Patient-specific induced pluripotent stem cells from cardiac progenitors recapitulate the models for cardiac chamber disorders

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Background: Zebrafish heart has shown to efficiently regenerate the lost myocardium after injury. Although the studies have indicated the genetic fingerprint essential for self-repair in lower vertebrate with single ventricle, yet, the genes potentially contributed to cardiac regeneration in human heart remain elusive. Here, we propose that the creation of disease-specific induced pluripotent stem (iPS) cells from patients with congenital heart malformation may provide an opportunity to uncover the genetic evidence for myocyte renewal in human.

Methods: Disease-specific iPS cells were generated from 15 patients including 10 single ventricle (SV) physiology and 5 biventricular (BV) hearts. Patient-derived cardiomyocytes (PCPs) were isolated and a combination of retroviruses encoding the human transcription factors Oct3/4, Sox2, KLF4, and c-Myc was transduced to isolate the cells for quantitative PCR and whole expression analysis. Bisulfite sequencing was assessed by using the primers amplifying the Oct3/4 and Nanog promoter regions.

Results: In culture, CPGs from SV hearts showed an enhanced proliferative potential compared with those from BV patients in consequence of more efficient IPS generation from these cells. Bisulfite sequencing analysis showed that Oct3/4 and Nanog promoter regions were demethylated in both types of IPS cells generated. Limiting dilution iPS cells from CPGs could form teratomas when injected into immunocompromised mice. Whole genome analysis revealed that Nck2, Tbx5, and Meliz were comparable between the CPGs isolated from SV and BV patients, consistent with similar calcium oscillation patterning in these cells. Inductive signals specific to second heart field development, including Isl1, Hand1, Wnt3a, GATA4, BMP type I receptor, and Bmp7, were significantly downregulated in SV-derived CPGs, however, Notch1 and Fox1 expressions increased remarkably compared with BV-derived CPGs. Upon cardiac differentiation, Nck2, Tbx5, Hand2, and Isl1 were significantly upregulated in BV-derived IPS cells, whereas these genes remained unchanged but GATA4 expression was enhanced in SV-derived IPS cells.

Conclusions: Our results suggest that factor-based reprogramming of patient-derived cardiac progenitors can efficiently generate disease-specific IPS cells. Single ventricle-derived CPGs and IPS cells have distinct characteristics during cardiac differentiation. Verification of genes prerequisite for zebrafish heart regeneration by using IPS cells may enable disease investigation and also facilitate the development of new cardiac regeneration therapy in human.

Electrophysiological integration of transplanted fetal and induced pluripotent stem cell-derived cardiomyocytes

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Purpose: The quality and the survival of transplanted fetal and induced pluripotent stem cell-derived cardiomyocytes (IPSCM) are regarded as promising cell type for cardiac regeneration. Verification of genes prerequisite for zebrafish heart regeneration by using IPS cells may enable disease investigation and also facilitate the development of new cardiac regeneration therapy in human.

Methods: We generated hiPSCs from keratinocytes from hair follicles and achieved directional cell-to-cell linkage of hiPS-CMs through one-year culture.

Results: We generated hiPSCs from keratinocytes from hair follicles, and achieved directional cell-to-cell linkage of hiPS-CMs through one-year culture.

Conclusions: We demonstrated the ultrastructural sarcomeric maturation process and achieved directional cell-to-cell linkage of hiPS-CMs through one-year culture.
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DPP4 inhibitor vildagliptin reverses diastolic left-ventricular dysfunction via the SDF-1alpha-dependent mechanisms in diabetes independently of glycemic control

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Purpose: Small molecule DPP4 inhibitors are widely used to treat diabetes. We aimed to explore clinical significances of DPP4 activity as the diagnostic marker and therapeutic target for diabetic heart failure by examining the effect of vildagliptin on diabetes-induced cardiac remodeling and diastolic left ventricular dysfunction (DHF) using streptozotocin-induced diabetic male rats (19 weeks old).

Methods and Results: Diabetes increased the cardiac DPP4 activity that exhibited. Cardiac catheterization and echocardiography revealed that vildagliptin (VIL; 10 mg/kg/day) ameliorated the diabetes-induced DHF (dp/dt; 6374.5±202.1 for veh and 9493.1±1115.4, Tau (msec); 20.0±1.7 (veh) and 15.5±3.2 (VIL), peak E (msec); 1.28±0.09 (veh) versus 1.49±0.2 (VIL), Dct (msec); 48.5±3.4 (veh) versus 23.2±0.2 (VIL)) independently of glycemic control. Immunohistochemical analysis revealed that vildagliptin treatment reversed the decline in the cardiomyocyte size and capillary density in diabetic rats. Cardiac SDF-1alpha level in the diabetic heart was decreased, which was reversed by VIL. The phosphorylation levels of eNOS and Akt were attenuated in diabetic subject and found that both reductions were reversed by VIL. We additionally evaluated the impact of genetic DPP4 deficiency using F344 rats and found that non-pharmacological loss of DPP4 activity consistently reversed the diabetes-induced DHF and remodeling.

Conclusions: These results suggest the ability of the model to recapitulate a disease phenotype. However additional experiments as well as further investigations into alterations in MYBPC3 protein levels and phosphorylation (western blot) as well as adenosin AT1Pase activity are currently being developed.

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Derivation and characterization of transgene free induced pluripotent stem cell derived cardiomyocytes from asian patient with long QT syndrome

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Purpose: Long QT syndromes are associated with prolonged ventricular repolarization and predisposed patients to risk of sudden cardiac death. We establish a new reporter in better understand electrical manifestations of Long QT Syndrome type 2 (LQTS2) in vitro.

Methods and Results: Dermal fibroblasts from a patient harboring a mutation of ASH1L (corresponding to C162T base pair) were transfected with keratin ion channel were reprogrammed using transgene free episomal based vectors to generate human induced pluripotent stem cells (hiPSC). They were differentiated into cardiomyocytes that manifested the LQT2S phenotype. While exhibiting both slower repolarization and cellular action potential (AP) prolongation compared to patient hiPSCs, they demonstrated prolonged repolarization period whereby field potential duration was significantly affected in comparison to normal controls (patient vs. control; 346±48 ms vs. 623±69 ms, p<0.05). Extracellular field potential recording following exposure of E-4031 in these LQT2 cardiomyocytes induced an overt ventricular tachycardia-like waveforms leading to contraction arrest. We further evaluated effects of commonly prescribed beta-blockers, in conjunction with beta-agonist stimulation, to mimic clinical management of such patients.

Conclusions: We report the first generation of viral-free hiPSC-derived cardiomyocytes from Asian patient with Long QT syndrome that respond appropriately to clinical drugs that could provide a clinical relevant model for LQT2 for better understanding of inherited cardiac arrhythmias.

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Human induced pluripotent stem cells as in vitro model for hypertrophic cardiomyopathy

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Purpose: The in vitro study of genetic diseases is thwart by many obstacles, especially because of the difficulty to obtain cardiomyocytes from patients and to expand and maintain those cells in long term cultures. Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by increased heart size and wall thickening in the absence of other cardiac or systemic diseases. It affects 1:500 individuals and is the leading cause of sudden cardiac death in young adults. In the Dutch population three founder mutations in the myosin binding protein C have been discovered, accounting for nearly one fourth of HCM cases in the Netherlands. MYBPC3 is a cardiac specific sarcomeric protein involved in modulations of force contraction modulation through intracellular calcium regulated phosphorylation. Recently it has become possible to reprogram somatic cells on Ca2+/calmodulin-dependent protein kinase II (CaMKII) as a mechanism of ROS increase working in the downstream of Ca overload using an animal model of diabetes mellitus.

Methods: Diabetes mellitus was induced by a single injection of STZ (60 mg/kg) into the tail vein of 250-300g Sprague-Dawley rats. Age matched control rats were injected with an equivalent volume of citrate buffer solution. Four weeks after the STZ injection, plasma glucose concentration of rats were ~300 mg/dL, and they were used for experiments.

Results: First, we confirmed that Ca level was increased in adult cardiomyocytes isolated from STZ-induced diabetic rat compared to those from control rat by ratiometric analysis of Fluo-3/Fura Red. Next, we investigated the ROS level in STZ-induced diabetic rat heart. Furthermore, the expressions of p47phox and p67phox, which are components of NADPH oxidase, were up-regulated in the heart of diabetic rats in a KN-93-inhibitable manner. These results indicate that activation of CaMKII works upstream of NADPH oxidase and increases ROS pro-

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Calmodulin kinase II dependent mitochondrial dysfunction by increased ROS production in STZ-induced diabetic rat heart

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Purpose: Increased reactive oxygen species (ROS) is one of the mechanisms of cardiac dysfunction in diabetes mellitus. In ESC congress 2011, we presented that sequential activation of Na-H exchanger and Na-Ca exchanger and subsequent Ca overload contributes to ROS increase using cultured neonatal cardiomyocytes exposed to high glucose concentration. In the present study, we focused on Ca2+/calmodulin-dependent protein kinase II (CaMKII) as a mechanism of ROS increase working in the downstream of Ca overload using an animal model of diabetes mellitus.

Methods: Diabetes mellitus was induced by a single injection of STZ (60 mg/kg) into the tail vein of 250-300g Sprague-Dawley rats. Age matched control rats were injected with an equivalent volume of citrate buffer solution. Four weeks after the STZ injection, plasma glucose concentration of rats were ~300 mg/dL, and they were used for experiments.

Results: First, we confirmed that Ca level was increased in adult cardiomyocytes isolated from STZ-induced diabetic rat compared to those from control rat by ratiometric analysis of Fluo-3/Fura Red. Next, we investigated the ROS level in the heart of diabetic rat. Level of 8-OhdG was significantly higher in STZ diabetic rats than that in control; however, this increase was attenuated by the treatment with KN-93, an inhibitor of CaMKII, and apocynin, a NADPH oxidase inhibitor. Consistently, the expression of phosphorylated CaMKII was up-regulated in STZ-induced diabetic cardiomyocytes but not in the control cardiomyocytes. In addition, a significant alteration in response to changes in extracellular calcium of HCM-iPS derived cardiomyocytes was observed compared to three independent control lines (determined by changes in beating frequency).

Conclusions: Our results propose a potential role for DPP4 activity in therapeutic target and diagnostic marker for diabetic heart failure.
The soluble guanylate cyclase activator cinaciguat improves cardiac dysfunction in diabetes mellitus

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Purpose: Patients with diabetes mellitus exhibit cardiovascular dysfunction along with increased oxidative stress and decreased nitric oxide – cyclic guanosine monophosphate (cGMP) signaling. It has been reported, that elevated intracellular cGMP-levels contribute to an effective cytoprotection against oxidative stress. In this study we investigated the effects of cinaciguat, a newly developed soluble guanylate cyclase activator on myocardial dysfunction in type 1 diabetes mellitus.

Methods: In male Sprague-Dawley rats diabetes was induced by a single ip. injection of streptozotocin (60mg/kg). In the treatment groups, cinaciguat (10mg/kg/d) was applied orally for 8 weeks. Rats of the control groups received vehicle for the same time. After the treatment left ventricular (LV) pressure-volume relations were measured by using a microtip Millar pressure-volume conductance catheter, and indexes of contractility (e.g. preload recruitable stroke work (PRSW)) were calculated. Blood plasma and myocardial tissue samples were collected for determination of cGMP-levels and immunohistochemical analysis, respectively. Myocardial gene expression analysis has been performed by quantitative real-time polymerase chain reaction (qRT-PCR).

Results: When compared to the non-diabetic controls, diabetic rats showed impaired left ventricular contractility (PRSW: 49.5±3.3 vs. 83.0±5.5mmHg, p<0.05) and a marked diastolic dysfunction (time constant of LV pressure decay, Tau: 17.3±0.8 vs. 10.3±0.3ms), which was significantly improved by cinaciguat (PRSW: 66.8±3.6mmHg, Tau: 14.9±0.6 ms in the diabetes-cinaciguat group). The treatment had no hemodynamic effects in non-diabetic control animals. Diabetic rats showed a significant reduction of cGMP levels (3.3±0.3 pmol/ml) in myocardial tissue samples after cinaciguat treatment. Efficacy of the therapy was reflected by markedly elevated levels of cGMP in the diabetes-cinaciguat group compared to control (44.2±11.4 vs. 16.2±2.0 pmol/ml plasma).

Conclusions: Our results demonstrate that cinaciguat prevents diabetes-associated deleterious myocardial changes and improves diabetic cardiac dysfunction in our rat model. Pharmacological soluble guanylate cyclase activation might represent a novel therapy approach for diabetic cardiomyopathy.

Conclusion: For the first time we directly recorded human mitoCx43 hemichannels which were inhibited by 43GAP27. Our results indicate endogenous protective adaptation mediated via enhanced basal mito-Cx43 hemichannel activity through hyperphosphorylation of the mitochondrial Cx43 fraction in heart failure.

Glucon-like peptide-1 receptor activation ameliorates cardiac steatosis and reverses pathological remodeling by quality control of mitochondria via cAMP/PKA axis

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Purpose: Glucagon-like peptide-1 receptor (GLP-1R) agonist exendin-4 facilitates cardiac contractility in systolic dysfunction model in rodents and patients with heart failure. However, the impact of GLP-1R on cardiac steatosis remains unclear.

Methods and Results: Male KK/AY mice (16-week-old) were allocated into exendin-4 (24 rmole/kg/day, 40 days; KK-ex4) and vehicle group (KK-v). Male C57BL6 mice were fed with high fat diet for 3 months (DIO) and subjected to exendin-4 treatment at the age of 16 week old (DIO-ex4 and DIO-v). KK-ex4 inhibited decline in heart weight (-16.5% vs KK-v) without body weight loss. Oil-red-O staining revealed that KK-ex4 and DIO-ex4 reduced cardiac steatosis. Echocardiography revealed that systolic function of DIO-v was suppressed (-13.8% vs control), which was restored in DIO-ex4 with reduced LVPWd (-11.1% vs DIO-v) and IVSd (-30.0% vs DIO-v). Myocardial fibrosis and tissue oxidative stress detected by DHE staining were reduced in KK-ex4 and DIO-ex4 (0.45±0.10 fold and 0.58±0.10 fold vs vehicle). Transmission electron microscopy revealed restoration of irregular alignment and increase in number of mitochondria with normal cristae in KK-ex4 and DIO-ex4. Mitochondria-specific dyes (MitoTracker Red) revealed decline in oxidative activity of cardiac mitochondria both in KK-ex4 and DIO-ex4. The levels of myocardial PINK/Parkin, the surrogate indicators for damaged mitochondria, were reduced both in KK-ex4 and DIO-ex4.

Conclusion: GLP-1R activation protects cardiac remodeling induced by steatosis through the restoring mitochondrial oxidative damage mediated by the activation of cAMP/PKA-dependent mechanisms.

Expression and physiological role of the novel adipokine nestatin-1 in cardiomyocytes

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Purpose: Nestatin-1 is a novel adipokine involved in the control of food intake and energy metabolism which shows anti-inflammatory properties. The role of this adipokine in cardiovascular physiology is unknown. In previous studies we determined that nestatin-1 is expressed in human, rat and mouse heart. Our aim now is to study the effect of this adipokine in cardiomyocytes and the possible regulation of nestatin-1 cardiac synthesis by diet and inflammatory mediators.

Methods: Real-time PCR was used to determine nestatin-1 mRNA levels in cultured neonatal cardiomyocytes of Sprague Dawley rats treated with TNF-α, dexamethasone and insulin. In heart tissue of rats fed with high fat diet for 16 weeks, we used real-time PCR to determine nestatin-1 cardiac mRNA levels and an ELISA to determine nestatin-1 plasma levels. Cardiomyocytes were treated with nestatin-1 and conofical microscopy was used to study the glucose transporter Glu-4 movilization. Finally, western blot was used to identify possible transducing signaling molecules (Erk, AMPK and AKT) after nestatin-1 treatment in cardiomyocytes.

Results: Cardiomyocytes treatment with 0.1-20 ng/ml TNF-α for 6-48 h induces an increase of nestatin-1 mRNA levels with a maximum stimulatory effect at 20 ng/ml for 24 h (p=0.0159; Fold-Change (FC)=1.16, n=5). Treatment with 0.1-100 nM dexamethasone for 6-48 h also increases of nestatin-1 mRNA levels with a maximum stimulatory effect at 100 nM for 24 h (p=0.0079; FC=2.457, n=5).

Figure 1. Typical mitochondria images by TEM
Adherence to the Mediterranean diet and albuminuria

Dietary omega-3 acid ethyl esters enhance omega-3

Influence of potassium intake on blood pressure of

p=0.039), whereas had lower heart rate (84 vs 87 bpm, p=0.014) and ACR lev-
to those with low KIDMED score exhibited higher systolic BP (117 vs 114 mmHg, (n=54), plasma creatinine
lected for 12 h (7 pm to 7 am) in the night previous to the hospital visit to as-
methods during a programmed visit to the University Hospital. Urine was col-
Brazil, was recruited to investigate cardiovascular risk factors. BP , anthropometry

Cardiac levels of this adipokine are modified by inflammatory and metabolic status.

Conclusions: In cardiomyocytes nesfatin-1 regulates glucose homeostasis. Car-
diac levels of this adipokine are modified by inflammatory and metabolic status.

Our work provides the first evidences about a potential role of nesfatin-1 in a paracrine/autocrine system at cardiac level.

NON PHARMACOLOGICAL TREATMENT IN HYPERTENSION

Adherence to the Mediterranean diet and albuminuria levels in adolescents: Emerging data from the Lyceum Leontio Albuminuria (3L) Study


Purpose: Mediterranean diet has favorable effects on the cardiovascular system, while albuminuria is associated with atherosclerosis progression. The aim of the study was to investigate the relationship of dietary habits with urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR), in a cohort of adoles-

Methods: A total of 365 adolescents 12-17 years of age (212 males, aged 13.9 years, office blood pressure (BP)=115/67 mmHg) that were included in the Lyceum Leontio Albuminuria (3L) study were considered for analysis. In all particip-
tors values were determined in a morning urine and for each adolescent a questionaire was completed on lifestyle and socio-economic characteris-
tics. Moreover, the Mediterranean Diet Quality Index for children and adolescents (KIDMED) was estimated and accordingly subjects were divided into those with optimal (≥7), average (4-7) and low (<4) score.

Results: Only 6.8% of the participants had optimal KIDMED score, whereas 51.2% had an average and 42% had a low score. Participants with at least aver-

KIDMED score (n=187) compared to those with low KIDMED score (n=153) had higher body mass index (22.2 vs 21.4 kg/m², p=0.043) and waist circum-
ference (77.6 vs 75.4 cm, p=0.044), spent more frequently time for sports ac-

In adolescents there is an inverse relation of KIDMED score with body mass index and waist circumference. The subgroups with optimal KIDMED score were leaner and spent more time for sports and leisure activities. They also had healthier eating habits than those with a lower KIDMED score.

Conclusions: A higher KIDMED score is associated with lower body mass index and waist circumference. The Mediterranean diet has a role in leptin levels and weight gain in children. Further studies are needed to investigate this relation in a larger population.

Influence of potassium intake on blood pressure of subjects with different levels of sodium consumption

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Background: Increase of potassium (K) intake has been recommended as a non
pharmacologic strategy to reduce blood pressure (BP) levels and hypertension in-
cidence. However, the benefits of such strategy in subjects with different patterns of sodium (Na) intake have not been evaluated. In this study we investigated in a population-based study the influence of the K intake on BP of individuals con-
suming low (<6 g/day) or high (>6 g/day) salt diets.

Methods: A random sample (n=1,661) of the adult (25-64 population) of Vitoria, Brazil, was recruited to investigate cardiovascular risk factors. BP, anthropometry and biochemical variables (lasting blood) were obtained according to standard methods during a programmed visit to the University Hospital. Urine was col-
gathered randomly from 7 am to 7 pm in the urine collected just before the hospital visit to assess Na, K and creatinine excretion. Individuals with inadequate urine collection (n=54), plasma creatinine >1.4 mg/dl (n=52) or under use of any hypertensive medication, including diuretics (n=270) were excluded from the present analysis.

Variables are shown as mean±standard deviation. Statistical significance was set atp<0.05.

Results: Data refer to 1,285 subjects (613 men, age >43±10 y). Hypertension (blood pressure >140/90 mmHg) was found in 31%, obesity (BMI>30 kg/m²) in 15.5% and diabetes (fasting glycemia >125 mg/dL) in 5.3%. Mean urinary Na and K excretion was 99±57 meq/L and 23±15 meq/L, giving a mean daily consump-
tion of 211 meq of Na and 78 meq of K. Higher K intake was associated with individuals older and with higher BMI and urinary Na excretion. Systolic and dias-
tolic BP mean levels were stable along quartiles of urinary K excretion. However, significant (P<0.001) decrease was observed for the systolic and diastolic BP adjusted for age, BMI and 12 h Na and creatinine excretion. Interestingly, the as-
sociation between K excretion (as surrogate of K intake) was lost in the subgroup of subjects (N=182) consuming >6 g salt/day (-1.20 g Na/12 h urine). In subjects consuming >6 g salt/day, the adjusted systolic and diastolic BP were, respectively, 7 mmHg and 3 mmHg lower in those in the upper urinary K excretion quartile (>28 mg/dL) as compared with those in the lowest one (<14 mg/dL).

Conclusion: Our data confirm based in data obtained in the general population that increasing the K intake may partially inhibit the hypertensive effect of high salt diets. This strategy seems to be more effective in high salt consumers.

Financial support – CNPq and FINEP

Dietary omega-3 acid ethyl esters enhance omega-3 index, attenuate myocardial arrhythmogenic substrate and protect from malignant arrhythmias in a model of human essential hypertension

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Background and Purpose: Hypertension-induced myocardial remodeling is known to be associated with increased propensity to malignant arrhythmias that can be attributed to impairment of cell-to-cell synchronization due to alterations in electrical coupling protein, connexin-43 (Cx43). Omega-3 fatty acids (omega-3) exert cardioprotective and antiarrhythmic effects in both experimental and clinical settings. We tested our hypothesis that dietary omega-3 intake can protect of hyperten-
sive rats from malignant arrhythmias via protection of intercellular communication ensured by Cx43 channels.

Design and Methods: Experiments were conducted on male spontaneously hy-
pertensive rats (SHR) at early (3month) and late (12 month) stage of diseases as well as age-matched normotensive Wistar rats. Untreated rats were compared with animals supplemented by omega-3 (EPA+DHA) ethyl esters. Vlček, Slovakia, 30 mg/day for two month. Blood pressure, body, heart and left ventri-
cle weights were monitored. Plasma and red blood cells (RBC) fatty acids profile (omega-3 index) was estimated by gas chromatography. Left ventricular tissues were taken for examination of Cx43 distribution (using immunostaining and electron microscopy) and expression (using immunoblotting). Expression of protein kinases C (PKC), which phosphorylates Cx43 was examined as well. Langendorff-
isolated hearts were used to test inducible VF.

Key results: Comparing to healthy rats the omega-3 index was lower in old SHR (0.7% vs 2.5%) and increased due to omega-3 intake in both groups to 2.3% and 4.8% in young and old SHR, respectively. Increase of Cx43 expression was also observed in young and decrease in old SHR. Hyperkalemic excitation of hearts but phosphorylated (functional) forms of Cx43 were suppressed in both SHR groups. In contrast, omega-3 intake diminished arrhythmogenic substrate, i.e. abnormal Cx43 distribution and attenuated significantly abnormal Cx43 ex-
pression and phosphorylation. The latter was linked with enhanced PKCe expression. Consequently, omega-3-treated SHR were less prone to inducible VF comparing to untreated rats.

Conclusions: Results indicate that hypertensive rats benefit from omega-3 fatty acids supplementation due to an increase of omega-3 index, alleviation of Cx43-related arrhythmogenic substrate and suppression of malignant arrhythmias. This work was supported by VEGA 2/0406/12 grant.

AT1 receptor blockade attenuates insulin resistance and myocardial remodeling in rats with diet-induced obesity

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Interactions between angiotensin II type 1 (AT1) receptor and insulin has clas-
sically resulted in insulin resistance and cardiomyopathy. This study evaluated the influence of AT1 receptor blocker losartan on insulin receptor/phosphotyrosine 3-kinase (P3K-kinase) pathway and myocardial remodeling in rats with diet-induced obesity.
Methods: Male Wistar-Kyoto rats (n=40) were subjected to a standard rat chow (C, 3.2kCal/g) or a hypercaloric diet (OB, 4.6kCal/g) for 30 weeks and then allocated into four groups: C, CL, OB, and OBL. L groups received losartan in drinking water (30mg/kg/day). After five weeks, body weight and adiposity, glycemia, and insulin serum concentration were evaluated. Systolic blood pressure was analyzed by tail plethysmography. Myocyte cross-sectional area and collagen intensity were measured in left ventricle histological sections stained with hematoxilin-eosin and picrosirius red, respectively. Myocardial total and tyrosine phosphorylated forms of insulin receptor β-subunit (IRβ) and PI3-kinase were visualized by Western blot. Statistical analysis: ANOVA and Tukey’s test.

Results: Both OB and OBL groups presented higher body weight and adiposity indexes than their respective controls (p<0.001). Glycemia, insulin serum concentration, and SBP were higher in OB than in C (p<0.05); these variables did not differ between CL and OB (p>0.05). Myocyte cross-sectional area (C 289±12; OB 332±23; CL 292±19; OBL 290±10μm²) was significantly higher in OB than in C and OBL. Collagen interstitial fractional volume (C 2.89±0.81; OB 4.81±0.41; CL 1.89±0.61; OBL 4.46±0.73%) was significantly higher in OB than in C. Western blot results are shown in the Table.

Conclusion: Losartan attenuates insulin resistance and myocardial remodeling in obese rats.

Support: RAPESP

NEW INSIGHTS IN MICRO AND MACROVASCULAR CORONARY ARTERY DISEASE

269 Plasma endothelin and adrenomedullin are associated with coronary conduit and microvascular function

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Purpose: Endothelin (ET-1) and adrenomedullin (ADM) are potent vasoactive peptides. ET-1 is a vasoconstrictor and an elevated level is associated with cardiovascular disease (CVD). ADM is a vasorelaxant and may result in protection from atherosclerosis in experimental studies. We sought to determine the relationship of ET-1 and ADM with coronary conduit and microvascular resistance.

Methods: Patients with chest pain syndromes having coronary angiography were recruited (n=32). Plasma ET-1 and ADM level were measured. Coronary flow mediated dilatation (FMD) was defined as percentage increase in coronary diameter during maximal hyperaemia as assessed by quantitative coronary angiography (QCA). Index of microcirculatory resistance (IMR) and coronary flow reserve (CFR) were measured by coronary pressure guidewire. Pearson’s correlation and linear regression analysis were used to determine the relationship between plasma biomarkers and coronary measures.

Results: Mean age was 66±9 year-old with 69% male. The sample included patients with hypertension (75%), dyslipidemia (84%), diabetes (34%) and current smokers (13%). Mean BMI was 33.6±6 kg/m² and 66% had prior coronary artery disease. The correlation between plasma biomarkers and coronary function is displayed in the table below.

For each 1pmol/L increase in ET-1, IMR increased by 7 units (95%CI 2.8, 10.5; p<0.01). For each 1pmol/L increase in ADM, CFR increased by 0.20 (95%CI 0.01, 0.40; p=0.04) and FMD increased by 0.92% (95%CI 0.29, 1.55; p=0.001). After adjustment gender, age, mean blood pressure, hypertension, dyslipidemia, BMI, and glucose and cholesterol, the relationship between ADM and CFR and FMD remained significant, the association between ET-1 and IMR (r=−0.79;95%CI 1.4, 10.0; p=0.01), and between ADM and FMD (r=−0.79;95%CI 0.45, 1.13; p<0.01) remained significant.

Conclusion: Significant independent relationships were found between plasma ET-1 and IMR, and plasma ADM with coronary FMD. Plasma vasoactive factors have differential effects on coronary conduit and coronary microvascular function.

Coronary microvascular dysfunction induced by primary hyperparathyroidism is restored after parathyroidectomy

E. Osto1, F. Fallo1, M.R. Pelizzo1, A. Maddalozzo1, F. Corbetti1, R. Montori2, R. Bellu1, T. Lucher1, S. Iliceto1, F. Tona1. 1University of Padua Polyclinic, Padua, Italy; 2University of Cagliari, Cardiology Clinic, Cagliari, Italy; 3Department of Cardiology, University Hospital and Cardiovascular Research, Institute of Physiology, University of Zürich, Zürich, Switzerland

Purpose: Symptomatic primary hyperparathyroidism (PHPT) is associated with increased cardiovascular mortality. However, data on the association between asymptomatic PHPT and cardiovascular risk are lacking. We assessed coronary flow reserve (CFR), as a marker of coronary microvascular function, in asymptomatic PHPT of recent onset.

Methods: We studied 100 PHPT patients (pts) (80 F, aged 58±12 years) without cardiovascular disease, and 50 controls matched for age and gender. CFR in the left anterior descending coronary artery (LAD) was detected by transcoronary

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251 Double blind, randomized, cross over, controlled clinical trial of nacl + chitosan 3% on high blood pressure parameters in association with diet and lifestyle recommendations

F.A. Allaert. Medical evaluation chaire esc, Dijon, France

Studycontext: Most of hypertensive patients have difficulties to reduce salt intake. We studied an association of Chitosan (chitine extract) with NaCl according a specific chemical procedure which could reduce the hypertensive power of the Cl.

Mainobjective: The main objectives was to compare the decrease of the high blood pressure parameter with Symbiosal (NaCl + Chitosan 3%) and with NaCl during the diet and lifestyle improvement period which must be prescribed to the patient before an eventual antihypertensive treatment.

Studydesign: Double blind, randomize, cross over, controlled clinical trial of Symbiosal (NaCl + Chitosan 3%) vs NaCl on two groups of 20 patients during two periods of 8weeks. Inclusion criteria: Men and women older than 18 years presenting a mild hypertension defined by a SBP between 140-159 mmHg and a DBP between 90-99 mmHg and having never been treated with antihypertensive drug.

Results: 40 patients were included in the ITTAnalysis and the effect of Symbiosal was available (decrease of 13.1±2.7 mmHg for SBP, 4.9±1.9 mmHg for DBP and 1.8±0.3% for IMR (C; 3.2Kcal/g) or a hypercaloric diet (OB; 4.6Kcal/g) for 30 weeks and then allo-

Variables Adrenomedullin Endothelin

<table>
<thead>
<tr>
<th>Coronary Flow Reserve</th>
<th>Index of Microcirculatory Resistance (units)</th>
<th>Coronary Flow Mediated Dilatation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>r=0.50 (p&lt;0.04)</td>
<td>r=0.47 (p&lt;0.01)</td>
<td>r=0.62 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Conclusion: Switching traditionalNaCl by Symbiosal significantly contributes to a bloodcontrol of hypertension in association to the lifestyle and dietrecommendations and may delay the prescription of antihypertensive drugs.

The music therapy in patients with hypertension and myocardial infarction; 12-year experience

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Unrelieved anxiety can produce an increase in sympathetic nervous system activity leading to an increase in cardiac workload. Patients who have clinical evidence of hypertension (HT) after acute myocardial infarction (AMI) have a poor prognosis. The purpose of this study was to evaluate the effectiveness of music therapy for reduction of new coronary events (NCE) in patients with HT and AMI after previous coronary artery bypass surgery (CABG).

Methods: 768 patients (males 79.8%, mean age 60.2±8.6 years) with AMI have been selected from the patients consecutively submitted from January 1990 to January 2012. HT was registered in 406 (53%) pts with AMI. All patients with HT were randomized and divided in 2 groups. Study group of 204 patients treated with music therapy and Control group of 202 patients with no music therapy. Each patient in study group underwent two sessions of medical therapy (12 minutes) in a day. Both groups were similar in baseline, post AMI characteristics and post AMI medical therapy.

Results: Comparing parameters of Study and Control group of patients in 12- year follow-up period. Statistic had lower anxiety score (r=−0.18, p=0.10) with statistically significant reduction in systolic blood pressure (p=0.004), diastolic blood pressure (p=0.0084), heart rate (p=0.0204), angina (p=0.0146), reinfarction (p=0.0216) and sudden deaths (p=0.004).

Conclusion: This study provides support for the use of music therapy in patients with HT and AMI to reduce blood pressure, heart rate and new coronary events expression. These effects of music therapy are probably because of decreasing in sympathetic nervous system activity.

270 Coronary microvascular dysfunction induced by primary hyperparathyroidism is restored after parathyroidectomy

E. Osto1, F. Fallo1, M.R. Pelizzo1, A. Maddalozzo1, F. Corbetti1, R. Montori2, R. Bellu1, T. Lucher1, S. Iliceto1, F. Tona1. 1University of Padua Polyclinic, Padua, Italy; 2University of Cagliari, Cardiology Clinic, Cagliari, Italy; 3Department of Cardiology, University Hospital and Cardiovascular Research, Institute of Physiology, University of Zürich, Zürich, Switzerland

Purpose: Symptomatic primary hyperparathyroidism (PHPT) is associated with increased cardiovascular mortality. However, data on the association between asymptomatic PHPT and cardiovascular risk are lacking. We assessed coronary flow reserve (CFR), as a marker of coronary microvascular function, in asymptomatic PHPT of recent onset.

Methods: We studied 100 PHPT patients (pts) (80 F, aged 58±12 years) without cardiovascular disease, and 50 controls matched for age and gender. CFR in the left anterior descending coronary artery (LAD) was detected by transcoronary...
Doppler echocardiography (TDE), at rest and during adenosine infusion. CFR was the ratio of hyperemic diastolic flow velocity (DFV) to resting DFV.

**Results:** In PHPT, CFR was lower than in controls (3.0±0.6 vs 3.8±0.7, p<0.001). A CFR was abnormal (<2.5) in 27 (27%) pts compared with controls (4%) (p=0.001). CFR was inversely related to parathyroid hormone (PTH) levels (r=-0.3, p<0.004). In pts with CFR ≤2.5 PTH was higher (28.4 [16.37] vs 18 [13-26] pmol/L, p=0.007) whereas calcium levels were similar (2.9±1.1 vs 2.8±2.3 mmol/L, p=0.2). At multivariable linear regression analysis, PTH and age were the only determinants of CFR (p=0.03 and p=0.01 respectively). At multiple logistic regression analysis only PTH increased the probability of CFR ≤2.5 (p=0.001).

In all 27 PHPT pts with CFR ≤2.5, parathyroidectomy normalized CFR (3.3±0.7 vs 2.1±0.5, p<0.0001).

**Conclusions:** PHT pts have coronary microvascular dysfunction which is completely restored after parathyroidectomy. PTH independently correlates with the coronary microvascular impairment, suggesting a crucial role of the hormone to explain the increased cardiovascular risk in PHPT.

## Relationship between leukocyte and subtype counts, low-grade inflammation and slow coronary flow phenomenon in patients with angiographically normal coronary arteries

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**Background:** Slow coronary flow (SCF) is an angiographic finding characterized by the slow reduction of epicardial coronary arteries in the absence of obstructive coronary disease. We aimed to investigate whether there is a positive correlation between leukocyte counts, high-sensitive C-reactive protein (hsCRP) and SCF determined by frame rates.

**Methods:** Forty-seven patients with NCA and SCF in all three coronary vessels and 30 sex and age matched control participants with NCA but without SCF were investigated. The quantification of the coronary flow was assessed by the thrombolyis in myocardial infarction (TIMI) frame count (TFC) in all coronary arteries.

**Results:** hsCRP was significantly positively correlated with mean TFC (r=0.52, p<0.001). Besides, leukocytes, neutrophils and monocytes were significantly positively related to mean TFC (r=0.35, p=0.002; r=0.29, p=0.009 and r=0.01, p=0.001, respectively). In multivariate analyses, only hsCRP (β=3.24, p=0.003) and monocyte count (β=0.39, p=0.003) were related to SCF determined by TFC.

**Table 1. The independent effects of hsCRP and monocytes on slow coronary flow phenomenon**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean TFC (Dependent variable)</th>
<th>SCF (Dependent variable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>0.1±0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Gendar (male)</td>
<td>0.4±0.9</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension, +</td>
<td>0.2±1.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus, +</td>
<td>0.1±1.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking, +</td>
<td>0.0±2.1</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>Hypertension + diabetes mellitus</td>
<td>2.3±2.1</td>
<td>0.0±1.1</td>
</tr>
<tr>
<td>HsCRP (mg/L)</td>
<td>1.5±2.1</td>
<td>0.347</td>
</tr>
<tr>
<td>Monocyte (×10^3/mm³)</td>
<td>0.02±0.01</td>
<td>0.534</td>
</tr>
<tr>
<td>Neutrophil (×10^3)</td>
<td>0.001±0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Conclusion:** Our results showed that circulating monocytes and low-grade inflammation predicted a slow coronary flow phenomenon, which may be pivotal for further studies searching the specific roles of monocytes and hsCRP on SCF phenomenon in coronary vasculature.

## Anemia and inflammation have an additive value in risk stratification of patients undergoing percutaneous coronary interventions

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**Aims:** We have previously showed that inflammation was associated with lower hemoglobin (Hb) concentrations in myocardial infarction (MI) patients prior to their percutaneous coronary intervention (PCI). We now aimed to analyze the additive value of Anemia and Inflammation on the outcomes of patients undergoing (PCI).

**Methods and Results:** We performed an analysis on prospectively collected data at a tertiary hospital cardiology laboratory between 2006-2011. Cox regression models were fitted for Hb and high sensitivity C-reactive protein (CRP) cutoffs and performed separately for MI and angioplastia (AP) patients. Major adverse cardiovascular events (MACE) were defined as all-cause mortality, MI and stroke. Follow up time was defined as the time form PCI to either MACE or November 20, 2011. Included were 1976 patients (865 with AP and 1111 with MI). The median follow up in the MI and the AP groups were 14 and 13 months, respectively. In the MI group, the risk of MACE during follow up was increased with the presence of either anemia (HR=2.1, p=0.07) or of elevated CRP (HR=1.9, p=0.04), while the presence of both increased the risk even further (HR=3.4, p=0.01). In the AP group, the risk of MACE was increased only in patients who had both anemia and elevated CRP (HR=2.9, p=0.01). In general, traditional risk factors as well as coronary disease severity did not predict adverse outcomes during the follow-up period.

**Conclusions:** Anemia and inflammation are independently and additively associated with MACE in MI patients.

## Increased levels of circulating endothelial microparticles and erythrocyte degradation products in microvascular angina

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**Purpose:** Microvascular angina (MVA) is a rare condition associated with myocardial ischemia and no evidence of epicardial coronary artery obstructive lesions. Although MVA is related to endothelial dysfunction, its precise pathophysiology still remains partially unknown. Enhanced hemolysis and free heme release can impair endothelial function, through direct endothelial injury and nitric oxide scavenging. We sought to investigate if MVA was associated increased hemolysis phenomenon that could lead to endothelial injury.

**Methods:** Patients without acute coronary syndromes who underwent a coronary angiography in our institution were screened for inclusion. Patients were classified in 3 groups, according to their clinical presentation and angiographic features: patients with stable CAD, patients with MVA (as defined by the Lanzer criteria) and subjects with cardiovascular risk factors (CRF) and no evidence of ischemia on non invasive medical test. Levels of endothelial (CD144a and CD31/-/-) EMPs, erythrocytes (CD35+ RBCMPs), platelets (CD41+ PMPs) and leukocytes-derived microparticles (CD11+ LMPs) were measured by flow cytometry methods on free platelets plasma samples. Levels of circulating free heme (CFH) were analyzed by absorption spectrophotometry methods.

**Results:** A total of n=104 subjects (62 ±6.1 ±2.5 years and 75% male gender) were included in the study (n=9 MVA patients, n=71 CAD patients and n=24 CRF patients). Patients with MVA displayed significantly higher levels of circulating RBCMPs (1485 ±657 ±241 ev/L) compared to CAD (672 ±25 ±1) and CRF patients (266 ±72 ev/L, p=0.01 ANOVA). Moreover, we also observed a significant increase in CFH levels in MVA patients (0.79 ±0.19 Units/L) compared to the others (0.44 ±0.03 and 0.66 ±0.10 Units/L, p=0.01 for all), suggesting an endothelial injury in these patients. No significant difference was observed for LMPs and PMPs levels between groups.

**Conclusions:** Patients with MVA have evidences of enhanced hemolysis with increases in circulating free heme and erythrocytes derived MPs levels as well as increased endothelial injury circulating biomarkers.

## Elevated plasma inflammatory markers and activated NF-kB in patients with coronary artery ectasia

**J. Li, J.-L. Nan, L. Li, C.-M. Yang, S.-P. Nie, Z.-C. Li, Z.-C. Li on behalf of the Lian-Jun Li. Division of Dyslipidemia, Cardiovascular Medicine, Fu Wai Hospital, Peking Union Medical College and, Beijing, China, People's Republic of China**

**Background:** The role of inflammation in atherosclerosis is increasingly well known. However, there is a paucity of small sample size study, on the role of inflammation in coronary artery ectasia (CAE). The purpose of the present study was to investigate whether a chronic inflammatory status and activated nuclear factor-kB (NF-kB) pathway exists in patients with isolated CAE.

**Methods and Results:** A total of 107 consecutive patients with chest discomfort were enrolled in a multicenter manner, and the their plasma levels of high-sensitivity C-reactive protein (CRP) and interleukin-6 (IL-6) were examined by ELISA on admission. NF-kB activity derived from circulating white blood cells in 63 patients with non-obstructive isolated CAE and 44 age- and sex-matched angiographically normal coronary controls was determined by electrophoretic mobility shift assay. The NF-kB activity showed as a band, and value calcula...
Paradoxical preservation of NO signalling in Takotsubo cardiomyopathy

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Introduction: Takotsubo cardiomyopathy (TTC) is characterized by the sudden development of segmental (usually periapical) left ventricular systolic dysfunction, usually in post-menopausal women and often after acute severe stress. To date, little information is available concerning the mechanisms(s) underlying this presumably ‘chemical’ asymmetric myocardial process, other than evidence of associated catecholamine secretion. We tested the hypothesis that TTC might also be associated with impairment of nitric oxide (NO)-based signalling.

Methods: In 56 patients with TTC, we utilized (1) platelet responsiveness to NO and (2) plasma levels of asymmetric dimethylarginine (ADMA) as indices of potential NO effect. Additionally, endothelial progenitor cell (EPC) counts, which are partially NO-dependent, were evaluated. We sought correlations between these parameters, measured at the time of diagnosis and 3 months thereafter, and (1) severity of TTC episodes and (2) extent of recovery after 3 months. An aging female population sample (n = 110) was used for control purposes.

Results: Surprisingly, platelet NO responsiveness was substantially elevated (p = 0.005) and ADMA concentrations lowered (p = 0.005) in TTC vs. control subjects both acutely and after 3 months (Figure 1). Furthermore, extent of platelet NO responsiveness correlated directly with several markers of severity of TTC attacks. However, ADMA levels were predictive of markers of incomplete recovery at 3 months (p = 0.001).

Conclusions: In conclusion, (1) TTC is associated with “paradoxical” integrity of NO signalling and (2) there is a direct relationship between tissue NO responsive-ness and severity of TTC episodes. Acute NO generation may both contribute to the extent of acute myocardial injury and to subsequent rapid recovery in TTC.

Coronary flow reserve versus CT scan study to differentiate non-ischemic from ischemic dilated cardiomyopathy

F. Rigo1, N. Gabazzi2, E. Grolla1, C. Rewerber1, G. Ossena2, 1d’Angelo Hospital Department of Cardiology, Mestre-Venice, Italy; 2Hospital ‘dell’Angelo’, Department of Cardiology, Mestre-Venice, Italy

Background: Discriminating the underlying mechanism of dilated cardiomyopathy represents a key for proper management and therapy with significant impact for patient outcome.

Aim: To compare the diagnostic value of an integrated study based on coronary flow reserve on left anterior descending coronary artery (CFR-LAD) and multidetector CT (CTA) scan in patients with unknown dilated cardiomyopathy (DCM).

Methods: Since 2009, we have prospectively enrolled 131 consecutive patients with DCM (95 males, mean age 63±16 years) who underwent dipyridamole (up to 0.84 mg/kg over 6’ stress echo with combined assessment of CFR-LAD by transthoracic Doppler. A value of CFR <2.0 was taken as abnormal. Within 7 days, a multidetector coronary CT, for both CaS and CTA assessment, was performed. Each patient underwent coronary angiography (CAG) within 30 days and a quantitatively assessed vessel stenosis ≥50% was considered significant.

Results: CFR-LAD (≥1.6) had an AUC=0.90, CaS (≥90) had an AUC=0.86 and the finding of at least 1 obstructive coronary stenosis (≥50%) with CTA had an AUC=0.96 in order to predict obstructive coronary artery disease (CAD) at coronary angiography, configuring an ischemic DCM.

Conclusions: Conventional risk factors for coronary disease were fairly useful in predicting DCM due to coronary disease (global chi square=42.0). By progressively adding CaS, CFR-LAD and finally CTA, we provided increasingly accurate information (p<0.001 for all sequential comparisons) for predicting the underlying cause of DCM correctly.

Table 1

<table>
<thead>
<tr>
<th>No</th>
<th>Chemosensitivity</th>
<th>Hemodynamic response to transient hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L/min%</td>
<td>SBP slope mmHg%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR slope bpm%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SVR slope dyn s cm⁻¹%</td>
</tr>
<tr>
<td>Control</td>
<td>0.22±0.25</td>
<td>0.41±0.28</td>
</tr>
<tr>
<td>CHF low chemosensitivity</td>
<td>0.03±0.19</td>
<td>0.57±0.28</td>
</tr>
<tr>
<td>CHF high chemosensitivity</td>
<td>1.11±0.32</td>
<td>1.17±0.71</td>
</tr>
</tbody>
</table>

*p < 0.05 CHF high CHS vs control, p < 0.05 CHF high CHS vs. CHF low CHS.

Conclusions: In CHF patients, despite comprehensive neurohumoral blockage high peripheral CHS is related to augmented SBP, HR and SVR response to hypoxia. As such patients often experience episodes of transient desaturations, they are prone to disadvantageous haemodynamic changes, which may contribute to disease progression.
Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients

J-C. Reil1, J-C. Tardif2, I. Ford3, S.M. Lloyd4, E. O’Meara4, M. Komajda5, J. Borre6, L. Tavazzi7, K. Svensson2, M. Boerm1 on behalf of SHIFT echocardiography substudy investigators.

Purpose: The effective arterial elastance (Ea) represents resistive and pulsatile afterload of the heart derived from the pressure volume (PV) diagram. Heart rate modulates Ea, and, therefore, afterload burden. It was the aim of this study to investigate whether selective heart rate reduction with ivabradine reduces afterload of patients with systolic heart failure included in the echocardiographic substudy of the SHIFT trial.

Methods and results: 275 patients with systolic heart failure (EF ≤ 35%) treated either with placebo (n=132) or ivabradine (up to 7.5 mg bid; n=143) were included. Ea, vascular compliance (VC) and end-systolic elastance (Ees) were calculated at baseline and after 8 months of treatment. Blood pressure was measured by auscultation (7.5 ± 2 mm Hg) and left ventricular end-diastolic volume (EDV) were assessed by echocardiography. At baseline Ea, VC, heart rate and Ees did not differ significantly between groups treated with placebo or ivabradine. After 8 months of treatment heart rate was significantly reduced in the ivabradine group (p < 0.0001) and was accompanied by marked reduction in Ea (p < 0.001) and improved VC (p < 0.0048). Because Ees remained unchanged (p>0.59), ventricular-arterial coupling worsened markedly (p < 0.003) resulting in a higher stroke volume (p < 0.0001), and a decrease EDV (p < 0.0002) in the ivabradine treated patients.

Conclusion: Selective heart rate reduction by ivabradine improved vascular compliance, while reducing Ea, which might contribute to the beneficial effect of selective heart rate reduction in patients with systolic heart failure and help to explain the good hemodynamic tolerability of the lower heart rate.

Serum tenascin-c levels might be a candidate biomarker for myocardial nonconception

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Background & Purpose: Myocardial nonconception (MN) is a rare form of congenital cardiomyopathy which is assumed to occur secondary to interruption of the normal myocardial morphogenesis. Tenasin-C (TN-C), an extracellular matrix glycoprotein that appears in several important steps of embryonic development such as the initial differentiation of cardiomyocytes or coronary vasculogenesis, but it is not detected in a normal adult myocardium. The clinical significance of TN-C levels has not yet been studied in patients with MN. The aim of this study is to elucidate whether serum TN-C levels might be a useful biomarker for MN.

Methods: Serum TN-C levels were measured by ELISA in 50 MN patients both with/without systolic dysfunction and 23 normal controls. Systolic dysfunction was defined as EF ≤ 40. Mann-Whitney U test and ROC curve analysis were done.

Results: Of 51 MN patients, 24 MN (47%) patients had systolic dysfunction (mean age 38±18) and 27 MN patients (53%) had normal systolic function (mean age 36±16). The mean age of controls was compatible with the patients (mean age 37±16). The mean levels of serum TN-C were significantly higher than that of controls, while stroke volume and TN-C levels with systolic dysfunction (26±10 ng/ml) and diastolic (26±8 ng/ml, respectively, p < 0.001). No significance was observed between two groups of MN patients regarding TN-C levels (p>0.8). ROC curve analysis revealed that TN-C value of 11.7 ng/ml was related to MN with 100% sensitivity and specificity and the results were compatible for all patients with systolic dysfunction or not.

Conclusion: TN-C might be a candidate biomarker for MN patients and seems not to be affected by systolic function.

Measurement of anti beta-1-adrenoreceptor auto-antibodies in heart failure by a cellular ELISA assay

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Background: Auto-antibodies directed against the second extracellular loop of the cardiac beta-1-adrenergic receptor (β1-AR) contribute to the pathogenesis of heart failure, such as dilated cardiomyopathy (DCM) and Chagas disease. Various assays have been used to detect these autoantibodies, and the reported prevalence of positive patients varied depending on the assay method.

Methods: We analysed sera from 164 patients with DCM (ejection fraction < 45%) and from 110 healthy volunteers with an existing method, and compared it to a novel cellular ELISA using the full transgene for the human β1-AR. This novel assay was designed in strong analogy to the most reliable anti-TSH receptor antibody ELISA used in Graves’ disease diagnostics (‘third generation assay’), and also uses a competition with a monoclonal anti-receptor antibody which specifically recognizes the relevant epitope of the β1AR.

Results: The assay was validated and showed high reproducibility; clear cut-off values were determined. Anti-β1-AR antibody titers (determined as inhibition of monoclonal antibody binding) were significantly higher when sera were depleted from antibodies by protein G column purification. In contrast, a previously used ELISA conducted with a 26-mer peptide derived from the second extracellular loop of β1-AR resulted in high false positive rates, so that no specific identification of DCM patients was achieved.

Conclusion: We have established a simple screening assay which identifies auto-antibodies directed against the β1-AR in human sera. These auto-antibodies can be detected and quantified with high reproducibility in high throughput screening. The specificity of the novel assay is markedly superior to existing assays. The assay was validated according to “good laboratory practice” (GLP), and now serves as a companion bio-diagnostic assay to develop and control individualized therapies in antibody-positive patients.

Pregnancy after in vitro fertilization is associated with an increased incidence of pulmonary and venous thromboembolism

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Objective: To estimate the risk of pulmonary embolism (PE) and venous thromboembolism (VTE) in pregnancy after in vitro fertilization (IVF).

Design: A cross-sectional study in Sweden of all women who had given birth from 1990 to 2008 after undergoing in vitro fertilization (IVF) and individually matched women from the Swedish Medical Birth Register (unexposed women).

Participants: 23,498 women who had given birth to a child after IVF between 1990 and 2008 and 116,960 individually matched women.

Main outcome measures: Risk of PE and VTE during the trimesters of pregnancy.

Results: The proportion of pregnancies complicated by VTE was 4.2/1000 (n=99) exposed vs 3.5/1000 (n=291) in unexposed. The reported incidence of DVT was 0.7/1000 (n=17) vs 0.5/1000 (n=14) exposed vs unexposed, respectively. The risk of VTE was increased during all trimesters but in particular during the first trimester (1.5/1000 in exposed vs 0.3/1000 in unexposed; odds ratio, 4.74; 95% CI, 3.00 to 7.47). The proportion of women suffering PE during the first trimester was 3.0/1000 as compared to 0.4/1000 in controls (odds ratio, 6.98; 95% CI 2.22 to 21.98).

Conclusions: IVF is associated with a substantially increased risk of PE and VTE in women during the first part of the pregnancy. As PE is a leading cause of maternal mortality and a condition where clinical suspicion is critical to diagnosis, the knowledge and an awareness of this risk of IVF is important to practicing physicians.

Risk of PE and VTE during all trimesters but in particular during the first trimester of pregnancy after IVF.
Short term prognosis in acute pulmonary embolism: external validation of the European Society of Cardiology prognostic model

C. Becattini1, F. Casazza2, A. Bongarzoni2, C. Forgione3, C. Cuccia1, L. Ranzoni1, F. Porro2, L. Pignataro4, G. Agnelli1, U. University of Perugia, Perugia, Italy; 2San Carlo Borromeo Hospital, Milan, Italy; 3Foundation Poliambulananza - Institute Hosp, Brescia, Italy; 4Santa Maria della Misericordia Hospital, Ravio, Italy; 5Foundation IRCCS Ca’ Granda Ospedale Policlinico, Milan, Italy

Purpose: The aim of this study is to externally validate the prognostic model proposed by the European Society of Cardiology (ESC) in patients with acute pulmonary embolism (PE) included in the Italian Pulmonary Embolism Registry (IPER).

Methods: IPER is a web-based registry including patients with acute PE hospitalized in Cardiology, Emergency or Internal Medicine Departments in Italy.

Results: 1716 consecutive patients with confirmed acute PE were enrolled in IPER. Hemodynamic impairment was the main independent predictor for in-hospital death (HR 6.4, 95% CI 4.3 to 9.6, p < 0.001), along with age > 75 and bed-rest. Echocardiography and troponin were obtained in 869 of 1516 hemodynamically stable patients (57%). In-hospital death or clinical deterioration occurred in 8.6% (95% CI 5.9 to 11.7%) patients with both RVD and elevated troponin levels, in 4.7% (95% CI 2.4 to 7.0%) patients with RVD or elevated troponin and in 0.6% (4/643) of the patients with no RVD and normal troponin levels. Among hemodynamically stable patients, the risk for in-hospital death or clinical deterioration was higher in those with both RVD and elevated troponin (adjusted HR 7.3; 95% CI 3.17-17.5; p < 0.001) and in those with RVD or elevated troponin (adjusted HR 4.3; 95% CI 1.18-17.7; p: 0.05) as compared with those without these markers (Figure). The risk for in-hospital death was higher in patients with both RVD and elevated troponin (HR 5.9; 95% CI 1.12-2.3; p < 0.01), than in patients with RVD or elevated troponin. None of the patients with no RVD and normal troponin died.

Conclusions: The ESC prognostic model can be used for risk stratification of hemodynamically stable patients with acute PE.

Inconsistencies in the use of cardiac biomarkers or echocardiography in patients with acute non-massive pulmonary embolism

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Background: Cardiac biomarkers and echocardiography for assessing right ventricular function are recommended to risk stratify patients with acute non-massive pulmonary embolism (PE) but their use and effect on the management and clinical outcomes in daily practice remains unclear.

Methods and Results: Overall, 587 patients with acute non-massive PE from 18 hospitals were enrolled in the Swiss Venous Thromboembolism Registry (SWIVETER): 178 (30%) neither had a biomarker test nor an echocardiographic evaluation. Among the 409 (70%) patients with biomarkers or echocardiography, 164 (41%) had troponin only, and 47 (11%) had echocardiographic evaluation only: 210 (51%) had at least one positive test and 67 (16%) had positive biomarkers and right ventricular dysfunction. Syncope (OR 3.49, 95% CI 1.17-10.15; p = 0.022), heart rate > 110 beats/min (OR 2.91, 95% CI 1.37-3.91; p = 0.002), and increasing age per year (OR 1.02, 95% CI 1.01-1.04; p = 0.001) were independently associated with testing of cardiac risk; outpatient status at the time of PE diagnosis (OR 2.24, 95% CI 1.49-3.36; p < 0.001), cancer (OR 1.81, 95% CI 1.17-2.79; p = 0.008), and proposed PE (OR 1.58, 95% CI 1.05-2.40; p = 0.029) were associated with its absence. The hospitalization rates were 93% vs. 80% without testing (p = 0.001), and the ICU admission rates were 6% vs 5%, respectively (p = 0.78). Thrombolyis or embolomcytectomy were performed in 4.9% with vs. 2.8% without testing (p = 0.29). In comparison to risk-stratified patients without any positive test, there was more frequent use of thrombolysis or embolomcytectomy in patients with at least one positive test (7.1% vs. 2.5%; p = 0.039) and in patients with positive biomarkers and right ventricular dysfunction (14.9% vs. 2.5%; p = 0.001). The 30-day rates of mortality or PE recurrence were 3.2% with vs. 7.4% without testing (p = 0.001).

Conclusions: In hemodynamically stable patients with acute PE, biomarker testing and echocardiographic evaluation are currently used inconsistently and rarely in combination. With such lack of systematic use, their utility in guiding PE management is extremely low.

Prognostic significance of tricuspid annular displacement in normotensive patients with acute symptomatic pulmonary embolism

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Background: The tricuspid plane systolic excursion (TAPSE) is an emerging prognostic indicator in patients with acute symptomatic pulmonary embolism (PE). However, outcome implications of TAPSE have not been analyzed in the context of routine clinical practice and in a multicenter study.

Methods and Results: We prospectively examined 782 normotensive patients with acute PE enrolled in the PROTECT study (NCT00880737); of those, 35 patients died (4.5%); 95% confidence interval (0.3% to 9.9%), and 65 (7.9%; 95% CI, 5.2% to 8.8%) suffered a complicated course within the 30-days of follow-up. Compared with patients with a TAPSE greater than 1.6 cm, those with a TAPSE of ≤ 1.6 cm or systolic pulmonary artery pressure ≥ 31 + 16.7 mm Hg vs. 40 ± 15.5 mm Hg (P < 0.001), right ventricle end-diastolic diameter (3.5 ± 0.8 cm vs. 3.0 ± 0.6 cm, P < 0.001), and right ventricle to left ventricle end-diastolic diameter (1.0 ± 0.3 vs. 0.8 ± 0.2, P < 0.001). Patients with a TAPSE of 1.6 cm or less had a higher prevalence of right ventricular free wall hypokinesia (68% vs. 11%, P < 0.001). Patients with a TAPSE of 1.6 cm or less at the time of acute PE diagnosis were significantly more likely to die from any cause during follow-up (hazard ratio [HR] 2.3; 95% CI 1.2 to 4.7, P = 0.02). A TAPSE of 1.6 cm or less at the time of presentation was also independently, significantly associated with PE-related death (HR 4.4; 95% CI 1.3 to 15.3, P = 0.02).

Conclusions: In normotensive patients with acute symptomatic PE, TAPSE powerfully reflects right ventricular function. For these patients, TAPSE is independently predictive of survival.
Plasma MR-proADM is superior to NT-proBNP for all-cause short term mortality prediction in acute pulmonary embolism


Objective: NT-proBNP reflects RV dysfunction and according to ESC guidelines can be used for risk stratification in APE. Pseudodemuldenium, secreted by failing heart, was proposed to be a predictor of short-term mortality in acute heart failure and adds prognostic value to NT-proBNP for diagnosis and prognosis in AHE. We hypothesized that MR-proADM plasma levels are related to the severity of APE and predicts short term mortality in APE. We also compared prognostic values of MR-proADM and NT-proBNP for prediction of early mortality in APE.

Method and materials: We studied 98 consecutive pts (51F/47M, 59.6±18.4 yr) with confirmed spiral CT APE. On admission, echocardiography was performed and blood samples were collected for MR-proADM (Thermo Fisher Scientific, BRAHMS Hennigsdorf, Germany) and NT-proBNP (bioMérieux, l’Etolle, France). MR-proADM concentrations were also measured for 40 healthy individuals (38F/14M).

Results: Our study group included 5 pts with high-risk APE, 66 pts with intermediate-risk APE and 27 pts with low-risk APE. Median of MR-proADM and NT-proBNP concentrations shows table 1. Six pts (6.1%) died during 30-pts observation. MR-proADM was higher in non-survivors than in survivors 2.12 nmol/L (1.54–4.22), vs. 0.91 nmol/L (0.38–4.749, p=0.003, and vs. control group 0.85 nmol/L (0.30–1.9), p=0.01. The AUC of the MR-proADM and NT-proBNP ROC curve for predicting all-cause mortality was 0.935 (CI 0.86–0.98) and 0.844 (CI 0.75-0.91), respectively. Cut-off value for MR-proADM 1.6nmol/L showed sensitivity of 100%, specificity 88%, PPV 35.2% and NPV 100% for all-cause mortality. MR-proADM and NT-proBNP plasma levels were predictors of 30-day all-cause mortality in unfavorable Cox’s proportional hazard regression analysis HR 1,65 (CI 1,21-2,25, p=0.01) and HR 1,0 (CI 1,00-1,02, p=0.09), respectively. In multivariable model MR-proADM but not NT-proBNP was significant prognostic predictor of all-cause mortality HR 61,47 (95% CI 6.56-576,30, p=0.0028).

Conclusion: NT-proBNP and MR-proADM are important risk markers in APE. However, MR-proADM is superior to NT-proBNP for all-cause short term mortality prediction in APE.

351 Echocardiographic determinants of maximal exercise capacity in asymptomatic patients with primary mitral regurgitation

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Background: Despite a symptom-based management recommended by both EBM and AHA guidelines in patients with primary mitral regurgitation (MR), the assessment of maximal exercise capacity (MEC) is rarely performed and its determinants remain unknown. We sought to assess MEC and to identify its determinants in asymptomatic patients with primary MR.

Method and results: We prospectively studied 63 asymptomatic patients (60±13 years, 52% of male) with at least moderate MR (regurgitant volume (ReGVR) ≥30mL) and preserved left ventricular (LV) systolic function (LV ejection fraction >60%, LV end-systolic diameter <45 mm) in whom comprehensive resting and exercise echocardiography and cardiopulmonary exercise test were performed. MEC was assessed using peak exercise VO2 and varied extensively among the patients (mean: 23.6±7.7 mL/kg/min; range: 12.9–44.2 mL/kg/min).

According to the median of peak VO2, patients with reduced MEC were significantly older (p=0.005) and were more frequently women (p=0.02). There was no significant difference between the 2 groups (reduced vs. preserved MEC) regarding demographic and clinical data and medication. However, patients with reduced MEC had significantly (p=0.05) more frequent women (p=0.02). There was no other difference between the 2 groups (reduced vs. preserved MEC) regarding demographic and clinical data and medication.

According to the median of peak VO2, patients with reduced MEC were significantly older (p=0.05) and were more frequently women (p=0.02). There was no other difference between the 2 groups (reduced vs. preserved MEC) regarding demographic and clinical data and medication.

In 434 patients underwent surgical anuloplasty for chronic ischemic mitral regurgitation and 100 controls, posterior and lateral displacement of papillary muscles (PMs), the AML and posterior mitral leaflet (PML) tethering angles and their ratio, coaptation length and their ratio (L/S), and their ratio (L/S) were measured before and at follow up (mean [Interquartile range] 44.7 months (25.9-66.4)). Patients were divided in 5 Groups on the basis of the preoperative AML tethering angle α: Group 1, normal/low (< 27.30) AML tetherng (n=51), Group 2, mild (27.30-32.1) AML tetherng (n=97), Group 3, moderate (32.2–36.9) AML tetherng (n=98), Group 4, moderate-severe (36.0–39.5) AML tetherng (n=100) and Group 5, severe (39.6-45°) AML tetherng (n=98).

Results: Subjects with AML tetherng ≥moderate-severe had preoperatively a more symmetric tethering (p<0.001), a more accentuated anterior papillary muscle displacement (p<0.001) and a larger anterior local remodeling (p<0.001).

Regression of MR was significantly higher in patients with moderate-severe/severe AML tetherng (p<0.001). Postoperatively, tetherng of posterior leaflet increased (p<0.001) and it was predominant without difference between groups, resulting in a more asymmetric tethering in most of patients with reduced MR (p<0.001).
Valvular heart disease: beyond the valve / Imaging for electrophysiologist: the spectrum gets broader

354 Tricuspid annulus systolic velocity as a parameter for optimized right ventricular function for predicting clinical outcome after MitraClip implantation

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Background: Interventional implantation of MitraClip is increasingly used as an alternative therapeutic option for patients with severe mitral valve regurgitation and high intraoperative risk. The purpose of this study was the evaluation of right ventricular function on clinical outcome after MitraClip implantation.

Methods: Right ventricular function was evaluated by echocardiography before and after MitraClip implantation from March 2009 to April 2011 in 68 consecutive patients (age 73±16y; LVEF 35.8%; NT-proBNP 6705±8908pg/ml; 60% CK). The indication for MitraClip-implantation was a functional mitral valve regurgitation grade 3 or severe mitral valve prolapses with high surgical risk (mean log Euroscore 34). All patients were followed up at our centre regularly. A combined endpoint (overall mortality, LVAD, surgery of mitral valve, futile implantation) was evaluated by Kaplan-Meier-analysis.

Results: Overall there were 29 combined endpoint events. Patients with reduced tricuspid annulus systolic velocity (TASV<10cm/s) had significantly more events as patients with higher TASV (univariate Cox-model HR 2.995%CI: 1.0-5.5). In contrast TAPSE, right ventricular diameter and graduated tricuspid valve regurgitation showed no significance.

Conclusion: An impaired right ventricular function is a significant predictor for a poorer medium term outcome in patients with high-grade mitral valve regurgitation after MitraClip implantation. The evaluation of the TASV by echocardiography before intervention is recommended.

355 Left ventricular shape and mass impact apical rotation in patients with aortic regurgitation. A speckle-tracking echocardiography study

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Background: Apical rotation, an essential determinant of left ventricular (LV) twist and twist over a wide range of loading conditions, is considered an effective noninvasive index of global LV function. Chronic aortic regurgitation is a condition associated with a unique pattern of LV overloading, both in volume and pressure, leading to LV remodeling.

Purpose: To study the impact of LV shape and mass on systolic and diastolic LV apical rotation assessed by speckle-tracking echocardiography (STE) in patients with chronic AR.

Methods: We prospectively enrolled 42 consecutive patients (47±17.6 years, 33 men) with moderate-severe and severe chronic AR and 30 age- and gender-matched normal subjects (45±18.0 years, 21 men). Exclusion criteria for the patients with AR were LV ejection fraction (LVEF) ≤50%, significant coronary artery disease, more than mild mitral regurgitation, non-sinus rhythm. A comprehensive echocardiogram was performed in all patients. Systolic apical rotation and rotation rate and diastolic apical rotation rate were measured from two-dimensional greyscale LV parasternal apical short-axis images by STE using a dedicated software (2D strain, EchoPac, GE Healthcare). Global LV geometry was assessed using a sphericity index defined as LV end-diastolic volume divided by the volume of a sphere with the same diameter as the LV end-diastolic longitudinal length, as previously described.

Results: Left ventricular EF was similar in both groups (60±4% in AR group vs 61±3% in control group, p=0.27). Patients in AR group had significantly higher LV diameters and volumes and LV mass (all p <0.001). Peak systolic apical rotation was significantly lower in the AR group as compared to normal subjects (13.1±7.6 vs 17.8±6.3°, p=0.007). Peak diastolic apical rotation rate was also significantly lower in the AR group (-81.2±38.2 vs -107.7±34.8°/s, p=0.004). Peak systolic apical rotation had an inverse correlation with LV sphericity index (r=-0.41, p<0.007) and did not correlate with LV mass index (r=−0.18, p=0.26). Peak diastolic apical rotation rate correlated significantly both with LV sphericity index (r=0.44, p=0.003) and LV mass index (r=−0.45, p=0.003).

Conclusions: The shape and mass of a remodeled LV have an impact on systolic and diastolic apical rotation in patients with significant chronic AR and normal LVEF. These parameters of LV rotation could identify early LV dysfunction (before EF declines) and may be used for monitoring asymptomatic patients with severe AR.

356 The impairment of endocardial radial strain is related to aortic stenosis severity in patients with aortic stenosis and preserved left ventricular ejection fraction using two-dimensional speckle tracking

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Background: Myocardial function is heterogeneous in different myocardial layers. Recently, 2-dimensional speckle-tracking echocardiography has been used to define myocardial deformation parameters of the left ventricular (LV) segment. This study aimed to investigate strain in subendocardial and subepicardial layers in patients with aortic stenosis (AS) and preserved LV ejection fraction (LVEF) using speckle-tracking echocardiography.

Methods: Parasternal short-axis and apical long-axis views of the left ventricle were acquired at the mid-papillary level in 35 control subjects and 32 patients with AS and preserved LVEF. Radial, circumferential strain in subendocardial and subepicardial layers at the posterior and antero-septal segments were calculated.

Results: There was no significant difference in circumferential strain in subendocardial and subepicardial layers between the control subjects and the patients with AS. Similarly, there was no significant difference in epicardial radial strain at the posterior and antero-septal segments between the control subjects and the patients with AS. AS patients had significantly decreased values of endocardial radial strain compared with those in controls (antero-septal: 18.2±14.8 vs. 34.5±14.8, p<0.005; posterior: 25.2±14.8 vs. 32.6±12.6, p<0.05). In the AS group, endocardial radial strain in the posterior and antero-septal segments was significantly correlated with the aortic valve area (posterior: r=−0.31, p<0.05; antero-septal: r=−0.33, p<0.05).

Conclusion: Patients with AS and preserved LVEF have impaired longitudinal strain and endocardial radial strain, although circumferential strain and epicardial radial strain are preserved. Despite preserved LVEF, endocardial radial strain gradually decreased as increasing AS severity.}

IMAGING FOR ELECTROPHYSIOLOGIST: THE SPECTRUM GETS BROADER

373 Role of the cardiovascular magnetic resonance in patients with ventricular arrhythmia of unknown cause and non-diagnostic echocardiography


Introduction: Significant ventricular arrhythmia (here defined as > 1000 ectopics per 24 hours, or ventricular tachycardia) may itself have adverse consequences and/or may point to an underlying structural heart disease. In patients with significant ventricular arrhythmia and normal or non-diagnostic echocardiography, we hypothesized that cardiovascular magnetic resonance (CMR) may detect significant, previously unrecognized structural heart disease.
Silent cerebral embolism after PVAC and irrigated-tip ablation for atrial fibrillation: incidence and clinical implications. Results from the CE-AF trial pilot

Purpose: Catheter ablation is an effective treatment for atrial fibrillation (AF). Silent thromboembolism occurs more frequently than clinical strokes. The aim of this pilot was to study silent cerebral embolism during ablation with an irrigated-tip catheter (Thermocool) and a non-cooled, decapolar duty-cycled catheter (PVAC).

Methods: 15 Patients undergoing a first ablation of paroxysmal AF were prospectively randomized in a 2:1 fashion to PVAC or Thermocool, respectively. A diffusion-weighted cerebral MRI was performed 1 day before and after the procedure. Blood samples were obtained before, during and after ablation for determination of endothelial damage and coagulation factors. Development of microembolic signals (MES) during the procedure was evaluated by Transcranial Doppler ultrasonography. Extended neuropsychological testing was performed 1 day before and 1 day after the ablation. If a new lesion was observed on MRI after ablation, a 3-month follow-up scan was performed.

Results: Baseline characteristics including sex, age, left atrial size, CHA2DS2-VASc and INR were comparable between both groups. In the Thermocool-group, no new MES lesions were detected. In the PVAC-group, 2 patients developed a new microembolus (<5 mm) and 1 patient showed a microbleed after ablation, all located in the cerebellum. At 3 months follow-up, MRI showed remainder lesions. A newly developed algorithm using ECs could correctly identify scar during epicardial EAM in the absence of a thick fat layer. In areas covered by a fat layer, BV, as well as UV, were not bipurpolar voltage (BV), Electrogram characteristics (EC) and unipolar voltage (UV) may allow detection of scar covered with fat and intramural scar.

Conclusions: CE-CMR might be helpful to plan the approach needed, epicardial or endocardial, before the procedure, as well as to target the VT ablation.

Scar, viable myocardium or fat during epicardial electroanatomical mapping for ventricular tachycardia ablation: validation of mapping parameters by integration of multi-detector CT and MRI

Purpose: To identify scar from fat during epicardial electroanatomical mapping (EAM), as both decrease bipurpolar voltage (BV). Electrogram characteristics (EC) and unipolar voltage (UV) may allow detection of scar covered with fat and intramural scar.

Methods: Ten pts (7 male, age 55±12 years) with VT and non-ischemic cardiomyopathy underwent epicardial EAM with real-time integration of CT-derived fat and contrast-enhanced-CT-derived scar (example provided in Figure). BV, UV and EC (duration and morphology (double equal, fragmented, late potential, other abnormal)) were correlated with the presence of fat and scar. Ablation target sites were also evaluated for BV, UV and EC.

Results: The optimal cutoff values to differentiate between scar and viable myocardium at sites devoid of fat were 1.81mV for BV and 7.95mV for UV. BV and UV electrogram duration distinguished scar from viable myocardium in areas covered with <2.8mm fat (p<0.001), but not with ≥2.8mm fat (p=NS). In contrast, electogram morphology could also detect scar covered with ≥2.8mm fat (p=0.01). A newly developed algorithm using ECs could correctly identify scar with a sensitivity of 61%. Intramural scar could be detected with unipolar voltage, not with bipurpolar voltage. At 86% of ablation target sites UV was <7.95mV, as compared to 75% for BV (<1.81mV) and pathological EC.

Conclusions: Both BV<1.81mV and UV<7.95mV are useful for detection of scar during epicardial EAM in the absence of a thick fat layer. In areas covered by a thick layer of fat, EC are superior for identification of scar. A newly developed algorithm combining UV and EC can distinguish between scar and viable myocardium. Intramural scar can be detected with unipolar voltage, not with bipurpolar voltage.
Methods: Prospective observational study of patients referred to AF catheter ablation. Before the procedure, CMR with LA angiography was performed, in order to characterize LA anatomy, volume and ejection fraction. Atrial fibrosis was analyzed in post-processing with clinical data blinding: qualitative (presence of late enhancement in each atrial wall and in the peri-ostial regions) and quantitative (mass of fibrotic tissue) evaluation was performed.

Results: Twenty-eight patients were enrolled (82% male; age 59±13 years). Right atrial fibrosis assessed by late enhancement was affected by either atrial LGE and transmural fibrosis in 10, or only atrial LGE in the other 18 patients. LA fibrosis was significantly more common in patients with persistent AF (93% vs. 50%; OR=14.0; P<0.001). LA fibrosis was similar in patients with paroxysmal or persistent AF. However, posterior wall fibrosis was significantly more common in patients with persistent AF (93% vs. 50%; OR=14.0; P<0.001). Late enhancement in each atrial wall and in the peri-ostial regions) and quantitatively (presence of late enhancement in each atrial wall and in the peri-ostial regions) could be related to atrial fibrosis.

Conclusions: LA fibrosis, determined by late enhancement, although not very significant in this population of patients referred to catheter ablation, tends to be related to atrial fibrosis and to progress with age. However, the clinical subtype of AF seems to depend more on the distribution of fibrosis, particularly on the involvement of the posterior wall, than on its amount. This finding could have implications in the planning of the ablation strategy in these patients.
poorer RVOT shortening. Further studies are warranted to identify echocardiographic predictors of high risk.

HEART FAILURE: FROM BENCH TO BEDSIDE

P381 Left ventricular dyssynchrony predicts limited exercise capacity in heart failure irrespective of ejection fraction
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Aim: The aim of this study was to prospectively examine functional echocardiographic parameters that correlate and predict 6 minute walk test (6-MWT) results in patients with heart failure (HF).

Methods: In 147 HF patients (mean age 61±11 years, 50.3±male), a 6-MWT and an echo-Doppler study were performed in the same day. Global LV dysynchrony was indirectly assessed by total isovolumic time - T'IVT [in s/min; calculated as: 60 – (total ejection time – total filling time)], and Tei index (T'I-Te/Te). These were divided into two groups based on the 6-MWT distance (Group I: ≤300m, Group II: >300m).

Results: The 6-MWT correlated with T'IVT (r=0.48, p<0.001) and Tei index (r=0.27, p<0.05) but not for EF or LVID sy, LVID di or IVST. Group I patients had lower hemoglobin level (p=0.02), lower EF (p=0.003), larger left atrium (p=0.02), thicker interventricular septum (p=0.02), lower A wave (p=0.004), higher E/A ratio (p=0.004), higher E/e' ratio (p=0.003), longer IVST (p=0.003), and longer T'IVT (p=0.03), compared with Group II patients. In multivariate analysis, only T'IVT [r=0.28 (1.07:1.47), p=0.005], LV EF [r=0.947 (0.903-0.993), p=0.02], and E/A ratio [r=0.593 (0.315-0.972), p=0.004] independently predicted poor 6-MWT performance (<300m) in the group as a whole. No predictors for exercise tolerance were detected for HF-P (E/E'<8).

Conclusion: In patients with HF, the limited exercise capacity, assessed by 6-MWT, is mostly related to severity of global LV dysynchrony, more than EF or raised filling pressures.

P382 Health-related quality of life in patients with systolic and diastolic heart failure in Spain: is gender important?
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Purpose: Few studies have reported the impact of chronic heart failure upon quality of life within community samples. Further evidence of gender differences in HRQoL has been mainly provided by studies conducted in North America and Europe which are not available in the south of Europe. Whether these differences may be extrapolated to the geographical and socio-cultural context is not known. The aim of this study was to describe the HRQoL in ambulatory patients with systolic and diastolic CHF in Spain and to explore the self-perceived health status according to gender.

Methods: The VIDACI-CHF survey was designed to include 1200 consecutive patients with systolic HF seen in 120 hospitals in Spain in 2011. HRQoL was assessed at inclusion using the Kansas City Cardiomyopathy Questionnaire (KCCQ - specific for HF) and the generic EQ-5D questionnaire that includes the Visual Analogue Scale (VAS). The KCCQ was also assessed at 1 year.

Results: A total of 400 patients were available for this preliminary analysis. Overall, HRQoL was poor at baseline (mean VAS 59.6±20.7; mean EQ-5D index 0.74±0.22; KCCQ overall summary score: 58.3±24.8) compared to previously published studies. 32% of patients evaluated were women and they had a significant higher relative risk of reporting any complaint compared to men for mobility (28%), usual activities (15%) and pain/discomfort (24%) (all p-values<0.05) but not for self-care (19%) and anxiety/depression (8%). Women had worse scores for the EQ-5D (0.70±0.23 vs 0.76±0.21; p-value=0.028) and the KCCQ overall summary score (0.50±0.23 vs 0.61±0.23; p-value=0.031). There were also significant gender differences regarding the KCCQ scores in all domains (p-values<0.001). Women had worse scores for physical role limitation, pain, energy, physical functioning, social functioning, and emotional well-being (p-values<0.001) which may reflect a lower quality of life in women with heart failure.

Conclusion: In patients with systolic CHF, women had significantly worse health status and HRQoL compared to men. Women reported higher levels of deterioration in quality of life and HRQoL, possibly due to a lower quality of life in women with heart failure.

P383 Diastolic function is the most valuable predictive marker for peroperative acute heart failure in noncardiac surgery
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Background: Although perioperative risk stratification for non-cardiac surgery is essential, the predictive factors are still uncertain. We investigated herein the predictive factors for perioperative acute decompensated heart failure (ADHF) in patients with non-cardiac surgery.

Methods: We prospectively enrolled 129 patients into Group A (19 patients with peroperative ADHF) and Group B (110 patients without perioperative ADHF). ADHF was defined as the occurrence of heart failure-related symptoms and signs during hospitalization. The incidence of ADHF was analyzed using binary logistic regression with the presence of ADHF as the dependent variable.

Results: The incidence of ADHF was 15.2% (n=19) in Group A and 9.1% (n=10) in Group B. ADHF was significantly associated with preoperative use of diuretics (p<0.05), NYHA class (p<0.05), history of previous heart failure (p<0.01), and left ventricular ejection fraction (LVEF) (p<0.05) in univariate analysis. In multivariate analysis, LVEF was the most valuable predictive factor for ADHF with an adjusted odds ratio of 1.91 (p<0.05).

Conclusion: LVEF is an excellent predictive factor for development of peroperative ADHF in non-cardiac surgery.

P384 Progress of neurohumoral activation and diastolic function in patients with preserved left ventricular function in one-year follow-up
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Background: There is limited knowledge about the development and the correlation of neurohumoral activation and diastolic function in patients with and without diastolic dysfunction and diastolic heart failure. This study therefore investigated the progress and the association of neurohumoral activation as well as parameters of diastolic function in long term follow-up.

Methods: In the DIAS-CHF observational study n=1397 patients (±50years) with risk factors for heart failure or previously confirmed diagnosis of heart failure were prospectively included, of them n=1036 with normal systolic function (LVEF≥50%). Follow-up was performed at 12 months. Outcome parameters were changes in neurohumoral activation (logMR-proADM, logMR-proANP), exercise capacity (6-MWT) and diastolic function (E/é). Changes in these parameters were measured at baseline (BL) and follow-up (FU). Patients were classified as having E/é ≥8, E/é 8-15 and E/é <8 at both time points.

Results: At BL n=364 (35.1%) had E/é ≥8, n=570 (55.5%) had E/é 8-15 and n=102 (9.9%) had E/é <8. Age (64±17; 77±7; 76±3), sex (43,5±53,3/68,6), LVEF (61±2,5/61±6,6/61±6,0), 6-MWT (551±86,9/525±95,4/848,5±96,1I), NT-proBNP (116,3±145,0/72,3±169,1/525±96,1), MR-proADM (0,57±0,63/0,35±0,65/0,59±0,61), MR-proANP (88,6±104,4/62,5±90,4/50±61,8) and logMR-ProBNP (0,60±0,72/0,55±0,57/0,59±0,56) were significantly different between the three groups (all p<0.001). Also LAVI (78±59,7/60±56,2/74±53,7 mm²) was different across the groups, whereas LVEF did not differ between the three groups. In the univariate correlation analysis (Δ logMR-proADM, Δ logMR-proANP) were significantly correlated with the progress of diastolic function (ΔE/E) after one year (p=0.007, 0.002, 0.001). However, the multiple regression analysis revealed that only Δ logMR-proADM (p=0.004) and Δ logMR-proANP (p=0.001) were independently associated with changes in E/E after one year.

Conclusion: In patients with cardiovascular risk factors levels of NT-proBNP, MR-proADAM and MR-proANP were increased in dependency of the severity of their diastolic dysfunction. Furthermore, independent of other parameters the change of MR-proADAM and MR-proANP was associated with changes in diastolic function. However, this suggests that neurohumoral activation is linked to the severity of diastolic dysfunction and also has the potential to reflect changes of diastolic function during long term follow up.
Long-term therapy with capadenoson, a partial adenosine A1-receptor agonist, prevents calcium-overload and improves mitochondrial function in left ventricular myocardium of dogs with heart failure

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Background: Calcium overload and mitochondrial (MTO) dysfunction are hallmarks of failing left ventricular (LV) myocardium. The former occurs partly due to reduced sarcoplasmic reticulum (SR). SERCA-2a activity and expression and the latter, partly due to reduced expression of MTO uncoupling proteins (UCPs) responsible for maintaining MTO membrane potential and, consequently, ATP synthesis. We previously showed that capadenoson (CAP), a partial adenosine A1-receptor agonist, improves LV systolic function in dogs with chronic heart failure (HF). This study examined the effects of CAP on SERCA-2a activity and expression and on expression of UCP2 and UCP3 in LV myocardium of dogs with HF.

Methods: Studies were performed in 12 HF dogs randomized to 3 months oral monotherapy with CAP (7.5 mg twice daily, n=6) or no therapy at all (Control, n=6). Thapsigargin-sensitive SERCA-2a activity and affinity (Ka) were determined in LV tissue homogenate. SERCA-2a protein level normalized to calnexin (CNx) and MTO protein levels, was assessed by Western blotting. LV tissue from 6 normal (NL) dogs was used for comparison.

Results: Data are shown in table. SERCA-2a activity and expression were reduced significantly in Control dogs compared to NL. In CAP-treated HF dogs, SERCA-2a activity and expression were significantly increased compared to Controls to a final level not significantly different from NL. Thapsigargin-sensitive activity was significantly higher in CAP-treated HF dogs than in Control. Ka of SERCA-2a was significantly lower in Controls compared to NL. In CAP-treated HF dogs, Ka was significantly lower compared to Controls. These findings explain, in part, the improvement of LV function seen with long-term CAP therapy in dogs with HF.

Conclusions: In dogs with HF, long-term therapy with CAP attenuates calcium overload by up-regulating SERCA-2a activity and expression and improves mitochondrial function by improving protein levels of UCP2 and UCP3. These findings explain, in part, the improvement of LV function seen with long-term CAP therapy in dogs with HF.

G-CSF leads to a normalization of diastolic function in a mouse model of diastolic heart failure


Background: Nearly half of all patients with heart failure have a preserved ejec- tion fraction (HFpEF). The treatment of these patients represents a clinical challenge because contemporary therapeutic approaches failed to improve diastolic function. Fibrosis is a major point in the pathogenesis of HFpEF. As recent studies have shown, granulocyte colony-stimulating factor (G-CSF) modulates inflammatory reactions in a mouse model of diastolic heart failure and mice were randomized in an experimental group (G-CSF 300 µg/kg/min) via an osmotic pump. After four days, diastolic function was assessed by echocardiography and mice were randomized to a control group (saline). After 7 days, diastolic function was assessed in both groups and analyzed for potential confounding factors (i.e. age, gender, systolic and diastolic blood pressure and LV mass index). Interestingly, stimulation of human fibroblasts with osteopontin induced an increase in LOX expression and collagen cross-linking were strongly correlated with each other (r=0.759, <0.001) and protein (P<0.05) levels. Results: Whereas osteopontin and LOX expression were very scarce in normal hearts, it was high in failing hearts. Collagen cross-linking was increased (P<0.001) in HF patients compared with normal hearts. Osteopontin expression was directly correlated with LOX (r=0.466, P<0.05), collagen cross-linking (r=0.517, P<0.05), LV chamber stiffness (r=0.458, P<0.05), and pulmonary capillary wedge pressure (r=0.588, P<0.01) in all HF patients. Additionally, LOX and collagen cross-linking were strongly correlated with each other (r=0.709, P<0.005) and directly correlated with LV chamber stiffness (r=0.459, P<0.05 r=0.716, P<0.005; respectively) and pulmonary capillary wedge pressure (r=0.588, P<0.01 r=0.771, r=0.01; respectively). These correlations remained significant after adjusting for potential confounding factors (i.e. age, gender, LV). Furthermore, the study revealed an increased expression of Jmjd1a and Jmjd2a in failing hearts compared to normal hearts. Although the mechanisms of ANP and BNP reactivation are incompletely understood, epigenetic modifications may play an important role. Histone acetylation and methylation affect the conformation of chromatin, which in turn governs the accessibility of DNA for transcription factors. Here, we characterized histone modifica- tions in the promoter regions of ANP and BNP in human failing myocardium and analyzed the underlying mechanisms of epigenetic modifications.

Methods and Results: In human failing myocardium (n=16), ANP and BNP expression and function were increased (P<0.05 vs. NL;† P<0.001) and protein (P<0.05†) levels. Osteopontin was associated with increased LOX and collagen cross-linking in the hypertensive failing human heart.

Conclusion: Osteopontin is associated with increased LOX and collagen cross-linking in the hypertensive failing human heart. In addition, osteopontin and LOX may be involved in the development of LV stiffness and increased left-sided filling pressures in these patients, suggesting that the osteopontin/LOX axis might facilitate the deposition of stiff collagen and the subsequent alteration of LV diastolic mechanical properties in the hypertensive failing heart.
50% in neonatal cardiac myocytes increased H3K9 methylation (~3-4 fold) at the ANP promoter and reduced ANP and BNP expression by 13±2% and 15±1%, respectively. In contrast, siRNA of either Jmjd1a or Jmjd2a alone did not affect ANP or BNP expression.

Conclusions: Jmjd1a and Jmjd2a control ANP and BNP expression via demethylation of H3K9 and dissociation of HP-1 from the promoter regions of ANP and BNP, respectively. In contrast, siRNA of either Jmjd1a or Jmjd2a alone did not affect ANP and BNP expression.

Understanding Lipid Metabolism and Designing Future Therapies for Dyslipidemia

Large scale reverse siRNA-transfection: a novel tool to dissect regulators of lipid metabolism in human macrophages

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Objective: Reverse siRNA-transfection has previously been used as a high-throughput transfection tool in immortalized cell lines such as HeLa cells. In order to identify new regulators of macrophage lipid metabolism with possible relevance for cardiovascular disease, we sought to apply this technology to primary human monocyte-derived macrophages isolated from human blood and differentially macrophages.

Methods and Results: Human blood-derived monocytes were obtained from blood by negative bead isolation and seeded onto 96- and 384-well plates pre-coated with siRNA for reverse transfection. Macrophage differentiation was induced by stimulation with 100ng/ml M-CSF for three days. To detect changes in lipid metabolism we then used four different assays: cellular uptake of fluorescent-labeled (1) native or (2) oxidized low-density lipoproteins (DiI(ox)LDL), (3) intracellular free cholesterol by staining with Filipin and (4) lipid uptake of fluorescent-labeled (1) native or (2) oxidized low-density lipoproteins (DiI(ox)LDL).

These effects of CETPi may be mechanistically linked to enhanced cholesterol efflux from β-cells. Whether CETPi inhibition mitigates against harmful post-prandial glucose elevations after chronic therapy warrants further investigation.


Increased symmetric dimethylarginine level is the most powerful factor associated with low HDL Density Lipoprotein in patients with acute myocardial infarction

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Purpose: Dimethylarginines such as asymmetric dimethylarginine (ADMA) and SDMA (its symmetrical stereoisomer) are novel modulating pathways for cardiovascular oxidative stress and endothelial dysfunction. High Density Lipoprotein (HDL) has been found to exert important endothelial atheroprotective effects and low levels of HDL cholesterol are associated with an increased risk of acute myocardial infarction in patients with acute myocardial infarction. In this study, we investigated the relationship between HDL and dimethylarginines serum levels.

Methods: Blood samples from 373 consecutive patients hospitalized ≥24 hours after acute MI were taken on admission. Blood lipids were determined using automated enzymatic methods and Low Density Lipoprotein-cholesterol was calculated by Friedewald formula. Serum levels of ADMA, SDMA and L-arginine (L-arg) were determined using high-performance liquid chromatography. Patients with low HDL cholesterol (<0.40 mg/dl for men and <0.50 mg/dl for women) were compared with patients with higher HDL cholesterol.

Results: Most patients (228/373 (61.6%)) had low HDL levels. Patients with low HDL cholesterol were 97% (p<0.001), with higher body mass index (73±3 vs. 63±3 kg/m², p=0.010), abdominal obesity (50 vs. 38%, p<0.023) and waist circumference (101±10 vs. 97±7 cm, p=0.035) than patients with higher HDL levels. HDL was also associated with higher triglycerides (1.36±0.45 vs. 0.92±0.35 mmol/l, p=0.001), LDL (1.27±0.27 vs. 1.20±0.30 mmol/dl, p=0.045) but non HDL cholesterol (1.58±0.30 vs. 1.38±0.30 mmol/dl, p<0.001). Chronic medications including statin and fibrate and other risk factors including diabetes and prior MI were similar for the 2 groups. ADMA levels were markedly higher (+30%) in low HDL group (0.86±0.27 vs. 0.53±0.25 μmol/l, p<0.001), while SDMA and L-arg levels were similar for the 2 groups (0.57±0.31 vs. 0.62±0.55 μmol/l, p=0.13 and 107±54 vs. 102±54 μmol/l, p=0.150, respectively). ADMA, but not SDMA, was strongly correlated with HDL (r=0.329, p<0.001 and r=0.063, p=0.22). By multivariate analysis, ADMA level was the only independent low factor associated with low HDL levels (r=0.74, 95% CI: 3.44-16.08), even when adjusted for confounding (female (OR (95%CI): 3.37 (1.71-6.66), total cholesterol (OR (95%CI): 0.33 (0.17-0.61)), and triglyceride (OR (95%CI): 4.39 (2.64-7.29).

Conclusion: Our large prospective study showed for the first time in MI patients that reduced HDL was associated with increased levels of ADMA, but not of SDMA levels. Our data suggest that increased CV risk associated with low HDL-cholesterol could be partly mediated through ADMA-related effects.

Increased cholesterol efflux is associated with reductions in arterial wall area and inflammation as assessed by MR and FDG-PET imaging in humans: analysis of the dal-PLAQUE study

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Purpose: The relation between cholesterol efflux (CEF) capacity (a metric of high-density lipoprotein function), and changes in arterial wall biology and structure is unknown. We conducted a post-hoc analysis of the dal-PLAQUE study which evaluated the effect of dalteparin, a cholesterol ester transfer protein (CEPT) modulator) to assess those relationships.

Methods: 130 patients with coronary heart disease (CHD) or CHD risk equivalents (aged 18–75 years) were randomized to dalteparin vs placebo. At 0, 3 and
Dysfunctional high density lipoprotein (HDL) from patients with chronic kidney disease (CKD) increases arterial blood pressure: role of TLR-2 and endothelial NO synthase

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Background: Patients with chronic kidney disease (CKD) exhibit a high cardiovascular morbidity and mortality, even in the early stages, and frequently develop hypertension. Patients with advanced CKD have an uremic dyslipidemia, characterized by low levels of total cholesterol, low density lipoprotein and HDL cholesterol. In addition to its role in reverse cholesterol transport, HDL from healthy subjects (HS) exerts several potential vasoprotective effects. Thus, we compared endothelial effects of HDL from CKD patients and HS and potential consequences for blood pressure response.

Methods: HDL was isolated from patients with CKD (K/DQOOL stadium II, IV, V, each n=15) and healthy subjects (n=15) by sequential ultracentrifugation. The effect of HDL on endothelial nitric oxide production (NO) was assessed by electron spin resonance (ESR) spectroscopy. To evaluate the effect of HDL on systolic blood pressure (SBP) in vivo, HDL was injected into wild type and eNOS-deficient mice. The expression of VCAM-1 and endothelial mononuclear cell (MNC) adhesion was assessed to quantify HDL’s anti-inflammatory capacity. Moreover, the endothelial repair capacity of HDL was assessed in vitro and vivo, using a gap closure assay and carotid injury model in nude mice.

Results: HDL from CKD patients markedly inhibited endothelial NO production (70% by HDL of these patients; P<0.05), even in incipient CKD. TLR2, but not TLR4 inhibition, prevented the inhibitory effects of HDL-CKD on endothelial NO production. In vivo, HDL reduced blood pressure (−10.7±1.1 mmHg; P<0.05), while healthy HDL reduced SBP (−11.2±1.7 mmHg; P<0.05). Notably, HDL from patients with CKD induced basal endothelial VCAM-1 expression and promoted endothelial MNC adhesion, while HDL from healthy subjects did not, suggesting a change to a proinflammatory particle. In vitro gap closure and in vivo reendothelialization after carotid injury were suppressed by HDL of CKD patients.

Conclusion: Our data demonstrate for the first time that endothelial-protective effects of HDL are considerably impaired in patients with CKD independently of the severity of CKD. Furthermore, HDL may be involved in initiation and aggravation of hypertension in these patients. This reveals a new potentially important pathomechanism of cardiovascular disease in patients with incipient CKD.

Efficacy, safety and tolerability of 150 mg Q2W dose of the anti-PCSK9 mAb, REGN727/SAR365353: data from 3 phase 2 studies

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Purpose: Proprotein convertase subtilisin/kexin type 9 serum protease (PCSK9) plays a pivotal role in LDL receptor (LDLR) degradation. Gain-of-function mutations of PCSK9 in humans result in hypercholesterolemia, while loss-of-function mutations are associated with low LDL-cholesterol (LDL-C) and significantly reduced coronary heart disease risk. REGN727/SAR365353, a fully human monoclonal antibody targeted to PCSK9, has been evaluated in 3 recently completed phase 2 studies, DF11565 (NCT01288443), DF11566 (NCT01288469), and R727-CL-1003 (NCT01268676). We present a combined analysis from these 3 studies to assess the efficacy and safety profile of REGN727.

Methods: A total of 365 patients with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [FH] or non-FH) and LDL-C <100 mg/dl on background lipid-lowering therapies which included a statin, were enrolled in 3 dose-blind, randomized, placebo-controlled phase 2 studies of 8- to 12-week treatment durations. At randomization, 77 patients were administered placebo, 167 received any other regimen of REGN727 and 108 received 150 mg REGN727 every 2 weeks (Q2W) for 2 weeks (Q2W), 31 patients from DF11565, 61 from DF11566 and 16 from R727-CL-1003). The 150 mg Q2W dose was selected for analysis as it was common to all 3 studies.

Results: REGN727 150 mg Q2W resulted in robust reductions in LDL-C with mean percent reductions from baseline ranging from -66.2% to -71.8% as compared to placebo (-5.7% to -8.9%) by week 12 in studies DF11565 and R727-CL-1003. In study DF11566, mean percent reductions from baseline ranged from -66.7% to -72.3% as compared to -17.7% for placebo by week 8. We also observed similar reductions at earlier time points and reductions in other apoB-containing lipid parameters. Additionally, modest increases in HDL-C and apoA1, along with reductions in Lp(a) were observed. REGN727 155 mg Q2W was tolerated and exhibited no clearly adverse event signal compared to placebo. Among those patients who received at least one dose of REGN727 150 mg Q2W (safety population, n=108), adverse events occurring in ≥10% of patients included dizziness, nausea, headache, diarrhea, and injection-site reactions. In this treatment group, there were 0 deaths, 1 SAE and 2 discontinuations as compared to 0 deaths, 2 SAEs and 4 discontinuations for patients on placebo (safety population, n=77).

Conclusion: In Phase 2 studies, REGN727 150 mg Q2W provides robust reductions in LDL-C and other atherogenic lipoproteins while providing a good safety and tolerability profile.

OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENT

Ambulatory blood pressure measurement-mandatory for blood pressure monitoring in treated hypertensive patients?

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Purpose: In epidemiological and clinical studies 24-hour ambulatory blood pressure monitoring (ABPM) for hypertension management has been shown to be superior in predicting cardiovascular events to office blood pressure (BP) readings and recent guidelines recommend ABPM in the diagnostic set up (in NICE now routinely mandatory). But the usefulness of ABPM has only been scarcely examined in cohorts of treated hypertensive patients.

Methods: In this non-interventional study conducted in Germany (3A-Registry in 899 general practitioners’ offices, office BP and ambulatory blood pressure (ABP) was measured in 3826 hypertensive patients, enrolled for 1 year in the registry, with 3.0±1.6 antihypertensive agents. In this cohort (54.4% males, mean age 64.2 years), mean systolic and diastolic office BP was 156/90 mmHg and mean systolic and diastolic 24-hour ABP was 146/85 mmHg.

Results: Patients were categorized in controlled BP (office BP ≤140/90 mmHg, ABP 24-hour ≤130/80 mmHg) and uncontrolled BP (office BP ≥140/90 mmHg, ABP 24-hour ≥130/80 mmHg) groups, according to ESC-ESH 2009 guidelines. 50.5% of the patients had controlled office BP values, and with ABPM 23.7% had controlled values. Percentage of patients with office BP values ≤140/90 mmHg and ABP values ≥130/80 mmHg was 32.9%, indicating masked hypertensive BP despite antihypertensive therapy. In contrast, only 6.1% of the patients with ABP values ≤130/80 mmHg had office BP ≥140/90 mmHg indicating some ‘white coat effect’

Understanding lipid metabolism and designing future therapies for dyslipidemia / Out-of-office blood pressure measurement
Ambulatory blood pressure and dipping-pattern after catheter-based renal sympathetic denervation in patients with resistant hypertension

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Background: Catheter-based renal sympathetic denervation (RD) in patients with resistant hypertension has been shown to reduce sympathetic drive and office blood pressure. Ambulatory blood pressure monitoring (ABPM) is mandatory in every patient with uncontrolled hypertension. Nighttime systolic pressure and non-dipping is associated with cardiovascular morbidity and mortality. The influence of RD on ambulatory blood pressure (ABPM) and dipping pattern has not been studied in details.

Methods and Results: Eighty patients with resistant hypertension were included in the study. Systolic and diastolic blood pressure (SBP/DBP) as well as ABPM (24h systolic, 24h diastolic, 24h DBP, heart rate [HR] average) and dipping-pattern were analyzed prior to, and at 3 and 6 months follow-up. RD reduced office SBP and DBP at 3 and 6 months by 20.9/7.1 mmHg and 25.9/3.3 mmHg (p<0.001, respectively). After 3 and 6 months 24-hour average SBP/DBP was reduced by 8.6/4.5 mmHg (p=0.019/0.025) and 11.5/6.5 mmHg (p=0.018/0.022), respectively. Average SBP/DBP were lowered at 3 and 6 months follow-up at daytime by 9.2/5.4 mmHg (p=0.010/0.001) and 11.9/7.1 mmHg (p=0.001/0.001) and at nighttime by 6.2/5.1 mmHg (p=0.002/0.004) and 10.25/1.1 mmHg (p=0.001/0.001), respectively. Renal denervation also reduced maximum SBP by -12.8 mmHg at 3 months and by -14.7 mmHg at 6 months follow-up (p<0.001 and p<0.001). Six months after RD 21 patients had an improvement in their dipping-pattern.

Conclusion: Beside significant reductions in office SBP and DBP, RD also reduced the nighttime, daytime and nighttime SBP and DBP as well as maximum SBP after 3 and 6 months. RD has the impact to improve dipping-pattern in at least some patients.

Central blood pressure variability is related to carotid intima-media thickness whereas nocturnal central blood pressure fall is related to left ventricular mass in untreated hypertensives

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There is an evidence that central systolic pressure (CSP) is strongly correlated with target organ damage than peripheral systolic pressure (PSP). The relation between organ damage and CSP variability and 24-h CSP profile is unknown. Therefore, the aim of the study was to evaluate the relationship between 24-h CSP profile as well as CSP variability and left ventricular mass (LVM), LV and left atrial (LA) dimensions; carotid intima-media thickness (IMT), and microalbuminuria.

Methods: The study group consisted of 50 patients with newly diagnosed, untreated hypertension (age 40.4±11.5 years, 35 men) and 50 normotensive subjects (age 38.3±12.0 years, 35 men). Applanation tonometry of the radial artery and “point forward moving average” method has been used to derive 24-hour CSP (Bpno). 24-hour peripheral blood pressure (BP) was measured using Space-labs device. The nocturnal pressure fall was defined as the pressure difference between hours of diurnal activity and nocturnal rest divided by average BP obtained during the entire 24-hour PSP variability was estimated using standard deviation of all measurements during 24-hours (24SD), during the hours of diurnal activity (DSD), and during the hours of nocturnal rest (nSD). The independent relations were assessed using the general linear model.

Results: The 24-hour peripheral BP was 136.0±7.2/84.9±6.3 mmHg in hypertensives vs. 120.9±6.4/74.7±5.5 mmHg in normotensives (p<0.05) for both; CSP was 129.5±10.6 mmHg and 110.5±12.4 mmHg (p<0.05), respectively. Nocturnal CSP fall was lower compared to PSP fall (8.0±4.3% vs. 12.4±4.7%, p<0.002). Nocturnal systolic pressure fall was similar in subjects with and without hypertension (central: 7.9±4.5% vs. 8.1±4.1%, p=NS peripheral: 11.4±4.7% vs. 12.4±4.7%, p=NS). Both 24-hour CSP and 24-hour PSP is independently related to IMT and LVM index. Nocturnal CSP fall was independently related to LVM index (standardized regression coefficient:standard error: -0.32±0.16, p=0.05), LV systolic diameter (-0.38±0.14, p<0.01), and LA volume (0.15±0.15, p<0.05) in hypertensives whereas in whose association was found in normotensives. Nocturnal PSP fall was not related to any of these parameters. IMT was related to CSP variability (24SD:-0.40±0.14, p=0.01; dSD: -0.35±0.15, p<0.05; nID: 0.25±0.13, p<0.05) in hypertensive only. IMT was not related to PSP variability.

Conclusion: Central systolic pressure variability is related to carotid IMT whereas nocturnal CSP fall is related to LVM and LV geometry in untreated hypertensives.

Out-of-office blood pressure measurement, but not office blood pressure is a determinant of B-type natriuretic peptide levels in untreated essential hypertension

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Background: B-type natriuretic peptide (BNP) is a marker of elevated left ventricular (LV) filling pressure or myocardial stretch, as well as a risk marker of cardiovascular diseases. However, increased BNP levels in treated hypertensives, in association with out-of-office blood pressure (out-of-OBP) and LV geometry remain to be examined.

Methods: 245 elderly hypertensive patients (mean age, 74 years; men: 38%) underwent ambulatory BP measurement (ABPM) (30-min intervals), trans-thoracic echocardiography, and measurement of plasma BNP concentration.

Results: Logarithmically transformed BNP concentration (LnBNP) correlated with body mass index, eGFR, 24-hour systolic BP, nighttime BP, but not OBP of grade 2 hypertension. It also correlated with left atrial dimension, relative wall thickness, but not with LV mass index (LVM). In the multiple linear regression analysis, nighttime BP and eGFR independently predicted LnBNP after adjusting for age, sex, BMI, smoking habit, dyslipidemia, diastolic BP, 24 mean systolic pressure, variability of each one BP parameter was independently related to PWV (systolicSB: b = -0.150, diastolicSB: b = -0.211 and pulse pressureSB: b = -0.283, p<0.05). Furthermore, in another model including the above confounding factors, the addition of respective SD value of the prediction of PWV by 24 mean systolic BP, 24 mean diastolic BP and 24 mean pulse pressure (for systolicSB: r change from 0.280 to 0.312, for diastolicSB: r change from 0.224 to 0.271 and for pulse pressureSB: r change from 0.342 to 0.403 respectively, p<0.01).

Conclusions: In untreated patients with newly diagnosed essential hypertension reduced blood pressure variability (systolic, diastolic, pulse pressure) was significantly and inversely related with increased BNP variability analysis. After adjustment for age, sex, BMI, smoking habit, dyslipidemia, diastolic BP, 24 mean systolic pressure, variability of each one BP parameter was independently related to PWV (systolicSB: b = -0.150, diastolicSB: b = -0.211 and pulse pressureSB: b = -0.283, p<0.05). Furthermore, in another model including the above confounding factors, the addition of respective SD value of the prediction of PWV by 24 mean systolic BP, 24 mean diastolic BP and 24 mean pulse pressure (for systolicSB: r change from 0.280 to 0.312, for diastolicSB: r change from 0.224 to 0.271 and for pulse pressureSB: r change from 0.342 to 0.403 respectively, p<0.01).

Conclusion: Central systolic pressure variability is related to carotid IMT whereas nocturnal CSP fall is related to LVM and LV geometry in untreated hypertensives.
REGIONAL CEREBRAL BLOOD FLOW AND CIRCADIAN BLOOD PRESSURE PROFILE IN PATIENTS WITH METABOLIC SYNDROME: EFFECT OF COMBINED ANTIHYPERTENSIVE THERAPY

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Purpose: Study of regional cerebral blood flow (rCBF) in patients with metabolic syndrome (MetS), revealing of interrelation between parameters of blood pressure monitoring and the results of brain perfusion single photon emission computed tomography (SPECT), as well as estimation of combined antihypertensive therapy on cerebral perfusion.

Methods: Twenty-four patients with MetS were investigated by brain SPECT with 99mTc-HMPAO and blood pressure monitoring before and after 6 months of antihypertensive therapy, sustained-release verapamil in combination with indapamide sustained release or enalapril. Regional cerebral blood flow (rCBF) (ml/100g/min) was calculated. All patients had no focal neurological symptoms. Fifteen patients of similar age without angiographic signs of carotid atherosclerosis, cardiac arrhythmia, coronary artery disease and arterial hypertension, neurological and psychiatric disorders were investigated as control group.

Results: All patients with MetS showed a decrease in rCBF in all regions of the brain compared with the control group. The most pronounced decrease in perfusion in all subjects was found in the temporal, occipital and upper frontal regions (p<0.001). Antihypertensive therapy with verapamil and indapamide for 24 weeks led to an increase of CBF by 7% in the left temporal region (p<0.009). The combination of verapamil and enalapril improved CBF over a larger range of study areas. Thus, the increase in rCBF we observed in the right lower frontal (p=0.007), temporal (p=0.01), upper frontal (p=0.01), anterior parietal and in the posterior parietal lobes on both sides (p=0.009 and p=0.003, respectively) There was a direct correlation between the degree of nocturnal diastolic blood pressure reduction and values of rCBF in the right temporal region (R= -0.5, p<0.04), which confirms the danger of excessive loss of blood pressure in hypertensive patients during sleep.

Conclusions: Our results suggest that patients with MetS even without focal neurological symptomatology have marked signs of rCBF disorders. Combination antihypertensive therapy has a positive effect on cerebral perfusion.

CARDIOVASCULAR RISK ASSESSMENT IN CLINICAL APPLICATION

ASSOCIATION OF HEART RATE ON ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN THE GENERAL POPULATION DURING LONG-TERM FOLLOW-UP

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Purpose: Increased resting heart rate (HR) has been proposed as a risk factor for all-cause (AC) mortality. The effect of an increased HR on cardiovascular (CV) mortality is not equivocal. We hypothesize that monitoring the change in HR over a four years period could be an independent risk factor for AC and CV mortality in the general population.

Methods: From the Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort (N=8592), 7189 subjects had no previous history of CV disease and were not on beta-blocker therapy on both HR measurements. Between 1997 and 2001, HR was measured after 10 minutes rest. Baseline HR was divided into: low (<80th percentile), normal (80th percentile), and high (>80th percentile). Changes in HR were defined in the same manner: decreased (<5bpm), unchanged (±5bpm), and increased (>5bpm). After the second HR measurement, HR was measured again after 3.5 years. Between measurements, HR change was calculated and the median follow-up was 6.3 years (range 5.8-6.9). Multivariable Cox proportional hazard analyses were performed, adjusting HR for age, gender, smoking, systolic blood pressure, cholesterol and the biomarkers C-reactive protein, high-sensitive Troponin-T and N-terminal pro-B-type natriuretic peptide.

Results: At baseline, mean age was 48±12 years and 49% of subjects were male. Mean HR was 70±10bmp and mean change in HR was -0.2±7.5bmp (p=0.045 vs. baseline). There were 472 deaths (6.6%), of which 89 (18.9%) of CV origin. Using Cox-proportional hazard analyses, high baseline resting HR was associated with AC mortality (1.5-fold increase, CI: 1.0-2.2%; p=0.006, compared to low resting HR), but not with CV mortality (p=0.763). Over 4 years, 1238 subjects decreased in HR, 3377 subjects remained unchanged and 1137 subjects had an increased HR (mean change -1.0, -0.1 and 1.0 bpm, respectively). Subjects with an increased HR had two-fold increased risk for AC (2.1 CI: 1.0-4.4; p=0.047) and six-fold increased risk for CV mortality (6.0, CI: 1.8-19.9; p=0.004), both compared to subjects with decreased HR.

Conclusions: In a middle aged general population, a single measurement of increased resting HR is associated with increased AC mortality, but not with increased CV mortality. In contrast, a change in HR of >5bmp over 4 years, was associated with a major, six-fold increased risk for CV mortality, whereas risk for AC mortality was only two-fold increased during further follow-up. Serial HR measure-ments may be more informative with regard to mortality risk, especially of CV origin.

CORONARY ARTERY CALCIFICATION SCORE AS TOOL FOR RISK ASSESSMENT AMONG FAMILIES WITH PREVIOUS CORONARY ARTERY DISEASE

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Introduction: A family history (FHx) of premature coronary artery disease (CAD) is a risk factor for CAD. Notwithstanding its value for families at risk, FHx provides no information on individual familial disease and arterial hypertension, neurological and psychiatric disorders were investigated as control group.

Methods: We performed a case-control study in asymptomatic individuals (n=722) to assess the association between a positive FHx and elevated CAC scores. Furthermore, we performed a post-hoc analysis on the St. Francis Heart Study (n=138) to calculate the 10-year risk of future CAD in individuals with a positive FHx and elevated CAC (>80th percentile).

Results: In the case-control study, individuals with a positive FHx had an increased risk for elevated CAD (odds ratio (OR) 1.93 (95% CI 1.31-2.84); p<0.05). Furthermore, in a multivariable regression analysis, a positive FHx was associated with absence of CAC (OR 2.82 (95% CI 1.72-4.61); p<0.05) and with CAC score >80th percentile (OR 4.65 (95% CI 2.63-8.24); p<0.05). The post-hoc analysis showed that for those with a CAC >80th percentile, after 3.5 years follow-up, individuals with a positive FHx had an increased risk for cardiovascular events (HR 1.96; 95% CI 1.06-3.61; p=0.05) compared to those with a negative FHx.

Conclusion: CAC scores in individuals with a FHx of premature CAD show a marked, dichotomous distribution compared to those with a negative FHx. The individuals with positive FHx and elevated CAC scores have a marked increase of future cardiovascular events. These findings indicate that CAC score individuates the risk within families with positive FHx.

RISK FACTORS OF VENOUS THROMBOEMBOLISM AMONG PREGNANT WOMEN- A NATIONWIDE CASE-CONTROL STUDY

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Purpose: Pregnant women are at increased risk of a venous thromboembolism (VTE) compared to non-pregnant women. We aimed to assess potential lifestyle risk factors (smoking, body mass index (BMI), and use of pharmacotherapy) for VTE in pregnant women.

Methods: Using individual-level linkage of Danish nationwide administrative registries, we included all women with their first pregnancy between 1997 and 2009. We excluded women with prior VTE, and previous VTE in four pregnant women (controls). The risk of VTE associated with pharmacotherapy during pregnancy, BMI, smoking, and parity (number of childbirths) was investigated using conditional logistic regression.

Results: Among 518,103 pregnant women, there were 419 cases. The cases and non-cases did not differ in age (mean age 29.9 and 29.6 years respectively, p=0.16). Cases more often had a history of prior VTE within the last 5 years (9.07% vs. 0.14%, p<0.001). After matching there were no difference between cases and controls in parity, BMI and the matching variables. Using conditional logistic regression we found no association between VTE during pregnancy and
smoking, BMI, or parity (Figure). Use of psycholeptic drugs (antipsychotics, anxiolytics and hypnotics and sedatives) during pregnancy increased the risk of VTE (Figure 1).

Conclusions: In this nationwide case-control study of pregnant women, we — surprisingly — found no association between the risk of VTE during pregnancy and smoking or obesity. The risk of VTE was increased among women using psycholeptic drugs during pregnancy. Further studies are warranted to investigate whether this risk is caused by the underlying psychiatric disease or the medication itself.

Elevated resting heart rate is a risk factor for mortality independent of physical fitness (VO2max)

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Purpose: Elevated resting heart rate has been shown to be associated with mortality. However, it is still undetermined whether resting heart rate is merely a marker of physical fitness or an independent risk factor. We studied the relationship between resting heart rate, physical fitness (VO2max), and mortality.

Methods: A prospective study of middle-aged employed men without known cardiovascular disease. Resting heart rate was assessed from the ECG, physical fitness (VO2max) was determined by the Åstrand bicycle ergometer test. Only subjects with sinus rhythm were included.

Results: 2964 subjects were followed for 16 years. 1180 deaths occurred. Resting heart rate was inversely related to physical fitness (p<0.001). Resting heart rate in the highest vs lowest quintile predicted mortality after adjusting for age (1.6, 95% CI 1.1-2.3), 1.4 (1.1-1.8) and 1.3 (1.0-1.7) among participants aged 50-55, 55-60, 60-65, 65-70 and 70+ years, respectively (p for trend <0.0001). Only 18 of 1742 (1.0%) participants did not have at least 1 PAC on Holter monitoring. Sex was not associated with PAC occurrence (p=0.27). In stepwise logistic regression models, significant predictors for PAC occurrence were age (β per year 0.05, 95% confidence interval (CI) 0.04-0.06, p<0.0001), height (β per cm 0.02, 95% CI 0.01-0.03, p=0.001), log-transformed pro-B-type natriuretic peptides (β per log-unit 0.44, 95% CI 0.34-0.54, p<0.0001), elevated high sensitivity troponin levels ≥0.014 μg/L (β compared to reference level <0.003 μg/L, 25th, 95% CI 0.09-0.40, p<0.002) and HDL cholesterol (β per mmol/L 0.22, 95% CI 0.03-0.40, p=0.02). Elevated blood pressure, body mass index and a history of cardiovascular disease were not significantly related to PAC occurrence.

Conclusions: To our knowledge, this is the first study of risk factors for PAC occurrence in a representative sample of the general population aged 50 years or older. PAC occurrence is common and independently associated with age, height, natriuretic peptide levels, troponin levels and HDL cholesterol. The underlying mechanisms of these relationships need to be addressed in future studies.

Atrial fibrillation is a strong independent risk factor for ischemic heart disease mortality

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Purpose: Atrial fibrillation (AF) is a common sustained arrhythmia and is well known as a major risk factor for thrombo-embolic stroke and heart failure. However, the association of AF and ischemic heart disease (IHD) remains controversial. Although it has been reported that AF is a predictor of death and coronary artery events in patients with coronary artery disease in some small clinical studies, the information about an association between AF and IHD mortality is not enough. The aim of this study was to evaluate the association between AF and risk of IHD mortality among general population.

Methods: A total of 30,693 male and 59,884 female aged 40-79 years without history of heart diseases and CI who completed health checkups in Ibaraki prefecture, Japan, in 1993, enrolled into this study and were followed-up through 2006. The hazard ratios (HR) and 95% confidence intervals (95%CI) of AF for cause-specific mortality by using a multivariable Cox proportional hazards regression model were analyzed.

Results: AF was significantly associated with excess risk of total death (HR [95%CI]; 1.93 [1.59-2.33]), all-cause vascular mortality (3.87 [2.99-5.02]), CI mortality (5.38 [3.59-7.56]), and IHD mortality (4.97 [2.95-7.44]) in multivariable analyses. Furthermore, AF was the strongest predictor for IHD mortality among conventional risk factors including hypertension (1.56 [1.33-1.84]), diabetes mellitus (1.81 [1.36-2.40]), dyslipidemia (1.06 [0.86-1.31]) or smoking (2.05 [1.62-2.59]).

Conclusions: In this large-scale community-based cohort study, AF was strongly associated with increased risk of IHD mortality as well as risk of CI mortality.

Prevalence and risk factors

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Purpose: The occurrence of premature atrial contractions (PACs) is an independent predictor of incident atrial fibrillation and other adverse outcomes, including stroke and death. However, little is known about PAC prevalence in the general population and risk factors for PAC occurrence.

Methods: We performed a cross-sectional analysis among participants of the population-based Swiss cohort Study on Air Pollution and Lung Diseases in Adults (SAPALDIA). At the SAPALDIA follow-up visit in 2002, 24-hour Holter electrocardiograms were performed in 1742 (10.7%) after prearranged 40 years or older. PACs were identified by a coupling interval to the preceding QRS complex <80% of the mean RR interval before the event, and a QRS duration of <0.12 seconds unless aberration was suspected. Stepwise multivariable linear regression models were constructed to determine independent correlates for the number of PACs per hour (log-transformed).

Results: The median number (interquartile range) of PACs per hour was 0.8 (0.4-1.8), 1.1 (0.5-2.4), 1.4 (0.7-4.6), 2.3 (0.8-6.9) and 2.6 (1.2-6.5) among participants aged 50-55, 55-60, 60-65, 65-70 and 70+ years, respectively (p for trend <0.0001). Only 18 of 1742 (1.0%) participants did not have at least 1 PAC on Holter monitoring. Sex was not associated with PAC occurrence (p=0.27). In stepwise logistic regression models, significant predictors for PAC occurrence were age (β per year 0.05, 95% confidence interval (CI) 0.04-0.06, p<0.0001), height (β per cm 0.02, 95% CI 0.01-0.03, p=0.001), log-transformed pro-B-type natriuretic peptides (β per log-unit 0.44, 95% CI 0.34-0.54, p<0.0001), elevated high sensitivity troponin levels ≥0.014 μg/L (β compared to reference level <0.003 μg/L, 25th, 95% CI 0.09-0.40, p<0.002) and HDL cholesterol (β per mmol/L 0.22, 95% CI 0.03-0.40, p=0.02). Elevated blood pressure, body mass index and a history of cardiovascular disease were not significantly related to PAC occurrence.

Conclusions: To our knowledge, this is the first study of risk factors for PAC occurrence in a representative sample of the general population aged 50 years or older. PAC occurrence is common and independently associated with age, height, natriuretic peptide levels, troponin levels and HDL cholesterol. The underlying mechanisms of these relationships need to be addressed in future studies.

Genetic testing for platelet inhibition: why are we not doing it?

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Objectives: This study sought to determine the impact of a global platelet hyperreactivity — both to arachidonic acid and ADP — as the possible prognostic marker of per- and long-term thrombotic events in patients with acute coronary syndromes (ACS) undergoing an invasive procedure.

Background: High on-clipidogrel platelet reactivity has been found to be associated with high risk of ischemic events after percutaneous coronary interventions (PCI). Some data have found that the real adverse prognostic marker is the presence of a global high on-treatment platelet hyperreactivity (GHPH) identified by the measurement of platelet function induced by both arachidonic acid and aspirin.

Methods: Prospective, observational, referral center cohort study of 1772 consecutive patients with ACS undergoing PCI from April 2005 to April 2009 at the Division of Cardiology of Careggi Hospital, Florence, Italy in whom platelet reactivity was prospectively assessed by light transmission aggregometry by 10 micromolar ADP and by 1 arachidonic acid (AA). The primary end-point was a composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up.

Results: GHPH was documented in 152/1772 (8.6%); isolated HPR by ADP was found in 96/1772 (5.6%) and isolated HPR by AA in 21/1772 (1.2%). The pri-
Personalized antiplatelet treatment after percutaneous coronary intervention: the MADONNA study

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Background: Clopidogrel nonresponsiveness is associated with adverse clinical outcome.

Objectives: We aimed to investigate whether individualized antiplatelet treatment is an effective and safe strategy.

Methods: This was a prospective controlled study with a follow-up of 1-month. Responsiveness to clopidogrel was assessed by multiple electrode aggregometry (MEA) in 798 patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). In the guided group (n=403) clopidogrel nonresponders received repeated loading doses of clopidogrel (up to 4 loading doses of 600mg) or prasugrel (60mg), in the non-guided group (n=395) clopidogrel nonresponders did not undergo any change of treatment.

Results: Twenty six percent of patients (n=106) were classified as nonresponders in the guided group. Of them 56 received a prasugrel loading dose of 60mg and 50 were reloaded with 600mg of clopidogrel. All prasugrel non-responders reached a sufficient level of platelet inhibition whereas 14% (n=7) of clopidogrel nonresponders did not undergo any change of treatment.

Conclusion: personalization of treatment in patients undergoing PCI reduces periprocedural myocardial infarction and improves clinical outcomes in patients with clopidogrel nonresponsiveness.

558 Ticapigrer or prasagrel in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Purpose: Few data exist about the onset of action and the extent of platelet inhibition after ticagrelor or prasugrel loading dose (LD) in patients with STEMI. We aimed to compare the antiplatelet effect of ticagrelor versus prasugrel in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods: This was a prospective, randomized, single-center study of parallel design. Antiplatelet-naive STEMI patients, undergoing PCI were randomized in a 1:1 ratio either: prasugrel 60mg LD/10mg maintenance dose-MD or ticagrelor 180mg LD/90mgx2 MD. Platelet reactivity (PR) was assessed at 0 hour (pre randomization), 1, 2, 6, 24 hours and at day 5 with the VerifyNow assay (in PR units-PRU, with a value<230 indicating high on-treatment platelet reactivity-HTPR).

Results: Thirty-eight patients were randomized (76.3% men, age 60.2±1.3 years). There was no difference in patient’s characteristics between ticagrelor (N=18) and prasugrel (N=20) group. The primary end point of PR at hour 1 did not differ significantly between groups. There was a trend towards lower PR with prasugrel compared to ticagrelor at hour 2 (Table 1). HTPR rate remained high in both groups at hour 1 (72.2% for ticagrelor vs 70.0% for prasugrel, p=1.0). There was a trend towards lower HTPR rate with prasugrel compared to ticagrelor at hour 2 (31.1% vs 56.2% respectively, p=0.02). Beyond hour 6 both agents effectively reduced PR.

Table 1. Platelet reactivity analysis

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<th>Ticagrelor</th>
<th>Prasugrel</th>
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<tr>
<td>PR 0H</td>
<td>N=18</td>
<td>N=20</td>
<td>0.8</td>
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<tr>
<td>PR 1H</td>
<td>N=18</td>
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<td>PR 2H</td>
<td>N=16</td>
<td>N=19</td>
<td>0.1</td>
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<tr>
<td>PR 4H</td>
<td>N=16</td>
<td>N=19</td>
<td>0.9</td>
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<td>PR 24H</td>
<td>N=15</td>
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AngioCor-A model with treatment as fixed effect and PR 0H as a covariate. Values represent least squares estimates (95% CIs) with a p-value for the treatment effect.

Conclusions: Patients with STEMI undergoing PCI exhibit similarly high PR early after treatment with either prasugrel or ticagrelor. Apart from a trend towards better platelet inhibition with prasugrel compared to ticagrelor 2 hours post LD, both agents effectively treated HTPR thereafter.

598 Prasugrel is associated with higher levels of P2Y12 blockade and less periprocedural myonecrosis than clopidogrel in patients undergoing coronary angioplasty for stable coronary artery disease

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Aim: Clopidogrel treatment along with aspirin is considered the "gold standard" antiplatelet regimen in patients undergoing percutaneous coronary intervention (PCI). Prasugrel is a novel thienopyridine with more potent antiplatelet effect than clopidogrel. We assessed the response to clopidogrel and prasugrel with a point-of-care assay (Verify Now) in patients undergoing elective PCI. Number of periprocedural myocardial infarctions (PMI) was recorded and relation to antiplatelet regimen used was evaluated. Patients under chronic aspirin therapy undergoing elective PCI were randomised to either clopidogrel (n=51, 600mg loading and 75mg maintenance dose) or prasugrel (n=53, 60mg loading and 10mg maintenance dose) therapy. Response to P2Y12 inhibition was measured with P2Y12 Reaction Units (PRU) and % inhibition of PRU. PRU was defined as a post-procedural trponent-i increase more than 3 times the 95th percentile of the upper reference limit.

Results: Clinical characteristics and baseline platelet reactivity did not differ significantly among the 2 groups. No difference was found for aspirin response assessed by ARU (79.9±20.4% for clopidogrel vs 85±6% for prasugrel, p=0.23). PRU was significantly lower and % inhibition P2Y12 was significantly higher in prasugrel compared to clopidogrel group (38±4 vs 232±106, p<0.001 and 87±14 vs 31±26%, p<0.001, respectively) (Figure). PMI occurred in 24 (33%) patients, 17 (46%) in patients receiving clopidogrel and 7 (19%) in patients receiving prasugrel (p=0.024).

CYP2C19*2 and *17 alleles have a significant impact on the platelet response and bleeding risk in patients treated with prasugrel after acute coronary syndrome

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Background: Clopidogrel and Prasugrel are thienopyridine which need transformation to active metabolites via the cytochrome P450. CYP2C19*2 “loss of function” allele and CYP2C19*17 “gain of function” allele have been linked with re
spouse to clopidogrel and clinical outcomes. While previous data did not show significant influence of these alleles on response to loading dose of prasugrel, the effect on chronic response to prasugrel and bleeding risk has not been well investigated. We therefore designed the present study to answer this question.

Methods and Results: 213 patients undergoing successful coronary stenting for acute coronary syndrome and discharged with prasugrel 10 mg daily were prospectively included. Prasugrel Response was assessed at one month with the PRI VASP and High on-treatment Platelet reactivity (HTPR) defined as PRI VASP >50% and “hyper response” as PRI VASP < 8% (95th percentile), Platelet reactivity assessed by ADP-induced aggregation. CYP2C19*2 and CYP2C19*17 genotyping were performed. At one month, carriers of “loss of function” 2 allele had significantly higher PRI VASP than non carriers (33±15% vs. 27±14%, p <0.03) and higher rate of HTPR (16% vs. 4%, p<0.01). Conversely, carriers of 17 “gain of function” allele had significantly lower PRI VASP than non carriers (25±13% vs. 31±15%, p=0.03, p=0.01), lower rate of HTPR (1% vs. 10%, p=0.02), higher rate of “hyper response” (11% vs. 3%, p=0.02) and higher rate of bleeding complications than non carriers: 22% vs. 11%, (OR 95%CI: 2.5 [1.2-5.4]; p=0.02).

Conclusion: The present study shows a significant influence of CYP2C19*2 and 17 allele on response to chronic treatment by prasugrel 10 mg daily and occurrence of bleeding complications.

Differential effects of platelet transfusion on correction of the bleeding time in prasugrel and ticagrelor treated rats

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Purpose: Clinical trials have shown that dual antiplatelet therapy, aspirin plus novel P2Y12 inhibitors, result in superior efficacy regarding major adverse cardiovascular events in patients with acute coronary syndrome. However, an increased number of bleeding events in certain patient groups has also been reported. Platelet transfusion is a treatment option in such patients. In the present study, effects of platelet transfusion on bleeding time were compared in rats treated with prasugrel, the 3rd generation thienopyridine, and ticagrelor, a non-thienopyridine P2Y12 antagonist.

Methods: Vehicle, or doses of prasugrel (10 mg/kg, p.o.) and ticagrelor (30 mg/kg, p.o.) that resulted in similar levels of platelet inhibition were administered to rats 1 week after the loading dose of platelet inhibitors. Platelet transfusions of PRP (platelet rich plasma) were given at 24 h after the loading dose of platelet inhibitors. Platelet transfusions were performed with vehicle, or doses of prasugrel (10 mg/kg, p.o.) and ticagrelor (30 mg/kg, p.o.). The number of bleeding events in certain patient groups has also been reported.

Results: Both prasugrel and ticagrelor significantly prolonged the bleeding time compared to vehicle-treated control groups (p<0.001 and p=0.01, respectively, both n=14). Platelet transfusion resulted in similar significant increases in blood platelet numbers in both prasugrel- and ticagrelor-treated animals. In contrast, red blood cell numbers were not changed by platelet transfusion in all groups tested. In the prasugrel-treated group, platelet transfusion caused significant shortening of bleeding time (p<0.05, n=13). In the ticagrelor-treated group, by contrast, platelet transfusion showed no influence on bleeding time (p>0.05, n=14).

Conclusion: The present results indicate that the prolongation of bleeding time by high-dose prasugrel was significantly reversed by platelet transfusion. However, bleeding time prolongation associated with ticagrelor was not lessened under the experimental conditions employed. The disparity in findings between prasugrel- and ticagrelor-treated animals may reflect the different reversibility profiles of the two agents.

HEART FAILURE MEDICATION: BENCH TO PRACTICE

478 Long-acting loop diuretic alosineamide is superior to short-acting furosemide in treatment of congestive heart failure: the J-MELODIC study

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Purpose: It is unknown what kind of loop diuretics is optimal for the treatment of patients with chronic heart failure (CHF). A previous animal study reported that the administration of alosineamide, a long-acting loop diuretic, improved mortality rate in a hypertensive heart failure model compared to furosemide, a short-acting one. We conducted J-MELODIC (Japanese Multicenter Evaluation of Long-acting Diuretics in Congestive heart failure) to compare therapeutic effects of alosineamide and furosemide in patients with CHF.

Methods: In this multicenter, prospective, randomized, open, blinded endpoint trial, we compared effects of alosineamide and furosemide in patients with CHF with New York Heart Association class II or III symptoms. 320 patients (160 patients in each group, mean age 71 years) were followed up for a minimum of 2 years. We considered 40 mg furosemide to be equivalent to 60 mg alosineamide based on the result of a previous clinical pharmacology study. Electrocardiography, echocardiography, chest X-ray and blood sample were examined at the study entry and every 12 months after the randomization. The primary endpoint was a composite of cardiovascular death or unplanned admission to hospital for congestive heart failure.

Results: Etiologies of heart failure were ischemic heart disease (33%), dilated cardiomyopathy (22%), and others (45%). Median left ventricular ejection fraction (LVEF) was 51%. During a median follow-up of 35.2 months, the primary endpoint occurred in 21 patients in the alosineamide group and 34 patients in the furosemide group (hazard ratio, 0.55, 95% confidence interval [CI], 0.32 to 0.95; P=0.03). Hazard ratio for the patients with LVEF < 50% was tended to be lower than that for patients with LVEF > 50% (0.42 [95% CI], 0.20-0.85) vs. 0.79 (0.36-1.21), P=0.25. Among the secondary endpoints, unplanned admission to hospital for congestive heart failure or a need for modification of the treatment for heart failure were also reduced in the alosineamide group compared to the furosemide group (hazard ratio, 0.60, 95% CI, 0.36 to 0.99; P=0.046). Increase in plasma BNP concentration after 1 year randomization was tended to be lower in the alosineamide group than in the furosemide group (3% vs. 25%; P=0.06). Changes in norepinephrine were not different between the 2 groups.

Conclusion: Alosineamide, compared to furosemide, improved the prognosis of patients with CHF.

479 Comparison of carvedilol, nebivolol and bisoprolol on cardiological function in moderate heart failure patients

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Purpose: Several β blockers are available for heart failure (HF) treatment but only few comparative data among molecules are available. We compared Carvedilol (β1,β2,β3 blocker) (C), Bisoprolol (β1 blocker) (B), and Nebivolol (β1 blocker with NO releasing activity) (N).

Methods: We included 61 moderate HF patients (age 61±9 years) in stable clinical conditions. Patients were randomized to receive, for 2 months, C, B, N in a blind, cross-over design. Averaged daily dose were 25.6±12.5, 4.8±2.4 and 5.0±2.4 mg for C, B, N, respectively. At the end of each period, patients underwent: spirometry with lung diffusion measure (DLco and its subcomponents Dm, Dl (CO), Vc, Peripheric CO2 sensitivity (L/min/mmHg) and VE/VCO2 slope.

Results: The main results are summarized in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>B</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLO (mL/min/mmHg)</td>
<td>26.3±3.1</td>
<td>30.4±3.8</td>
<td>30.4±3.8</td>
</tr>
<tr>
<td>VO2 (mL/min/kg)</td>
<td>26.9±4.1</td>
<td>29.0±4.4</td>
<td>28.8±4.5</td>
</tr>
<tr>
<td>VE/VCO2 slope</td>
<td>2.4±0.3</td>
<td>2.6±0.3</td>
<td>2.8±0.3</td>
</tr>
<tr>
<td>CCB (L/min/mmHg)</td>
<td>2.6±1.2</td>
<td>3.0±1.3</td>
<td>2.8±1.2</td>
</tr>
<tr>
<td>CCB (mL/min/mmHg)</td>
<td>2.6±1.2</td>
<td>3.0±1.3</td>
<td>2.8±1.2</td>
</tr>
<tr>
<td>DLO &gt; Lung diffusion for CO2</td>
<td>&lt;0.05 vs C and DMC</td>
<td>Vs. C</td>
<td>&lt;0.05 vs C and DMC</td>
</tr>
</tbody>
</table>

Conclusion: Nebivolol and bisoprolol were beneficial, C was deleterious.

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and Vc), chemoreceptor sensitivity to CO2 and maximal cardiopulmonary exercise test.

Results: (table): No significant difference were observed in lung mechanics and peak exercise heart rate. On C membrane diffusion and exercise capacity were worse while ventilation efficiency, as measured by VE/VCO2 slope, better than on B or N. Both peripheral and central sensitivity to CO2 were higher with B than with C.

Conclusions: β-blockers differently affected cardiopulmonary function in patients with moderate HF. B and N caused an amelioration in lung diffusion in comparison with C and B, after exercise performance, the former due to a lesser interference with β2-mediated alveolar fluid clearance. C, however, allowed a better ventilation efficiency during exercise likely due to a different chemoreceptor modulation. Results from this study could represent a basis for identifying the best match between a specific beta blocker compound and a specific HF patient.

480 Is there a relationship between adequacy of medical therapy for heart failure and results of imaging of sympathetic neuronal status using 123I metaiodobenzoxylguanidine (miBG)?

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Purpose: Heart failure (HF) medications such as beta blockers, ACE inhibitors, angiotensin receptor blockers (ARB) and aldosterone antagonists have both direct and indirect effects on the cardiac sympathetic nervous system. This study examined the relationship between doses of these drugs and myocardial sympathetic innervation assessed by 123I-miBG imaging.

Methods: Medication data for 782 HF subjects (81% male; 82% NYHA class II, 18% class III; 65% ischemic, 35% non-ischemic) with left ventricular ejection fraction (LVEF) ≤ 35% (mean 27%) were reviewed. All subjects were enrolled in a US/Europe clinical trial which required subjects to be on a stable regimen of guidelines-based medical therapy. Based upon clinical trial results and HF guidelines, a panel of 3 cardiologists rated dosage for each medication category on a 0-5 scale - 0: inadequate, 2: adequate, 4-5: maximally achieved. For ACE and ARB combined, total scores could range from 0 to 9. Cardiac 123I-miBG uptake was quantified as the heart/muscle tissue ratio (H/M) on 4-hour anterior planar images. The relationships between medication scores, H/M, and outcome events (composite of HF progression, arrhythmic events, and cardiac death) during median 17 months follow-up were examined using correlation and Cox proportional hazards methods.

Results: Mean total medication score was 4.7; most common scores were 4 and 5 (each n=142 (18%)). Only 123 subjects (16%) were judged to be receiving adequate doses (score ≥ 4) of all 3 medication categories. Mean H/M did not differ as a function of total medication score (range 1.41-1.47). However, for subjects with low (0-3), intermediate (4-6), and high scores (7-9), those who experienced events had significantly lower mean H/M (Table).

<table>
<thead>
<tr>
<th>Total Medication Score</th>
<th>No.Subjects with Event</th>
<th>H/M</th>
<th>Subjects without Event</th>
<th>H/M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>221</td>
<td>1.35</td>
<td>185</td>
<td>1.48</td>
</tr>
<tr>
<td>4-5</td>
<td>124</td>
<td>1.41</td>
<td>271</td>
<td>1.46</td>
</tr>
<tr>
<td>7-9</td>
<td>156</td>
<td>1.38</td>
<td>99</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Conclusion: Regardless of the intensity of HF medical therapy, patients with poorer myocardial sympathetic innervation as determined using 123I-miBG imaging are at increased risk for adverse outcomes. The optimal approach to use of 123I-miBG uptake measurements as an indicator of adequacy of HF medication dosages remains to be defined.

481 Prescription frequencies, dosing and clinical effects of heart failure drugs in the randomised INH-study

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Background: Therapy according to guidelines improves outcomes in heart failure patients. To investigate the prospective INH substudy investigated changes in prescription frequencies and dosages of betablockers (BB), angiotensin inhibitors (ACEI) or receptor blockers (ARB) and corresponding clinical effects in both study arms (one receiving HeartNetCare-HFTM (HNC) = telephoned, nurse-coordinated monitoring and individualised coaching, education; other arm was usual care (UC)).

Methods: 715 patients with systolic heart failure (ejection fraction < 40%) were randomised (UC=363, HNC=n=352, 69±12 yrs, 29% women, mean ejection fraction 30%). HNC-patients received education regarding drugs, uptitration of BB and ACEI/ARB was an principal HNC-goal. UC-patients received standard care, but uptitration of drugs was recommended to general practitioners. Type and dosages of drugs, quality of life (Short Form Questionnaire SF-36) and NYHA class were assessed both at baseline (BL) and follow up (FU).

Results: At BL 80% (HNC: 81. UC 79%, NS) of patients received a BB and 88% (HNC: 89, UC 87%, NS) ACEI/ARB. The mean equivalence dosage for BB was based on the recomended maximum of p-blockers for NYHA class III (HNC: 34, UC: 38%, NS) and for ACE/ARB 43% (HNC 44, UC 41%, NS). 40% of patients were in NYHA III/IV (HNC 43, UC 36%, NS), and mean SF-36 physical function score was 46 (HNC 48, UC 44, NS). About 70% of patients had BB (p<0.05) and each arm -1% of patients were on ACE/ARB (p=0.99). Mean equivalence dosages for BB increased by +8% in HNC and +4% in UC (P <0.001). For ACE/ARB the changes were +9 ±2% (p=0.009). Overall, in HNC uptitration of BB and ACEI/ARB was achieved in 53, in UC in 43.5% (p<0.003). Here, NYHA-class changed by -0.43 and -0.11 (p<0.001), and physical function scores by -8.1 and -2.0 (p<0.004). In patients without uptitration NYHA-class changed by -0.29 in both arms (p=0.96) and physical function score by +3.3 (HNC) and +5.3 (UC) (p<0.05).

Conclusions: While BB and ACEI/ARB are often prescribed, dosing according to guidelines is not always possible. Even with personalised coaching full uptitration is feasible only in a minority of patients. However, compared with UC, uptitration HNC-patients gained significantly more in quality of life and NYHA class, which suggests, that uptitration may require careful supervision to achieve maximum benefits for the patients.

482 Lung Impedance guided preemptive treatment of evolving pulmonary congestion-edema in course of acute myocardial infarction reduces use of furosemide

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Background: Patients sustaining an acute myocardial infarction (AMI) frequently develop pulmonary congestion-edema (PEd) during hospitalization. Treatment is initiated after the appearance signs of lung fluid content (LFC) increase. Ongoing monitoring of LFC may enable to predict impending PEd and prompt preemptive therapy. Late treatment beginning of PEd may require more diuretics.

Aims: We sought to find out whether non-invasive lung impedance (LI) guided preemptive treatment of evolving PEd in the course of acute myocardial infarction reduces dosage of furosemide administered in comparison with common practice.

Methods: LI was measured by a method based on transverse distribution of electromagnetic energy through the chest which is more sensitive than current methods. We previously found that an LI decrease of 12-14% from baseline level, when patients are still asymptomatic, reflects the beginning of transition from interstitial to alveolar edema. In this study we evaluated the effect of preemptive LI-guided therapy on furosemide dosage required to treat evolving PEd.

Results: 222 AMI consecutive patients asymptomatic at admission in which an LI decrease of 12-14% from initial level was recorded during monitoring were randomized into two groups (2:1). Groups were well matched for demographic, laboratory parameters, perfusion type and in-hospital therapy. Patients were monitored for 116±50 hours. Treatment for PEd was started in group 1 patients (common practice) only after symptom appearance (LI decrease 25.3±6.5% from initial) while group 2 patients diuretic preemptive therapy was begun at an asymptomatic stage when LI decreased by 12-14%. All group 1 patients but only 11% of patients from group 2 developed moderate to severe clinically and roentgenologically proven PEd (p < 0.001). During admission group 1 patients were treated with more furosemide than group 2 patients (131±37 mg vs. 184±159 mg, p=0.007). Time from LI decrease to 12-14% to initiation of therapy with furosemide was longer in group 1 by 545±539 minutes than in group 2 (p=0.001). Patients of group 1 and 2 required furosemide treatment more than 5 days in 12% and 14% of cases, respectively.

Conclusions: Preemptive LI-guided therapy with furosemide in AMI patients is initiated earlier than in common practice and is effective in halting evolving PEd. Preemptive treatment translates into better clinical outcome and lower furosemide dosage.

483 Acute intravenous infusion of human stresscopin (JNJ-39588146) improves left ventricular systolic function without increasing myocardial oxygen consumption in dogs with advanced heart failure

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Background: JNJ-39588146/human Stresscopin (STC) is a newly identified peptide that binds selectively and with high affinity to CRF type 2 receptor (CRFR2). This study examined the acute effects of intravenous administration of escalating doses of STC on left ventricular (LV) systolic function in dogs with advanced heart failure (HF).

Methods: Studies were performed in 7 anesthetized dogs with intracoronary microembolization-induced HF. Each dog received both STC and volume matched vehicle control (Veh, 5mM acetate/D5W) administered one week
apart in random order. STC was administered as a 60 min low dose (LD) infusion (2.2ng/kg/min), followed by a 60 min intermediate dose (ID) infusion (7.3ng/kg/min). Hemodynamic and ventriculographic measurements were made at baseline, prior to drug administration, and at the end of each 60 min drug or vehicle infusion. Measurements included LV ejection fraction (EF), end-systolic volume, end-diastolic volume, stroke volume (SV), LV end-diastolic pressure (EDP) and myocardial oxygen consumption (MVO2).

Results: Data are shown in the table. Neither STC nor Veh had any significant effect on heart rate or systolic blood pressure. Veh infusions had no effect on EF, ESV, SV, EDP or MVO2. In contrast, compared to Veh, STC significantly increased EF and significantly lowered ESV and EDP in a dose-dependent fashion without increasing MVO2. In addition, STC was safe and did not elicit de novo cardiac arrhythmias.

Conclusions: In dogs with advanced HF, acute intravenous administration of STC preserved LV systolic function while decreasing heart rate or MVO2 without decreasing systemic pressure. These findings support the continued development of STC for the treatment of patients with acute HF syndromes.

**RISK STRATIFICATION FOR SUDDEN CARDIAC DEATH: A CONTINUUM PROCESS**

### 503

**A blood test for sudden death risk**

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**Background:** Human heart failure (HF) is associated with decreased cardiac voltage-gated sodium channel current (encoded by SCNSA), and the changes have been implicated in the increased risk of sudden death in HF. In heart failure (HF), SCNSA has two truncated mRNA alternative splicing variants that are upregulated with a concomitant decrease in the full-length transcript. These variants encode prematurely truncated, nonfunctional sodium channels. In this study, we evaluated whether white blood cell (WBC) sodium channel mRNA splicing varied as a function of the presence of HF or malignant arrhythmias as measured by appropriate implanted cardio-de fibrillator (ICD) shocks.

**Methods:** One hundred eighty adult patients were recruited into this study, 45 controls without HF (Ejection Fraction (EF) > 40%) and 135 with HF (EF < 35%). Patients with congenital heart disease, infections, and inflammatory conditions were excluded. The splicing factor expression profile was investigated by gene array assay in circulating WBCs of HF patients. The mRNA abundances of SCNSA and SCNSA variants were determined by real-time PCR. The expressions of SCNSA and SCNSA variants were compared with heart tissues in HF or control patients.

**Results:** Gene array comparisons between normal human and heart failure tissues and WBCs correlated. Two variants were shown to have significant differences in the age, race, gender, NYHA class, coronary artery disease, QRS duration, ACE-inhibitor and antiarrhythmic use among the groups. No significant differences were noted in the presence of HF or malignant arrhythmias as measured by appropriate implanted cardio-de fibrillator (ICD) shocks.

**Conclusions:** In heart failure (HF), SCNSA splice variants are correlated with the presence of HF or malignant arrhythmias as measured by appropriate implanted cardio-de fibrillator (ICD) shocks.

### 504

**Early repolarization and prolonged filtered QRS duration associated with sudden cardiac death for a long term follow-up in patients with chronic heart failure**

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**Background:** Early repolarization pattern (ERP) is known to be associated with sudden cardiac death (SCD) in healthy subjects. Recently, it has been reported that ERP would be associated with SCD in patients with old myocardial infarction in the case-control study. However, there is no information available on the prognostic significance of ERP in chronic heart failure (CHF) patients, in relation to ventricular late potential (VLP) detected by signal-averaged electrocardiogram (SAE). We sought to prospectively investigate whether ERP would be associated with SCD in CHF patients, and whether the combination of ERP and VLP would improve the prediction of SCD.

**Methods:** The study population consisted of 129 consecutive outpatients with mild to moderate systolic heart failure with LVEF ≥ 40%. All patients underwent the standard 12-lead electrocardiogram and SAE at enrollment, and we assessed the presence of ERP using the criteria of j-point elevation ≥ 0.1 mV in at least 2 inferior or lateral leads. The duration of filtered QRS (IQRs), the RMS voltage for the last 40 ms of filtered QRS (RMS40), and the WBC low amplitude signal (<40 μV) in the terminal portion of filtered QRS (LAS40) were measured on the vector magnitude of SAE. Abnormal values for these 3 parameters were assessed at enrollment ≥ 130 ms, RMS40 < 17 μV, and LAS40 ≥ 40 μs. VLP was defined by the presence of 2 or more abnormal values. The primary endpoint of this study was SCD.

**Results:** At the entry, 16 had ERP and 63 had VLP. During the follow up period of 6.7±3.6 years, 26 patients had SCD. The incidence of SCD was significantly higher in patients with than without ERP (68% vs 14%, p<0.0001). Although patients with SCD trend to have VLP more frequently than those without SCD (24% vs 16%, p=0.03), IQRs was significantly longer in patients with SCD (144±15 ms vs 132±17 ms, p=0.02). A multivariate Cox analysis revealed that ERP hazard ratio (HR) 3.9, 95% CI 1.7 to 8.9, p=0.001 and abnormal IQRs (HR 3.1, 95% CI 1.1 to 8.6, p=0.03) significantly associated with SCD. In Kaplan-Meier analysis, it was shown that patients with SCD was significantly often observed in patients with than without ERP (63 [10/16%] vs. 14 [16/13%], p=0.001). HR of a combination of ERP and abnormal IQRs for prediction of SCD was 14.4 (95% CI 4.4 to 47.3), which was 3.7-fold of the HR of ERP only.

**Conclusions:** ERP would be associated with an increased risk of SCD in CHF patients. The combination of ERP and prolonged IQRs could improve the power to predict for SCD in patients with CHF.
**Predictors, in-hospital, short and long term prognosis of**

**Delayed CE-MRI quantification for predicting left cardiac arrest complicating a first STEMI was a strong independent predictor of**

**Conclusions:** The presence of ER increases the risk for VT/VF or sudden death occurrences in the chronic phase of AMIs, and may become a useful tool for deciding an indication for an implantable cardioverter defibrillator.

**Concomitant early repolarization increases the occurrence of sustained ventricular tachyarrhythmias and sudden death in the chronic phase of an acute myocardial infarction**

**Purpose:** We recently demonstrated that the presence of early repolarization (ER) increased the risk of ventricular fibrillation (VF) occurrences in the early phase of acute myocardial infarctions (AMIs). However, it is unknown whether there is an association between ER and VF occurrences in the chronic phase of an AMI.

**Methods:** This study included 974 patients with AMIs (67±12 years; 742 male; 232 female) who underwent successful percutaneous coronary intervention. The primary endpoint was occurrence of sustained ventricular tachyarrhythmias (VT/VF) or sudden death after discharge from the AMI hospitalization. We evaluated the presence of ER from the ECGs recorded at pre-discharge. ER was electrocardiographically defined as a QRS-ST junction elevation of >0.15mV from baseline in at least 2 inferior or lateral leads, manifested as QRS slurring or notching. We also analyzed the localization (inferior or lateral leads), amplitude, morphology (notching or slurring), and ST segment characteristics (upsloping or horizontal/descending) of ER to evaluate the significance of the ER pattern.

**Figure 1. ROC of 3 different c-o of infarct sizing**

**Conclusion:** In the context of STEMI, FWHM is a tough and reproducible algorithm to quantitatively assess delayed hyperenhancement, greatly related to functional prognosis at 3 months follow-up.

**Delayed CE-MRI quantification for predicting left ventricular remodelling after acute myocardial infarction**

**Purpose:** To aim the interest of quantitative versus qualitative assessment of myocardial hyperenhancement in the setting of a first reperfusion ST-elevation myocardial infarction (STEMI). Several methods were tested across their capacity to predict left ventricular (LV) remodelling at 3 months.

**Methods:** CE-MRI was performed on day 5 and after a period of 3 months in 92 patients with STEMI. LV scar and scar parameters were assessed visually (by using a four scale score) and quantitatively on day 5 and at 3 months. Dichotomous thresholds were defined first visually (VISUAL), then by 2.5 and 6 standard deviations above remote myocardium, and by the full-width at half-maximum (FWHM) method.

**Results:** All infarct sizing methods showed great relation to LV remodelling at 3 months (R²=0.92) (Hyperintensity). Univariate predictors of an LVEF/s superior to 70 ml/m² were: heart failure, CK peak and infarct size at day 5. FWHM was shown to be the best of all quantitative methods. An infarct size superior to 44 grams was related to LVEF=s>70ml/m² with a sensitivity of 0.8 and a specificity of 0.925. FWHM reproducibility was good (r=0.989 p=0.0001, Bland Altman bias of 0.8).

**Conclusions:** Treatment of decompensated left-sided heart failure lowers right ventricular pulsatile load and increases the pulmonary arterial time constant**

**Purpose:** Treatment of decompensated left-sided heart failure (HF) and independently prognosticates. We examined how decongestive treatment of left-sided HF influences the RV afterload components pulmonary vascular resistance (PVR) and pulmonary arterial capacitance (PAC) (stroke volume/pulmonary pulse pressure) which are supposed to have an inverse hyperbolic relationship in such way that their product (PVR x PAC, the pulmonary arterial time constant) forms a constant.

**Methods:** Changes in PVR, PAC and t were analyzed in 75 patients in whom hemodynamically tailored treatment of acute decompensated HF resulted in a decrease in pulmonary capillary wedge pressure (PCWP) of 10 mmHg or more.

**Results:** In our patient cohort (age 57±13 years, EF 24±13%), decongestive treatment with diuretics (99%), nitroprusside (75%) and inotropes (41%) resulted in a decrease in PCWP (31±17 to 16±5 mmHg, p<0.001) and an increase in CI (1.3±0.84 to 2.67±1.63 mmHg/sec, p<0.001). PVR decreased from 270±165 to 211±88 dynes sec cm⁻² (p=0.20±0.12 to 0.16±0.07 mmHg/sec/ml, p=0.002) and PAC increased more obviously from 1.65±0.64 to 2.61±1.42 ml/mmHg (p<0.0001) (Fig). The product of PVR and PAC (time constant) increased from

**Risk stratification for sudden cardiac death: a continuum process / The heart in pulmonary hypertension**

**THE HEART IN PULMONARY HYPERTENSION**

**Delayed CE-MRI quantification for predicting left ventricular remodelling after acute myocardial infarction**

**Conclusions:** The presence of ER increases the risk of VT/VF or sudden death occurrences in the chronic phase of AMIs, and may become a useful tool for deciding an indication for an implantable cardioverter defibrillator.
Right ventricular dyssynchrony impairs left ventricular performance in patients with pulmonary hypertension


Purpose: Pulmonary hypertension may cause right ventricular (RV) dyssynchrony and subsequently, through inter-ventricular interaction, left ventricular (LV) dyssynchrony. The aim of our study was to assess the influence of RV dyssynchrony on LV performance in patients with pulmonary hypertension.

Methods: Eighty-seven patients with pulmonary hypertension and LV ejection fraction (EF) ≤ 50% (age 65±15 years, RVSP 64±21 mmHg) were evaluated. Ventricular dyssynchrony was defined as the standard deviation of the time to peak longitudinal strain of 6 segments of the RV (RV-SD) and the LV (LV-SD) in the apical 4 chamber view as assessed with speckle tracking echocardiography.

Results: The patient population was divided according to the median RV-SD value of 54 ms. Pulmonary hypertension patients with RV-SD > 54 ms had significantly worse NYHA functional class (2.3±0.8 vs. 2.7±0.7, p<0.01), LV EF (50±8.6% vs. 56±6.8%, p=0.001), wider QRS duration (116±32 ms vs. 102±27 ms, p=0.04) and higher LV-SD (57±19 ms vs. 40±17 ms, p=0.001). A significant correlation between RV-SD and LV-SD (r=0.48, p<0.001) and between RV-SD and EF (r=-0.34, p=0.001) was observed (figure 1 A and B). After multiple linear regression analysis, RV-SD was significantly associated with LV-SD (beta 0.3, 95% CI 0.16 – 0.45, p<0.001).

Conclusion: RV dyssynchrony is associated with LV dyssynchrony and impairment of LV performance in patients with pulmonary hypertension. This suggests that LV and RV function are interrelated in pulmonary hypertension.

Exaggerated exercise induced pulmonary artery pressure increase in systemic sclerosis patients predominantly results from left ventricular diastolic dysfunction

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Background: Recent data suggest that there is an unexpectedly high prevalence of inappropriate pulmonary artery pressure responses to exercise among patients with systemic sclerosis (SSc).

Purpose: We evaluated the frequency and aetiology of exaggerated pulmonary artery pressure response (EPAPR) during exercise in SSc patients.

Methods: This study included 111 consecutive, otherwise healthy pts (101F, 10M, mean age 54±15 years) with SSc. Trans-thoracic echocardiography (TTE) followed by exercise Doppler-echocardiography (EDE) were performed with Philips IE33. A positive exercise test was defined when at least 20 mmHg increase of tricuspid regurgitation peak gradient (TRPG) was observed. An right heart catheterization (RHC) with exercise was performed in EPAPR patients and in pts with echocardiographically suspected PH (resting TRPG > 31 mmHg).

Results: According to the TEE and EDE, 30 patients were referred to RHC. Finally, RHC was performed in 16 patients (16 pts resting TRPG > 31 mmHg) and 4 with normal resting TRPG and EPAPR. In 15 (75%) of them an excessive, exercised induced, significant increase of postcapillary PAP was observed (mean exercise PAP 45±12.7 mmHg, mean exercise pulmonary capillary wedge pressure-PCWP 23±1±6.1 mmHg). While in remaining 3 pts pulmonary arterial hypertension and 2 pts exercised induced significant increase of precapillary PAP was diagnosed. Interestingly, mean left atrium (LA) diameter was significantly greater in an inappropiate, exercise induced increase of postcapillary PAP (38±5±5 vs. 35±3±5 mm, p<0.03) than in pts with normal exercise response. In this group significantly greater mean value of E/E of mitral lateral annulus was observed (7.9±3±25 vs 6.3±1±9, p<0.03). In the univariate logistic regression analysis was shown that the diameter of LA (OR 1.199, 95% CI 1.029-1.396, p = 0.019) was the parameter that increased the chance of inappropriate, exercise induced, increased of postcapillary PAP.

Conclusions: In SSc patients the excessive increase, exercise induced post-capillary pulmonary artery pressure is caused in most cases by left ventricular diastolic dysfunction and not by pulmonary arterial hypertension.
Assessment of right ventriculo-pulmonary arterial coupling in patients with pulmonary hypertension

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Purpose: Right ventricular (RV) failure is an important prognostic determinant in patients with pulmonary hypertension (PH). However, little is known about RV-pulmonary arterial (PA) coupling in PH patients. Accordingly we assessed PA effective elastance (Ea, index of arterial load), RV maximal end-systolic elastance (Ees, index of intrinsic contractility) and the time to peak-elastance to cycle length ratio (%Tpe) using single-beat estimation of RV pressure-volume relationship.

Method: Twenty-six patients with chronic PH (PH group; 49±20 years old, 16 females, and WHO class 2.4±0.5) and twenty-one patients with heart failure without PH (HF group; 71±12 years old, 6 females, and NYHA functional 2.3±0.5) were evaluated. All patients underwent pressure recording by PressureWire (St. Jude Medical, Inc., St. Paul, MN) via Swan-Ganz catheter. We estimated the maximal RV pressure of isovolumic beats (Pmax) and %Tpe using by extrapolated sin curve fitted to RV pressure in isovolumic period and detected end-systolic pressure (Pes) using by second derivative curve of PA pressure. Ees was assessed as the slope of Pmax-derived end-systolic pressure-volume relationships, Ees as the slope of extrinsically-end-systolic relation, and coupling efficiency as the Ees-to-Ea ratio (Ees/Ea). We measured augmentation index (AI) of PA to assess pressure reflection.

Results: Mean RV pressure was higher in PH group than in HF group (46±15 mmHg vs. 33±11 mmHg, P < 0.001) before cardiac index was comparable. Ees was higher in PH group than in HF group (0.47±0.04 mmHg/mL vs. 0.39±0.02 mmHg/mL, P < 0.001) and was also higher in PH group (1.17±0.76 dyne*sec*cm-5 vs. 0.33±0.18 mmHg/mL, P < 0.001). Ees/Ea was significantly lower in PH group than in HF group (0.65±0.29 vs. 1.37±0.81, P < 0.001). The AI was higher than in HF group (29.7±4.3% vs. 23.4±9.3%, P < 0.001) and %Tpe was longer in PH group than in HF group (0.74±0.29 vs. 0.65±0.23, P < 0.001).

Conclusions: 1) In PH group, pressure reflection augments the RV afterload. 2) RV-PAP coupling was worse in PH group than in HF group (0.65 vs. 1.37 mmHg/mL, P = 0.005) and Ea was also higher in PH group (1.17 vs. 0.33 mmHg/mL, P < 0.001). EA showed significant correlation with the %Tpe (R = 0.779, P < 0.001). Ees showed positive correlation with the AI (R = 0.295, P = 0.044). Multivariate analysis revealed that logarithm of Ea was the independent predictor of %Tpe (% = 0.001).

Remarkable effectiveness of percutaneous transluminal pulmonary angioplasty for hemodynamics and long-term prognosis in patients with distal-type chronic thromboembolic pulmonary hypertension

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Background: Pulmonary thromboendarterectomy is an established treatment for chronic thromboembolic pulmonary hypertension (CTEPH), resulting in significant improvement in right ventricular hemodynamics. However, this surgical treatment is limited to the central-type CTEPH and is not feasible for distal-type CTEPH. Indeed, CTEPH still remains a serious condition with a poor prognosis due to the lack of effective treatment. Optical coherence tomography (OCT) is an interferometer-based imaging modality to produce a 2-D image of optical reflectivity from internal tissue microstructures. In the present study, in order to develop an effective and safe treatment for CTEPH, we examined the effectiveness of our modified methods of percutaneous transluminal pulmonary angioplasty (PTPA) combined with OCT evaluation.

Methods: From July 2009 to February 2012, we prospectively enrolled 20 consecutive patients with d-CTEPH, including 2 patients of post-thromboendarterectomy with residual PH (d-CTEPH). Indeed, d-CTEPH still remains a serious condition with a poor prognosis due to the lack of effective treatment. Optical coherence tomography (OCT) is an interferometer-based imaging modality to produce a 2-D image of optical reflectivity from internal tissue microstructures. In the present study, in order to develop an effective and safe treatment for d-CTEPH, we examined the effectiveness of our modified methods of percutaneous transluminal pulmonary angioplasty (PTPA) combined with OCT evaluation.

Results: The pulmonary vasodilator therapy significantly improved cardiac index (CI; 2.25±0.53 to 2.78±0.71 L/min/m2, P < 0.05) and plasma levels of brain natriuretic peptide (BNP; 274±355 to 62±98 pg/dL, P < 0.05), but did not decrease PAP or pulmonary vascular resistance (PVR). Then, we performed PTPA (4±2 procedure for 3±7 lesions), resulting in additional significant improvement of mean PAP (40.5±9.9 to 27.6±3.9 mmHg, P < 0.01) and PVR (612±237 to 337±131 dyn*sec*cm-5, P < 0.01). OCT examination revealed that PTPA destroyed the typical flaps and webs in PA and shifted them to the pulmonary artery walls. The cohort of d-CTEPH was mild hypoxemia in 10 out of 18 patients, which was successfully managed with oxygen and non-invasive positive pressure ventilation without intubation. Importantly, epoprostenol therapy was successfully terminated in 7 out of the 18 patients and no patient died during the mean follow-up periods of 15 months, resulting in the significant improvement of prognosis compared with the historical controls (n = 38) (P < 0.05).

Conclusion: PTPA combined with conventional vasodilator treatment markedly improves pulmonary hemodynamics and long-term prognosis of patients with d-CTEPH, although the procedure should be carefully performed in a step-wise manner to prevent major complications.
normal O blood group human myocardium and skeletal muscle, blindly from clinical and genetic diagnosis. Control groups for AHA and AIDA included sera from patients with non-inflammatory cardiac disease (NCD) (n=160), 80 male, aged 35±12, with ischemic heart failure (n=141), 131 male, aged 51±12, and normal blood donors (n=270, 123 male, aged 35±11). Cascade mutation screening of five ARVC genes, e.g. plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP-2), desmolgin-2 (DSC-2), desmocollin-2 (DSC-2) was wabsent in 137 of the 164 pts.

Results: The frequencies of AHA and of AIDA were higher (31%: 15%) in ARVC than in NCD (1%: 4%), ischemic heart failure (1%: 2%) or normal subjects (2.5%: 0%; p<0.0001; p<0.0001 respectively). Of the 137 genotyped, 40 (29%) pts were pts.

Conclusions: The detection of serum AIDA suggests autoimmune involvement in the pathogenesis of desmosomal mutation associated ARVC.

Detailed histomorphologic and molecular analysis of myocarditis in the rat as an approach to identify novel molecular targets facilitating imaging of myocardial inflammation
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Myocarditis is characterized by inflammation, myocyte necrosis/apoptosis and subsequent fibrotic replacement of heart muscle. In the human, about 30% of myocarditis cases develop DCM. Because the clinical picture of myocarditis is multi-faceted, its diagnosis is difficult. We therefore screened for novel suitable tools for the detection of myocardial inflammation in acute myocarditis (EAM).

Methods: N=45 female Lewis rats were immunized with (pg) cardiac myosin (CM) emulsified in CFA and injected with heat killed B. Pertussis on days 0 and 3. Rats were boosted on days 7, 14, and 28. Myosin-antibody titers were fol- lowed by RT-PCR. RNA from cardiac tissue by echocardiography, respectively. On day 21 the animals underwent MRI (T2 or T2'Flash sequences). Rats were sacri ficed and consecutive heart sections were stained with Hematoxylin/Eosin (HE), Masson Goldner trichrome (MG), and compared with MRI findings. Mononuclear cells were detected with an anti CD-68 antibody. RNA isolated from apical car diac tissues was screened for the expression of pro-inflammatory and pro-fibrotic markers including somatostatin and integrins alpha-v beta-3, and of genes in volved in cardiac function.

Results: Sera from immunized rats strongly reacted against cardiac myosin. Echocardiography and MRI on days 18-21 revealed large pericardial effusion. MRI employing iron contrast agents (SPIO) as well as stained heart sections from immunized rats revealed massive cell infiltrates and severe fibrosis. Analysis of the time course of macrophage infiltration vs. fibrosis revealed that infiltration takes place following day 14 to 28. Disappearance of macrophages leads to replace ment fibrosis in formerly invaded myocardial areas. This finding was confirmed by the time-dependent differential expression of cytokines in the myocardium; in particular, macrophage M1 was found to be high (-50-fold) up-regulated. Induced phenotypes could be categorized as an early or late phase of myocarditis. Histol ogy correlated well with ex-vivo MRI images showing maximal infiltrates in same areas. Immunohistochemical data suggesting that iron particles are suitable for the detection of acute inflammation.

Conclusion: Cytokines like oncostatin M which are specifically expressed in the inflamed heart might serve as molecular targets for the detection of acute myocarditis. Moreover, integrins alpha-v beta-3 and/or somatostatin may be labeled with nuclear tracers and detected by PET-scans. Thus, these molecular targets might serve to develop novel ligand-based MRI and/or nuclear contrast agents to image myocardial inflammation in vivo.

Is improvement of the left ventricular systolic function in patients with new-onset dilated cardiomyopathy related to the presence of virus or inflammation in endomyocardial biopsy?
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Background and aim of the study: The analysis of endomyocardial biopsy (EMB) tissue using polymerase chain reaction (PCR) and immunochemistry currently represent a gold standard for diagnoses of inflammatory di lated cardiomyopathy (DCM). However, there is conflicting evidence regarding the prognostic significance of viral and/or myocardial inflammation persistence. Therefore, we aimed to prospectively evaluate the course of the left ventricular (LV) systolic function in patients with new-onset DCM who underwent endomyocardial biopsy (EMB).

Methods: In 96 consecutive patients (52±11 years; 28 women) with new-onset unexpected DCM (symptoms of heart failure lasting <12 months), EMB spec- imens were studied by immunohistochemistry and by PCR focused on detection of herpetic viruses, enteroviruses, adenoviruses, parvovirus B19 and Borella burgdorferi (EF) and was echocardiographically analyzed at baseline and after 6 months follow-up. All subjects with Bb positivity were specifically treated by ceftriaxone and not included in further analysis. Results: Viral genome was found in 35 patients (37%) and Bb genome was present in 21 subjects (22%). Myocardial inflammation was detected in 35 pa- tients (37%), out of whom viral agent was present in 10 (11%) and Bb in 7 (7%) viral myocardial agent and/or virus persistence. Thirty six patients with either viral persistence and/or myocardial inflam mation and 33 subjects with negative EMB results were all treated only by con ventional heart failure medical therapy. There was no significant difference be tween these 2 groups regarding LV EF at the time of diagnosis (EF 28±6% vs. 29±8%; p=NS). During 6 months follow-up, LV EF significantly improved in both groups (44±10% and 42±12%, respectively; p<0.05). The degree of the LV EF improvement did not differ between the groups.

Conclusions: In more than half of the patients with new-onset DCM, myocardial inflammation and/or microbial agent persistence is present. Therefore, inflamma tory DCM may represent a frequent cause of new-onset DCM. However, con ventional heart failure therapy is associated with similar improvement in LV EF in patients with new-onset DCM regardless of the presence or absence of myocardial inflammation and/or virus persistence. This might be either due to low impact of viral persistence and/or myocardial inflammation on prognosis of affected sub jects or by underdiagnosing of inflammatory DCM by current techniques.

Beneficial actions of the natural triterpene oleanolic acid in an experimental model of myocarditis: a potential therapeutic role
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Purpose: Myocarditis and dilated cardiomyopathy represent the acute and chronic phases of an inflammatory disease of the myocardium, for which no stan dardized treatment is currently available. Oleanolic acid (OA), a natural triterpene widely distributed among higher plants, exhibits a variety of beneficial health prop erties. OA is found in numerous products of the Mediterranean diet, including olive oil, and is the major component of many traditional herbal remedies. Se veral experimental approaches have shown its cardioprotective actions, and re cently, it has been proven to be effective for the treatment of Th1 mediated chronic inflammatory diseases, but its effect on inflammatory heart disorders has not been addressed yet. In this study, we investigated the effectiveness of OA in prevention/treatment of myocarditis in an experimental autoimmune model that mimics human myocarditis and dilated cardiomyopathy.

Methods and Results: OA was administered at the time (prophylactic, OA0) or 21 days (therapeutic, OA21) after disease induction in BALB/c mice with a myc oglobulin peptide. At days 21 of 65 post-immunization animals were sacrificed and both blood samples and hearts were collected. The levels of functional (BNP) and inflammation (Galectin-3, IL-17, IL-6, TNFα and IL-10) markers, as well as IgG and IgM in sera and heart lavage were detected by ELISAs. We found that, at both ad ministered regimens, OA dramatically lessened the disease severity, which was characterized by a reduction in heart weight/body weight ratio and heart weight, fibrotic ratio and myocardial edema. OA treatment reduced BNP and lower anti-cardiac myosin IgG and IgM titers, compared with the group that received no drug. Histological analysis of the heart showed that OA significantly reduced the infiltration of inflammatory cells, fibrosis and calcium deposits, whereas such effect was not found in placebo-treated EAM mice. Furthermore, levels of the pro inflammatory and profibrotic cytokines galectin-3, IL-6, IL-17 and TNFα in serum and heart tissue of the OA-treated EAM animals were significantly less than of the standardized treatment EAM mice, while anti-inflammatory IL-10 was markedly upregulated. Collectively, these results suggest that OA ameliorates experimental autoimmune myocarditis by interfering with both the Th1/Th2/Th17 balance and the generation of cardiac-specific autoantibodies.

Conclusions: OA may be considered a molecular switch for immune responses that improves cardiac function and hence contributes to prevent the development of postmyocarditis dilated cardiomyopathy.

Acute myocarditis mimicking ST-segment elevation myocardial infarction: relation between electrocardiographic changes and myocardial damage as assessed by cardiac troponins
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Purpose: Acute myocarditis (AM) may occasionally mimic ST-segment elevation
myocardial infarction (STEMI), since patients may present with chest pain, electrocardiographic (ECG) changes and cardiac troponin elevation. Scarce data are available about the clinical meaning of ECG changes in this group of patients; particularly, few is known about the relation between ECG changes and myocardial damage assessed by cardiac magnetic resonance (CMR) imaging.

Methods: 22 consecutive patients (17 males, mean age 42±10 years) with dia
diagnosis of AM and clinical presentation mimicking STEMI were included. STEMI was ruled out by invasive coronary angiography. AM was diagnosed according to CMR “Lake Louise” criteria, when at least 2 of the following features were present: 1) regional or global myocardial oedema (increased signal intensity in T2W images); 2) hyperaemia (early gadolinium enhancement in post-contrast T1W images) and 3) myocardial necrosis with non-ischemic regional distribution (late gadolinium enhancement (LGE) in inversion recovery-prepared gadolinium-enhanced T1W images). The following ECG changes were recorded: site of ST-segment elevation, sum of ST-segment elevation (sumSTE), time to normalization of ST-segment elevation, evolution to T-wave inversion. The relation between ECG changes and the presence and extent of LGE, expressed as % of left ventricular (LV) mass (%LV LGE), was evaluated.

Results: ST-segment elevation was observed in inferior or anterior lateral leads in 14 (64%) patients, and in lateral or anterolateral leads in 8 (36%) patients. SumSTE was 4.2±2.2 and normalization of ST-segment elevation occurred ≥24 hours from clinical presentation in 14 (64%) patients. Evolution to T-wave inversion was observed within 7 days in 16 (73%) patients. CMR showed LGE in all patients: %LV LGE was 8.7±7.0%. Topographic agreement between site of ST-segment elevation and LGE was 49%; no relation was found between SumSTE and %LV LGE (p=0.10). Patients with reperfusion of ST ≥24 hours from clinical presentation had lower %LV LGE, compared to remaining patients (6.5±4.3% versus 13.2±8.7%; p=0.035). Similarly, patients showing ECG evolution to T-wave inversion had higher %LV LGE, compared to patients with normalized ECG (10.1±6.2% versus 4.5±8.1%; p=0.049).

Conclusions: ECG changes poorly predict location and extent of myocardial damage in patients with AM and clinical presentation mimicking STEMI. However, clinical ECG features, such as time to normalization of ST-segment elevation and evolution to T-wave inversion, may help to identify patients with larger area of myocardial injury.

CARDIAC MAGNETIC RESONANCE SPELLS THE FUTURE

Assessment of the warranty time of dobutamine cardiovascular magnetic resonance imaging in 3138 consecutive patients. A bi-center study focusing on wall motion and late gadolinium enhancement

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Purpose: To determine the prognostic value of wall motion assessment during high-dose dobutamine stress cardiovascular magnetic resonance (CMR) imaging (DGMR) for the prediction of outcome in a large patient cohort and within a long follow-up duration.

Methods: Consecutive patients with suspected or known coronary artery disease underwent CMR at two experienced cardiac centers, using a standard protocol with 1.5T Philips MR-scanners. Wall motion was assessed at rest and during high-dose stress followed by late gadolinium enhancement (LGE) imaging. Outcome data were based on hard cardiac events defined as cardiac death and non-fatal myocardial infarction as well as “late” revascularization performed ≥3 months after the scans were prospectively collected at least 6 months after DCMR.

Results: Follow-up data were available in 3138 consecutive patients (mean follow-up 3.3±1.7 years, range 0.5 and 9.7 years). Hard cardiac events occurred in 183 (5.8%) patients during the follow-up period. In 589 (18.8%) patients early revascularization was performed within 90 days after the MR-examination and 257 (8.2%) patients underwent late revascularization. Multivariable analysis showed that inducible wall motion abnormalities (WMA), LGE and resting WMA were independent predictors of hard events (hazard ratio (HR) of 6.5, 95% confid

dence interval (CI):4.6-9.3; 2.2, 95%CI=1-2.4 and 1.6, 95%CI=1-2.3, respectively, p<0.001 for all). Within the first 3 years of follow-up excellent outcomes were recorded for patients with normal wall motion during stress (annual hard cardiac event rate of 0.6% and revascularization rate of 1.6%). Over the following 3 years of follow-up however, annual event rates rose for both hard events and revascularization to 1.6% and 3.2%, respectively.

Conclusion: Within the first 3 years after DCMR excellent outcomes (annual hard cardiac event rate <1%) are recorded in patients with normal findings.

Long-term prognosis of adenosine perfusion cardiac magnetic resonance imaging in consecutive patients

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Background: Adenosine perfusion cardiac magnetic resonance imaging (CMR) has established for the detection of coronary artery disease (CAD) due to its high diagnostic accuracy. However, little is known about long-term prognosis in large consecutive patient cohorts. Aim of our prospective study was to evaluate long-term prognosis of adenosine perfusion CMR in consecutive patients presenting with stable angina and intermediate to high CAD risk.

Methods: 1,152 consecutive patients underwent adenosine perfusion CMR in a 1.5T whole-body CMR. After acquisition of cine sequences for the evaluation of left and right ventricular volumes and function first-pass perfusion of a gadolinium-based contrast agent (0.1 mmol/kg) was evaluated after three minutes of adeno

sine infusion (140 μg/kg/min) using a steady-state free-precession sequence. Ten minutes after contrast administration late gadolinium enhancement images were acquired for visualization of myocardial necrosis. All images were evaluated by two blinded observers in consensus. Patients were followed for 5 years. Primary combined end-point was defined as cardiovascular death, non-fatal myocardial infarction and stroke.

Results: Reversible perfusion deficit was diagnosed in 308 (28.7%) patients. Pri

mary endpoint occurred in 86 patients during observation. Patients with primary endpoint had significantly more often a reversible perfusion deficit (49 [15.9%] vs. 27 [4.4%, p=0.001]). Logistic regression revealed reversible perfusion deficit to be an independent predictor for occurrence of a primary endpoint (HR 3.05). In case of no perfusion deficit event-free 5-years survival was 95.6%.

Conclusion: CMR predicts long-term outcome and enables an independent risk assessment for long-term event-free survival. Patients without perfusion deficit have a low risk of event occurrence within 5 years.

Final infarct size by cardiovascular magnetic resonance in patients with st elevation myocardial infarction predicts long-term clinical outcome

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Purpose: Tailored treatment and risk assessment in patients following ST eleva

tion myocardial infarction (STEMI) is based almost exclusively on left ventricular (LV) ejection fraction (EF). Assessment of final infarct size in addition to LVEF may improve the prognostic evaluation. Thus the purpose of this study is to evaluate the prognostic importance of final infarct size by cardiovascular magnetic resonance (CMR) in patients with STEMI.

Methods: In 309 patients with STEMI final infarct size was measured by late gadolinium enhancement CMR 3 months after initial admission. The clinical end

point was a composite of all-cause mortality and admission for heart failure.

Results: During the follow-up period of median 807 (IQR 669-1117) days there were 35 events (5 non-cardiac deaths, 3 cardiac deaths, and 27 admissions for heart failure). Patients with final CMR size ≥ median had significantly more event rates than patients with final infarct size < median (17% versus 6%; Log rank p=0.002). In a multivariable Cox regression analysis, including age, stent implantation, peak troponin T, LVEF, LV volume index, and heart rate, final infarct size remained significantly associated with the occurrence of subsequent events (adjusted hazard ratio 1.13 per 1% increase (1.05-1.21); p=0.001). The overall Wald chi2 value of a model including known risk factors was 47.3, which increased to 57.9 when final infarct size was added (p=0.001 for the difference).

Conclusion: Assessment of final infarct size by CMR 3 months after STEMI provides strong independent prognostic information incremental to known risk factors including LVEF.

Grace score and cardiac magnetic resonance for predicting cardiac events after hospital discharge in patients with ST segment elevation acute myocardial infarction


Purpose: Grace Score permits an early stratification of the risk of events in pa

ients with ST segment elevation acute myocardial infarction (STEMI). Cardiac magnetic resonance (CMR) is the reference imaging technique for the complete non invasive characterization of the structural consequences of STEMI. Prognos
tic implications of a combined analysis of Grace Score and CMR to predict events after hospital discharge in STEMI patients has not been analyzed yet.

Methods: We prospectively included 461 patients admitted with STEMI. Grace Score was determined at the time of admission. CMR was carried out in the first week post-STEMI and a quantitative (9% of ventricular mass) and semi-
quantitative analysis (number of segments with late gadolinium enhancement (LGE) in > 50% of wall thickness) of the extent of infarction were performed. Events during follow-up (death, myocardial infarction, re-admission for heart failure) were registered.

Results: Of the 461 patients included CMR was performed in 390 patients; 71 patients were excluded due to events during hospitalization or contraindication to CMR. During a median follow-up of 644 days 17 deaths, 26 infarctions and 26 re-hospitalizations for heart failure were detected; 52 patients (13%) had a first post-discharge event. The event rate in patients with low (≤ 125), intermediate (126-249) and high (> 250) risk in Grace Score was 6/106 (6%), 20/156 (13%) and 26/126 (21%) respectively (p < 0.01). The percentage of infarct mass was greater in high risk patients (20±15%, 20±14%, 25±16%, p = 0.01) but the Grace score showed a weak association (area under the curve 0.58 [0.52 to 0.63]) with extensive infarcts (> 20%, median) and did not significantly relate to ejection fraction. In the multivariate analysis, independent predictors of events were high risk Grace Score (3.4 [1.4 to 8.3], p = 0.007) and extent of the infarction (number of segments) (1.3 [1.2-1.4], p = 0.001). Risk of events was higher in patients with >5 segments (23/296, 8%) vs. 29/92, 31%, p = 0.001. The extent of infarction in 0.5 or >5 segments allowed to discriminate the event risk in patients with low (1% vs. 23%, p = 0.001), intermediate (10% vs. 23%, p = 0.05) and high (11% vs. 46%, p < 0.001) risk in Grace Score.

Conclusions: Our results illustrate that for predicting events in patients with STI clinical assessment and the use of sophisticated techniques are both useful. Grace Score permits a simple and early risk stratification that can be optimized by determining the extent of the infarction with CMR.

Cardiovascular risk profile, long term survival and stress cardiac magnetic resonance imaging guided catheterization. a post-hoc analysis of a natural experiment
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Purpose: Stress cardiac magnetic resonance imaging (CMR) as test for coronary ischemia before catheterization was still not recommended 2003. A decision on coronary angiography (CA) was based on clinical judgment (history, risk profile, exercise ECG) and optional CMR. This approach simulated a “quasi-randomization” of two diagnostic pathways (CMR-CA vs. CA).
Methods: A group of patients with CMR guided CA (CMRCA) (N=220) was compared to a matched control group of patients with CA indicated by standard evaluation (SECA) (N=644). The retrospective study included patients with suspected coronary artery disease from 2003-2004. Long term follow-up of selected hard events (death, PCI, CABG) was performed. To control the impact of cardiovascular risk the Framingham score was calculated and each group was subgrouped by the median score into a group with higher (CMRCA, HR, SECA, HR) and with lower risk (CMRCA LR, SECA LR). Kaplan-Meier plots, Cox regression and rank statistics were used to evaluate outcome as index variable for effectiveness.

Results: PCI, CABG, death and number of hospital admissions were significantly higher in the SECA group (34%, 20%, 11%, 97%) than in the CMRCA group (1%, 6%, 8%, 35%). Survival was significantly better in CMRCA (p=0.006 log – rank). Though CMRCA was not no significant difference of Framingham score between CMRCA and SECA, the Kaplan Meier plot demonstrated a significant impact of the risk profile on survival. Adjustment for revascularization demonstrated a significant impact (<0.0001) of CABG on survival.

Conclusion: CMRCA was significantly more effective in terms of death and hospitalization than SECA. Revascularization and cardiovascular risk had some impact on survival, but do not account for this difference.

Diagnostic value of cardiac magnetic resonance imaging in patients presenting with chest pain, troponin elevation and unobstructed coronary arteries
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Background: Among patients presenting with chest pain, troponin elevation and non obstructed coronary arteries, diagnosis is important for prognostic stratification and treatment. However, many conditions can lead to this presentation. We sought to assess the diagnostic value of cardiac magnetic resonance imaging (CMR) in this setting.

Methods: From January 2009 to December 2011, 89 consecutive patients with chest pain, troponin elevation and unobstructed coronary arteries were included in this study. A post-hoc analysis of a natural experiment and treatment. However, many conditions can lead to this presentation. We sought to assess the diagnostic value of cardiac magnetic resonance imaging (CMR) in this setting.

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NT-proBNP for risk stratification in atrial fibrillation during treatment with apixaban or warfarin

L.C. Wallentin1, C. Christersson2, A. Siegbahn3, M. Schollin4, J.H. Alexander5, M. Härma6, E.M. Hylek7, J. Horowitz8, M.J. McMurtry9, C.B. Granger1, L. Wallentin1, 2Uppsala University, Department of Medical Sciences, Clinical Chemistry, Upplands Väsby, Sweden; 2Uppsala University, Department of Medical Sciences, Cardiology, Upplands Väsby, Sweden; 3Uppsala University, Department of Medical Sciences, Ophthalmology, Upplands Väsby, Sweden; 4Uppsala University, UCR-Upplands Clinical Research Center, Upplands Väsby, Sweden; 5Duke Clinical Research Institute, Duke University Medical Center, Durham, United States of America; 6Bristol-Myers Squibb, Princeton, NJ, United States of America; 7Boston University Medical Center, Boston, United States of America; 8University of Adelaide, Adelaide, Australia; 9University of Glasgow, Glasgow, United Kingdom

Background: Plasma NT-proBNP concentration is predictive of death and cardiovascular events in healthy elderly subjects and in patients with heart failure. We evaluated the prognostic value of NT-proBNP in patients with atrial fibrillation (AF) and investigated the interaction between NT-proBNP and the effect of treatment with apixaban versus warfarin, taking account of the CHADS2 score and other biomarkers.

Methods: The ARISTOTLE trial randomized 16,201 patients to apixaban 5 mg twice daily or warfarin. NT-proBNP and other biomarkers were measured at randomization in 14,879 patients. Efficacy and safety outcomes were compared across quartiles of NT-proBNP adjusted for the CHADS2 score and other biomarkers. Also the effect of apixaban versus warfarin was compared within NT-proBNP quartiles.

Results: There was a continuous and strong relationship between NT-proBNP concentration and stroke, mortality, and major bleeding. The prognostic information provided by NT-proBNP was independent of and additive to the CHADS2 score and other biomarkers. Apixaban consistently reduced stroke, mortality and bleeding, regardless of NT-proBNP level (Table).

Conclusions: NT-proBNP is an independent additional risk factor for stroke, death and major bleeding in atrial fibrillation. Apixaban led to better outcomes than warfarin, irrespective of NT-proBNP concentration.

Assessment of stroke risk in the PROTECT AF trial according to CHADS2-VASc scores and final follow-up results

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1Herzzentrum Leipzig, Leipzig, Germany; 2CardioVascular Care Center Frankfurt, Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany; 3Mount Sinai School of Medicine, New York, United States of America

Purpose: Thromboembolic stroke originating from the left atrial appendage (LAA) is a major cause of morbidity in patients with atrial fibrillation (AF). The WATCHMAN device uses a self-expanding nitinol frame covered with permeable fabric to close the LAA and prevent embolization of LAA thrombi in patients with non-valvular AF. In the PROTECT AF trial, the WATCHMAN device was noninferior to warfarin for the prevention of stroke, CV or unexplained death, and systemic embolization at the primary endpoint of 600 patient-year (pt-y) follow-up. Approximately 32% of patients in this study had a baseline CHADS2 score of 1, indicating intermediate stroke risk according to this score. Recently, the CHADS2-VASc score has been shown to more accurately differentiate stroke risk in AF patients than the CHADS2 score. The post-hoc analysis of the PROTECT AF trial evaluates patients according to CHADS2-VASc score to better determine true stroke risk and presents final follow-up results for the study.

Methods: In PROTECT AF, patients with AF and a CHADS2 score ≥1 were randomized to receive either WATCHMAN plus warfarin ×45 days (WATCHMAN group; n=463) or warfarin alone indefinitely (control group; n=444). Follow-up continued until the primary efficacy variable reached 1500 pt-y.

Results: The mean CHADS2-VASc score was 3.4±1.5 (range 1 to 9) for the WATCHMAN group and 3.7±1.6 (range 1 to 8) for the control group (P=0.03). A total of 4264/463 (92.0%) of patients in the WATCHMAN group and 231/244 (94.7%) of patients in the control group had a CHADS2-VASc score ≥2. Overall, 1707/207 (12.5%) patients had a prior MI, 263/707 (37.2%) were aged 74 years, and 210/707 (29.7%) were female. After 1500 pt-y of follow-up, the WATCHMAN group had a 29% lower rate of efficacy events compared with control (relative risk: 0.71 [95% credible interval: 0.44, 1.30]; Prob >0.999 for non-inferiority). According to the CHADS2-VASc scoring system, the predicted stroke rate for scores between 3 and 4 would be 3.2%/yr (CHADS2-VASc score=3.0) to 4.0%/yr (CHADS2-VASc score=4.0); in contrast, at 1500 pt-y, the stroke rate in PROTECT AF was 2.9%/yr (21 events/1025.3 pt-y) for WATCHMAN versus 5.7% (15 events/562.7 pt-y) for warfarin.

Conclusions: According to the CHADS2-VASc scoring system, 93% of patients in the PROTECT AF study had a risk score ≥2, indicating a high risk of stroke. At 1500 pt-y of follow-up, the relative risk of stroke, cardiac death, or embolization was 0.71 (0.44, 1.30) for WATCHMAN versus warfarin alone, confirming the WATCHMAN device is an alternative treatment option to warfarin in this patient population.

Increased levels of D-dimer identity patients with atrial fibrillation at high risk for bleeding an ARISTOTLE substudy

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Purpose: Increased concentrations of markers of activated coagulation, such as D-dimer, indicate abnormal thrombogenesis. We evaluated D-dimer as an independent risk marker for bleeding in patients with atrial fibrillation and the effect of apixaban and warfarin across quartiles of D-dimer.

Methods: In the ARISTOTLE trial, 18,201 patients with atrial fibrillation were randomized to apixaban 5 mg twice daily or warfarin. D-dimer was analyzed in 14,878 patients before starting the study treatment. The relationship between quartiles of D-dimer levels and major or clinical relevant non-major bleeding was evaluated by Cox proportional hazard models adjusting for the HAS-BLED bleeding risk score and randomized treatment.

Results: There was a strong and positive association between higher D-dimer level and increased bleeding (p<0.0001) across all HAS-BLED score categories. The significant reduction in bleeding with apixaban as compared with warfarin was consistent regardless of D-dimer level.

D-dimer levels in relation to bleeding

<table>
<thead>
<tr>
<th>D-dimer (μg/L)</th>
<th>Whole group</th>
<th>Major or Clinically Relevant Non-Major Bleeding (N=1368)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hazard ratio</td>
<td>Apixaban vs Warfarin (HR (95% CI))</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>Warfarin (N=7482)</td>
</tr>
<tr>
<td>&gt;713-1250</td>
<td>6.49 (4.47-9.39)</td>
<td>0.70 (0.58-0.88)</td>
</tr>
<tr>
<td>&gt;1250</td>
<td>5.19 (3.44-7.67)</td>
<td>0.71 (0.58-0.86)</td>
</tr>
<tr>
<td>&gt;528-713</td>
<td>4.90 (3.10-7.53)</td>
<td>0.71 (0.58-0.85)</td>
</tr>
<tr>
<td>&gt;363-528</td>
<td>3.63 (2.10-6.26)</td>
<td>0.71 (0.58-0.85)</td>
</tr>
<tr>
<td>&gt;363</td>
<td>2.89 (1.78-4.78)</td>
<td>0.71 (0.58-0.85)</td>
</tr>
</tbody>
</table>

Conclusion: In patients with atrial fibrillation, levels of D-dimer are strongly and independently associated with higher risk of major and clinical relevant non-major bleeding. Compared with warfarin, apixaban caused significantly less bleeding across patients with all levels of D-dimer measured at baseline.

Abstract P551 — Table 1. Outcomes in relation to NT-proBNP ng/L

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Biomarker level</th>
<th>All patients, N=14,879 (95% CI)</th>
<th>Apixaban, N=7479 (95% CI)</th>
<th>Apixaban vs Warfarin (HR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>&gt;363-715</td>
<td>54 (0.74) 1.48 (1.05-2.09)</td>
<td>51 (0.74) 1.40 (1.03-1.88)</td>
<td>0.75 (0.44-1.28)</td>
</tr>
<tr>
<td>Death</td>
<td>&lt;1250</td>
<td>112 (1.58) 1.99 (1.43-2.78)</td>
<td>105 (1.48) 1.53 (1.15-2.02)</td>
<td>0.82 (0.57-1.15)</td>
</tr>
<tr>
<td>Major</td>
<td>&gt;363</td>
<td>157 (2.12) 1.05 (0.83-1.32)</td>
<td>123 (1.72) 1.26 (0.94-1.70)</td>
<td>0.81 (0.63-1.05)</td>
</tr>
</tbody>
</table>

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Effect of apixaban on all-cause mortality in atrial fibrillation: an imputed placebo analysis

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Purpose: ARISTOTLE demonstrated the superiority of apixaban over warfarin in preventing stroke or systemic embolism (SEE). AVERROES showed the superiority of apixaban over aspirin in preventing SEE. We used a meta-analysis of earlier warfarin vs. placebo/control (P/C), and aspirin vs. P/C, trials to make an indirect comparison between apixaban and P/C on mortality.

Methods: The meta-analysis of Hart et al. (Regan LA, Aguilar MI (Ann Int Med 2007) included 6 warfarin vs. P/C trials (n=2900 patients) and 7 aspirin vs. P/C trials (n=8895). The method of Bucher HC, Guyatt GH, Griffith LE, Walter SD (J Clin Epidemiol 1997) was used to make an indirect comparison of odds ratios (OR).

Results: The meta-analysis reported 143 deaths (in 1450 patients) on P/C and 110 deaths (1450 pts) on warfarin, OR 0.74 (0.57, 0.97). In ARISTOTLE there were 9081 deaths on warfarin and 633 deaths (9120 pts) on apixaban, OR 0.89 (0.79, 0.99). An indirect comparison of apixaban with P/C gives an estimated apixaban/placebo OR for death of 0.65 (0.50, 0.88), p=0.004. The meta-analysis reported 204 deaths (1993 pts) on P/C and 184 deaths (1902 patients) on aspirin, OR 0.86 (0.69, 1.07). In AVERROES, there were 140 deaths (2791 pts) on aspirin and 111 deaths (2807 pts) on apixaban, OR 0.79 (0.62, 1.02). Indirect comparison of apixaban with P/C gives an estimated apixaban/placebo OR of 0.7156 NVAF patients were included. Bleeding rates per 100 person years were calculated by HAS-BLED score for risk of bleeding (i.e. low = 0, moderate = 1-2, high >3) and compared with other risk scores. Both comparisons combined gives an estimated apixaban/placebo OR for death of 0.66 (0.53, 0.82), p=0.002 (Figure).

Conclusions: This imputed placebo analysis suggests that apixaban significantly reduces all-cause mortality by about one third in patients with AF.

Risk of bleeding in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project

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Background: Oral anticoagulation (OAC) is associated with increased bleeding risk in patients with non-valvular atrial fibrillation (NVAF). The HAS-BLED score, a novel risk prediction tool for bleeding in NVAF patients, requires further validation in real world populations with long-term follow-up and comparison with alternative risk scores.

Methods: Among NVAF patients in a 4 hospital-institution between 2000 and 2010, those with complete data regarding OAC were included. Stroke and bleeding rates were calculated by HAS-BLED score for risk of bleeding (i.e. low = 0, moderate = 1-2, high >3) and compared with other risk scores. Risk factors were investigated by Cox regression.

Results: 7156 NVAF patients were included. Bleeding rates per 100 person years were 1.26 (1.07,1.47), 0.74 (0.67,0.83) and 0.38 (0.28,0.51) in high-risk, moderate-risk and low-risk patients respectively, as measured by HAS-BLED score (p=0.001, Table 1). In multivariate analyses, age >75 (HR 1.42,95% CI 1.14-1.76), age 65-74 (1.31,1.14-1.51), and labile INR >2.5 (2.71,2.11-3.45), anaemia (2.69,1.27-4.88) and heart failure (1.23,1.01-1.50) increased bleeding risk. The HAS-BLED system (C-statistic 0.61,0.58-0.65) performed comparably with other bleeding risk scores.

Conclusions: In this large 'real world' NVAF population, there were differences in rates of bleeding, stroke/TE and mortality by bleeding risk, but only age, alcohol, anaemia and heart failure increased bleeding risk in multivariate analyses. The HAS-BLED score predicted 10-year bleeding risk accurately and was comparable with other bleeding risk stratification systems.

Atrial fibrillation: antithrombotic treatment and beyond

P557 Antithrombotic treatment patterns for stroke prevention in relation to age: insights from the Global Anticoagulant Registry in the FIELD (GARFIELD)

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Oral anticoagulation (OAC) is highly effective reducing the risk of stroke and mortality, compared to placebo/control (P/C), with atrial fibrillation (AF), and a decision of thromboprophylaxis has classically been based on stroke risk. Clinical scores for bleeding risk estimation are much less well validated than stroke risk scales. Despite the clear net clinical benefit of OAC in AF patients at risk for stroke, major bleeding events, especially intracranial bleeds, may be devastating when they do occur. HAS-BLED bleeding risk score is recommended to assist in estimating major bleeding risk in AF patients. By the other way, the ATRIA study group has recently proposed a new bleeding risk scale. The aim of our study was to assess the new ATRIA bleeding score in a large cohort of stable chronically anticoagulated AF patients, compared with the well-validated HAS-BLED score.

Methods: We recruited 928 consecutive patients (45% male; 76 (70-81) years of age) with AF who were on steady OAC for at least 6 months (INR 2.0-3.0). During a median follow-up of 952 [IQR: 785-1071] days, all bleeding events were recorded. Bleeding events were defined as serious based on the 2005 ISTH criteria. Both HAS-BLED and ATRIA scores were calculated based on medical history; and were compared as quantitative (per point) or as dichotomized (low-moderate vs high risk) variables. Model performance was evaluated by calculating c-statistics, and the improvement in predictive accuracy was evaluated using net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Results: HAS-BLED and ATRIA scores were 2 [IQR: 2-3] and 3 [IQR: 1-3], respectively. During the follow-up, 77 (8.2%) patients had a serious bleeding event [annual rate 3.2%], including 15 intracranial hemorrhages (annual rate 0.6%), 45 gastrointestinal bleeds (annual rate 1.8%) and 8 bleeding-related deaths (annual rate 0.24%). HAS-BLED score showed a slightly superior model performance to ATRIA as dichotomized as quantitative variable. The NRI were 14% (as quantitative) and 19% (as dichotomized), whereas the IDI was 7% for both analyses (all p >0.05). The probability of correctly predicting serious bleeding events using the HAS-BLED was particularity reflected in the percentage of events correctly reclassified.

Conclusions: In anticoagulated AF patients, HAS-BLED shows significantly better prediction ability than the weighted (and more complex) ATRIA score. Our findings reinforce the incremental utility of the HAS-BLED score over other bleeding risk scores in patients with AF.
over 500 sites randomly selected from lists representative of national AF care settings and geographies. Eligible patients are ≥ 18 years old, newly diagnosed with non-valvular AF, with ≥ 1 additional investigator-determined stroke risk factor, not limited to risk factors included in existing risk scores. Risk score stratification used the baseline patient characteristics captured to assign a CHADS2 score to each patient enrolled.

Results: Data from 10,504 AF patients from cohort 1 were available; 8.5% had a CHADS2 score of 0, 36.3% a score of 1 and 55.2% a score of 2. In patients at low risk for stroke, total use of OACs increased in patients aged ≤ 65 years. In patients at high risk for stroke the use of OACs was highest in the group aged 65-74 years (72.1%) and lowest in the group aged ≥ 75 years (66.5%).

Table 1. Anthrombotic use according to age group and CHADS2 score: cohort 1 data

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>CHADS2 score 0</th>
<th>CHADS2 score 1</th>
<th>CHADS2 score 2</th>
</tr>
</thead>
</table>

OACs only 41.1% 48.6% 48.8% 50.8% 51.9% 51.8% OACs + antiplatelets (APs) 10.1% 11.7% 10.3% 17.6% 20.2% 14.7%

Conclusions: These observational data suggest that OAC use is influenced by risk for stroke and by age. Total OAC use is more frequent in high-risk than in low-risk patients in all age groups. In patients at low risk, total OAC use is less frequent in the group aged < 65 years, whereas in patients at high risk total OAC use is least frequent in the group aged ≥ 75 years.

Abstract P559

High sensitivity troponin-T for risk stratification in atrial fibrillation during treatment with apixaban or warfarin

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Purpose: Slight elevations of troponin levels are prognostic for cardiovascular events in a variety of conditions. We assessed high-sensitivity troponin-T (hs-TnT) in relation to outcomes with apixaban versus warfarin in patients with atrial fibrillation (AF) in addition to the CHADS2 risk score and other biomarkers.

Methods: The ARISTOTLE trial randomized 18,201 patients with AF to apixaban 5 mg twice daily or warfarin. Hs-TnT and other biomarkers were measured at baseline and during the trial. The levels of hs-TnT were strongly and continuously related to stroke, mortality and bleeding regardless of the hs-TnT level at entry in patients with AF in our institution were identified and followed up to 2000-2010 for mortality, stroke and bleeding events. Among 8122 consecutive patients with AF, 791 major bleeding events were recorded during a follow-up of 871.3±1097.5 days. Rate of bleeding events was calculated for the low, moderate and high risk subgroups of patients using the new HAS-BLED score and we then compared its predictive value with 4 previously published bleeding risk schemas (Shrier, HEMORR2HAGES, Beyth, and Kuijer).

Results: Of the 5 tested schemas, the HAS-BLED score performed best in multi-

P559 How well are atrial fibrillation (AF) patients in the real world represented in the Contemporary Novel Oral Anticoagulant (NOAC) AF trials?

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Purpose: Baseline data of AF patients in NOAC trials compared to real world data of AF patients.

Methods: AF patients identified in 4 RW data sources were compared to AF patients in 3 contemporary RCT studies (ARISTOTLE, RE-LY and ROCKET-AF) by baseline characteristics including CHADS2 risk score data. Sources: General Practice Research Database (GPRD) in the UK, the Swedish Hospital Discharge Register, claims data from I3 InVision Data Mart and PharmMetrics in the US. Results: Descriptive results show (Table) that the RW populations have a higher proportion of ≥ 75 yrs and slightly more females compared to the RCTs. Similar CHADS2 scores (except ROCKET-AF) were observed between the RCTs and RW data. 2-fold more AF patients in the RCTs had a history of hypertension, and a higher use of beta blockers and statins. More RCT patients had a prior stroke.

Table 1. Randomized Clinical Trials vs. Real World Observational Cohorts

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ARISTOTLE</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>SHDR</th>
<th>Pharmetrics</th>
<th>GPRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>18.201</td>
<td>18.113</td>
<td>14.269</td>
<td>94.175</td>
<td>182.678</td>
<td>227.595</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>70</td>
<td>71.5</td>
<td>73.1</td>
<td>71.1</td>
<td>76.5</td>
<td>75.9</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>10</td>
<td>10.1</td>
<td>11.7</td>
<td>10.3</td>
<td>17.6</td>
<td>20.2</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>72</td>
<td>76</td>
<td>78</td>
<td>74</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Beta blocker (%)</td>
<td>61</td>
<td>63</td>
<td>65</td>
<td>67</td>
<td>69</td>
<td>71</td>
</tr>
</tbody>
</table>

Conclusions: Females and ≥ 75 yrs are under-represented in the RCTs. I3 and Pharmetrics under-represent those ≥ 65 and older so the differences in the RW may be greater than represented here. Beta blockers are used substantially more in the RCTs. The drug use rates are lower in the RW cohorts despite fairly similar baseline characteristics, which may be an indicator of less adequate treatment in the RW. Some differences observed between the studies may be due to differences in how conditions were defined. As new therapies come to market, comparative effectiveness studies will be executed. Evaluating baseline data including co-morbidity conditions and concomitant medications will be important as we assess the benefits and potential risks of NOACs in the RW.

P560 Predicting bleeding risk in patients with atrial fibrillation: comparison of several risk scores in a real world community based cohort study

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The risk of bleeding in patients with atrial fibrillation (AF) is not homogenous. Several risk stratification schemas for bleeding have been proposed but some of them are based on complex scoring systems that are difficult to apply in clinical practice, and few have been validated in levels above the normal range (≥ 14 ng/L). The prognostic information by hs-TnT was additive to the CHADS2 risk score and other biomarkers. Apixaban consistently reduced stroke, mortality and bleeding regardless of the hs-TnT level at entry (Table).

Conclusions: Hs-TnT is an important additional risk factor for stroke, death and major bleeding in atrial fibrillation. The benefits with apixaban are maintained across different hs-TnT levels.
High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with chronic atrial fibrillation

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1University General Hospital Morales Meseguer, Murcia, Spain; 2Hospital Universitario Virgen de la Arrixaca, Murcia, Murcia, Spain; 3City Hospital, Centre for Cardiovascular Sciences, Birmingham, United Kingdom;

Detectable high sensitivity troponin T (hsTnT) in subjects without cardiovascular disease has been associated with incident coronary heart disease, mortality and heart failure. Inflammation plays a central role in atherosclerosis and AF patients associated high incidence of atherothrombotic events. There are limited data on the prognostic role of biomarkers in anticoagulated patients with atrial fibrillation (AF). We evaluated the prognostic value of hsTnT and high sensitivity interleukin-6 (hsIL6, as inflammatory marker) in a large cohort of AF patients taking oral anticoagulant therapy (OAC).

Methods: We studied 930 patients (50% male; median age 76 years [IQR 70-81]) with permanent AF who were stabilised (for at least 6 months) on OAC (INRs 2.0-3.0). hsTnT and hsIL6 levels were quantified by electrochemiluminescence immunoassay at baseline. The lower limit of detection of these assays was 3.3pg/mL for hsTnT and 1.5pg/mL for hsIL6. Patients were followed-up for up to 2 years, and adverse events (thrombotic and vascular events, mortality and major bleeding) were recorded.

Results: Both hsTnT and hsIL6 were detectable in 770 patients (80%). Median (IQR) values of hsTnT were 8.86 (4.24-15.21) pg/mL, and 291 (31%) patients had hsTnT levels above 13 pg/mL. Median (IQR) values of hsIL6 were 3.45 (1.93-5.70) pg/mL. Median follow-up was 957 (784-1087) days, and during this period, 96 (3.57%) died whilst 107 patients had an adverse cardiovascular event (3.14%). On univariate analysis, both high hsTnT and high hsIL6 remained significantly associated with prognosis even after adjusting for CHADS2 score, with adjusted hazard ratios (HRs) of 2.21 (1.46-3.35, p < 0.001) for hsTnT and 1.97 (1.30-2.92, p < 0.002) for hsIL6, for adverse cardiovascular events. For all cause mortality, the HRs were 1.79 (1.13-2.83, p = 0.013) and 2.48 (1.60-3.85, p < 0.001), respectively. The integrated discrimination index (IDI) values of clinical risk scores (CHADS2 and CHA2DS2-VASc) were improved by the addition of hs-TnT or hsIL6 (all p < 0.05). And importantly, IDI values of both clinical scores were improved after adding both biomarkers for death and cardiovascular events (all p < 0.05).

Conclusion: In a large ‘real world’ cohort of anticoagulated AF patients, both hsTnT and hsIL6 levels provided complementary prognostic information to the clinical risk scores (CHA2DS2-VASc and CHADS2) for prediction of long-term cardiovascular events and death, suggesting that these biomarkers may potentially be used to refine clinical risk stratification in AF.

Patterns of antithrombotic therapy and type of atrial fibrillation: insights from the Global Anticoagulant Registry In the FIELD (GARFIELD)


1University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 2Thrombosis Research Institute, London, United Kingdom; 3Department of Medicine, Tokai University, Kanagawa, Japan; 4Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands; 5Harvard Medical School, Brigham and Women’s Hospital, Department of Medicine, Boston, United States of America; 6Technical University of Munich, Munich, Germany; 7University Hospital Jean-Minjoz, Besançon, France.

Background: Oral anticoagulation (OAC) is recommended for all patients with atrial fibrillation (AF) at moderate to high risk of stroke and without contraindications, irrespective of type of AF. We sought to compare rates of antithrombotic use according to CHADS2 score and type of AF in an international cohort of patients from the Global Anticoagulant Registry in the FIELD (GARFIELD).

Methods: In this worldwide registry, patients with newly diagnosed AF will be enrolled in 5 sequential prospective cohorts in up to 1000 sites and 50 countries. The first cohort includes an international validation group. Eligibility criteria include age ≥ 18, HR ≥ 7.0, ≥ 2 risk factors for stroke (past history of stroke, transient ischemic attack or other stroke, or AF of > 1 year duration, hypertension, diabetes mellitus, age > 75 years), and being on OAC therapy. The primary aim is to compare rates of OAC use across the entire GARFIELD database, according to type of AF.

Conclusions: These observational data from real-world practice suggest low rates of OAC use in patients with paroxysmal AF across all CHADS2 risk groups. A notable proportion of patients at low risk of stroke received OAC therapy. These data highlight discrepancies between clinical practice patterns and guideline recommendations.

Cost-effectiveness of apixaban against other novel oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation


1University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; 2United Biosource Corporation, Bangkok, Thailand; 3Bristol Myers Squibb, Princeton, NJ, United States of America; 4Pfizer, Inc., New York City, NY, United States of America; 5United States of America; 6United Biosource Corporation, London, United Kingdom; 7Bristol Myers Squibb, Wallingford, CT, United States of America; 8St. Michael’s Hospital, Toronto, Canada

Purpose: Apixaban (5 mg BID) is a factor Xa inhibitor studied in trials of stroke prevention in atrial fibrillation compared to warfarin and aspirin. Two other novel anticoagulants (NOACs) are dabigatran, a direct thrombin inhibitor (available as 150 mg BID and 110 mg BID in Europe) and rivaroxaban (20mg QD). This study evaluated the cost effectiveness of apixaban against other NOACs from the UK National Health Services (NHS) perspective.

Methods: A Markov model was developed to evaluate the clinical and economic impact of apixaban versus other NOACs over lifetime from a payer perspective. Pair-wise direct treatment comparisons were conducted against other NOACs using ARISTOTLE, RE-LY and ROCKET-AF trial results for the following end-points: ischemic stroke, hemorrhagic stroke, intracranial hemorrhage excluding subarachnoid hemorrhage, other major bleedings, clinically relevant non-major, myo-cardial infarction and treatment discontinuations. The analyses of event rate outcomes for efficacy and safety end-points were conducted on intent-to-treat (ITT) and modified ITT (mITT) basis, respectively. Outcome measures were life years gained (LYs) and quality adjusted life years gained (QALYs). Medical costs were estimated in 2010 GBP and discounted at 3.5% per year. Incremental cost effectiveness ratio (ICER) below £20,000/QALY was deemed acceptable for the purposes of these analyses.

Results: Apixaban was found to potentially increase life-expectancy versus other NOACs, dabigatran (both doses) and rivaroxaban, over lifetime horizon. These gains were achieved at nominal increase in costs over lifetime which were associated with expected increase in life-expectancy and potentially higher drug acquisition costs which could be incurred due to less number of discontinuations anticipated on apixaban versus other NOACs. One-way and probabilistic sensitivity analyses indicated that results were robust over a wide range of inputs.

Cost-effectiveness of NOACs versus other NOACs at lifetime horizon

<table>
<thead>
<tr>
<th>Comparator</th>
<th>ΔCost over lifetime</th>
<th>ΔLY over lifetime</th>
<th>ΔQALY over lifetime</th>
<th>ICER (£20,000/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>£972</td>
<td>0.085</td>
<td>0.076</td>
<td>12,762/QALY</td>
</tr>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>£734</td>
<td>0.118</td>
<td>0.188</td>
<td>£6,735/QALY</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg QD</td>
<td>£670</td>
<td>0.076</td>
<td>0.051</td>
<td>£4,436/QALY</td>
</tr>
</tbody>
</table>

Conclusions: Based on the results of CE model, apixaban will be the cost-effective alternative to dabigatran 150 mg BID, dabigatran 110 mg BID and rivaroxaban 20 mg QD.
**P564**

**Left atrial thrombus in anticoagulated patients undergoing catheter ablation for atrial fibrillation: who is not at risk?**

E. Bertaglia, F.C. Zoppo, G. Brandolin, Mirano Public Hospital, Italy

**Purpose:** Aim of this study was to investigate incidence and predictors of left atrial (LA) thrombus in fully anticoagulated patients undergoing catheter ablation for atrial fibrillation (AF) in order to confirm the safety of current recommendations in selecting patients in whom preablation transoesophageal echocardiogram (TOE) could be avoided.

**Methods:** We joined personal data collected in 429 patients who performed preablation TOE in Germany, Austria and Italy with a therapeutic INR of at least four consecutive weeks, with those of patients with similar characteristics obtained from two previously published papers. Several combinations of clinical and echocardiographic parameters were tested to identify the best compromise between safety and reduction of useless TOE.

**Results:** A total of 1353 patients were analyzed. AT preablation TOE, a left appendage thrombus was found in 30 patients (2.2%). Following current recommendations, that is to perform TOE in anticoagulated patients only if AF is persistent and present at the moment of ablation, TOE utilization would have been reduced by 48.7%, but LA thrombus have been missed in 8/1353 (0.59%) patients. Combinations of clinical and echocardiographic parameters we have tested in term of unsuccessful detection of LA thrombus and reduction of useless TOE are presented in the Table.

**Conclusions:** In fully anticoagulated patients prevalence of LA thrombus at TOE is low but not negligible (2.2%). Current recommendations on preablation TOE do not guarantee patients' safety. Preablation TOE could be safely avoided only in patients with a CHA2DS2-VASc score of 0. This choice reduces the utilization of TOE in more than 4% of candidates to AF ablation catheter.

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**P565**

**Antithrombotic treatment of patients with atrial fibrillation and acute coronary syndrome: Results from the AFibACS Registry (as part of the Berlin Myocardial Infarction Registry)**

S. Behrens, C. Hegenbarth, B. Maier, E. Braun, H. Schulz, R. Schoeller, H. Schülehen, H. Theres on behalf of BMIR.1 Vivantes Humboldt Hospital, Berlin, Germany; 2 Berlin Myocardial Infarction Registry at TU Berlin, Charité-Campus Mitte, Berlin, Germany; 3 Vivantes Berlin, Berlin, Germany; 4 Vivantes Auguste-Viktoria Hospital, Berlin, Germany; 5 Charité - University Medicine Berlin, Campus Mitte, Berlin, Germany

**Background:** Guidelines for the management of atrial fibrillation (AF) recommend strategies for the treatment of patients with AF and acute coronary syndrome (ACS) and define who should receive triple therapy (VKA, ASA, and Clopidogrel). Our study aims to show how guidelines are implemented in Berlin, which complications occur, and whether new antithrombotic drugs are being used in everyday practice.

**Method:** A total of 795 patients with all types of AF (first diagnosed, paroxysmal, persistent, long-standing persistent, permanent) and ACS were included between 1 April 2008 and 30 June 2011. The CHA2DS2-VASc score and data on the HAS-BLED score, as well as on hospital treatment and outcome were collected for each patient.

**Results:** In 510 (out of 795) patients, a stent was implanted (n=179 DES;n=331 BMS), 62 received a PTCA, and 223 experienced no intervention. Patients treated without stent (n=285) were older (79.5 vs. 74.6 years, **p** < 0.001), had a higher mortality rate (n=25, 8.8% vs. 4.2%, **p**=0.03), and suffered from previous stroke more often (19.3% versus 14.1%, **p**=0.056). According to the guidelines, patients with a HAS-BLED score ≥ 3 should be treated with a BMS stent. This was the case in 63.3% in our study. A total of 7.5% of interventionally treated patients (with stent) died in the hospital, compared to 21.8% not treated with a stent (n=2, **p**<0.001).

**Table 1. Antithrombotic and anticoagulative treatment at discharge according to CHA2DS2-VASc score for patients discharged (n=644)**

<table>
<thead>
<tr>
<th>CHA2DS2-VASc</th>
<th>Triple ASA (n=261)</th>
<th>ASA + Clopidogrel (n=140)</th>
<th>ASA or Clopidogrel (n=103)</th>
<th>Other combination</th>
<th>Left atrium (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (4.3%)</td>
<td>6 (23.1%)</td>
<td>27 (26.5%)</td>
<td>–</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>1-2</td>
<td>13 (5.0%)</td>
<td>8 (32.7%)</td>
<td>25 (25.0%)</td>
<td>1 (4.1%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>187 (71.4%)</td>
<td>107 (44.0%)</td>
<td>102 (46.2%)</td>
<td>12 (61.9%)</td>
<td>2 (12.5%)</td>
</tr>
</tbody>
</table>

**Conclusion:** 1. ACS patients with AF and a HAS-BLED-Score ≥ 3 received BMS more often than DES. However, approximately one-third of patients received DES.

2. In ACS patients with AF, pharmacological antithrombotic treatment was focused primarily for ACS; VKA for stroke prevention was administered less often.

3. Further data analyses will show whether guidelines are implemented more often in everyday treatment of ACS patients with AF.

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**P566**

**Risk of stroke, myocardial infarction, bleeding and death in patients with incident atrial fibrillation: a cohort study of primary care in the UK**

C. Martínez1, S. Riedbrock1, T. Evers2. 1Pharmaeppi.com, Frankfurt, Germany; 2 Bayer Pharma AG, Wuppertal, Germany

**Purpose:** To estimate the risk of stroke and other outcomes in patients with incident atrial fibrillation (AF) and to describe effectiveness and persistence with anticoagulant and antiplatelet agents.

**Methods:** Patient data were retrieved from general practices in England via the General Practice Research Database and linked to data from the Hospital Episode Statistics and death data from the Office for National Statistics. Cases of incident non-valvular AF between 2001–2009 were followed-up over 1 year for the occurrence of stroke, myocardial infarction (MI), bleeding and all-cause mortality. Kaplan-Meier estimates of cumulative incidence were derived for each outcome, stratified by use of warfarin and adjusted by use of acetylsalicylic acid (ASA). Conclusions: Results: Of 30,311 patients with incident AF, 996 had stroke, 898 had MI, 242 had major bleeding and 4467 died. Cumulative incidence of 15.9% for all-cause mortality, 3.8% for stroke, 3.4% for MI and 0.9% for major bleeding. The risk of stroke, MI and all-cause mortality was highest within 30 days of AF diagnosis. When compared with warfarin users, patients treated with ASA alone were more likely to have a stroke (adjusted HR 1.76 [95% CI 1.43–2.18]) or MI (1.38 [1.11–1.72]) but were less likely to have major bleeding (0.61 [0.42–0.89]). Persistence with warfarin was 27% at 1 year.

**Conclusions:** All-cause mortality was the most frequent outcome of incident AF, whereas major bleeding was less likely than stroke or MI. Warfarin persistence was low.

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**P567**

**Efficacy and safety of short-term anticoagulation after cardioversion in atrial fibrillation patients with low thromboembolic risk**

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**Background:** Patients with AF lasting more than 48 h required anticoagulants prior to and after cardioversion. The short-term postcardioversion anticoagulation (STPA) with low molecular weight heparin (LMWH) can decrease the risk of bleeding and does not require in regular INR monitoring. Objective: The purpose of our study was to evaluate the efficacy and safety of STPA with second postcardioversion TEE and the evaluation of thrombosis markers such as D-dimers and soluble fibrin monomer complexes (SFMC) in patients with persistent non-valvular AF.

**Methods:** 62 patients with AF lasting more than 48 h and low risk ([CHA2DS2VASc score]≤ 1) were included. The exclusion criteria were acute thrombosis or thrombomembolism, intracranial hemorrhage; gastro-intestinal bleeding or acute peptic ulcer within previous 3 months; urgent cardioversion; contradictions to TEE, to LMWH or oral anticoagulant. 30 patients were treated with enoxaparin 1 mg/kg subcutaneously twice a day 24 h before and 7 days after cardioversion, whereas another 31 patients received conventional therapy with warfarin. All subjects were underwent TEE before cardioversion in order to exclude LA/LAA thrombus. Second TEE was performed 7–10 days after cardioversion to examine LAA contractile function. In enoxaparin group anticoagulation therapy was discontinued if LAA emptying velocity was > 25 cm/s (in absence of “atrial stunning”), otherwise patients received warfarin for 3 weeks. In patients prior to and 7 days and 1 month after cardioversion blood samples was taken for D-dimers and SFMC assays. The follow-up period was 1 month.

**Results:** Subjects in both groups were similar with respect to demographic, clinical and echocardiographic characteristic at the beginning of the study. Reduction of major bleeding was less likely than stroke or MI. Enoxaparin patients had lower risk of thromboembolic complications (95% CI 0.19–0.84) compared to warfarin patients with LMWH (95% CI 0.45–0.90). In enoxaparin group anticoagulation therapy was discontinued if LAA emptying velocity was > 25 cm/s (in absence of “atrial stunning”), otherwise patients received warfarin for 3 weeks. In patients prior to and 7 days and 1 month after cardioversion blood samples was taken for D-dimers and SFMC assays. The follow-up period was 1 month.

**Conclusions:** Subjects in both groups were similar with respect to demographic, clinical and echocardiographic characteristic at the beginning of the study. Reduction of major bleeding was less likely than stroke or MI. Enoxaparin patients had lower risk of thromboembolic complications (95% CI 0.19–0.84) compared to warfarin patients with LMWH (95% CI 0.45–0.90).
Quality of anticoagulation and bleeding and thrombotic risk in relation to CHADS2 score: analysis of the AF cohort of EPICA study

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Purpose: The quality of anticoagulation expressed as time in therapeutic range (TTR) is associated to both bleeding and thrombotic events during vitamin K antagonists treatment. It is unknown if TTR in patients with Atrial Fibrillation (AF) is related to their baseline stroke risk. Aim of this study is to evaluate TTR in relation to CHADS2 score in the AF cohort of EPICA Study (1).

Methods: We defined patients with TTR<60% as adequately anticoagulated. We calculated the distribution of patients with TTR<60% and the rate of bleeding and thrombotic events in relation to CHADS2 score.

Results: We studied 2015 AF patients (males 45%; median age 83 years, range 80-103) enrolled in the AMADEUS clinical trial. The total quality of anticoagulation measured using TTR was 66% and the rate of bleeding and thrombotic events in relation to CHADS2 score is reported in Table 1.

Conclusions: As expected, the rate of major bleedings and of thrombotic events increase with CHADS2 score. Instead, no difference in the quality of anticoagulation is found in relation to CHADS2 score.

Renaal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial

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Background: Limited data are available on the impact of indices of renal function on the outcome of anticoagulated AF patients, who do not have severe renal impairment.

Methods: We performed a post hoc analysis of the AMADEUS study to assess the impact of renal function on safety and efficacy outcomes of vitamin K antagonists treatment. It is unknown if TTR in patients with Atrial Fibrillation (AF) is associated to stroke risk. The AMADEUS trial was a multicentre, randomised, study that compared fixed-dose idraparinux with adjusted dose oral VKA therapy in patients with AF. The primary efficacy outcome was the composite of stroke or systemic embolism (SE). The principal safety outcome was clinically relevant bleeding.

Results: The AMADEUS study randomized 2290 patients in the VKA arm (65% men, mean age 70.2±9.1, 2257 (98%) patients had creatinine clearance (CrCl) >30 ml/min. In total 251 (11%) safety and 60 (2.6%) efficacy endpoints occurred. On adjusted Cox proportional hazards analysis, patients at the middle-top tertiles of serum creatinine (Cr) (<86 umol/L) had significantly increased risk for stroke or death (HR 1.72, 95% CI 1.07-2.75) compared to patients in the lowest tertile (<60 umol/L) (Table 1). Patients with serum Cr between 86-102 umol/L (middle tertile) had 2.6-fold higher risk of stroke/SE compared to patients in the lowest tertile (<60 umol/L), whilst those in the top tertile (>102 umol/L) had 3.3-fold higher risk. Serum Cr affected the quality of anticoagulation as reflected by the lower time in therapeutic range (TTR) in the highest Cr tertile compared to the middle/lowest tertiles (55±2% vs. 58±2% respectively, p<0.05). However, TTR was not independently associated with the efficacy outcome (HR 0.4, 95% CI 0.1-1.7, p=0.2). No association was established between serum Cr and bleeding risk, nor between baseline CrCl and either efficacy or safety outcomes.

Conclusion: In an anticoagulated cohort of AF patients, serum Cr (but not CrCl) was independently associated with stroke and SE. Serum Cr may be a simple predictor of thromboembolism in anticoagulated AF patients without severe renal impairment.

Intensive educational intervention improves time in therapeutic range in atrial fibrillation patients initiating warfarin: results from the TREAT study

D.E. Smith, H.M. Paterson, G.Y.H. Lip, D.A. Lane on behalf of University Centre for Cardiovascular Science. Center for Cardiovascular Sciences, Birmingham, United Kingdom

Purpose: Stroke thromboprophylaxis in atrial fibrillation (AF) is dependent upon time spent within the target therapeutic INR range (TTR) (2.0 to 3.0). This randomized controlled trial (ISRCTN89952605) examined the effect of an intensive educational intervention on TTR among AF patients initiating warfarin compared to usual care.

Methods: Warfarin-naive AF patients were randomised (stratified by age, sex and centre (specialist vs. non-specialist)) to receive the intervention, consisting of group sessions (2-8 patients) with the trial team, educational booklet, “expert-patient” focused DVD, and worksheets, or usual care (warfarin clinic). Primary endpoint was TTR, assessed by Rosendahl method, during the first 6 months of therapy.

Results: 97 patients were recruited: intervention [n=43; mean (SD) age 72.5 (7.4) years, 29 men; median (IQR) CHADS2 score 2 (1-3)] and usual care [n=54; mean (SD) age 73.2 (8.7) years, 34 men; median (IQR) CHADS2 score 2 (1-3)] (see Table). No significant demographic or clinical differences at baseline between the groups were evident. Patients receiving the intensive educational intervention had significantly higher TTR compared to those receiving usual care (78.5% vs. 66.7%, p<0.001). Patients receiving usual care spent significantly more time with sub-therapeutic INRs.

Conclusions: Intensive education can improve TTR in AF patients and potentially help improve clinical outcomes. Improving education provision for AF patients is essential to ensure efficacious treatment.

Independent predictors of mortality in patients with non-valvular atrial fibrillation: results from ROCKET AF

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Purpose: Identifying risk factors for mortality may help guide interventions in AF. Methods: Patients with non-valvular AF were randomized to rivaroxaban or dose-adjusted warfarin. Cox proportional hazards regression was used to identify factors associated with all-cause mortality in 17,171 intention to treat patients.

Results: See Table 1 (p. 57). Median age was 73; mean CHADS2 was 3.5. Over a median follow-up of 1.94 yrs, 1214 (8.7%) pts died. Of these, median age was 76, men CHADS2 was 3.6, 48% had prior stroke/TIA. Independent predictors of increased mortality were decreasing CrCl, COPD, male sex, PVD, increasing age, diabetes, HF, tachycardia, residence in Latin America, and prior stroke/TIA (C-index 0.670). Alcohol use and higher BMI were associated with a decreased risk of death. When baseline medications, including prior VKAs (HR 0.77; 95% CI 0.68–0.87) and antithrombinics (HR 1.04; 95% CI 0.87–1.24), were included as candidate variables the C-index improved to 0.689.

Conclusions: The strongest predictors of mortality were reduced renal function, COPD, male sex, PVD, and age.

Table 1. Hazard ratios for stroke and SE

<table>
<thead>
<tr>
<th>CR</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical terms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine tertiles</td>
<td></td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Creatinine tertiles (86–102 umol/L)</td>
<td>2.6</td>
<td>1.2–5.7</td>
<td>0.013</td>
</tr>
<tr>
<td>Creatinine tertiles (&gt;102 umol/L)</td>
<td>4.3</td>
<td>1.5–7.2</td>
<td>0.002</td>
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<td>Model adjusted for age, sex, previous stroke or transient ischemic attack, hypertension, left ventricular systolic dysfunction and diabetes. SE, systemic embolism; HR, hazard ratio; CI, confidence interval.</td>
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Safety and efficacy of switching to antiplatelet agent after successful catheter ablation of atrial fibrillation

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Introduction: The current guidelines for anti-thrombotic treatment are equal before and after successful radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF). However, warfarin has a significant risk of major bleeding. Therefore, we evaluated safety and the strategy switching from warfarin to anti-platelet agent (APLT) regardless of CHADS2 score after confirming no AF recurrence at 3rd month after procedure.

Methods: Among 708 patients (age, 56.8±11.1 year; male 77.1%; paroxysmal AF 67.9%, persistent AF 32.1%, CHADS2 score, 0.9±1.0) who did not show clinical recurrence after RFCA, 358 patients were assigned into switching from warfarin to APLT at 3rd month after RFCA (APLT group; CHADS2 score 0.8±1.0) and 350 patients into conventional anti-thrombotic strategy according to CHADS2 score (Conv group; CHADS2 score 0.9±1.0, p=0.708). We compared thromboembolic risk, major hemorrhage risk, and event of overall stroke.

Results: 1. During 12.1±5.8 months follow-up, one patient in APLT group (0.28%) and 4 patients in Conv group (1.14%) developed major thrombotic or hemorrhagic events (p=0.542). 2. In APLT group, a patient with CHADS2 score 4 had transient ischemic attack on admission warfarin. 3. Among 707 patients (44%) were on warfarin. We compared thromboembolic risk, major hemorrhage risk, and event of overall stroke.

Conclusion: Switching to APLT after successful AF ablation might be a relatively safe and effective anti-thrombotic strategy reducing major hemorrhagic risk in patients with low CHADS2 score and high HAS-BLED score. However, strict rhythm monitoring for AF recurrence is mandatory.

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Conclusions: LA function measured by TTE added to the CHADS2 or the CHADS2-VASc scores may improve the predictive value of presence of SEC and thrombus, especially in clinically low risk group. In clinic, anti-coagulation may be considered to prevent embolism in patients with low risk score when they have LA dysfunction.

Anti-thrombotic therapy and atrial fibrillation in Scotland: results of a national audit

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Introduction and Methods: GP practices across Scotland were invited to participate in an audit of the management of atrial fibrillation (AF) as part of a national audit of Clinical Standards in Heart Disease by Health Improvement Scotland. A primary care database interrogation tool was developed to identify patients with AF, extract relevant data and calculate a CHADS2 score for each patient.

Results: 248 practices with a total practice population of 1,376,834 contributed data. 19,470 patients with AF were identified (prevalence 1.4%) including 18,165 patients with non-valvular AF. The majority of patients with non-valvular AF (56%) were in a high risk group for stroke (CHADS2=2) and the most prevalent risk factors overall were age >75 (75%) and hypertension (50%). Formal stroke risk assessment was rarely recorded in primary care (<1%). 79% of patients with AF were prescribed some form of anti-thrombotic therapy, either anti-platelet or warfarin (Table). In the high risk group (CHADS2=2) not on warfarin, a minority of patients had recorded exclusion criteria for warfarin (10%). In patients with non-valvular AF who had a prior history of ischaemic stroke or TIA, less than half (44%) were on warfarin.

Anti-thrombotic use by CHADS2 score

Stroke risk Stroke score Number of patients with AF (% of total) Number of patients on anti-platelet (% of group) Number of patients on warfarin and anti-platelet (% of group)

CHADS2=0 819 (32%) 1019 (32%) 69 (22%)
CHADS2=1 5338 (28%) 2039 (38%) 1829 (35%) 511 (4%)
CHADS2=2 9691 (58%) 3778 (39%) 3967 (41%) 357 (4%)

Conclusion: In Scotland, patients with AF are not receiving anti-thrombotic therapy according to guidelines. Patients at high risk of stroke are undertreated with warfarin and those at low risk of stroke are over prescribed warfarin. Strategies to improve appropriate anti-coagulant use in this group include routine use of simple stroke risk stratification.

Increased prevalence of anxiety and depression in atrial fibrillation patients following oral anticoagulant treatment initiation

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Purpose: Evidence suggests atrial fibrillation (AF) confers an increased risk of psychological morbidity, particularly anxiety, which may affect the subsequent management and treatment adherence. Few studies have studied psychological factors over time in AF patients.

Method: Warfarin-naive AF patients were followed up for 6 months after commencing warfarin. Anxiety and depression, and quality of life (QoL) were assessed at baseline, 1, 2 and 6 months using the Hospital Anxiety and Depression Scale (HADS) and AF-QoL-18, respectively.

Results: 97 patients (mean (SD) age 72.9 (9.2) years, 63 men; median (IQR) CHADS2 score 2 (1-3)) were recruited. Median anxiety and depression scores increased significantly between baseline and 1 month (p<0.001) and remained elevated over the 6-month period. The prevalence of depression cases doubled from baseline to month 1 (25.5% to 56.5%), as did the prevalence of anxiety (41.5% to 95.4%). QoL remained unchanged over time.

Conclusion: Anxiety and depression levels increase significantly following commencement of warfarin. Standardised psychological screening at warfarin clinics
could identify such patients, with a targeted psychological intervention as appropriate to reduce psychological morbidity.

**Net clinical benefit of apixaban among patients with atrial fibrillation**

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**Purpose:** Atrial fibrillation (AF) increases stroke risk, warranting oral anticoagulation (OAC) in high-risk patients. Vitamin K antagonists, previously the only OAC, were commonly underutilised, partly due to inconveniences. We therefore evaluated the theoretical impact on clinical outcomes by apixaban, a new OAC, in Europe.

**Methods:** Based on a large European prospective cohort we identified all high-risk (CHA2DS2-VASc score ≥2) patients with non-valvular AF and one follow-up. First, occurrence of stroke/TIA, major bleeding and all-cause mortality were stratified according to antithrombotic regimen. We included all European AF patients who would translate into the annual prevention of 24,378 deaths, 59,762 strokes per year and 5,531 major bleedings.

**Conclusion:** Based on this modelling exercise utilization of apixaban for thromboprophylaxis could provide a profound annual mathematical net clinical benefit in major life events and survival.

**Cost-effectiveness of dabigatran etexilate versus warfarin for stroke prevention in patients with non-valvular atrial fibrillation in the public and private healthcare system in Brazil**

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**Objectives:** To compare costs and effectiveness of dabigatran etexilate (DAB) versus warfarin (WAR) in patients with Non-Valvular Atrial Fibrillation (NVAF) from a private and public health care system perspective in Brazil.

**Methods:** A Markov model was built to compare DAB versus WAR to derive the incremental cost effectiveness ratio (ICER) of DAB (150 mg BID or 110 mg BID), based on the international literature and a modified Delphi panel with Brazilian experts (local clinical practice pattern on the management of NVAF patients) assuming in the model a hypothetical population considering similar profile of the RELY trial. The model estimated the number of ischemic and hemorrhagic strokes, systemic embolisms, intracranial hemorrhages, transient ischemic attacks, extracranial hemorrhages, minor bleeds and acute myocardial infarctions associated with the respective treatments. To each clinical event costs, disabilities and/or reduction in quality of life, and risk of death were assigned. Only direct medical costs were considered and a discount rate of 5% was assumed, according to Brazilian HTA guidelines. A probabilistic sensitivity analysis was designed to assess uncertainty.

**Results:** Under both, the private and public perspective, DAB was associated with additional 0.30 life years gained (LY) (9.42 life year for DAB versus 9.11 life year for WAR), additional 0.35 QALYs (7.25 QALYs for DAB versus 6.91 QALYs for WAR) and demonstrated a lower incidence of intracranial events versus WAR, resulting in lower event costs (R$ 4,030.31 for DAB versus R$ 4,828.38 for WAR) in the public health care system and R$ 8,767.99 for DAB versus R$ 11,539.30 for WAR in the private healthcare system and follow-up costs (R$ 8,549.87 for DAB versus R$ 9,530.77 for WAR in the public healthcare system and R$ 16,275.83 for DAB versus R$ 19,444.25 for WAR in the private healthcare system). The ICER for both DAB versus WAR was R$ 39,744.00 (95% CI: R$ 25,252.48–R$ 22,160.20) from the private perspective.

**Conclusion:** Results suggest that DAB can be cost-effective for stroke prevention when used instead of WAR in NVAF patients in Brazil, given that the ICERS were below the threshold of other technologies reimbursed.
pendage (LAA) dysfunction and thrombi in patients with persistent nonvalvar atrial fibrillation (AF).

**Methods:** Transesophageal echocardiography (TEE) were performed in 229 nonvalvar patients: mean age 63.9±8.6 years and mean AF episode duration 7.3 months. In the 41.05% of cases current episode was first. The mean CHADS2/CHADS2/Vasc score was 1.8. Severe SEC was found in 7.9% and LAA thrombus in 6.2% of cases. LAA velocity <5 cm/s was found in 24.45% of cases. There was significant correlation between CHADS2/CHADS2/Vasc score and density of SEC (r=0.34, p=0.002). We found that CHADS2/CHADS2/Vasc score ≥ 4 significantly associated with SEC (OR 4.6 (95% CI 3.6-5.7), p=0.005; with LAA velocity <5 cm/s OR 4.9 (4.3 5.64), p=0.0002 and LAA thrombus OR 6.2 (CI 5.1-6.3), p=0.0007.

In addition, we calculated that 33% cases of LAA thrombi and 17% of SEC cases were found in patients with a low CHADS2/CHADS2/Vasc score 1, and that 40% of the LAA thrombi and 55.6% of SEC 4+ were revealed in the first case of the persistent AF episode.

**Conclusions:** Therefore we concluded that although high CHADS2/CHADS2/Vasc score may be useful also for prognosis of LAA disturbances in patients with persistent nonvalvar AF, performing of TEE even in cases with low CHADS2/CHADS2/Vasc score is of importance for more complete stroke risk estimation.

**P583**

**Predictors of left atrium appendage clot detection despite on-target warfarin prevention for atrial fibrillation**

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**Introduction:** The antithrombotic management in atrial fibrillation (AF) is currently based on CHADS2 or CHADS2/Vasc scores. The prevalence of left atrium (L) thrombi in AF patients has been reported up to 10%. We tried to correlate L LA thrombus appendage (LAA) thrombus detection with clinical predictors, in warfarin patients.

**Methods and Results:** A cohort of 430 study patients (mean age of 63.9±8.6 years), all in oral anticoagulant (OAC) and undergoing PVI was assessed with transesophageal echo (TEE).

In 10/430 (2.3%) an LA thrombus was found despite therapeutic OAC (mean INR 2.6±0.6, range 2.0-3.8) over the previous 4 weeks. Two study groups were then identified: 1) T-positive group = with LAA thrombus 2) T-negative group = without LAA thrombus.

The Tpositive patients had higher CHADS2 score (1.5±0.7 versus 0.7±0.8; p=0.004), a lower LVEF (54.7±9.8 versus 60.2±7.4; p=0.02), and a larger LA size (LA diameter: 56.12±2.6 mm versus 46.6±5.5 mm, p=0.001). In the multivariate model only a larger LA size (OR 1.2±95% CI 1.07-1.48; p=0.006) predicted LAA thrombus.

In further 42/430 (9.8%) patients an LA spontaneous echo-contrast (SEC) was detected. Thus, cumulatively 52/430 (12.1%) study patients were found to have both LAA thrombi or SEC. The LA size continued to predict also both the thrombi and SEC presence (OR 1.19 95% CI 1.07-1.2; p=0.001).

**Conclusions:** We found a 2.3% prevalence of LA thrombi (up to 12.1% when and SEC presence (OR 1.14 95% CI 97.1-1.2; p=0.004), a lower LVEF (54.7±9.8 versus 60.2±7.4; p=0.02), and a larger LA size (LA diameter: 56.12±2.6 mm versus 46.6±5.5 mm, p=0.001). In the multivariate model only a larger LA size (OR 1.2±95% CI 1.07-1.48; p=0.006) predicted LAA thrombus.

**P584**

**Thromboembolic risk prediction in an atrial fibrillation cohort from AF-BAR study, comparison between CHADS2, CHADS2/VASC and physician awareness**


**Purpose:** The aim was to evaluate the performance of the different thromboembolic risk (CHADS2,CHA2DS2VASC) assessment scores in comparison with the primary physician awareness about this risk, in a cohort of Atrial Fibrillation (AF) patients (p) from AF-BAR study followed by primary care physicians (PCP) during a near 3 year period.

**Methods:** AF-BAR was a cross-sectional study made with collaboration of 35 PCP. During a 3 month period in 2008, 796p with previous history of AF were included. Follow-up was done by clinical review or telephone contact and death or CV events were recorded, as well as the cause of death. A survey about thromboembolic risk of the patients was answered by PCP for 754p (94.7%).

**Results:** 754p were analysed, first episode 86p (11.4%) recurrent AF in 143p (19%), and permanent AF in 521p (69.6%). Mean age 74.6±9.2 years, 51.7% men, older than 75y, 46.3% female, 76.8% hypertension, 24.4% diabetes, 12.6% previous heart failure, 8% previous TIA or stroke, 10.2% vascular disease. Mean CHADS2 1.8±1.1, mean CHADS2/VASC 2.9±1.4. Estimated risk by physicians was divided in low risk 30.1%, moderate 40.3% and high 29.6%. Distinction for CHADS2 was low 9.9%, moderate 29.6% and 60.5%. The number of embolic events was 29 (3.8%) with median follow up of 1119 days, anticoagulation was used in 576p (76.4%). The receiver-operator characteristic curve to discriminate individuals who will or will not have embolic event during follow-up based on their score showed the next area under curve (AUC) for physician risk assessment 0.640 (95% CI 0.600-0.675)CHADS2 0.578 (0.542-0.613); CHADS2/VASC 0.605 (0.569-0.640), without statistical differences between the 3 embolic risk prediction schemes (Figure 1)

**Figure 1. ROC curve comparison**

**Conclusions:** Physicians showed similar performance in comparison with established risk scores

**P585**

**Specific von Willebrand factor origin and thromboembolic risk in patients with paroxysmal and persistent atrial fibrillation**

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**Purpose:** Abnormal plasma levels of von Willebrand factor (vWF) have been found in atrial fibrillation (AF), but the origin of this marker of pro-thrombotic risk is not clear. We hypothesised that multiple dosages at different levels of the cir-
culatory tree would help to identify the origin of vWF and to assess the role of the endothelium in the thromboembolic risk associated with AF.

Methods: Using a case-control study, 43 patients with paroxysmal (Px) and 38 with persistent (Ps) AF were compared to 15 control (Ct) subjects. Peripheral (Pp), left atrial (LA) and coronary sinus (CS) blood samples were obtained during routine catheterization, prior to ablation. Serum levels of vWF in all three sites were measured by immunoturbidimetric assay.

Results: Compared to Ct, patients with Ps AF had higher LA blood levels of vWF (113±51 UI/dL vs. 81±30 UI/dL, p<0.02), but similar Pp and CS levels (both p>0.05). Patients with Ps AF had higher levels of vWF in Pp (122±62 UI/dL vs. 89±37 UI/dL, p=0.04), LA (138±50 UI/dL vs. 81±30 UI/dL, p=0.004), and CS (133±49 UI/dL vs. 82±24 UI/dL, p=0.03) blood samples, compared to Ct patients. LA levels of vWF were significantly higher in Ps than in Ps AF group (p=0.02). In the AF group, subjects at high risk of stroke (CHADS2/SAVASc score ≥2) had significantly higher vWF levels compared to patients at low and intermediate risk (CHADS2/SAVASc score =0) (126±57 UI/dL vs. 103±49 UI/dL, p=0.04).

Conclusions: In patients with Ps AF, the source of vWF appears to be limited to the atrial endocardium. In patients with Ps AF, both atrial endocardium and vascular endothelium are the main sources of vWF. These findings suggest specific thromboembolic risk patterns in patients with different clinical forms of AF. High LA thrombi levels of vWF in both Ps and Ps AF patients could explain the similar risk of stroke observed in these patients.

P586 Individual approach to antithrombotic management in non-valvular atrial fibrillation patients undergoing electrical cardioversion

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Purpose: The goal of the study was to evaluate the prevalence and characteristics of left atrial appendage (LAA) and right atrial appendage (RAA) thrombi in non-valvular atrial fibrillation (NVAF) patients undergoing transesophageal echocardiography (TOE) before electrical cardioversion (ECV); to determine the relationship of CHADS2/SAVASc score with atrial appendages thrombi; to evaluate the importance of TOE-guided strategy of oral anticoagulant (OAC) therapy before ECV.

Methods: A total of 112 patients with NVAF, who underwent TOE before ECV, were included in the study.

Results: The mean age of participants was 60.5±0.9 years. 72% were men. 60.7% of patients had arterial hypertension, 6.2%-coronary artery disease, 60.7%-were obese. The mean term of last AF episode was 5.2±1.3 months. The majority of the patients (67.8%) fell into the high-risk group as CHADS2/SAVASc score ≥2, 27.7% were in the moderate-risk group and 4.5% had CHADS2/SAVASc score of 0. Transesophageal echocardiography (TEE) was done in all patients after at least 3 weeks of effective OAC therapy. Precedence cardioversion TOE detected LAA/RAA thrombi in 30 patients (27%). The severity of thrombi was as follows: moderate-29% and severe-1%. Thrombi in the LAA were discovered in 19 patients (17%). Thrombi in the RAA were discovered in 11 patients (10%). Thrombus organization after 3 weeks has been observed in 38% of patients. Thrombus organization after 3 weeks has been observed in 38% of patients. Cerebral ischemia was observed in these patients. Among these patients, 26% had ischemic strokes and bleeding complications. The mean term of last AF episode was 5.2±1.3 months. The mean term of last AF episode was 5.2±1.3 months.

Conclusions: Our study shows, that prevalence of LAA and RAA thrombi is very high. In patients with CHADS2/SAVASc score ≥2 OAC therapy is recommended, in patients with CHADS2/SAVASc score of 0-1 TOE is recommended for more accurate thrombo-embolism risk assessment and selection of thrombo-embolism prevention strategy. Approach of TOE-guided ECV must be selected in all patients, because it gives the opportunity to mark patients for course of OAC therapy more persistent (Ps) AF. The importance of TOE detection of LAA/RAA thrombi in atrial fibrillation patients is not an obstacle in making decision of rhythm control therapy.

P587 Relationship between CHADS2 score and prophylactic efficacy during antiarrhythmic drugs therapy in patients with paroxysmal atrial fibrillation

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Background: CHADS2 score is a useful scheme for risk stratification of thromboembolism, whereas there has been little information in its usefulness for evaluation of antiarrhythmic drugs therapy (AAD). This study included 459 paroxysmal atrial fibrillation patients age 66±12 years, mean follow up 50±35 months and prophylactic efficacy was analyzed on the basis of CHADS2 score.

Methods: (1) Survival rates free from AF recurrence at 1, 6, 12 and 24 months were 97%,74%,63% and 47% in score-0 group (N=152), 92%,68%,59% and 46% in score-2 group (N=84), 87%,65%,51% and 35% in score-3 group (N=43), and 68%,50%,36% and 18% in score-4 group (N=22), respectively (P<0.05;score-0, score-1 or score-2 versus score-4 group). (2) Survival rates free from conversion to permanent AF at 12,36,60 and 90 months were 96%,84%,71% and 69% in score-0 group, 97%,91%,89% and 88% in score-1 group, 96%,93%,88% and 83% in score-2 group, 91%,74%,67% and 60% in score-3 group, and 91%,82%,68% and 55% in score-4 group, respectively (P<0.01; score-0, score-1 or score-2 versus score-4 group). (3) In a multivariate logistic regression analysis adjusted for age and sex, CHADS2 score were associated with AF recurrence (odds ratio [OR] 1.45, 95% confidence interval [CI] 1.16-1.81, P<0.001) and conversion to permanent AF during AAD (OR 1.64, 95% CI 1.04-2.69, P<0.001).

Conclusion: CHADS2 score is a useful scheme not only for risk stratification of thromboembolism but also for outcome of AAD in patients with paroxysmal AF.

P588 Safety and efficacy of Dabigatran in patients undergoing left atrial ablation procedures: a case-matched analysis

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Background: Periprocedural anticoagulation strategy during left atrial catheter ablation is still much discussed. Recently, Dabigatran as novel, oral, reversible, direct thrombin inhibitor has been approved for the prevention of stroke in patients with nonvalvular atrial fibrillation. Safety, management and periprocedural potential complications are still unknown.

Objective: Evaluate the efficacy and safety of Dabigatran during left atrial ablation procedures (LAAPs).

Methods: We conducted a case-match analysis considering the variables age, gender, body mass index, creatinine levels, left atrium dimensions, type of arrhythmia. Between May 2010 and January 2012 LAAPs were performed in 27 patients of Dabigatran. Preprocedural INR value, baseline and procedural antiplatelet measurement, heparin doses adjusted for the body weight (and time of procedure) and evaluation for ischemic strokes and bleeding complications were conducted in all patients.

Results: In the Dabigatran group baseline ACT was higher (170±52;32.8±84.19±19.62; p<0.001). Furthermore less heparin was needed to achieve an ACT between 250 and 300s (7965±2.4176.9±1067.9±3.2861.02, p<0.007). One patient under Dabigatran had a periprocedural thrombotic stroke and recovered partially after 13 days follow-up. No major hemorrhagic complications occurred. Minor bleeding complications (gyn hematuria) occurred in 2 patients on Dabigatran and in 4 patients with continuous warfarinization.
Influence of CYP2C9 gene polymorphism on warfarin efficacy in Uzbek patients with long term atrial fibrillation


Aim: To study of 2*3 polymorphisms of CYP2C9 gene and its carriage association with warfarin induced hypocoagulation in Uzbek patients with atrial fibrillation (AF).

Methods: Study included 92 patients of both sexes (60.5% males) in the age from 38 to 76 years (average age 60.7±9.02 years) with long lasting (5.2±1.6 month inaverage) AF, having not less than 2 risk factors of thromboembolic complica-
tions on CHA2DS2VASc and have not previously received warfarin. Warfarin was prescribed in addition to basic therapy in initial dose of 2.5±0.3mg/day with control of International Normalized Ratio (INR). Hypocoagulation noted in INR<3.

Results: After genotyping on CYP2C9*2 polymorphism it was revealed that 85 patients (91.4%) have homozygous CYP2C9*1/*1 genotype, CYP2C9*1/*2 heterozygous genotype– 7 patients (7.53%) and 1 (1.08%) patient has CYP2C9*2/*2 genotype. Referring to CYP2C9*3 polymorphism it was found that all 92 patients havehomozygous genotype CYP2C9*2/*2.

Conclusions: In this study homozygous CYP2C9*2/*2 allele carriers have no hypocoagulation during 3 months after starting warfarin prescribed in addition to basic therapy in initial dose of 2.5-5.0mg/day with control of International Normalized Ratio (INR).

Organized electrocardiographic pattern of atrial fibrillation on ECG predicts successful electric cardioversion


Introduction: Fibrillatory waves in atrial fibrillation (AF) may be related with structural or mechanical properties of the atria. ECG pattern of AF at the moment of electrical cardioversion (ECV) may predict the probability of conversion to sinus rhythm (SR).

Methods: We analyzed the morphology of the fibrillatory waves in lead V1 and inferior leads in 237 consecutive patients (65±12 year-old; 57% male) admitted for ECV of persistent AF. Severe valvular disease, valvular prosthesis and severely dilated atria were excluded. The voltage and duration of the P wave after successful ECV was evaluated.

Results: We identified two ECG patterns of AF prior to ECV: Type I (organized fibrillatory activity into visible and regular waves in V1 and/or II, III or aVF) 75% (n=178), Type II (without any visible organized activity). Success of ECV was performed in 82% of patients. The success rate for each pattern was 90.4% for Type I and 55.9% for Type II (p<0.001). There were no differences in atrial size or the presence of cardiomyopathy. Type II pattern was associated with lower voltage (0.06±0.04 vs 0.12±0.05 mV; p<0.001) and a shorter duration (68±20 vs. 81±25 ms; p<0.01) of the P wave in V1 in SR. Type II pattern was also identified in older patients (68±10 vs 64±12 year-old; p<0.03) and associated to a higher presence of echocardiographic "smoke" (85% vs 66% p=0.02).

ATRIAL FIBRILLATION: SOLVING COMPLEX PROBLEMS

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Purpose: No proper data is available from Patna, India on AtrialFibril-
lation (AF). Most of the informations are from the west, which has dif-
ferent predisposing factors and management. Goal of the study is to knowabout details of predisposing conditions and etiological factors and also to define in treatment specialty the problem of anticoagulation.

Method: From single centre at Patna, India, patients of AtrialFibrilation were en-
rolled from 2008 to 2011. Average aged from 35 to 88 years. The peak incidence was 70 to 80 years and male female ratio was 55:45%. Patientcharacteristics such as Atrial fibrillation and AFib Patter, reasons for found, history of atrial fibrillation and their pattern were recorded. Various etiological factors were as follows. Rheumatic Heart Disease, (RHD, mostly mitral valve disease) 41%Hypertension 32%, Diabetes 5.12%, Heart failure (systolic) 19.23%, Coronary artery disease 11.3%, Lone Atrial Fibrillation 10%, Hypertrophic cardiomyopa-thy 1.28%, Thyroid disorders both Hyperthyroidism 5.12% and Hypothyroidism 5.12%, Chronic Obstructive Pulmonary Disease 2.56%, AluminumPhosphate Poi-
sioning 1.28%. Out of total 156 patients 18 were paroxysmal (11.53%). 62 pa-
tients (39.74%) were on oral anticoagulants. Proper INR wasmaintained in less than half (≠20). Two cases had strong family history of AF. Number of prosthetic valve were 18 out of 156 (11.53%), 4 patients of mitrvalvalve prostheses were replaced due to thrombosis, one case converted torsus rhytmus thromb-
ysis. Prosthetic mitral valve and post mitralvalvotomy cases had refractory AF. Number of embolism 3.64% which includedperipheral as well as intra-cerebral. Youngest patient a 15 year old boy treated with Radio Frequency Ablation (RFA) for permanent cure. Drugs used wereastematically controlling due to patient, beta-
blockers and calcium channelblockers apart from anti platelets, ace inhibitors and statins. Atrial Fibrillation and Beta blockers were commontreatment which was success-
ful in pharmacological conversion in ≤20% cases.

Result: The RHD is the commonest cause in this study followed by hyper-
tension and heart failure. Level of anticoagulation is 39.7% and INR control is
<20%.Incidence of Embolism is surprisingly low despite prior anti coagulation.

Conclusion: This study highlights the commonest cause of AF beingRHD com-
pared to west were Hypertension is the commonest. The persistent antithrom-
atry AF is very common due to enlarged and diseased left atrium in longstanding mitral valve disease despite valvotomy and replacement of valve.Overall anticoagulation level is far from satisfactory. The RFA for AF is stillvnot popular.
Degree of atrial structural remodeling determines improvement in ejection fraction after catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction

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Background: Restoration of sinus rhythm by catheter ablation in patients with atrial fibrillation (AF) promises to be an effective therapy to simultaneously improve left ventricular (LV) systolic function, however it is unclear as to which patients may benefit from this therapy. We assessed the improvement in LV ejection fraction (LVEF) in patients with different stages of atrial structural remodeling.

Methods: One hundred-five patients with impaired LV systolic function (LVEF ≤ 50%) who underwent an LGE-MRI prior to ablation for AF were included in this retrospective analysis. We quantified left atrial fibrosis using LGE-MRI and grouped patients into four stages based on the percentage of fibrosis (minimal=0-15%, mild=15-35%, moderate=35-60%, extensive= ≥60%). LV remodeling was determined both prior to and 3 months following pulmonary vein ablation with posterior wall and septal debulking.

Results: The average pre-ablation LVEF in patients with minimal fibrosis (n=3) was 41.7±6.8%, 38.3±7.6% in patients with mild fibrosis (n=48), 41.2±9.1% in patients with moderate fibrosis (n=39) and 39.9±9.7% in patients with extensive fibrosis (n=15; P=0.45). While the overall average increase in LVEF following ablation was 11.3±8.4%, greatest increase was seen in patients with less extensive LA fibrosis (minimal=13.3±7.6% and mild= 14.1±8.5%). Patients with moderate and extensive fibrosis had an average EF improvement of 9.6±8.0% and 5.9±6.0%, respectively.

Conclusion: In patients with LV systolic dysfunction, a low fibrosis in the left atrium was associated with greater improvement in LVEF after catheter ablation for AF.

Characteristics of atrial fibrillation ablation in routine practice: In-hospital results of a French registry of more than 1000 procedures

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Purpose: This atrial fibrillation (AF) ablation registry was conducted in order to describe the current epidemiology of patients undergoing AF ablation, the techniques used and the results obtained in routine practice in France. We report here the in-hospital data.

Methods: Data were prospectively collected in 6 medium-high volume French centers. All consecutive patients who underwent an atrial fibrillation or a left atrial macro-reentry ablation procedure were included in the registry within a period of 6 to 18 months according to centers.

Results: From January 2010 to December 2011, 1097 consecutive complex left atrial ablation procedures were collected. Patients were predominantly males (75%) with a mean age of 59±10 years old. The targeted arrhythmia was paroxysmal AF in 57%, persistent AF in 32%, long-standing AF in 4% or left atrial macro-reentry secondary to a previous AF ablation in 7%. Of interest, redo procedures represented 27% of the overall procedures. Pulmonary vein isolation (PVI) was attempted in 96% of the cases, the roof line in 40% and the left isthmus line in 16%. Complex fractionated atrial electrograms were targeted in 20% of procedures. The procedures were most often performed with an irrigated-tip RF ablation catheter (75%) and a 3D navigation system was used in 68% of the procedures. PVI was performed with a cryoballon in 21% or with phased RF technology tools in 3% of the cases. The mean procedure time was 142±56 min, with a mean amount of X-ray exposure of 56±43 Gray.cm². Surprisingly, X-ray exposure was not significantly less when 3D navigation system was used (46±32 vs 49±35 Gray.cm²; p=0.31). The overall complication rate was 6.7%. Tamponade occurred in 14 patients (1.3%, requiring surgical drainage in 2 pts) and responsible of death in 1); stroke was documented in 5 pts (0.4%), phrenic nerve palsy was observed in 8 pts during cryoballon procedures only (8/234, 3.4%). Gastrointestinal bleeding occurred in 14 patients (pts, 1.3%, requiring surgical drainage in 2 pts and requiring surgical treatment in 3); Hemoptysis, complete AV block, cardiogenic shock, documented in 1 pt respectively.

Conclusion: This prospective registry allows to get a real vision of how and to whom are performed complex left atrial ablation procedures in routine practice. Detailed data analysis might raise potential issues on which preventive action might further reduce procedures complication rate.

Contribution of left ventricular diastolic function to left atrial mechanical function in patients with paroxysmal atrial fibrillation

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Purpose: Among diverse mechanisms leading to electroanatomical remodeling of left atrium (LA) in paroxysmal atrial fibrillation (PAF), left ventricular (LV) diastolic dysfunction would be one of the major contributors. The aim of this study was to evaluate the association between LV diastolic function and LA mechanical function.

Methods: We included 286 patients with PAF (male 73%, 57±11 years old) who underwent radiofrequency catheter ablation (RFCA). The patients had undergone transthoracic echocardiography, transesophageal echocardiography, and cardiac computed tomography before RFCA. LA voltage map was obtained using the NavX contact mapping system.

Results: Patients with impaired LA mechanical function (n=142; LAA-FV<58cm/s) revealed a larger LA diameter (p=0.040), indexed LA volume (p=0.017), lower LAA voltage (p=0.047), higher CHADS2 score (p=0.009) and higher rate of cerebrovascular events (p=0.025) than in those with good LA mechanical function (n=144; LAA-FV>58cm/s). In simple correlation analysis, early mitral filling/mitral annular annular velocity ratio (E/E') was significantly correlated

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with LAA-FV (r=0.19, p=0.004) and LA voltage (r=0.22, p=0.007). These associations were stronger for subjects ≥55 years of age and LA diameter ≥40mm (LAA-FV, r=0.39, p<0.001; LA voltage, r=0.31, p=0.03). E/E’ was an independent predictor of LA mechanical function (β=0.19, p=0.021) even after controlling for age, gender, LA diameter and comorbidities.

**Conclusion:** LA mechanical function and its electroanatomical remodeling are closely related to one another, and both of them are under the influence of left ventricular diastolic function in PAF. The contribution of LV diastolic function to LA mechanical dysfunction was especially important to older patients with large LA diameter.

**High left atrial pressure and its responsiveness to isoproterenol infusion are related to the degree of electroanatomical remodeling of left atrium in patients with atrial fibrillation**

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**Background:** Although left atrial pressure (LAP) may affect to atrial remodeling, their direct relationship has not yet been elucidated. The purpose of this study was to compare the clinical, imaging, and electrophysiological data of different area with LAP in patients with atrial fibrillation (AF) who underwent radiofrequency catheter ablation (RFCA).

**Methods:** We measured both LAP during sinus rhythm (SR) and AF in 311 patients (76.1% male, 57.4±11.5 years, 68.6% paroxysmal AF) who underwent catheter ablation, and change of LAP during isoproterenol infusion in 140 of them. We compared LAPAF, LAPSR, LA volume and voltage with LAP.

**Results:** 1. In patients with mean LAPSR:13mmHg, LA size (42.9±6.9 vs. 40.1±5.8mm, p<0.001), LA volume (141.0±49.7 vs. 122.3±39.2ml, p=0.006), body weight (71.1±11.0 vs. 68.3±10.9kg, p=0.037), and proportion of persistent AF (93.6% vs. 21.1%, p=0.010) were greater than those with LAPSR:13mmHg. These findings were consistent when we compared LAPAF:13mmHg and LAPAF:13mmHg. 2. During isoproterenol infusion, LAPSR reduced from 2.6±6.0 vs. 5.3±3.64.4mmHg to 16.8±11.0±0.5±5.6/1±1.6±4.1mmHg at heart rate 110 bpm (p<0.001). 3. The patients with ∆LAPSR <3mmHg were older (60.0±11.2 vs. 54.9±11.5 years, p=0.009) and had lower endocardial voltage of LA (1.2±0.6 vs. 1.5±0.9 mV, p=0.028) than those with ∆LAPSR >3mmHg.

**Conclusion:** Elevated LAPSR and LAPAF were closely related to greater LA volume and body weight, and more likely persistent AF. Less significant reduction of LAPSR during isoproterenol infusion was observed in older patients with lower endocardial voltage of LA, suggesting elevated LAP associated with poor function and delayed afterdepolarization, as well as steepest maximum slope of AP90 restoration curve (RC) compared to the other 3 groups (Figure). CFAE with high DF site had a longer AP90 and effective refractory period (ERP) compared to the non-CFAE with high DF. It possesses most depolarized resting membrane potential (RMP), highest incidence of early afterdepolarization and delayed afterdepolarization, as well as steepest maximum slope of AP90 and ERP cementing that POAF are more likely to be AF-related arrhythmo-generative sites.

**Impact of ranolazine in preventing postoperative atrial fibrillation in patients after on-pump coronary artery bypass graft surgery**

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**Purpose:** Atrial fibrillation is a common complication of acute coronary syndrome (ACS) and it increases the mortality risk. The use of digitalis in coronary artery disease is controversial and usually considered unfavorable. NFAD is a new approach that is known on the influence of digitalis in patients with ACS in the long-term outcome. Our purpose was to investigate the relationship between presence of AF/FL during ACS and digitalis treatment over 12 year mortality and to determine which treatment is associated with the highest rate of survival.

**Methods:** We prospectively studied 557 unselected patients enrolled in three Intensive Care Units with ACS who were discharged alive. They were followed up for 12 years (The ABC study on ACS). Patients with AF/FL during the 1st week of hospitalization (n=57, median age (IQ) 75 (67-81) years, females 39%) were compared with those with steady sinus rhythm (n=500, median age (IQ) 65 (58-73) years, females 28%). Twenty-one percent of the patients in sinus rhythm (SR) received digoxin during follow up at the median dose of 0.125mg/day, and 65% among AF/FL patients. Statistic beyond basic analysis was carried out by using Cox proportional hazard regression, polynomial logistic regression and interaction analysis. All survival analysis were made at univariable and multivariable level.

**Results:** After 12-year of follow up, 48% of the patients in sinus rhythm and 79% of those in AF/FL had died (p < 0.0001). At adjusted Cox survival analysis, AF/FL did not result independently associated to all-cause mortality. At ad-
justed logistic polynomial regression analysis, AF/FL resulted associated to an excess of mortality due to sudden death (SD) (adjusted HR=2.9; 95%CI=1.2-7.2; p=0.002). Digitalis treatment showed a negative (protective) interaction for all-cause mortality (HR=0.3; 95%CI=0.2-0.5; p=0.002). This protective effect was linked chiefly to SD (adjusted HR=0.1; 95%CI=0.03-0.4; p=0.0003). Even after adjustment for age, gender, heart failure and heart rate the (protective) interaction remained strong (HR=0.3; 95%CI=0.2-0.6). p=0.002 and HR=0.1, 95%CI=0.03-0.4; p=0.0004 respectively for all-cause mortality and SD).

Conclusions: Treatment with low dose digitalis during follow up appears to have an independent long term beneficial effects in subjects with ACS and AF/FL at baseline, chiefly affecting SD.

### P600

**In-hospital prognosis in patients with atrial fibrillation during acute myocardial infarction**

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**Introduction:** Acute myocardial infarction (AMI) is frequently related to presence of atrial fibrillation (AF). The aim of our study was to evaluate the clinical and prognostic importance of AF in patients with AMI.

**Methods:** A total of 479 unselected, consecutive patients admitted to the intensive care unit (ICU) of Conegliano General hospital, with definite AMI, between January 1st 2001 and December 31st 2002. The variables examined were related to patients’ hospitalization. Cutoff factors: revascularization therapy and presence of AF/fibrillation, divided by new onset AF, chronic AF and AF preceding the admission to the hospital. The end point was major adverse cardiovascular event (heart failure, re-AMI and death). We compared the patients with AF and those with sinus rhythm, using monovariate analysis models (Chi square and Student Test) and a model of multiple logistic regression to evaluate the clinical predictors of AF and mortality.

**Results:** 106 out of 479 AMI patients were affected by AF. In particular 20 patients had previous episodes of AF, 39 had chronic AF and 47 had new onset AF, during the hospitalization. Compared to patients with sinus rhythm during hospitalization, those with AF were older (77 vs 67 years), more often affected by hypertension (69.7% vs 57.2%), with lower ejection fraction (48.6% vs 54.0%) and larger left atrium on echocardiography (47.2 ± 41.7 mm on sagittal axis), more often affected by ischemic stroke preceding the current hospitalization (11.6% vs 4.3%), more often affected by 3 vessels coronary artery disease (55.8% vs 36.9%), heart failure (43.7% vs 20.1%) and death (12.5% vs 6.0%) during the indexed hospitalization. At multivariable analysis, AF was independently associated to higher in-hospital mortality (OR 1.75; 95% CI 1.2-2.1; p=0.03), alongside age and left atrium on echocardiography. In the subsets of patients, there were no difference between patients with chronic AF and patients with new onset AF. Chronic atrial fibrillation was not associated with a higher incidence of 3 vessel coronary artery disease.

**Conclusion:** AF is independently associated to higher in-hospital mortality after AMI, whether AF is chronic or new onset.

### P601

**Assessment of atrial conduction time in patients with systemic lupus erythematosus**

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**Objectives:** Systemic lupus erythematosus (SLE) is an autoimmune disorder resulting in multisystemic inflammatory damage. Recent articles reports that 20 to 30% of deaths in patients with SLE have cardiovascular origin. The aim of this study was to investigate the atrial conduction time in patients with SLE by using high-usefulness tissue Doppler echocardiography (TDD).

**Methods:** The study population included 56 patients with SLE (49 female; mean age=46±12.2 years, and mean disease duration=30.7±10.9 months) and 45 healthy subjects as control group (39 female; mean age = 45±8.1±12.3 Years). P wave dispersion (PWD) was evaluated using 12 lead electrocardiogram. The timing of atrial contractions (PA) was measured as the interval between the onset of P wave on electrocardiogram and the beginning of A-wave on TDI. Atrial electrical conduction time (ECD) was calculated from the lateral (PA lateral), septal (PA septal) and posterior (PA posterior) annulus of the left atrium. Mean ECD was calculated as the mean of the three PA annuli.

**Results:** PA lateral and PA septal were significantly longer in patients with SLE than control subjects (66.7±15.9 vs 56.5±13.7, p=0.001 and 53.5±15.0 vs 45.9±14.5 ms, p=0.006, respectively). Interal (PA lateral – PA tricuspid) and interatrial (PA septal – PA tricuspid) electrical conduction delay (ECD) were significantly longer in SLE groups (25.5±9.7 vs 19.9±8.3, p=0.003 and 13.3±9.7 vs 6.6±8.0 ms, p=0.002, respectively). Similarly, maximum P-wave duration and PWD were significantly longer in patients with SLE than control subjects (104.9±13.5 vs 98.1±15.1, p=0.001 and 24±6:7±4.2 vs 0.001, respectively). There were significant positive correlations between the disease duration and interatrial ECD (r=0.611, p=0.001) and intraatrial ECD (r=0.565, p<0.001). Positive correlation was also present between the disease duration and PWD (r=0.45, p<0.001).

**Conclusion:** Atrial ECD is prolonged in patients with SLE. We have also showed that PWD, intraatrial and interatrial ECD were significantly correlated with disease duration. This study calls attention to measurement of atrial conduction time may be clinically helpful in the definition of cardiac involvement.

### P602

**Total atrial conduction time predicts symptoms and quality of life impact in paroxysmal atrial fibrillation patients**

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**Background:** Paroxysmal atrial fibrillation (PAF) is a common arrhythmia with multiple presenting symptoms. Total atrial conduction time (TACT [time from the start of the p-wave in lead II to A’ of the left atrial wall – Figure 1]) has been identified as a risk marker of AF occurrence and as a predictor of AF ablation success. It can be hypothesised that patients with shorter TACTs will be more symptomatic from AF episodes due to the loss of loss of atrial function. A’ alone has also been correlated with success rates of PAF ablation. The ratio of A’ to VTI in S PVT has not previously been described but may indicate the proportion of atrial input into overall cardiac output.

**Methods:** 18 patients (age 64±3.7 yrs, 11 females) undergoing pulmonary vein isolation (PVI) for paroxysmal AF were implanted with monitoring devices at District General Hospital were enrolled. An ECHO was performed immediately prior to ablation. TACT, A’ and the ratio of A’ to S VTI were all calculated. Visual analogue scores (VAS), specific symptom prevalence score and the SF36 questionnaires were used to evaluate symptom and quality of life burden. The VAS, specific symptom prevalence score and SF36 score were compared to the TACT, A’ and the A’/VTI ratio.

**Results:** A’ and the A’/VTI ratio did not correlate with VAS, specific symptom prevalence score or SF36 scores. TACT correlated well with all 3 scores (Fig. 1).

**Conclusion:** Short TACT correlated well with high symptomatic and reduced quality of life scores suggesting that atrial function impacts on the symptom burden in patients with PAF. This may contribute some explanation to why some patients are highly symptomatic with low burdens of arrhythmia whilst others are symptom free.

### P603

**What are the best predictors of spontaneous conversion in non valvular AF patients?**

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Spontaneous conversion (SC) occurs in atrial fibrillation patients with a frequency varying from 16% to 72%. Identifying patients prone to have a SC remains challenging in clinical practice. We investigated whether MR-proANP and Copeptine could predict SC in non valvular AF patients.

**Methods:** Transthoracic echocardiography (TTE) and venous blood test were performed in 460 consecutive AF patients with an ECG documented AF. MR-proANP and Copeptine were retrospectively measured using immunoassays assays. SC was defined as the occurrence of sinus rhythm between the time of admission and before TEE guided cardioversion.

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Baseline patients’ characteristics are depicted in table 1. SC occurred in 217 pa-
tients (47%). MR-proANP and Copeptine blood levels were significantly lower in patients with SC compared to those without, LVEF = 40%, left atrial diameter > 20 mm or left atrial diameter < 40 mm were more frequently observed in patients without SC. In the multivariable logistic regression model, only AF onset <48h (OR=4.82, 95%CI: 3.05-7.21), and TTE parameters (left ventricular ejection fraction (LVEF) <40% and left atrial area > 20 cm² or left atrial diameter > 40 mm) (OR= 2.34, 95%CI: 1.48-3.70) were independently associated with non SC.

Conclusion: MR-pro ANP and copeptine level were significantly lower in patients with SC compared to those without. In multivariate analysis, LVEF < 40% and/or left atrial area > 20 cm² were independently associated with infrquent SC.

### P604 Ventricular repolarization changes following catheter ablation of atrial fibrillation

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**Background:** Atrial fibrillation (AF) leads to dispersion of ventricular refractoriness and QT prolongation has been demonstrated following DC cardioversion. We studied ventricular depolarization changes following catheter ablation of AF.

**Methods:** 471 patients with AF undergoing ablation at the University of Utah were included. Anti-arrhythmic drugs were discontinued at least 4 half-lives prior to ablation. We measured QT and QTc intervals pre- and immediately post- and 3 months following catheter ablation. Patient demographics/comorbidities including drug use were included in the analysis.

**Results:** 231 patients (49.9%) had paroxysmal and 240 (51.1%) had persistent AF. 52.0% patients were prescribed beta-blockers or calcium channel blockers prior to ablation. 10.2% were prescribed class 1 and 7.2% class III AADs. Compared to pre-ablation, immediately post- QT and QTc intervals were significantly longer: 403.6±43.8 vs 410.0±45.8; p=0.01 (QT) and 437.8±33.8 vs 454.7±31.5; p=0.01 (QTc). At 3 months, QT and QTc intervals remained prolonged compared to pre-ablation: 403.6±43.7 vs 412.6±43.0; p=0.01 (QT) and 437.1±33.3 vs 443.6±36.1; p=0.01 (QTc). Comparing immediately post- to 3-months post-ablation, the mean QTc shortened from 453.8±30.8 to 443.5±32.5; p=0.01 while the QT interval was not significantly different. QT and QTc intervals remained significant insusggroup analysis by AF type, baseline and recurrent AF after ablation and prior drug treatment.

**Conclusions:** Catheter ablation of atrial fibrillation is associated with acute prolongation of ventricular repolarization. This is independent of AF type, drug treatment or recurrence AF.

### P606 Landiolol hydrochloride: prevention of atrial fibrillation after open-heart surgery

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**Purpose:** Postoperative atrial fibrillation (AF) is one of the most common compli-
cations after open-heart surgery and can result in increased surgical mortality. Landiolol hydrochloride, an ultrashort-acting beta-blocker, was introduced in 2002. Although its effectiveness for prevention of postoperative AF is becoming clear, few randomized studies which include all types of open-heart surgery have been performed. The aims of this study were to evaluate whether landiolol hydrochloride contributes to the prevention of postoperative AF, and to evaluate the influence of landiolol hydrochloride on perioperative echocardiography findings.

**Methods:** From May 2010 to January 2012, a total of 141 patients (97 men, 44 women; mean age, 70.3±8.9 years) undergoing scheduled open-heart surgery (61 coronary artery bypass grafting, 46 valve surgery, 19 thoracic aorta surgery, 21 bypass grafting and valve surgery, 2 others) were randomly divided into two groups. Group L (n = 73) received landiolol hydrochloride postoperatively and Group C (n = 68) did not. Patients with previous AF and undergoing emergency surgery were excluded. Landiolol hydrochloride 2–3 mcg/kg/min was started soon after arrival in the intensive care unit after surgery and was continued for 48 hours. The occurrence of postoperative AF, prevalence of postoperative echocardiographic parameters, preoperative and postoperative cardiac function were evaluated using echocardiography, and several other perioperative factors were also evaluated.

**Results:** There were no significant differences between the two groups in base-
line patient characteristics or echocardiographic findings. Postoperative AF oc-
curred during infusion in 3 patients (4.1%) in Group L and 17 patients (25.0%) in Group C (p = 0.0005). From the time the infusion was stopped until discharge, 17 patients (23.3%) in Group L and 15 patients (22.1%) in Group C developed AF (p = 1.0000). There were no significant differences between the two groups in postoperative left ventricular ejection fraction (Group L: 62.2±13.5, Group C: 64.6±13.1, p = 0.437) or other echocardiographic findings. Multivariate analysis revealed that not receiving postoperative landiolol hydrochloride was a significant risk factor for postoperative AF (odds ratio 0.2, 95% confidence interval 0.05 to 0.82, p = 0.0054).

**Conclusions:** Landiolol hydrochloride is effective in decreasing the incidence of postoperative AF without disturbing left ventricular function. Landiolol hydrochloride is recommended for all patients undergoing open-heart surgery because of its minimally suppressive effect on cardiovascular performance.

### P607 Left ventricular fibrosis in atrial fibrillation: A novel mechanism for heart failure and arrhythmia progression

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**Background:** Excessive atrial fibrosis is involved in pathogenesis of atrial fibril-
ation (AF), but little is known on leftventricular (LV) fibrotic status in AF. In this study the presence of abnormal LV fibrosis in AF vs. its impact on cardiac function, as well as the possible association with arterial stiffness (i.e., systemic cardiovascular fibrosis) and parameters of endothelial activation, dysfunction and inflammation, is explored.

**Methods:** We performed a cross-sectional study to compare severity of LV fibrosis in permanent AF, paroxysmal AF and AF-free “disease controls” and “healthy controls”. LVfibrosis was quantified by calibrated integrated backscatter (cIB) using echocardiography-based acoustic densitometry (Philips iE33 Bothel, WA, USAwith off-line QLAB software). Arterial stiffness was assessed by pulse wave velocity; plasma markers of endothelial activation (E-selectin), endothelial damage/ dysfunction (vonWillebrand factors) were measured by ELISA; microvascular endothelial function was evaluated by laser Doppler flowmetry.

**Results:** There were more severe LV fibrosis (i.e., lower cIB) in both paroxysmal AF and permanentAF compared to AF-free controls (p < 0.001), with more LV fibrosis in permanent vs. paroxysmal AF (p=0.002) (Table). Low cIB was indepen-
dent association with high E/A ratio (diastolic dysfunction) after adjustment for age, sex, systolic blood pressure, history of hypertension, diabetes, and CVD.
0.24, p=0.032), but it was not significantly associated with LV ejection fraction or arrhythmia progression (paroxysmal vs permanent AF).

More severe LV fibrosis (i.e., lower cIB) was significantly correlated with advanced age (r=-0.40, p<0.001), higher systolic blood pressure (r=0.37, p<0.001), heart rate (r=-0.21, p=0.048), and left atrial volume (r=0.23, p=0.029). We found no significant association between LV fibrosis and parameters of arterial stiffness, meaning 51% and 55% of the variance was explained by Willebrand factor or E-seleciton.

Comparison of LV fibrosis between patients

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<td>cIB (dB)</td>
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### Conclusion

Abnormal LV fibrosis may be responsible for diastolic dysfunction and the high rate of heart failure with preserved ejection fraction in subjects with AF, but not arrhythmia progression. Given the high burden of heart failure in AF patients, LV fibrosis may become a novel therapeutic target in the future.

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### P608 Sub-optimal heart rate and rhythm control post-hospitalisation in high risk patients with chronic atrial fibrillation: the value of therapeutic ECG Holter monitoring

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#### Purpose:
Regardless of the therapeutic merits of “rate versus rhythm” control in managing chronic atrial fibrillation (AF), it is imperative to determine if the physician-nominated target is being achieved, particularly in patients at high risk for progressive cardiac dysfunction and future thrombo-embolic events. However, this data is rarely assessed.

#### Methods:
As part of a multicentre, randomised controlled trial of a nurse-led, home-based, AF-specific management program vs. usual post-discharge care, we have recruited a large cohort of patients discharged from hospital with chronic forms of AF. We report on the underlying rhythm and heart rate captured on 24 hour ECG Holter monitoring at a home visit (7-14 days post-discharge) of 122 patients randomised into the intervention arm.Aim of this study was to determine if patients displayed controlled (sustained heart rate <90 beats/min), uncontrolled (<20% of recording time sustained at >90bpm) or labile (>5 episodes of >90bpm for ≥20% of recording time) rates.

#### Results:
Mean age 72±11 years, 56% were male and 88% and 9% were diagnosed with persistent or permanent AF. At hospital discharge, 70% and 30% of patients were being managed as “rate” vs. “rhythm” control. During post-discharge Holter monitoring, of the 36 patients nominated for rhythm control, 59% had detected episodes of AF (33±45% of recording time). Of the 86 patients nominated for rate control, 55% were in AF for 100% of the recording time. Overall, three distinct heart rate phenotypes were evident. Almost half (47%) had a controlled heart rate during monitoring. However, 31% of patients displayed an uncontrolled rate, while the remainder (22%) showed a distinctly labile heart rate. Those patients assigned to rhythm control were more likely to display a controlled rate compared to rate controlled patients (62% vs. 42%; OR 2.4, 95% CI 1.0 to 5.8, p<0.049). Conversely, those assigned rate control were more likely to display an uncontrolled rate (36% vs. 17%) or labile (22% vs. 21%) heart rate. Clinically significant arrhythmias (other than AF) were identified in 49% of patients overall including extreme bradycardia/pauses (35%), supraventricular tachycardia (15%) and ventricular tachycardia (7%).

#### Conclusions:
These data confirm the potential value of routinely applying post-discharge, ECG Holter monitoring of heart rate/rhythm to further stratify risk and inform therapeutic choices in recently hospitalised patients with chronic AF. We found three distinct phenotypes of heart rate control—two of which were clinically significant, requiring intervention.

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### P609 Who is the optimal patient for cryo balloon ablation


#### Background:
Although ablation of atrial fibrillation with the cryoballon (CB) technique and irrigated tip catheter (RF) is widely used the question what a therapy is more appropriate for a given patient was not investigated. Aim of this study was to identify cohort of patients in whom CB ablation may be more successful, based on recently proposed in our institution risk score (RS)

#### Methods:
A total of 848 consecutive pts (age=58±6; history of AF=5, male=59%, PAF=38%, LAESD=75±5; hypertension=58%, DM=61, metabolic syndrome (MetS) = 341, LVEF=60%, LA area=20.91 cm2, BSA = 2.06 m2, GFR=88.85 mL/min) treated in our institution from 2005 to 2010 were enrolled. Pulmonary vein isolation (PVI) was performed either with cryoballoon technique (n=329) or circumferential PVI (n=519) with a 3.5mm irrigated tip catheter. A 7-day Holter monitoring was performed at each follow-up visit. Any episode of documented AF/LAT after an initial 3-months blanking period were considered as clinical endpoint. The RS was constructed based on 4 clinical parameters: Non PAF, enlarged LA area (LA area/BSA > 11.5), reduced GFR (< 68 mL/min) and MetS. The constructed score reached maximum value of 4 if all parameters were met.

#### Results:
Out of 848 patients 424 (50.0%) remained in sinus rhythm (SR) within median follow up of 35 months. The proportion of maintained SR was (28±6% (63.6%) vs. 65/84 (77.4%); p<0.03), 68/117 (58.1%) vs. 74/124 (59.7%); p<.78), 60/112 (53.6%) vs. 37/82 (45.1%); p<.29), 75/211 (35.5%) vs. 10/35 (28%); p=.88, and 6/34 (17.6%) vs. 9/4 (0%); p<.31 for RF vs. CB and RS =0,1,2,3, and 4, respectively.

#### Conclusion:
In patients with RS=0 both ablation techniques seems to be not differing in the efficacy. However in patients with lone PAF without concomitant factors CB ablation may be more effective.
Catheter ablation of atrial fibrillation: radiofrequency catheter ablation for redo procedures after pulmonary vein isolation with the cryoballoon technique - long-term follow-up results

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Catheter ablation has become the first line of therapy in patients with symptomatic, recurrent, drug-refractory atrial fibrillation. Cryoballoon ablation has been shown to be a safe and effective technique for pulmonary vein isolation. However, the arrhythmia recurrence rate is high after cryoballoon ablation procedures and there are no established strategies for redo procedures in these patients. Therefore, we have summarized our initial experience with two different strategies for redo procedures using radiofrequency catheter ablation.

Methods: Fifty-five patients (paroxysmal AF: 37 patients, persistent AF: 18 patients) had to undergo a redo procedure after initially successful circumferential PV isolation with the cryoballoon technique (Arctic Front Balloon, CryoCath Technologies). The redo ablation procedures were performed using a segmental approach or a circumferential ablation strategy (CARTO, Biosense Webster) depending on the intra-procedural findings.

Results: During the redo procedure, a mean number of 2.3±0.4 re-conducting PVs were detected (using a circular mapping catheter). In 47 patients, a segmental approach was sufficient to eliminate the residual PV conduction because there were only a few recovered PV foci. In the remaining 8 patients, a circumferential ablation strategy was used because of a complete recovery of the PV-LA conduction. All recovered PVs could be isolated successfully again. At 30-month follow-up, 80% of all patients were free from an arrhythmia recurrence (44/55 patients). There were no major complications.

Conclusion: In patients with an initial circumferential PV isolation with the cryoballoon technique, a repeat ablation procedure can be performed safely and effectively using radiofrequency catheter ablation. In most cases only a few re-conducting PV foci were found and therefore, a segmental re-ablation approach seems to be sufficient in the majority of patients.

Relationship between symptoms and arrhythmia burden in patients with atrial fibrillation

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Purpose: The few studies evaluating the relationship between symptoms and baseline arrhythmia burden in patients with atrial fibrillation (AF) lack continuous electrical monitoring, which is an important limitation.

Methods: We have studied the relationship between symptoms and arrhythmia burden in 50 patients with symptomatic drug-refractory paroxysmal AF referred for ablation, which underwent implantation of an internal loop recorder with AF detection algorithms (Reveal XT, Medtronic) at least 1 month before ablation. Immediately before ablation, patients fulfilled the Brigham AF Specific Symptoms Scale Checklist. This test provided a semi quantitative evaluation of patients’ symptoms (palpitations, dyspnea, chest pain and fatigue) during the previous month.

Results: 39 men and 11 women, with a median (P25, P75) age of 56 (44, 61) years were included in this study. The prevalence of hypertension, diabetes and structural heart disease was 28%, 12% and 16% respectively. The anteroposterior LA diameter at parasternal long-axis view was 42 (39, 46) mm. The pre-ablation monitoring period lasted for 38 (30, 65) days. During this period, 68% of patients had AF or atrial flutter recurrences. These patients had a median of 14 (6, 43) AF episodes. Cumulated arrhythmia burden was 89 (18, 320) hours, which was equivalent to 10 (2, 33) of time. Maximum duration of AF episodes was 15 (7, 53) hours. None of these variables was significantly associated with patients’ symptoms (Figure 1).

Conclusions: This study shows that the type and frequency of symptoms in patients with recurrent paroxysmal AF are not significantly correlated to arrhythmia burden. This finding supports the need to consider both issues independently during follow-up, particularly at the time of evaluating the results of a therapy.

Geometrical characterization of tricuspid valve remodeling with real time 3D echocardiography in patients undergoing mitral valve surgery: translational study

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Purpose: The aim of this study was to assess the way the right ventricle and tricuspid valve remodel in patients with post-capillary pulmonary hypertension who are undergoing mitral valve repair for degenerative mitral valve disease. The functional and morphological changes of the right ventricle (RV) as well as tricuspid apparatus in post-capillary pulmonary hypertension remains elusive.

Methods: A total of 34 consecutive patients were prospectively recruited. All of them had degenerative mitral valve regurgitation which required mitral valve repair (MR). Twenty age and gender matched healthy volunteers were also studied to serve as controls. Real-time 3 Dimensional echocardiography (3DE) was used to assess RV volumes and tricuspid valve mobility, before and 6 months after the operation.

Results: Overall, RV diastolic volumes (ml) were greater and RV EF (%) lower in MR compared to healthy volunteers (105.2±17.4 ml vs. 74.5±13.8 ml, p<0.001) and (59.6±5.1% vs. 69.3±8.4%, p=0.0044) respectively. When RV volume was corrected by body surface area, a significant difference remained (75.8±7.3 vs. 65.9±10.2 ml/m2, p=0.017). A significant reduction of RV volumes post repair (RV-end-diastolic volume: 80.8±17.4 vs. 75.1±12.9 ml/m2, p=0.02) and higher ApoB/ApoA-I ratio (0.48±0.17 vs. 0.41±0.11, p=0.004). On multivariate analysis, increased ApoB/ApoA-I ratio (Odds ratio [OR]=1.41, 95% confidence interval [CI]: [1.01-1.82] p=0.02) and the use of bisphosphonates (OR=3.57, 95%CI: 1.14-10.8 p=0.02) were the strongest independent predictors of SVD. Presence of metabolic syndrome, higher HOMA index, and absence of statin therapy were independently associated with increased ApoB/ApoA-I ratio.

Conclusion: This study demonstrates a strong independent association between elevated ApoB/ApoA-I ratio and increased risk of structural degeneration of aortic bioprosthetic valves. Randomized trials are needed to determine if behavioral or pharmacological interventions aiming at the improvement of the ApoB/ApoA-I ratio (i.e. the balance of proatherogenic and antiatherogenic lipoproteins) could prevent or slow bioprosthetic valve degeneration.
vs. 109.4±17.3 ms), reduction of tricuspid annular diameter (2.82±0.13 cm vs. 2.40±0.16 cm) and improvement of tricuspid leaflet angulation. RVEF remained unchanged (66.8±6.8% vs. 66.5±6.2%).

Conclusions: Mitral valve repair benefits RV remodeling and improves the geometric and functional features of tricuspid valvular apparatus.

**P616**

Hybrid thoracoscopic surgery for AF in patients with prior failed catheter ablation or enlarged atria: benefit of electrophysiological measurements

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**Introduction:** Recently, it was reported that non-hybrid thoracoscopic pulmonary vein ablation (TPVI) is effective and safe in patients with a prior failed catheter ablation or large atria and hypertension. We hypothesize that additional perioperative epicardial electrophysiological confirmation of conduction block across all ablation lines might add to the success of TPVI in these patients. We retrospectively studied the clinical outcome of patients undergoing hybrid-TPVI with previous failed catheter ablation or large atria or hypertension.

**Methods:** Patients were included for analysis if they had 1) a failed previous catheter ablation, 2) left atrial diameter of ≥44 mm or 3) hypertension with a left atrial diameter of 40-44 mm and underwent bilateral TPVI. Ganglionated plexus were ablated and the left atrial appendage was excluded. Patients with new-onset left atrial AF received additional left atrial lesions (consisting of a superior and a trigone line). Epicardial electrophysiological measurements were performed to assess conduction block across pulmonary vein lines and linear ablation lines. Patients were followed-up with Holter monitoring every three months after the procedure for one year. Primary endpoint was freedom of any left atrial arrhythmia >30 seconds without the use of anti-arrhythmic drugs at one year follow up.

**Results:** Out of a total of 58 patients undergoing hybrid-TPVI for AF between 2008 and 2010, 27 (n=11 paroxysmal AF; n=16 non-paroxysmal AF) met the inclusion criteria (n=16 previous catheter ablation, n=11 enlarged atria >44 mm). Mean age was 58 years (range 43-77 years), 85% (23/27) were male and mean left atrial diameter was 50.0±5.8 mm (range 40-61 mm). Primary endpoint was reached by 74% (91% paroxysmal, 63% non-paroxysmal). Patients with a prior catheter ablation had a success rate of 75% and 73% in patients with an enlarged left atrium. There were 6 (22%) procedural adverse events; 2 stenotomas, 2 hemotheroma, 1 pneumothorax and 1 pneumonia.

**Conclusion:** Hybrid-TPVI is effective and safe in patients with an enlarged left atrium or a failed catheter ablation. Our data show that periprocedural electrophysiological evaluation of conduction block across all ablation lines might increase the success of TPVI in this patient population, without increasing the rate of adverse events.

**P617**

Frequency and causes of stroke during or after transcatheter aortic valve implantation

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**Purpose:** Transcatheter aortic valve implantation (TAVI) is invariably associated with the risk of clinically manifest transient or irreversible neurologic impairment. We sought to investigate the incidence and causes of clinically manifest stroke during TAVI.

**Methods:** A total of 214 consecutive patients underwent TAVI with the Medtronic-CoreValve System between November 2005 and September 2011 in our institution. Stroke was defined by the Valve Academic Research Consortium recommendations. Its cause was established by (i) analyzing the time of onset of symptoms, (ii) correlating the symptoms with computed tomography (CT) detected deficits in the brain and (iii) by analyzing the time course of potential co-existing causes of stroke in addition to a multivariate analysis to determine independent predictors.

**Results:** Stroke occurred in 19 patients (9%) and was major in 10 (5%), minor in 3 (1%) and transient (TIA) in 6 (3%). The onset of symptoms was early (<24 hours) in 8 patients (42%) and delayed (>24 hours) in 11 (58%). Brain CT scan showed a cortical infarct in 8 patients (42%), a lacunar infarct in 5 (26%), hemorrhage in 1 (5%) but no abnormalities in 5 (26%). Independent determinants of stroke were new-onset atrial fibrillation after TAVI (OR: 4.4; 95% CI: 1.2-15.6) and baseline atrial fibrillation grade II (OR: 3.2; 95% CI: 1.1-9.9).

**Conclusion:** The incidence of stroke was 9% which was more than half occurred >24 hours after the procedure. New-onset atrial fibrillation was associated with a 4.4-fold increased risk of stroke. These findings indicate that improvements in postoperative care after TAVI are equally if not more important for the reduction of periprocedural stroke than preventive measures during the procedure.

**P618**

Matched-pairs analysis of results and quality of life after total arterial multi-vessel revascularization via antero-lateral mini-thoracotomy compared to sternotomy

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**Total arterial multi-vessel coronary revascularization through a left-sided mini-thoracotomy is technically challenging and described only in few cases. This study presents the results of this new technique of off-pump myocardial revascularization. Using the matched-pairs analysis these results will be compared to those of patients with complete sternotomy for total arterial off-pump revascularization. Between September 2008 and December 2011 195 patients underwent minimally invasive total-arterial multi-vessel off-pump myocardial revascularization via left sided mini-thoracotomy (group M). For the first 142 patients of group M we found a matching patient operated via a conventional sternotomy using both internal mammary arteries (group C). Intraoperative data were similar in both groups. A SF-36 questionnaire was given to the patients on average of 9 months postoperatively.**

In the minimally-invasive revascularization group, there has been no cerebrovascular stroke, one patient died because of sudden arrhythmia. One patient had a perioperative myocardial infarction because of a graft problem and received an immediate revision of the affected anastomosis.

In the matched-pairs analysis (n=142) the ventilation time (4.3±4.1h vs. 5.9±3.5h, p=0.001) and the over-all hospital stay (9.5±2.3d vs. 11.7±5.3d, p=0.001) were significantly shorter for patients of group M. In the SF-36 survey, the patients showed a significant improvement regarding physical role functioning (p=0.002) and emotional role functioning (p=0.009). No patient reported a myocardial infarction or a cerebro-vascular stroke within the follow-up period. The minimally invasive off-pump myocardial revascularization via left mini-thoracotomy is a feasible and safe procedure. It is equivalent to conventional sternotomy. Shorter ventilation time and shorter hospital stay demonstrate a faster recovery after mini-thoracotomy. Furthermore, this minimally invasive access allows an improvement of postoperative quality of life.

**P619**

5 year follow up of 500 totally endoscopic coronary bypass operations

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**Background:** Robotic totally endoscopic coronary artery bypass grafting (TECAB) was introduced a decade ago in the field of cardiac surgery. Since then it was further developed and refined. Beating heart procedures as well as multi-vessel TECAB is now reality at dedicated centers. We overlook a ten year period of TECAB experience and we report our 5 year outcome with regard to major adverse cardiac and cerebrovascular events (MACCE).

**Methods:** Between June 2001 and June 2011, 500 patients (73% male), mean age: 60±9, mean EuroSCORE= 2.3±2.1, underwent TECAB in two institutions. Single, double, triple and quadruple TECAB was performed in 334, 150, 15 and 1 patients respectively. The majority of the patients were operated on the arrested heart (n=390, 78%).

**Results:** After a mean follow up time of 24±26 months MACCE occurred in 69 (14%) patients. The freedom from MACCE was 86%, 82%, and 80% at 1, 3, and 5 years following TECAB. Univariate analysis showed EuroSCORE (p=0.02), STS-score (p<0.001), age (p=0.034), serum creatinin (p=0.007) preoperative need of...
Right ventricular analysis by speckle tracking echocardiography in patients undergoing left ventricular assist device

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Background: Right ventricular (RV) systolic function has a critical role in determining the clinical outcome and the success of using left ventricular assist devices (LVADs), in patients with refractory heart failure. RV deformation analysis by speckle tracking echocardiography (STE) has recently allowed a deeper analysis of RV longitudinal function. The aim of the study was to evaluate right ventricular function by speckle tracking echocardiography (STE) in patients with advanced heart failure before and after LVAD implant.

Methods: Transthoracic echo-Doppler was performed in 9 patients referred for LVAD implant at baseline and with serial echocardiograms after LVAD implant (Jarvik 2000). In a subgroup of patients an additional intermediate echo evaluation, after intra-aortic balloon pump (IABP) implant, was performed. All echocardiographic images were analyzed off-line to calculate the free wall RV longitudinal strain (RVLS).

Results: All patients, except two, which presented the lowest RVLS values at baseline, showed a progressive increase of RVLS after LVAD implant. Analyzing five patients undergone to IABP as an intermediate step, it was clear that only patients that presented an increase of RVLS after IABP implant, showed progressive increase of RVLS levels after LVAD implant. Three patients, that did not experienced an increase of RVLS after IABP implant, presented a RV failure after LVAD implant.

Conclusions: This new parameter of RV myocardial deformation, RVLS, may help to predict the clinical recovery. In addition the decreased RVLS into considerable levels can predict clinical recovery leading to weaning off VA-ECMO.

Figure 1. RV strain in subgroup IABP/LVAD

Prognostic impact of dramatic alteration of mixed oxygen saturation on the氧e serum sodium recovery from veno-arterial extracorporeal membrane oxygenation

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Background: Although low mixed venous oxygen saturation (SvO2) from pulmonary artery blood indicates circulatory collapse in general, the clinical significance of SvO2 during veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has not been evaluated.

Methods & Results: We divided 30 patients treated with VA-ECMO for hemodynamic deterioration due to cardiovascular diseases into 2 groups according to having a period of SvO2 >75% during VA-ECMO (Group A; n=19) or not (Group B; n=11). While VA-ECMO was weaned off without severely-deteriorated cardiac output indicated by end-tidal CO2 (ETCO2) <10 mmHg or left ventricular ejection time (LVET) <100 msec in 10 of 11 (88%) of Group B, only 9 of 19 (47%) could show similar results in Group A (P<0.01). A dramatic decrease of SvO2 (85±12→69±7%) was observed together with an increased cardiac index (0.5±0.7→2.3±0.9 L/min/m²), ETCO2 (7.9±26.6%), and LVET (144±49→227±47 msec) whenever VA-ECMO was subsequently weaned off in survivors of Group A. On the other hand, the rest of Group A patients with sustained high SvO2 (79±12%) during the course never recovered from hemodynamic deterioration requiring VA-ECMO until death (figure).

Conclusion: Extraordinarily high SvO2 of >75% is a useful indicator for severely impaired cardiac output during VA-ECMO and reversed SvO2 to considerable levels can predict the clinical recovery. In addition the decreased SvO2 into considerable levels can predict clinical recovery leading to weaning off VA-ECMO.

Arterial vascular complications in peripheral ECMO support


Introduction: Extracorporeal membrane oxygenation (ECMO) is a life-saving technique for patients with acute refractory cardiopulmonary dysfunction. Arterial complication related to femoral cannulation remain an important concern occurring in 3.2% and 28%. We report complications and compare outcomes between the percutaneous and open approaches for femoral artery cannulation.

Patients and methods: One hundred and seven patients undergoing peripheral veno-arterial ECMO support were prospectively included. In all patients venoarterial ECMO was instituted by means of peripheral cannulation through the groin. The Seldinger's technique was used for percutaneous approach. While surgical exposure and cannulation of femoral vessels under direct visual control was employed for the open approach. Whenever possible antegrade perfusion of the ipsilateral lower limb was performed through the superficial femoral artery. Explanation of the ECMO support for both approaches was performed according to a standardized surgical procedure.

Results: ECMO support was required for cardiac arrest (34 patients, 32%), cardiogenic shock (28 patients, 27%) or following cardiac surgery (31 patients 29%). 92 cases were performed through open access (group A) and 15 percutaneously (group B). In 44 cases, a 6 Fr catheter was inserted for limb perfusion, (40 in group A and 4 in group B).

ECMO support was maintained for 7.4 days (1-40): 7.8 days (1-40) in group A and 4.9 days (1-12) in group B. Thirty-day mortality was 56% (60% in group A and 53% in group B). Vascular complications are described in the Table.

Table 1. Arterial vascular complications of venoarterial ECMO support

<table>
<thead>
<tr>
<th>Patients (n=107)</th>
<th>Group A (n=92)</th>
<th>Group B (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular comp.</td>
<td>16 (15%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Limb ischemia</td>
<td>7 (6.5%)</td>
<td>6 (6.5%)</td>
</tr>
<tr>
<td>Dissection</td>
<td>3 (2.8%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2 (1.9%)</td>
<td>0</td>
</tr>
<tr>
<td>No arterial flow</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusion: Femoral vessels cannulation for ECMO support remains a prompt approach for cardiopulmonary failure but is associated with high rate of early vascular complications. Routine distal limb perfusion catheter SvO2 to considerable levels can predict clinical recovery leading to weaning off VA-ECMOC.

Mid-term neurologic complications after off-pump coronary artery bypass grafting with and without aortic manipulation

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Objective: The aim of this study was to assess the impact of ascending aortic manipulation in off-pump coronary artery bypass grafting (OPCAB) on neurologic complications.

Patients and Method: Of 336 patients who underwent isolated OPCAB between 1998 and 2011, aorta was not touched at all in 264 patients (group A), aorta was manipulated by side-biting clamp or proximal anastomosis in 72 patients (group B). Preoperative characteristics and mid-term survival, cardiac and neurologic event were investigated.

Results: Average follow up period was 2.9±2.5 years. Postoperative neurologic complications within 1 month occurred in 1 patient in group A (0.4%) and 1
patient in group B (1.4%) (p=0.38). On univariate analysis, age was not different between group A (67.3±8.0) and group B (68.9±9.1) (p=0.15). Preoperative left ventricular ejection fraction was not different between group A (56.4±16.0%) and group B (63.6±16.0%) (p=0.51). The prevalence of triple vessel disease (group A 40.9% vs group B 61.1%; p=0.0003) and left main trunk disease (group A 30.7% vs group B 47.2%; p=0.01) was lower in group A than in group B. The number of diseased vessels (group A 2.18±0.76 vs group B 2.58±0.57; p=0.001) and the number of bypass graft (group A 2.18±0.97 vs group B 3.00±0.97; p=0.0001) was also lower in group A than in group B. The prevalence of preoperative atrial fibrillation (group A 4.2% vs group B 2.8%; p=0.74) and the incidence of new-onset postoperative atrial fibrillation (group A 34.6% vs group B 37.3%; p=0.86) were not different between groups. Survival rate, freedom from major adverse cardiac event were not different between groups (p=0.87, p=0.51, respectively in order by Log rank test). But the rate of freedom from neurological complications was significantly lower in group A (p=0.0006 by Log-rank test). Cox hazard model revealed that atrial manipulation (p=0.004, OR 6.16, 95% CI 1.9-21.6) and preoperative atrial fibrillation (p=0.001, OR 14.0, 95% CI 2.7-72.5) were the risk factors for the neurological complications.

Conclusions: Although the incidence of immediate postoperative neurological complications was different between with or without atrioventricular manipulations in OPCAB cases, mid-term neurological complications was lower in OPCAB cases without aortic manipulations.

**Conclusion:** The MYPRE -CABG strategy is a feasible, safe and efficient way for surgical coronary revascularization. Removing diseased plaques through endarterectomy and replacing diseased endothelium with arterial conduits does not increase acute risk but may favorably impact on long-term outcome.

**Methods:** We prospectively studied 383 patients undergoing CABG in a single center. Demographic and clinical data were collected preoperatively. The glomerular filtration rate (GFR) was evaluated before surgery and coronary angiography according to the MDRD-equation. We defined CKD when GFR < 60ml/min/1.73m². Patients were categorized into 3 groups (group 1: no CKD prior to surgery; group 2: CKD before coronary angiography and surgery; group 3: no CKD before coronary angiography and surgery). Multivariable Cox proportional hazard analysis was performed to determine the independent prognostic factors.

The primary outcome was long-term total mortality. The secondary outcome was composite, combining long-term death, acute coronary syndrome, stroke and coronary revascularization.

**Results:** During a median follow-up of 39±14 months, poorer prognosis was observed in groups 2 and 3 vs group 1 (figure 1). In the multivariate analysis adjusting for confounders, we found an increased risk of mortality (hazard ratio (HR) and 95% confidence interval: 3.9 [1.1-12.8]; p=0.04) in group 3 compared to group 1, but no significant risk was found in group 2 (mortality: HR 1.1 [0.5-2.4]; p=0.79).

**Conclusions:** Recent perioperative renal dysfunction occurring between coronary angiography and surgery is an independent predictor of long-term mortality.

**Conclusion:** The MYPRE -CABG strategy is a feasible, safe and efficient way for surgical coronary revascularization. Removing diseased plaques through endarterectomy and replacing diseased endothelium with arterial conduits does not increase acute risk but may favorably impact on long-term outcome.

**Methods:** Five year follow-up of on-pump versus off pump coronary artery bypass surgery in elderly patients - the MASS III trial

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**Purpose:** Advanced age is associated with increased mortality and morbidity in patients undergoing coronary artery bypass grafting (CABG), which may be a consequence of cardiopulmonary bypass. Thus, off-pump surgery may have an increased benefit in elderly patients. We aim to evaluate cardiac events and long-term outcomes in elderly patients with stable coronary artery disease and preserved left ventricular ejection fraction undergoing off-pump and on-pump CABG.

**Methods:** The MASS III was a single-center randomized trial that evaluate 308 patients with stable coronary artery disease and preserved ventricular function assigned for off-pump (n=155) or on-pump (n=153) CABG. Of this, 176 (58.3%) patients had 60 years or older at the time of randomization (of-pump=88 and
on-pump=46). Primary composite end points were death, myocardial infarction, further revascularization (surgery or angioplasty), or stroke.

Results: The two randomized groups were well-matched for baseline demographic, clinical, and angiographic characteristics. The mean age was 67.2 ± 5.9 years. After 5-year follow-up, there were no significant differences between on-pump and off-pump groups in the composite end points: 27.9% vs 21.1% (hazard ratio 1:77, 95% CI 0.87 to 1.59, p=0.29). Figure 1. Six patients (7.0%) died in the on-pump group compared with 10 (11.1%) in the off-pump group (hazard ratio 0.78, 95% CI 0.47 to 1.29; p=0.33). On-pump patients had a higher incidence of postoperative stroke or myocardial infarction: 13 (15.1%) vs 5 (5.6%); p=0.036.

Conclusions: Patients undergoing off-pump surgery had a lower incidence of in-hospital stroke or myocardial infarction. This finding did not add benefit in clinical outcomes at 5-years follow-up.

Conclusions: The EuroSCORE I overestimates mortality in octagenerians submitted to isolated CABG. The EuroSCORE II approximates to the actual mortality, but showed no higher discriminatory power for 30 days mortality in very old age patients (70+).

Purpose: The aim of this study is to evaluate the performance of the EuroSCORE and the EuroSCORE II as mortality predictor at 30 days in very old patients (VOP) that underwent isolated coronary artery bypass grafting (CABG).

Methods: Retrospective analysis from a single center of 198 patients with ≥ 80 years of age undergoing CABG between July 2003 and October 2010, mean age 83±2 years old, 62% men. The mean of EuroSCORE I was 11.4±8.9 and the mean of EuroSCORE II was 4.2±3.4. The area under the ROC curve (AUC), or - statistics-C, was used as a measure of the discriminatory power of both scores for predicting mortality to 30 days and the test used to adjust the model was the Hosmer-Lemeshow. It has been calculated through their ROC curves the best cut-off for each respective score.

Results: Of 198 patients 95% have a full follow-up time of 30 days. During this period there were 8 (4%) deaths, of which 6 (3%) have been in-hospital. The EuroSCORE I is not a good predictor of mortality at 30 days (AUC: 0.65; 0.58-0.72; p=0.16; Hosmer-Lemeshow: p=0.787); the EuroSCORE II showed reasonable discriminatory power (AUC: 0.71; 0.63-0.77; p=0.05; Hosmer-Lemeshow: p=0.331), although when compared to the EuroSCORE I I haven’t shown superiority (AUC: 0.05; 0.08-0.19; p=0.423). Both scores had high negative predictive values (97%), with the best cut-off in this population of 16.6% and 9.0% for the EuroSCORE I and II, respectively.

Evaluation of the EUROSCORE II as predictor of 30 days mortality in very old age patients (≥ 80) submitted to isolated coronary artery bypass grafting


Utility of combined administration of magnesium sulfate and corticosteroids in prevention of postoperative complications and outcomes in patients undergoing coronary surgery

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Background: Cardiac surgery and cardiopulmonary bypass (CPB) induce an acute inflammatory response contributing to postoperative morbidity and complications including myocardial dysfunction, atrial fibrillation, acute lung injury and postoperative bleeding.

Objectives: The objective of this study is to evaluate the impact of a three-day hydrocortisone hemisuccinate (HCHS) and magnesium sulfate (MS) administration on the occurrence of postoperative complications in coronary surgery with CPB.

Materials and Methods: This is a retrospective study that involved 129 patients who underwent coronary surgery with CPB. The patients were divided into 2 groups: Group 1 (G1=64 patients) comprising those who didn’t receive the study protocol and group 2 (G2=65patients) consisted of patients in whom we performed a combined administration of MS and HCHS. The anesthesiology protocol and CPB were the same for all patients in both groups.

Results: There were no differences between the two groups in terms of demographics features and preoperative treatment. The length of mechanical ventilation was higher in G1 (p=0.02). Both the 2 groups were similar concerning the incidence of postoperative bleeding. The incidence of postoperative atrial fibrillation (AF) was significantly higher in G1 (23% vs 6%, p=0.006). SIRS and severe SIRS were significantly more frequent in G1 (respectively 62% vs 35% and 32% vs 16%). CRP levels were also higher in G1 in comparison with G2 (201.33±74.08 vs 142.47±52.57; p=0.002). Duration of intensive care unit stay (ICU) was significantly longer in G1 (7.57±3.54 vs 5.73±2.8, p=0.025). Finally, the overall postoperative mortality was higher in G1: (7 cases vs 3, p<0.05).

Conclusion: Prevention of postoperative complications by combined administration of magnesium sulfate and corticosteroids decreased the incidence of FA, SIRS, the duration of ICU stay and the postoperative mortality.

P631 Long-term outcomes in 714 subjects after endoscopic aorto-coronary artery bypass grafting (EACAB): single-centre registry data

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Purpose: The assessment of long-term outcomes in consecutive patients who underwent EACAB over a 12-year period.

Methods: The study included 714 patients, 581 males (81.4%), aged 57.9±9.7 years who underwent EACAB from Apr 1998 till Dec 2009. A prospective registry analysis was performed to estimate the incidence of major adverse events and cardiac-cerebrovascular events (MACCE), including all-cause death, myocardial infarction, stroke or TIA, and the need of repeated coronary revascularization (with assessment whether it was related to a target vessel, LAD, or not). Risk factors of MACCE incidence were estimated on the basis of demographics and clinical data.

Results: The time of observation was 2122±1313 days (median = 1918.5, maximal = 4661 days). The MACCE occurrence was 10.8% (77 patients), with the need of revascularization as the most frequent complication (50 patients, 7%); the second was death (19subjects, 2.7%), then myocardial infarction (17 cases, 2.4%), and the less frequent was stroke/TIA (7 patients, 1%). None of the subjects required CABG. Cardiac death concerned 10/19 persons (52.6%). PCI for myocardial infarction was performed in 10/17 patients (58.8%). Target vessel PCI was done in 19/50 cases (38%), including two patients with myocardial infarction. On the basis of cumulative survival analysis it was revealed that subjects after EACAB had survival ratio of 96.1% in a long-term follow-up. Event-free survival (MACCE-free) was 85.3%. Myocardial-infarction-free survival was 96.9%. PCI-free survival was 90.5%. Stroke/TIA-free survival was 96.2%. Older age (> 57 y), ejection fraction <50%, previous PCI and NYHA class II (vs I) were risk factors for both death and the overall MACCE incidence in a follow-up (p<0.05).

Conclusions: EACAB ensures good long-term therapeutic results in stable high survival, and MACCE-free survival. The most frequent complication in a long-term observation is a need of repeated PCI. The variables which shortsens survival and MACCE-free survival are: older age, lower ejection fraction, previous PCI and moderate heart failure by NYHA class.

P632 Evolution of ventricular function in patients with stable coronary artery disease submitted to on-pump or off-pump coronary artery bypass graft in MASS III trial

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Purpose: Ventricular function is a major determinant of prognosis in patients with coronary artery disease (CAD). Few data are available to assess the evolution of ventricular function among patients submitted to off-pump coronary artery bypass graft surgery (OPCAB). To compare the evolution of ventricular function in a long-term follow-up among patients with stable CAD submitted to OPCAB or On-Pump coronary artery bypass graft (ONCAB).

Methods: Patients with stable CAD and preserved systolic left ventricular function were randomized to OPCAB or ONCAB and followed for 5 years. Patients who underwent a new evaluation of ventricular function in this follow-up were studied. Left ventricle ejection fraction (LVEF) was assessed by echocardiogram.

Results: Of 308 patients randomized to OPCAB (n=155) or ONCAB (n=153), 91 had a new assessment of ventricular function by echocardiogram in a 5-year follow-up: 49 in OPCAB group and 42 in ONCAB group. In ONCAB group the initial and final mean of LVEF was respectively 59.85% and 56.16% (p<0.10). In OPCAB group the initial and final mean of LVEF was respectively 59.18% and 56.07% (p<0.17).
Conclusion: There was no difference in the evolution of LVEF among patients with stable CAD randomized to ONCAB or OPCAB in a 5-year follow-up.

Conclusions: Thirty-day event rates after cardiac surgery may be influenced by “competing risks” in which lower 30-day mortality rates at individual hospitals may confer higher probability of subsequent readmission. There may be key differences between the diagnostic prognostic indicators that predict early post-discharge mortality and readmission.

Conclusions: The observed 30-day mortality rate of 2.6% was substantially lower than the expected rate of 5.9%, while the observed 30-day readmission rate of 12.2% was included in the study. The mean age was 57 ± 8 years. One hundred and one pts were alive by the time of the study (86.3%) and 81 pts (80.2%) were free of major cardiac events. The CAR patency was evaluated either by coronary angiography (64 pts) or by coronary computed tomography (25 pts). Eight asymptomatic pts refused these procedures and 4 with metastatic cancer were not assessed. At 10 years, patency rate of the CAR was 94% (84/89). In case of associated LAD endarterectomy, the patency rate was 92% (12/13). CAR is a worthwhile technique with good patency rate at 10 years. Exclusion of plaques or endarterectomized wall in case of diffuse disease seems beneficial for these extensive critical coronary lesions.

Conclusions: For off-pump diabetic patients presented the same incidence of composite endpoints compared with on-pump CABG. Few data are available on the effects of off-pump coronary artery bypass graft surgery (OPCAB) on cardiac events and long-term clinical outcomes in this population.

Conclusions: In this analysis, off-pump diabetic patients were presented the same incidence of composite endpoints compared with on-pump CABG.

Conclusions: Mean follow-up was 118±11 months. One hundred and one pts were alive by the time of the study (86.3%) and 81 pts (80.2%) were free of major cardiac events. The CAR patency was evaluated either by coronary angiography (64 pts) or by coronary computed tomography (25 pts). Eight asymptomatic pts refused these procedures and 4 with metastatic cancer were not assessed. At 10 years, patency rate of the CAR was 94% (84/89). In case of associated LAD endarterectomy, the patency rate was 92% (12/13). CAR is a worthwhile technique with good patency rate at 10 years. Exclusion of plaques or endarterectomized wall in case of diffuse disease seems beneficial for these extensive critical coronary lesions.

Conclusions: The two randomized groups were well-matched for major baseline demographic, clinical, and angiographic characteristics. After 5-year follow-up, the primary composite end point was not different between groups (event-free survival 83.7% vs 93.7%, p = 0.15).

Conclusions: For off-pump diabetic patients presented the same incidence of composite endpoints compared with on-pump CABG.

Conclusions: The observed 30-day mortality rate of 2.6% was substantially lower than the expected rate of 5.9%, while the observed 30-day readmission rate of 12.2% was included in the study. The mean age was 57 ± 8 years. One hundred and one pts were alive by the time of the study (86.3%) and 81 pts (80.2%) were free of major cardiac events. The CAR patency was evaluated either by coronary angiography (64 pts) or by coronary computed tomography (25 pts). Eight asymptomatic pts refused these procedures and 4 with metastatic cancer were not assessed. At 10 years, patency rate of the CAR was 94% (84/89). In case of associated LAD endarterectomy, the patency rate was 92% (12/13). CAR is a worthwhile technique with good patency rate at 10 years. Exclusion of plaques or endarterectomized wall in case of diffuse disease seems beneficial for these extensive critical coronary lesions.
Background: Modern coronary stents include design features that provide greater flexibility to improve deliverability in complex lesions. The platinum-chromium everolimus-eluting stent (Promus Element) has implemented these requirements consistently in a unique scaffold design. Recently, inadvertent longitudinal stent compression during percutaneous coronary intervention (PCI) was noted with this platform. (Figure A: angiography; B: OCT). Aim of this study was to evaluate frequency of longitudinal stent compression during PCI, and define patient and lesion related predictors for this complication.

Methods: All coronary cases treated with an Element stent from January 1, 2010 to October 31, 2011 were analyzed for documented longitudinal stent compression. We compared baseline characteristics and periprocedural data between patients with and without longitudinal stent compression and assessed predictors for this event by multiple logistic regression models.

Results: During 22 months 2,936 Promus Element stents were placed in 1,295 patients and 1,392 PCI cases with 2,839 atherosclerotic lesions. Mean age was 67±11 years, 21.9% were women. Longitudinal compression was reported in 20 patients (1.44%), 20 lesions (0.70%), and 0.68% of all stents. Significant differences were found for number of stents (per case: \( p < 0.001 \); per lesion: \( p = 0.024 \)), total stent length (\( p = 0.003 \)), ostial segment (\( p < 0.001 \)), and vessel angulation (\( p = 0.002 \)). Ostial segments, number of stents, and the presence of a bifurcation were the only significant predictors (odds ratio [95% CI]: 8.33 [3.30 to 21.28], 1.57 [1.01 to 2.45], 0.57 [0.36 to 0.93], respectively).

Conclusion: Longitudinal compression of the Element stent is a rare complication and occurs more frequently in ostial or bifurcation lesions and with multiple stents.

Long term prognostic value of high-sensitivity troponin I after elective percutaneous coronary interventions


Background: High-sensitivity cardiac troponin (hs-cTnI) assays could improve the detection of myocardial damage after percutaneous coronary intervention (PCI) and the prediction of subsequent adverse events. Aim of our study was to evaluate the prognostic value of hs-cTnI measured after successful PCI.

Methods: 931 consecutive patients with normal baseline cTnI levels (upper reference limit, URL = 0.04 ng/mL) underwent elective and angiographically successful PCI in our Institution. In this population we evaluated the correlation between hs-cTnI levels 24 hours after PCI and major adverse coronary events at a median follow-up of 3.0 years.

Results: Postprocedural hs-cTnI levels above the URL were common (68.9% of the study population) and met the definition of type 4a myocardial infarction (MI) in 51.9% of patients. Abnormal cTnI levels, even in the range of type 4a MI, were associated with severe coronary atherosclerosis and complex interventions, but failed to predict subsequent cardiac mortality or MI. At univariate analysis only higher levels of hs-cTnI (10 times the URL) were associated with an increased risk of cardiac death (HR 2.16, 95% CI 1.07 to 5.17; \( p = 0.03 \)) and target vessel failure (HR 1.56, 95% CI 1.02 to 2.42; \( p = 0.02 \)). After adjustment for concomitant risk factors hs-cTnI levels above 10 times the URL were independent predictors of target vessel failure only.

Conclusions: In a large single-centre population elective PCI patients, hs-cTnI elevation was common and was associated with more complex interventions. However elevated cTnI levels failed to predict long term mortality and MI occurrence.
Methods: Consecutive patients with STEMI undergoing primary PCI in a single tertiary cardiac center were enrolled. No-reflow was defined by means of angiography as the presence of myocardial blush grade 0 or 1 at the end of primary PCI. The SYNTAX score was calculated by 2 independent cardiologists who were blinded to no-reflow assessment. A multiple logistic regression analysis, with the calculation of odds ratios (OR) with 95% confidence intervals (CI), was performed, entering SYNTAX score either as continuous variable or as dichotomous variable (i.e. SYNTAX score ≥ 32) in addition to sex, age, main cardiovascular risk factors and known predictors of no-reflow such as anterior myocardial infarction, time from symptom onset, infarct size, admission stent thrombosis, thrombectomy use. A two-tailed p-value < 0.05 was considered statistically significant.

Results: A total of 371 patients, median age 65.3 yrs-old (54.8-73.7, 25th-75th percentile), 266 (72.2%) males, were enrolled. Baseline median value of SYNTAX score was 16 (9.5-23.5, 25th-75th percentile). Patients with no-reflow presented significantly higher values of SYNTAX score as compared to those without no-reflow (18.7 median (10-26.5, 25th-75th percentile) vs. 14 (9-21.5), p=0.017). The incidence of no-reflow was significantly higher in patients with SYNTAX score ≥ 32 than in patients with SYNTAX score < 32 (13.9% vs. 5.1%, p=0.003). At multiple logistic regression analysis, SYNTAX score as continuous variable (OR 1.03, 95% CI 1.003-1.05, p=0.025) or SYNTAX score >32 (OR 2.74, 95% CI 1.23-6.12, p=0.014) was an independent predictor of no-reflow.

Conclusions: In patients with STEMI undergoing primary PCI, high SYNTAX scores are an independent predictor of no-reflow.

Conclusions: Even a small increase in CK-MB levels after PCI is associated with significantly higher risk of late mortality. Efforts to routinely monitor periprocedural CK-MB level may help to improve the long-term clinical outcomes following PCI.
patients with CIN were associated with higher mean serum troponin (1.22 vs 0.86, p=0.007) and mean hospital stay duration (5.36 vs 4.44, p=0.026). Patients who developed CIN had an elevation in urine NGAL as early as 2 hours after PCI, compared to those who did not develop CIN (see graph).

Conclusions: NGAL may be a useful tool in a multi-ethnic Asian population to facilitate earlier diagnosis of CIN. Larger population studies are needed to validate the cut-off values and clinical benefits of NGAL for earlier diagnosis of CIN.

ST peak during primary percutaneous coronary intervention predicts final infarct size, left ventricular function and clinical outcome

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Purpose: One third of patients treated with primary PCI develop an secondary increase in electrocardiographic ST-segment elevation (ST peak) during reperfusion. The prognostic importance of ST peak remains unknown and the association with final infarct size is not fully elucidated. Thus the purpose of this study is to determine the association between a ST peak, and final infarct size and clinical outcome in patients treated with primary percutaneous coronary intervention (PCI).

Methods: Continuous ST monitoring was performed in 363 STEMI patients from arrival at the PCI centre until 90 minutes after revascularisation. Patients were stratified according to no-ST peak or ST peak. Final infarct size and ejection fraction was assessed by cardiovascular magnetic resonance. All-cause mortality, cardiac mortality and cardiac event rate (cardiac death and admission for heart failure) were examined. Results: Patients with ST peak had larger final infarct size (14% vs. 10%; p=0.003) and a lower ejection fraction (53% vs. 57%; p=0.022). At follow-up after median 913 days no difference in all-cause mortality was observed (8% vs. 5%; p=0.46), whereas cardiac mortality (8% vs. 3%; p=0.047) and cardiac event rate (19% vs. 10%; p=0.018) were both higher among patients with ST peak. In a multivariable Cox regression analysis, including ST resolution and ejection fraction, ST peak during primary PCI remained significantly associated with cardiac events (adjusted hazard ratio 2.03 (1.08-3.82)).

Conclusions: ST peak occurring during PCI is related to larger final infarct size, a reduced left ventricular ejection fraction, and adverse clinical outcome.

Predictors of persistent renal dysfunction after acute kidney injury in percutaneous coronary intervention

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Backgrounds: Percutaneous coronary intervention (PCI) is often complicated by acute kidney injury (AKI) and resulting in permanent renal dysfunction or restoration of normal renal function. However factors associated with clinical course of AKI are not well known. The aim of the present study is to investigate factors which predict the clinical course of AKI whether to transient kidney injury or permanent renal dysfunction.

Methods: From January 2004 to December 2009. 7382 patients without history of end stage renal disease or kidney transplantation were selected from COACT (CathOlic medical center percutaneous Coronary intervention) registry. Mean follow up period was 26 months. 474 patients diagnosed with acute kidney injury after PCI were selected and stratified into two categories; AKI with transient renal dysfunction within 2 weeks (transient AKI), and AKI leading to persistent renal dysfunction (persistent kidney injury). The definition of AKI is according to the Acute Kidney Injury Network criteria. After comparison of baseline characteristics, logistic regression analysis was performed to evaluate factors predicting either transient AKI or persistent kidney injury.

Results: From 2004 to 2009, 7382 patients entered the clinical database. Relative risk for vascular complications was calculated and univariate analysis was performed in subgroups (“PCI”, “Diagnostic” and “All patients” by age group). The complication rate for patients ≥80 years and to look for potential predictors of access site complications. The complication rate for patients ≥80 years was 3.2%, for patients aged 65-79 1.9%, and for individuals younger than 65 years 1.2%.

Conclusions: Proteinuria and eGFR < 60 mg/dl is significant predictors of persistent renal dysfunction after PCI.

Remote ischemic pre-conditioning attenuates the contrast-induced kidney injury in patients with moderate chronic kidney disease

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Background: Contrast-induced acute kidney injury (CI-AKI) is a common complication associated with coronary angiography and percutaneous coronary intervention. Although the most effective prevention strategy for CI-AKI is hydration, the effectiveness is not sufficient. Recent studies have shown that remote ischemic preconditioning (RIPC) can preserve kidney function in patients undergoing cardiovascular surgery. However, the impact of RIPC on CI-AKI remains unknown. This study was designed to test the hypothesis that RIPC can attenuate CI-AKI in patients with moderate chronic kidney disease.

Methods and Results: Fifty-two patients undergoing elective angiographic procedures with moderate chronic kidney disease (an estimated glomerular filtration rate from 30 to 60 ml/min/1.73 m²) were randomly assigned to the RIPC group (n=26) or the control group (n=26). The baseline characteristics of the two groups were similar. RIPC consisted of intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff on the innominate arm site 3 days before PCI. From January 2004 to December 2009, 7382 patients without history of end stage renal disease or kidney transplantation were selected from COACT (CathOlic medical center percutaneous Coronary intervention) registry. Mean follow up period was 26 months. 474 patients diagnosed with acute kidney injury after PCI were selected and stratified into two categories; AKI with transient re-sarcotin (mCRP), pentraxin-3, derivatives of reactive oxidative metabolites (D-ROMs) and asymmetric dimethylarginine (ADMA) were measured before and 24h, 48h after angiography. Although L-FABP-based CI-AKI was developed in 7 patients of the control group (26.9%), there were 2 patient with CI-AKI in the RIPC group (7.7%). At 24h increase of L-FABP levels in the control group was significantly larger than that of the RIPC group (7.1±8.7 vs. 3.1±5.6 μg/l Cr, P=0.05), suggesting that RIPC attenuates CI-AKI. To explore the mechanism for suppressed L-FABP levels in RIPC group, contributing factors of CI-AKI were analyzed. Neither hsCRP nor pentraxin-3 was significant between two groups. However, the change of serum ADMA level was significantly higher in the RIPC group than in the control group (40.6%±15.0 vs. 10.8%±12.7%, P=0.04), and DROMs levels were tendency to be lower in the RIPC group compared with the control group (P=0.06).

Conclusions: Our results suggest that RIPC attenuates the L-FABP-based CI-AKI in patients undergoing angiographic procedures. This beneficial effect might be mediated by decreasing ADMA level.

Vascular femoral complications of percutaneous coronary intervention (PCI) and diagnostic catheterization in octogenarians: How high is the risk?

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Objectives: As consequence of the demographic change in Western countries, invasive coronary catheterization procedures are increasingly performed in patients above the age of 80 years. At the moment, decisions for invasive versus conservative treatment in octogenarians are based on limited clinical data in this age group. The true rate of vascular complications of catheterization procedures in different age groups is currently unknown. Aim of this study was therefore to investigate the femoral vascular complication rates in patients >65 years, between 65 and 79 years, and in patients ≤80 years and to look for potential predictors of complications.

Methods: 42,628 diagnostic and interventional catheterization procedures in a high-volume center from 2005-2009 were entered in this prospective registry study. Relative risk for vascular complications was calculated and univariate analysis was performed in subgroups (“PCI”, “Diagnostic” and “All patients” by age group). The complication rate for patients ≥80 years and to look for potential predictors of access site complications. The complication rate for patients ≥80 years was 3.3%, for patients aged 65-79 1.9%, and for individuals younger than 65 years 1.2%.

Conclusions: Proteinuria and eGFR < 60 mg/dl is significant predictors of persistent renal dysfunction after PCI.

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Multivariate regression analysis: factor

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Conclusion: Proteinuria and eGFR < 60 mg/dl is significant predictors of persistent renal dysfunction after PCI.
such as preexistent antithrombotic/antiaggregation therapy and renal insufficiency may help to further optimize access management.

Clinical outcomes of unprotected left main PCI and correlation with the type of adjunctive antithrombotic therapy: a pooled analysis from REPLACE-2, ACUITY and HORIZONS-AMI trials


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Background: Recent data suggest that stenting of the unprotected left main coronary artery (ULMCA) may be an acceptable alternative to bypass surgery. PCI-related risk is increased among patients with ULMCA primarily due to extensive co-morbidity. The aim of this study was to evaluate the impact of randomized antithrombotic therapy on net clinical outcome after stenting of the ULMCA.

Methods: This is an analysis of 177 patients with ULMCA from a pooled dataset of 14,326 patients treated with aspirin and clopidogrel who underwent PCI in 3 large randomized trials comparing treatment with heparin plus a glycoprotein IIb/IIIa inhibitor (GP IIb/IIIa) or bivalirudin alone, including the REPLACE-2 (Randomized Evaluation of PCI Linking Angiography to Reduced Clinical Events), ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) and HORIZONS-AMI (Harmonizing Outcome With Revascularization and Stents in Acute Myocardial Infarction) trials. 30-day clinical outcomes were evaluated.

Results: Patients with ULMCA represented a higher risk cohort. Overall net adverse clinical outcomes and non-CABG major bleeding occurred more frequently in patients undergoing PCI of ULMCA compared to the overall study population patients (NACE: 19.8 vs. 10.6, p=0.001; Major Bleeding: 9.6% versus 4.6, p=0.001). In the ULMCA group, bivalirudin was associated with significantly less non-CABG major bleeding compared to heparin plus GP IIb/IIIa (4.5% versus 14.6%, RR 0.3, 95% CI 0.2-0.6, p=0.003). The composite ischemic endpoint death, MI, TVR at 30 days was similar in both treatment groups (11.4 vs. 12.4, respectively, RR 0.9, 95% CI 0.5-1.7, p=0.513) resulting in a net adverse clinical benefit for bivalirudin over heparin + GP IIb/IIIa (14.8% vs. 24.7%; RR 0.53, p=0.039).

Conclusions: Among patients undergoing either elective or urgent PCI of ULMCA, bivalirudin was associated with significantly reduced incidence of major bleeding, similar rates of ischemic events and improved net clinical outcome. Bivalirudin may be the preferred anticoagulation strategy in this high-risk group of PCI patients exhibiting a high risk for both thrombotic and bleeding events.

Clinical outcomes of unprotected left main PCI and correlation with the type of adjunctive antithrombotic therapy: a pooled analysis from REPLACE-2, ACUITY and HORIZONS-AMI trials

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Objectives: This study evaluated the predictive value of hyperuricemia for risk of CI-AKI in patients with relatively normal serum creatinine (SCr) who were undergoing PCI.

Methods and Results: A total of 788 patients with relatively normal baseline SCr (≤1.5 mg/dl) undergoing PCI were prospectively enrolled and divided into two groups (hyperuricemic group, n = 211, and normouricemic group, n = 577). CI-AKI occurred in 17 (8.1%) of the hyperuricemic group and 8 (1.4%) of the normouricemic group (P = 0.001). In-hospital mortality (2.4% vs. 0.3%, P = 0.007) and the cumulative 1-year mortality (P = 0.007) were higher in the hyperuricemic group.

Multivariate analysis, adjusting for potential confounding factors, resulted in an odds ratio for CI-AKI in the hyperuricemic group, as compared with the normouricemic group, of 5.3 (95% confidence interval, 1.99-14.58, P = 0.001).

Conclusion: Hyperuricemia was significantly associated with the risk of CI-AKI in patients with relatively normal SCr after PCI. This needs further prospective trials aimed at examining the effect of uric-acid-lowering therapies for prevention of CI-AKI.

Long term prognosis of contrast induced nephropathy: a prospective study with 3 years follow-up

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Purpose: The increased incidence of long-term adverse events (AE) after CI-AKI is derived from retrospective analyses of large databases and observational studies of patients. The aim of the present study was to prospectively evaluate, at short and long-term follow-up, the incidence, the predictors of CI and the occurrence of CI-related AE, in a population at risk for acute kidney injury undergoing coronary angiography.

Methods: 216 patients at risk for CI, were included in the study and completed all the in-hospital observation mandated by the protocol, including determinations of serum creatinine (SCr) and glomerular filtration rate (GFR), at 12, 24 and 48 hours after exposure to contrast media. CI was defined as an acute impairment of renal function, expressed as a relative increase in SC concentration of at least 25% within 48 hours after exposure to contrast media.

Results: A total of 788 patients at risk for CI-AKI, were included in the study and completed all the in-hospital observation mandated by the protocol, including determinations of serum creatinine (SCr) and glomerular filtration rate (GFR), at 12, 24 and 48 hours after exposure to contrast media. CI was defined as an acute impairment of renal function, expressed as a relative increase in SC concentration of at least 25% within 48 hours after exposure to contrast media.

Conclusions: Our findings do no support a direct correlation between in-hospital development of CI and long-term incidence of AE. The study shows a significant relationship between any in-hospital reduction of GFR and the occurrence of AE at long-term, independently of the occurrence of CI as conventionally defined.

Clinical predictors of contrast-induced nephropathy in the patients undergoing emergent versus elective percutaneous coronary interventions

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Purpose: The aim of this study was to evaluate an incidence and clinical predictors of contrast-induced nephropathy (CIN) in the patients undergoing emergent percutaneous coronary intervention (PCI) who had ST-elevated myocardial infarction (STEMI) and unstable angina pectoris/non-STEMI (UAP/NSTEMI), and elective PCI who had stable AP.

Methods: We enrolled 1309 stable AP (70.3±9.7 year-old, 77%male), 343 UAP/NSTEMI (69.3±11.9 year-old, 77%male) and 62 CIN-related AE, in a population at risk for acute kidney injury undergoing percutaneous coronary intervention.

Results: Incidence of CIN was gradually increased among three groups (stable AP vs. UAP/NSTEMI vs. STEMI, 4.2%, 10.8%, 16.9%, p<0.05) (Figure 1). Among emergent CV/GFR subgroups, incidence of CIN was also gradually increased among three groups (Figure 2). Multivariate logistic regression analysis showed that the significant predictors of CI were emergent PCI (OR 2.19, 95%CI 1.82-2.62, p<0.001), low ejection fraction (EF<40%, OR 2.29, 95%CI 1.43-3.68, p<0.001), low Hb (Hb<10g/dl OR 2.06, 95%CI 1.50-2.80, p<0.001) after adjusting for multiple confounders. The risk of CI was significantly associated with increasing CV/GFR in stable AP group (p<0.05), but not associated in UAP/NSTEMI and STEMI groups.

Table 1. Multivariate analysis associating CI-AKI risk indicators

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperuricemia</td>
<td>5.38</td>
<td>1.99-15.58</td>
<td>0.007</td>
</tr>
<tr>
<td>Gendar (female)</td>
<td>0.96</td>
<td>0.33-2.81</td>
<td>0.942</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>0.55</td>
<td>1.51-10.42</td>
<td>0.027</td>
</tr>
<tr>
<td>CCI&lt;40 min</td>
<td>0.21</td>
<td>0.15-1.59</td>
<td>0.207</td>
</tr>
<tr>
<td>Multivessel coronary disease</td>
<td>1.10</td>
<td>0.34-3.54</td>
<td>0.875</td>
</tr>
<tr>
<td>Emergent PCI</td>
<td>3.66</td>
<td>1.43-9.55</td>
<td>0.008</td>
</tr>
<tr>
<td>LVEF &lt; 40%</td>
<td>1.86</td>
<td>0.50-6.87</td>
<td>0.550</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.89</td>
<td>0.64-5.59</td>
<td>0.352</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.61</td>
<td>1.08-2.02</td>
<td>0.416</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>0.34</td>
<td>1.00-12.02</td>
<td>0.054</td>
</tr>
<tr>
<td>IABP</td>
<td>7.29</td>
<td>2.09-23.15</td>
<td>0.001</td>
</tr>
<tr>
<td>Exceeding MCD</td>
<td>1.84</td>
<td>0.31-11.10</td>
<td>0.550</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.16</td>
<td>0.36-3.72</td>
<td>0.800</td>
</tr>
<tr>
<td>Diuretic usage</td>
<td>4.87</td>
<td>1.87-12.69</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Risk factors for the development of coronary stent thrombosis

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Purpose: Despite major advances in coronary stent technology, stent thrombosis (ST) remains the “achilles heel” of percutaneous coronary intervention, with an incidence of 0.5-4% and a mortality rate of 20-40%. Although there are many patient, procedural and lesion-related predictors for ST, there are no risk-scoring systems to guide the use of newer, more potent antplatelet agents. Therefore, the existing literature was reviewed to develop this.

Methods: Bibliographic databases including MEDLINE, EMBASE, the cochrane databases, database of abstracts of reviews of effects and the health technology assessment database were searched from 1990 to 2010 to identify relevant studies. Studies were included if they had at least 1000 participants or at least 50 cases and if they estimated the effects of risk factors using multivariate analyses. A total of 24 studies with risk factors for early ST (<30days) and 14 studies with risk factors for late ST (30 days to 1 year) were used. Data were pooled according to reporting of similar risk factors between each study.

Results: The risk factors identified to predict early stent thrombosis with pooled OR/HR (95% confidence intervals in brackets) were acute MI at presentation, 13.1 (9.5-18.2), STEMI at presentation, 4.2 (3.0-6.0), bifurcation lesion, 2.7 (2.0-3.6), thrombus at baseline, 2.5 (1.5-4.1), ACS at presentation, 2.4 (1.9-3.0), previous CHF or CHF at presentation, 2.2 (1.4-3.5), renal insufficiency, 2.1 (1.1-1.2), diabetes mellitus, 2.1 (1.7-2.5) and current smoking, 1.48 (1.18-1.86).

For late stent thrombosis, the risk factors identified with pooled OR/HR were renal insufficiency, 5.4 (2.4-12.2), premature antplatelet discontinuation, 5.3 (3.2-8.6), bifurcation lesion, 3.9 (2.1-7.4), diabetes mellitus, 2.7 (2.0-4.0) and age, 0.97 (0.95-0.99).

For data for very late ST (>1 year) were sparse.

Conclusions: There are many risk factors for ST with a clinical need to develop an individualised risk scoring system to aid decision making with regards to antiplatelet regimens. A delphi RAND process has been devised to elicit expert opinion on ST risk factors. This involves sending a questionnaire to several experts requesting their views on the impact of each individual risk factor on the development of early, late and very late ST. Bayesian methods will then be used to combine this with the results of the literature review to develop a weighted scoring system to predict ST according to the odds ratio for each risk factor. This will be available to present early this year.

Effect of iv or oral N-acetylcyesteine in the prevention of contrast-induced nephropathy in patients with moderate to severe renal insufficiency

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Background: The effect of N-acetylcyesteine (NAC) to prevent contrast-induced nephropathy (CIN) in patients with moderate to severe renal insufficiency undergoing intravascular interventions remains questionable.

Methods: This study is a single center, prospective clinical trial. We studied 251 patients undergoing elective intra-arterial procedure with estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m² calculated by MDRD formulae. Patients were randomly assigned 1 of 3 prophylactic regimens: infusion of 0.9% saline (1 cc/kg/hr) for 12 hours before and 12 hours after the procedure (group 1), or NAC orally (1200 mg) every 12 hours for 24 hr prior and 48 hr after the procedure plus saline (group 2), or NAC IV for 1 hr (2400 mg) prior and 6 hr (4800 mg) after the procedure plus saline (group 3). Contrast-induced nephropathy was defined as an increase in serum creatinine level ≤25% or 0.5 mg/dl after 48 hours.

Results: There were no significant differences among groups regarding baseline demographic properties except mean volume of contrast agent administered which was lower in group 3 (table). Prevalence of CIN was 7.2% in group 1, 12.2% in group 2 and 10.7% in group 3, which was statistically insignificant (p < 0.5).

Conclusions: STEMI patients undergoing PCI regardless of CIV/GFRI were at high risk for CIN. Minimizing contrast dose on the basis e-GFR might be valuable in reducing the risk of CIN in stable AP group.

High incidence of radial artery occlusions in transradial coronary catheterization on ongoing oral anticoagulation: Is an additional heparin bolus warranted?

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Purpose: In patients with uninterrupted oral anticoagulation the radial artery approach has been advocated as the optimal strategy for arterial access during cardiac catheterization. However, it remains unclear if patients under full oral anticoagulation (INR 2.0 - 3.0) who do not receive additional heparin treatment during the catheterization procedure are at an increased risk for radial artery occlusion (RAO). Aim of our study was therefore to investigate the incidence of access-site complications (radial artery occlusion (RAO), av-fistula, pseudoaneurysm, major bleeding) with high-resolution vascular ultrasound after transradial cardiac catheterization.

Methods: Between 11/2010 - 01/2011 a total of 33 consecutive patients aged 72.4±8.7 years (66.7% male) with ongoing oral anticoagulation were prospectively enrolled in the registry. The procedure was performed using 5 F sheaths in 29 patients (87.9%) and 6 F sheaths in 4 patients. Duplex ultrasound was obtained in each patient before discharge. Patients undergoing diagnostic catheterization only did not receive heparin during the procedure, whereas in patients undergoing PCI an additional bolus of 5000 IE of unfractionated heparin was given intravenously.

Results: A total of 30 patients underwent diagnostic catheterization and in 3 patients a PCI was performed. 4 patients presented in the setting of acute coronary syndromes. The mean international normalized ratio was 2.3±0.5 (min. 1.7, max. 3.6). The incidence of RAO in Duplex sonography was 33.3% (11 patients), all of which received a diagnostic coronary catheterization. Interestingly, RAO was only seen in patients who underwent diagnostic angiography using 5 F sheaths. No patient presented with a critical limb ischemia. There was no evidence of av-fistulas or pseudoaneurysms. We did not see any case of major bleeding requiring transfusion therapy. Procedural success was achieved in 97%, one patients required cross-over to femoral access because of vascular spasm.

Conclusion: The transradial approach for coronary angiography proved to be safe with regard to bleeding complications in patients with ongoing oral anticoagulation. However, the incidence of radial artery occlusion was higher than expected from our prospective radial access registry data in non-coagulated patients. This pilot study therefore raises the question whether an additional heparin bolus needs to be administered in patients undergoing trans-radial coronary angiography on full oral anticoagulation. This question will be addressed in a prospective randomized trial shortly.

Effect of Angiotensin Receptor Blockers on long term aortic events in medically treated patients with type B acute aortic dissection

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Background: Although antihypertensive therapy is the standard of care for type B aortic dissection in both acute and chronic phases, the mortality of patients with type B aortic dissection treated with medication in the chronic phase remains
high. This retrospective case-control study aimed to explore the effect of angiotensin receptor blockers (ARBs) on the outcomes of medically treated patients with type B aortic dissection treated with medication in the chronic phase.

Methods: A total of 87 patients with type B AD were enrolled; mean age was 65.3±12.0 years and the mean follow-up period was 19.5±17.7 months. All patients received anti-hypertensive therapy according to the guideline for standard care of acute aortic dissection, and were followed up by a physician’s examination and enhanced computed tomography. Unfavorable outcome in the chronic phase was defined as death, surgical repair, or progression of dissecting aorta.

Results: The group with unfavorable outcomes (unfavorable group) consisted of 31 type B aortic dissection patients in the chronic phase; the remaining 56 patients had favorable outcomes (favorable group). The incidence of true lumen compression, false lumen expansion, false to true lumen ratio, and maximum dissection diameter were significantly greater (P<0.002, P=0.041, P=0.042, and P<0.011, respectively), and thrombosed false lumen was significantly less frequently observed (P<0.002). Cox regression analysis showed that male sex, non-ambulatory status, ejection fraction (EF), and presence of CVD were independent predictors of all-cause death (Wilcoxon’s test, P=0.048).

Conclusion: This case-control study indicated that administration of ARBs was significantly associated with a decreased risk for death, surgical repair, or progression of dissection in type B aortic dissection patients. The prognosis of type B aortic dissection patients appears to improve by administration of ARB in the long term.

**Predictors of early mortality in patients with critical limb ischemia caused by isolated below-the-knee artery disease**

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Background: Previous study suggests that critical limb ischemia (CLI) patients who are unlikely to live 2 years are probably better served by Endovascular treatment (EVT) first revascularization. In this study, we sought to investigate the predictors of early mortality in patients with CLI caused by isolated below-the-knee (BTK) artery disease.

Methods: This study was a multicenter retrospective observational study of prospectively maintained database. From March 2004 to June 2011, total of 884 patients with CLI who underwent angioplasty for de novo isolated BTK artery disease.

Results: Mean follow-up period was 589±527 days. Thirty-eight percent had non-ambulatory status, and 24% had cerebrovascular disease (CVD). Mean body mass index (BMI) was 21.6±3.3, serum albumin level was 3.5±0.6 g/dl, ejection fraction (EF) was 59±14%. All-cause death within two years was accounted for 25.0%. Cox multivariate analysis was performed to determine predictors in the unfavorable outcome group. Among the independent risk factors, EF, and presence of CVD were independent predictors of all-cause death within 2 years.

### Predictors of early mortality

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>BMI&lt;18</td>
<td>2.17 (1.57-2.93)</td>
<td>0.000</td>
</tr>
<tr>
<td>Albumin&lt;3.5g/dl</td>
<td>2.70 (2.03-3.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-ambulatory</td>
<td>3.39 (2.56-4.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb&lt;13.0g/dl</td>
<td>1.46 (1.10-1.94)</td>
<td>0.009</td>
</tr>
<tr>
<td>EF&lt;45%</td>
<td>2.19 (1.63-2.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD</td>
<td>1.78 (1.36-2.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>1.91 (1.27-2.87)</td>
<td>0.002</td>
</tr>
<tr>
<td>CFP&lt;1.64-29</td>
<td>2.22 (1.84-3.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ABI&lt;0.6</td>
<td>1.57 (1.12-2.19)</td>
<td>0.006</td>
</tr>
<tr>
<td>Rutherford class 4-6</td>
<td>1.93 (1.57-2.39)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: In patients with CLI caused by isolated BTK disease, BMI, serum albumin level, non-ambulatory status, EF, and presence of CVD were the independent predictors of early mortality. Patients who have these predictors may indicate EVT first revascularization.

**P659**

Prevalence and clinical outcome of polyvascular atherosclerotic disease in patients undergoing coronary intervention

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Background: There is a high rate of cardiovascular events in patients after PCI, but the prevalence and effects of PolyVD have not been evaluated in these patients. The goal of the study was to evaluate the prevalence and outcomes of polyvascular disease (PolyVD) (defined as lower extremity artery disease [LEAD], carotid artery disease [CaAD], renal artery disease [RAD], and abdominal aortic aneurysm [AAA]) in patients undergoing percutaneous coronary intervention (PCI).

Methods: The subjects were 1597 patients who underwent PCI and were prospectively enrolled in the study. The carotid, renal and peripheral arteries and abdominal aorta were simultaneously evaluated using duple ultrasound and the ankle-brachial index to evaluate the presence of PolyVD. This study was performed at a single center over 24 months. Clinical follow-up was completed in 1559/1597 patients (97.6%). The primary endpoint was major adverse cardiovascular events (MACE: death, myocardial infarction, and stroke).

Results: PolyVD was found in 446 of 1597 cases (27.9%), MACE was significantly higher in the PolyVD group compared to patients (n=1151) with coronary artery disease (CAD) alone (17.9% vs. 6.5%, P<0.0001). All-cause mortality and the incidence of stroke were significantly higher in the PolyVD group (14.1% vs. 4.3%, P<0.0001, 3.6% vs. 12%, P=0.006, respectively). The incidence of myocardial infarction (MI) was similar in the two groups (3.7% vs. 1.3%, P=0.08). The adjusted hazard ratios for MACE in patients with 1, 2, and 3 arterial beds (compared with CAD alone) increased from 1.64 to 1.74 to 10.62 (P<0.0001)

**P660**

Long-term clinical outcome after primary stenting for subclavian artery disease

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Background: Little is known about long-term clinical outcomes after endovascular therapy (EVT) for subclavian artery disease (SCD). The aim of this study was to investigate the long-term clinical outcome after primary stenting for SCD.

Methods: From January 2001 to December 2010, 83 patients (34% female, 69.9±8.6 years old, 86% left subclavian disease,) underwent successful primary stenting for de novo SCD. Mean lesion length was 27.9±12.7 mm, chronic total occlusion was included in 27%. Outcome measures were primary and secondary patency and all-cause mortality for SCD. Primary patency was defined as treated vessel without restenosis (defined as >2.5 of peak systolic velocity ratio by duplex and first repeat revascularization. Secondary patency was defined as target vessel which subsequently become totally occluded and is reopened by repeat revascularization. Initial success was defined as >30% of residual stenosis without complications.

Result: The mean follow-up interval was 48±34 months. Initial success was...
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achieved in 93% and complication rate was 8%. Primary patency at 1-3- and 5-year were 97%, 91% and 85%, respectively. Secondary patency was 100% during follow-up period. On multivariate analysis, female gender (p<0.02), and ventricular artery stenosis (p<0.01), were independent predictors of primary pa-
tency. Overall survival rates were 90%, 79%, 68% at 1-3- and 5-years. On multivariate analysis, age (P>0.02), chronic kidney disease (P=0.003), dialysis (P>0.004), were independent predictors of all cause mortality.

Conclusion: Primary stenting for SCD was safe and was effective for the long-term clinical follow-up period.

Left ventricular contractility impairment in Marfan patients is related to increased aortic stiffness


Introduction: Previous studies demonstrated aortic stiffening in Marfan patients by magnetic resonance imaging (MRI). Therefore, left ventricular (LV) contractility could be impaired due to an increased afterload. We aimed to establish the relationship between LV contractility and aorta distensibility in Marfan patients.

Methods: MRI and echocardiographic evaluation was performed in 27 Marfan patients and 15 matched for age, sex, and body surface area controls. Mean time between studies was 4.4±3.6 months. Ascending aorta distensibility and ascending-to-
abdominal pulse wave velocity (PWV) were analyzed by MRI LV volumes, ejection fraction, septobasal tissue Doppler velocity (TDV), global longitudinal strain (GLS) and septobasal longitudinal strain (LS) were determined by echocardiogra-

Results: LV ejection fraction was similar between Marfan patients and controls. Telediastolic and telesystolic indexed volumes were greater in Marfan compared with controls. Septobasal TDV were similar between Marfan and controls (6.2±0.5 cm/s, p=0.503). However, GLS and septobasal LS were lower in Mar-

fan compared with controls (-17.1% vs -18.9%, p=0.045 and -19.6% vs -15.6%, p=0.004). Ascending aorta distensibility and ascending-to-abdominal PWV by MRI were impaired in Marfan compared with controls (2.6±4.6 mm/m2 10-2, p=0.001 and 4.0 vs 4.9 m/s, p=0.030). Septobasal TDV was not correlated ei-

ther with ascending aorta distensibility or PWV. However, GLS and septobasal LS correlated positively with PWV (r=0.392, p=0.035 and r=0.664, p<0.001).

Conclusions: Marfan patients have impaired LV contractility and a stiffened aorta. Furthermore, LV contractility is correlated with aortic distensibility. These results provide better insight into the ventriculo-aortic interdependence in Marfan patients.

MRI evaluation of ascending aorta biophysics: new functional indexes and their relationship with aortic size


1 Sant’Anna School of Advanced Studies, Sector of Medicine, Pisa, Italy; 2 Fondazione Toscana Galbani Monasterio, Department of Cardiac Surgery, 5 Pataviniucchi Heart Hospital, Pisa, Italy; 3 Gabriele Monasterio Foundation-CNR Toscana, MRI Laboratory, Pisa, Italy; 4 Institute of Clinical Physiology of CNR, Pisa, Italy

Purpose: Ascending aorta aneurysm is one of the most common cause of death in cardiovascular patients. Prophylactic surgery to avoid higher mortality due to dissection is recommended at a aortic diameter of 5.5 cm in otherwise healthy patients. Nevertheless, there are several limitations of this criteria. Aortic size index allows to stratifies patients according to the level of risk of dissection/rupture, enabling appropriate surgical decision-making. Recently two new MRI indexes of aortic wall distension and recoil during cardiac cycle were developed. We evaluated two new MRI derived functional indexes to describe the elastic properties of ascending aorta in patients with different aortic size index.

Methods: We evaluated two new MRI-derived functional indexes to describe the elastic properties of ascending aorta in patients with different aortic size index. The MRI images has been followed and MRSD and MRDR were calculated enabling appropriate surgical decision-making. Two new indexes were calculated as cross-sectional area of the proximal ascending aorta (5 mm above the sino-
tubular junction) measured in each cardiac phase was indexed for the maximal cross-sectional area and indexed for the time between the two cardiac phases.

Results: Age (48±10 yrs.; 17 males) undergoing surgery for ascending aorta aneurysm were enrolled in the study. All the patients underwent comprehensive cardiac MRI study. A standard protocol to ac-
quire the MRI images has been followed and MRSD and MRDR were calculated with a regression coefficient equation for ascending aorta (5 mm above the sino-
tubular junction) measured in each cardiac phase was indexed for the maximal cross-sectional area and indexed for the time between the two cardiac phases. Ascending aorta distensibility and ascending-to-abdominal PWV by MRI were impaired in Marfan compared with controls (2.6±4.6 mm/m2 10-2, p=0.001 and 4.0 vs 4.9 m/s, p=0.030). Septobasal TDV was not correlated ei-

ther with ascending aorta distensibility or PWV. However, GLS and septobasal LS correlated positively with PWV (r=0.392, p=0.035 and r=0.664, p<0.001).

Conclusions: Marfan patients have impaired LV contractility and a stiffened aorta. Furthermore, LV contractility is correlated with aortic distensibility. These results provide better insight into the ventriculo-aortic interdependence in Marfan patients.

Background: Epicardial adipose tissue (EAT), localized beneath the visceral pericardium, is a metabolically active endocrine and paracrine organ with possible interactions within the heart. Recent studies identified possible roles of uric acid induced oxidative stress and increased inflammatory status in the pathogenesis of ascending aortic aneurysms. This study was to investigate the relationship between LV contractility and aorta distensibility in Marfan patients.

EAT, uric acid (UA) and C-reactive protein (CRP) levels are independently related to ascending aortic dilatation.

Method: Sensu UA, LV ejection fraction (EF), LV end-systolic wall thick and LV wall thickness were assessed in 38 patients with ascending aortic dilatation (dilated ascending aorta; DAA group ≥ 37 mm) vs. 107 subjects with normal aortic diameter (Normal AD group < 37 mm).

Results: EAT thickness was significantly higher in DAA group compared to normal AD group (mean 3.6±2.7 vs. 5.4±2.2 mm, p<0.001) as well as age (53±10 vs. 48±9 yrs, p=0.004), the presence of hypertension (54% vs. 30%, p=0.009) and uric acid levels (6.0±1.4 vs. 5.2±1.1 mg/dL, p<0.001). There was a strong corre-
lation between EAT thickness and ascending aortic diameter (r=0.521, p<0.001). When we performed multiple logistic regression analysis, EAT thickness (OR: 1.429, 95% CI: 1.108-1.843, p=0.006), BMI (OR: 1.169, 95% CI: 1.032-1.347, p<0.014) and uric acid levels (OR: 1.727, 95% CI: 1.078-2.766, p=0.023) were related to ascending aortic dilatation.

Conclusions: This is the first study displaying an independent relationship between LV EAT thickness and ascending aortic diameter. Based on our findings, increased epicardial and total visceral adipose tissue UA and possibly associated endothelial dysfunction may be suggested as a mechanism of ascending dilatation.

The evaluation of peripheral artery disease among patients with atherosclerotic thoracic aortic aneurysm undergoing scheduled surgical therapy

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Purpose: Patients suffering from atherosclerotic thoracic aortic aneurysm are often associated with peripheral artery disease (PAD). We evaluated PAD preoper-
atively, and analyzed the outcome of patients with and without PAD comparatively.

Methods: From January 2000 to June 2011, 201 consecutive patients with atherosclerotic thoracic aortic aneurysm underwent scheduled surgical therapy for thoracic aortic grafting, 103, (51.7%); thoracic aortic grafting, 39; descending thoracic aortic grafting, 14; thoraco-abdominal aortic grafting). Extra-cranial carotid and verte-
bral artery disease (ECVAD) was evaluated by MRI. Coronary artery disease (CAD) was evaluated by CAG, MDCT and scintigram. Lower extremity arterial disease (LEAD) was diagnosed by ABI less than 0.9. Abdominal aortic aneurysm (AAA) was evaluated by CT. All patients with PAD were treated simultaneously or within 90 days of aortic surgery.

Results: There were 19 patients (9.5%) with ECVAD, 55 patients (27.4%) with PAD, 16 patients (8.0%) with LEAD and 35 (17.3%) with AAA. All patients were divided into two groups. The group A consisted of 113 patients without PAD, and the group B was consisted of 88 patients with PAD. The mean age and rates of diabetes, hyperlipidemia, and intra-cranial lesion in the group B were higher than in the group A, significantly. Preoperative renal function (e-GFR) in the group A was 91.4 (81.6-101.8) ml/min/1.73 m2, and in the group B was 78.8 (69.4-88.1) ml/min/1.73 m2. The survival rates at 96 months after the operation were 62.6±6.6% and 59.8±8.4% in the group A and
Advanced glycation endproducts are elevated and predictive for mortality in patients with peripheral arterial occlusive disease

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Background/hypotheses: Advanced glycation endproducts (AGEs) are sugar-modified proteins which accumulate during normal ageing. AGEs are particularly increased during oxidative and glyceremic stress and play an important role in the formation of atherosclerosis. The predictive value of AGEs for mortality has been proven in diabetes mellitus (DM), renal insufficiency and after myocardial infarction. AGEs in peripheral arterial occlusive disease (PAOD) have never been studied. We hypothesize that AGEs are increased in PAOD and predictive for mortality.

Methods: A total of 514 patients with PAOD and 171 age-matched controls were included. For a cross-sectional study, cohort A (n=286) was measured in 2007-2008 and cohort B (n=250) in 2010-2011. AGEs were quantified non-invasively by skin autofluorescence (SAF) measurements. Cardiovascular risk factors were inventoried. The prospective follow-up study on mortality was done in cohort A. Independent parameters (tests, Chi-square tests, Kaplan-Meier and Cox regression analysis) were performed. In linear regression analysis, AGEs level was the dependent and cardiovascular risk factors were the independent variables. A p-value of <0.05 was considered statistically significant (SPSS 19.0).

Results: The mean age of patients and controls was 65 (SD 11) years. Mean standard deviations of the MD, denoting good inter and intra-observer agreement. Across both genders, the mean diameter for the AA was 20.0 ± 0.3 mm. SD was 23.6 ± 2.8 mm and PAoA was 26.0 ± 3.1 mm. Upper normal limits were 24.8, 35.8, 29.2 and 32.2 mm respectively. At univariate analysis smoking was a significant predictor of increasing dimensions at all 4 levels, whereas an inverse relationship was demonstrated between DM and AA and STJ dimensions.

Conclusions: This study describes BSA-indexed normative reference dimensions of the adult aortic root at 4 levels. The normative data will be useful in planning future investigations for patients noted to have dilated aortic roots in the course of coronary angiography and left ventriculography. This information may assist in electing which patients should be referred for additional imaging of the ascending aorta.
were studied. The remaining 59 patients were included. Mean age (standard deviation) at stent implantation was 28 (10.5) years, 56% male, 63% had native CoAo, 54 patients (92%) were on antihypertensive therapy before stenting, with 33 (61%) on multiple drugs (2 to 7). Minimal diameter of coarctation was 6 (2.7) mm. Twenty patients (34%) had transverse aorta/aorta diaphragm level (T ao/DiaphAo) < 0.8.

A total of 64 stents were implanted, of which 39% were covered. A second procedure was performed in 9 patients (15%) because of multistage procedure (n=4), growth (n=2), stent fracture (n=2) and neointima (n=1). Invasive gradient decreased from 46 (18) mmHg to 5 (5.5) mmHg. There were no major complications nor mortality.

It was possible to discontinue one or more antihypertensive drugs in 39 patients (66%) and 22 patients (37%) became free of medication. Patients who remained medication free were younger 21.6 (7.7) versus 31.4 (15.9) years, p < 0.009; had a lower Doppler gradient [38.9 (19.1) vs 58.3 (19.9) mmHg, p < 0.001] and a lower invasive gradient before intervention [38.8 (14.4) versus 52.8 (23.5) mmHg, p < 0.001]. Gradients immediately after stenting were also lower in this group [2.3 (3.6) versus 6.7 (8.5) mmHg, p < 0.026]. In medication free patients, final stent di-ameter correlated with BSA (p < 0.035). In patients with T ao/DiaphAo < 0.8, 46% remained medication free, but with T ao/DiaphAo > 0.8 only 23% did not require medication at long term. Results were similar for native CoAo and ReCoAo. In a mean follow up of 4.8 (2.9) years, one patient died of stroke 4 years after the early 3-year period before the setting-up of SOS-Aorta, including: RAA 10 (RAA), Stanford type A dissection (AD), or Type B (BD), and traumatic rupture (TR).

The average number of patients treated annually for SAA was 58 (9). One hundred and forty patients treated for SAA: ruptured aneurysm of the thoracic or abdominal aorta (T ao/AbAo), 54 patients (92%) were on antihypertensive therapy before stenting, with lower initial gradients, larger T ao/DiaphAo and lower immediate residual gradients.

**P669 An emergency center for acute aortic syndromes (SOS-Aorta): feasibility and impact**


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**Purpose:** Acute aortic syndromes (AAS) represent a wide range of life-threatening pathologies. Their management should be immediate and multidisciplinary, but is often delayed by the difficulty to find a dedicated center. We assessed the feasibility and the impact of an immediate, round-the-clock, protocolized management of patients with SAA on the number of patients and on their short-term survival.

**Methods:** In January 2009 we set up the SOS-Aorta center, in a university hospital regrouping intensivists, cardio-vascular and endovascular surgeons available around the clock. A dedicated phone number was created. Patients were immediately accepted in an intensive care unit dedicated for traumatized and unstable patients, with immediate access to the CT-scan and/or the operating room. An information campaign was done to communicate the phone number and the SOS-Aorta center on the internet.

**Results:** A total of 451 patients were admitted in our emergency center for SAA over the 6 year period (174 before and 287 after the setting-up of SOS-Aorta). The average number of patients treated annually for SAA was 58±6.6 in the early 3 year period before the setting-up of SOS-Aorta, including: RAA 10±5, 28±3 AD, 18±2 BD and 6±1 TR. It increased significantly to 96±17 (p < 0.05) over the 3 years following the setting-up of SOS-Aorta, including: RAA 21±6.1 (p < 0.05), 42±3.6 AD (p < 0.05), 23±5.2 BD (p < 0.01), and 9±3.1 TR (p < 0.07). The overall in-hospital mortality rate of patients treated for SAA in the early period was 36.4±1.84%; 50% for RAA, 53% for AD, 12% for BD, and 22% for TR. It decreased significantly to 21.6% (p < 0.01) after the creation of SOS-Aorta: 23% for RAA (p < 0.05), 30% for AD (p < 0.01), 9% for the BD (p = 0.01), and 9% for TR (p < 0.05).

**Conclusion:** Setting-up a SOS-Aorta center offering an immediate, round-the-clock, multidisciplinary management, has significantly increased the number of patients admitted for a SAA, thereby improving the experience of all teams’ members. It resulted in our center, in a significant improvement of in-hospital mortality for these patients with otherwise immediate severe prognosis.

**P670 Perioperative cardiac arrest in patients undergoing percutaneous coronary intervention: the prevalence and association with coronary disease severity**

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**Purpose:** As an indicator of multilocal atherosclerosis, peripheral artery disease (PAD) has known to be an important marker in risk stratification of patients with coronary artery disease (CAD). We sought to determine the prevalence of PAD in patients with coronary disease and show the relation between ankle-brachial index (ABI) and severity of CAD.

**Methods:** The study was carried out at single center from August 2009 to August 2011. A total 711 patients with CAD undergoing percutaneous coronary intervention (PCI) were enrolled. Diagnosis of PAD was made using the ABI of 0.9 or less and more than 1.3 with 0.7 or less toe-brachial index. To assess the severity of CAD, we investigated whether multi-vestel and left main coronary lesion was involved or not.

**Results:** The prevalence of PAD was 12.8% (Right, left ABI: 0.71±0.15, 0.73±0.15) in all patients. 23.9% among patients over 70 years and did not differ between genders (13.4% vs 10.9%, p = 0.435). Patients with PAD had higher prevalence of left main coronary disease (14.3% vs 5.8%, p=0.003) and more frequently involved multi-vestel lesion (74.9% vs 52.1%, p < 0.001). Alternatively, patients with PAD had a higher prevalence of left main coronary disease than those presented with acute coronary syndrome, which was not statistically significant (14% vs 12.1%, p=0.386). In relation to ABI < 0.9, 46% had ABI < 0.8, 46% had ABI < 0.7, 54% had ABI < 0.6. PAD had higher prevalence in patients presented with atherosclerotic coronary disease than those presented with acute coronary syndrome, which was not statistically significant (14% vs 12.1%, p=0.386).

**Conclusion:** Our study confirmed a high prevalence of PAD in patients with coronary artery disease. ABI-based PAD screening should be implemented in all patients with coronary artery disease, especially in those with severe extent.

**P671 Local carotid wave speed by radiofrequency-based ultrasound vs carotid-femoral pulse wave velocity for estimate of large artery stiffness in the clinical setting: similarities and differences**

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New radiofrequency-based ultrasound techniques (RF-US) allow accurate estimates of local wave speed (WS), an index of large artery stiffness, in superficial arteries, that may be of potential clinical usefulness for vascular age assessment and cardiovascular (CV) risk stratification. Aim of the study was to compare carotid WS (C-WS) with carotid-femoral pulse wave velocity (PWV), an established marker of aortic stiffness and predictor of CV risk, and to evaluate their associations with age and CV risk factors in subjects without CV disease.

**Methods:** In 530 subjects free of clinical CV disease (158 normals, NL; 165 hypertensives, HT; 170 diabetics, DM; and 29 obese, OB; 305 males; age range 18-73 years), PWV was measured by Complior (Alam, Vincennes, France), and C-WS was assessed by RF-US using a different stiffness index from arterial disten-

**Results:** A total of 451 patients were admitted in our emergency center for SAA over the 6 year period (174 before and 287 after the setting-up of SOS-Aorta). The average number of patients treated annually for SAA was 58±6.6 in the early 3 year period before the setting-up of SOS-Aorta, including: RAA 10±5, 28±3 AD, 18±2 BD and 6±1 TR. It increased significantly to 96±17 (p < 0.05) over the 3 years following the setting-up of SOS-Aorta, including: RAA 21±6.1 (p < 0.05), 42±3.6 AD (p < 0.05), 23±5.2 BD (p < 0.01), and 9±3.1 TR (p < 0.07). The overall in-hospital mortality rate of patients treated for SAA in the early period was 36.4±1.84%; 50% for RAA, 53% for AD, 12% for BD, and 22% for TR. It decreased significantly to 21.6% (p < 0.01) after the creation of SOS-Aorta: 23% for RAA (p < 0.05), 30% for AD (p < 0.01), 9% for the BD (p = 0.01), and 9% for TR (p < 0.05).

**Conclusion:** Setting-up a SOS-Aorta center offering an immediate, round-the-clock, multidisciplinary management, has significantly increased the number of patients admitted for a SAA, thereby improving the experience of all teams’ members. It resulted in our center, in a significant improvement of in-hospital mortality for these patients with otherwise immediate severe prognosis.
Independent predictors of operative mortality in acute aortic syndromes


Purpose: Type A Acute Aortic Syndromes (TA-AAS) have still high morbidity and mortality despite advances in management and therapy. Multiple clinical findings upon presentation, various lesion extension and low annual operative center-volume are elements that yield to difficult data evaluation. Few studies have shown that some variables are predictors of poor operative outcome. We review our experience in the treatment of 200 consecutive surgical cases of TA-AAS and analyzed the preoperative variables associated with operative mortality.

Methods: Several variables (180) have been collected related to demographic, anamnestic, clinical and interventional characteristics at ER presentation, diagnosis establishment and operative table. Those parameters have been correlated to operative mortality. The variables which diverged at initial univariate analysis (p < 0.05) become covariates in Cox regression model.

Results: From March 1993 to December 2011, 200 consecutive patients under- went repair for TA-AAS (acute aortic dissection= 182, intramural hematoma= 14 and penetrating ulcer= 4). Operative mortality was 28% (57 Pts). Main parameters associated with the operative mortality are listed in the following table. However, at multivariate analysis independent predictors for operative mortality were: 1) Shock or cardiac tamponade at onset (HR= 0.42; IC 0.18-0.94; p=0.03); 2) Pulse deficit at onset (HR=0.504; IC 0.254-1.00; p=0.05); 3) New cardiac tamponade at OR (HR=0.453; IC 0.204-1.008; p=0.05).

Conclusions: Our data show that variables which express a severe hemodynamic impairment (shock or cardiac tamponade) or broad lesion extension at the level of the vascular tree (pulse deficit) are independent predictors of operative mortality, rather than surgical strategy adopted.

Mortality for peripheral artery disease and coronary artery disease in the Korean population: 5-15 years follow-up

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The objective of this study is to analyze long-term survival of the subjects with peripheral artery disease (PAD), and coronary artery disease (CAD).

The sample included 4,526 Korean patients aged ≥45 years who were hospitalized from 1994 through 2004. 405 subjects had PAD confirmed by computed tomography angiography, while 3,475 subjects had CAD confirmed by cardiac catheterization among PAD or CAD patients. Mortality data were obtained from all participants between 1994 and 2009 from the Statistics Korea. All-cause mortality was measured at 5 to 15 years.

The mean age (years) of PAD subjects was 65.1 (±8.4) and that of CAD subjects was 62.4 (±8.7) (p < 0.001). For age, 45 to 64 year-old group was 45.2% in PAD and 59.6% in CAD. During the 5 to 15 years follow-up, all-cause cumulative mortality rate were 31.8% in PAD and 28.2% in CAD. The mean survival time was 8.77 (±0.24) years in PAD and 11.4 (±0.8) years in CAD. Ten years survival rate was 59% in PAD and 71% in CAD. The independent predictors of mortality were included, but not limited to, age, diabetes, and chronic kidney disease (CKD) in PAD and age, male gender, diabetes, dyslipidemia, smoking, CKD and anemia in CAD. Interestingly, overweight and obesity showed lower hazard ratio in PAD or CAD group.

Elective repair of abdominal aortic aneurysm in patients over 85 years old: results from a 60 patients monocentric cohort

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Purpose: Due to aging population, increasing screening of abdominal aortic aneurysms (AAA) and diffusion of minimally invasive surgical techniques, proportion raise of older patients are eligible for AAA elective repair. Few data exist in the literature on the expected benefits and risks ratio of such prophylactic intervention on this old population. The purpose of this single-center study was to evaluate the short- and medium-term results of AAA repair in patients older than 85 years.

Methods: Between 2004 and 2011, data of all patients over 85 years-old and treated for an elective AAA in our university center were collected prospectively. In line with current recommendations, patients were treated by endovascular repair (EVAR) in case of suitable anatomy. Open repair (OR) was performed in patients with poor anatomy or iliac arteries preventing endoluminal access. The proportion of repair (EVAR or OR), and the short- and mid-term postoperative results were analyzed. Primary endpoints were 30-day mortality rate and actuarial survival rate.

Results: Of the 1016 patients operated electively for an AAA during the 8-year period studied, 60 patients (5.9%) were aged ≥85 years (54 men, mean age = 87±2 years), with a mean AAA diameter of 63.1±10.2 mm. Twenty nine (48%) were treated by EVAR and 31 by OR. The global 30-day mortality rate was 3.3% (EVAR=3.4%, OR=3.2%, p=NS). The median of follow-up was 30 months (range 3-63). Postoperative actuarial survival rates at 1, 3 and 5 years were similar, 90%, 79% and 64%. No patient died of AAA related cause during the follow-up.

Conclusions: Elective repair of AAA in patients over 85 years old is associated with acceptable perioperative mortality and life expectancy. The survival rates return to the ones of population with same age without AAA. Although EVAR does not present a significant benefit on postoperative mortality compared to OR in our series, it seems reasonable to propose this less invasive treatment as first-line when the anatomical conditions are suitable.

Racial differences in acute aortic dissection: insights from the International Registry of Acute Aortic Dissection

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Background: Few data exist on race-related differences in demographics, medical history, clinical presentation, diagnostic findings, management, and outcomes in patients presenting with acute aortic dissection (AAD).

Methods: Accordingly, we evaluated 3,354 patients (mean age 62±15.3 years; 36.4% women) enrolled in 13 United States centers participating to International Registry of Acute Aortic Dissection (IRAD). Race was recorded as black in 14% of these patients.

Results: Type B AAD was more frequent in the black patient cohort (52.4% vs 39.3% in whites, p<0.001). Black patients were younger accounting for 20% AAD patients under 40, but only 5% of those ≥70 years. Furthermore they were more likely to have a history of cocaine abuse (12% vs. 1.6%, p<0.001), hypertension (89.7% vs. 73.9%, p<0.001) and diabetes (13.2% vs 6.4%, p<0.001). In contrast, they were less likely to have a history of bicuspid aortic valve (1.8% vs. 5.8%, p<0.029), Marfan Syndrome (1.6% vs. 4.2%, p=0.099), iatrogenic AAD (0.5% vs. 4.5%, p<0.010) and prior AAD repair (7.7% vs. 12.8%, p=0.047). Pre-existing features similar to the exception of more frequent abdominal pain (44.6% vs. 30.6%, p<0.001) and electrocardiographic evidence of left ventricular hypertrophy (44.2% vs. 20.1%, p<0.001). Use of various imaging modalities and management of AAD (medical vs invasive) similar in the 2 groups. Complication of hypertension/shock/cardiac tamponade was less common (7.6% vs. 20.1%, p<0.001) whereas acute kidney failure more common (41.0% vs 21.7%, p<0.001) in blacks with AAD. In- hospital mortality was similar in the 2 groups (14.3% in black patients vs 19.1% in white patients, p= 0.10).
Conclusions: Our study provides important insights into the clinical characteristics and outcomes of patients with AAD. Despite younger age, similar management and a lower incidence of hypotension/shock/cardiopulmonary tamponade, blacks have similar mortality compared with whites with AAD. These findings may have implications in terms of optimizing societal efforts to prevent, diagnose earlier, and more effectively treat AAD in black patients.

Intraoperative flowmetry for assessment of the success of vertebral artery reconstruction

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Objective: Intraoperative ultrasound has become an integral part of surgical procedures and influences on both the intermediate intraoperative course and long-term outcome. Unlike coronary and carotid surgery vascular arteries (VA) reconstruction is not provided by flowmetry. This study reviewed our experience with intraoperative ultrasound evaluation of graft performance in third vertebral artery segment.

Material and Methods: We prospectively evaluated 30 patients (pts) (mean age 53 years) with vertebral basilar insufficiency who had undergone VA reconstruction due to lesion of its 2-3 segments. In all cases flow and pulsatility index (PI) of VA in situ and in 1st and 2nd cervical vertebrae, internal carotid artery (ICA) and external carotid artery (ECA) prior to intervention and all anastomosis components following the reconstruction were measured by intraoperative flowmeter.

Results: Successful rate of VA revascularization was achieved in 86.6%. Recurrence of vertebral basilar insufficiency was revealed in 4 pts (13.4%). No death or acute cerebrovascular events were observed. PI of ECA and volume flow griefs from the VA after operation were significant predictors of bypass patency (P < 0.05). Mean flow volume in VA increased on 22.0 ml/min (95% CI 17.2-26.7), PI of ECA decreased by 23.3%. (95% CI 10.9-35.8) intraoperatively. Pts with acute thrombosis had significantly lower VFG (p=0.03) compared to pts with uneventful period flow. Mean PI of vertebral arteries was 5.5 in control state and higher in postoperative period (p=0.02).

Conclusions: The intraoperative flowmetry is rapid noninvasive and sensitive technique. This procedure allows to assess accurately the third segment of vertebral artery anastomosis. A poor VFG and high ECA PI after VA reconstruction can alert surgeons to potential difficulties with donor vessel, anastomosis or recipient vessel during surgery.

Aortic diameter predicts acute type a aortic dissection in marfan patients but not in non-marfan patients


Purpose: Among the parameters considered during watchful follow-up for the genesis of acute type A aortic dissection, aortic size has been considered a cardinal factor. Preventive surgery of the aorta in asymptomatic patients on the basis of size alone is still controversial in patient populations lacking risk factors for aortic dissection. The aim of this study was to assess the feasibility of aortic diameter as a current criterion for elective aortic surgery to prevent the development of aortic dissection in non-Marfan and Marfan (MFS) patients.

Method: We reviewed the data for patients diagnosed with acute type A aortic dissection from December 1994 to March 2009 at our institute. Results: A total of 237 patients who presented with acute type A aortic dissection were enrolled, of which 31 were diagnosed with MFS. The maximal ascending aorta size was 46.7 mm (42.9–51.6) in non-MFS patients and 58.5 mm (43.8–64.9) in MFS patients (p < 0.001). Two-thirds (74.1%) of MFS patients had a maximal aortic root size ≥ 45 mm. However, 86.9% of the 206 non-MFS patients had aortic diameters < 55 mm. Non-MFS patients presenting with an aortic size < 55 mm developed aortic dissection at a younger age and had a higher body mass index than those with aortic sizes ≥ 55 mm.

Conclusion: Aortic diameter is of limited value and is not a critical parameter for aortic dissection in non-MFS patients.

MULTIDETECTOR COMPUTED TOMOGRAPHY IN DIAGNOSIS AND CHARACTERIZATION OF CORONARY ARTERY DISEASE

Relationship of dyspnea and typical angina to coronary artery plaque severity, distribution, composition and risk

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Objective: Dyspnea and typical angina are associated with poor prognosis, although their relative risk to mortality in relation to coronary artery disease (CAD) characteristics has not been examined. The aim of this study was to evaluate coronary plaque distribution, severity, composition and risk among individuals undergoing coronary CT angiography (CCTA) presenting with versus without dyspnea or typical angina as a chief complaint.

Methods: We studied 1443 consecutive individuals (mean age 61 years, 61.6% men) undergoing CCTA, comprised of 170 individuals with dyspnea, 249 individuals with typical angina (TypAng), and 1024 individuals without dyspnea or TypAng (Reference group). Multivariable logistic regression was performed to evaluate the association of Dyspnea or TypAng to the presence of obstructive CAD (≥70% diameter stenosis); plaque distribution determined by a segment involvement score [15] (defined as the total number of segments with plaque); and plaque composition (categorized as noncalcified, mixed, calcified). Risk of mortality in relation to Dyspnea or TypAng was evaluated with multivariable Cox proportional hazards models.

Results: During a follow-up of 2.9±1.0 years, 63 individuals died (4.4% of total population): 17 (10.0%) with Dyspnea; 13 (5.2%) with TypAng; and 33 (3.2%) in the Reference group. By multivariable logistic regression, both Dyspnea (OR 2.1, 95% CI 1.2-3.5, p=0.01) and TypAng (OR 1.8, 95% CI 1.1-2.9, p=0.03) were associated with the presence of obstructive CAD when compared to Reference individuals, but neither symptom type was associated with greater plaque distribution or any plaque composition type. Despite similarities in rates of obstructive CAD, those with Dyspnea experienced a 3-fold higher mortality (3.3%/year vs. 1.1%/year, p=0.001) compared to Reference individuals, while those with Typang did not (1.0%/year vs. 1.1%/year, p=0.03). By multivariable Cox models, individuals with Dyspnea experienced higher mortality risk (HR 2.3, 95% CI 1.2-4.3, p=0.008) yet those with Typang did not (HR 1.1, 95% CI 0.5-2.1, p=0.73).

Conclusion: Both Dyspnea and TypAng are associated with increased prevalence of obstructive CAD, which is associated with heightened risk of mortality in individuals with Dyspnea but not TypAng. Dyspnea was a worse prognosis for individuals with Dyspnea warrants further investigation.

P679 Prospectively-triggered, 320-row cardiac CT angiography increases aspirin but not statin prescriptions compared to myocardial perfusion imaging in low-risk, symptomatic patients in the emergency room

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Purpose: Compared to myocardial perfusion imaging (MPI), prospectively-triggered, 320-row volumetric cardiac computed tomography (CTA) reduces the length of stay (LOS), hospital cost, and radiation exposure in low risk, symptomatic patients presenting to the ER with chest pain, a non-ischemic ECG, and negative initial cardiac markers, were evaluated by either CTA or MPI based on the discretion of the treating physician. LOS, total cost, radiation dose, prescription rates of statins and aspirin, and lipids were compared between those undergoing CTA vs. MPI. Prospectively triggered, contrast-enhanced CTA was performed on a 320 detector row platform (Aquilion ONE; Toshiba, Tustin, CA; Tube Voltage 120-35V, Tube current 300-550 mA). Marin-Whitney test was utilized to compare non-normally distributed variables and chi-square test was used to compare categorical variables; p < 0.05 was considered test significant.

Results: There were 107 patients (52±12.4 years, 42% M, BMI 31.7) evaluated by CTA and 105 patients by MPI (59±13.2, 38% M, BMI 29.3). As seen in the Table, prescription rates for aspirin were significantly higher in those undergoing CTA. LOS, radiation dose, and total hospital cost were significantly lower in the CTA group.

Cardiac CTA vs. MPI in ER patients

Table: Cardiac CTA (Median 25%-75%) Nuclear (Median 25%-75%) P Value

- LOS (hours) 21.7 [10.3–30.5] 25.4 [18.2–43.9] P=0.001
- Cost (US$) 1321 [800–2219] 1536 [1257–2287] P=0.0078
- Radiation Dose (mSV) 5.2 [2.4–10.2] 13.0 [12.1–13.7] P<0.0001
- Statin Rx at Discharge 40% 46% P=0.40
- Aspirin Rx at Discharge 58% 40% P=0.012

Conclusions: In a ‘real-world’ population of low risk patients presenting to the ER with chest pain, prospectively-triggered volumetric CTA as a first line test may be the dominant strategy by reducing LOS, hospital cost and radiation dose. Compared to MPI, CTA did not influence rates of statin prescription at discharge, but was associated with an increase in aspirin prescriptions.

P680 Coronary artery ectasia and coronary calcification: pathological relation or just an association?

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Introduction: Coronary artery ectasia (CAE) is considered a variant of coronary artery atherosclerosis, however, a definite link is not yet confirmed. The aim of this study was to evaluate the prevalence of CAE, angiographic characteristics, its
Coronary atherosclerosis and circulating biomarkers in patients with suspected coronary artery disease (MDCT).

Methods: We prospectively enrolled 2600 patients (mean age 55±10 years) who were scheduled for computed tomography coronary angiography (CTCA). CTCA was performed using 64-MDCT scanner with dedicated software for calcium measurement. CAE was defined as an arterial segment with a diameter of ≥1.5 times the diameter of the adjacent normal segment. The presence of ≥70% diameter stenosis of any major epicardial vessel was considered an obstructive lesion (OL).

Results: CAE was encountered in 192 (7.4%) patients with male gender predominance (88%). Only 16.2% of CAE patients had no detectable atherosclerotic lesion. OL was shown in 37% of patients in the non ectatic segments. Left anterior descending coronary artery was the most commonly affected vessel followed by right coronary artery. According to Markis classification, type I was present in 44 (22.9%) patients, type II in 34 (17.7%), type III in 38 (19.8%) and type IV in 76 (39.6%) patients. Despite that patients with and without CAE had comparable age, the former group had higher coronary artery calcium score (CACS) (408±168 vs. 0.002; 0.002). Of 192 patients with CAE, 86 (44.8%) had CACS >0. Only 8.6% of ectatic coronary segments showed various degrees of intimal calcification. Pearson’s correlation coefficients showed negative correlation between CAC and Markis classification of CAE (r=-0.036, p=0.005). Ascending aorta aneurysm was found in 5 (2.6%) patients with CAE vs. 4 (0.17%) patients without CAE. P=0.000.

Conclusion: CTCA is a feasible technique to identify and evaluate morphology of CAE. It may have an important diagnostic role; help delineation of CAE and the associated atherosclerotic burden.

**P681**

Coronary atherosclerosis and circulating biomarkers in patients with opposite for risk factor profiles and no clinical ischamic heart disease. CAPRIE study: preliminary findings

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Purpose: To identify distinctive anatomical and biological features in patients who develop coronary artery disease (CAD) despite a low risk factor (RF) profile (“outlier”).

Methods: Coronary multidetector computed tomography (MDCT) and circulating biomarkers were centrally analyzed in 110 patients with LVEF>50% subdivided into three groups based on CAD extent and RF (family history, hypertension, dyslipidemia, smoking, diabetes). Group 1: 56 without CAD and <1 RF excluded diabetes (No-CAD/low-RF); group 2: 28 “outliers” with diffuse CAD (CAD/low-RF), and group 3: 26 with diffuse CAD and ≥3 RF (CAD/high-RF).

Results: CAD/low-RF showed angiographic findings similar to CAD/high-RF. In contrast, stenosis severity and plaque composition were different in CAD/low-RF. Circulating hs-cTnT, C-reactive protein and creatinine were not different between the two CAD groups but were significantly higher in CAD/high-RF than in no-CAD/low-RF.

**P682**

Impact of serum uric acid levels on the characteristics of coronary plaques using computed tomography angiography

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Background: Uric acid may have effects on vascular remodeling and atherosclerosis. The purpose of this study was to evaluate the relationship between serum uric acid (SUA) levels and presence of coronary vulnerable plaque assessed by computed tomography angiography (CTA).

Methods: Five hundred twenty-nine patients with suspected coronary artery disease (CAD) underwent 64-slice CTA to evaluate the prevalence of CAD and plaque morphology. Coronary vulnerable plaque was defined as positive vessel remodeling (PR) (R-I>1.1) and low-attenuation plaques (LAP) (<50 Hounsfield Units). SUA level was divided into 4 groups: <5, 5 to <6, 6 to <6.8, ≥6.8 mg/dl. Results: The number of vulnerable plaques per patient was significantly higher in patients with high SUA level (Figure, P=0.002). In multivariate logistic analysis, C-reactive protein and SUA were independent risk factors that adjusted for gender, age, smoking, hypertension, dyslipidemia, diabetes mellitus and estimated glomerular filtration rate, the patients whose SUA level 5 to <6mg/dl, 6 to <6.8mg/dl, and ≥6.8mg/dl had odds ratio (OR) of 1.194 (95% CI: 0.773-2.078, P=0.525), 1.306 (95% CI: 0.085-2.510, P=0.382), 2.622 (95% CI: 1.643-4.541, P<0.002) respectively, for prediction of coronary vulnerable plaque, compared with those whose SUA level was <5 mg/dl.

Conclusion: SUA level was associated with the presence of coronary vulnerable plaques. Assessment of SUA level may be useful to identify the high-risk patients with suspected CAD, and SUA may have a pathophysiologic effect on atherosclerosis.

**P683**

Levels of circulating microRNA miR-145 and high-sensitive cardiac Troponin T show a different correlation with coronary plaque burden and characteristics as assessed by cardiac computed tomography

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Background: MicroRNA-145 and hsTnT are biomarkers for coronary artery disease (CAD). However, there is no data on patients with subclinical atherosclerosis. Coronary CT angiography permits to quantify atherosclerotic plaque. We investigated the correlation between coronary plaque burden assessed by MDCT, miR-145 plasma and hsTnT serum levels in patients without known CAD.

Methods: 33 patients underwent MDCT for exclusion of CAD. Plasma levels of miR-145 and serum levels of hsTnT were determined before scan. MiRNAs were quantified by real-time PCR and normalization to spiked c.elegans miRNA. TnT serum levels of hs-TnT were determined before scan. MiRNAs were investigated the correlation between coronary plaque burden assessed by MDCT, miR-145 plasma and hs-TnT serum levels in patients without known CAD.

Results: MI-R145 levels were lower in patients with plaque (0.09±0.07fmol/ml, n=24) as compared to patients without (0.23±0.18fmol/ml, n=9, p=0.006). They were inversely correlated to plaque number (p=0.02 for >1 plaque vs. no plaque). MiR-145 levels in patients with predominantly non-calcified plaques (0.05±0.04fmol/ml, n=6), were lower than in patients with calcified plaques (0.14±0.07fmol/ml, n=8). Serum levels of hsTnT were different: For patients with coronary plaque serum levels were higher than for those without (6.4±4 vs. 3.3±0.7pg/ml, p=0.05). The number of plaques was proportionally correlated with hs-TnT levels (p<0.01 for >1 plaque vs. no plaque). Plateau type did not have any influence on cTnT levels.

Conclusion: The presence of coronary plaque is associated with alterations in serum levels of miR-145 and hsTnT. Plasma levels of miR-145 are down-regulated in the presence of plaque, while serum levels of hsTnT are positively correlated to coronary artery plaque burden.
The effect of LDLR-negative genotype on CT-coronary atherosclerosis in asymptomatic, statin treated patients with heterozygous familial hypercholesterolemia

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Background: In asymptomatic patients with heterozygous familial hypercholesterolemia (FH), the influence of LDL receptor (R) mutational status on coronary atherosclerosis is largely unknown. We measured plaque burden by means of CT coronary angiography in patients with FH.

Methods and Results: One hundred and forty four clinically diagnosed FH patients (92 men; mean age 52±8) underwent LDLR mutational screening. We distinguished two groups: A) 54 patients (38%) with LDLR-negative mutations and B) 90 patients (62%) with either LDLR-defective (d) or LDLR-unidentified (u) mutations. The plaque burden score was the primary endpoint defined as the integrated sum of the stenosis severity and number of diseased coronary artery segments (score=1 for <20-50% stenosis, score=2 for >50-70% stenosis and score=3 for >70% stenosis) (median, IQR). The primary analysis was the comparison of plaque burden between groups A and B and additionally between LDLR d and LDLR-u mutational FH. The median plaque burden score in group A was significantly higher as compared to group B (4 (4-5) and 2 (0-6); P=0.031). There was no significant difference in plaque burden score between LDLR-d and LDLR-u mutational FH.

Conclusion: LDLR-negative mutational status in asymptomatic statin treated FH patients is associated with the highest extent of subclinical CT-coronary atherosclerosis.

Cardiac Ct for clinical decision making results of a 8-years follow-up

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Aim: The diagnostic accuracy of cardiac multi-detector row computed tomography angiography (MDCTA) is well studied, but the prognostic value of MDCTA described in the most studies on short-term follow-up. Therefore, the aim of this study was to determine the long-term prognostic value of MDCTA.

Methods and Results: Our study included 210 patients (138 men, age 67±11 years) referred to our outpatient clinic because of unclear chest pain. 8 years after MDCTA, a clinical follow-up was performed by telephone reporting, reaplication of invasive coronary angiography (ICA), need for revascularization, cardiac death and myocardial infarction.

Follow-up information on 180 patients (85%) could be obtained. During a mean follow-up of 86±9.6 months we observed 54 index events in 50 pts (71%). These pts were significantly older (72±9 years vs. 66±11 years, p<0.001), had more 2 cardiovascular risk factors (48% vs. 21.5%, p<0.05), and the Agatston-Score was significantly higher (1205±622 vs. 190±62, p<0.001). Ten index events were deaths, four were of cardiac origin. Two myocardial infarctions occurred. 100% of event free survival in the group of exclusion of CAD was documented. Furthermore, the event free survival rate dropped to 45% (n=27/60) in pts with significant CAD.

Conclusions: Even after 8 years of follow-up MDCTA was found to be prognostic important in pts with unclear chest pain. Especially, the absence of any CAD provided an excellent prognosis. In contrast, the cardiac event rate increased in pts with proven CAD and in pts with non-diagnostic image quality.

Can computed tomography coronary angiography (CTCA) be used as a non-invasive estimate of the SYNTAX score?

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Purpose: The SYNTAX score is used for evaluation of patients with complex coronary artery disease undergoing revascularisation. It is usually calculated offline, meaning that in suitable patients, percutaneous intervention is performed at a later date. The ability to non-invasively estimate SYNTAX score would allow the heart team to recommend optimal treatment prior to invasive coronary angiography (ICA), thus enabling the diagnostic and therapeutic procedure to be performed at the same session. We aimed to test the agreement between CTCA and ICA in patients who had undergone both procedures within a 2 month period and had at least one significant stenosis by ICA.

Methods: CTCA scans were performed on a 64 slice scanner following injection of 80ml IV contrast medium. SYNTAX score was independently and blindly calculated by 2 experienced readers of CCTA and 2 invasive cardiologists in 104 patients, age 57±10, with significant (>50%) stenoses in 1.7±0.7 vessels. Calcium score averaged 597±727 Agatston units.

Results: Agreement between ICA and CCTA for conventional vessel based analysis (presence of >50% stenosis per vessel) was good with kappa 0.66 and sensitivity, specificity and accuracy of 79%, 93% and 83%, respectively. The mean SYNTAX score was 14.5±10.0 by ICA and 10.2±6.8 by CTCA with a significant underestimation of 20±18.8 by CCTA (p<0.001). Weighted kappa was 0.33, indicating only fair agreement. If only good quality CCTA’s were used, kappa improved to 0.56. Analysis of the causes of the bias showed ICA to identify more lesions per patient (2.2±1.3 vs. 1.7±1.0, p<0.001), while the mean score per lesion was not different (6.4 vs. 5.9, p=0.64). SYNTAX score per lesion showed good agreement (Kappa=0.69). Regarding various components of the SYNTAX score, CCTA identified 12/24 occlusions (kappa 0.6); agreement for calcified lesions was fair (kappa 0.36), while agreement regarding bifurcation lesions and long lesions was poor. Inter-rater agreement was good for ICA (kappa 0.84) and moderate for CCTA (kappa 0.51).

Conclusion: CCTA, despite having a good agreement by conventional vessel based analysis, showed only a fair agreement for the calculation of SYNTAX score, and cannot be currently used as a substitute for diagnostic ICA for this purpose.

Impact of visceral abdominal adipose tissue on unstable coronary plaque formation detected by multidetector computed tomography in non-diabetic patients

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Background: Visceral abdominal adipose tissue (VAT) may play an active role in the coronary plaque, since visceral adipose tissue secretes many inflammatory cytokines. This study investigated the relation between VAT and unstable coronary plaques detected by multidetector computed tomography (MDCT).

Methods: We measured VAT and determined presence and characteristics of coronary plaques using MDCT in consecutive 161 patients suspected of coronary artery disease (88 men; age, 64±13 years). Unstable plaque was defined as the plaque with an attenuation less than 50 HU.

Results: The unstable plaque was detected in 19% subjects. The VAT in patients with unstable plaque was significantly greater than that in patients without unstable plaque (120±60 mm3 vs. 89±70 mm3, median±IQR, p<0.01). Patients with unstable plaque had higher age (p=0.03), greater percentage of male (p<0.01), higher prevalence of diabetes (p<0.01), lower HDL-cholesterol (p=0.02), and higher HemoglobinA1c (p<0.01). When all subjects were categorized on the basis into three groups, low VAT group (<62 cm2, n=34), moderate VAT (62<cm2<116 cm2, n=32), moderate VAT (>116 cm2, n=34), the presences of patients with unstable plaque were 8%, 19%, 29%, respectively, p=0.02. In all subjects, multi- variant logistic regression analysis revealed that high VAT tended to be associate with the presence of unstable plaques (odds ratio; 2.69, p=0.11). However, sub-analysis according to diabetes demonstrated that those associations remained significant only in non-diabetic patients (odds ratio; 4.92, 95%CI; 1.27 to 110.1, p=0.03), but not in diabetic patients.

Conclusion: VAT is a significant and independent risk factor for unstable coronary plaques.

The impact of chronic kidney disease in the development of coronary atherosclerosis: 128 Multi-slice Ct study

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Aim: The several reports have mentioned that chronic kidney disease (CKD) is associated with the occurrence of cardiovascular event. The aim of this study is to investigate the correlation between CKD stage and the prevalence of coronary atherosclerosis using Multi-slice computed tomography (MSCT).

Methods: We investigated consecutive 865 cases underwent 128-MSCT for evaluation of suspected coronary artery disease. We investigated the correlation between CKD stage (stage 1:GFR>90, 2: eGFR<60–90, 3a:eGFR<50–60, 3b: eGFR<50–30), various measurements, and severity of coronary artery atherosclerosis by MSCT.

Results: The results are shown in the table. The severity of coronary artery atherosclerosis such as Agatston score, the prevalence of coronary artery plaque, and significant stenosis was significantly higher in the advanced CKD patients.
Conclusions: In our study, the severity of coronary artery atherosclerosis was significantly higher in the patients with advanced OKD stage. Increased OKD stage seems to contribute to the development of coronary artery atherosclerosis.

Coronary computed tomography angiography predicting major adverse cardiac events

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Objective: Framingham study discovers the coronary risk factor by long term follow-up. However, the prediction of events is only moderate accurate. The plaque characteristics by Coronary Computed Tomography Angiography (CCTA) may be more accurate in predicting the events.

Methods: The patients who underwent CCTA from Jan 2008 to Feb 2010 were included in the study. Any patients who later developed acute ST elevated myocardial infarction (STEMI), non ST elevated acute myocardial infarction (NSTEMI) or cardiac death after CCTA was considered a MACE. Both grayscale and color coding analysis of the plaque were performed. The plaque score system was established to quantify the lesions. The plaques were classified into the complex lesion, severe localized stenosis, positive remodeling, mild to moderate lesions, drug eluting stent, complete occlusion, defused moderate lesions and calcification. The plaque score times the number of segments was the total plaque score. Event risk was calculated as follow: death point 3, heart failure point 2, STEMI point 1, NSTEMI 1, 0.5, multiplied by the number of abnormal segments. Clinical Plaque score—plaque score × [modified ACEF score]. Two-way analysis of variance and linear regression were performed between clinical plaque score and event risk score.

Results: A total of 8557 consecutive cases of CCTA were performed in the institution. Among them 25 patients developed MACE after CCTA, including 6 cases of deaths, 2 cases of heart failure, 11 cases of STEMI and 6 cases of NSTEMI. Of the 6 deaths 4 revealed complex lesions which included erosive lesions, chronic occlusion, calcified plaque, soft plaque, fibrous plaque and ulcers on the color coded CCTA. One patient died of DES thrombosis without significant stenosis on CCTA. One patient had only moderate lesion on CCTA before the death. Two patients suffered from heart failure. They all belonged to the complex lesions. Of the 5 heart failures who suffered from STEMI, 4 patients had severe localized stenosis, 3 cases had only moderate lesions and 1 had DES on CCTA before the MACE. Of the 6 patients who suffered from NSTEMI, 2 had severe localized stenosis, 2 and severe localized stenosis on CCTA before the MACE. The complex lesions and severe localized stenosis were the powerful predictors of MACE.

Conclusion: The plaque characteristics of CCTA are predictive of MACE. The plaque characteristics of CCTA are predictive of MACE. The plaque characteristics of CCTA are predictive of MACE. The plaque characteristics of CCTA are predictive of MACE.

Detection of significant coronary artery disease using computed tomography coronary angiography in patients with aortic stenosis referred for surgical aortic valve replacement

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1. Rigshospitalet · Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; 2. Rigshospitalet · Copenhagen University Hospital, Department of Radiology, Copenhagen, Denmark; 3. Roskilde Hospital, Roskilde, Denmark; 4. Rigshospitalet · Copenhagen University Hospital, Heart Centre, Department of Cardiothoracic Surgery, Copenhagen, Denmark

Purpose: The diagnostic accuracy of computed tomography coronary angiography (CTCA) to identify significant coronary artery disease was evaluated in patients referred for surgical aortic valve replacement. In patients referred for aortic valve replacement a pre-surgical assessment of coronary artery disease is mandatory to determine the possible need for additional arterial bypass grafting. CTCA has been useful for detection of significant coronary disease in other populations, but coronary calcification due to advanced age and predominately male gender, may limit the use of CTCA in patients with aortic stenosis.

Methods: Between March 2008 and March 2010 a total of 181 consecutive patients scheduled for aortic valve replacement were included. All patients underwent pre-surgical CTCA (64- or 160-detector (n=60 CT scanner) as well as an invasive coronary angiography. CTCA and invasive coronary angiography analyses were performed blinded to each other. Significant coronary artery disease was defined as a stenosis > 70%.

Results: The mean (SD) age was 71 (9) years and 59% were male. The prevalence of significant coronary artery stenosis by invasive coronary angiography was 36%. Average heart rate during CTCA was 65 (16) beats per minute and median (range) coronary artery calcium score was 529 (0-8599) by Agatston score. On coronary vessel level 97% of vessels (705/724) were considered evaluable. The vessel-by-vessel sensitivity was 61% and specificity 94%. On a patient-by-patient level 94% of patients (171/181) were considered fully evaluable and CTCA had a sensitivity of 68%, specificity of 91%, a positive predictive value of 81% and a negative predictive value of 83%. Multivariate logistic regression analysis identified advanced age, coronary artery calcium score > 400 and heart rate > 62 beats per minute as independent predictors of invasive coronary angiography/CTCA disagreement. Excluding all patients > 70 years old resulted in: sensitivity 82%, specificity 96%, positive predictive value 95% and negative predictive value 92% (n=71).

Conclusion: In patients referred for surgical aortic valve replacement the diagnostic accuracy of CTCA to identify significant coronary artery disease was found to be moderate. Results may be improved by selecting patients with age < 70 years, coronary artery calcium score ≤ 400 and by lowering the heart rate to ≤ 62 beats per minute.
P692

Prognostic value of coronary computed tomography angiography during 5 years of follow up in patients with suspected coronary artery disease

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Background: The capability of coronary CT angiography (CCTA) to predict subsequent cardiac events is well known. However, the follow-up period is limited to approximately 2 years in most studies; data on prognosis over five years of follow up are very limited.

Methods: We analyzed 1453 patients with suspected coronary artery disease (CAD) undergoing CCTA between December 2003 and November 2006. Amongst other known CCTA parameters, the number of abnormal segments (having either a nonstenotic plaque or a stenosis) and presence of nonobstructive and obstructive CAD were recorded. Endpoint was the occurrence of hard cardiac events defined as all cause death or nonfatal myocardial infarction.

Results: During a median follow-up of 5.6 years (IQR 5.1 to 6.2 years), there were 58 hard cardiac events. The annual event rate ranged from 0.2% for patients normal coronary arteries to 0.7% and 1.2% for patients with nonobstructive and obstructive CAD resp. (see Figure below). Both the presence of (non)obstructive CAD and the number of abnormal segments significantly improved the predictive value of the Morise score as best clinical risk predictor (p=0.003 and p<0.001 resp.).

Conclusion: The 5 year follow-up results after CCTA extend the available follow up data, confirming that the exclusion of atherosclerotic changes in CCTA is associated with an excellent prognosis during 5 years. Both the presence of obstructive CAD and the number of abnormal segments in CCTA improve the predictive value of clinical risk assessment.

P693

A comparative cost impact study of cardiac forrester and coronary calcium score criteria given by NICE at rapid access chest pain clinics

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Purpose: NICE clinical guideline 95 (CG95) proposed the use of a Diamond Forrester (DF) calculator to determine cardiac investigations for patients with stable chest pain in the UK. Patients with DF scores <10 do not require further investigation; 10-29% calcium score CT (CS); 30-60% stress imaging; and >60% invasive angiography (IA). For those patients receiving a CS, a score of 0 requires no further investigation; 1-400 CT angiogram (CTCA); and >400 IA.

Method: This study was part of an ongoing RCT evaluating the cost effectiveness of cardiac CT as a primary investigation for stable patients. The sub-study evaluated the cost of DF and CS as risk stratification tools to guide the diagnostic tests.

DFs were calculated in 250 patients who proceeded to CS and CTCA performed on a 64 detector platform. CTCA was taken as the reference point for coronary artery disease (CAD) severity, with disease classified via the most significant lesion from none to severe. The theoretical number and cost of investigations was determined using the two models - the DF and the CS criteria.

Results: From January to December 2011 a total number of 107 patients underwent contrast MDCT for different indications. All patients were simultaneously examined within 7 days by TEE. The presence of LAA thrombi/filling defects were assessed and statistically analyzed.

Results: From a total number of 107 patients examined by MDCT the filling defect was found in 11 (10.3%) patients. Using the TEE, LAA thrombi were detected in 9 (8.4%) patients. With TEE as a reference method the sensitivity of MDCT in LAA thrombi detection was 90% (95% confidence interval [CI]: 89.3-91.6%), specificity 90% (95% CI: 89.3-91.6%), diagnostic accuracy 90% (95% CI: 89.3-91.6%). The agreement of both methods for the detection of LA thrombi was high: in 96 patients there were no thrombi detected using MDCT and TEE, in 6 patients there were thrombi found using MDCT and TEE, in 5 patients there were thrombi detected using MDCT but not proven by TEE (kappa = 0.683 [95% CI: 0.544-0.831]).

Conclusion: 256 MDCT is a noninvasive imaging method with high sensitivity, specificity and diagnostic accuracy for LAA thrombi detection. When compared to TEE, this method is burdened with radiation exposure.

Abstract P693 – Table 1. Projected costing of CG95 using both CG95DF and CG95CS

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<th>Patients with typical pain only (n=98)</th>
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P695

Aortic prosthetic heart valve motion during the cardiac cycle: implications for multidetector-row computed tomography imaging

P. Symersky1, J. Habetz2, B.A.J.M. De Mol1, R.P.J. Budde2, J. Hausleiter. German Heart Center, Munich, Germany

Introduction: The presence of left atrial appendage (LAA) thrombi is the important risk factor for cardioembolic stroke. Transeophageal echocardiography (TEE) is not recognized as a gold standard for detecting intracardiac thrombi.

Aim: To assess the diagnostic accuracy of 256 multidetector CT (MDCT) in LAA thrombi detection in patients undergoing MDCT for different indications compared to TEE as a reference diagnostic modality.

Methods: From January to December 2011 a total number of 107 patients underwent contrast MDCT for different indications. All patients were simultaneously examined within 7 days by TEE. The presence of LA thrombi/filling defects were assessed and statistically analyzed.

Results: From a total number of 107 patients examined by MDCT the filling defect was found in 11 (10.3%) patients. Using the TEE, LA thrombi were detected in 9 (8.4%) patients. With TEE as a reference method the sensitivity of MDCT in LAA thrombi detection was 90% (95% confidence interval [CI]: 89.3-91.6%), specificity 90% (95% CI: 89.3-91.6%), diagnostic accuracy 90% (95% CI: 89.3-91.6%). The agreement of both methods for the detection of LA thrombi was high: in 96 patients there were no thrombi detected using MDCT and TEE, in 6 patients there were thrombi found using MDCT and TEE, in 5 patients there were thrombi detected using MDCT but not proven by TEE (kappa = 0.683 [95% CI: 0.544-0.831]).

Conclusion: 256 MDCT is a noninvasive imaging method with high sensitivity, specificity and diagnostic accuracy for LAA thrombi detection. When compared to TEE, this method is burdened with radiation exposure.

Abstract P695 – Table 1. Projected costing of CG95 using both CG95DF and CG95CS

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</table>
Association between atrial fibrillation recurrence and thoracic and pericardial fat volume change after radiofrequency catheter ablation: assessment by 320-slice computed tomography

M. Motooka, Y. Hayama, S. Nakajima, M. Miyake, T. Tamura, H. Kondo, K. Kaitani, C. Izumi, Y. Nakagawa. Tenni Hospital, Tenni, Japan

Background: Left atrial (LA) remodeling has been reported to be an important factor in atrial fibrillation (AF) recurrence after pulmonary vein (PV) radiofrequency catheter ablation (RFCA). We hypothesized that multi-slice computed tomography (MSCT) would be useful for the evaluation of patients post PV isolation by delineating LA and PV remodeling.

Materials and methods: Fifty-four patients (62.8 ± 9.3 years, 48 males) with non-paroxysmal AF were enrolled. MSCT was performed before and after RFCA. Images were reconstructed at 16 phases of one cardiac cycle (from 5% to 95% of the R-R interval). Using multi-planar reconstruction, the location of the PV ostium was defined, and the ejection fraction (EF) of each PV was calculated as the volume change at the first 10 mm from the ostium using Simpson's disc methods. The maximal LA volume and the EF of LA and each PV (right superior PV: RSPV, right inferior PV: RIPV, left superior PV: LSPV, left inferior PV: LIPV) were calculated before and after RFCA. Patients were divided into two groups according to AF recurrence. The maximal LA volume and the EF of LA and each PV were calculated and compared before and after RFCA in the two groups.

Results: The maximal LA volume significantly decreased after RFCA in both groups. In patients with AF recurrence (n=22), the EF of LA and each PV did not change significantly. However, in patients without AF recurrence (n=32), the EF of LA significantly improved and the EF of PV significantly decreased in RSPV, RIPV, and LSPV (see Table).

Conclusion: It is suggested that PV contraction is retained in patients with AF recurrence. MSCT may have clinical implications for the non-invasive evaluation of pulmonary vein isolation procedural success and follow-up.

Association between thoracic and pericardial fat volume change after radiofrequency catheter ablation: assessment by 320-slice computed tomography

Results: PVF and TFV were significantly higher in patients with significant coronary artery stenosis (p < 0.001). Logistic regression was done p value was 0.54 for PVF, and 0.003 for TFV. Partial correlation was done controlling for age and BMI, R = 0.39 for TFV, and 0.56 for PVF, p < 0.0001 for both.

Conclusion: PVF and TFV are significantly higher in patients with significant coronary artery stenosis. TFV is more indicative for significant coronary artery disease. TFV and PVF are predictive of significant coronary artery stenosis beyond and independent from body mass index and age.

Comparison of size of ilio-femoral system in different populations: implication on transcatheter aortic valve implantation access route

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Aim: To demonstrate the variation in size of ilio-femoral arteries among different ethnic origins which affects the feasibility of utilizing the femoral access (requiring 18 Fr sheath) as an alternative access route for transcatheter aortic valve implantation (TAVI) and potential vascular access complication rate.

Method: From Jan 2011, in two institutions (Hospital in London, United Kingdom and Hospital in Hong Kong, China), first 100 patients aged 70 or above undergoing contrast-enhanced computed tomography (CT) scan with femoral artery visualization were recruited. Indications for CT, background demographics, iliac and femoral artery size and degree of calcifications were analyzed. Minimal luminal diameters on each side of ilio-femoral artery were identified and compared. Degree of calcifications was evaluated and graded: no calcification (0), mild calcification (1), moderate calcification (2) and heavy/circumferential calcification (3).

Results: 100 patients in each institution (with similar age, sex and incidences of DM, HT and PVD) who underwent contrast-enhanced CT were recruited. In Chinese population, the average minimal diameters of ilio-femoral arteries were 6.4 ± 1.7 mm (R-side) and 6.2 ± 2.0 mm (L-side) while those in Caucasian population were 8.2 ± 1.5 mm (R-side) and 7.5 ± 1.5 mm (L-side). Degrees of vessel calcifications were 1.0 ± 0.9 (R-side), 3.3 ± 1.0 (L-side) in the former and 1.3 ± 1.0 (R-side), 1.4 ± 1.1 (L-side) in the latter. Comparing the larger side of ilio-femoral arteries in the two populations, Chinese population has a significantly smaller caliber of ilio-femoral arteries (p < 0.05 vs 8.4 ± 1.4 mm, p < 0.001) but with similar degree of calcifications (p = 0.19 for R, 0.49 for L).

Conclusion: In selected Chinese population, the possibility of safely utilizing femoral access for TAVI requiring 18 Fr sheath might be lower when compared with Caucasian who generally has larger caliber ilio-femoral arteries. Careful case selection or consideration for alternative access route might be needed in TAVI candidates to prevent vascular complications.
CT characteristics of coronary arteries in 4 types of aortic aneurysms evaluated for surgery.

Ascending aortic aneurysms complicated less vulnerable plaques than abdominal aortic aneurysms

Background: Evaluation of coronary artery anatomy is recommended prior to great vessel surgical intervention. The underlying pathophysiology of abdominal aortic aneurysms (AAA) is often systemic atherosclerosis, and that of thoracic aortic aneurysms (TAA) is connective tissue or inflammatory disease. To study this, we carried out ECG gated 320 slice CT in subjects with TAA and AAA who were being evaluated coronary arteries for possible surgical intervention.

Materials and Methods: 66 asymptomatic subjects (36 with TAA only (19 male, mean age 73±19 years, maximum diameter of TAA 53±4.95mm), who were being evaluated for possible surgical intervention, underwent retrospective ECG gated 320 slice CT (Aquilion one) for preoperative evaluation of coronary arteries.

Results: In coronary arteries, frequency of calcified plaques were significantly lower in descending TAA (33%) than AAA group (87%, P<0.01). That of mixed plaques were significantly lower in ascending TAA (20%) than AAA (70%) and AAA group (57%, P<0.01). Frequency of non-calciﬁed plaques were signiﬁcantly lower in ascending TAA (30%) than AAA group (60%, P=0.02). That of outward remodeling were signiﬁcantly lower in ascending TAA (5%) than descending TAA (50%) and AAA group (40%) (both P<0.01). That of luminal stenosis more than 50% were signiﬁcantly lower in ascending TAA (20%) than AAA group (70%, P<0.01).

Conclusions: Ascending TAA had coronary arteries which characteristically tended to less vulnerable coronary plaques especially when compared with AAA group. This information may be useful for cardiovascular surgeons.

Systolic and diastolic parameters of the aortic annulus in patients scheduled for transcatheter aortic valve implantation (TAVI)

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Purpose: The exact evaluation of the aortic annulus dimensions in patients with high-grade aortic stenosis, scheduled for TAVI, is essential. It is unknown whether these parameters should be measured in systole or diastole and to what extent they differ between the phases.

Methods: Consecutive echocardiography-triggered CT angiography data sets of 75 patients, scheduled for TAVI, were analysed. The diameters in short- and long-axis view, the area and circumference of the aortic annulus were analysed by two independent observers in systolic (35%) and diastolic reconstructions (75%) of the RR-cycle. Inter- and intraobserver variability were assessed. Systolic and diastolic parameters were compared to each other.

Results: There was no statistical significant difference between systolic and diastolic diameters of short: (2.13±0.21cm vs. 2.07±0.22cm) and long-axis view diameters (2.64±0.29cm vs. 2.62±0.32cm), the area (4.82±0.86cm² vs. 4.69±1.01cm²) and circumference (7.94±0.72cm vs. 7.84±0.87cm) of the aortic annulus. Interobserver variability results are shown in the table. Intraobserver results showed signiﬁcant differences of short- and long-axis view diameters in systolic reconstructions (2.07±0.23cm vs. 2.12±0.23cm, P = 0.004 and 2.60±0.23cm vs. 2.64±0.31cm, P = 0.003), whereas in diastolic reconstructions, there was no significant difference of all aortic annulus parameters.

Conclusions: Dimensions of the aortic annulus in CT imaging do not differ signiﬁcantly between systolic and diastolic data sets. Interobserver variability is independent of the reconstructed phase.

Increased epicardial adipose tissue volume predicts presence of insulin resistance and coronary artery disease in non-obese subjects without metabolic syndrome

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Background: It is well known that obesity and overabundance of visceral fat are important risk factors of coronary artery disease (CAD). Visceral fat produces various adipokines which are associated with development of CAD. Recently, epicardial adipose tissue (EAT) was also reported to secrete various adipokines such as tumor necrosis factor-alpha, resistin and monocyte chemotactic protein-1. It is currently reported that EAT volume is significantly associated with insulin resistance (IR) and CAD in patients with obesity or metabolic syndrome. However, it remains determined whether EAT volume is associated with IR and CAD even in lean subjects.

Methods and Results: We prospectively studied 624 consecutive patients who underwent multi detector computed tomography (MDCT) at the Yamagata University Hospital between January 2009 and June 2011. Obesity was deﬁned as body mass index (BMI) ≥ 25 kg/m² and metabolic syndrome was deﬁned according to the criteria from the National Cholesterol Education Program Adult Treatment Panel III. After we excluded 385 patients with obesity or metabolic syndrome, 239 patients were enrolled in the present study. EAT volume was measured by using 64-slice MDCT. There were 102 (42.7%) subjects with IR (homeostasis model assessment-IR > 2.5) and 88 (36.8%) subjects with CAD. Subjects with IR had higher EAT volume, higher BMI, higher serum low-density lipoprotein cholesterol level and higher prevalence of CAD compared with those without IR. Subjects with CAD were younger and showed higher EAT volume, lower serum high-density lipoprotein cholesterol level and higher prevalence of IR compared with those without CAD. After adjustment of age, gender, and BMI, increased EAT volume (35 ml of mean EAT volume) was independently associated with IR (hazard ratio 2.6, 95% conﬁdence interval 1.5-4.8). Increased EAT volume was also associated with CAD (hazard ratio 1.9, 95% conﬁdence interval 1.0-3.6) after adjustment of age, gender, BMI and presence of IR.

Conclusion: Increased EAT volume may play a key role in development of IR and CAD even in non-obese subjects without metabolic syndrome.

Conformational pulsatile changes of the aortic annulus: impact on prosthesi size by computed tomography for transcatheter aortic valve replacement (TAVR)

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Objectives: To investigate pulsatile changes of the aortic annulus and their impact on prosthesi size by computed tomography (CT).

Background: Precise non-invasive prosthesis sizing is a prerequisite for transcatheter aortic valve replacement (TAVR).

Material and Methods: 110 patients with severe aortic stenosis (mean age 82.9±8.8 years, mean aortic valve area 0.69±0.18cm²) underwent ECO-gated CT. The aortic annulus dimensions were planimetrically assessed as area-derived (AAR = 2π x (CSA/n)) and perimeter-derived (DP = P/π) diameter in 5% increments of RR. Hypothetical prosthesis sizing was based on DA and DP (23mm prosthesis for <22mm; 26mm: 22-25mm; 29mm: >25mm) and compared between maxi...
Peri-atrial epicardial adipose tissue is associated with new-onset non-valvular atrial fibrillation

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Purpose: Obesity is a risk factor for the development of atrial fibrillation (AF), however distribution of body fat varies in each patient. Epicardial adipose tissue (EAT) is recognized as an important inflammatory tissue, which may exert deleterious effects on the adjacent left atrial (LA) wall. The aim of this study was to investigate the relationship between peri-atrial EAT and new-onset non-valvular AF in patients with coronary artery disease (CAD), using multidetector computed tomography (MDCT).

Methods: The study consisted of 279 CAD patients (176 men; age, 65±10 years) with no history of AF who underwent MDCT examination. EAT volume was calculated as the sum of EAT area and subsequently divided into peri-atrial and peri-ventricular EAT. The classical cut-offs to future AF, LA volume and, the total- and peri-atrial EAT volumes by MDCT were analyzed.

Results: During follow-up of 3.3 years, AF occurred in 17 (6.1%) patients including 13 paroxysmal AF and 4 persistent AF. Patients with a higher body mass index were likely to be older, had higher level of serum C-reactive protein, had larger volumes of left ventricular mass, LA, total EAT, and peri-atrial EAT, compared to those without AF (all p<0.05). Cox hazard model analysis indicated that the presence of diabetes, LA, and peri-atrial EAT volumes (p=0.01; p<0.001, and p=0.001, respectively) were independent predictors for future AF. The sensitivity and specificity for the prediction of AF using peri-atrial EAT index of ≥27 m/m² were 88% and 92%, respectively. Patients with increased peri-atrial EAT volume were at higher risk of new-onset AF than those without increased peri-atrial EAT volume (Figure).

Conclusions: This MDCT study demonstrated that peri-atrial EAT volume predicted new-onset AF in patients with CAD, independent of LA enlargement.

MULTIDETECTOR COMPUTED TOMOGRAPHY: TECHNOLOGICAL ISSUES

CORONARY ARTERY CALCIUM SCORING: INFLUENCE OF ADAPTIVE STATISTICAL ITERATIVE RECONSTRUCTION USING 64-MDCT

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Background: Assessment of coronary artery calcification is increasingly used for cardiovascular risk stratification. We evaluated the reliability of calcium-scoring results using a novel iterative reconstruction algorithm (ASIR) on a high-definition 64-slice CT scanner, as such data is lacking.

Methods and Results: In 50 consecutive patients Agatston scores, calcium mass and volume score were assessed. Comparisons were performed between groups using filtered back projection (FBP) and 20-100% ASIR algorithms. Calcium score was measured in the coronary arteries, signal and noise were measured.

Accuracy of prospectively ECG-triggered very-low-dose coronary DSCT angiography using iterative reconstruction for the detection of coronary artery stenosis: comparison with invasive catheterization

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Introduction: Raw-data based iterative reconstruction (IR) allows substantial reduction of image noise and hence the use of very low dose data acquisition protocols in coronary CT angiography. We evaluated image quality of IR and its diagnostic accuracy compared to invasive catheterization.

Methods: 30 symptomatic patients (age: 62±11 years, BMI: 27.9±2.9 kg/m², heart rate: 58±6 bpm after beta blocking) with an intermediate likelihood for coronary artery disease underwent coronary dual-source CT (DSCT) angiography (prospectively ECG-triggered at 70% of RR-interval, 100kV, 165 mAs, 2×128x0.6mm collimation, 60mL contrast at 6ml/sec) prior to invasive catheterization. DSCT images were reconstructed both using standard filtered back projection (FBP) and IR algorithms. Subsequently, the accuracy to detect significant coronary artery stenosis (>50%) was assessed for FBP and IR by two independent observers blinded to the results of invasive catheterization. Additionally, differences in subjective image quality (0 to 3 points), image noise, signal- and contrast-to-noise-ratios (SNR, CNR) were determined between FBP and IR. Mean effective radiation dose was calculated based on the dose-length product.

Results: Mean DLP and effective radiation dose of prospectively ECG-triggered coronary DSCT angiography was 47.3 mGy·cm and 0.65±0.05 mSv. IR led to significantly improved image quality in comparison to standard FBP (image quality score: 2.4±0.6 vs. 1.9±0.7 points, p<0.01; image noise: 45.1±13 vs. 51.1±12 HU, p<0.05; SNR: 12.8±9 vs. 9.3±0.5, p<0.05; CNR: 14.9±9 vs. 10.3±0.5, p<0.05). In standard FBP reconstructions, sensitivity, specificity, PPV and NPV of DSCT angiography to detect significant coronary artery stenoses were 86% (67%), 83% (92%), 65% (80%), 95% (19/20) on a per-patient and 80% (8/10), 95% (10/11), 62% (6/10), 98% (10/10) on a per-patient basis. After IR, values improved to 100% (7/7), 97% (10/10) (20/20), 70% (7/10), 100% (10/10) per patient and to 90% (9/10), 96% (10/11), 69% (8/12), 99% (10/10) per vessel.

Conclusion: Raw-data based iterative reconstruction along with prospective ECG-triggering improves diagnostic accuracy for detection of coronary artery stenosis when compared to standard filtered back projection and allows substantial reduction of radiation exposure in coronary DSCT angiography.

Should computed tomography coronary angiography be aborted when the calcium score exceeds a certain threshold in patients with chest pain?

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Introduction: There is an ongoing debate about whether a computed tomography coronary angiography (CTCA) should be aborted when the calcium score (CS) exceeds a certain threshold in patients with chest pain. The aim of this study was to discover whether specific “cutpoints” regarding coronary artery CS could be used to abort CTCA in patients with chest pain.

Methods: 294 consecutive patients evaluated for chest pain, without known coronary artery disease and submitted for 64-CT between January 2007 and December 2010 were enrolled. Subjects underwent Agatston CS and CTCA using current 64-slice technology.

Results: Severe coronary stenoses were noted in 75 of 294 (25.1%) patients on CTCA. A very high prevalence of severe coronary stenoses was found in patients with CS≥400 (87.0%). The CS had area under the ROC curve 0.86 to predict severe coronary stenoses on CTCA. The best discriminant cut-off point was CS≥400 (sensitivity of 55.3%, specificity of 83.5, positive predictive value of 85.8%, negative predictive value of 84.0%). Multivariant logistic regression
Objective: To determine the impact of an ECG-triggered computed tomography angiography (CTA) utilizing high-pitch spiral dual source CT on radiation dose and image quality of the heart and vascular access site prior to Transcatheter Aortic Valve Implantation (TAVI).

Methods: This was a retrospective analysis of consecutive patients evaluated for TAVI. The patients were divided into three groups based on the CTA protocol used: spiral CTA without ECG gating (non-gated, n=13), spiral CTA with retrospective ECG gating (gated spiral, n=12); and high-pitch dual-source CTA (gated flash, n=18). The effective radiation dose was calculated from the given total Dose Length Product (DLP) multiplied by conversion factor of 0.016 (average for chest, abdomen and pelvis). The image quality was determined by calculating the contrast-to-noise ratio (CNR) in aortic root and iliofemoral arteries.

Results: A total of 43 patients (age 75±8 years, males were 72%) were included. The body mass index was 31.1±9.4. The total amount of contrast per exam was 95±11 mL (no significant difference between the groups). The effective radiation dose was significantly lower in patients who underwent gated flash compared to the gated spiral and non-gated CT; the median was 5.6 vs. 29.9 and 16.6 mSv, respectively, p<0.0001 (figure1). The image quality was well maintained across all the groups; the root CNR was 21.8±10.4, 14.0±6.5 and 19.7±9.1; the femoral artery CNR was 17.1±7.4, 10.2±4.5 and 15.0±7.6 in non-gated, gated spiral and gated flash CT respectively.

Conclusion: High-pitch prospectively triggered CTA is an attractive protocol to assess the entire aorta and iliofemoral arteries in evaluating patients prior to TAVI. It is associated with a significantly lower radiation dose while maintaining sufficient image quality.
**Premedication with beta blocking agents for coronary CT angiography: analysis of efficacy and safety in the German cardiac CT registry**

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**Objectives:** Premedication with beta blocking agents is recommended for heart rate control prior to coronary CT angiography. However, there is insufficient data about the use in daily practice, effectiveness and safety issues of beta blockers for this purpose.

**Methods:** Patient characteristics and peri-intravenous parameters of patients undergoing coronary CT angiography were submitted by ten experienced centers to the German Cardiac CT Registry. A total of 3203 patients were analyzed with regards to the use of beta blockers, procedural data such as heart rate and peri-procedural complications.

**Results:** Of 3203 patients included into the registry (mean age 60±12 years; 38% female), 2414 received beta blockers (75.4% of all patients). 1443 received only intravenous, 628 patients only oral beta blockers (63.9% and 26% of all patients on beta blocking agents). Both i.v. and oral beta blocking agents were administered in 243 patients (10.1%, respectively). Mean heart rate during CT was 67.3 ± 17.0 bpm. It was significantly higher for patients on beta blockers (mean/max heart rate 59.8 ± 8.4 bpm/67.9 ± 27.3 bpm) than for patients without (mean/max heart rate 59.1 ± 10.8 bpm/67.9 ± 22.7 bpm, p < 0.001/p<0.05). Oral was more effective than i.v. and combined beta blockade (mean/max heart rate 57.8 ± 6.8 bpm/67.0 ± 30.1 bpm and 62.0 ± 6.7 bpm/69.0 ± 15.8 bpm, p < 0.001 for both). The rate of patients with all vessels evaluable for stenoses was insignificantly higher in patients on beta blockers (96.3% vs. 94.9%, p = 0.19). Peri-procedural complications were rare (33 of 3203 patients, only 7 patients with adverse events attributable to pre-procedural medical treatment) and did not show any significant differences for patients with and without beta blockers.

**Conclusions:** Beta blockers are consistently used for heart rate control prior to coronary CT angiography, with oral being more effective than i.v. - beta blockade.

**The usefulness of landiolol, an ultra-short-acting beta1-adrenergic blocker, for 256-slice cardiac computed tomography with iterative reconstruction**

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**Background:** The hybrid iterative reconstruction (IR) technique for 256-slice coronary computed tomography (CT) with improved temporal resolution can reduce radiation exposure and provide sufficient image quality. Furthermore, the administration of a short-term β-blocker is the first-line option for effective heart rate (HR) reduction and reducing motion artifacts during coronary CT angiography.

**Purpose:** The aim of this study was to evaluate the efficacy of the administration of intravenous landiolol, an ultra-short-acting cardioselective β-blocker, for both reduction of the radiation dose and improving the image quality using CT angiography with high temporal resolution and an IR algorithm (IDose).

**Methods:** A total of 400 patients with HRs ≥ 65 beats/min before 256-slice coronary CT were prospectively randomized to a β-blocker (n=200) or a control group (n=200). Landiolol (0.25 mg/kg) was administered intravenously before 256-slice CT scanning in the β-blocker group. IR was provided with moderate level (IDose level 4) and a helical scan with tube current modulation was performed in all patients. The radiation dose and image quality were systematically analyzed. The image quality of all coronary segments was graded on a 4-point scale (1=best to 4=worst) by two experienced observers.

**Results:** Intravenous landiolol was administered in 200 patients without adverse events. The mean HRs were significantly reduced (76±8.10 to 63±10.3, p<0.01) 4 minutes after administration of landiolol, and 68% of patients showed an HR<65 beats/min. The mean effective radiation dose in the β-blocker group was lower than that in the control group (4.20±1.46 vs. 5.05±2.03 mSv, p<0.01).

The image quality was grater in the β-blocker than that in the control group (1.08±0.11 vs. 1.21±0.20, p<0.01).

**Conclusion:** Intravenous landiolol administration is useful to both reduce radiation exposure and improve image quality of IR CT.

**How the use of iterative reconstruction affects assessment of patients with stable chest pain**

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**Purpose:** This study was designed to evaluate the impact of a novel iterative reconstruction (IR) algorithm on cardiac computed tomography (CT) image quality and effective radiation dose (ED).

**Methods:** As a sub-study of the larger CAPP (CT for Assessment of Pain and Plaque) trial, this study enrolled 250 consecutive patients with stable chest pain. The CAPP study was designed to evaluate the implementation of NICE guideline 95 on patients with stable chest pain. CT examinations were performed on a 64 multi-detector scanner. Scan protocols were patient specific and at the discretion of imaging clinician. Images were reconstructed with either a standard filtered back-projection (FBP) or IR. Image noise was measured within regions of interest (ROI), and image quality was qualitatively assessed by two clinicians blinded to the reconstruction method. Images were also assessed for the presence of noise artefacts.

**Results:** 4 patients withdrew. 246 patients (140 males) underwent cardiac CT. 124 consecutive patients underwent image reconstruction with FBP (72 with retrospective and 52 with prospective) and 122 patients underwent scanning with IR (112 with retrospective and 10 with prospective). Demographics are in Table 1. The mean estimated EDs were 8.3 mSv (FBP) and 4.4 mSv (IR) (dose savings of 47% using IR for retrospective cohorts and 6.5 mSv (FBP) and 4.3 mSv (IR) (dose savings of 34%) (p < 0.0001). There was no statistical difference in noise or mean attenuation in the ROIs. The mean IR image quality score was 3.7 ± 1.0 compared to 3.3 ± 1.2 for FBP images (p < 0.001). 29 of the 52 FBP prospective studies had staircase artefacts, with 2 of the 10 IR demonstrating the same.

**Conclusion:** IR in cardiac CT offers substantial ED reduction without compromise in image quality. This work suggests IR influenced clinical practice, as its availability promoted the use of retrospective protocol with practitioners opting for its diagnostic reassurance.

**Prospective randomized trial on radiation dose estimates of CT angiography in patients scanned with a high-pitch-first strategy: the PROTECTION II trial**

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**Background:** Concerns have been raised about the radiation exposure during coronary CT angiographies (CCTAs). For a prospectively ECG-triggered high-pitch first strategy and even conventional submillisecond radiation doses have been reported for CCTA, but it is unclear, whether image quality is maintained when compared to conventional CCTA. The multi-center, prospective, randomized PROTECTION II study investigates the impact of the high-pitch CT protocol on image quality and radiation dose.

**Methods:** 303 patients with suspected coronary artery disease and low and stable heart rate were randomized to either a high-pitch-first or a conventional-first CCTA strategy. In the conventional-first CCTA arm, ECG-triggered axial or ECG-gated low-pitch helical CT data acquisitions were used. If image quality was defined insufficient with the first CCTA scan, a second scan was performed. The primary study endpoint was to show the diagnostic non-inferiority of the high-pitch scan protocol, which was assessed by a 4-point image quality grading score (1: nondiagnostic to 4: excellent image quality; predefined non-inferiority margin of 0.25 score points). Total radiation dose, the need for a second CCTA scan as well as the rate of downstream testing during 30-day follow-up were assessed as secondary endpoints.

**Results:** 150 and 153 patients were randomized to high-pitch-first and conventional-first CCTA groups, respectively. The mean heart rate and BMI were 57.6 ± 6.0 bpm and 26.5 ± 3.7 kg/m², respectively. A second CCTA scan was performed in 14.0% and 9.2% of patients in the high-pitch-first and conventional-first groups, respectively (P = 0.187). The resulting total CCTA dose was 2.05 ± 2.4 mSv

**Abstract P713 – Table 1. Demographics and CT data**
Influence of heart rate on the accuracy of dual source CT for coronary stenosis detection in patients with intermediate likelihood of disease: results of the international multicenter MEDIC trial

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The accuracy of dual source CT (DSCT) for the detection of coronary artery stenosis depends on heart rate. In this study, we investigated the influence of heart rate on stenosis detection has in a sufficiently sized multicenter trial. We analyzed the results of an international multicenter trial (“Multicenter Evaluation of Dual source CT coronary angiography in patients with Intermediate likelihood of Coronary artery stenoses” - MEDIC) with 415 patients to determine the influence of heart rate in the accuracy of dual source coronary CT angiography.

Methods: In 6 international sites, 415 patients (30 - 80 years; suspected coronary artery disease with intermediate likelihood of coronary stenoses, no renal failure, no arrhythmias, Agatston score < 800) were investigated by contrast-enhanced DSCT in spiral mode without beta blockade and by invasive coronary angiography.

Results: Mean heart rate during DSCT was 67 ± 20 beats/min. Mean DLP was 424 ± 237 mGy*cm (5.9 mSv). In the entire patient group, sensitivity of DSCT for the detection of individuals with at least one coronary artery stenosis was 95% (104/110, 95%CI: 88% - 98%). Specificity was 95% (289/305, 95%CI: 92% - 97%), the positive predictive value was 84% (104/120) and the negative predictive value was 98% (289/295). Heart rate did not significantly influence accuracy (heart rate ≤ 60 minute: sensitivity 98%, specificity 94%, n = 145; heart rate > 60 minute: sensitivity 92%, specificity 95%, n = 270; p = n.s.).

Conclusions: In the largest multicenter trial to date concerning the detection of coronary artery stenoses by CT angiography, dual source CT demonstrated a high accuracy for the identification of patients with significant coronary lesions, which was independent of heart rate.

MULTIDETECTOR COMPUTED TOMOGRAPHY IN THE ASSESSMENT OF MYOCARDIAL PERFUSION

Adenosine-stress CT myocardial perfusion and CT coronary angiography for assessment of coronary artery disease: initial results

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Introduction: Computed tomography coronary angiography (CTCA) has been widely accepted as a reliable, non-invasive modality, when studying the coronary arteries. However, it cannot assess the functional implications of any detected coronary stenoses. A combination of adenosine stress myocardial CT perfusion (CTP) and CT angiography (CTCA) can be demonstrated if combined with myocardial stress CT perfusion scan (CTP). This is the first report of our experience, with the use of CTP in evaluating the severity of coronary artery disease (CAD).

Methods: Fourteen patients with angina symptoms, underwent a standardised stress CT (Aquilion ONE, Toshiba) protocol, consisted of prospectively ECG-triggered CTCA, which, in cases of ≥50% obstruction in any of the coronary arteries, was combined with rest/stress myocardial perfusion imaging (3 min iv adenosine infusion at 0.14 mg/kg/min and 5-20 mg iv metoprolol for baseline heart rate above 70 beats/min). An experienced cardiologist visually assessed myocardial perfusion defects, and CTP analysis was performed on transmural perfusion. On-rate/TPR (subendocardial attenuation density/ subepicardial attenuation density).

Results: All patients (63±9.86 years old, range 44-78; 9 males; with PCI history) completed the CT protocol without adverse events. Positive results were found in 5 of them. The referral reasons included extensive CAC (3 patients), >50% stenosis in one artery (8), stenosis in three arteries (3). Image quality was diagnostic in 228/238 territories. The mean coronary artery calcification score (CACs) in the 11 non-PCI patients was 1677 (min: 272; max: 6408); 3 patients with CACs>1000, 3 with CACS=401-1000, 5 with CACS=101-400. Mean resting TPR was 1.72 (min: 0.85, max: 5.1), with values >0.85 accepted as normal. Mean stress TPR was 1.27/min: 0.3, max: 3, n=14). In 16 territories with visually reported defect, mean rest TPR was 0.9 (min: 0.85, max: 1.4), while stress TPR was 0.66 (min: 0.3, max: 0.83); p=0.02. In the 206 normal territories the mean stress TPR was 1.812 (min: 0.9, max: 5.1) and the mean contrast TPR was 1.344 (min: 0.3, max: 3); p=0.004. In 4 territories with normal TPR, there was CTCA and CTP evidence of ischaemia.

Conclusions: The combination of CTA and CTP can identify ischemic defects due to coronary artery stenosis. TPR demonstrates good correlation with perfusion defects.

Discordance of anatomical and functional coronary stenoses assessed by 320-row computed tomography

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Background: It has been reported that computed tomography coronary angiography (CTCA) provides excellent diagnostic sensitivity for identifying coronary stenoses.

Aim: We sought to determine the diagnostic performance of 320-row CTCA and quantitative computed tomography coronary angiography (QCT) to predict the hemodynamic significance of de novo discrete coronary stenoses, using fractional flow reserve (FFR) as a reference standard.

Methods and Results: We investigated 26 vessels of 25 patients who underwent both 320-row CTCA before invasive coronary angiography and FFR measurement. Quantitative coronary angiography (QCA), QCT (cross-sectional area stenosis), and CT-density-derived stenosis assessment (CTDA) were performed to determine the severity of a stenosis that was compared with FFR measurement. A significant anatomical or functional stenosis was defined as > 50% diameter or 75% area stenosis, lumen CT density at most stenotic site < 200 HU, or an FFR < 0.80. A total of 26 stenoses were evaluated of which 69.2% (18 of 26) had an FFR > 0.80. The diagnostic accuracy of QCT, CTDA, and QCA to detect a hemodynamically significant coronary lesion was 42.3%, 42.3%, and 80.8%, respectively. Correlation between QCT and CTDA with FFR measurement was not significant or weak.

Conclusion: The anatomical assessment of the hemodynamic significance of
coronary stenoses determined by QCT, CTDI, or QCA does not correlate well with the functional assessment of FFR. Determining the hemodynamic significance of an angiographically intermediate stenosis remains mandatory for patient management.

Ct myocardial perfusion - correct scan timing for ischemia detection from time attenuation curves

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Purpose: CT Myocardial Perfusion Imaging (CTMPI) has been reported with various types of scanners. The 2nd generation dual-source scanners generate complete time-attenuation curves (TACs) for the heart & allow differentiation between normal & ischemic myocardium. For non-dual-source scanners relying on imaging at a single time point, the accurate identification of appropriate time to scan in detecting ischemia is less precise. We utilized the 128-slice DSCT to study the ideal imaging window for ischemia detection.

Methods: 25 patients with known reversible defects, as detected by nuclear perfusion imaging, underwent dipyridamole-stress CTMPI. Patients received 50cc of contrast was less than 50% of the maximum enhancement. TACs were computed for all 17 segments of the myocardium, and attenuation curves of healthy and ischemic segments were compared.

Results: The difference between healthy and ischemic myocardium ranged from 34HU at the optimal time for imaging to 12HU at a suboptimal (late) imaging time. Using maximum arterial enhancement as a reference time-point, there was a time window of 5 seconds before and after the peak, during which at least 60% of the maximum contrast could be detected in the myocardium. Outside this optimal window, the contrast was less than 50% of the maximum enhancement.

Conclusions: 1) The window of 10s implies that there is some latitude of scanning in the detection of ischemic defects.
2) However this relatively broad window may result in variability of estimation of size of ischemic defect, the quantitation being affected by exact scan timing.

Myocardial perfusion at rest is higher in women than in men

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Background: The clinical presentation of ischemic heart disease in women differs from men, which could reflect gender-related differences of normal physiology. With 320-multi detector computed tomography (MDCT) it has become possible to assess non-invasively regional and transmural myocardial perfusion in addition to coronary atherosclerosis. The aim of this study was in asymptomatic middle-aged to old individuals to evaluate potential gender-related differences of left ventricular myocardial perfusion measured as LV myocardial Attenuation Density/LV blood pool Attenuation Density (MyoAD-ratio) at rest and 2 Transmural Perfusion Ratio (TPR) as a measure of the endocardial perfusion relative to epicardial perfusion.

Methods and results: Myocardial perfusion at rest and coronary artery atherosclerosis was evaluated with MDCT in 206 asymptomatic women and 203 age matched men from the Copenhagen General Population Study. A significantly higher Global LV myocardial AD was found in women (97 vs. 84 Houndsfield Units, p<0.0001) (Figure 1). Left ventricular myocardial perfusion at rest (LV MyoAD-ratio) was higher in women compared with men (9% difference; p=0.039).

A multivariate analysis including age, gender, cardiovascular risk factors, coronary calcium score and presence of coronary stenosis, global LV MyoAD-ratio remained significantly higher in women than in men (p=0.045). No effect of cardiovascular risk factors on myocardial perfusion at rest was noted. TPR was slightly lower in women than in men (1.12 vs. 1.14; p<0.0019).

Conclusion: Left ventricular myocardial perfusion at rest is higher in women than men, independent of coronary atherosclerosis in asymptomatic subjects with risk factors.

Stress myocardial computed tomography perfusion imaging and fractional flow reserve in patients with calcified coronary plaques

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Purpose: Multidetector computed tomography (CT) angiography is limited in the ability to detect coronary stenosis with calcification. The objective of this study is to assess the usefulness of stress myocardial CT perfusion to detect functional coronary stenoses as determined by fractional flow reserve (FFR) in patients with calcified plaques.

Methods: In patients presenting with suspected coronary artery disease, the calcium scores were determined for each of the main coronary arteries before CT angiography. Patients who had at least one calcified vessel with Agatston score of ≥ 200 underwent 256 slice dipyridamole-stress CTMPI. The FFR was measured in the calcified vessels with ≥ 50 diameter stenosis on invasive angiography. FFR of 0.80 or less was considered hemodynamically significant.

Results: The FFR was measured in 58 calcified vessels (Agatston score 730.1±597.6) of 43 patients (Age 71.0±8.6 years, 74% male). Agatston score and FFR (0.80±0.12) were not significantly correlated (r = 0.03, p = 0.82). In the vessel-based analysis, CT perfusion had similar sensitivity (83% vs. 96%, p = 0.35), higher specificity (82% vs. 15%, p < 0.001), and higher diagnostic accuracy (83% vs. 48%, p < 0.001) for detection of hemodynamically significant stenosis as compared with CT angiography. The area under the receiver-operating characteristic curve for CT perfusion (0.83; 95% confidence interval [CI]: 0.71 to 0.94) was greater than that for CT angiography (0.55; 95% CI: 0.40 to 0.70).

Conclusions: Stress myocardial perfusion imaging with multidetector CT localizes calcified coronary plaques and offers feasible diagnostic performance in detecting functional coronary stenoses noninvasively in patients with calcified lesions.

Myocardial perfusion measured by cardiac 320-multidetector computer tomography in patients with coronary artery disease: a qualitative comparison study with cardiac magnetic resonance imaging

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Background: Multidetector computed tomography (CT) angiography has become a routine diagnostic tool in the assessment of coronary artery disease. The diagnostic accuracy of 320-multidetector CT perfusion imaging has been validated against coronary angiography. Patients who had at least one calcified vessel with Agatston score of ≥ 50% diameter stenosis were included. A total of 200 underwent 256 slice adenosine stress myocardial CT perfusion and CT angiography. The FFR was measured in the calcified vessels with ≥ 50 diameter stenosis on invasive angiography. FFR of 0.80 or less was considered hemodynamically significant.

Methods: In patients presenting with suspected coronary artery disease, the calcium scores were determined for each of the main coronary arteries before CT angiography. Patients who had at least one calcified vessel with Agatston score of ≥ 200 underwent 256 slice dipyridamole-stress CTMPI. The FFR was measured in the calcified vessels with ≥ 50 diameter stenosis on invasive angiography. FFR of 0.80 or less was considered hemodynamically significant.

Results: The FFR was measured in 58 calcified vessels (Agatston score 730.1±597.6) of 43 patients (Age 71.0±8.6 years, 74% male). Agatston score and FFR (0.80±0.12) were not significantly correlated (r = 0.03, p = 0.82). In the vessel-based analysis, CT perfusion had similar sensitivity (83% vs. 96%, p = 0.35), higher specificity (82% vs. 15%, p < 0.001), and higher diagnostic accuracy (83% vs. 48%, p < 0.001) for detection of hemodynamically significant stenosis as compared with CT angiography. The area under the receiver-operating characteristic curve for CT perfusion (0.83; 95% confidence interval [CI]: 0.71 to 0.94) was greater than that for CT angiography (0.55; 95% CI: 0.40 to 0.70).

Conclusions: Stress myocardial perfusion imaging with multidetector CT localizes calcified coronary plaques and offers feasible diagnostic performance in detecting functional coronary stenoses noninvasively in patients with calcified lesions.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>A. Diagnostic accuracy of stress perfusion images: CT qualitative against CMR qualitative</th>
<th>B. Diagnostic accuracy of rest perfusion images: CT qualitative against CMR qualitative</th>
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<tr>
<td></td>
<td>Sensitivity 0.482, Specificity 0.915, PPV 0.614, NPV 0.863, 95% CI 0.374-0.577, 0.885-0.942, 0.735-0.753, 0.835-0.888</td>
<td>Sensitivity 0.482, Specificity 0.915, PPV 0.614, NPV 0.863, 95% CI 0.374-0.577, 0.885-0.942, 0.735-0.753, 0.835-0.888</td>
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CT = computed tomography. CMR = cardiac magnetic resonance. PPV = positive predictive value. NPV = negative predictive value. CI = confidence interval.
The study complied with the Declaration of Helsinki.

Results: The qualitative CT analysis of stress images had a sensitivity of 100%, a specificity of 33.3%, Positive predictive value (PPV) of 86.7%, and negative predictive value (NPV) of 100% compared to the qualitative CMR stress analysis on a per patient basis, while the qualitative CT analysis of rest images had a sensitivity of 100%, a specificity of 66.7%, PPV of 50.0%, and NPV of 100% compared to the qualitative CMR rest analysis on a per patient basis to detect myocardial perfusion defects (Table 1).

Conclusions: Our study shows that 320-detector CT perfusion images can be used clinically with a high probability to detect myocardial perfusion defects compared to CMR both for the stress and rest images.

P723 Feasibility of coronary CT angiography for predicting the functional significance of stenosis severity in patient with intermediate coronary artery disease

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Purpose: Feasibility of coronary CT angiography (CCTA) in intermediate coronary artery disease (CAD) is not well elucidated. The purpose of this study was to evaluate the feasibility of CCTA in intermediate CAD by comparing with fractional flow reserve (FFR).

Methods: We enrolled 109 Patients (129 lesions) with intermediate CAD who underwent CCTA years after coronary angiography (CA) with FFR retrospectively. Intermediate CAD was defined as 30–70% diameter stenosis (DS), % assessed by CAG, and functionally significant stenosis was defined as FFR <0.8. Maximal hyperemia was induced by intracoronary continuous adenosine infusion using microcatheter. CCTA measurements included diameter stenosis and a stenosis calcium score. We divided 2 groups according to atastenosis calcium score for evaluation of calcium score effect assessing stenosis severity (group A: Calcium score <100, n=64, group B: calcium score ≥100, n=45).

Results: In intermediate coronary artery lesions, there was a weak negative correlation between FFR and DS assessed by CCTA (r=−0.248, p<0.005), whereas there was a moderate correlation between FFR versus DS assessed by CAG (r=−0.373, p<0.001) and FFR versus minimal luminal diameter (MLD) assessed by CAG (r=−0.400, p<0.001). The best cut-off value of DS assessed by CCTA to predict FFR<0.8 was 75.7% (47.4% sensitivity, 69.4% specificity, 55.1% positive predictive value, 62.5 negative predictive value, 59.7% accuracy, area under the ROC curve (AUC) = 0.573, 95% CI: 0.483-0.660). The accuracy of CCTA to predict FFR<0.8 was different between 2 groups (group A: AUC=0.576, 95% CI: 0.446-0.699 versus group B: AUC=0.575, 95% CI: 0.466-0.687). The correlation between FFR and DS of CCTA was: FFR Pearson's correlation coefficient 1 -0.248 -0.373 0.400 0.336 p-values 0.005 0.000 0.036 0.008 N 129 129 129 129

QCA: quantitative coronary analysis

Conclusions: CCTA may not be useful to predict the functional significance of stenosis severity in patients with intermediate CAD.

P724 Relationship between regional hyperaemic myocardial blood flow on dynamic dual-source computed tomography and coronary artery stenosis

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Purpose: To evaluate the relationship between regional myocardial blood flow (MBF) estimated in absolute terms by computed tomography and coronary percutaneous intervention (PCI) and cardiac artery bypass grafting (CABG).

Methods: We prospectively included 107 patients (mean age 62.8±10.0 years, 69% male) with stable anginal complaints and an intermediate to high pre-test likelihood for CAD based on Diamond and Forrester criteria. Hybrid SPECT/CTA was performed prior to CA in all patients. The study outcome was the treatment decision categorized as: no revascularization, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). These treatment decisions were made by a panel of two interventional cardiologists and one cardiothoracic surgeon in two steps: first based on the results of hybrid SPECT/CTA, and on a second occasion based on SPECT and CA. Percent agreement between the treatment decisions based on either hybrid SPECT/CTA or SPECT and CA was calculated separately for all patients. Secondly, three subgroups of patients were assessed: those with matched stenosis on CTA and corresponding ischemic myocardium on SPECT, with unmatched stenosis and CTA findings and those with normal findings on both SPECT and CTA.

Results: Revascularization (PCI or CABG) was necessary in 54 (50%) of patients based on SPECT and CA. Percent agreement of treatment decisions based on hybrid SPECT/CTA versus SPECT and CA was 92%. Percent agreement on the necessity of revascularization in group of patients with matched, unmatched and normal hybrid SPECT/CTA was 95%, 84% and 100% respectively. Percent agreement for the decisions on the method of revascularization (PCI versus CABG) was 74% overall.

Conclusions: Panel evaluation shows that patients could be accurately indicated and deferred from revascularization based on hybrid SPECT/CTA. In selected cases indications for percutaneous and possibly surgical revascularization could even be based on hybrid SPECT/CTA alone.

AORTIC VALVE DISEASE

P726 Normal aortic and pulmonary diameters correlates well with body length in children, but not with body weight

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Introduction: Most echocardiographic measurements of aortic and pulmonary diameter were established using body length only a few children. The measurements were seen in reference to body weight. Our impression was that body length correlates better to echocardiographic valve diameter than body weight.

Methods: We analysed our digital echocardiographic database starting from...
Abnormal aortic stiffness has been described in Marfan syndrome, but aortic mechanics in other heritable aortopathies are less well defined, as are factors significantly associated with aortic stiffness. Mechanical indices included stiffness (Stiff) and pulse wave velocity (PWV). Mechanical properties were compared between groups with stratification by common carotid artery (CCA) flow. Results: Severe AR was present in 48 patients (68%). We obtained optimal images of CCA flow in all cases. RI correlated better with AR severity by aortography than PWV (RI R=0.74, PWV R=0.70, p<0.001). Cut-off value of severe AR by RI was 0.89 (sensitivity 81%, specificity 82%, AUC=0.90). In patients with severe AR, eccentric AR was present in 18 patients. PWV of eccentric AR was smaller than that of central AR (5.3±2.7 vs. 8.6±3.9, p<0.001). However, there were no significant differences between RI (0.96±0.07 vs. 0.96±0.09, NS) of eccentric AR and that of central AR.

Conclusion: There is a linear correlation of body length to aortic and pulmonary diameter in children with the equation shown above. We integrated this formula in our echocardiographic program to display the normal values with the report.

Biomechanical properties of aorta in heritable aortopathy

R.W. Jeremy, K. Vis, A.A. De Wit. University of Sydney, Sydney, Australia

Abnormal aortic stiffness has been described in Marfan syndrome, but aortic mechanics in other heritable aortopathies are less well defined, as are changes in mechanical properties with age.

Aortic mechanics were calculated from simultaneous measurements of aortic root geometry (2D echo) and brachial blood pressure (BP, mmHg) in 218 patients: 69 controls, 55 Marfan, 47 bicuspid aortic valve (BAV) and 47 isolated familial aortopathy (TAAO). Mechanical indices included stiffness (Stiff) and pulse wave velocity (PWV). Mechanical properties were compared between groups with stratification for age (40 years = Group I, >40 years = Group II) by factorial ANOVA (SPSS 19). Factors predictive of aortic stiffness were identified by multiple linear regression. Aortic biomechanics are compared between groups in Table 1.

Abnormal biomechanics, manifest as increased aortic stiffness and pulse wave velocity, are a common feature in all aortopathy groups. In Marfan, aortic mechanics are abnormal in patients aged less than 40 years but similar to controls in patients over 40 years old. Aortic stiffness is even greater in patients with BAV and TAAO than in Marfan and is worse than in controls in all age groups. Independently, increased collagen stiffness is associated with aortic stiffness and age, gender, aortic diameter and mean blood pressure. These findings support a common mechanism of accelerated age-dependent collagen scar formation in the aorta in these heritable aortopathies, but severity appears to differ between the aortopathies.

Factors predictive of aortic stiffness were identified by multiple linear regression. Abnormal biomechanics are a common feature in all aortopathy groups. In Marfan, aortic mechanics are abnormal in patients aged less than 40 years but similar to controls in patients over 40 years old. Aortic stiffness is even greater in patients with BAV and TAAO than in Marfan and is worse than in controls in all age groups. Independently, increased collagen stiffness is associated with aortic stiffness and age, gender, aortic diameter and mean blood pressure. These findings support a common mechanism of accelerated age-dependent collagen scar formation in the aorta in these heritable aortopathies, but severity appears to differ between the aortopathies.

Aortic biomechanics

<table>
<thead>
<tr>
<th>Group</th>
<th>Control I</th>
<th>Control II</th>
<th>Marfan I</th>
<th>Marfan II</th>
<th>BAV I</th>
<th>BAV II</th>
<th>TAAD I</th>
<th>TAAD II</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>41±2</td>
<td>26±4</td>
<td>25±7</td>
<td>54±12</td>
<td>31±6</td>
<td>55±9</td>
<td>30±7</td>
<td>55±11</td>
</tr>
<tr>
<td>Age years</td>
<td>24±7</td>
<td>58±12</td>
<td>25±7</td>
<td>54±12</td>
<td>31±6</td>
<td>55±9</td>
<td>30±7</td>
<td>55±11</td>
</tr>
<tr>
<td>Aorta mm</td>
<td>29±3.8</td>
<td>31±4.3</td>
<td>46±5.6</td>
<td>44±3.4</td>
<td>42±1.6</td>
<td>46±5.4</td>
<td>39±6.4</td>
<td>44±4.7</td>
</tr>
<tr>
<td>BFP mean</td>
<td>86±9</td>
<td>92±7</td>
<td>83±8</td>
<td>87±6</td>
<td>91±1</td>
<td>93±1</td>
<td>89±6</td>
<td>96±7</td>
</tr>
<tr>
<td>Stiff</td>
<td>5.6±2.6</td>
<td>12.7±7.2</td>
<td>9.7±6.5</td>
<td>13.7±9.0</td>
<td>14.6±10.0</td>
<td>23.0±15.0</td>
<td>12.1±6.7</td>
<td>20.3±13.4</td>
</tr>
<tr>
<td>PWV mmHg</td>
<td>8.5±2.7</td>
<td>8.3±2.0</td>
<td>8.5±2.8</td>
<td>8.9±3.4</td>
<td>8.9±3.4</td>
<td>11.3±3.9</td>
<td>8.2±2.2</td>
<td>10.8±3.9</td>
</tr>
</tbody>
</table>

Mean ± s.d. *p<0.001 vs Control I; †p<0.001 vs Control II; ‡p<0.05 vs Marfan.
Clinical efficacy of doppler-echocardiographic indices in asymptomatic moderate or severe aortic stenosis with preserved ejection fraction: a comparison between resting and low-dose dobutamine values

Clinical Center of Serbia, Clinic for Cardiology, Belgrade, Serbia; Institute of Organizational Sciences, University of Belgrade, Belgrade, Serbia

Purpose: In aortic stenosis (AS) symptoms usually occur during exercise and, furthermore, most Doppler-echocardiographic indices that are used for assessing AS severity are not best. The aim of this study was to assess which hemodynamic parameter best accounts for the clinical outcome and to analyze the value of low-dose dobutamine testing (DT) in patients with moderate or severe, and preserved ejection fraction (EF).

Method: A total of 126 asymptomatic patients with aortic valve area (AVA) ≤ 1.5 cm² and EF > 50% were enrolled in this prospective study. The follow-up period was 14.2 ± 10.3 months. Mean age was 66.4 ± 10.3 years; 58.7% of males; mean EF was 72.0 ± 6.69%; mean pressure gradient (Pmean) was 41.9 ± 11.22 mmHg and average AVA 0.82 ± 0.22 cm². Patients with ≥ 2 maxvalvular regurgitation or mild mitral stenosis were excluded. The low-dose dobutamine infusion protocol was begun at 5 μg/kg/min body weight up to 20 μg/kg/min, titrated upwards at steps of 5 μg/kg/min every 3 min. The composite outcome endpoint (MACE) was defined as cardiac death, aortic valve replacement and hospitalization caused by AS. Patients according to patient’s medical record or referring physician.

Results: No patient experienced a serious adverse event during or after DT. A total of 70 patients had MACE (55.5%), of which 9 patients (7.14%) have died during follow-up. Univariate analysis showed that resting mean values of Vmax (maximal velocity), Pmean, AVEA, Zva (valvulo-arterial impedance), ELI (energy loss index), AVR (aortic valve resistance) and S’ were associated (p < 0.05) with MACE. The multivariate analysis revealed that only AVR (p = 0.007; HR = 1.04; CI = 1.01-1.06) was independently associated with MACE. Regarding death only, the univariate analysis showed that AVEA, Zva, ELI, SWL (stroke work loss), AVR, S’ and SAC (systemic arterial compliance) were associated (p < 0.05) with death. However, only Zva was independent predictor of death according to multivariate analysis (p = 0.017; HR = 3.244; CI = 1.69-6.309). Parameters that were not predictors of MACE, or death only, at rest, did not become predictors after DT either.

Conclusion: The AVR and Zva are the strongest predictors of MACE or death, respectively, in group of patients with asymptomatic moderate or severe AS and preserved EF. However, the assessment of Doppler-echocardiographic parameters during DT has no significance in predicting outcome, or suggesting when to intervene, in this group of patients.

Impact of global left ventricular hemodynamic load on maximal exercise capacity in patients with aortic stenosis

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Background: The determinants of maximal exercise capacity (MEX) in asymptomatic patients with moderate or severe AS are not fully understood. The aim of this study was to assess the relationship between MEX and the aortic valve stenosis severity using the aortic valve area (AVA) and the aortic valve regurgitation index (ARI).

Method: Asymptomatic patients with moderate or severe AS (n = 65, aortic valve area < 1.5 cm², 65 ± 14 years, 66% men) and preserved left ventricular (LV) systolic function were enrolled. All patients underwent echocardiographic examination and cardiovascular exercise test. LV hemodynamics were calculated using the standard formulas. LV ejection fraction was >50%, and LV systolic pressure was >110 mmHg. LV systolic function was assessed by indexed left ventricular ejection fraction. Patients with aortic valve regurgitation were excluded from study.

Results: Patients with low EF (≤ 53%) and patients with normal EF and low MWS (≥ 1.51 cm²/m²) achieved significantly lower MEX compared to patients with normal EF (p < 0.05). There was no other significant difference between the groups (n = 70) regarding demographic and clinical data. There was a significant correlation between peak VO2 and age, body mass index, LV stroke volume, mean flow rate, cardiac output, S’ and EF. LV ejection fraction, aortic valve area, mean pressure gradient, and AVA were independent predictors of MEX in the study population.

Conclusion: The AVA and Zva are the strongest predictors of MACE or death, respectively, in group of patients with asymptomatic moderate or severe AS and preserved EF. However, only Zva was independent predictor of death according to multivariate analysis. In asymptomatic patients with moderate or severe AS, MEX varies widely and is often lower than expected. Global LV hemodynamic load is the main Doppler-echocardiographic determinant of reduced MEX in these patients, further supporting the usefulness of this parameter for their clinical evaluation and management.

Aortic valve stenosis with or without surgery in dialysis patients; experience in a single dialysis center

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Backgrounds: Patients with chronic renal failure (CRF) have an elevated risk for the development of cardiovascular diseases. Aortic valve stenosis (AS) progresses more rapidly in patients with CRF than that in general population, however, aortic valve replacement (AVR) is not always performed due to associated comorbidities. The purpose of this study was to retrospectively evaluate the long-term prognosis of severe AS in CRF patients with or without performing AVR at the single hemodialysis center.

Methods and Results: Out of 1120 patients with CRF on maintenance hemodialysis at one dialysis center between January 2000 and December 2008, 188 patients (16.8%) were diagnosed as severe AS by routinely performed echocardiogram. AVR was performed in 42 patients (22.3%) (AVR group) and other 146 patients (77.4%) rejected the operation and treated only by medication (non-AVR group).

Conclusions: Medical therapy for AS in CRF patients resulted in poor long-term prognosis mainly due to cardiac events. Even though operative mortality was high in patients with CRF, AVR showed better long-term prognosis compared with medical therapy. Early surgical intervention should be warranted to improve operative outcomes in CRF patients with severe AS.

Midwall left ventricular systolic function in asymptomatic aortic valve stenosis: is it prognostically important? The SEAS study

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Purpose: Midwall fractional shortening (MWS) is used in hypertension for earlier identification of patients with left ventricular (LV) dysfunction and adverse cardiovascular (CV) outcome. Its performance has not been tested in patients with aortic stenosis (AS). This study aims to assess the relevance of measuring LV systolic function at midwall for CV risk assessment in asymptomatic AS.

Methods: 1720 patients with asymptomatic AS in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study were followed-up for 4.3 years. LV systolic function was assessed by biplane ejection fraction (EF) (low < 55%) and MWS (low if < 14%) at baseline and annual echocardiographic follow-up.

Results: Patients with low EF (n = 83) and patients with normal EF and low MWS (n = 318) at baseline had higher rate of major CV events than patients with both normal EF and MWS (p < 0.01, Figure). In Cox analyses including age, gender, study treatment, hypertension, severity of AS, and EF, low baseline MWS predicted a 43% increase in major CV events (95% CI 1.17-1.75) including 66% more CV death (95% CI 1.02-2.73), and 43% higher risk of AS-events (95% CI 1.16-1.76) (all p < 0.05). Low MWS over time predicted worse CV outcome with
The impact of atrial fibrillation on long-term clinical outcomes among patients with severe aortic stenosis undergoing transcatheter aortic valve implantation

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Background and Aim: Atrial fibrillation (Afib) impairs hemodynamic parameters by loss of atrio-ventricular synchrony and is a major risk factor for stroke. Degenerative aortic stenosis is the most common valvular heart disease and like Afib considered a disease of the elderly. Elderly patients considered high-risk for surgical aortic valve replacement are candidates for transcatheter aortic valve implantation (TAVI) with a prevalence of Afib in up to 50% of patients. The impact of Afib on long-term clinical outcomes in these patients is not well established. We therefore compared outcomes of patients with pre-existing or new-onset Afib with patients without Afib after TAVI.

Methods and Results: Between 8/2007 and 9/2010, 260 patients (age 83±6 years) with symptomatic, severe aortic stenosis (mean NYHA functional class 2.6±0.8) were included into a prospective single-center registry. Sixty-eight patients (26.2%) presented with Afib at baseline, and 21 patients (8.1%) developed new-onset Afib after TAVI. Compared to patients without Afib, those with had similar baseline characteristics including age (83±5 vs. 82±7, p=0.66), gender (female 61% vs. 54%, p=0.29), arterial hypertension (82% vs. 77%, p=0.31), diabetes (27% vs. 23%, p=0.53), chronic renal failure (74% vs. 68%, p=0.40), coronary artery disease (58% vs. 68%, p=0.11) and risk scores (CASS: 20±15 vs. 24±15, p=0.64). Patients with Afib more frequently had revascularization for coronary artery disease by either coronary artery bypass grafting (12% vs. 26%, p=0.009) or percutaneous coronary intervention (16% vs. 26%, p=0.05) than those without Afib.

At one year, all-cause mortality (31.5% versus 12.3%) was significantly higher in crude (HR 2.87, 95% CI 1.63-5.05, p<0.0003) and adjusted (HR 2.89, 95% CI 1.64-5.1, p=0.0002) analyses. Similarly, rates of cardiac death (8.6% vs. 22.5%, adjusted HR 2.84, 95%CI 1.45-5.55, p=0.002) were significantly increased among patients with as compared to those without Afib. Conversely, we recorded no differences with respect to major stroke (4.7% vs. 4.5%, adjusted HR 1.05, 95%CI 0.32-3.55, p=0.92) and life-threatening bleeding (11.7% vs. 11.2%, adjusted HR 0.94, 95% CI 0.42-2.12, p=0.68) between patients with and without Afib at one year of follow-up.

Conclusion: Afib frequently coexists with severe aortic stenosis in elderly patients who are candidates for TAVI. Although the risk of stroke and bleeding appears similar, Afib carries a nearly 3-fold increased risk of all-cause and cardiac mortality, which deserves further study.

Abdominal visceral adiposity and left ventricular hypertrophy in patients with aortic stenosis - results from the progressa study

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Background: We reported that metabolic syndrome (MetS) is associated with increased prevalence of LV concentric hypertrophy and impairment of LV systolic function, two risk factors for poor prognosis in AS patients. Excessive visceral fat accumulation could be one of the key causal factors underlying this association. The objective of this study was to examine the association between magnitude & distribution of adiposity and degree of LV hypertrophy and systolic dysfunction in AS patients.

Methods: 104 consecutive patients with AS were recruited in the PROGRESSA study and underwent Doppler-echocardiography and computed tomography (CT). As an estimate of the global LV hemodynamic load, we calculated the valve-arterial impedance (Zva). Abdominal visceral fat (AFT), subcutaneous fat (ASF), and total fat (ATF=AFV+ASF) areas were measured by CT between L4 and L5 lumbar vertebrae spaces. The AFV/ATF ratio was calculated to assess the portion of total fat deposited in the visceral compartment.

Results: Body mass index (BMI) correlated strongly with AVF, ASF and ATF (r=0.73, r=0.69 and r=0.86 respectively; all p<0.0001) but weakly with AVF/ATF ratio (r=0.23, p=0.02). Patients with AVF/ATF ratio >0.40 (i.e. median value) had higher prevalence of MetS (48 vs. 20%, p=0.003), hypertension (HTN: 86 vs. 57%, p<0.001), diabetes (30 vs. 12%, p=0.02), hyperlipidaemia (74 vs. 53%, p=0.03), and coronary artery disease (CAD: 56 vs. 25%, p=0.002) compared to those with AVF/ATF ratio <0.40. Peak aortic jet velocity was similar in both groups (Vpeak: 2.8±0.5 vs. 2.9±0.6 m/s, p=NS). LV mass index was higher in patients with AVF/ATF ratio >0.40 (LVM: 53±12 vs. 46±8 g/m², p=0.0007). In a multivariable model adjusted for age, gender, HTN, MetS, CAD, creatinin, valcurial calcification, Vpeak, and Zva, the two most powerful predictors of higher LVM were larger BMI (p=0.0001) and higher AVF/ATF ratio (p=0.03). Patients with AVF/ATF ratio >0.40 also had a lower LVEF (64±7 vs. 67±5%, p=0.2). In multivariable model adjusted for age, gender, HTN, CAD, and Zva, higher AVF/ATF ratio was associated with lower LVEF (p=0.04).

Conclusion: This study reports that the degree of global adiposity (as reflected by BMI) as well as the more extensive distribution of this adiposity within the visceral compartment (AVF/ATF ratio) (as reflected by AVF/ATF ratio) is independently associated with more pronounced LV hypertrophy and reduced LV systolic function in AS patients. These findings provide impetus for elaboration of interventional studies aiming at the reduction of obesity, and particular visceral obesity, in AS population.
measurements, plasma BNP levels and clinical outcome were studied. Mean follow-up was 27.5±24.2 months; mortality was gathered from Social Security Death Index and a Cox proportional hazards model was used to explore the association of BNP with all-cause mortality.

Results: Average BNP was 415±588 pg/dL and 85 pts (32%) had BNP ≥200 pg/dL. 137 pts (53%) were medically treated and 123 pts (47%) underwent AVR; over 27.5±24.2 months of follow-up, 105 pts (43%) died. 35 pts (14%) underwent AVR had BNP ≥200 pg/dL and medically treated 50 pts (59%) had BNP ≥200 pg/dL (p=0.12). BNP showed a significant univariate association with all-cause mortality (HR: 1.001 [95% CI: 1.000-1.001], p=0.001), and a BNP cut off value of 200 pg/dL remained a strong predictor of mortality (see Figure 1) (HR: 1.83 [95% CI: 1.097-3.052], p=0.021), independent of age (HR: 1.021 [95% CI: 0.991-1.052], p=0.17), LV EF (HR:0.993 [95% CI: 0.958-1.030], p=0.72) and valvular area impedance (Zva) (HR: 1.073 [95% CI: 0.884-1.303], p=0.48).

Conclusion: BNP cut off value of 200 pg/dL can help to predict adverse outcome in low gradient “severe” AS patients with preserved LVEF.

### Abstract P738

**Characteristics and prevalence of flow-gradient patterns in patients with severe aortic stenosis and preserved ejection fraction**

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**Background:** Paradoxical low-flow (LF), low-gradient (LG) severe aortic stenosis (AS) with preserved ejection fraction (EF) is reported to be a common entity associated with an adverse prognosis. Potential causes of discordant valve area and mean gradient include measurement error, small body size and high afterload, but their prevalence is still under debate. We investigated population characteristics of consecutive patients with severe AS using the newly proposed flow-gradient classification.

**Methods and Results:** An analysis was performed at our institution of all patients ≥18 years undergoing 2-D and Doppler echocardiography between 2006 and 2011 with severe AS and preserved EF (EF ≥50% and aortic valve area <1.0 cm²) (n=3,422). Patients were compared in 4 groups using the flow-gradient classification (Table): LF (stroke volume index <35 mL/m²), LG (mean gradient <40 mm Hg) (LF/LG), LF, high-gradient (HG, mean gradient ≥40 mm Hg) (LF/HG), normal-flow (NF), stroke volume index ≥35 mL/m², LG (NF/LG), and NF/HG.

**Conclusions:** LF severe AS with preserved EF is found in 30% of severe AS patients and is associated with female sex and small body size. However, paradoxical LF/LG severe AS characterized by high global afterload is less common and present in 5% of severe AS patients. Using the flow-gradient classification helps to further stratify groups according to hemodynamic findings that may have prognostic significance.

### Abstract P740

**Three-dimensional quantitative analysis of aortic valve apparatus in functional classification of aortic regurgitation**


**Purpose:** Recently, mechanism of aortic regurgitation (AR) can be analyzed from functional viewpoints. However, structural abnormality of aortic valve apparatus (AVAAP) has not been evaluated adequately. The purpose of this study was to clarify structural differences of AVAAP among functional classification of AR quantitatively by three-dimensional (3D) echocardiography.

**Methods:** Of consecutive 182 patients underwent elective surgical correction for pure AR from December 2007 to February 2011, 70 patients with single mechanism of tri-leaflet AR (Type I 20 patients, Type II 36 patients, Type III 16 patients ) and 15 controls were enrolled in this study. We acquired 3D datasets including T. Fukui, J. Umemura, S. Takanashi, T. Sumiyoshi. Sakakibara Heart Institute, Fuku, Japan

**Abstract P740 - Table. Flow Gradient Patterns in Severe AS**

<table>
<thead>
<tr>
<th>LF/LG (n=112)</th>
<th>LF/LG (n=115)</th>
<th>NF/LG (n=870)</th>
<th>NF/HG (n=2255)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76±16</td>
<td>74±16</td>
<td>77±16</td>
<td>77±16</td>
</tr>
<tr>
<td>Female sex</td>
<td>76 (50%)</td>
<td>100 (54%)</td>
<td>601 (85%)</td>
<td>1055 (47%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>34±17.9</td>
<td>28±7.5</td>
<td>27±4.5</td>
<td>28±4.5</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>2.1±0.3</td>
<td>1.9±0.2</td>
<td>1.8±0.2</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.6±0.15</td>
<td>0.8±0.12</td>
<td>0.8±0.12</td>
<td>0.8±0.12</td>
</tr>
<tr>
<td>Indexed aortic valve area (cm²/m²)</td>
<td>0.3±0.05</td>
<td>0.4±0.08</td>
<td>0.5±0.08</td>
<td>0.4±0.08</td>
</tr>
<tr>
<td>Left ventricular outflow tract diameter (cm)</td>
<td>2.0±0.30</td>
<td>2.05±0.20</td>
<td>2.08±0.15</td>
<td>2.20±0.18</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>64±14</td>
<td>60±11</td>
<td>79±12</td>
<td>99±12</td>
</tr>
<tr>
<td>Indexed stroke volume (mL/m²)</td>
<td>31±5</td>
<td>30±4</td>
<td>45±6</td>
<td>49±6</td>
</tr>
<tr>
<td>Valvular area impedance (mm Hg/mL/m²)</td>
<td>5.6±1.2</td>
<td>4.9±1.2</td>
<td>3.6±0.7</td>
<td>3.5±0.7</td>
</tr>
</tbody>
</table>

*Significance difference (p<0.05) compared with low flow (LF)/high gradient (HG) group; †significant difference with LF/Low gradient (LG) group; ‡significant difference with normal flow (NF)/LG group.*
Methods: Retrospective, single study, including 108 consecutive patients (pts) in the ninth decade of life, who underwent AVRS between July 2003 and November 2010. The predictive power was calculated by ROC (Receiver Operating Characteristic) curve, with a confidence interval (CI) of 95%.

Results: 108 pts were studied, mean age 83.1±2.2 years old. 62% females, 67.5% (66 pts) were in NYHA I and II and 37.0% (40 pts) had angina. 18.5% (20 pts) were diabetic, 67.0% (73) had creatinine clearance below 50 ml/min; extracardiac arteriopathy was found in 14.8% (16 pts), chronic obstructive pulmonary disease in 8.3% (9 pts). Left ventricular systolic dysfunction occurred in 25.8% (24 pts) and 4.6% (5 pts) had severe pulmonary hypertension. AVRS was elective in 91.7% (88 pts) of cases. Mean EuroScore I was 13.1±1.1 and mean euroSCORE II was 4.3±2.6. 30-day mortality was 5.7% (6 pts) and 1-year mortality was 4.3±2.8% (6 pts). The ROC curve AUC was 0.655 (CI 95%, 0.433-0.876) for euroSCORE II and 0.585 (CI 95%, 0.352-0.818) for euroSCORE I.

Conclusions: Isolated AVRS in octogenarians can be performed with a low 30-day and 1-year mortality, despite the increased perioperative risk. In this population, euroSCORE II was the best mortality predictor.

Conclusions: LA reverse remodeling and regression of LVH after AVR may be identified as a process in patients with severe aortic stenosis.

Background: In patients with severe aortic stenosis (AS), chronic pressure overload induces left ventricular hypertrophy (LVH) and left atrial (LA) enlargement. Aortic valve replacement (AVR) remains the most effective treatment for severe AS, and a regression in LVH after AVR has been reported. However, few data exist regarding the association between regression of LVH and LA reverse remodeling after AVR.

Methods: We retrospectively reviewed 268 consecutive patients who underwent AVR in our institution between 2006 and 2010. Among them, 105 patients (age: 76±8 years) who underwent surgery for severe AS, without any prior cardiac surgery were analyzed. Echocardiographic data were obtained before surgery, 1 month, 1 year, and 3 years after surgery.

Results: A significant reduction in both LV mass index and LA volume index were observed over time after surgery (Figure, both P<0.001). LA dilation was improved and reached plateau at 1 year after surgery, whereas LVH was improved and reached plateau at 1 year after surgery. There was no significant correlation between regression of LVH, defined as ≥20% reduction of LV mass, and LA reverse remodeling, defined as ≥25% reduction of LA volume (n=318, P=0.12). Preoperative LVH was the independent predictor of regression of LVH (odds ratio, 3.76; P=0.004), and preoperative LA dilation was the independent predictor of regression of LA dilation (odds ratio, 20.1; P<0.001).

Conclusion: LA reverse remodeling and regression of LVH after AVR may be independent processes, although AVR imparted beneficial effects on LV and LA structures over time. LA reverse remodeling preceded regression of LVH.

Conclusions: LA reverse remodeling and regression of LVH after AVR may be independent processes, although AVR imparted beneficial effects on LV and LA structures over time. LA reverse remodeling preceded regression of LVH.
not attain statistical significance. TDI-derived IVA, IVV index were found to be significantly increased after PMV from 1.71±0.54 m/s2 to 3.27±0.22 m/s2, and from 0.11±0.04 cm/s to 0.14±0.06 cm/s respectively with (P < 0.001) for all RV. Tei index significantly decreased from 0.49±0.025 to 0.31±0.21 (P < 0.01). Significant negative correlation could be established between IVA and PAP (before and after PMV) (r = -0.61, r = -0.58 respectively). Tei index (r = -0.72) and mean trans-mitral diastolic gradient (r = -0.74), whereas significant positive correlation was established between IVA and MVA (r = 0.68) with p<0.001 for all correlations.

Conclusion: TDI-derived IVA can be used as reliable, non invasive parameter to detect early improvement of RV function following PMV.

**P745**

Repeat percutaneous mitral valvuloplasty for patients with mitral valve restenosis: comparison with initial procedure and predictors of outcomes

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**Background:** Only a few reports have been published into redo PMV and data regarding its long term safety and efficacy are scarce.

**Objectives:** To explore the immediate and long-term outcome of repeat (redo) percutaneous mitral valvuloplasty (PMV) in a series of patients with mitral restenosis in comparison with initial PMV in the same series and to determine predictors of outcome.

**Methods:** Our study is retrospective enrolling 354 patients, hospitalized in the cardiology department between January 1996 and January 2011. The study group included 214 redo PMV procedures (mean age 47±10 years) who benefited from a redo PMV. All redo PMV procedures were performed using the Inoue balloon system. Procedural success was defined as 50% or more increase of mitral valve area (MVA) with a final MVA >1.5 cm², without major complications. Restenosis was defined as loss of >50% of the initial gain of MVA by the preceding PMV with a final MVA <1.5 cm².

**Results:** Successful procedural outcome was achieved in 81.1% of patients. There were no deaths and restenosis was noted in 40%. At one year, success was noted in 80% of patients who benefited from redo PMV as compared to the redo procedure (P < 0.05).

**Conclusion:** Repeat PMV is safe and provides good immediate results in patients with restenosis after successful first procedure. Long-term results of redo PMV are satisfactory and related mainly to the echo score.

**P746**

Quantification of mitral regurgitation by calculation of regurgitant volume: 3D left ventricular echocardiography versus PISA

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Quantification of mitral regurgitation (MR) by echocardiography is well established using several echo or Doppler parameters in which effective regurgitation orifice area (ERO) and regurgitant volume (RV) are the most commonly used. However, hemispheric assumptions allowing application of proximal isovelocity area (PISA) may be erroneous due to the complex mitral valve morphology (i.e. mitral valve prolapse). We hypothesized that 3D left ventricular echocardiography combined with aortic pulsed Doppler could obtain RV with high reliability and will allow a comparison of 2 methods (3D vs PISA) in presence of mitral regurgitation.

**Methods:** First, in 50 patients without MR, we compared LV ejection volumes (LVEV) from a full volume 3D echocardiographic acquisition and 2D Simpson method to the aortic stroke volume (ASV) obtained by Pulsed Doppler for validation of the 3D approach. Second, we analyzed 50 patients with different degree MR for comparison of the two approaches and verification of PISA RV values. Inter and intra observer variabilities were assessed for all techniques.

**Results:** Correlations and Bland-Altman analyses gave high adequacy between 3D LVEV and ASV compared to 2D and ASV (respectively 3D, r=0.96, y=0.91+0.4; 2D, y=0.90±0.06, mean error (ME) 95% confidence interval of error (CIE) [−0.84;−0.06] and 2D, r=0.81, y=0.79±0.08, 15.4±11.6%]. Variabilities averaged for 3D LVEV was 6.3% and 15.5±15.8±20% for 2D. In patients with mitral regurgitation, RV from PISA and 3D LVEV were 23.1±12ml and 24.5±11ml (p=0.37) and the fractional regurgitation 32.1±12% and 33.1±12% (p=0.63). However, mean error measurement was -1.37ml and 95% confidence interval of error was 17.90ml showing high discrepancy between the two methods. By selecting a cut-off of 5, 10, 15 ml, numbers of patients with uncorrected measurements was 48.5, 17 and 8.5%. When using ASE 4 grades classification, 25.7% of misclassified patients was obtained with PISA.

**Conclusion:** 3D LVEV method is robust and reliable for calculation of mitral regurgitant volumes with significant differences compared than those obtained with PISA which seems to be less adequate for all types of MR.

**P747**

Dynamic variation in mitral valve regurgitation is predominantly determined by alterations in flow velocity and less of regurgitant orifice area

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**Background:** Mitral valve regurgitant volume (MVRV) can be calculated as product of regurgitant orifice area and velocity time integral (VTI). Direct planimetry of anatomic regurgitant orifice area (AROA) can be accurately performed by 3D transthoracic echocardiography (3D TEE). To account for dynamic variations in mitral regurgitation (MR) during systole, serial planimetry and concordant analysis of flow during subintervals of systole may improve estimates of MVRV. We determined the impact of AROA and flow changes throughout systole on estimates of MVRV. MVRV derived by AROA and VTI were compared with MVRV obtained by 3D speckle tracking imaging (MRI).

**Methods:** 3D TEE and MRI were performed in 43 patients (age 71±11 years) with grade 2-4 MR. Etiology of MR was flail in 15 patients and functional in 28 patients. MVRV was expressed as sum of five systolic subintervals of equal duration. For each subinterval the AROA and the corresponding regurgitant VTI using the CW-Doppler signal were determined. Planimetry of AROA was performed using QLAB-software (Philips). MRI quantification of MVRV was performed by subtracting left ventricular stroke volume from aortic outflow volume.

**Results:** AROA derived MVRV correlated to MVRV determined by MRI (r=0.439, p<0.0032), AROA determined at five consecutive time points throughout systole varied only by 18% while the VTI of the subinterval with the highest flow was 120% of the subinterval with the lowest flow. Considering the etiology of MR, in both flail as well as functional MR greatest AROA and subinterval VTI were reached in the third quintile of systole.

**P748**

Left atrial strain relates to surgical indication in patients with severe organic mitral regurgitation: a 2D-speckle tracking study

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**Purpose:** To evaluate the effect of chronic severe organic mitral regurgitation (MR) on left atrial (LA) phasic function and its relationship with the presence of established criteria for surgical indication (SI).

**Methods:** 2D speckle tracking echocardiography-derived strain indices for LA reservoir, conduit and contractile function were assessed in 121 patients with chronic severe organic MR and 20 healthy controls. MR patients were divided according to the presence of no (n=46) versus ≥1 (n=75) criteria for SI according
to current guidelines: symptoms, left ventricular (LV) ejection fraction <60%, LV end-systolic diameter ≥40 mm, atrial fibrillation or pulmonary arterial pressure >50 mmHg.

Results: Impaired LA reservoir: 66% vs 30% (p<0.001), conduit (15 vs 5.05% vs 17.4±6.4%, p=0.02) and contractile (9.2±3.5% vs 14±3.3%, p<0.001) function was observed in MR patients as compared to controls. LA reservoir strain (LAx) showed the highest accuracy to identify the presence of SI (area under the ROC curve=0.8, CI 95% 0.72-0.87), and a cut-off value ≥24% predicted SI presence with a sensitivity and specificity of 76% and 72%, respectively. Multivariate analysis indicated LAx as an independent predictor of the presence of SI (OR 0.88, 95% CI 0.82-0.95, p=0.001). Additionally, likelihood ratio test showed LAx provides significant incremental value to predict SI over several clinical and echocardiographic variables (vena contracta width, E/E' and LA volume indexed to body surface area) (Figure).

Conclusion: Patients with severe organic MR are characterized by LA reservoir, conduit and contractile dysfunction. LAx is highly associated with the presence of guideline-based SI and may therefore be used as a surrogate measure for follow-up and clinical decision-making in these patients.

Mitral valve morphological abnormalities in severe aortic stenosis - a three-dimensional transesophageal echocardiographic study

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Purpose: Mitral regurgitation has been reported to accompany severe aortic stenosis (AS) in a significant proportion of cases. However, the mechanism underlying this association remains unclear. The aim of this study was to characterize the mitral apparatus using 3-dimensional (3D) transesophageal echocardiography (TEE) in patients with severe AS.

Methods: Ninety-four patients undergoing 3D TEE prior to transcatheter aortic valve implantation and 21 individuals free of structural heart disease (controls) were studied. The 3D morphology of the mitral annulus and leaflets and the aortomitral angle were measured offline using commercially available software.

Results: As summarized in the table, AS patients exhibited widening of the aortic root, increased mitral annular thickness and reduction in mitral annular height compared with controls. Despite contrasting clinical characteristics between AS patients and controls, the differences between groups in aortomitral and mitral annular height persisted after adjustment for age, coronary disease, left ventricular volume and mass, and relative wall thickness.

Conclusions: The MLs are abnormal in FMR: they are thicker, larger and less stretchable than normal mitral valve during systolic closure.

The loss of dynamic deformation of mitral leaflet in functional mitral regurgitation

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Purpose: The mitral leaflets (ML) in functional mitral regurgitation (FMR) has been considered structurally and functionally normal. We challenge this widely accepted concept using quantitative real-time three-dimensional echocardiography (RT3DE).

Methods: Transesophageal RT3DE of the mitral valve was acquired in 43 patients with FMR and 30 normal controls (NC). Leaflet thickness was measured in diastole. Dynamic changes of anterior and posterior leaflet surface area (AMLA and PMLA) were tracked in systolic valve closure using dedicated quantification software.

Results: In FMR, the ML was significantly thicker (2.71±0.03 vs 2.09±0.37mm, P<0.001) with significantly larger surface area (P<0.001) than normal. Dynamic deformation of the mitral leaflet surface area was evident in normal subjects. The mitral leaflet was stretched during systole with significantly increase by 25% in leaflet surface area from onset to end systole (AMA 4.94±1.13 to 5.72±1.15cm², PMLA 3.51±0.97 to 4.56±1.13cm², respectively, P<0.001), but showed no dynamic deformation with increase only by 0.8% in FMR (AMLA 7.26±1.85 to 7.42±1.84 cm², PMLA 6.41±1.94 to 6.30±1.83 cm², respectively, P=NS) (Figure).

Conclusions: The leaflet thickness was significantly greater in FMR than in NC. Despite dynamic deformation, leaflet surface area is stationary in FMR.

The discrepancy between 2D and 3D
was correlated with 2D-derived LV end-systolic dimension (r = 0.57, p < 0.001) there are some discrepancies between the two measurement (Figure). The cut-off value of 4 cm of LV end-systolic dimension failed to diagnose LV dilatation in 64.3% (Figure).

**Conclusion:** Pts with MR show major discrepancies between conventional and 3D derived parameters. Use of guideline criteria for LV enlargement may not represent the true volume-loading of the LV.

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**P752 Understanding of the etiology of degenerative mitral valve disease by echocardiography, surgeon and pathologist**

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**Purpose:** Degenerative mitral valve disease (DMVD) often results in severe mitral valve regurgitation due to leaflet prolapse or chordal rupture. To select the most appropriate repair technique a complete understanding of the underlying degenerative etiology (Barlow’s disease, BD or fibroelastic deficiency, FED) is mandatory. The purpose of this study was to determine the capability of transthoracic echocardiography to distinguish BD and FED compared with surgical and pathological findings.

**Methods:** Transthoracic echocardiograms were retrospectively compared with mobile leaflet length (M), anterior leaflet (AL) and posterior leaflet (PL) length, and surgeon description in 233 patients (mean age: 53.8±12.9) undergoing surgery for severe mitral regurgitation due to degenerative mitral valve disease at Almazov Federal Heart, Blood and Endocardiology Centre between 2000 and 2011. The analyzed echocardiographic features of DMVD included valvular thickening (≥5 mm), valve prolapse, flail leaflet due to ruptured chordae tendineae, and valvular calcification.

**Results:** The main pathologic findings by microscopy of valvular tissue specimens were myxomatous degeneration – in 100% and fibrosis – in 33.2% cases. Barlow’s disease was found in fewer cases than FED (25.8% vs. 74.2%) with very low variability between pathologist and surgeon (interclass correlation coefficient = 0.96).

Echocardiography had a very high diagnostic accuracy to identify the affected leaflet and scallop (0.91) and to determine valvaral thickening compared with surgical (0.81) and morphologic (0.87) description. In contrast, only in 76% transthoracic echocardiography was able to correctly identify ruptured chordae tendineae. The presence of valvular thickening, prolapse of the both mitral valve leaflets and annular enlargement had a high positive predictive value (0.92) in identification of Barlow’s disease. In contrast, the typical echocardiographic features of FED were thin leaflets, isolated prolapse of posterior leaflet scallop and chordal rupture (positive predictive value = 0.88).

**Conclusion:** Despite the introduction of three-dimensional transeosophageal echocardiography in routine practice, transthoracic echocardiography is the optimal noninvasive preoperative technique to determine the morphology and to identify possible etiologies of degenerative mitral valve disease.

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**P753 Evaluation the alteration of mitral valve structures in functional mitral regurgitation using real-time three-dimensional transeosophageal echocardiography**

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**Objective:** To investigate the geometric alterations of the mitral leaflets (MV) and annulus (MA) using real-time three-dimensional transeosophageal echocardiography (RT-3DTEE), and to clarify the effect of MV structures’ changes in FMR occurrence.

**Methods:** Twenty-five patients with paroxysmal supraventricular tachycardia, 25 isolated paroxysmal atrial fibrillation patients and 20 old myocardial infarction patients without functional mitral regurgitation (FMR) were enrolled as control. Twenty ischemic cardiomyopathy cases with FMR were ICM group. Standard RT-3DTEE evaluations were performed. The quantification parameters include: anterior-posterior diameter (APD), anterolateral-posteromedial (ALPMD), three dimensional annulus area circle (3DAA), two dimensional annulus area (DLAA), spherical Index (SI), non-planar angle (NPA), two dimensional annulus area fraction (2DAAF); tenting volume (TV); tenting height (TH); commissural diameter (CD), anterior leaflet area (ALA), posterior leaflet area (PLA), tenting volume index (TVI), tenting volume fraction (TVF), coaptation index (CI) (Fig. 1).

**Results:** There were significant difference of APD, ALPMD, NPA, AC, 2DAA, 3DAA, TV, TH, CD, ALA, PLA, TVI, CI, AAF in different groups (F=3.84, P=0.05). Correlation analysis revealed significant negative correlations between left ventricular dimension, left atrial dimension, left ventricular ejection fraction and MA, MV parameters except for SI, TVF and NPA (p=0.05).

**Conclusions:** The geometric and function alteration of MA and MV not only the final way of FMR, but also make the FMR worsen. The application of a series of new quantitative parameters in this study, including NPA, TV, CI, may help to make up the appropriate FMR therapeutic plans and assess the prognosis.

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**P754 Mitral valve remodelling caused by increased diastolic shear-stress mediated forces: observations in patients with a bicuspid aortic valve**


**Background:** Mitral valve (MV) leaflets enlarge as a response to increased systolic stress produced by leaflet tethering. However, flow-mediated shear-stress is the most important hemodynamic force responsible for physiological development of most vascular structures. Hypothesis: excentric aortic regurgitation (AR) in bicuspid aortic valve (BAV) patients rises diastolic shear-stress on the MV leaflet and could trigger leaflet remodelling.

**Methods and Results:** We applied cardiovascular magnetic resonance to characterize MV geometry in 65 BAV patients (43.16 years old, 86% male) and 22 control subjects. Anterior leaflet length (ALL), leaflet coaptation pattern (% of anterior leaflet projection onto the mitral annular diameter), tenting area (TA) and LV volume were measured. AR was graded as non-significant (Group I) or moderate-severe (Group II). RF > 25%. 23 patients had significant AR (Group II). Group II showed significantly higher values of ALL compared with Group I (3.6±0.5 cm vs 2.8±0.4 cm, p=0.001) with posterior displacement of the coaptation point (77±7 vs 68±9 mm, p=0.001). Despite larger LV volume in Group II (250±70 ml vs 194±48 ml, p=0.002), tethering forces were not higher (TA 1.01±0.2cm² vs 1.9±0.2cm², p=0.5). ALL was significantly higher in Group II compared with control subjects (3.6±0.5 vs 2.5±0.4 cm, p<0.001), however no differences were found with Group I. (2.5±0.4 vs 2.8±0.4, p=0.4). By multivariate regression ALL correlated with AR volume (p<0.001), but not with LV volume (p=0.6).

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**P755 Acute hemodynamic effects following percutaneous mitral valve therapy assessed by pressure-volume analysis**


**Background:** Percutaneous mitral valve repair (PMVR) is an evolving therapeu-
tic alternative for patients with mitral regurgitation (MR) with favorable long term efficacy in selected patients. The acute hemodynamic effects of this procedure however are still incompletely understood. We hereassessed changes of left ventricular hemodynamics during PMVR by pressure-volume relation analysis using a left ventricular conductance catheter.

**Methods and results:** Pressure-volume loops were recorded in 13 patients (age: 73±7y, 6 females) undergoing PMVR with the conductance catheter throughout the entire procedure. Patients with a baseline EF<30% (n=8, 3 functional MR, 5 degenerative MR) revealed acute ventricular unloading with a reduction of mean-EV (pre: 155±67, post: 143±62, p=0.14), pressure (EDP: pre: 11±2, post: 16±3 mmHg, p<0.03) and wall stress (WSED: pre: 36±9, post: 29±9 mmHg, p<0.03). Conversely, patients with an EF≥30% (n=6, 5 functional MR, 1 showed significant increases in EDV (pre: 320±69, post: 349±67, p<0.04), EDP (pre: 12±3, post: 16±3, p<0.02) and WSED (pre: 45±11, post: 67±8 mmHg, p<0.01). Simultaneous transesophageal echocardiographical assessment revealed normal forward stroke volume inpatients with EF<30%, which did not change after clip implantation. Incontrast, in patients with EF≥30% FSVs were reduced at baseline but showed asignificant increase following clip implantation.

**Discussion:** Our data suggest that changes in leftventricular hemodynamics following PMVR critically depend on on baseline leftventricular systolic function and may help to predict outcome in thesepatients.

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**P756 Three-dimensional echocardiography-guided assessment of vena contracta at rest predicts exercise-induced severe functional mitral regurgitation**

**Purpose:** To assess the value of the three-dimensional (3D) echocardiography-guided assessment of vena contracta (3DVC) at rest to predict exercise-induced changes in functional mitral regurgitation (FMR) in systolic heart failure (SHF)

**Methods:** The study population consisted of 42 patients (age 69±11y, 84% males, ejection fraction 30±9% with chronic systolic heart failure and mild-to-moderate FMR (≤2/4) at rest. All patients underwent Doppler 3D echocardiography at rest and during semi-supine bicycle exercise. Vena contracta area and its longest diameter (3DVC) were assessed at mid-systole.

**Results:** A total of 18 (43%) individuals showed a significant (≥20mm²) exercise-induced increase of FMR (effective regurgitant orifice rest vs. exercise; 17±5mm² vs. 42±10mm², p<0.001) (FMR increase) while 24 (57%) individuals did not (12±6mm² vs. 16±7mm², NS) (FMR stable). At rest, the FMR increase versus stable group had significantly larger 3DVC (7.6±1.8mm vs. 3.9±2.2mm, p<0.0001), higher prevalence of multiple jets (44% vs. 8%, p<0.01) and larger electromechanical dyssynchrony between the papillary muscles (87±46 ms vs.45±35 ms, p=0.002). In contrast, degree of left ventricular remodeling and mitral valve deformation were similar. The resting 3DVC ≥ 6.5 mm had the highest accuracy (AUC=0.84) to identify patients with significant exercise-induced FMR with a sensitivity of 88% and a specificity of 83% (Figure). The presence of multiple jets showed fair positive predictive value of 80% to predict exercise-induced increase in FMR.

**Conclusions:** The behavior of FMR during exercise can be accurately predicted from the assessment of the resting 3DVC.

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**P757 Left atrial and ventricular dilatation independently cause geometric change of mitral valve: Configuration analysis of functional mitral regurgitation by three-dimensional echocardiography**

**Aims:** To analyze geometric changes of mitral valve (MV) configuration in patients with severe mitral regurgitation (MR) by three-dimensional (3D) echocardiography.

**Methods:** Forty-three patients with mitral regurgitation were included. All patients underwent 2D and 3D transthoracic echocardiography and computed tomography. 3D MV configuration analysis was performed using PHILIPS QLAB software. MV configuration was assessed as a change of MV area, volume, and strain.

**Results:** The MV configuration was analyzed in 43 patients with severe MR (mean ejection fraction 35 ± 8%). The MV area, volume, and strain were significantly reduced in patients with severe MR compared to those with mild MR. The MV configuration was significantly altered in patients with severe MR, with a significant increase in MV area, volume, and strain compared to those with mild MR.

**Conclusion:** The MV configuration is significantly altered in patients with severe MR compared to those with mild MR. The MV configuration is likely to play a role in the development of severe MR.
Comparison of mitral annular calcification and other atherosclerosis risk factors, brachial/carotid intima-media thickness and angiographic extent of coronary artery disease

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Methods: We enrolled 146 consecutive patients with proven or suspected CAD who were referred for coronary angiography at our institution have been selected. The study is comprised of 63 men and 37 women aged 26-80 years (mean age 52.7±9.3). All patients underwent echocardiographic examination and Carotid and brachial arteries Duplex sonography before underwent coronary angiography. MAC was considered when the thickness of the intense echo-density overlying the anterior mitral annulus was greater than 1 mm by 2D echocardiography. We used the Gensini score for this study to test the burden of atherosclerosis. Results: Patients with MAC were more likely to be older than those without MAC (p=0.020). From all coronary traditional risk factors only diabetes mellitus was associated with MAC (p=0.017). The common carotid artery (CCA-IMT) and brachial artery-IMT values were significantly higher in the MAC subjects than without MAC (p=0.008, p=0.003, respectively). MAC was found to have higher Gensini score (46.22 vs 23.03, p=0.002). Plasma level of h-CRP, lipoprotein(a) and homocysteine values were not related with MAC. Presence of MAC was associated with multivessel CAD (p=0.002). Multivariate analysis identified women gender (p=0.035, p=0.23), BA-IMT (p=0.049, p=29.7), multivessel CAD (p=0.002, p=0.035) as independent predictors of MAC. Conclusion: The presence of MAC by echocardiography is highly associated with peripheric atherosclerosis and presence and extent of coronary atherosclerosis. This localization should be accepted a manifestation of later stage of atherosclerosis and thus, aggressive preventive approach, independent from the presence of risk factors, may be warranted to retard the atherosclerosis process.

Novel equations to calculate mitral valve area by mitral leaflet separation index

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Aim of this study is evaluation of the MLS index as a novel method for assessment of mitral valve area.

Methods: 2D Echocardiography was done in 50 patients with MS in this study: Group 1 consisted of 25 patients in sinus rhythm with mean age was 28.6±5.6 years. Four of the patients were male (16%), and 21 were female (84%). Six patients had mild,13 had moderate and 6 had severe Mitral stenosis. Group II consisted of 25 patients suffering from atrial fibrillation. The mean age was 37.5±9.8 years. Twelve of the patients were male (48%), 13 were female (52%). Three patients had mild,14 had moderate and 8 had severe Mitral stenosis. Patients with significant other valvular lesions or heavily calcified Mitral valve were excluded from the study. The MVA was assessed half time. MLS index was measured in end diastole, as the maximal separation at the tips of mitral leaflets in the parasternal long axis (PLX) and apical 4 chamber (A4C) views.

Results: ROC curves for group I demonstrated that:

In the PLX view, severe Mitral stenosis was predicted by a MVA of 8.05 mm less or more with a 62% sensitivity and 100% specificity for planimetry (MVA ≤ 8.05 + (0.162 × MLS), p=0.001) and MVA of 8.25 mm or less with a 85% sensitivity and 100% specificity for PHT (MVA ≤ 0.122 + (0.155 × MLS), p=0.003, p<0.01).

In the apical 4chamber view, severe Mitral stenosis was predicted by a MVA of 7.9 mm or less with a 82% sensitivity and 86% specificity for planimetry (MVA ≤ 0.268 + (0.176 × MLS), p=0.001), and 8.25 mm with a 81% sensitivity and 100% specificity for PHT (MVA ≤ 0.303 + (0.177 × MLS), p<0.001). Results for Group II demonstrated that:

In the PLX view, severe Mitral stenosis was predicted by a MVA of 7.25 mm or less with a 89% sensitivity and 90% specificity for planimetry (MVA ≤ 0.013 + (0.139 × MLS), p<0.001) and MVA of 7.75 mm or less with a 84% sensitivity and 100% specificity for PHT (MVA ≤ 0.203 + (0.168 × MLS), p<0.01). In the apical 4chamber view, severe Mitral stenosis was predicted by a MVA of 7.65 mm or less with a 93% sensitivity and 100% specificity for planimetry (MVA ≤ 0.122 + (0.152 × MLS), p<0.05), and 7.9 mm with a 84% sensitivity and 100% specificity for PHT (MVA ≤ 0.261 + (0.174 × MLS), p<0.040, P value <0.001) for both groups MVA by planimetry ≤ 0.304 + (0.052 × PLX view) (p<0.01) - the MLS index is a new and practical method for assessment of mitral stenosis severity and mitral valve area.

Comparison of mitral annular calcification and other atherosclerosis risk factors, brachial/carotid intima-media thickness and angiographic extent of coronary artery disease

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Comparison of arterial intracardiac echocardiography versus venous intracardiac echocardiography during mitral valvuloplasty

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Transesophageal echocardiography (TEE) and venous intracardiac echocardiography (ICE) are traditionally utilized to assess intertrial septal imaging and tenting effect of the fossa ovarii in patients undergoing percutaneous balloon mitral valvuloplasty (PBMV). The aim of this study was to assess the comparative efficacy and safety of arterial (intracoronary) ICE versus venous ICE with regard to TEE.
A cut-off value of left atrial remodeling parameters may predict the recurrence of atrial fibrillation after radiofrequency ablation concomitant to mitral valve surgery

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Though the benefit from the concomitant radiofrequency ablation and mitral valve surgery is high, the atrial fibrillation recurrence is possible in follow-up. The purpose of this study was to investigate the left atrial remodeling in patients undergoing ablation and mitral valve replacement and to determine the appropriate cut-off value of remodeling parameters to predict atrial fibrillation recurrence.

Methods: 66 consecutive patients with of atrial fibrillation (AF) and mitral valve disease underwent radiofrequency ablation and mitral valve surgery. Heart rhythm was evaluated before and 12 months post surgery. Biopsies of the posterior wall of the left atrium were obtained during the operation. The extent of fibrosis, myocyte diameter, intensity of inflammatory infiltrates, degree of myocytolysis and capillary density were determined. Transthoracic echocardiography was performed, and valvular disease and left atrial dimension were evaluated. A potential relationship between left atrial remodeling and these parameters was investigated, and a receiver-operating characteristic (ROC) curve was designed thereafter to identify a cut-off value of involved parameters that best predicted the recurrence of atrial fibrillation.

Results: Ten patients died and 1 patient was lost to follow-up. Heart rhythm at 12 months was used to divide the remaining 55 patients into two groups: group I, 34 with sinus rhythm; group II, 21 with AF. There was a significant difference in the median myocyte diameter (17.9 vs.3.5 μm vs. 20.3±4.6 μm; p=0.04), percentage of fibrosis (36.7±11.2% vs. 47.6±12.3%, p=0.009), inflammatory infiltrates (p=0.02) and percentage of left atrial diameter (5.03±0.7 cm vs. 5.5±0.8 cm; p=0.04) between groups I and II. No differences were found in capillary density (797.9±506.0/mm² vs 946.0±372.7/mm², p=0.3) and myocytolysis (p=0.4). According to the ROC curve cut-off value of 38.1% for fibrosis (p<0.001) and at 17.9 μm for myocyte diameter (p=0.01) predicted procedure failure (area under the curve 0.7). Cut-off value at 5.49 cm for left atrial size predicted procedure failure (area under the ROC curve 0.7, p<0.005).

Conclusions: These results suggest that a atrial fibrillation recurrence is strongly associated with a left atrial remodelling in patients with mitral valve disease and atrial fibrillation undergoing RF ablation concomitant to valvular surgery. The values of 38.1% for fibrosis, 17.9 μm for myocyte diameter and 5.49 cm for left atrial size allow us to predict the risk of atrial fibrillation recurrence in these patients.

Predicting post-operative outcomes after mitral valve surgery: additive value of three-dimensional echocardiography

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Purpose: Mitral regurgitation (MR) causes eccentric LV hypertrophy, therefore assessment of LV size using M-mode or 2D echo may be inaccurate. We sought the value of three-dimensional echocardiography (3DE) in predicting post-operative outcomes after mitral valve surgery.

Methods: We prospectively followed 84 cases with severe organic MR (73% men, age 61±11 years, 96% mitral valve prolapse, 4% ischemic MR) who underwent mitral valve surgery from Jan 2010 to Dec 2011. In addition to standard 2D echocardiography, three-dimensional echocardiography (3DE) was performed for accurate quantification of LV size. Patients were followed for post-operative development of atrial fibrillation (AF) and LV dysfunction (LVEF<50%) as an outcome. A multivariable regression analysis was performed to identify associations with events.

Results: Over 4.0±0.5 months, 23 patients had post-operative AF (22.5%) and 23 patients had post-operative LV EF dysfuction (24.7%). LVEF decreased from 57.4±1.24 pre-operatively to 50.7±1.33 post-operatively (p<0.001). Post-operative AF and LV dysfunction were predicted (R2=0.76) by mean 3D LV end-systolic volume index (LVEVSI) (HR 1.19 [95% CI 1.07-1.30], p<0.001), independent of age, gender, pre-operative AF, NYHA functional class, and LVEF. LVEVSI>100 mL/m² was the best cut-off value to predict post-operative events (sensitivity 90.9%, specificity 85.2%). Although arterial and venous ICE, and facilitates transseptal puncture in patients with mitral stenosis. In all patients on arterial ICE (p<0.001), however, the fossa ovalis and tip of the needle were well visualised in all patients on arterial ICE (p<0.001). Furthermore, the view of the fossa ovalis and tenting effect” was optimal in 11 patients on venous ICE, however, the fossa ovalis and tip of the needle were well visualised in all patients on venous ICE. The Altman test indicated that the 95% limits of agreement for the measurement of septal length were negatively correlated with each other (R2 = -0.218; p<0.001). Standard venous ICE generally tended to yield smaller values compared to TEE and arterial ICE for measurement of septal length. The Bland-Altman test indicated that the 95% limits of agreement for the measurement of septal diameter ranged from -11.0 to +8.0 mm (mean = -2.5 mm) between TEE and arterial ICE, -2.8 ±33.5 mm (mean =15.3 mm) between TEE and venous ICE, and -36.6 ±0.8 mm (mean =-17.9 mm) between venous and arterial ICE. Furthermore, the view of the fossa ovalis and “tenting effect” was optimal in 11 patients on venous ICE, however, the fossa ovalis and tip of the needle were well visualised in all patients on venous ICE. The Altman test indicated that the 95% limits of agreement for the measurement of septal length were negatively correlated with each other (R2 = -0.218; p<0.001). Standard venous ICE generally tended to yield smaller values compared to TEE and arterial ICE for measurement of septal length. The Bland-Altman test indicated that the 95% limits of agreement for the measurement of septal diameter ranged from -11.0 to +8.0 mm (mean = -2.5 mm) between TEE and arterial ICE, -2.8 ±33.5 mm (mean =15.3 mm) between TEE and venous ICE, and -36.6 ±0.8 mm (mean =-17.9 mm) between venous and arterial ICE. Furthermore, the view of the fossa ovalis and “tenting effect” was optimal in 11 patients on venous ICE, however, the fossa ovalis and tip of the needle were well visualised in all patients on venous ICE. The Altman test indicated that the 95% limits of agreement for the measurement of septal length were negatively correlated with each other (R2 = -0.218; p<0.001). Standard venous ICE generally tended to yield smaller values compared to TEE and arterial ICE for measurement of septal length. The Bland-Altman test indicated that the 95% limits of agreement for the measurement of septal diameter ranged from -11.0 to +8.0 mm (mean = -2.5 mm) between TEE and arterial ICE, -2.8 ±33.5 mm (mean =15.3 mm) between TEE and venous ICE, and -36.6 ±0.8 mm (mean =-17.9 mm) between venous and arterial ICE.
between the concentration of TGF-β1/2 and the progression of valve myxomatous and heart chambers’ remodeling after reconstructive surgery in MVP.

Methods: We examined 35 patients undergoing reconstructive surgery due MVP complicated by severe mitral insufficiency (mean age 62.5 ± 7.9 years, 46% - men). Additional group was formed from the 11 subjects with MVP (32.5 ± 11.3 years, 64% - men), have been the first generation offsprings of the ten operated patients. All echocardiographic measurements were performed using an ultrasonic system Vivid 7 Dimension (GE Healthcare). The levels of TGF-β1 and TGF-β2 in serum were determined by enzyme-linked immunosorbent assay using a test system Human Platinum ELISA (Bender MedSystems).

Results: High level of TGF-β1 (> 14.75 ng/ml) and/or TGF-β2 (> 2.0 ng/ml) was detected in majority (65%) of cases and correlated with the thickness of posterior leaflet (r = 0.67, p = 0.016), residual valve prolapse (r = 0.68, p = 0.007) and residual MR (r = 0.56; p = 0.01). In patients with high TGF-β1 level a significant decrease in LV longitudinal systolic (-13.5 ± 2.2% vs. -16.6 ± 2.3%; p = 0.008) and diastolic (1.14 ± 0.20 ± 1 vs. 1.34 ± 0.18 ± 1, p = 0.04) strain and SR (-0.89 ± 0.15 ± 1 vs. -1.14 ± 0.16 ± 1, p = 0.002).

In the nonoperated offsprings’ group high level of TGF-β1/2 observed in 73% (8 subjects). The concentration of TGF-1 was strongly correlated with the thickness of the posterior valve (r = 0.77, p = 0.01), with the thickening of the valves (r = 0.68; p = 0.021) and severity of mitral regurgitation (r = 0.69; p = 0.01).

Conclusions: TGF-β has a significant impact on the progression of valve myxomatous after reconstructive surgery. The high activity of TGF-β signaling pathway results also in reduction in LV function, probably due to TGF-β profibrotic activity.

(1) LASER-ASSISTED Mitral Valve Repair (LAMVR) vs. Transthoracic Valve Replacement (TTR) for Mitral Valve Regurgitation (MVR) - a randomized trial

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Value of exercise testing and deformation imaging before degerenerative mitral valve repair


Objectives: This study analyzes the association between pre-operative rest and exercise echocardiography and the six-month post-operative left ventricular ejection fraction (LVEF) in organic mitral regurgitation (MR).

Background: The left ventricular (LV) end-systolic diameter and the LVEF are correlated with the post-operative LVEF and the prognosis in patients with organic MR, but some patients still do not return to a 6-month post-operative normal LVEF despite having normal pre-operative diameters.

Methods: 88 patients (62.6 ± 1.4 yrs.) were prospectively recruited. They received a sub-maximal (for a complete echocardiography at rest and one at 110 ± 10/min) exercise stress echocardiography before MR repair, and all of the patients underwent an echocardiography 6 months after surgery. The exclusion criteria were coronary artery disease, other organic valvular diseases, uncontrolled arrhythmia and hemodynamic instability.

Results: All complete datasets with rest and exercise echocardiograms and underwent isolated mitral valve surgery. The global longitudinal strain (GLS) at rest (R = -0.42, p = 0.011) and exercise during (R = -0.36, p = 0.034) was correlated with the post-operative LVEF. Normalized for the LV end-systolic diameter, the GLS recorded during exercise was more closely correlated with and was the best predictor of the post-operative LVEF using a multivariable linear regression model. Normalized for LV end-systolic LV dimension, exercise GLS had, for a cut-off of -5.7% /mm, a sensitivity of 0.83, a specificity of 0.70, a negative predictive value of 0.64, a positive predictive value of 0.86 for predicting a 6-month post-operative LVEF of ≥ 50%.

Conclusions: GLS (%) recorded at rest and also during sub-maximal exercise improves the prediction of post-mitral valve repair LVEF.

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Preoperative atrial fibrillation predicts outcome after valve repair for mitral valve proplase

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Background: Guidelines recommend surgery, preferably mitral valve repair (MVR) for patients with severe organic mitral regurgitation (MR) and occurrence of atrial fibrillation (AF). The aim of this study is to assess the impact of preoperative AF on outcome in patients undergoing MVR for mitral valve prolapse (MVP).

Methods: Between 1991 and 2009, 335 consecutive patients underwent MVR for MR due to MVP (follow-up: mean duration 105 ± 50 months). Echocardiography was performed preoperatively and 9 to 12 months after surgery. Post operative left ventricular dysfunction (LVD) was defined as ejection fraction (EF) < 50%.

Results: There were 79 patients (23.6%) in AF at baseline. Preoperative EF decreased from 67.1 ± 9.7% to 58.9 ± 10.1% post operatively (p < 0.0001). Patients in AF were older (70 ± 9 vs. 65 ± 10 years, p < 0.0001), more often in NYHA III - IV class (p = 0.027), had a significantly higher EuroSCORE (4.53 ± 5.8 vs. 2.6 ± 2.4, p < 0.001) at baseline, patients in AF had a lower preoperative EF (64 ± 11 vs. 68 ± 9%, p = 0.002). Early mortality was 6.3% in patients with preoperative AF vs. 1.3% in sinus rhythm (p = 5, p = 0.046). Multivariate analysis did not identify AF as a predictor of early mortality whereas EuroSCORE (p: 0.0001) and low pre-operative EF < 60% (p = 0.019) were independent risk factors for early mortality. On multivariate analysis adjusted for EuroSCORE, NYHA III - IV class and preoperative LVEF, preoperative AF was identified as an independent predictors of overall mortality (OR 1.34; p = 0.02) and of occurrence of heart failure (OR 1.55, p = 0.028). After adjustment for gender, EuroSCORE, NYHA III-IV class and preoperative EF, preoperative AF and pre-operative EF were the 2 predictors of early mortality (OR 2.06, p = 0.038 and OR 1.04, p = 0.027 respectively). Post-operative LVD was associated with more than 2.5 – fold increase risk of cardiac death and/or heart failure during follow-up (HR 2.67 (1.41 - 5.08); p = 0.0003).

Conclusion: Preoperative AF is an independent predictor of long term mortality and of post-operative LVD after MVR for MVP.

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Reasons for an insufficient procedural result in patients treated with the mitrACLIP for mitral regurgitation

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Background: Treatment in the US EVEREST-trial required strict adherence to inclusion and exclusion criteria. In Europe patients could be treated outside of clinical trials and the MitraClip has been in patients that would have been excluded from the US trial. We analysed 114 consecutive patients that were treated in our clinic to detect predictors of a treatment failure or of an only partially successful treatment.

Methods: Between March 2009 and November 2011 114 procedures in 109 patients (age 73 ± 16, LVEF 34.7 , NTproBNP 6802 ± 8195 pg/ml, 62% male) were performed by two interventionalists. Treatment was for moderate-severe or severe functional or degenerative mitral regurgitation. Failure or partial success was defined as: clip not implanted, clip implanted but death during same hospitalization, partial detachment that could not be repaired, residual regurgitation of ≥ grade II.

Results: In 3 patients we were unable to implant a Clip. 2 of these patients had marked enlargement of the right atrium (47 cm² and 46 cm² in 4ch vs. 28.5 ± 11.7 cm² in entire group), the third patient had a flail width of 17 mm. In 2 further patients, the mitral regurgitation deteriorated as a result of several graspers, in both cases caused by structural damage to the leaflets, not the result of chordal rupture. In 15 patients (13.2%) the residual mitral regurgitation was ≥ grade II. Of these 15 patients were among the first 20 patients treated in our clinic and presumably reflect a learning curve. Among the remaining 7 patients ≥ grade II regurgitation were 2 with Barlow’s disease (none successfully treated), 3 after mitral valve repair with anuloplasty (1 successfully treated), 4 with marked thickening of the leaflets (2 successfully treated) and 1 patient with a purely commissural prolapse (none successfully treated). Death was in 2 cases due to acute procedural deterioration (one of mitral regurgitation = Tier EuroSCORE (p < 0.0001) and one patient without operation because of instability). 5 additional patients died from progressive heart failure despite unsuccessful implantation of a clip.

Conclusion: After the learning curve the following morphologies are associated with poor procedural success: strong enlargement of the right atrium, Barlow’s disease, prior mitral valve repair with anuloplasty-ring, thickening of the leaflets to more than 3mm and purely commissural prolapse. The grasping of the leaflets can endanger the structural integrity of the leaflet by a mechanism distinct from chordal rupture. In patients with terminal heart failure the prognosis is probably unaltered by the procedure.
Background: Percutaneous techniques to treat severe aortic stenosis (AS) or significant mitral regurgitation (MR) in patients deemed at high surgical risk have shown to be safe and efficacious in either clinical entity. For AS, transcatheater aortic valve replacement (TAVR) using the Sapien/Sapien XT prosthesis (Edwards Lifesciences) via transfemoral (TF) or transapical (TA) access or the CoreValve (Medtronic) via TF access has become a viable therapeutic option, whereas in MR, considerable clinical experience has been gained with transvenous/transseptal implantation of the MitraClip (MC) device (Abbott Vascular, Abbott Park, IL, USA). To date, little information is available on transcatheater treatment for both AS and MR in the same patient.

Methods and Results: By March 2011, 285 TAVR and 233 MC procedures had been performed at our center. Eleven patients (78±6.6 years; 9 men [82%]) underwent both TAVR and MC implantation. In the first 8 patients treated, TAVR (5 TA, 3 TF) preceded MC by a median of 648 days (range, 4 to 348) days, whereas in the last 3 patients, TAVR (2 TA, 1 TF) was performed in a single session. All TAVR procedures (7 Sapien [4] Sapien XT [3]) to MC by a median of 60 days after MitraClip therapy.

Post T AVR, no patient had transvalvular aortic regurgitation (AR); minor (grade 1) AR was caused by functional or degenerative valve disease or mitral valve prolapse. Most patients had no surgical treatment or highly increased surgical risk (32±19.8% of patients with severe MR with small periprocedural risk). The poor prognosis in patients with end-stage heart failure and significantly reduced LVEF. The obtained results are comparable to results achieved in patients with preserved LVEF. Therefore, percutaneous mitral valve repair represents a treatment option in patients with significant MR and low LVEF.

Echocardiographic parameters in functional mitral regurgitation predicting therapy failure after MitraClip

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Background: The interventional reconstruction of the mitral valve with the MitraClip device has become an effective treatment in high-risk patients with functional mitral regurgitation (MR). Predicting therapy success based on echocardiographic data is difficult. FMR is due to complex pathologies of the left ventricle. Studies on the therapy success after surgical reconstruction have shown that several parameters, such as a negative paravalvular AR, are predictive of clinical benefit from transcatheter-based double-valve intervention remain to be determined.

Aims: The implantation of MitraClip is a new treatment for severe mitral regurgitation (MR) of patients, who are inoperable or at high risk for conventional operation. This study reports the follow up data of patients implanted with MitraClip in our heart center to evaluate the clinical benefit of this procedure.

Methods: This study enclosed 97 consecutive implantation procedures in 92 patients (age 73±16.0 years; LVEF 34%; NT-proBNP 5945±6639 pg/mL) between March 2009 and November 2011 in our center. The severe mitral regurgitation was caused by functional or degenerative valve disease or mitral valve prolapse. Most patients had no surgical treatment option or highly increased surgical risk due to reduced LVEF or concomitant diseases. 3 (3%) implantation procedures were unsuccessful. In 5 patients the implantation procedures were redone due to MR progress. 6 patients needed conventional heart surgery despite high operative risk. Therapy failure was defined as a MR reduction of less than one grade in every patient.

Results: 9 (9%) patients died in the first 6 months, both groups mainly due to severe therapy-resistant end-stage heart failure. The 73 patients alive after 6 months showed a significant improvement in NT-proBNP, LVEF, NYHA class, 6 minutes walk test and quality of life. The MR was reduced at least by half in every patient. The 6mWT showed a trend to longer walking distances (248±115 to 347±123m, P=0.064 vs. 304±118 to 389±125m, P=NS). NYHA class improved from group 1 from 3.0±0.5 to 1.3±1.1 (P<0.001) and in group 2 from 3.0±0.5 to 1.8±1.0 (P<0.01) and from 3.4±0.5 to 1.8±1.0 (P<0.01), respectively. NT-proBNPs decreased in group 1 from 58±10 patients 5±11mmol/L (P<0.01) and from 30.8±12.9 to 32.7±10.8mmHg (P<0.001) in group 2. The LV diameters and volumina demonstrated a trend to smaller dimensions at follow-up.

Conclusion: At mid-term follow-up, the percutaneous MitraClip edge-to-edge treatment provided significant clinical benefits in selected patients with severe heart failure and significantly reduced LVEF. The obtained results are comparable to results achieved in patients with preserved LVEF. Therefore, percutaneous mitral valve repair represents a treatment option in patients with significant MR and low LVEF.

Clinical outcome and patient selection criteria for MitraClip therapy in patients with severe mitral regurgitation and high surgical risk

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SIRT3 deficiency impairs cardiac function but not contractile recovery following ischemia-reperfusion

SIRT3 deficiency impairs cardiac function but not contractile recovery following ischemia-reperfusion. In contrast, SIRT3 may be expendable for contractile recovery following ischemia-reperfusion. Thus, we hypothesized that reduced SIRT3 expression may contribute to contractile dysfunction in failing hearts. In 8 week-old mice lacking SIRT3 (SIRT3 KO), heart weight-to-tibia length ratios were significantly increased (+18%; p<0.05) compared to wildtype (WT) mice, indicating cardiac hypertrophy. In isolated working hearts, left ventricular developed pressure (LVDevP) was decreased before and after ischemia in SIRT3 KO compared to WT, however, percental recovery of LVDevP following ischemia-reperfusion was similar in WT and SIRT3 KO (LVDevP 88±16 vs. 87±3.2%; n.s.). Similarly, CE and coronary flow showed equal rates of recovery. Thus, lack of SIRT3 causes cardiac hypertrophy and may impair contractile function in the heart, suggesting that reduced expression of SIRT3 in failing hearts may contribute to cardiac dysfunction. In contrast, SIRT3 may be expendable for contractile recovery following ischemia-reperfusion.

**Methods & Results:**

LVDevP was decreased before and after ischemia in SIRT3 KO compared to WT. However, percental recovery of LVDevP following ischemia-reperfusion was similar in WT and SIRT3 KO (LVDevP 88±16 vs. 87±3.2%; n.s.). Similarly, CE and coronary flow showed equal rates of recovery. Thus, lack of SIRT3 causes cardiac hypertrophy and may impair contractile function in the heart, suggesting that reduced expression of SIRT3 in failing hearts may contribute to cardiac dysfunction. In contrast, SIRT3 may be expendable for contractile recovery following ischemia-reperfusion.
gaining of reperfusion and achieved a better recovery of pH during further reperfusion. In the presence of both GS3-βi-inhibitors during the application of NH4Cl and its washout, the pH recovery was 3-fold delayed compared to controls indicating an inhibition of the Na+/H+ exchanger. These data suggest a major role of Na+/H+ exchanger in the delayed pH-recovery in cardiomyocytes through GS3-βi-inhibition.

**Propose:** Extracellular RNA (eRNA), released after tissue trauma, ischemia or damage, has been shown to exert prothrombotic and hyperpermeability-inducing functions, which are prevented by Ribonuclease1 (RNase1) treatment in vivo. Following ischemia and myocardial necrosis during reperfusion, the presence of eRNA (as collector for cytokines and coagulation proteases) might potentiate the development of rigot contracture. Here, the potential contribution of the eRNA/RNase1 -system in ischemia/reperfusion (I/R) injury was investigated in isolated rat hearts in a Langendorff system.

Methods: Lactate dehydrogenase (LDH) release, a marker of cell damage/necrosis, as well as eRNA and RNase-activity were determined in the perfusate before and during reperfusion (120 min) following 45 min of ischemia. To study the performance of RNase1 on physiological parameters, left ventricular (LV) pressure was continuously recorded. RNase1 was added in different concentrations to the perfusion buffer, starting 3 min before the ischemic phase and maintained for the whole duration of the experiment.

**Results:** In the initial period of reperfusion (following the ischemia phase) there was a sharp increase in LDH release (32.8±3.0 U/g dry tissue), a prominent initial peak of eRNA (52.9±33.3 ng/ml) followed by a prolonged high level of eRNA between 15 and 60 min of reperfusion. Only very low endogenous RNase1-activity was found in the perfusate. Treatment with RNase1 in a concentration-dependent manner induced a lower and delayed increase in diastolic pressure during reperfusion, indicating a less severe rigot contracture. In addition, functional recovery of heart tissue after 30 min reperfusion was preserved as indicated by increased of LV developed pressure (I/R: 53±4.7% vs. baseline; p=0.03). Finally, RNase1 reduced the severity of the maximal hypercontracture (I/R: 67.8±8 mmHg; RNase1-treatment: 19.3±3 mmHg; p=0.05) during the initial reperfusion phase and prevented the initial LDH release (16.3±2.0 U/g dry tissue, 30 min after reperfusion), indicating less myocardial damage and protection against necrosis.

**Conclusion:** eRNA is released from the rat heart during I/R and may contribute to the outcome of injury. RNase1 intervention appears to be a new potential therapeutic strategy to protect the heart from ischemia and reperfusion injury.

**Results:** In the non-r-IPC, infarct size was 40.8±3.1%. r-IPC decreased infarct size to 16.4±3.5% (p<0.05). The section of vague nerves or the atropine administration during r-IPC protocol abolished the effect of r-IPC on infarct size (43.2±3.4% and 37.6±3.1%, respectively). Vagal stimulation mimicked the effect of r-IPC, decreasing infarct size to 15.2±4.7% (p<0.05). The femoral and sciatic nerves section only partially abolished the effect of r-IPC (p<NS). However, the spinal cord section (T9-T10) completely abrogated the effect of r-IPC on the infarct size (44.2±5.4%; p<0.05).

**Conclusion:** Hindlimb ischemia in r-IPC activates a neural afferent pathway that reaches the heart via the vague nerve (afferent pathway) and contributes to cardioprotection. The beneficial effect of r-IPC may be mediated by acetylcholine, since it was blocked by atropine.
A method of studying the course of myocardial ischemia and reperfusion in rats in vivo

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Background: The use of MRI for the study of ischemia and its consequences in small animals has been limited by the need for a thoracotomy and operative occlusion of the coronary arteries. The trauma of the surgery may be an important confounder in this open-chest model. The closure of the coronaries with a suture would not allow multiple occlusion-reperfusion cycles, and has limited the study of ischemia-reperfusion in small animals.

Objective: To develop a "closed chest" model of ischemia-reperfusion, which would allow ischemia and infarction to be studied in real-time while the rat is in MRI imaging.

Materials and Methods: We developed a method of implanting a balloon occluder to the left coronary artery. Male Sprague Dawley rats (n=12, weight 360±30g) were anesthetized and then intubated. The heart was exposed by an incision in the fourth rib space. The occluder was then secured loosely to the myocardium with a 6-0 non-absorbable suture. Occlusion and reperfusion of the coronary vessels was confirmed by visual inspection (blanching of the left ventricle) and by ECG (ST-segment elevation and normalization) on brief inflation and deflation of the balloon. The tubing of the occluder was then tunneled to the back of the rat and exposed in the infra scapular area. The animals were then allowed to recover from the operation for at least 5 days.

For coronary occlusion and MRI scanning, rats were again anesthetized, the tubing was connected to a syringe, and animals were placed in the MRI scanner.

Results: There was a very low mortality rate for the implantation of the coronary occluder (8.3%). Inflation of the occluder on the MRI table resulted in myocardial ischemia in all animals as documented by ECG, and allowed the effects of ischemia and reperfusion on myocardial edema and function to be studied serially before, during, and after coronary occlusion. The changes in ECG were visible on the standard Philips console. There was no visible artifact from the occluder on any of the images.

Conclusions: The use of a pre-implanted balloon occluder allows for studying of the effects of single or repeated myocardial ischemia and reperfusion with MRI in real-time in a closed-chest rat model. As the current treatment of myocardial infarction is urgent revascularization, this model is more clinically relevant than a simple infarction model. A more physiologically suitable model should aid the study of the complex mechanisms involved.

N-acetylcysteine ameliorates infarction-induced myocardial fibrosis

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Purpose: Excessive production and deposition of extracellular matrix proteins is a feature after myocardial infarction. Excessive fibrosis is an important substrate for ventricular vulnerability. Reactive oxygen species contributes to collagen synthesis through the activation of RhoA. We assessed whether the antioxidant N-acetylcysteine could attenuate myocardial fibrosis after myocardial infarction, evaluating connective tissue growth factor signal transduction mechanism that is responsible for extracellular matrix deposition and antiarrhythmia.

Methods: Male Wistar rats after ligation coronary artery were randomized to either vehicle, or N-acetylcysteine for 4 weeks.

Results: Post-infarction was associated with increased oxidant release, as measured by myocardial glutathione and superoxide, and dithiothreitol fluorescent staining. RhoA/ROCK activation after myocardial infarction was observed by increasing RhoA localization from the cytoplasm to the membrane and phosphorylating the ROCK substrate myosin phosphatase target subunit 1. N-acetylcysteine diminished myocardial fibrosis by inhibiting RhoA/ROCK activation without alteration of TGF-β1 levels. A Rho inhibitor, C3 exoenzyme, and 2 ROCK inhibitors, Y27632 and Y27662 demonstrated that myocardial telomerase is up-regulated in a factor expression. Arrhythmic scores during programmed stimulation in the vehicle-treated infarcted rats were significantly higher than that in those treated with N-acetylcysteine. NAC administration could be helpful in preventing early remodeling process, which involves the cellular aging signalling machinery.

Conclusion: These results indicate that N-acetylcysteine as a glutathione precursor can expedite the attenuation of infarction-induced myocardial fibrosis probably through the inhibition of TGF-β1-dependent Rho/ROCK activity and thus plays a critical role in the beneficial effect on arrhythmogenic response to programmed electrical stimulation.

Dynamic regulation of myocardial telomere biology in the infarcted mouse heart

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Introduction: The incidence of cardiovascular disease rises with age. The aging process on the level of organs and cells is finely regulated and involves the accumulation of irreversible DNA damage and the erosion of telomeres. Oxidative stress-induced DNA damage may induce premature stress-induced senescence of ischemic cardiomyocytes. Telomerase has been shown to protect cardiovascular cells from mitochondrial oxidative stress. In this study, we analyzed whether myocardial ischemia impacts on telomere biology and cellular senescence in the infarcted mouse heart.

Methods and results: C57Bl/6 mice (male, 10 weeks old, n=6 per group) were exposed to anterior myocardial ischemia induced by proximal ligation of the left anterior descending (LAD) coronary artery or sham operation. Infarct size and localization were verified by cardiac MRI. Sham-operated and mice with myocardial infarction were analyzed 3 days, 7 days, 4 weeks after LAD ligation and myocardial infarct zone and remote zone were compared with respect to the telomere and senescence status as measured by telomere repeat amplification protocols. A standard dilution curve of Human Embryonic Kidney (HEK) cells with high telomerase activity was used as positive control. The experiment revealed that 3 days after LAD ligation, telomerase activity was elevated in the infarct zone, but not in the remote zone of the hearts. 7 days after myocardial infarction, telomerase was up-regulated both, in the infarct zone and the remote zone. This effect was even more pronounced 4 weeks after LAD ligation. Corresponding to telomerase elevation, telomere repeat binding factor (TRF) 2 protein expression was up-regulated in the infarct zone after three days and in both areas at 7 days and 4 weeks. At the same time, apoptosis regulators (p53, CHK2 and bax) and senescence regulators (p16) were up-regulated in the infarcted hearts as an indicator of a complex cellular remodeling process, which involves the cellular aging signalling machinery.

Conclusion: Our data show that myocardial ischemia impacts on telomere biology and cellular senescence in the infarcted mouse heart.
**Protective role of Prothymosin alpha against cardiac ischemic injury**

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**Purpose:** The human Prothymosin alpha (PTα) gene encodes a 12.5 kDa highly acidic nuclear protein that is widely expressed in mammalian tissues including the heart and, importantly, is detectable also in blood serum. During apoptosis or necrosis, PTα is released from cells and is able to exert an autocrine-paracrine cytoprotective effect. Since the role of PTα in the heart is still unknown, the aim of the present study has been to test whether PTα might have a similar protective action in cardiomyocytes following ischemia.

**Methods:** Acute myocardial infarction (AMI) was induced in mice by surgical ligation of the left anterior coronary artery (LCA). Sham-operated animals underwent the same surgical procedure without occlusion of the LCA. All the animals were sacrificed 1 or 7 days post-surgery to perform molecular and histological analyses. For in vitro evaluations, neonatal rat cardiomyocytes underwent simulated ischemia for 6 hours or ischemia/reperfusion for 16 hours. Furthermore, a recombinant murine PTα (PTαr) was expressed and purified to test its effects both in vitro and in vivo.

**Results:** Seven days post-AMI, PTαr expression levels were significantly increased in both blood serum and cardiac tissues compared to Sham animals. Moreover, myocardial ischemia induced PTαr translocation from the nucleus to the cytoplasm and plasma membrane in cardiomyocytes in the peri- and infarcted regions. Furthermore, in vitro experiments confirmed that in cardiomyocytes, exposed to ischemia or IR, PTαr protein levels were upregulated compared to non-toxic cells, and the protein was also released from cells since it was detectable in the medium of ischemic cultured cells. Importantly, the treatment of cardiomyocytes with PTαr was shown to be lower in groups 3 and 4 than in group 2 (all p < 0.001). The angiogenic markers (protein expression: eNOS; IF staining: CD31+ and vWF+ cells; small number of vessels in CLI region) were higher in group 5 than in groups 2 to 4, and higher in groups 3 and 4 than in group 2 (all p < 0.001).

**Conclusion:** Combined cistostatol-clopidogrel therapy is superior to either one alone in improving ischemia in rodent CLI.

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**Inhibition of mitochondrial benzodiazepine receptor protects cardiomyocytes against reoxygenation injury**

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It has been shown that inhibition of the mitochondrial benzodiazepine receptors (mBzR) exhibits cardio-protective effects towards development of arrhythmia during ischemia and reperfusion. The aim of the present study was to investigate, whether inhibition of mBzR protects isolated cardiomyocytes against reoxygenation induced Ca2+-oscillations and hypercontracture and to analyze, whether this is due to an interaction with the mitochondrial permeability transition pores (MPTP).

Isolated rat cardiomyocytes were superfused anoxically (60 min; 100% N2; no-glucose; pH 6.4) and then reperfused with a normoxic buffer (20 min; 21% O2; 2.5 mM glucose; pH 7.4). In addition to cell length measurement, cytosolic Ca2+ and MPTP opening were measured by the fluorescence indicators Fura-2 and Calcine, respectively. The mBzR inhibitor 4-Cl'-DZP (10 μM), the activator of the mBzR, N,N-Diethyl-2-(4-fluorophenyl)indole-3-acetamide (FGN; 4.6 μM) or the direct inhibitor of the MPTP, Cyclosporine A (Cap A; 500 nM) were administered during reperfusion.

Application of 4-Cl'-DZP during reperfusion markedly reduced the amplitude and frequency of cytosolic Ca2+ oscillations (Ca2+-amplitude in the 5th min of reperfusion [a.u.]: control: 9.94 ± 1.83; 4-Cl'-DZP: 2.26 ± 0.68; n=12; p<0.05 vs. control). The extent of hypercontracture was also significantly reduced by 4-Cl'-DZP (cell length at the end of reperfusion [% of end-diastolic fluorescence]: control: 60.95 ± 3.59; 4-Cl'-DZP: 74.98 ± 2.44; Cap A: 74.64 ± 3.79; FGN: 48.82 ± 2.57, p<0.05 vs. control). The data of the present study show, that inhibition of the mBzR has a protective effect on reoxygenated cardiomyocytes as the development of Ca2+-oscillations and hypercontracture is decreased. Furthermore, the data demonstrate a reduced opening of MPTP, indicating a stabilization of the mitochondrial membrane potential, Δψm.

Altogether, these mechanisms lead to a protection of cardiomyocytes against reoxygenation-induced injury and reperfusion-induced arrhythmia.
Cardiac morphology and function in migfilin deficient mice due to experimental pressure overload

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Background: Migfilin, a protein associated with cell adhesions and the cytoskeleton, is essential for cardiac hypertrophy by inducing transcription of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), among others. In vivo, migfilin is involved in cardiac hypertrophy and function is unknown.

Methods: Migfilin wild type (WT) and knock out (KO) mice were examined at baseline and after one and three weeks of pressure overload, induced by transverse aortic constriction (TAC). mRNA and protein expression of cardiac hypertrophy and function markers were measured.

Results: In KO mice, ANP and BNP mRNA expression was significantly lower when compared to WT mice (both, p < 0.05) and basal mRNA expression was increased by 2 weeks of pressure overload (p < 0.05). Moreover, ANP and BNP protein expression was increased in KO mice compared to WT at baseline (p < 0.05) and after 3 weeks of pressure overload (p < 0.05). Furthermore, ANP and BNP expression was increased by 2 weeks of pressure overload in KO mice (both, p < 0.05).

Conclusion: Migfilin plays an essential role in cardiac hypertrophy and function is unknown.

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Signaling modules involved in myocardial pathology

Cardiac morphology and function in migfilin deficient mice due to experimental pressure overload

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Conclusion: Migfilin plays an essential role in cardiac hypertrophy and function is unknown.
Inhibition of GSK-3beta augments 5-HT2B receptor blockade induced protection in angiotensin-II-induced cardiac hypertrophy in rats
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Glycogen synthase kinase-3β (GSK-3β) is a multifunctional Serine/Threonine kinase that performs a crucial role in regulating cardiac hypertrophy. The purpose of the current study was to identify and dissect the intracellular signaling mechanisms that link 5-HT2B receptor (5-HT2B) blockade and GSK-3β pathway in angiotensin-II induced cardiac hypertrophy. 5-HT2B receptor antagonist, SB-204741 (1 mg/kg, i.p.) or GSK-3β inhibitor, SB-216763 (0.6 mg/kg, i.p.) plus SB-204741 were administered in angiotensin-II (100 ng/kg/min, s.c.) treated rats for 28 days. SB-204741, treatment significantly (P<0.05) alleviated salt induced hypertension markers (creatinine kinase-MB, c-reactive protein, brain natriuretic peptide and malondialdehyde), myocyte area, TNF-α level and bolstered the anti-oxidant defense system (glutathione peroxidase and Manganese-superoxide dismutase). Moreover, this improvement was associated with anti-hypertrophic response was well coupled with increased expression of GSK-3α and GSK-3β, phosphorylation of Akt/GSK-3β/ESOs/IκBα and suppression of 5-HT2B, Nox4 and IκBα/NF-κB protein expressions in angiotensin-II insulted myocardium. Furthermore, the resistance to anti-apoptotic potential as measured by decreased TUNEL positivity, Bax expression and upregulated Bcl2 expression.

Mechanical stretch via transforming growth factor-beta1 activates microRNA-208a to regulate hypertrophy in cultured rat cardiomyocytes
K.-G. Shyu, B.-W. Wang. Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan

Purpose: MicroRNAs (miRs) and mechanical stress play a key role in cardiac hypertrophy. MiR208A is essential for expression of the genes involved in cardiac hypertrophic growth. The relationship between miR208A and mechanical stress in cultured cardiomyocytes has not been investigated yet. The molecular mechanisms underlying miR208A induced hypertrophy of cardiomyocytes by mechanical stress is poorly understood. We sought to investigate whether miR208A is a critical regulator in cardiomyocyte hypertrophy under mechanical stretch. Methods: Neonatal rat cardiomyocytes grown on a flexible membrane base were stretched via vacuum to 20% of maximum elongation at 60 cycles/min. TaqMan® microRNA real-time quantitative analysis was used to quantify microRNA expression. Western blot was used to measure hypertrophic protein expression. Quantitative sandwich enzyme immunoassay was used to measure transforming growth factor-beta1 (TGF-β1) in the culture medium. Protein synthesis of cultured cardiomyocytes was measured by 3H-proline incorporation assay. Results: Mechanical stretch significantly enhanced miR208A expression after 4 h of stretch. Stretch significantly induced cardiomyocyte hypertrophic protein expression such as β-myosin heavy chain (MHCβ), thyroid hormone receptor-associated protein 1, myostatin, connexin, 40, GATA4 and brain natriuretic peptide. MHCα was not induced by stretch. Overexpression of miR208A significantly decreased myocyte area, TNFα and interstitial fibrosis. Exogenous addition of TGF-β1- resistant cell line of 208A combined protein significantly increased miR208A expression and pretreatment with TGF-β1 antibody attenuated the miR208A expression induced by stretch. Mechanical stretch and overexpression of miR208A increased protein synthesis concomitantly while miR208A attenuated the protein synthesis induced by stretch overexpression of miR208A. Conclusions: Cyclic mechanical stretch enhances miR208A expression in cultured rat cardiomyocytes. MiR208A plays a role in stretch-induced cardiac hypertrophy. The stretch-induced miR208A is mediated by TGF-β1.

Mechanical stretch significantly increased Fib6 expression after 72h of ischemia but enhanced by increase in workload in remote myocardium with increased workload, mice subjected to transversal aortic constriction (T AC) with a gradient of 40 mmHg were used. RTPCR analysis showed 2.4 fold increased Fib6 expression after 7d of T AC (n=5, p<0.001) but not yet after 24h MI/R. To assess regulation of Fib6 in myocardium we performed T AC in cmc-G13-KOs. Four weeks after T AC, control hearts showed increased LVW/TL (mg/mm), with TGF-β1 or stretch induced gene expression of ANP and β-MHC was reduced by G12/13-deficient mice, we generated tamoxifen-inducible, cardiomyocyte-specific knockouts of Gα13. As a pressure-overload model, transverse aortic constriction (TAC) surgery was performed. LVW/TL (mg/mm), myocardial thickness and LVW/TL (mg/mm). TGF-β1 or stretch induced gene expression of ANP and β-MHC was reduced in cmc-G13-KO compared with controls. EF was preserved compared to wildtype mice.

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MicroRNAs (miRs) and mechanical stress play a key role in cardiac hypertrophy. MiR208A is essential for expression of the genes involved in cardiac hypertrophic growth. The relationship between miR208A and mechanical stretch in cultured cardiomyocytes has not been investigated yet. The molecular mechanisms underlying miR208A induced hypertrophy of cardiomyocytes by mechanical stress is poorly understood. We sought to investigate whether miR208A is a critical regulator in cardiomyocyte hypertrophy under mechanical stretch. Methods: Neonatal rat cardiomyocytes grown on a flexible membrane base were stretched via vacuum to 20% of maximum elongation at 60 cycles/min. TaqMan® microRNA real-time quantitative analysis was used to quantify microRNA expression. Western blot was used to measure hypertrophic protein expression. Quantitative sandwich enzyme immunoassay was used to measure transforming growth factor-beta1 (TGF-β1) in the culture medium. Protein synthesis of cultured cardiomyocytes was measured by 3H-proline incorporation assay. Results: Mechanical stretch significantly enhanced miR208A expression after 4 h of stretch. Stretch significantly induced cardiomyocyte hypertrophic protein expression such as β-myosin heavy chain (MHCβ), thyroid hormone receptor-associated protein 1, myostatin, connexin, 40, GATA4 and brain natriuretic peptide. MHCα was not induced by stretch. Overexpression of miR208A significantly decreased myocyte area, TNFα and interstitial fibrosis. Exogenous addition of TGF-β1-resistant cell line of 208A combined protein significantly increased miR208A expression and pretreatment with TGF-β1 antibody attenuated the miR208A expression induced by stretch. Mechanical stretch and overexpression of miR208A increased protein synthesis concomitantly while miR208A attenuated the protein synthesis induced by stretch overexpression of miR208A. Conclusions: Cyclic mechanical stretch enhances miR208A expression in cultured rat cardiomyocytes. MiR208A plays a role in stretch-induced cardiac hypertrophy. The stretch-induced miR208A is mediated by TGF-β1.

Myocardial hypertrophy is the adaptive response of the heart to pressure overload. A variety of in vivo studies indicated that G-protein coupled receptors (GPCRs) agonists induce heart remodeling through heteromeric G-proteins of the Gq/11 family. However, these GPCRs can also activate the G12/13 family which has been shown to regulate vascular smooth muscle contraction in a RhoA-dependent manner. We examine in this study whether G12/13 signaling contributes to cardiac remodeling. Methods: To circumvent this embryonic lethality in G13-deficient mice, we generated tamoxifen-inducible, cardiomyocyte-specific knockouts of Gα13 (cmc-G13-KO). As a pressure-overload model, transverse aortic constriction (TAC) surgery was performed. LVW/TL (mg/mm), myocardial thickness and LVW/TL (mg/mm). TGF-β1 or stretch induced gene expression of ANP and β-MHC was reduced in cmc-G13-KO compared with controls. EF was preserved compared to wildtype mice.

Mechanical stretch and overexpression of miR208A increased protein synthesis concomitantly while miR208A attenuated the protein synthesis induced by stretch overexpression of miR208A. Conclusions: Cyclic mechanical stretch enhances miR208A expression in cultured rat cardiomyocytes. MiR208A plays a role in stretch-induced cardiac hypertrophy. The stretch-induced miR208A is mediated by TGF-β1.
Micro-RNA 146a: a new kid on the block in the pathophysiology of cardiac hypertrophy and hypertensive heart failure, and a promising therapeutic target

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Background: Cardiac hypertrophy is one of the key processes in the transition from a healthy heart to cardiac failure in hypertensive heart disease. The present study investigated whether the genetic or pharmacological knockdown, in contrast to constitutively overexpression of micro-RNA 146a (miR-146a) may affect cardiac hypertrophy upon a pressure overload stimulus.

Methods: MiR-146a knockout (KO), wild-type (WT) and miR-146a cardiomyocyte-specific overexpressing transgene (TG) C57Bl6/N mice were exposed to angiotensin-II 2.5 mg/kg/day during 4 weeks. Next, miR-146a was pharmacologically blocked by administering specific miR-146a antagomirs. Functional analysis with echocardiography was performed. All mice were sacrificed and hearts were dissected for further histological and molecular analysis.

Results: Upon pressure overload, miR-146a expression levels decrease both in mice submitted to 4 weeks of Ang-II, and in cardiomyocytes in vitro stimulated with angiotensin-I. Ang-II infusion significantly increased the heart weight (normalized to tibia length) in the WT mice (HWT/L = 7, but not in the KO (HWT/L = 6), where the hypertrophic response was severely blunted (p<0.05). Echocardiographic analysis showed a preserved fractional shortening (FS) in KO mice (FS = 0%), whereas FS was severely decreased in the WT (FS = -25%, p<0.05). The reduced hypertrophic response and preserved cardiac function in the miR-146a KO mice went along with a significant reduction in the number of CD45+ inflammatory cells compared to the WT littermates (90 cells/mm2 in WT versus 50 cells/mm2 in KO, p<0.05). These findings were confirmed when blocking miR-146a with antagomirs: in fact, hypertrophy in response to AngII was significantly reduced in the anti-miR-146a group compared to the control scrambled group one (HWT/L = 10 in scrambled versus 8 in antimir group, p<0.01). In line with reduced hypertrophy when miR-146a is lacking, its overexpression in cardiomyocytes in TG mice resulted in a spontaneous development of cardiac hypertrophy, further accentuated upon Ang-II-administration (HWT/L = 5,5 in WT SHAM versus 8 in WT ANG, p<0.01). Following Ang-II infusion and Ang-II treatment with the PAR-1 antagonist, the number of CD34+/CXCR4+ cells among total peripheral blood mononuclear cells were significantly increased. Moreover, the infarct size was the smallest in the LE+G group (14.0 ± 2.5%) than in the control group (29 ± 5.4%), G group (23 ± 5.6%) or LE group (17 ± 3.7%). Western blot analysis showed the highest expression of phosphorylated-Akt and p-ERK in the ischemic myocardium at 14 days of reperfusion. To determine the participation of endothelial progenitor cells (EPCs) in the protection of the anti-miR-146a group, compared to the control scrambled group, the number of circulating EPCs was counted using FACS analysis 7 days after reperfusion.

Results: The infarct size was the smallest in the LE+G group (14.0 ± 2.5%) than in the control group (29 ± 5.4%), G group (23 ± 5.6%) or LE group (17 ± 3.7%). Western blot analysis showed the highest expression of phosphorylated-Akt and p-ERK in the ischemic myocardium at 14 days of reperfusion. To determine the participation of endothelial progenitor cells (EPCs) in the protection of the anti-miR-146a group, compared to the control scrambled group, the number of circulating EPCs was counted using FACS analysis 7 days after reperfusion.

Conclusions: Absence or inhibition of microRNA-146a blunts the hypertrophic response and cardiac failure upon pressure overload, whereas its overexpression in cardiomyocytes increases hypertrophy. MicroRNA-146a thus represents a new strategy for the treatment of myocardial infarction.

F16618, an antagonist of the protease activated receptor 1 reduces the atrial remodeling in a rat model of Chronic Heart Failure

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Purpose: Atrial fibrillation (AF) complicates the atrial remodelling characterized by increased expression of PAR-1 and PAR-1. It also prevented the decrease in ErbB2 and ErbB4 gene expression, but had no significant effect on the LV dysfunction.

Methods: Rats underwent either thoracotomy only (SHAM) or thoracotomy with cardiomegaly (CM). Neonatal rat cardiac myocytes and fibroblasts were transduced with adenoviral vectors encoding either wild-type FOXO3a (WT-FOXO3a), constitutive-active FOXO3a (TM-FOXO3a) or GFP as control. Effects on potential target gene expression were assessed by real-time qPCR. Western blotting was used to confirm the targeted gene expression in the left ventricle. Ex vivo cultures of CD34+CXCR4+ cells among total peripheral blood mononuclear cells were significantly increased. Moreover, the infarct size was the smallest in the LE+G group (14.0 ± 2.5%) than in the control group (29 ± 5.4%), G group (23 ± 5.6%) or LE group (17 ± 3.7%). Western blot analysis showed the highest expression of phosphorylated-Akt and p-ERK in the ischemic myocardium at 14 days of reperfusion. To determine the participation of endothelial progenitor cells (EPCs) in the protection of the anti-miR-146a group, compared to the control scrambled group, the number of circulating EPCs was counted using FACS analysis 7 days after reperfusion.

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Conclusions: Absence or inhibition of microRNA-146a blunts the hypertrophic response and cardiac failure upon pressure overload, whereas its overexpression in cardiomyocytes increases hypertrophy. MicroRNA-146a thus represents a new strategy for the treatment of myocardial infarction.

The forhead-transcription factor Foxo3a regulates MMP-13 expression, implications for cardiac remodeling

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Purpose: Structural alterations of cardiac extracellular matrix occur as a result of pathological processes, e.g., inflammation or ischemia/reperfusion injury. Matrix metalloproteinases (MMPs) are proteolytic enzymes which play a pivotal role in stress induced matrix remodeling. FOXO transcription factors are important stress-activated regulators of cell cycle and size. Therefore, we hypothesized that FOXO3a modulates the expression of MMPs thereby coordinating matrix remodeling.

Methods: Neonatal rat cardiac myocytes and fibroblasts were transduced with adenoviral vectors encoding either wild-type FOXO3a (WT-FOXO3a), constitutive-active FOXO3a (TM-FOXO3a) or GFP as control. Effects on potential target genes were assessed by qRT-PCR. Western blotting was used to confirm the targeted gene expression in the left ventricle. Ex vivo cultures of CD34+CXCR4+ cells among total peripheral blood mononuclear cells were significantly increased. Moreover, the infarct size was the smallest in the LE+G group (14.0 ± 2.5%) than in the control group (29 ± 5.4%), G group (23 ± 5.6%) or LE group (17 ± 3.7%). Western blot analysis showed the highest expression of phosphorylated-Akt and p-ERK in the ischemic myocardium at 14 days of reperfusion. To determine the participation of endothelial progenitor cells (EPCs) in the protection of the anti-miR-146a group, compared to the control scrambled group, the number of circulating EPCs was counted using FACS analysis 7 days after reperfusion.

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Conclusions: Combination of post-infarct treatment with G-CSF and EPO-liposomes SLX markedly reduced the infarct size via EPCs mobilization and upregulation of p-Akt and p-ERK in the ischemic myocardium. This may provide a new strategy for the treatment of myocardial infarction.
Conclusion: In conclusion our results implicate FOXO3a directly in the regulation of MPP13 expression. FOXO3a might play an important role in controlling extracellular matrix remodeling processes under cardiovascular stress and injury such as inflammation and myocardial infarction. Thus, targeting FOXO3a might have therapeutic potential.

P802 Eya4 mediates the development of acquired cardiac hypertrophy

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Introduction: We previously showed that a mutation in the transcription cofactor “Eyes absent” (Eya4) leads to late-onset familial dilated cardiomyopathy and heart failure. A precise role for Eya4 in the myocardium has not yet been identified. It appears to be a negative regulator of the protein kinase inhibitor p27kip1 (p27), a protein shown to regulate hypertrophic responses in the adult cardiomyocyte. This study was aimed to explore the role of Eya4 in angiogenin II (ATII)-induced cardiac hypertrophy.

Methods and results: We constructed a transgenic mouse model with a constitutive overexpression of HA-tagged Eya4. Wildtype and Eya4 overexpressing mice were challenged with ATII via osmotic minipumps for four weeks to induce cardiac hypertrophy. First analysis of these animals using magnetic resonance imaging to visualize cardiac structures in detail showed that in response to the sustained ATII stimulation, the Eya4 overexpressing mice exhibited a phenotype with significantly increased parameters of hypertrophy: LV free wall diameter as measured in T2 MRI was 1.7±0.2 mm in Eya4 mice with ATII compared to 1.3±0.2 mm in WT mice with ATII. This was also confirmed by HW/BW ratio, hemodynamic measurements and cell size measurements. Histology also affirmed the results of the MR imaging. Moreover, Eya4 overexpression induced a significant suppression of p27 protein expression which is in agreement with our in vitro data. We confirmed our hypothesis, that Eya4 suppresses p27 expression which facilitates development of myocardial hypertrophy.

Conclusion: In summary, we previously identified a mutation in Eya4 to disturb cardiac physiology. We now provide evidence that Eya4 is also involved in forms of acquired heart disease. It seems to suppress p27, thereby augmenting ATII induced cardiac hypertrophy.

P803 The transcription cofactor Eya4 is crucial in the development of heart disease

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Introduction: We identified a mutation in the human transcription cofactor Eya4 (E193) to cause terminal heart failure preceded by sensorineural hearing loss. Eya4 proteins lack DNA-binding and nuclear translocation sequences and therefore must interact with real transcription factors, including Six family members. The cyclin-dependent kinase inhibitor p27kip1 (p27), which inhibits hypertrophic growth in adult cardiomyocytes, is one of the few known Eya-Six targets expressed in the heart. We hypothesize that Eya4-Six1 regulates targets relevant to sustain normal cardiac function via p27.

Methods and results: We examined the correlation of Eya4 and the mutant E193 overexpression upon p27 in permanent mammalian cell lines and primary cardiac myocytes. Westernblot analysis demonstrated that an overexpression of Eya4, with a constitutive overexpression of Eya4 led to a significant suppression of p27, whereas E193 had no effect on p27 levels; knockdown of Eya4 via siRNA exerted opposing effects. Promoter studies using a p27 promoter fragment including Six1 consensus sites revealed that the constitutive suppression of p27 by Eya4 was released after targeting one of the Six1 consensus sites; E193 had no effect on p27 promoter activity. We constructed a transgenic mouse model with a constitutive myocardial overexpression of HA-tagged E193 to study the effect of a disturbed Eya4-Six1 complex upon cardiac physiology. Magnetic resonance imaging to visualize cardiac structures in detail also in vivo. Overexpression of HA-tagged Eya4 overexpression of Eya4 in mice leads to an age related onset of cardiomyopathy similar to patients carrying the E193 mutation. H&E-staining showed dilatation of the LV associated with a thinning of the myocardial wall. PS1-staining showed interstitial fibrosis of the myocardial tissue which is characteristic for cardiac disease.

Conclusion: In summary, we identified a mutation in Eya4 to cause DCM. Eya4/Six1 seems to suppress the expression of p27, an important inhibitor of the development of hypertrophy in postmitotic cardiomyocytes. Our transgenic mouse model with overexpression of the Eya4 mutant E193 supports our hypothesis whereas the dysfunctional E193 mutant could not suppress p27, finally leading to an age related onset of cardiomyopathy.

P804 Alogliptin reverses cardiac remodeling and dysfunction induced by pressure overload through the GLP-1/cAMP-mediated mitophagy

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Purpose: Dipeptidyl peptidase-4 (DPP4) inactivation protects heart from pathological remodeling and higher mortality induced by acute myocardial infarction. However, the impact of DPP4 inhibition on the chronic heart failure induced by pressure overload (TAC) remains uncertain.

Methods and Results: Male 10-week-old C57BL6 mice were randomly allocated into 6 groups: sham and TAC treated with (sham/ALO, TAC/ALO) or without (sham/CTL, TAC/CTL) alogliptin (10 mg/kg/day) or exendin-4, a potent GLP-1 receptor agonist (24 nmole/kg/day) (n=5-6). Echocardiogram revealed that TAC/CTL exhibited cardiac hypertrophy and their systolic and diastolic left ventricular functions were impaired 4 week after exposure to pressure overload, which were reversed by alogliptin treatment. Alogliptin increased circulating GLP-1 levels, which induced cardiac elevation of cAMP AMP levels. Administration of exendin-4 consistently reversed the left-ventricular dysfunction induced by pressure-overload via increase in cardiac cyclic AMP concentration. Of note, both alogliptin and exendin-4 had no effect on cardiac angiogenesis. PINK/Parkin accumulated on the mitochondrial outer membrane fraction of each heart extract revealed that alogliptin and exendin-4 treatment ameliorated mitochondrial damages induced by pressure overload.

Conclusion: The present study demonstrates that the GLP-1/cAMP axis protects heart from pressure-overload-induced chronic heart failure via activation of mitophagy.

P805 Lack of adiponectin receptor 1 impairs mitochondrial function in the heart

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Adiponectin is an adipocyte-derived hormone that regulates energy metabolism in various tissues via adiponectin receptors 1 and 2. In skeletal muscle, lack of adiponectin receptor 1 results in impaired mitochondrial respiratory capacity due to decreased expression of mitochondrial electron transport chain subunits, cumulated via decreased AMPK/SIRT1/PGC-1alpha signaling. In the heart, both adiponectin receptors are expressed, but their function is incompletely understood. We hypothesized that lack of adiponectin receptor 1 impairs mitochondrial function in the heart. 10 week-old adiponectin receptor 1 knockout mice (AdipoR1) showed impairment in mitochondrial respiratory capacity of saponin-permeabilized cardiac fibers (16.3±0.6 vs. 18.8±0.5 nmolO2/min/mg.p<0.05) and enzymatic activity of mitochondrial electron transport chain complexes (complex I -28%, complex II -25%, complex IV -20%; all p<0.05). This functional impairment was accompanied by a decrease in AMPK phosphorylation (-21%), SIRT1 activity (-11%), PGC-Talpha protein expression (-20%), and expression of electron transport chain subunits on the mRNA (COX II -36%, COX II 52%, SDH -41%) and protein level (complex IV -15%) in AdipoR1. In addition, electron transport chain analysis revealed an 11% decrease in myocardial mitochondrial volume density in AdipoR1. In contrast, hearts of mice lacking adiponectin receptor 2 showed no impairment of electron transport chain activity, AMPK phosphorylation, SIRT1 activity, and expression of electron transport chain subunits. Thus, lack of adiponectin receptor 1 but not adiponectin receptor 2 impairs mitochondrial function in the heart, at least in part due to impaired AMPK/SIRT1/PGC-Talpha signaling. Adiponectin receptors regulate, at least in part, distinct signaling pathways in the heart.
The effect of estrogen receptor agonists on hypertension-induced oxidative stress of cardiac and renal tissue in rats

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Although endogenous ovarian estrogen is known to offer cardiovascular benefit and vascular protection in pre-menopausal women, there is still a debate in the literature whether hormone replacement therapy decreases or even increases the risk of cardiovascular disease. We aimed to investigate the effects of the estrogen receptor agonists on the cardio-vascular and renal functions of 2 kidney-1 clip (2K1C) hypertensive rats.

Female Sprague-Dawley rats (250-300 g) were divided into 2K1C and 2K1C-ovariectomy (OVX) groups. Both groups received either estrogen receptor-β (ER-β) agonist diarylpropiolnitrile (DPN), 1 mg/kg/day or estrogen receptor-α (ER-α) agonist propylpyrazolotetrazol (PPT); 1 mg/kg/day starting at the third week following the surgery and continuing for 6 weeks. Indirect blood pressure (BP) recordings were obtained to verify hypertension. At the end of the 9th week, the animals were decapitated. In the kidney and cardiac samples, malondialdehyde (MDA) and glutathione (GSH) levels, superoxide dismutase (SOD), catalase (CAT) and myeloperoxidase (MPO) activities were determined. Statistical analysis was carried out using Mann-Whitney U test and Student’s t test.

2K1C hypertension resulted in increased BP and caused significant decreases in cardiac and renal MDA and GSH levels and CAT activities and increased SOD activities in both groups of O VX and NO-OVX groups. PPT treatment reduced BP in both O VX (p < 0.01) and NO-OVX (p < 0.01) groups. On the other hand, PPT and DPN treatments restored cardiac MDA levels and MPO activities in both groups (p < 0.05-0.01), while PPT treatment restored cardiac GSH content (p < 0.05) and increased SOD activity (p < 0.05) in OVX hypertensive rats. Even though PPT and DPN treatments had no effect on MDA and GSH contents in the kidney either in O VX or NO-OVX groups, PPT and DPN treatments restored cardiac GSH content (p < 0.05-0.01) in O VX hypertensive rats. DPN treatment increased SOD activity in renal tissue in O VX (p < 0.01) and NO-OVX (p < 0.05) groups.

The findings demonstrate that hypertension-induced oxidative damage of the cardiac and renal tissue was reduced by both ER-β and ER-α agonists, while ER-α agonist was more efficient in ameliorating cardiac oxidative stress. Thus, in the presence of cardiac protective effects of endogenous ovarian hormones, the agonists that mimic the cardioprotection via the ER-α receptors, or in part via the ER-β receptors, have the potential to reduce the risk of cardiovascular disease.

Evidence for a reciprocal down-regulation between beta-1-adrenergic receptor and sphingosine-1-phosphate receptor 1

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Purpose: Sphingosine-1-phosphate receptor 1 (SIP1) and β-1-adrenergic receptor (β1AR) belong to the superfamily of G-protein coupled receptors (GPCRs), whose function is regulated by the G-protein coupled receptor kinase-2 (GRK-2), and are strongly expressed in cardiomyocytes. Since β1AR and SIP1 couple to G-proteins with opposite effects on adenyl cyclase/cyclase, these two receptors might be expected to negatively antagonize each other’s signaling when they are co-stimulated in the same cell. In the present study we evaluated a possible cross-talk between these two receptors, that actually has never been investigated.

Methods: We used HEK293 cells expressing mouse wild type β1AR (WT/1AR) or 2 mutants lacking, respectively: the putative PKA (PKA-s1AR) or GRK (GRK-s1AR) phosphorylation sites. All cells were transiently transfected with SIP1. By confocal microscopy experiments we evaluated receptor-receptor interaction following isoprotidine (ISO; β2AR agonist) or sphingosine (SIP1 agonist) internalization, while β1AR and SIP1 couple to G-proteins with opposite effects on adenyl cyclase/cyclase, these two receptors might be expected to negatively antagonize each other’s signaling when they are co-stimulated. We co-transfected HEK293 cells with β1AR alone, β1AR and SIP1 co-transfected HEK293 cells following the respective agonist stimulation. Interestingly, this reciprocal downregulation was accompanied to a sustained GRK2 upregulation. The same phenomenon was observed in PKA-s1AR cells after stimulation with either ISO or SIP1. Notably, this receptor-receptor interaction was not observed in GRK-s1AR cells. In fact, ISO stimulation induced GRK2, while not SIP1 internalization, while SIP1 stimulation downregulated GRK2. Interestingly the lack of reciprocal downregulation prevented ISO- and SIP1-dependent GRK2 upregulation. In order to verify this observation in vivo, we used 2 experimental animal models in which β1AR is known to be downregulated following overstimulation. In line with our in vitro results, we observed that cardiac SIP1 plasma membrane levels were significantly reduced in both ISO 7d mice in or HF rats compared to the respective control groups.

Conclusions: These results provide a biochemical and functional evidence of a direct connection between SIP1 and β1AR that appears to be GRK2 dependent. Importantly, this reciprocal downregulation was observed also in vivo both after chronic β1AR overstimulation or in a clinically relevant experimental model of HF, which is known to be characterized by sympathetic nervous system overdrive.

Vildagliptin, a dipeptidyl peptidase-4 inhibitor, prevents cardiac hypertrophy and diastolic dysfunction induced by chronic beta-1-adrenergic stimulation in rats


Background: Congestive heart failure with left ventricular (LV) diastolic dysfunction and preserved ejection fraction is often observed in hypertensive patients; however, the effective treatment of diastolic heart failure has not been established. Recent studies showed that dipeptidyl peptidase-4 (DPP4) inhibitors, which increase circulating GLP1 level, have cardio-protective effects. Accordingly, the current study elucidated whether vildagliptin prevents the development of LV hypertrophy and diastolic dysfunction in isoproterenol (ISO)-induced hypertrophied rat hearts.

Methods: Male Wistar rats (9 weeks old) received a vehicle (control, n=5), ISO subcutaneously (2.4 mg/kg/day, n=20) or ISO subcutaneously + vildagliptin with oral administration (30mg/kg/day, n=20) for 7 days. Cardiac catheterization and echocardiographic study were performed one week after ISO-infusion to evaluate S1P1 cardiac plasma membrane levels.

Results: After 7 days, LV hypertrophy in ISO + vildagliptin was significantly decreased compared with those in ISO (Heart weight/body weight, Vehicle: 3.19±0.42, ISO: 4.43±0.39, ISO + vildagliptin: 4.14±0.29, p < 0.05). Cardiac catheterization and echocardiographic study showed that increased LV end-diastolic pressure in ISO was ameliorated in ISO + vildagliptin (Vehicle: 2.7±1.1, ISO: 3.5±1.1 or ISO + vildagliptin: 2.1±0.5 mmHg, p < 0.05), and prolonged time constant of LV relaxation (Tau) improved in ISO + vildagliptin (Vehicle: 9.4±0.9, ISO: 11.1±2.3 or ISO + vildagliptin: 9.4±1.1ms, p < 0.05), although heart rate, LV systolic pressure, and max (+) dP/dt did not differ among three groups. Furthermore, echocardiographic study showed the shortened deceleration time as a LV diastolic function time in ISO was significantly improved compared with those in ISO + vildagliptin (Vehicle: 43.8±4.3, ISO: 40.2±2.9 or ISO + vildagliptin: 43.0±2.7 ms, p < 0.05); however, increased LV wall thickness in ISO did not decrease in ISO + vildagliptin. Real-time quantitative PCR revealed that these effects were accompanied with the attenuation of decreases in molecules associated with glycemic metabolism such as glucose transporter type 4 and pyruvate dehydrogenase phosphate catalytic subunit 1, and increase in insulin growth factor 1 associated with cardiac hypertrophy.

Conclusion: This study demonstrated that administration of vildagliptin exerts a therapeutic effect on the development of LV hypertrophy and diastolic dysfunction.
Influence of angiotensin-II type 1 receptor blockade on mitogen-activated protein kinases in myocardium of obese rats

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Besides nutritional and metabolic disorders, obesity has been associated with cardiac remodeling in rodents. However, the physiopathological mechanisms involved in obesity-stimulated cardiac phenotypic plasticity are poorly understood. This study evaluated the influence of angiotensin-II type 1 (AT1) receptor blockade on the expression of mitogen-activated protein kinase (MAPK) expression and parameters of cardiac remodeling in rats with diet-induced obesity.

Methods: Male Wistar-Kyoto rats (n=40) were subjected to standard rat chow (C: 3.2kcal/g) or hypercaloric diet (OB: 4.8kcal/g) for 30 weeks and then assigned to three groups; C, OB, and OBL. OBL received losartan in drinking water (30mg/kg/day). After five weeks, body weight (BW), adiposity, triacylglycerol (TG), and serum leptin concentration were analyzed. Cardiac structure and left ventricular function were assessed by echocardiography. Myocardial morphology was evaluated in histological sections. Myosin heavy chain (MyHC) isoforms were analyzed by polyacrylamide gel electrophoresis. Total levels of MAPK ERK and JNK were measured by Western blot. Statistical analysis: ANOVA and Bonferroni test.

Results: OB presented higher values of BW, adiposity, TG, and leptin than C (p<0.05). Losartan treatment decreased TG concentration [C 96±28; OB 132±0.03; OBL 92±17mg/dL]. Intestinal collagen cross-sectional area and nuclear volume, and MyHC α-isoforms ratio were higher in OB than C. Intertitial collagen and MyHC α/α-isoforms ratio (C 0.48±0.06; OB 1.12±0.45; OBL 1.16±0.35) did not differ between OB and OBL.

Conclusion: Losartan modulates MAPK pathway protein expression and attenuates cardiac remodeling in obese rats.

Support: FAPESP

Cardioprotection through S-nitros(yl)ation of macrophage migration inhibitory factor


Purpose: Macrophage migration inhibitory factor (MIF) is a structurally unique inflammatory cytokine that controls cellular signaling in human physiology and disease through both extra- and intracellular processes. MIF has been shown to mediate both disease-exacerbating and beneficial effects, but the underlying mechanism(s) controlling these diverse functions are poorly understood. Here we have identified S-nitrosylation modification of MIF which regulates the beneficial functional phenotype of MIF in myocardial infarction.

Methods and Results: S-nitrosidine (SNO) analysis on MIF using chemiluminescence detection revealed that MIF can be S-nitrosylated (SNO-MIF) by S-nitrosothiol (SNO) via S-nitrosothiol (SNO) formation, whereas the CXXC-derived cysteine residues of MIF remained unaffected. S-Nitrosothiol (SNO) detection was performed by mass spectrometric analysis. S-nitrosylation modification of MIF at cysteine 118 was site-specifically modified by S-nitrosylation, whereas the CXXC-derived cysteine residues of MIF remained unaffected. S-Nitrosylation (SNO-MIF) of MIF by S-nitrosothiol (SNO) formation was shown to be a post-translational modification of MIF that regulates its functional phenotype in myocardial infarction.

Glucocorticoid ameliorated early cardiac dysfunction after coronary microembolization by suppressing TGF-beta/p38 and CTGF expression

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Objectives: This study was designed to evidence the protective effect of glucocorticoid therapy on cardiac dysfunction after coronary microembolization (CME), and clarified its mechanism with the expression of TGF-β1/p38 and CTGF.

Methods: A total of fourteen mini-pigs were subjected to this study, including Sham-operation group (n=4), CME group (n=6) and Glucocorticoid therapy group (n=4). Measurement of cardiac function was performed by transthoracic echocardiography. Left ventricular end-diastolic volume (LVEDV) was measured by transthoracic echocardiography. Left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were determined by contrast MRI. CTGF and Smad3 were also detected by western blot or immunohistochemistry. Total collagen expression was demonstrated by Masson trichrome stain.

Results: Compared with Sham-operation group, the values of left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were increased in the CME group (p<0.05). Left ventricular ejection fraction (LVEF) was decreased (62±2 vs. 82±2, P<0.05). Methylprednisolone therapy greatly improved LVEF after CME, especially at 6th hour after CME. Cardiac magnetic resonance imaging was performed to evaluate cardiac function at baseline, 6th hour and 1 week after CME. Serum TGF-β1, CTGF and Smad3 were also detected by western blot or immunohistochemistry. Total collagen expression was demonstrated by Masson trichrome stain.

Conclusion: Glucocorticoids could ameliorate early cardiac dysfunction after coronary microembolization by suppressing TGF-beta/p38 and CTGF expression.
The association between different monocyte subsets and coronary collateral development

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Purpose: Increased circulating monocyte count has been found to be related with greater coronary collateral development. In this study, we aimed to find any possible relationship between the levels of circulating monocyte subsets and coronary collateral development.

Methods: Patients who had > 95% stenosis of at least one major coronary artery in their first coronary angiogram were included consecutively in this study. Collateral development was graded as good and poor according to Cohen-Rentrop method. Blood samples underwent cytometric analysis for determination of monocyte subsets.

Results: Out of 105 patients, 55 had good, 50 had poor coronary collateral development. When the baseline characteristics were compared, the monocyte subsets were significantly higher in the good collateral group (p < 0.001). With cytometric analysis, CD14+CD16- levels were significantly higher in the good collateral group (2.17 ± 1.14 vs 1.22 ± 0.83, p = 0.01). When a multivariate analysis was performed, increased CD14+CD16- levels remained significantly associated with good collateral development.

Conclusions: Our present results are the first to show a significant association between increased circulating CD14+CD16- monocyte levels and good coronary collateral development. Further studies are needed to better understand the relationship between different subsets of monocytes and collateralization.

Lack of effect of simvastatin on structural remodeling in animal model of chagasic cardiomyopathy


Purpose: Chagasic cardiomyopathy (CM) is characterized by a large amount of fibrosis and inflammation. As simvastatin (simva) has anti-inflammatory effects, we hypothesized that it could be an important drug in the treatment of patients with CM. The purpose was to evaluate simva in the myocardium remodeling and inflammation in an animal model of CM.

Methods: 123 hamsters were divided into controls (25), simva1-controls with simvastatin 10mg/kg/day (25), simva2-infected treated from the beginning with the same dose of simva (25), simva2-infected treated after 4 months (24); infect-untreated (24). Follow-up of 10 months. Intercollagenal collateral volume fraction (ICVF) and LV measurement were made using cine MRI. The role of simva in reducing inflammation was analyzed by measuring inflammatory cytokines.

Results: In controls (Simva1=189±133days; Simva2=150±124; Infect=138±123) lived less than controls (C=257±80; Simva2=283±58) (p<0.05) with no difference among infected groups. ICVF-LV (%) was greater in infected (Simva1=3.88±1.14; Simva2=2.22±0.64; Infect=4.38±0.83) than in controls (C=1.12±0.31; Simva2=2.18±0.73) (p<0.05) with no difference among infected groups. ICVF-LV (%) was greater in infected animals (Simva1=1.83±1.01; Simva2=1.52±0.73; Infect=3.01±0.66) than in controls (C=0.68±0.31; Simva2=0.81±0.28) (p<0.05) with no difference among infected. MMPI was higher in infected groups (Simva1=2384±2441; Simva2=2297±4091; Infect=2392±2042) compared to controls (C=954±2332; Simva4=544±1123) (p<0.05) with no difference among infected. TNFalpha did not differ between different infected groups (Simva1=5.33±3.66; Simva2=4.44±1.77; Infect=4.13±3.04). IFNgamma in infected groups (Simva1=4.7±3.56; Simva2=4.46±2.08; Infect=4.21±2.09) was higher than in controls (C=8.50±2.59; Simva1=8.84±2.53) (p<0.05) with no difference among infected. IL10 in infected animals (Simva1=9.07±4.62; Simva2=7.76±4.77; Infect=8.11±4.48) did not differ and the values were greater than controls (C=14.11±4.40; Simva2=12.55±3.90) (p<0.05).

Conclusions: Simva did not attenuate deposition of interstitial collagen,did not change dynamics of collagen degradation,did not decrease inflammation, and did not reduce mortality.

Antibody against oncostatin M receptor-beta attenuates left ventricular remodeling in an inflammatory model of cardiomyopathy

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Purpose: Heart failure (HF) is often the consequence of damage to the myocardium during which remodeling and de-differentiation of cardiomyocytes is observed. During the course of the disease the infiltration of the myocardium with inflammatory cells is well recognized and becomes nowadays a major focus of research. We hypothesized that oncostatin M (OSM) a cytokine mainly restricted to the myocardium, could play an important role in the development of the OSM receptor-β (Δ1) on cardiomyocytes.

Methods: We used a mouse model of cardiomyopathy based on the heart specific over expression of monocyte chemoattractant protein-1 (MCP-1) leading to massive infiltration by macrophages and HF after 6 months. Samples from mice and from patients with endstage HF were analyzed by Western blot (WB), confocal microscopy, ZE-analysis combined with mass spectrometry (2DE-MS) and immunofluorescence (IF) at various time points. Functional analysis was performed by cine MRI. The role of OSM was assessed by blocking OSM receptor-βΔ1.

Results: Mice showed ventricular dilatation and heart failure as well as massive infiltration of the myocardium with macrophages. 2DE-MS and WB analysis revealed more than 10 re-expressed proteins such as ANP, desmin and α-smooth muscle actin. Confocal microscopy showed clear localization of re-expressed proteins to cardiomyocytes. We found up-regulation of the OSM receptor-βΔ1 coinciding with de-differentiation and remodeling of cardiomyocytes in failing hearts. Activation of the OSM signaling pathway correlated with enhanced MEK/ERK signaling. Blockage of OSM with a neutralizing antibody or genetic deletion of the
**TRIF-dependent inflammation promotes afterload-induced cardiac remodeling**

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**Background and objective:** Inflammatory cells and cytokines contribute to myocardial and vascular remodeling. The role of TRF-domain-containing adapter-inducing interferon-β (TRIF) and interferon regulatory factor-3 (IRF3)-dependent inflammatory signaling during myocardial hypertrophy is incompletely understood.

**Methods and results:** Afterload-induced myocardial remodeling induced by trans-aortic constriction (TAC) in C57Bl/6J wildtype (WT) and in C57Bl/6J TRIF-/- mice was compared to sham surgery (sham). Twenty-eight 5/6-nephrectomized male Wistar rats were supplemented with high VK ("OKDK") or with low VK ("OKD"). TRIF-/- mice showed reduced CD3 T-cell (8.1±2.0-fold vs. sham, p<0.001) and increase of TGFbeta protein expression was more pronounced in WT than in TRIF-/- mice following TAC (54±9% vs. WT, p=0.05; 317±5% vs. WT, p<0.001) in WT (p<0.005 TRIF+/- vs. WT). Cardiovascular structure increased similarly in TRIF-/- (130±6%, p<0.01) and in WT animals (119±3%, p<0.05) relative to sham. However, ventricular (LV) posterior wall thickness (echocardiography) and left ventricular mass increased less in TRIF-/- (115±11%, p<0.05, n=12, respectively) than in WT animals (150±14%, p<0.05, and 154±9%, p<0.01, respectively). Capillary density was almost unchanged in TRIF-/- mice (123±20%, p=ns), but significantly reduced in TAC-WT mice (74±2%, p<0.01 compared to their sham controls). The number of cardiomyocytes/mm² was reduced in WT following TAC (54±8, p<0.005, but not in TRIF-/- mice (83±1%, p=ns). Myocardial fibrosis was more pronounced in WT following TAC (19±0.1±1% collagen content) than in TRIF-/- mice (8±0.2±0.3, p<0.001 TRIF-/- vs. WT), and increase of TGFbeta protein expression was more pronounced in WT (318±5% of sham-operated controls) than in TRIF-/- mice (111±15% of sham-operated controls; p=0.05 TRIF-/- vs. WT).

**Conclusion:** TRIF-dependent inflammatory signaling plays an important role in the regulation of fibrosis and capillarisation during pressure overload-dependent cardiac remodeling in mice. Further studies are needed to investigate whether inhibition of TRIF-signaling can positively modulate afterload-induced myocardial remodeling.

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**Stimulating anti-beta1-receptor antibodies and kidney function: reno-cardial cross talk and its relevance for worsening cardiac function**

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Stimulating antibodies directed against the beta1-adenoreceptor (beta1-ABS) induce cardiac diastolic failure and atrial fibrillation in rats. After immunization, antibody-positive animals within the first 6 months develop a hypertensive phenotype (increase in blood pressure, hypertrophy), which then evolves into a dilated cardiomyopathic phenotype. As beta1-receptors (beta1-AR) are also highly expressed in the kidney, we hypothesized that the early hypertensive phenotype might—in part—also rely on a stimulation of renal beta1-AR.

**Methods:** Cardiomyopathy was induced in n=40 Lewis rats by monthly immunization with beta1-ELIQUIST fusion protein. Antibody-positive animals were followed every 3 months by ELISA and by echocardiography, respectively. In addition, plasma renin activity and 24h-urine were analysed every month. Every 3 months inulin- and PAH-clearance was inversely assessed to determine glomerular filtration rate (GFR), renal plasma flow (RPF), and fractional excretion (FE) rates before the rats were sacrificed, and heart & kidneys subjected to further hemodynamic & molecular analysis.

**Results:** Stimulating the kidneys by beta1-ABS resulted in renal beta1-AR desensitization and reduction in beta1-AR mRNA-levels. In the first 6 months, renal mRNA-levels continuously increased, indicating cross-activation by stimulated ANF in renal-producing juxtaglomerular cells. After 6 months of inulin-renin expression-decreased. This finding fits well with the observed transient increase in plasma renin activity and the subsequent mild GFR-increase in immunized animals, pointing to renin-mediated functional hyperfiltration followed by angiotensin-II mediated feedback mechanisms which hindered further renin-production. After 12 months sodium (Na) levels in 24h-urine samples decreased comparable with a beta1-abs-mediated increase in Na-reabsorption in the distal tubulus. Increases in Na-reabsorption negatively affect renin-secretion, which was confirmed by plasma renin-activity assays. The reabsorption of other electrolytes (Ca++, K+, Mg2+) was not affected. In contrast, urine albumin loss increased substantially, indicating upregulating glomerular and proximal tubular damage, whereas the lack of urinary macromolecules (IgG) precluded a whole range-impairment of the glomerular basement membrane within 12 months of immunization.

**Conclusion:** Our findings demonstrate that stimulating beta1-abs appear in fact to be able to alter renal function, which might indirectly contribute to worsen the induced cardiovascular phenotype.

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**Viakorin K supplementation rescues procalcific vascular mRNA alterations in a rat model of chronic kidney disease**

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**Background:** Vascular calcification (VC) is a predictor of cardiovascular disease. Patients with chronic kidney disease (CKD) suffer from severe vascular calcifications (VC). Osteocalcin (OC) is a small, circulating protein that is synthesized by osteoblasts and is a potent inhibitor of VC. It remains unclear whether vitamin K-dependent proteins and anti-vascular disease afforded by vitamin K-dependent proteins in a murine model of CKD.

**Methods:** Twenty-eight 5/6-nephrectomized male Wistar rats were supplemented with high VK ("OKDK") or with low VK ("OKD"). Twenty-Four rats were treated as controls ("Con"; "ConK"). All animals were followed longitudinally up to 12 weeks for vital parameters, serum chemistry, creatinine clearance and cardiac function. After 12 weeks tissue calcium content and mRNA expression of calcium regulating proteins was analyzed.

**Results:** After 12 weeks all CKD-rats developed significant renal insufficiency with increased creatinine serum levels and typical functional cardiovascular alterations (hypertension increased interventricular septal wall dimensions). Moreover, we detected profound calcification (von Kossa staining) in kidneys of all CKD-rats, while cardiovascular tissues remained predominantly healthy. Nevertheless, we detected significant CKD- and VK-induced alterations in aortic gene regulation, even before calcification became macroscopically evident: CKD itself induced reduction of Sm22-alpha mRNA levels (-3.0-fold; p<0.01*), reduced MGP-expression (-2.2-fold; p<0.014) and a trend towards increased periostin mRNA levels. Controversely effects in the aortic mRNA repertoire could be induced by VK-supplementation in ConK-rats, mirrored by induction of MGP (11.4-fold; p=0.09), a trend to increased levels of Sm22-alpha (3.6-fold; p=0.02) and downregulation of peristin (-4-fold; p<0.05) compared to controls. As a matter of fact, CKD-induced procalcific mRNA alterations were abolished by VK-supplementation.

**Conclusions:** CKD induces procalcific cardiovascular mRNA alterations even after macroscopic calcification arises. We demonstrated for the first time that VK-supplementation rescues CKD-induced vascular mRNA alteration and VK-dependent proteins involved in calcification (MGP) and remodeling (periostin).
Evaluation of the national institute for clinical excellence mini-GRACE risk scores for acute myocardial infarction: the myocardial ischaemia national audit project (MINAP) 2003 to 2009


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Purpose: Comparative provider performance for acute coronary syndromes often requires patient level adjustment. The GRACE risk score considers case mix; however, national registries, such as the Myocardial Ischaemia National Audit Project (MINAP) do not collect all 8 GRACE variables. We investigated performance of the mini-GRACE (MG) and adjusted mini-GRACE (AMG) models, developed by the National Institute for Clinical Excellence (NICE), for use in MINAP.

Methods: In-hospital and 6-month all-cause mortality was regressed on predictors using the scoring system and coefficients described by the GRACE investigators to generate the MG and AMG models. The MG model predictors included age, admission systolic blood pressure and heart rate; cardiac arrest, elevated troponin and ST deviation on presenting ECG. The AMG model in addition included an estimation of renal failure and heart failure. For this, a creatinine below 200 μmol/L was given a score of 5, and a creatinine above 200 μmol/L a score of 20, and patients who were prescribed a loop diuretic scored 20 points. Calibration, accuracy, discrimination and clinical reclassification for in-hospital and 6-month all-cause mortality models MG and AMG were studied in 462650 patients hospitalized with acute myocardial infarction (AMI) from 1 January 2003 to 30 October 2009.

Results: There were 308324 MG and 134304 AMG complete cases. In-hospital mortality model calibration, Hosmer-Lemeshow goodness of fit test (H-L), for MG and AMG was: STEMI P=0.25 and P=0.03; NSTEMI P=0.96, respectively. MG and AMG model accuracy, Brier score: STEMI 0.05 and 0.05, NSTEMI 0.05 and 0.05; and discrimination, C-statistic (95%CI): STEMI 0.90 (0.89-0.91) and 0.86 (0.85-0.88) and 0.87 (0.86-0.87), respectively. MG and AMG model accuracy, Brier score: STEMI 0.09 and 0.08, NSTEMI 0.12 and 0.10; and discrimination: STEMI 0.84 (0.83-0.84) and 0.85 (0.85-0.86), NSTEMI 0.80 (0.79-0.80) and 0.82 (0.81-0.82). NRI for AMI: 12.5%.

Conclusions: The MG and AMG risk scores for in-hospital and 6-month mortality show good performance in the wider spectrum of AMI phenotypes and clinical subgroups. Overall the AMG model performed better across performance indices, but was limited by the number of complete cases.

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Inversive relationship between treated cardiovascular risk factors and mortality among patients with first-time myocardial infarction - a nationwide study

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Purpose: Diabetes, hypertension and dyslipidemia are known risk factors for a poor prognosis following myocardial infarction (MI). However, with more efficient treatment these risk factors may not be prognostic important. We conducted this study to investigate the association between the number of treated CHD risk factors and the prognosis among a population of patients with first-time MI.

Methods: Patients aged ≥30 years admitted with first-time MI during 1997-2009 were identified by individual-level-linkage of nationwide registries in Denmark. Use of antidiabetic drugs, statins and antihypertensive drugs 180 days before MI was used as proxy for prevalent diabetes mellitus, dyslipidemia and hypertension, respectively. The association between number of treated CHD risk factors and 30 days mortality were estimated by age stratified logistic regression analyses.

Results: A total of 128,418 patients were admitted with first-time MI, 67.1% had at least 1 of the 3 risk factors. There was an inverse relationship between number of CHD risk factors and 30 days mortality (Odds Ratio (OR), 95% confidence intervals [95% CI] – 1 risk factor, OR 0.75 [0.72-0.77], 2 risk factors, OR 0.63 [0.59-0.66] and 3 risk factors, OR 0.43 [0.38-0.49]). We stratified the analyses due to interaction with age (figure).
Evidence of coronary artery disease (CAD) in a cohort of essential hypertensive patients.

Methods: We followed up 1128 essential hypertensives (mean age 56.1 years, 587 males, blood pressure (BP)=144±9 mmHg) free of cardiovascular disease for a mean period of 6 years. All subjects had at least one annual visit and at baseline underwent complete echocardiographic study for estimation of LVMII and blood sampling for assessment of metabolic profile. Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP) and the distribution of PWV was split by the median (18.3 cm/s) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Moreover, LV hypertrophy (LHV) was defined as LVMII ≥125 g/m² in males and LVMII ≥110 g/m² in females, while CAD was defined as the history of myocardial infarction or significant coronary stenosis revealed by angiography or coronary revascularization procedure.

Results: The incidence of CAD over the follow-up period was 2.83%. Hypertensives who developed CAD (n=32) compared to those without CAD at follow-up (n=1096) had at baseline higher waist circumference (101.8±11.1 vs 97.2±11.9 cm, p=0.033), LVMII (123.7±22.9 vs 107.4±24.2 g/m², p=0.014), prevalence of LHV (46% vs 30%, p=0.027) and prevalence of high PWV levels (69% vs 48%, p=0.019). No difference was observed between hypertensives with CAD and those without CAD with respect to baseline office BP, serum creatinine and lipid levels (p>NS for all). By univariate Cox regression analysis it was revealed that high PWV levels predicted CAD (hazard ratio=2.657, p=0.008). However, in multivariate Cox regression model, waist circumference (hazard ratio=1.016, p=0.04) and LVMII (hazard ratio=1.023, p=0.018) but not high baseline PWV turned out to be independent predictors of CAD.

Conclusions: In essential hypertensive patients LVMII predicts future development of CAD, whereas high baseline PWV exhibits no independent prognostic value. The findings support that LVMII constitutes a superior prognosticator of events than PWV and its estimation is essential in order to improve overall risk stratification in hypertensive patients.

Multiple siblings or mother with myocardial infarction are primarily responsible for familial clustering - a nationwide study

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Purpose: The importance of parents and siblings in familial clustering of myocardial infarction (MI) is controversial. We performed the hitherto largest study of clustering of MI in first degree relatives.

Methods: This study is a nationwide register-based cohort study. The study population was combined from two large databases, the Danish civil registration system and The Danish National Registry on Patients. For sibships the first sibling to have a MI would be defined as the proband. The date of the MI of the proband would be the start of risk time for the rest of the siblings. If more than 1 sibling in a sibship had a MI, a new analysis was made (without including the first proband) and the second sibling to have a MI would be the new proband and the rest of the siblings in the sibship would start a new risk time, from the date of the new proband’s MI. Further when a parent was the proband the children’s risk time was compared using Cox proportional hazards regression with the lean BMI (23.5 kg/m²) as the reference group. The RR are adjusted for sex, age and co-morbidities according to the Charlson index of co-morbidities.

Results: We identified 10181 siblings to 7254 cases of MI. For 101 sibships more than one sibling had a MI. Furthermore we identified 54164 offspring of 29147 mothers who developed CAD (n=32) compared to those without CAD at follow-up. We found that maternal proband 2.45 (95% CI 1.99-2.22, p=0.001), More than one sibling proband 3.74 (95% CI 1.56-8.99, p=0.003), Maternal proband 2.34 (95% CI 1.80-3.04, p<0.001) and More than one sibling proband 3.74 (95% CI 1.56-8.99, p=0.003) had a higher risk for MI compared to the reference group. The RR are adjusted for sex, age and co-morbidities according to the Charlson index.

Conclusion: Familial clustering of MI is particularly strong in the presence of a maternal MI and multiple siblings with MI.

Risk factors for coronary heart disease and survival after myocardial infarction: evidence of a paradox?

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Purpose: Several risk factors for coronary heart disease (CHD) have been associated with improved in-hospital survival after myocardial infarction (MI). We aimed to confirm this paradox and assess whether it extends to long-term outcome.

Methods: We examined the relation between the presence of 4 modifiable risk factors for CHD (hypertension, dyslipidemia, smoking and diabetes mellitus) and mortality in 14 434 consecutive patients admitted with an MI to a coronary care unit from 1985 to 2008. Patients were categorized according to the presence or absence of at least one CHD risk factor.

Results: Two-thirds of MI patients (n = 10 003) had at least one risk factor for CHD on hospital admission. Hypertension was present in 35%, dyslipidemia in 28%, diabetes mellitus in 14%, and 32% were current smokers. Age-adjusted cumulative 30-day mortality was lower in patients with at least one CHD risk factor as opposed to no such risk factors (5% vs. 7%). In multivariate analysis, the presence of at least one CHD risk factor was associated with a favorable 30-day survival after MI (adjusted OR 0.72, 95%CI: 0.62-0.83). On the long-term, this paradox completely disappeared (adjusted 20-year hazard ratio [HR] 1.1, 95%CI: 1.0-1.1).

Conclusions: The presence of at least one modifiable coronary heart disease risk factor was associated with improved short-term outcome after MI. On the long-term, this paradox disappeared. Future studies should seek for possibilities to improve short-term outcome in patients without coronary heart disease risk factors.

Risk factor assessment for the prevention of premature cardiovascular disease in clinical practice

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Purpose: To examine the extent of risk factor (RF) assessment in primary care
Effect modification of dietary n-3 fatty acids on cardiovascular mortality risk by resting heart rate in Japanese general population: NIPPON DATA80

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Purpose: Multiple lines of evidence have shown that a higher dietary intake of n-3 fatty acids (FAs) reduces the risk of cardiovascular diseases (CVDs). Meanwhile, increased resting heart rate (RHR) has been reported to be an independent predictor of CVDs. Identification of measures for preventing CVD risk associated with increased RHR is therefore of considerable clinical and public health importance. We assessed the hypothesis that a higher n-3 FAs intake would attenuate the elevation of mortality risk by increased RHR.

Methods: A total of 8,807 community-dwelling individuals (55.7% women, mean age of 48.3 years), none of whom had anti-hypertensive drugs and prior CVDs, from the general population of Japan were included in the analysis. The primary endpoint was CVD mortality, and secondary endpoint was cardiac mortality during a mean follow-up of 20.4±6.1 years. Dietary n-3 FAs intake was estimated using a modified household food weighing method. The RHR measurement was obtained from 3 consecutive intervals between R waves on 12-leads electrocardiography (ECG). Cox models were used to calculate hazard ratios (HRs) per 10 beats per minute of RHR (95% confidence interval [95%CI]) adjusted for potential confounders, including ECG findings (left ventricular hypertrophy, suspected coronary heart disease) and nutritional parameters (saturated FAs, sodium and potassium intake, and fiber intake).

Results: Of the 8,807 participants, 617 individuals died from CVDs, and of these, 314 were from cardiac causes. Among men, in the lowest (<0.93kcal) tertile of n-3 FAs group, increased RHR was associated with elevated risk of CVD (HR, 1.18; 95%CI, 1.02-1.39), and cardiac RHR (HR, 1.29; 95%CI, 1.01-1.63). In contrast, in the middle (0.93-1.19kcal) and highest (1.20; >1kcal) tertile, both HRs did not show statistically significant for CVD (HR, 0.74; 95%CI, 0.61-1.44 and HR, 0.91; 95%CI, 0.72-1.15, respectively), and cardiac mortality (HR, 0.90; 95%CI, 0.66-1.21 and HR, 0.99; 95%CI, 0.69-1.43, respectively). For interaction between n-3 FAs and RHR was significant in CVD mortality (p=0.009) and marginally significantly in cardiac mortality (p=0.060) in men, including the first 5 years of follow-up did not substantially alter the results. Among women, those relationships were not observed.

Conclusions: An elevated risk of CVD, and cardiac mortality related to increased RHR would be attenuated in individuals with higher dietary intake of n-3 FAs in Japanese men, suggesting that a higher n-3 FAs intake may prevent long-term mortality risk associated with increased RHR.
Investigation of sex differences in noninvasive vascular function

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Background: Sex differences in cardiovascular disease susceptibility have been reported. The relation of noninvasive vascular function measures to sex, female sex hormones, menopausal status and reproductive history is little understood.

Methods: We assessed menstrual cycle, reproductive history and simultaneous measurement of flow-mediated dilation (FMD) of the brachial artery and peripheral arterial tonometry in 454 women (mean age 40.4 ± 16.1 years) and 100 men (mean age 44.7 ± 15.3 years). Plasma estradiol, progesterone, luteinizing hormone, and follicle stimulating hormone were measured.

Results: In regression analyses, endothelial function was blunted in men compared to women irrespective of menopausal status and adjustment for classical cardiovascular risk factors and sex hormone concentrations. In women, vascular reactivity changed during the menstrual cycle with a mid-cyclic peak and correlated with estradiol concentrations for FMD, r = 0.13, P < 0.0066, and inversely with progesterone for baseline pulse amplitudes, r = -0.14, P < 0.035 and brachial artery diameter decreased by age, r = -0.103, P = 0.035. Multivariable adjusted regression models adjusted for age, sex, and menopausal status showed a relation of estradiol with FMD, beta 0.658, 95% confidence interval (CI) 0.084 to 1.292, P = 0.025 in women. Age at menarche (beta 0.070, 95% CI 0.039 to 0.101, P < 0.001) and breastfeeding duration (beta -0.006, 95% CI -0.011 to -0.001, P = 0.036) were related to brachial artery diameter. Age at menarche was related to FMD (beta -0.455, 95% CI -0.886 to -0.023, P < 0.009).

Conclusions: We observed sex differences for noninvasive conduit artery and peripheral arterial function with better vascular reactivity in women. Differences were not fully explained by female sex hormones and menopausal status. Age at menarche and duration of breastfeeding were also related to vascular function.

Physiological polymorphisms associated with coronary artery disease in patients with previous low cardiovascular risk by traditional risk factors

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Several studies have attempted to link genetic polymorphisms with the onset of coronary artery disease (CAD). The added risk from each polymorphism is relatively low, with an Odds Ratio (OR) of about 1.1 or 1.2, much lower than the usually associated with traditional risk factors (TRF). Therefore, it becomes relevant to understand the cause of vascular disease, in patients without TRF and try to assess genetic factors associated with these situations.

Objective: The aim of this study was to evaluate genetic factors associated with vascular disease development in patients without TRF.

Methods: A case-control study was performed. This study included 1032 inpatients (915 consecutive coronary patients with CAD and 117 patients without major cardiovascular risk factors (without diabetes, smoking habits, hypertension or severe dyslipidemia), mean age 54.9 years, 67.7% male and 837 controls without CAD, mean age 54.6 years, 71.8% male and 857 controls without CAD, mean age 54.6 years, 71.8% male). Cases and controls were gender- and age-matched (p = 0.578 and 0.367, respectively). We evaluated 16 genetic variants, previously associated with CAD, using specific primers. We analyzed Hardy-Weinberg equilibrium and the genotypic and allelic distribution of CAD risk was determined using a bivariate analysis (3x2) for each polymorphism, calculating the OR and 95% CI.

Results: In patients with low cardiovascular risk, only three polymorphisms, namely: PCSK9 AA (OR=1.94, p=0.011); rs1333049 CC (OR=1.49, p=0.017) and PON 55 MM (OR=1.49, p=0.050) have shown an increased risk of CAD. The homozygous wild genotypes were protective. On the other hand, the polymorphism normally associated with CAD, ACE DD genotype, was found to be significantly associated with CAD, suggesting that its mechanism of action may depend on the traditional risk factors.

Conclusions: The present study discloses some polymorphic variants associated with CAD, in patients without major traditional risk factors and, apparently, low risk. In these really high risk patients, it will be important, in the future, define early intervention preventive programs.

Who is at low risk for cardiovascular disease? An assessment of different definitions

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Purpose: To assess the prevalence and trends of low cardiovascular risk factor (RF) profile in the Swiss population according to different definitions

Methods: Population-based cross-sectional study of 6170 subjects (3241 women) aged 35-75 years living in Lausanne, Switzerland. Trends were assessed using data from the Swiss MONICA population surveys conducted in 1984-6 (N=3300), 1988-9 (N=3331) and 1992-3 (N=3133) and restricted to the same age group. Seven different definitions of low RF profile were used.

Results: Prevalence of low RF profile varied between 6.5% (95% confidence interval 5.9-7.1) and 9.7% (9.0-10.5) depending on the definition used. The prevalence was inversely related to the number of criteria used and higher in other countries. Irrespective of the definition used, the prevalence of low RF profile was higher in women and in physically active participants, and decreased with increasing age or in the presence of a family history of cardiovascular disease (table). The prevalence of low RF profile increased from 3.8% (3.1-4.5) in 1984-6 to 6.7% (6.1-7.3) in 2004-5; using the same other definition, the results were 5.9% (5.1-6.8) and 7.9% (7.0-9.5), respectively.

Conclusion: The prevalence of low RF profile varies according to the criteria used; this prevalence is relatively high and increasing in the Swiss population, which might partly explain the low and decreasing trend in cardiovascular mortality rates.

Comparison of different cardiac risk scores for coronary artery disease in women: do female-specific risk factors matter?

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Background: The estimation of the pre-test probability of coronary artery disease (CAD) in women is often difficult, due to a different clinical presentation compared to men. Meanwhile, cardiovascular diseases remain the leading cause of death in women, urging the need for more accurate risk assessment scores. The aims of our study were to compare the accuracy of several definitions and scoring systems of CAD risk assessment in predicting the likelihood of obstructive CAD on CT coronary angiography (CTCA) in women and to explore which female-specific risk factors were independent predictors for obstructive CAD on CTCA, and if adding these factors to usual risk assessment scores would improve their accuracy.

Methods: Data was obtained from a cohort of 228 female patients undergoing clinical CAD assessment for CT and referred for CTCA. Obstructive CAD was defined as ≥ 50% luminal stenosis on CTCA. Pre-test probability for CAD was calculated according to the Diamond and Forrester score, New Score, Duke Clinical Score, and the updated Diamond and Forrester score. Female specific factors were obtained using a written questionnaire. Pre-test probability scores were compared with ROC analysis.

Results: ROC analysis showed that only the New Score and the extended Diamond & Forrester model were significantly related to women's risk factors and only identified female-specific risk factors. The updated Diamond and Forrester score was used for Net Reclassification Improvement (NRI) analyses, since the New Score already accounts for estrogen status. Adding GDM and estrogen status to the updated Diamond and Forrester score resulted in a significant NRI (p = 0.04).

Conclusion: Adding female-specific risk factors to the cardiac pre-test probability score significantly improves their accuracy in predicting the presence of symptomatic CAD in women.

C-Reactive Protein (CRP) and mortality to cardiovascular diseases

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Inflammation seems to be a component in the development of atherosclerotic cardiovascular diseases. Highly sensitive (hs) C-Reactive Protein (hsCRP) is a good marker of inflammatory processes. Our aim was to determine the role of hsCRP in the prediction of cardiovascular mortality. The study group consisted of 1019 middle-aged Finnish subjects in our randomly recruited, population-based cohort (OPERA=Oulu Project Evaluating Risk of Atherosclerosis) initiated in 1991. Mortality was followed for 18 years up to 2009 in the national death register. hsCRP was determined using commercial Ellia kit.
Analysis of covariance and logistic regression were used in the statistical analysis. In the follow-up years 1991-2009, the subjects who deceased due to cardiovascular and noncardiovascular events had higher hsCRP values. 6.24 μg/ml (SE 0.77) and 5.19 μg/ml (SE 0.80) respectively, when compared to the subjects alive. The statistical analysis of hsCRP was log-transformed and adjusted by age and sex. Plasma hsCRP levels at the baseline of the 18 year follow up in relation to mortality are shown in the figure. The columns are mean values and the bars standard errors (adjusted by age and sex; p-value for trend in ANCOVA = 0.001). Interestingly, the hsCRP values did not differ significantly between those who died due to cardiovascular and those due to noncardiovascular causes. When the cohort was divided into hsCRP tertiles the odds ratio for total mortality was 3.1 (95% CI=2.0-3.1; p<0.001) in the highest compared to the lowest tertile.

Figure 1

In conclusion, elevated hsCRP is associated with both cardiovascular and noncardiovascular mortality suggesting that hsCRP is a nonspecific marker for mortality.

P839 Hysterectomy with ovarian conservation in young women associates with higher cardiovascular risk: a nationwide cohort study

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Objectives: We aimed to investigate the exact influence of hysterectomy with ovarian conservation on the risk of cardiovascular events, with adjustment for traditional risk factors.

Background: Hysterectomy is a common procedure for treatment of numerous gynecologic diseases. However, its association with the risk of cardiovascular events remains controversial.

Methods: A nationwide population-based study using the Taiwan National Health Insurance database from the 1 million sampling cohort data set was conducted. A total of 8059 women who underwent hysterectomy with ovarian conservation during 1997 to 2009 were identified. The control group consisted of 32,236 women without hysterectomy by matching age at operation, hypertension, diabetes, dyslipidemia and surgery date.

Results: A total of 806 strokes, 986 coronary heart diseases (CHD), and 1055 cardiovascular diseases (CVD) developed during a median 6.97 years follow-up. The difference was not significant between women with and without hysterectomy for CHD (3.37 vs. 3.06 per 1000 person-year, p = 0.23), stroke (3.17 vs. 2.87, p = 0.28) and CVD (4.27 vs. 3.79, p = 0.14). However, of the women who underwent hysterectomy with before 45 years, the hazard ratio of hysterectomy was 1.95 (1.40-2.72) for stroke and 1.60 (1.20-2.12) for cardiovascular events. (Figure)

Figure 1

Conclusions: The association between hysterectomy and the risk of cardiovascular disease was different according to the patients’ age at operation. The excess risk of cardiovascular events, mainly driven by the development of stroke, was observed in women had hysterectomy with ovarian conservation before 45 years and remained significant even after accounting for baseline cardiovascular risk factors.

P838 Are there ethnic differences in the association between family history of cardiovascular disease and prevalent cardiovascular disease in the UK?

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Purpose: Family history of cardiovascular disease is an established risk factor for developing cardiovascular disease and provides a potential tool for identifying individuals with high cardiovascular risk. There are ethnic inequalities in cardiovascular disease prevalence in the UK, with higher coronary heart disease prevalence in Indian and Pakistani groups and higher stroke incidence in Black ethnic groups compared to the White population. The purpose of this study was to investigate whether there are ethnic differences in the association between family history of cardiovascular disease and prevalent cardiovascular disease in the UK.

Methods: Cross-sectional analysis of the Health Survey for England 2003, 2004 and 2006 was performed. This large, annual survey collects self-reported health and lifestyle information, and in 2006 contained a boosted sample of the largest ethnic minority groups in England. 15,605 adults aged 40-74 years from 6 ethnic groups (White, Black Caribbean, Indian, Pakistani, Bangladeshi and Irish) were included. Odds ratios (ORs) were calculated to investigate the association between family history of parental cardiovascular disease and prevalent cardiovascular disease in all age groups, and between younger and older age groups.

Results: An increased risk of cardiovascular disease associated with a positive family history was observed in all ethnic groups and was significantly increased in the Indian (OR: 2.5, 95% CI:1.4, 4.3), Irish (OR: 2.0, 95% CI: 1.3, 3.3) and White (OR: 1.6, 95% CI: 1.4, 1.9) groups, with the highest ORs in the Indian and Irish groups. These ethnic differences remained consistent between men and women in all age groups, and between younger and older age groups.

Conclusions: Ethnic differences in the association between family history of cardiovascular disease and prevalent cardiovascular disease were observed in this multietnic sample. This may have implications for the use of family history as a tool for identifying individuals with high cardiovascular risk as its performance may vary between ethnic groups. Whilst this study was based on ethnic groups in the UK these findings will be relevant to audiences from other countries where this approach could also be applied. Further research is being carried out to model ethnic differences in the use of family history in screening for high cardiovascular risk.

P840 Grade 1 hypertension is associated with an increase in myocardial infarction even in the very elderly patients; analysis from 3100 autopsy cases

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Background: Although the risk of vascular events rises with increasing blood pressures (BP) above 115/75mmHg, the association of BP and events attenuates with advancing ages. Even after HYVET showed the efficacy of antihypertensive treatment in octogenarians, target BP for the very elderly remains to be examined.

Methods: We studied 3100 consecutive autopsy cases (1589 men, 1511 women, median 81 years old) at a general geriatric hospital. They deceased of various illnesses. We related office systolic BP to myocardial infarction (MI) determined by autopsy. The atherosclerosis of the intra-cranial artery (A-CA) and the most severe coronary artery stenosis (CS) were also semi-quantitatively evaluated.

Results: Average office BPs were 141±1/80±1/60±1mmHg. The age of death correlated negatively with heart weight (r=-0.54, p=0.003) and kidney weight (r=-0.416, p<0.001), but correlated positively with office systolic BP (r=0.111), BUN (r=0.182), A-CA (r=0.289), and CS (r=0.126), all p<0.001. In the logistic re-
5-HTTLPR polymorphism and stroke. Findings from WOBASZ study

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Purpose: The carriers of short allele of 5-HTTLPR gene are more susceptible to higher secretion of noradrenaline, so they could have the higher cardiovascular risk, higher risk of repeated cardiovascular events versus other interrelations, and higher risk of hypertension which could be associated with stroke. We try to evaluate the association between polymorphism of 5-HTTLPR and self-reported history of stroke in person aged 20-74.

Methods: The genotyping of 5-HTTLPR s/s was made in 1823 persons, examined in the frame of WOBASZ study, in 2003-2005. The stroke history was assessed based on answers to the questionnaire. Using logistic regression analysis we evaluated the association between genotypes: at least one s allele (ss or ss sL) vs LL, and as dummy variable (ss vs ss LS and ss LL).

Results: Out of 1823 persons, 1.7% of them had the history of stroke. Persons with stroke history had the ss genotype significantly more often than LL genotype (25.0% vs 12.6%, p < 0.0001). Being a carrier of at least one s allele of 5HTTLPR gene (ss or sL) compared to LL genotype was associated with more than twice higher frequency of stroke in adult Polish WOBASZ population.

Conclusions: The analyzed polymorphism of 5HTTLPR was associated with higher frequency of stroke in adult Polish WOBASZ population.

Lifetime risk algorithm identifies more patients with carotid and femoral plaques than 10 year or 30 year framingham risk algorithms

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Background: Cardiovascular disease (CVD) is the leading cause of death in the United States. Current CVD prediction algorithms are successful in recognizing underlying risk factors in populations but have failed to identify those at highest risk due to underlying disease. We compared a newer algorithm, "Lifetime Risk" (LR), with 10 yr and 30 yr Framingham Risk Score (FRS) algorithms in the identification of subjects with femoral or carotid plaque.

Methods: We studied 809 adults between ages 20 and 60 with exclusions of previous CVD: myocardial infarction, angina, stroke or claudication. Both 10- and 30-yr FRS as well as LR were calculated and subjects categorized into low-, intermediate- and high-risk groups. Ultrasound examination of both carotid and femoral arteries was performed in the transverse and longitudinal planes. Wilcoxon signed-rank test was used to assess agreement between the algorithms for classifying those with plaque across risk groups.

Results: LR placed ≥50% of all subjects with plaques in the high-risk group. For women 20 to 60 and men <50, this allocation of subjects with underlying disease was significantly better than 10 yr FRS (p < 0.001, p < 0.001) and 30 yr FRS (p < 0.01, p < 0.05) (Table 1).

Conclusions: Our study showed LR was superior to both 10 yr and 30 yr FRS in assigning subjects with plaques to the high-risk category for women aged 20 to 60 yr and for men aged ≥50 yr.

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The aim of this paper is to describe the differences in values of LDL-cholesterol which arise when using two different methods of measuring LDL-cholesterol, both equally used in clinical laboratories: the direct method and indirect method by calculation according to Friedewald formula, in real world laboratories.

Methods: A multicenter international prospective cross-sectional study. Each of thirteen laboratories from Slovakia and the Czech Republic provided a set of data from at least 200 patients in its normal operation, in which we measured values of total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were measured by direct method (LDL-D). For each patient the value of LDL-cholesterol was grossed up using the Friedewald indirect method (LDL-F). We compared the consistency in classification of patients into groups according to the treatment goals of LDL-cholesterol using the direct or indirect method of assessment. According to European guidelines on cardiovascular disease prevention, the Fourth Joint Task Force (2007) the treatment goals of LDL-cholesterol are, in various clinical situations, 2, 2,5 and 3 mmol/L.

Results: The ratio of average values of LDL-F compared to the average values of LDL-D is in the range 91.9% to 190.3%. In 6 laboratories the average LDL-F is lower than the average LDL-D: in 7 laboratories the average LDL-F is higher than the average LDL-D. The Pearson correlation coefficient r is between 0.6575 (95% CI 0,6430 – 0,6699) to 0,9795 (95% CI 0,9667 – 0,9894). The correlation coefficient in 10 laboratories was above 0.9 and under 0.9 in the 3 laboratories. For each laboratory the number of discordant or discordant inclusions in the appropriate category were calculated from the goals of LDL-cholesterol measured by both methods. The number of discordant results is in the range of 14 to 57%. If we consider LDL-D as a standard method, the LDL-F values obtained put patients at higher levels of risk ranging from 0 to 55%, to lower levels of risk ranging from 1,5 to 31,5%.

Conclusion: The differences in values obtained among real world laboratories are enormous. The suggested lipidic screening includes LDL-cholesterol, but two equally used methods are not interchangeable. Our results support efforts to replace the determination of LDL-cholesterol with other laboratory parameters.
**Cardiovascular risk profile in high risk primary care patients not treated with lipid-lowering treatment**

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**Purpose:** There is a paucity of data on the prevalence of high cardiovascular risk (HCVR) calculated with risk algorithms within a primary prevention population. The goal of the present study was to assess cardiovascular risk profile in high risk primary care patients not treated with lipid-lowering treatment.

**Methods:** This observational study was conducted among a sample of 1,147 general practitioners. All men and women aged 50 and 60 years and older, with at least one additional cardiovascular risk (CVR) factor among: smoking, high blood pressure (HBP), type 2 diabetes, low HDL-cholesterol (<0.40 g/L), in primary prevention, not treated for dyslipidemia, and attending a primary care clinic over a week, were included in the study. A questionnaire filled-in by the physician enabled calculation of the cardiovascular risk and age of arteries according to SCORE risk equation. Half of the patients in primary prevention aged 50/60 years over represented in the highest CVR region compared to the lowest: uncontrolled HBP: 44%; type 2 diabetes: 21%; smoking: 21%. According to SCORE, the prevalence of HCVR reached 50% in men and women (49% vs. 51%, respectively). Age had the highest impact on CVR assessment: the prevalence of HCVR was increased by 4.6 fold in men between 55 and 65 years old and by 7 fold in women between 60 and 65 years old. Moreover, half of the patients aged 60 to 64 years had a 6.7 year increase of their arterial age compared to their real age.

**Results:** The influence of age on CVD risk assessment was confirmed across French regions with the highest HCVR prevalence (54%) in the Mediterranean population (oldest population in France, and the lowest HCVR prevalence (47%) in the Northeast population (the youngest population in France in this study) (p<0.01). The adjustment by age and gender reduced regional disparities with a 52% and 48% prevalence of HCVR in both regions. Beside age, 3 other risk factors were over represented in the highest CVR region compared to the lowest: uncontrollable HBP, renal impairment and left ventricular hypertrophy.

**Conclusions:** Half of the patients in primary prevention aged 50/60 years (men/women) or more with at least one risk factor and not receiving a lipid-lowering treatment presented a high risk of cardiovascular event assessed by SCORE risk equation. Thus, assessing cardiovascular risk with risk equation appears particularly useful in this specific group of patients. Beside age, which had the strongest impact on risk estimation, other risk factors may be screened to improve the management of HCVR.

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**Serum hemoglobin predicts long-term mortality in patients with carotid atherosclerosis**


**Aims:** Anemia is associated with cardiovascular outcome in healthy individuals but its impact on outcome in patients with cardiovascular disease has not been fully understood as yet. Therefore, we assessed the long-term influence of serum hemoglobin on all-cause and cardiovascular mortality in patients with atherosclerotic disease.

**Methods and Results:** We prospectively studied 1065 of 1286 consecutive patients with asymptomatic carotid atherosclerosis. During a median follow-up of 6.2 years, corresponding to 5551 overall person-years, 275 (25.8%) patients died. Continuous measures of serum hemoglobin displayed a significant protective effect on all-cause mortality and cardiovascular mortality (adjusted HR [increase of 1-SD of hemoglobin] 0.73, 95%CI 0.64–0.83, p<0.001) and 0.76, 95%CI 0.64–0.89; p<0.001, respectively). The cumulative 6-year survival rates were 61%, 79%, 80% and 81% in the first, second, third and fourth quartile of serum hemoglobin (log rank p<0.001). Patients within the first quartile (<12.9 g/dL) had a significantly increased risk for all-cause mortality (adjusted HR 1.93, 95%CI 1.46–2.54, p<0.001) and cardiovascular mortality (adjusted HR 1.68, 95%CI 1.19–2.36, p<0.001) compared to patients with higher levels.

**Conclusion:** Our study demonstrates a significant association with hemoglobin levels and all-cause and cardiovascular mortality in patients with carotid atherosclerosis. Nevertheless, further research, in terms of randomized controlled trials, is needed to validate these findings and to evaluate potential therapeutic interventions.

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**Relationship between erectile dysfunction and chronotropic response to exercise testing in middle-aged hypertensive men**

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**Purpose:** Hypertension is the most common comorbidity in men with erectile dysfunction (ED). ED may carry an incremental predictive value for future cardiovascular events. Chronotropic incompetence, or an inability to increase heart rate during exercise, independently predicts death. The purpose of this study was to evaluate the association between ED and chronotropic index (CI) during EST in middle-aged hypertensive men.

**Methods:** 97 non-diabetic, hypertensive (Grade II-III) ED patients (55±9 y/o) and 32 age-matched hypertensive men without ED underwent maximal EST under the standard Bruce protocol. CI was calculated as ([HRpeak – HRrest]/220 – age) x 100. The CI was considered abnormal when <0.8 in patients not taking beta-blockers. All men with ED underwent penile color Doppler and peak systolic velocity (PSV) was measured as an index of penile vascular disease. Reduced PSV is associated with increased risk for cardiovascular events as well as the degree and distribution of atherosclerotic lesions.

**Results:** ED patients had a substantially reduced CI (left plot) and a higher prevalence of abnormal CI (42 vs 21%) than nonED subjects (all P<0.01). After adjusting for age and blood pressure, CI was decreased (0.78±0.20 vs 0.89±0.19) and prevalence of abnormal CI was increased (48 vs 17%) in patients with severe arterial insufficiency (PSV<25 cm/s) compared to subjects with higher Doppler velocities (P<0.001). The combination of severe penile arterial disease (PSV<25 cm/s) with an abnormal CI (≤0.8) showed a greater effect on 10-year risk of a CV event (right plot).

**Conclusions:** Our findings indicate that chronotropic response to exercise testing is significantly associated with the presence and severity of ED among hypertensive patients.
Use of national intervention coronary registry data as cardiovascular surveillance system in developing countries

G. Saade, A. Sarissi, G. Ghanem, J. Haddad, S. Arnaout, S. Dada, and 48% three or more.

patients had no vessels diseased, 27% had one vessel diseased, 24.6% had two
giography in 74.5% of cases: unstable angina (44.9%), stable angina (19.1%),
was reported in around 42.5% of the patient sample. The other most commonly
ported CVD risk factor reaching a prevalence of around 62%. Similarly, smoking
and completed one-year follow-up. The biomarkers were obtained simultaneously
patients had blood sampled for prospective assessment of the prognostic value
We enrolled 329 asymptomatic ambulatory hemodialysis patients. All
are available for troponin I and troponin T, but little is known about the ability of
Purpose:

The majority of patients were men (67%) who are at a significantly younger age
32824 were angiographies and 8054 PCI. Patients' ages ranged between 18 and
98 asymptomatic pts (33 males, 65 females; screening group) undergone MED
98 interesting news from large epidemiological studies and registries / Cardiovascular risk assessment: what's new?

CARDIOVASCULAR RISK ASSESSMENT: WHAT'S NEW?

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Head-to-head comparison of cardiac high-sensitive troponin I, high-sensitive troponin T and NT-proBNP for risk stratification in asymptomatic patients with end-stage renal disease

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Purpose: Cardiac troponin T (TnT) is recommended as mortality risk stratification tool in end-stage renal disease (ESRD) patients, since TnT is considered to be superior to troponin I (TnI) in ability to predict mortality. NT-proBNP is also shown to be a predictor of mortality in this population. However, there is no head-to-head comparison study for these three markers. Moreover, new high-sensitivity assays are available for troponin I and troponin T, but little is known about the ability of these high-sensitivity assays in predicting prognosis in ESRD patients.

Methods: We enrolled 329 asymptomatic ambulatory hemodialysis patients. All patients had blood sampled for prospective assessment of the prognostic value and completed one-year follow-up. The biomarkers were obtained simultaneously just before dialysis. All patients were followed-up for combined cardiovascular endpoint (CCE) including acute coronary syndrome, stroke, amputation due to critical limb ischemia, and cardiovascular death. The predictive abilities of high-sensitive TnI (hsTnI), high-sensitive TnT (hsTnT), and NT-proBNP were compared by area under the curve (AUC).

Results: At baseline, the median hsTnI and hsTnT levels were 13 ng/L (IQR: 6-29) and 64 ng/L (IQR: 39-94), respectively. There were 50 CCEs during one year follow-up. In multivariate analyses, hsTnI (P = 0.01), hsTnT (P < 0.001) and NT-proBNP (P = 0.05) remained as independent predictors for CCE. The AUC of hsTnI for predicting CCE was superior to both hsTnI (0.83 vs 0.75, P = 0.04) and NT-proBNP (0.83 vs 0.70, P = 0.004); however, there was no significant difference between the AUC for hsTnT and NT-proBNP (P = 0.04). In head-to-head comparison, hsTnT was superior to hsTnI and NT-proBNP for providing prognostic information in asymptomatic ESRD patients.

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Reduction of adverse cardiovascular events in patients with severe psoriasis treated with biologic agents or methotrexate: a Danish real-world cohort study

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Purpose: Psoriasis is a chronic inflammatory disorder associated with cardiovascular morbidity and mortality. Systemic anti-inflammatory drugs, including biologic agents, are widely used in the treatment of patients with moderate to severe psoriasis and cardiovascular events in this patient population are rare. The aim of this study was to assess the potential of cardiovascular events in treatment-naive patients with severe psoriasis and to compare the risk of cardiovascular events in treatment-naive patients treated with methotrexate, biologic therapies, or other therapies: e.g., retinoids, cyclosporine, and phototherapy in Denmark from 2007 to 2009.

Methods: A total of 2,400 patients with severe psoriasis, including 693 patients treated with biologic agents were identified. Patients treated with biologic agents were younger at baseline (46.6 ± 12.9 vs. 53.7 ± 15.2 years) and were more often men (68.7% vs. 47.5%) compared to patients not treated with biologic agents. Incidence rates and 95% confidence intervals (CIs) for the composite endpoint were 6.0 (CI 2.7-13.4), 17.3 (CI 12.3-24.3), and 44.5 (CI 34.6-57.0) for patients treated with biologic agents, methotrexate, and other therapies, respectively. Corresponding HRs for a composite cardiovascular endpoint, i.e., cardiovascular death, myocardial infarction, and stroke in patients with severe psoriasis treated with biologic agents, methotrexate, or other therapies was 0.48 (CI 0.12-0.64) and 0.65 (CI 0.42-1.00) for patients treated with biologic agents and methotrexate, respectively. Corresponding HRs for a composite cardiovascular endpoint, i.e., cardiovascular death, myocardial infarction, and stroke compared to patients treated with other therapies.

Conclusion: In a nationwide study of patients with severe psoriasis, systemic anti-inflammatory treatment with biologic agents or methotrexate was associated with lower risk of a composite endpoint of death, myocardial infarction, and stroke compared to patients treated with other therapies.

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Late cardiac damages after chest radiotherapy: a long-term follow-up and screening project

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Introduction: Mediastinal (MED) and left chest wall (LCW) radiotherapy (RT) may cause several late damages to the heart: constrictive pericarditis (CP), valvular (VHD) or coronary artery (CAD) disease, left ventricular dysfunction (LVD), RT cardiotoxicity is usually incidentally detected when the patients (pts) become symptomatic. Few prospective screening studies on asymptomatic pts have been carried on so far.

Methods: We prospectively studied by echocardiography (ECOG) and stress test 98 asymptomatic pts (33 males, 65 females; screening group) undergoing MED (n=81); 80 lymphomas, 1 thymoma) or LCW (n=17, all breast cancer) RT from 1974 to 2004, and followed up for up to 37 years after RT. Age at treatment ranged from 8 to 64 (median 33); 84 pts also received cardiological examinations (ECG). Radiation burden ranged from 16 to 50 Gy, median 40. The follow-up (FU) lasted 6-37 years, mean 17, median 16. A total of 449 ECHO and 167 stress tests were done.

Results: Significant cardiac abnormalities were detected in 23/98 (23%) pts undergoing screening: 10 males, 13 females, aged 40-76 (mean 56). At ECHO we observed LVD in 9 pts (one of them had also CAD) and VHD in 3 requiring surgery in one. Stress test revealed ischemia in 9 pts (7 silent, 2 with angina; 6 needed cardiac revascularization). We observed 7 more patients (not on screening) who presented because of cardiac symptoms: 3 males, 4 females, 3 with critical limb ischemia, and cardiovascular death. The predictive abilities of high-sensitive TnI (hsTnI), high-sensitive TnT (hsTnT), and NT-proBNP were compared by area under the curve (AUC).

Conclusion: In head-to-head comparison, hsTnT was superior to hsTnI and NT-proBNP for providing prognostic information in asymptomatic ESRD patients.

Figure 1. ROC curves and AUC for CCE
severe LVD, 2 with acute myocardial infarction (AMI), 2 with symptomatic VHD. Overall, cardiotoxicity was evident 1 to 35 years after RT (mean 17). Age at treatment was 14 to 64 (mean 37), at toxicity detection 36 to 76 (mean 54). As regards LVD (n=12), all the pts had received also cardiotoxic chemotherapy and 3 of them had associated CAD; the interval from RT was 1-27 years (mean and median 12). Seven of 12 pts with CAD had also dyslipidemia; the time from RT was 2-26 years (mean 16, median 19). For VHD (n=6) the interval was 16-35 (mean 26, median 27) years. Among the screening group, in 22/23 pts symptomatic events were prevented by timely treatments; only one had AMI 2 years after a negative stress test.

**Conclusions:** At long-term follow-up a significant percentage of pts treated with RT are at risk of clinically relevant heart disease at a rather young age. LVD is usually detected in pts treated with both RT and CT, and is clinically evident earlier; CAO and VHD occur later. CAD is clinically silent in most cases. In pts treated with MED or LCW radiotherapy we suggest a long-term follow-up with ECHO and stress test, mostly for those treated >20 years ago, to prevent life-threatening events.

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**Clinical impact of the morphologic classification of coronary spasm in ergonovine provocation test**


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**Background:** Coronary vasospasm plays a key role in provoking myocardial ischemia, acute myocardial infarction (AMI) and sudden cardiac death (SCD) in variant angina. But there are little data about the adverse cardiac events according to morphologic type of provoked spasm.

**Method:** A consecutive 164 patients with clinically suspected variant angina were performed ergonovine provocation test without significant stenosis (≥ 50% diameter stenosis) and total 105 patients with a positive provocation test were enrolled. Coronary vasospasm was defined as a transient vessel narrowing (~ 90%) which was associated with angina and/or ST-depressive or elevated changes. These patients were divided to three groups according to the extent of coronary spasm: Focal type, segmental type and diffuse type. We compared the occurrence rates of 12-month adverse cardiac events (MACEs) such as death, AMI, re-hospitalization due to angina during 1 year follow up and AMI or SCD as initial presentation.

**Results:** There were no significant differences in baseline characteristics between three groups, including use of calcium channel blockers and/or nitrates. During follow up period, one arrhythmic death occurred in focal type. There are no differences in SCD or AMI between three groups. But, when we compared the two groups (non-diffuse type vs diffuse type), focal and segmental type (non-diffuse type) tend to have higher incidence rates of SCD or AMI than diffuse type (11.9% vs 2.4%, p = 0.082). Combined MACEs rates were significantly higher in diffuse type than focal and segmental type (37% vs 44.4% vs 18.5%, p = 0.018).

**Conclusion:** Focal and segmental type of coronary spasm in provocation test was significantly associated with adverse cardiac events at 12-month follow up in patient with vasospastic angina. These results suggest that focal and segmental type of coronary spasm may need more intensive treatment for variant angina.

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**A variant in the epithelial sodium channel affects the arterial stiffness in a portuguese population**

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**Pulse Wave Velocity (PWV)** is a simple, non-invasive and sensitive method, widely used as an index of arterial stiffness. This parameter has been shown as an important risk marker for cardiovascular mortality and morbidity. The sodium channel gene (SCNN1G), located on human chromosome 16p12, encodes the gamma subunit of the epithelial sodium channel. Minor polymorphic changes in its promoter region may result in an increased sodium channel activity and have been associated to arterial hypertension and consequently higher PWV values.

**Objective:** The aim of this study is to evaluate whether this variant in the epithelial sodium channel affects the PWV values and, consequently, the arterial stiffness in a Portuguese population.

**Methods:** An epidemiological study with 863 individuals (51.3% male, mean age 49.8 ± 7.6 years) was performed and all the PWV measurements were distributed in quartiles according to the increasing values of this parameter. The first quartile consisted of 250 men with a mean age 47.5 ± 7.2 years and a PWV: 5.8 m/s, the forth quartile included 187 individuals with a mean age 52.3 ± 7.1 years and a PWV: 10.2 m/s. As PWV is strongly reliant on age, some individuals were excluded from each group (after fixing this variable) and two groups with 177 individuals and similar mean age were established. These were compared in terms of SCNN1G A173G variant frequency. Categorical variables were presented by the respective frequency and analyzed by χ2 test or Fisher’s exact test. Continuous variables were expressed as mean±standard deviation and compared by using Student’s t-test or Mann Whitney. In order to investigate which variables significantly influence the increase of PWV, a multivariate analysis was performed with all the confounding variables. P-values < 0.05 were considered significant.

**Results:** The GG SCNN1G A173G variant was significant and independently associated with the increase of PWV values (OR>1.95, p=0.048 together with male sex (OR=2.88, p=0.0001), arterial hypertension (OR=4.06, p<0.0001) and heart rate (OR=1.03, p=0.005).

**Conclusions:** According to our results, this variant increases the PWV values and, consequently, reduces the arterial distensibility in our population, independently of arterial hypertension. The individuals carrying this polymorphism, which is associated with a lower capacity to manage the sodium and water, may present, in the future, a higher risk of cardiovascular complications benefiting from a more careful prevention.
Characterization of cocaine cardiotoxicity with cardiovascular magnetic resonance at 3T

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Cocaine is a highly addictive drug with potentially cardiovascular lethal effects. The real prevalence and features of cocaine cardiotoxicity are unknown as they have been evaluated only in selected groups. We aimed to assess using a comprehensive 3T cardiovascular magnetic resonance (3TCMR) protocol in consecutive cocaine addicts.

Methods: Consecutive, non-selected, cocaine abusers first attending a rehabilitation clinic were recruited. Medical history and examination, ECG, blood test and 3TCMR were done. CMR protocol included TrueFISP cine for measurement of left and right ventricular (LV, RV) volumes and ejection fraction (EF), ST/strain sequences, dipyradimole (0.4mg/kg) myocardial perfusion study with gadolinium-DTPA (0.1mmol/kg), myocardial late gadolinium enhancement (LGE) and T2WST study of the aorta. Images were analyzed by 2 independent, blinded observers and compared to those of 90 age and gender-matched healthy controls previously reported.

Results: 94 cocaine abusers were initially included. One subject had a sudden cardiac death 2 days before 3TCMR and another individual had to be excluded because he was diagnosed of previously unknown hypertrophic cardiomyopathy. Finally, 92 consecutive cocaine abusers were included (13 females, 37.7±5 years, age range 22-53 yrs, 77.7±0.8yrs of addiction). Only 4 patients referred mild cardiovascular symptoms (palpitations during abuse). In a per-group analysis, end-systolic volumes were slightly enlarged (LV:318±24±2 m³/mL, RV:38±10 vs 28±3±m³/mL, all P<0.001) and so was the LV mass index (80±13 vs 69±4±g/cm³, P<0.001), while EF was significantly decreased (LV:59±6 vs 68±4±%, RV: 55±5 vs 61±%, all P<0.001) and the LV end-diastolic volume was increased (13.9±4.1 vs 12±4.1, all P<0.001). The real prevalence and features of cocaine cardiotoxicity are unknown as they have been evaluated only in selected groups. We aimed to assess using a comprehensive 3T cardiovascular magnetic resonance (3TCMR) protocol in consecutive cocaine addicts.

Conclusions: 3TCMR detected cardiovascular disease of variable degree in 69% of this cohort of consecutive, non-selected, cocaine abusers. The main findings were decrease in LV and RV EF, increase in LV mass index and presence of myocardial LGE, which in the majority of cases was suggestive of previous myocardial infarction.

Association of omega-3 polyunsaturated fatty acids with cardiac arrestorsclerosis in patients on haemodialysis

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Background: Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have beneficial effects against cardiovascular disease. In haemodialysis (HD) patients, blood levels of n-3 PUFAs have been reported to be more suboptimal compared to general population due to consumption of inadequate amounts of dietary fish. However, the association between n-3 PUFAs levels and cardiovascular risk has been little studied in HD patients with cardiac arrestorsclerosis. We investigated the association of n-3 PUFAs levels with carotid arrestorsclerosis in HD patients.

Methods: Carotid ultrasound was performed in 461 HD patients (male 67%, age 67.1±10.4 years). Intima-medial thickness (IMT), intima-media thickness (IMT), and plaques (PS) in common carotid artery were measured. Carotid arrestorsclerosis was defined as IMT > 0.5mm and/or PS > 5.0mm. The levels of n-6 PUFAs [dihomo-γ-linolenic acid (DGLA) and arachidonic acid (AA)] and n-3 PUFAs [icosapentaeonic acid (EPA) and docosahexaenoic acid (DHA)] were also measured.

Results: Carotid arrestorsclerosis was seen in 94 patients (20.4%). Individual PUFAs were comparable between patients with and without cardiac arrestorsclerosis. However, the ratio of EPA/AA and that of n-3/n-6 PUFAs were significantly lower in patients with cardiac arrestorsclerosis compared to those without (0.43±0.29 vs. 0.53±0.44, p = 0.027 and 0.94±0.43 vs 1.07±0.55, p = 0.036, respectively). After adjustment of the confounders, the ratio of EPA/AA and that of n-3/n-6 PUFAs were independently associated with carotid arrestorsclerosis, respectively. In addition, C-index for carotid arrestorsclerosis was significantly greater in an established risk model with EPA/AA ratio and n-3/n-6 ratio than in the established risk model alone (Table).

Conclusion: Levels of both EPA/AA ratio and n-3/n-6 PUFAs ratio are closely associated with incidence of carotid arrestorsclerosis in patients on HD.

Enhancement of cardioankle vascular index induced by the 2011 earthquake in Tohoku, Japan

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Background: It is known that the frequency of cardiovascular events increases just after a huge earthquake. Cardio-ankle vascular stiffness index (CAVI) represents the stiffness of the aorta, femoral artery and tibial artery as a whole. The most conspicuous feature of CAVI is a blood pressure-independency at measuring aortic stiffness.

CAVI increases with age and in many arteriosclerotic diseases, such as coronary artery disease, carotidarteriosclerosis, chronic kidney disease and cerebrovascular disease, and is related to many coronary risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking status, body mass index, previous history of cardiovascular diseases, serum albumin, and C-reactive protein.

Enhancement of CAVI just after a huge earthquake. Cardio-ankle vascular stiffness index (CAVI) represents the stiffness of the aorta, femoral artery and tibial artery as a whole. The most conspicuous feature of CAVI is a blood pressure-independency at measuring aortic stiffness.

C.AVI increases with age and in many arteriosclerotic diseases, such as coronary artery disease, carotidarteriosclerosis, chronic kidney disease and cerebrovascular disease, and is related to many coronary risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking status, body mass index, previous history of cardiovascular diseases, serum albumin, and C-reactive protein.

Conclusion: It was found that the frequency of cardiovascular events increases just after a huge earthquake.

Aim: To reveal the relationship between psychological stress and the aortic hardening using CAVI.

Methods: We felt large psychological stress by the fear of the huge earthquake. Cardio-ankle vascular stiffness index (CAVI) represents the stiffness of the aorta, femoral artery and tibial artery as a whole. The most conspicuous feature of CAVI is a blood pressure-independency at measuring aortic stiffness.
Ankle blood pressure and dementia - a prospective follow-up study

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Background and objective: To investigate the relationship between ankle blood pressure and clinically incident dementia. The ankle blood pressure may be a useful indicator of arterial stiffness but very few studies have considered the independent value of the ankle blood pressure without indexing it to the brachial blood pressure (ABI-index).

Methods: This prospective follow-up study is based on individuals (mean age 50 years, 68% male) referred to a symptom-limited exercise test between the August 1989 and December 1995. A cohort of 3859 subjects free of dementia and vascular disease at baseline was followed for 18 years. The significance of ankle blood pressure as a predictor of incident dementia was analyzed using Cox proportional hazard models, controlling for several confounders including brachial systolic blood pressure.

Results: Clinically incident dementia was observed in 123 (3%) of the 3859 participants during the mean follow-up period of 18 years. Altogether, 592 patients had a vascular event (15%). Patients with incident dementia were older than those without dementia and the majority of them were women. Significant associations were found between the elevated ankle blood pressure at baseline and clinically incident dementia during the follow-up. In persons with normal resting and exercise brachial blood pressure but elevated ankle blood pressure the hazard ratio was 1.58 (95% CI 1.04 – 2.40, p=0.03, adjusted for age and sex) and 1.59-fold (95% CI 1.00 – 2.66, p=0.05) in the wider model (adjusted for age, sex, resting systolic blood pressure, smoking and early parental cardiovascular diseases). On the other hand, good physical exercise capacity at baseline, measured as METs, was significantly protective (p=0.01) from dementia.

Conclusion: These results suggest that the ankle blood pressure has an independent value as a marker of arterial stiffness and subclinical atherosclerosis. Elevated ankle blood pressure in persons with otherwise normal blood pressure may indicate increased risk of cardiovascular complications and dementia.

Increased cardiovascular morbidity and mortality in apparently healthy middle-aged men and women with frequent episodes of leg cramps

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Purpose: Leg cramps are a common and bothering symptom, especially in the elderly. The prognostic significance of this phenomenon is unknown. We aimed to investigate the prognostic value of leg cramps and a thorough examination of the lower extremity arteries in a prospective epidemiological study.

Method: A total of 678 healthy men and women between the age of 55 and 75, included in the Copenhagen Holter Study, reported either to have 1. Never leg cramps, 2. Seldom leg cramps or 3. Often or daily leg cramps. The abdominal aorta was similarly assessed.

Results: 47 (6.9%) subjects had often/daily episodes of leg cramps. Cramps were more frequent among women than men, 9.6% vs 5% (p=0.03) and were associated with an increased risk of reaching the combined cardiovascular end-point, HR=2.57 (1.26-5.22), p=0.009. This association remained significant after correcting for traditional risk factors, and intermittent claudication, HR=2.54 (1.23-5.25), p=0.01. Leg cramps were not associated with all-cause mortality, HR=1.38 (0.67-2.85), p=0.38.

In 243 (36.4%) subjects palpable pulse was absent in 1 or more regions and was not associated with the 1st cardiovascular endpoints (HR=1.47 [0.87-2.46], p=0.15) or all-cause mortality (HR=1.32 [0.86-2.03], p=0.21). In 49 (7.3%) subjects pulse was absent in 4 or more regions and neither was this finding associated with endpoints.

Conclusion: In apparently healthy subjects frequent leg cramps are associated with increased cardiovascular risk. The absence of palpable pulse did not have prognostic value. These findings give reason to reconsider leg cramps as a pure benign phenomenon.

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Abstract P863 - Table 1

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Quartile values (mg/L)</th>
<th>HR (95% CI) for CHD events after 1 year</th>
<th>P</th>
<th>HR (95% CI) for CHD events after 1 year</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hsCRP, adjusted for conventional risk factors</td>
<td>1.22</td>
<td>1.00 (0.79-1.26)</td>
<td>0.31</td>
<td>1.00 (0.79-1.26)</td>
<td>0.31</td>
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<td></td>
<td>1.22 to 2.43</td>
<td>0.89 (0.77-1.02)</td>
<td>0.31</td>
<td>0.91 (0.75-1.12)</td>
<td>0.31</td>
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<td></td>
<td>2.43 to 4.78</td>
<td>1.00 (0.79 to 1.27)</td>
<td>0.31</td>
<td>1.02 (0.83 to 1.26)</td>
<td>0.31</td>
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<td></td>
<td>&gt;4.78</td>
<td>1.15 (0.88 to 1.49)</td>
<td>0.34</td>
<td>1.24 (0.98 to 1.56)</td>
<td>0.34</td>
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<tr>
<td>Change in hsCRP, adjusted for conventional risk factors</td>
<td>-0.99</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.99 to -0.04</td>
<td>0.81 (0.63 to 1.04)</td>
<td>0.34</td>
<td>0.83 (0.67 to 1.03)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>-0.04 to 0.875</td>
<td>0.97 (0.76 to 1.24)</td>
<td>0.34</td>
<td>0.95 (0.77 to 1.19)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>&gt;0.875</td>
<td>1.11 (0.90 to 1.37)</td>
<td>0.22</td>
<td>1.12 (0.93 to 1.35)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
P864 Relationship between plasma choline and betaine levels and risk of acute myocardial infarction in patients with stable coronary heart disease

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Purpose: High plasma choline and its derivative betaine have been associated with cardiovascular disease, and circulating choline levels predict adverse events in patients with acute coronary syndrome. We studied relations of plasma choline and betaine to long-term risk of acute myocardial infarction (AMI) in patients with stable angina pectoris (SAP).

Methods: Samples were obtained from 2568 participants in the Western Norway B-Vitamin Intervention Trial (WENBIT). Hazard ratios (HR) (95% confidence interval) were calculated per quartile increment, using Cox regression analyses adjusted for age, sex, fasting status, smoking, body mass index, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, LDL-cholesterol and medication and stratified by study site.

Results: During a mean (SD) follow-up of 4.8 (1.4) years, 8.3% suffered from AMI. Plasma choline was not associated with AMI (HR 0.99 (0.87, 1.14), p=0.91) in the total population. However, the relationship of plasma choline with risk of AMI was significantly modified by smoking (p<0.001), showing increased risk in non-smokers (HR 1.24 (1.02, 1.51), p=0.033) and decreased risk in smokers (HR 0.77 (0.62, 0.94), p=0.010). Plasma betaine was not associated with AMI (HR 0.99 (0.87, 1.13), p=0.74), and did not interact.

Conclusion: In SAP patients, high plasma choline is associated with increased risk of AMI in non-smokers, but with decreased risk in smokers. These results motivate further research into the relation between atherosclerosis, smoking and choline metabolism.

P865 Pulse wave velocity as a predictor of cardiovascular events in coronary artery disease

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2Volgograd State Medical University, Volgograd Regional Cardiology Centre, Volgograd, Russian Federation

Pulse wave velocity (PWV) is a well known marker of end organ damage in patients (pts) with arterial hypertension. As for pts with coronary artery disease (CAD), there are limited data and it remains unclear whether the change in PWV motivates further research into the relation between atherosclerosis, smoking and cardiovascular disease.

Materials and methods: 160 pts (68% male) with proven CAD (mean age 58.8 ± 12.0 years) were included. PWV was measured as the average value of PWV at the aortic arch (first measurement) and femoral artery (second measurement) using the applanation tonometry. PWV was calculated as the difference between two points of measurement divided by the distance between these points. The obtained values of PWV were divided into 3 groups, depending on the PWV (Figure). The first group included 94 pts with PWV > 12 m/s. It was found that the probability of major cardiovascular events in the total population was 58.8%, 160 pts (68% male) with proven CAD (mean age 58.8 ± 12.1 years), normal blood pressure and left ventricular ejection fraction were >50%.

Results: The average value of PWV was 11.5 ± 5.0 m/s in pts with normal blood pressure and left ventricular ejection fraction. PWV was significantly modified by smoking (p<0.001), showing increased risk in non-smokers (HR 1.24 (1.02, 1.51), p=0.033) and decreased risk in smokers (HR 0.77 (0.62, 0.94), p=0.010). Pts with CAD were divided into 3 groups, depending on the PWV (Figure). The first group included 94 pts with PWV > 12 m/s. It was found that the probability of major cardiovascular events in the total population was 58.8%, 160 pts (68% male) with proven CAD (mean age 58.8 ± 12.1 years), normal blood pressure and left ventricular ejection fraction were >50%.

Conclusion: In SAP patients, high plasma choline is associated with increased risk of AMI in non-smokers, but with decreased risk in smokers. These results motivate further research into the relation between atherosclerosis, smoking and choline metabolism.

P866 Combination of serum albumin, C-reactive protein and body mass index improves the predicting of cardiovascular mortality in end-stage renal disease patients who started hemodialysis therapy

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Purpose: Malnutrition and chronic inflammation statuses are highly prevalent in patients with end-stage renal disease (ESRD). We investigated the interaction among serum albumin, C-reactive protein (CRP) and body mass index (BMI) at initiation of hemodialysis (HD) therapy as a predictor of cardiovascular (CV) mortality in ESRD patients.

Methods: 1,228 consecutive ESRD patients who were stably induced into HD therapy were enrolled. To clarify the joint role of these valuables, serum albumin <3.5g/dL, serum CRP >4.0mg/L and BMI <19.6kg/m2 were defined as risk factors using ROC analysis, thereafter, the patients were divided into groups according to the number of risk factors; patients without any factors (group 0, n=314), with one factor (group 1, n=409), with two factors (group 2, n=385) and with all factors (group 3, n=120). They were followed up for 10 years.

Results: Serum albumin, CRP and BMI were individually independent predictors for CV mortality (HR 0.64, 95%CI 0.41-0.98, p=0.042; HR 1.01, 95%CI 1.00-1.02, p=0.0039 and HR 0.89, 95%CI 0.82-0.97, p=0.0088, respectively). Regarding the joint role of these factors, 10-year survival rates for CV mortality were 74.7%, 78.5% and 72.5% among group 0, 1, and 3, respectively (p=0.0001). Adjusted HRs were 2.28 (95%CI 1.92-5.09), group 1 vs. 0), 3.82 (95%CI 1.76-8.25) for group 2 vs. 0) and 6.75 (95%CI 2.91-15.6) for group 3 vs. 0), respectively. In addition, C-index for CV mortality significantly increased in a model including the number of risk factors compared to other models (Table). Similar results were also seen for all-cause mortality.

C-index of various models for mortality

<table>
<thead>
<tr>
<th>Model</th>
<th>C-index (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic model</td>
<td>0.614 (0.506-0.671)</td>
<td>reference</td>
</tr>
<tr>
<td>Basic model + albumin</td>
<td>0.669 (0.609-0.72)</td>
<td>0.016</td>
</tr>
<tr>
<td>Basic model + CRP</td>
<td>0.693 (0.642-0.745)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Basic model + BMI</td>
<td>0.692 (0.642-0.743)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Basic model + number of risks</td>
<td>0.754 (0.710-0.798)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusion: Serum albumin, CRP and BMI at starting HD therapy were independent predictors for CV mortality in ESRD patients, individually. Furthermore, combination of these valuables could more accurately predict the mortality than these valuables alone.

P867 The predictive value of preoperative B-type natriuretic peptide for major adverse cardiac/noncardiac events in patients undergoing noncardiac, nonvascular surgery

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Background: The prognostic role of B-type natriuretic peptide (BNP) measurement before noncardiac surgery is unclear. We aimed to determine the impact of preoperative BNP levels on perioperative cardiovascular and noncardiac outcomes in patients undergoing nonemergent, major noncardiothoracic surgery.

Methods and Results: A total of 1340 patients were prospectively followed up for a minimum of 3 months after noncardiothoracic, nonvascular surgery. Patients older than 18 years who underwent an elective, nonday case, open surgical procedure were enrolled. Demographics, comorbidities, preoperative (medications, electrocardiography, echocardiography, laboratory results) and postoperative data were evaluated for their association with the occurrence of perioperative adverse events. The perioperative cardiovascular complications were defined as the occurrence of severe arrhythmias requiring treatment, acute heart failure, acute coronary syndrome (including unstable angina), deep venous thrombosis, pulmonary embolism, arterial thromboembolic events, acute cardioembolic stroke and nonfatal cardiac arrest. Non-cardiovascular complications were lobar pneumonia, major and minor bleeding, acute renal failure requiring dialysis, respiratory failure requiring intubation for >2 days or reintubation, wound infection, and bacteremia. Eighteen patients (1.3%) died during the study period. Cardiovascular complications occurred in 145 patients (10.8%), and noncardiac complications developed in 159 patients (11.9%). Preoperative BNP levels were significantly higher in patients with perioperative cardiovascular events in comparison to those without cardiovascular events (362.8 ± 513.2 vs 91.1 ± 80.6 mg/L, p < 0.0001), and in patients with non-cardiac complications in comparison to those without noncardiovascular events (137.5 ± 102.4 vs 80.6 ± 73.7 mg/L p < 0.0001). Patients who died had also higher BNP levels (485.4 ± 419.6 vs 154.4 ± 144.8 mg/L, p < 0.0001) compared to survivors. The optimal cut-off level, sensitivity, and specificity of BNP levels to distinguish the deceased group from the survival group were 245 mg/L, 75.0% and 73.0%, respectively.
Conclusions: Preoperative BNP levels may predict not only perioperative cardiovascular events and mortality but also noncardiovascular complications in patients undergoing noncardiac, nonvascular surgery.

Incremental value of endogenous sex hormones as determinants of subclinical atherosclerosis in apparently healthy postmenopausal women

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Introduction: Although controversial, accumulating evidence suggest that endogenous sex hormones may play a pivotal role in mechanisms mediating accelerated atherosclerosis in postmenopausal women. We aimed to assess the incremental value of endogenous sex hormones over traditional risk factors to detect the presence of subclinical atherosclerosis in a sample of apparently healthy postmenopausal women.

Methods: In this cross-sectional study, serum follicle-stimulating hormone, luteinizing hormone, estradiol, testosterone, sex hormone-binding globulin, dehydroepiandrosterone sulfate (DHEAS), and 1,4-androstenedione were measured in 424 healthy postmenopausal women consecutively recruited from the Menopause Clinic of an academic hospital. Pulse wave velocity (PWV), flow mediated dilatation (FMD), augmentation index (AI), stiffness index (SI) and intima media thickness (IMT) in the carotid and common femoral arteries were measured in all women. The presence of subclinical atherosclerosis was defined by the presence of one or more of the following: IMT > 0.9 mm and/or the presence of an atherosclerotic plaque at any site and PWV above the reference values for age matched European population with risk factors.

Results: The free androgen index (FAI) was an independent determinant of PWV (β= 0.935, p=0.008) and inversely (β= −0.081, p=0.05) correlated with FMD. Total testosterone was independently associated with common carotid IMT (β= 0.215, p<0.001) and the presence of subclinical atherosclerosis (β= 1.7, p=0.001). In contrast, estradiol was inversely associated with stiffness index (β= −0.187, p=0.03) and IMT in the femoral arteries (β= −0.233, p<0.001). Total testosterone incrementally determined elevated common carotid IMT (p=0.02) and the presence of subclinical atherosclerosis (p=0.045) and FAI predicted abnormal PWV (p=0.034) over the core model of traditional risk factors. Finally, net reclassification improvement (NRI) was significant for the presence of subclinical atherosclerosis (NRI=2.44, p=0.015) and increased common carotid IMT (NRI= 0.224, p=0.003) when adding testosterone over a core model including traditional risk factors.

Discussion: Estrogens were associated with favorable while androgens with adverse cardiovascular effects in postmenopausal women. However, among the sex hormones assessed in this study, testosterone provided the highest incremental value and more accurate reclassification over traditional risk factors as a determinant of the presence of subclinical atherosclerosis.

Purpose: Obstructive Sleep Apnea Syndrome (OSAS) is a common airways disease recognized as an independent cardiovascular risk factor. It is often associated with obesity, diabetes and dyslipidemia. Its patho-physiological consequences (hypoxia, hypercapnia, micro- arousals, sympathetic hyperactivity, oxidative stress, systemic inflammation and hypercoagulability) are implicated in the development of hypertension, endothelial dysfunction and higher intima-media thickness (IMT) values, all elements known to lead to atherosclerosis. The study aim was to demonstrate a relationship between OSAS duration and IMT values and to confirm how OSAS severity could influence IMT (a marker of atherosclerosis).

Methods: We enrolled 156 patients (125 men, mean age: 60±12 years) affected by OSAS of different severity: 111 (71%) were in CPAP therapy; some of the population were also affected by hypertension [38 (65%)], dyslipidemia [52 (33%)] and diabetes [38 (24%)].

Results: We found a statistically significant higher IMT value in patients with longer-lasting disease (OSAS duration in IMT < 0.9 mm: 146±126 months vs OSAS duration in IMT > 0.9 mm: 247±153 months; p=0.001). OSAS severity is positively related to IMT values. We found a positive relationship between IMT and OSAS duration [r=0.34; p<0.001] and between AHI and IMT [r=0.51; p<0.001].

Conclusions: Our study shows that the duration of OSAS and its severity are important factor related with higher values of IMT and hence with a higher risk of atherosclerosis.

Plasma Lp(a) concentration shows modest predictive power for coronary heart disease events: results from the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial

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Background: Lp(a) has been an elusive risk factor for CHD. Population studies and meta-analyses show association between Lp(a) and first-ever CHD events among people with high global risk, but there is a paucity of evidence from population-levels with overt CHD with stable symptoms. We tested the potential association of CHD events (death or nonfatal MI) with Lp(a) concentration and interactions with treatment and conventional risk factors in patients with prior clinical CHD (myocardial infarction (MI) or hospitalization for unstable angina) randomly allocated to pravastatin or placebo.

Methods: Plasma samples were available from 7863 patients (6530 men and 1333 women, mean age 62 years) at baseline. The prognostic value of Lp(a) on each outcome was assessed by fitting proportional hazards models by base-line biomarker quartile. Hazard ratios (HR) by quartile of Lp(a) levels were first adjusted for treatment and sex (Model 1) and then additionally adjusted for diabetes, smoking, hypertension, major lipid classes including apoB and apoA-I, age, WBC, eGFR, BMI, and other CVD at baseline (Model 2).

Results: Lp(a) was not associated with the primary outcome, coronary events (P=0.15, Model 1; P=0.09, Model 2). Total CHD events (CHD death, nonfatal MI, unstable angina, revascularization) showed a significant trend with biomarker concentration (P=0.02, Model 1; P=0.03, Model 2) owing to subjects with the highest levels (table). There was no association with stroke or total mortality.

Conclusions: In contrast to the relatively consistent predictive strength of Lp(a) for future CHD events in subjects without prior clinical disease, our findings suggest a much weaker influence of Lp(a) among patients with pre-existing stable CHD.

Hs-CRP, PC-PLC and MCP-1 as independent predictors of cardiac events in patients with acute coronary syndrome

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Background: The purpose of this study is to investigate the predictive value of high-sensitive C-reactive protein (hs-CRP), secretory phospholipase A2 (sPLA2), phospholipidhydrolyse-specific phospholipase C (PC-PLC), soluble CD40 ligand (sCD40L), interleukin-6 (IL-6), myeloperoxidase (MPO) and monocye chemoattractant protein-1 (MCP-1) to cardiac events in patients with acute coronary syndrome (ACS).

Methods: We enrolled 337 patients with ACS in this study. The peripheral concentrations of hs-CRP, sPLA2, sCD40L, IL-6, MPO and MCP-1 were
assayed. Each patient underwent a continuous follow-up of one time every 6 months. The main end point included relapsed unstable angina pectoris, myocardial infarction, sudden cardiac death and coronary revascularization. Cox proportion risk model was used to evaluate the predictive power of conventional cardiac risk factors and inflammation biomarkers to cardiac events. 

Results: The average follow-up period was 26 months. There were 36 censored patients. The median follow-up time was 22 months. The primary end point was clinical outcome. Age, smoking, hypertension and diabetes possessed predictive power to cardiac events (hazard ratio: 1.04, 2.75, 2.44, 2.09, respectively, all p < 0.05). Cox-CP, PC-PLC and MCP-1 could independently predict cardiac events beyond conventional cardiac risk factors in patients with ACS (hazard ratio: 1.21, 1.02 and 2.04, respectively). Cox-CP above 3 pg/ml, PC-PLC above 84.9 mU/ml and MCP-1 above 101.2 pg/ml could significantly increase the cumulative hazard for cardiac events (p < 0.05).

Conclusion: Cox-CP, PC-PLC and MCP-1 possess independent predictive value to cardiac events beyond conventional cardiac risk factors in patients with acute coronary syndrome.

Predictive value of neutrophil to lymphocyte ratio in clinical outcomes of non-ST elevation myocardial infarction and unstable angina pectoris: 3-years follow-up

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Background: Neutrophil to lymphocyte (NLR) is the strongest white blood cell predictor of adverse outcomes for stable coronary artery disease and mortality in patients presenting with ST-segment elevation myocardial infarction. We sought to determine the prognostic value of NLR in non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).

Methods: A total of 368 (mean age 59.22±11.93; 234 males, 74 females) patients with NSTEMI and UAP were prospectively evaluated. Admission NLR was measured as part of the automated complete blood count. The study population was formed at the two tertiary hospitals based on admission NLR values. A high NLR (n=110) was defined as a value in the third tertile (≥3.04), and a low NLR (n=206) was defined as a value in the lower two tertiles (<3.04). Patients were followed for clinical outcomes for up to 3-years after discharge.

Results: Kaplan-Meier survival analysis showed 3-years mortality rate of 21.6% in patients with high NLR versus 3% in low NLR group (p<0.001). In a receiver operating characteristic curve analysis, a NLR value of 3.4 ± 1.27 as an effective cut-point in NSTEMI and UAP of 3-years cardiovascular mortality (area under curve=0.86, 95% confidence interval 0.8 to 0.92). A NLR value of 3.04 identified as an effective cut-point in NSTEMI and UAP of 3-years cardiovascular mortality (area under curve=0.86, 95% confidence interval 0.8 to 0.92).

Conclusion: Admission NLR is strongly, and independent predictor of 3-years cardiovascular mortality.

The farnesoid X receptor -1G>T polymorphism is associated with the lipid response to rosuvastatin in Chinese patients with hyperlipidaemia

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Purpose: Drug transporters play an important role in statin disposition and efficacy. The bile-acid-activated nuclear receptor farnesoid X receptor (FXR) regulates multiple drug transporters involved in statin disposition in addition to maintaining hepatic bile acid, glucose and lipoprotein homeostasis. This study examined whether a functional single nucleotide polymorphism (SNP) in FXR (-1G>T) influences the lipid-lowering effect of rosuvastatin.

Methods: In a total of 385 Chinese patients with hyperlipidaemia including 166 with familial hypercholesterolaemia who had been treated with rosuvastatin 10 mg daily for at least 4 weeks, the associations between the FXR -1G>T SNP and lipid responses to rosuvastatin were analyzed. Of these patients, 314 had GG genotype, 68 were heterozygous and 3 were homozygous for the T variant allele.

The frequency of the T variant allele was 9.9% and the genotype distribution was in Hardy-Weinberg equilibrium (P=0.05).

Results: The FXR -1G>T SNP was significantly associated with LDL-C and total cholesterol response to rosuvastatin. The three subjects homozygous for TT appeared to have the greatest LDL-C response to rosuvastatin, whereas the heterozygous had intermediate responses which were significantly different from those in homozygotes for the wild-type allele (t=-2.047, P=1.010 vs. 1.010). The genotype distribution in Hardy-Weinberg equilibrium (P=0.05).

Results: The PXR -1G>T SNP was significantly associated with LDL-C and total cholesterol response to rosuvastatin. The three subjects homozygous for TT appeared to have the greatest LDL-C response to rosuvastatin, whereas the heterozygous had intermediate responses which were significantly different from those in homozygotes for the wild-type allele: 62.4±7.1% vs. 55.1±6.0%, P=0.008, and 52.6±6.0% vs. 32.6±5.0%, P=0.005.

Conclusions: C-IMT and C-plaques as well as a pathological LAD velocity were the most predictive parameters, building a significant additional diagnostic value for the prediction of CAD. This integrated ultrasound application is a promising noninvasive assessment of preclinical atherosclerosis.

Do changes in HDL-C after increasing the dose of atorvastatin have prognostic significance?

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Purpose: High-density lipoprotein cholesterol (HDL-C) levels are predictive of major cardiovascular events (MCEs). Whether on-treatment changes in HDL-C related to outcomes has not been well defined.

Methods: In the Treating to New Targets (TNT) trial, 10,001 patients with stable coronary disease were randomized to 10 or 80 mg/day of atorvastatin and followed for a mean of 4.9 years. Mean low-density lipoprotein cholesterol (LDL-C) levels during follow-up was 101 mg/dL (2.6 mmol/L) in the 10-mg arm and 77 mg/dL (2.0 mmol/L) in the 80-mg arm. This difference was associated with a 22% relative risk reduction in MCEs (P=0.0002). We have previously shown that on-treatment HDL-C levels in TNT are a strong predictor of MCEs (NEJM 2007;357:1301). In this new post-hoc analysis of TNT data, we examined the relation of HDL-C changes within the first 3 months of atorvastatin therapy.
and subsequent MCEs using Cox proportional hazards regression. For this analysis, we excluded 236 patients with either incomplete data or an event before the 3-month visit.

Results: From baseline (after an 8-week run-in on 10 mg of atorvastatin) to the next visit at 3 months, HDL-C levels increased from 47.16±10.8 mg/dL (1.22±0.28 mmol/L; mean±SD) to 47.49±11.0 mg/dL (1.23±0.28 mmol/L) in the ticagrelor group, and decreased from 47.47±11.1 mg/dL (1.23±0.29 mmol/L) to 47.01±11.3 mg/dL (1.22±0.29 mmol/L) in the group that had been increased to 80 mg atorvastatin at baseline (P=0.001 for the change difference between groups). Patients were divided into quintiles of HDL-C change, ranging in the 80-mg arm from -7.75±3.8 mg/dL (±0.20±0.11 mmol/L) to Q1 to +7.75±4.1 mg/dL (±0.20±0.11 mmol/L) in Q5. Change in HDL-C was not predictive of subsequent MCEs in the entire group; the adjusted hazard ratio per 1-mg/dL (0.03 mmol/L) increase in HDL-C was 0.997 (95% confidence interval: 0.984–1.010, P=0.65). The rate of MCEs was 9.6% in Q1 and 9.6% in Q5. Changes in HDL-C were similarly not predictive in the 10-mg and 80-mg groups when examined separately. At visits after 3 months, approximately 70% of patients did not remain in the same quintile of HDL-C change as at 3 months. In comparing categories from 3 months to later visits, both the weighted kappa statistic and Kendall's T alpha-b coefficient were <0.30, indicating marginal concordance.

Conclusions: Although on-treatment HDL-C levels are strong predictors of MCEs, change in HDL-C at 3 months was not predictive. This may be due to subsequent variation in HDL-C levels despite a constant atorvastatin dose.

Serial cystatin C measurements and changes in glomerular filtration rate as predictors for death or myocardial infarction in ACS patients

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Purpose: During treatment of acute coronary syndrome (ACS) with ticagrelor there is a transient slight increase in renal markers as compared to clopidogrel. We investigated if the increase in renal markers corresponded to changes in outcome with an improved risk prediction in discharge samples.

Methods: In the Platelet inhibition and patient Outcomes trial (PLATO) plasma cystatin C concentration were determined from samples taken within 24 hours of symptom onset (baseline) and at discharge. The cystatin C concentrations were log-transformed and evaluated in a multivariable Cox regression analysis including: background characteristics, previous cardiovascular disease, coronary interventions and established risk factors as well as log-transformed biomarkers NT-proBNP and troponin I. The primary endpoint was in-hospital cardiovascular death or myocardial infarction. C-statistics and Integrated Discrimination Improvement (IDI) were obtained to evaluate the incremental predictive ability of cystatin C.

Results: Cystatin C concentrations were available in 2133 ticagrelor- and 2162 clopidogrel-treated patients with mean concentrations at baseline (0.86 mg/L and 0.86 mg/L) and discharge (1.01 mg/L and 0.97 mg/L; p<0.0005) respectively. Median change and interquartile intervals for ticagrelor and clopidogrel treated patients were 0.12 (0.02-0.27) mg/L and 0.10 (0.04-0.25) mg/L respectively. Multivariable c-statistics and the relative IDI of the primary outcome after hospitalisation for the cystatin C concentration were 0.60 and 5.2% at baseline and 0.684 and 4.5% at discharge respectively (n=4034).

Conclusions: Cystatin C concentrations increase in the majority of patients with ACS during hospitalization. The discharge cystatin C concentration does not improve risk prediction. The initial transient increase in cystatin C concentrations in ticagrelor-compared to clopidogrel-treated patients is not associated with any difference in long-term outcome.

The value of pretest risk stratification before coronary computed tomographic angiography and myocardial perfusion imaging

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Purpose: Coronary computed tomographic angiography (CCTA) and myocardial perfusion imaging (MPI) are established tests for detecting coronary artery stenosis and ischemia, respectively, in coronary artery disease (CAD). However, the value of pretest risk stratification prior to imaging is not well established. Our aim was to investigate the value of the Duke Risk Model and the Duke Treadmill Score as pre-tests for assessing significant CAD as determined by CCTA and MPI, respectively.

Methods: We studied 197 Asian patients with suspected ischemia who underwent both CCTA and SPECT MPI. We applied our dataset to (i) the Duke Risk Model probability for significant CAD, calculated from a physician’s initial assessment of patient’s history, physical examination and ECG, and (ii) to the Duke Treadmill Score calculated as (exercise duration – 5 × maximal ST-segment depression) – 4 × treadmill angina index). The treadmill score was applied to the exercise stress group, and decreased MPI. Statistical analysis used logistic regression with calculation of area (AUC) under the Receiver Operating Characteristic (ROC) curve.

Results: Our analysis demonstrated that the Duke Risk Model (DRM) was a statistically significant predictor of severe coronary stenosis (>70%) as measured by CCTA (AUC=0.778, p < 0.0001), and ischemia as determined by MPI (AUC=0.611, p < 0.0004). At the DRM cutoff of 0.20, the NPV for ischemia was 90% (prevalence=24%), with 26% of the population exhibiting a DRM risk >0.20. At the DRM cutoff of 0.12, the NPV for ischemia was 90% (prevalence=24%), with 26% of the population exhibiting a DRM risk >0.12. The Duke Treadmill Score calculated as [exercise duration – (5 × rate of change)] – 4 × treadmill angina index). The treadmill score was applied to the exercise stress group, and decreased MPI. Statistical analysis used logistic regression with calculation of area (AUC) under the Receiver Operating Characteristic (ROC) curve.

Conclusions: Our analysis demonstrated that the Duke Risk Model calculated from a physician’s initial assessment of patient’s history, physical examination and ECG may be useful as a pretest selection tool to predict ischemia as determined by MPI and severe coronary stenosis (>70%) as determined by CCTA. In contrast, we found that the Duke Treadmill Score may be useful for predicting severe coronary stenosis, but not presence of ischemia. In our population, Duke Risk Model cutoffs of 0.20 and 0.12 achieved negative predictive values of 100% and 90% in excluding severe stenosis and ischemia, respectively. Our findings need to be assessed prospectively.

ARTERIAL STIFFNESS AND PULSE WAVE VELOCITY

Relationship between arterial stiffness, cardiac baroreflex sensitivity and blood pressure variability in normotensive healthy adults

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Purpose: An increased arterial stiffness has been proposed as a likely mechanism for a reduced cardiac baroreflex sensitivity (BRS) and the associated increases in 24-h blood pressure (BP) variability. Aim of the present study was to explore this issue in a group of 90 normotensive (Systolic BP 107±19 mmHg, diastolic BP 66.7±7.7 mmHg), non-obese, healthy adults (mean age 48±10 yrs, 50% F) from the city of Medellín, Colombia.

Methods: BRS was assessed by computer analysis of 10 min beat-to-beat BP and ECG recordings obtained while in resting supine. The linear regression slope of spontaneous concomitant increases or decreases in systolic (SBP) and RR interval (SRBP+RR and SRBPIRIR slope respectively) were calculated, averaged and expressed as total slope of BRS (mmHg/mmHg). Simultaneous recordings of pulse wave velocity (PWV) were obtained by means of a previously validated oscillometric device for ambulatory BP monitoring with inbuilt transfer-function like method, and pulse wave velocity (PWV, m/s) and other indices of arterial stiffness were calculated. Pulse wave velocity was assessed separately for systolic and diastolic (D) BP as 24 h standard deviation (SD), weighted 24h SD (wSD), daytime and night-time SD from 24h ABPM.

Results: In multiple linear regression analysis arterial stiffness (as assessed through PWV), had the strongest effect on BRS variation (beta=−0.49, p < 0.0001), followed by HR and male sex. No significant effect was observed for age or MAP on BRS in this selected cohort (See Table). A similar independent analysis showed a significant inverse relationship between BRS and daytime SBP SD (beta=−0.23, p=0.039).

Predictors of cardiac BRS

Variable (means±SD) Regression Coefficient 95% CI Beta Coefficient P value RT

PWV (12±1.5 m/s) −3.619 −5.6, −2.2 −0.503 −0.0001 0.25
HR (94±21.6 bpm) −0.436 −0.6, −0.2 −0.344 −0.0001 0.14
Sex (male) −4.373 −8.4, −0.3 −0.212 0.029 0.04
Age (48±11 yrs) −0.7, −0.3 −0.187 0.047
MAP (79±18.8 mmHg) −0.019 −0.4, 0.2 −0.077 0.759 −
R Squared for the model including only significant variables (PWV, sex, HR) 0.342

Conclusion: Our findings suggest that in normotensive otherwise healthy adults, decreased BRS and, indirectly, the associated increased day-time BPV might be largely explained by an increased arterial stiffness, independently of age and BP levels.
Relationship between arterial stiffness and circadian pattern of blood pressure


A total of 419 patients (66.8±16.4 years, 80.4% men) were enrolled in this study. All patients received measurements of supine brachial and carotid systolic (SBP) and diastolic (DBP) pressures, carotid-femoral pulse wave velocity (cf-PWV), carotid augmentation index (cAI), carotid augmented pressure (cAP), and reflected wave amplitude (Pb) from a decomposed carotid pressure wave. Orthostatic blood pressures were measured after a 3-minute standing. Orthostatic hypotension was defined as a reduction of >10% in the DBP as isolated diastolic non-dipping and reduction of >10% in both SBP and DBP as diastolic and systolic non-dipping. For adjustment of age, population was divided into 2 groups: old group (≥55 years old, 213, 107 males), young group (55 years-old, 560, 234 males).

Results: old vs. young group, the mean BP of 24-hour ABPM, gender and body mass index were not statistically different. Multivariate analysis showed that isolated diastolic non-dipping was correlated with arterial stiffness expressed as augmentation index at rest and during exercise (p=0.009, 0.018 and 0.011, respectively). No statistical difference among circadian BP patterns was demonstrated in old group.

Conclusion: In present study, the isolated diastolic non-dipper was closely related with arterial stiffness in patients with HTN and pre-HTN under 55 years old. Arterial stiffness might be closely related with the pattern of non-dipping in young patients with HTN and pre-HTN.

Wave reflection intensity but not arterial stiffness is a major determinant of postural hypotension


Purpose: Orthostatic hypotension (OH), represents an important cause of hospitalization and functional impairment. Vascular aging is considered a major predisposing factor for OH. Our aim was to investigate the relative importance of arterial stiffness and wave reflection in the determination of orthostatic hypotension.

Methods: A total of 419 patients (66.8±16.4 years, 80.4% men) were enrolled in this study. All patients received measurements of supine brachial and carotid systolic (SBP) and diastolic (DBP) pressures, carotid-femoral pulse wave velocity (cf-PWV), carotid augmentation index (cAI), carotid augmented pressure (cAP), and reflected wave amplitude (Pb) from a decomposed carotid pressure wave. Orthostatic blood pressures were measured after a 3-minute standing. Orthostatic hypotension was defined as a 20-mmHg fall in SBP or a 10-mmHg drop in DBP.

Results: 89 patients with OH were identified and compared to 360 patients without OH and with similar diagnoses and uses of BP/hypertensive medications. Patients with OH compared to controls were older and had higher serum creatinine (Cr) and lower hemoglobin (Hgb) levels, as well as higher brachial and carotid SBP and PP (p < 0.05). In addition, they also had higher cf-PWV, cAP and Pb. However, cAI and cAP were similar between the 2 groups. In multivariate analyses adjusting for age, Hgb and Cr levels, the significantly independent determinants of OH included supine brachial and carotid SBPs, cAP [odds ratio per 1-s.d. and 95% confidence interval: 1.37 (1.01-1.85), P<0.04], and Pb [1.59 (1.01-2.39), P<0.03], but not cAI or cf-PWV.

Conclusion: Our data indicate that wave reflection intensity, rather than arterial stiffness is a major determinant of postural hypotension.

Gender differences in pulse wave velocity in young healthy adults at rest and exercise - the wellheart study

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Background: Elderly women have increased aortic stiffness, measured by pulse wave velocity (PWV), and show little increase in PWV with pharmacological inotropic stress. The aim of this study was to examine gender-related differences in aortic stiffness at rest and during physiological exercise stress in young non-athletic subjects.

Methods and results: Eighteen healthy subjects without known cardiovascular disease (mean age 28 years; male=10, all non-smokers) underwent cardiovascular magnetic resonance (CMR) imaging at rest and supine bicycle exercise for cine and in-plane flow with high temporal resolution (Figure 1). At rest both genders demonstrated similar haemodynamic parameters and PWV. To achieve 85% of the age-predicted heart rate (APHR), men required significantly greater workload (p<0.00) and showed higher systolic blood pressure (BP, p<0.03) than women. Imaging at 60% APHR, sustained by hand-grip exercise, revealed an increase in stroke volume and cardiac index in men (p<0.05), whereas women showed no change in PWV (p=0.02), whereas women showed only a trend towards a difference (p=0.09).

Conclusions: In young healthy non-athletic males there is a greater increase in PWV and systolic BP than women. Our findings concord with previous observations in elderly populations during inotropic stress and inform on the gender differences in vascular performance with stress and ageing.

Factors influencing the increase of pulse wave velocity in a Portuguese population


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Pulse wave velocity (PWV) has emerged as a new marker of cardiovascular risk and currently is used as an index of arterial distensibility. Several factors have been associated with contradictory results with increasing PWV.

Objective: In this study we intend to evaluate whether there is any association between genetic, demographic, metabolic, nutritional and inflammatory markers with increase of PWV.

Methods: This study included 1195 participants with a mean age 50.6±7.5 years and 50% of them were male. We analyzed in the participants genetic polymorphisms; ACE I/D, AT1R A1166C, CYP11B2 C344T, ACE A202020I, ADI1 G460W, GNB3 C825T, ADR1i Arg389Gly, ADR1i R16G, SCNN1A (His173G), and AGT1235 MT. As well as demographic factors such as age and gender, other factors as systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate; biochemical factors as Homocysteine, Protein C high sensitivity and pathologies as obesity, diabetes, dyslipidemia and PWV. The PWV carotid-femoral was calculated using a computerized automatic registration (COMPILOR).

Regarding to the statistical analysis, we evaluated the relationship of each factor with PWV. A logistic regression model to determine which variables were associated significantly and independently to the increase of PWV was developed. Categorical variables are presented by their frequency. For data analysis we used chi-square test or Fisher’s exact probability, as appropriate. We calculated the odds ratio and the 95% confidence interval. The threshold of significance was p < 0.05. Data analysis was performed using the statistical software SPSS for Windows version 19.0.

Results: After logistic regression, variables that remained in the equation and influence the increase of PWV were age OR = 1.15 (1.11 to 1.18) p < 0.0001; gender OR = 2.98 (1.92 to 4.64) p < 0.0001; systolic blood pressure OR = 1.03 (1.01 to 1.04) p = 0.005; diastolic blood pressure OR = 1.06 (1.03 to 1.10) p < 0.0001; Heart Rate OR = 1.02 (1.00 - 1.04) p = 0.019; Homocysteine OR = 0.87
Endothelial dysfunction, pulse wave velocity and augmentation index are correlated in subjects with systemic arterial hypertension?


Direct evidence of a relationship between endothelial function and more definitive measures of arterial stiffness is studied in patients with cardiovascular disease and risk factors, but the relationship between endothelial function and Pulse Wave Velocity (PWV), the gold standard measure of stiffness, has been described partially. Aim of our study was to evaluate a positive correlation between results of two non-invasive methodologies: endothelial-dependent vasodilatation (FMD) by right brachial scanning validated procedure and PWV and Augmentation Index (AIx) by using a simple upper arm cuff and an analysis of the oscillometric pressure wave (Arteriograph), in subjects with recent diagnosis of systemic arterial hypertension compared with healthy young people.

Methods: We have studied 100 subjects, 50 healthy and 50 with a new diagnosis of systemic arterial hypertension without medications. All of the subjects were free of dyslipidemia, diabetes, previous cardiovascular event, arrhythmias, heart failure.

Clinical and hemodynamic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normotensives (n=50)</th>
<th>Hypertensives (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDF</td>
<td>36.7</td>
<td>9.4%</td>
</tr>
<tr>
<td>Gender, m/f</td>
<td>27/23</td>
<td>30/20</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.1</td>
<td>25.5</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
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<td>194.8</td>
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<tr>
<td>Triglyceride, mg/dl</td>
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<td>117.1</td>
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<tr>
<td>Glucose, mg/dl</td>
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<td>81.1</td>
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<tr>
<td>Peripheral SBP, mmHg</td>
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<tr>
<td>Peripheral DBP, mmHg</td>
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<td>95.5</td>
</tr>
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<td>Central SBP, mmHg</td>
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<tr>
<td>MAP, mmHg</td>
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<td>HRL, bpm</td>
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<tr>
<td>Augmentation Index, %</td>
<td>22.2%</td>
<td>27.7%</td>
</tr>
<tr>
<td>PWV, %</td>
<td>8.7</td>
<td>11.5</td>
</tr>
<tr>
<td>MDF</td>
<td>21.8%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

Results in the table: Robust statistical correlation was found among different early preclinical parameters, FMD differentiates better the two population.

Stage 1 hypertensive subjects may improve small artery compliance practising regular physical activity

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Purpose: The aim of this study was to investigate the effect of regular physical activity on small artery compliance (C) in stage 1 hypertensive subjects.

Methods: We studied 365 never treated stage 1 hypertensive subjects (mean age=38 yrs, blood pressure=145±92 mmHg, % of women=28%). Subjects were divided into 2 groups: sedentary (n=261) and physically active (n=104). We measured C with a tonometer sensor array (HDI-CR200 device) by obtaining radial arterial pulse waves. We repeated C measurements in 152 subjects (sedinetary n=110, physically active n=42) after 6 years of follow-up.

Results: Resting heart rate (HR) was lower in physically active subjects (70±10 vs 76±10 bpm, p<0.001). The lower was the heart rate, the higher was the compliance (p<0.0008). In an ANCOVA analysis, C (adjusted for age, gender, BMI, lifestyle factors, parental hypertension and blood pressure) was greater in the physically active group compared to the sedentary group (7.2±0.2 vs 6.4±0.1 mmHg/m² x 10, p<0.004). When total cholesterol, triglycerides and glucose were included in the analysis, the association remained highly significant (p<0.001). After 6 years, we repeated C measurements and C remained unchanged in sedentary subjects (n=110) but slightly increased in physically active subjects (n=42). In a 2-way repeated-measure ANCOVA, taking into account also antihypertensive therapy (n=82), physical activity had a significant effect on C (p<0.001) especially in women (p=0.024).

Conclusions: Young-to-middle age stage 1 hypertensive subjects performing regular physical activity have a more elevated small artery compliance compared to their sedentary peers. The relationship is independent from the effects of exercise on HR, BMI, blood pressure and metabolic parameters, persist over time and is stronger in women than in men.

The influence of change of autonomic balance by reactive hyperemia maneuver on conduit arterial and resistant arterial endothelial function tests

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Background: While the maneuver of reactive hyperemia in the assessment of endothelial function is thought to affect sympathetic/parsympathetic nerve activities, the details of the effects of such change of autonomic activities on endothelial function have not been clarified. This study was conducted to examine the influence of the changes of sympathetic/parsympathetic nerve activities during the maneuver of reactive hyperemia on conduit arterial and resistant arterial endothelial function.

Methods: In 36 subjects with hypertension (age 62±9 years old), flow-mediated vasodilatation of brachial artery assessed by ultrasound examination (FMD) (conduit arterial function) and peripheral reactive hyperemia assessed by laser Doppler (LasDOP) (resistant arterial endothelial function) were conducted. Reactive hyperemia was induced by the 5 minutes’ clamp of forearm blood flow. Heart rate was continuously monitored throughout this reactive hyperemia, and high frequency domain (HF), low frequency domain (LF) and their ratio (LF/HF) were obtained in every 5 minutes’ interval. Then, percent change of HF (perHF) (HF value after the hyperemia – HF value before the hyperemia), percent change of LF (perLF), and percent change of LF/HF (perLF/HF) were calculated.

Results: FMD had a significant correlation with neither perHF (r=0.09, p=0.59), nor perLF (r=0.06, p=0.74). On the other hand, LasDOP had significant correlations with perHF (r=0.36, p=0.05) and perLFH (r=0.35, p=0.05), but not with perLFH (r=-0.07, p=0.69).

Conclusion: The change of sympathetic/parsympathetic nerve activities caused by the maneuver of reactive hyperemia affect resistant arterial endothelial function, but not conduit arterial endothelial function. This influence should be taken into account for interpretation of data of resistant arterial endothelial function.

Advanced oxidation protein products’ level in serum is positively correlated with intima-media thickness in carotid arteries

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Objective: Oxidative stress raises considerable interest in pathophysiology of cardiovascular disease. The objective of the study was to evaluate oxidative stress markers (dimethylated L-arginine (ADMA), symmetric dimethyl-L-arginine (SDMA), oxidised low density lipoproteins (ox-LDL) and advanced oxidation protein products (AOPPs)) in essential hypertension and search for possible relations between oxidative stress markers and arterial remodeling assessed by intima-media thickness (IMT).

Design and Methods: We recruited 50 families at the Outpatient Hypertension Clinic (hypertensive index person with at least 3 first-degree relatives, at least one relative hypertensive) altogether 217 subjects; male 114 and 103 female. Blood pressure was measures in the morning.

Cases (2 x 3 consecutive measurements). Hypertension was defined as use of antihypertensive drugs and/or blood pressure >140/90 mmHg. In every subject carotid intima-media thickness (IMT) was measured with Vivid GE 7 device. For the measurement of oxidative stress markers we collected fasting blood samples in the morning.

Results: The study group included 155 hypertensive subjects. Hypertensive and normotensive subjects differed in terms of age, blood pressure and carotid IMT (respectively 49±15.2 vs 37±14.7 years, p<0.001; 144±22/185±11 mmHg vs 127±5±11/79±8 mmHg, p<0.001 for both; 0.63±0.16 vs 0.53±0.13 mm, p<0.001). We found a significant positive correlation between AOPP and IMT (r=0.16, p=0.024) in our study group. In multivariate analyses carotid IMT was related with AOPP (r=0.013, p=0.037) after adjustment for, BMI, uric acid, eGFR, smoking status and pulse pressure.

Conclusion: The observed significant relation between advanced oxidation protein products and intima-media thickness in carotid arteries in hypertensive subjects might suggest role of the oxidative stress in the pathogenesis of arterial wall remodeling in the natural history of hypertension.

Arterial stiffness and pulse wave velocity / Aorta and carotid arteries

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P890 Analysis of aortic characteristic impedance in the time domain: validation using computer simulation

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Purpose: In arterial windkessel (WK) models, characteristic impedance (Zc) denotes the resistance of the proximal aorta and is a key determinant of LV afterload. Zc is commonly approximated as the ratio between pressure (P) to flow (Q) into the aortic root in the interval 10 – 30 ms after aortic valve opening, however few comparative studies exist to support this choice of interval. We wished to identify the optimal time interval for Zc estimation.

Methods: 60 recordings of LV outflow by pulsed-wave Doppler were digitised using custom software and entered into computer simulation in the frequency domain after discrete Fourier transform (DFT). Each flow was coupled to 10 simulated 4-element WK arterial trees, producing n=600 sets of P and Q. Randomly chosen values were used for: stroke volume (50 – 90 mL), heart rate (55 – 85 bpm), blood inertia (0 – 0.025 mmHg.s/mL), arterial compliance (0.8 – 2.0 mL/mmHg) and systemic vascular resistance (1.0 – 2.5 mmHg.s/mL).

Results: When fitting a WK model to measured aortic P and Q, Zc should be estimated in the interval 3 – 12 ms after aortic valve opening. Zc is a key determinant of cardiac afterload and this finding is of importance for haemodynamic parameter estimation.

Figure. 1. Difference between true vs. estimated Zc.

Conclusions: When fitting a WK model to measured aortic P and Q, Zc should be estimated in the interval 3 – 12 ms after aortic valve opening. Zc is a key determinant of cardiac afterload and this finding is of importance for haemodynamic parameter estimation.

P891 Impact of leg blood pressure and body posture changes on aortic root diameter

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Purposes: Increased aortic root diameter (AoRD) is associated with higher cardiovascular mortality. The mechanical load imposed by the systemic circulation is considered a determinant of aortic remodeling. However, casual brachial blood pressure (BP) measurements exhibit low or no ability to predict AoRD. BP levels are not constant along the arterial tree. This study evaluated brachial and leg BP levels in supine and orthostatic postures and investigated the relationship between these measurements and AoRD.

Methods: Two samples were enrolled. Sample A included 130 nonsmoker, non-diabetic, normotensive and nonolimpemic. Sample B comprised 197 subjects with at least one of the following cardiovascular risk factors: smoking, hypertension or diabetes mellitus. They were evaluated by clinical history, anthropometry, analysis of metabolic parameters, echocardiography, and had their BP measured in the arm and calf in supine and orthostatic positions. All values were expressed as mean±standard error. Unpaired t-test was used to compare continuous variables. A p-value <0.05 was considered significant.

Results: Among all BP measurements, leg supine SBP and leg orthostatic diastolic BP (DBP) exhibited the highest correlation coefficients with AoRD in sample A (r=0.36, p<0.001) and sample B (r=0.30, p<0.01), respectively. Among brachial BP measurements, orthostatic DBP and supine SBP showed the strongest correlation with AoRD in sample A (r=0.46, p<0.01) and sample B (r=0.26, p<0.01), respectively. Further variables that presented significant univariate correlation with AoRD were then included in linear regression models.

Conclusions: In hypertensive population, brachial SBP and leg orthostatic DBP are associated with AoRD. Among BP measurements, leg orthostatic DBP and supine SBP showed the strongest correlation with AoRD in sample A and sample B, respectively. Further variables that presented significant univariate correlation with AoRD were then included in linear regression models. In sample A, leg supine SBP (r=0.36, p<0.001), LVM index (r=0.20, p<0.01) and body surface area (r=0.39, p<0.01) were associated with AoRD in a model that still included age, gender and brachial orthostatic DBP as independent variables. In sample B, leg orthostatic DBP (r=0.22, p<0.01), LVM index (r=0.12, p<0.01) and body surface area (r=0.37, p<0.01) were associated with AoRD in a model adjusted for age, gender, diabetes mellitus, hypertension, brachial supine SBP and triglycerides.

Conclusion: This study demonstrated that leg BP was associated with AoRD in
individuals with or without cardiovascular risk factors and body posture played a role in this relationship. These findings suggest that leg BP evaluation might be an alternative approach in order to predict AoRD.

### Ascending aortic dilatation: a new landmark for orthostatic hypotension

**Method:** We followed up 1128 essential hypertensives (mean age 56.1 years, 587 males, office blood pressure (BP) = 144/91 mmHg) free of cardiovascular disease for a mean period of 6 years. All subjects had at least one annual visit and had undergone complete echocardiographic study for estimation of LVMI and blood sampling for assessment of metabolic profile. Arterial stiffness was evaluated based on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP) and the distribution of PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Moreover, LV hypertrophy (LHV) was defined as LVMI ≥ 125 g/m² in males and LVMI ≥ 110 g/m² in females, while CAD was defined as the history of myocardial infarction or significant coronary artery stenosis revealed by angiography or coronary revascularization procedure. 

**Results:** The incidence of CAD over the follow-up period was 2.83%. Hypertensives who developed CAD (n=32) compared to those without CAD at follow-up (n=1096) had at baseline higher waist circumference (101.6 ± 11.1 vs 97.2 ± 11.9 cm, p=0.033), LVMI (123.7 ± 22.9 vs 107.2 ± 24.2 g/m², p=0.014), prevalence of LVH (46% vs 25%, p=0.027) and prevalence of high PWV levels (69% vs 48%, p=0.019). No difference was observed between hypertensives with CAD and those without CAD with respect to office BP serum creatinine and lipid levels (p=NS for all). By univariate Cox regression analysis it was revealed that high baseline PWV levels predicted CAD (hazard ratio=2.657, p=0.008). However, in multivariate Cox regression model, waist circumference (hazard ratio=1.016, p=0.04) and LVMI (hazard ratio=1.023, p=0.018) but not high baseline PWV turned out to be independent predictors of CAD.

**Conclusion:** In essential hypertensives patients LVMI predicts future development of CAD, whereas high baseline PWV exhibits no independent prognostic value. These findings support that LVMI constitutes a superior prognosticator of events than PWV and its estimation is essential in order to improve overall risk stratification in hypertension.

**References:**


### Leg blood pressure measured in orthostatic posture is a predictor of left ventricular mass in normotensive subjects

**Method:** From 2008 to 2010, we evaluated 115 healthy Japanese men and women aged 20-70 years, for whom we could obtain all available data. We excluded 3 subjects with stroke, 2 with heart failure, and 3 with atrial fibrillation. From the remaining 110 subjects, we obtained leg blood pressure using the oscillometric method (Complior SP) and the distribution of PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Moreover, LV hypertrophy (LHV) was defined as LVMI ≥ 125 g/m² in males and LVMI ≥ 110 g/m² in females, while CAD was defined as the history of myocardial infarction or significant coronary artery stenosis revealed by angiography or coronary revascularization procedure. These findings support that LVMI constitutes a superior prognosticator of events than PWV and its estimation is essential in order to improve overall risk stratification in hypertension.

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**References:**


### Pulse wave velocity versus left ventricular mass as determinants of Coronary Artery Disease in patients with essential hypertension: data from a Greek 6-year-follow-up study

**Method:** We followed up 1128 essential hypertensives (mean age 56.1 years, 587 males, office blood pressure (BP) = 144/91 mmHg) free of cardiovascular disease for a mean period of 6 years. All subjects had at least one annual visit and had undergone complete echocardiographic study for estimation of LVMI and blood sampling for assessment of metabolic profile. Arterial stiffness was evaluated based on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP) and the distribution of PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Moreover, LV hypertrophy (LHV) was defined as LVMI ≥ 125 g/m² in males and LVMI ≥ 110 g/m² in females, while CAD was defined as the history of myocardial infarction or significant coronary artery stenosis revealed by angiography or coronary revascularization procedure. These findings support that LVMI constitutes a superior prognosticator of events than PWV and its estimation is essential in order to improve overall risk stratification in hypertension.

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**Conclusion:** In essential hypertensives patients LVMI predicts future development of CAD, whereas high baseline PWV exhibits no independent prognostic value. These findings support that LVMI constitutes a superior prognosticator of events than PWV and its estimation is essential in order to improve overall risk stratification in hypertension.

**References:**

Methods: We enrolled 371 hypertensive patients (236 men, 68±10 years) with diastolic dysfunction and preserved LV systolic function (ejection fraction > 50%) who had not achieved treatment goal with standard doses of angiotensin convert- ing enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). We changed ACEi or ARB to a combination of Losartan/HCTZ and followed patients for 24 weeks, and examine a change in septal mitral annular velocity during diastole (e') and the ratio of mitral inflow velocity to e' velocity (E/e') from the baseline to the end of follow-up. Patients were divided into quartiles of baseline PP.

Results: After 24-weeks-treatment of Losartan/HCTZ, the SBP, DBP and PP signifi- cantly decreased by 23.11 and 12 mmHg, respectively. The patient with higher PP are significantly older and had more comorbid disorders with higher SBP. The increase in e' velocity and decrease in E/e' ratio were greater in the highest PP quartiles (Figure 1), and correlated with the decrease in PP respectively (e': r= 0.25, p<0.0001, E/e': r=-0.23, p<0.0001).

Conclusions: Treatment with Losartan/HCTZ is associated with the improvement of LV systolic and diastolic function and relaxation in hypertensive patients with diastolic dysfunction and high PP.

Retinal vascular deterioration is accompanied by adverse cardiac remodeling in essential hypertension

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Purpose: In the setting of essential hypertension, scarce data exist re- garding the associations between retinal vascular alterations and cardiac remodel- ing process. We assessed the hypothesis that there might be a link between fundus vascular changes and echocardiographically derived parameters of car- diac maladaptation.

Methods: Our study population consisted of 229 stage I-II never treated essen- tial hypertensive subjects (aged 62±10 years, 120 female, office blood pressure 155/92 mmHg), free of clinically evident cardiovascular disease. All participants underwent routine blood test analysis, 24 hour ambulatory blood pressure moni- toring (ABPM), complete echocardiographic study and fundoscopy examination. The subjects were divided into five categories according to Scheie's fundus grad- ing system of severity (0, I, II, III, IV: normal, arteriolar narrowing, arteriovenous nipping, hemorrhages-exudates and papilloedema respectively).

Results: The five groups did not differ concerning age, sex, basic ABPM param- eters, as well as their metabolic profile (fasting glucose, serum lipids, uric acid). Deterioration of the retinal vascular category was associated with a statistically significant impairment of ejection fraction (63.2±2% vs 61.1±8% vs 60.3±2.2% vs 58.2±1.5% vs 56.1±2.4%, respectively, all p<0.01) accompanied by an in- crease in interventricular septum enddiastolic thickness (9.9±0.24 vs 10.0±0.28 vs 10.3±0.35 vs 10.4±0.40 vs 10.7±0.45 mm, respectively, p=0.013) and left atrial anteroposterior diameter (37.0±7.0 vs 39.1±1.1 vs 39.2±1.2 vs 41.0±0.31 vs 42.0±1.53 mm, p=0.029). On the contrary, the five categories did not differ re- garding left atrial volume (p=0.287), left atrial volume index (p=0.319) and posteri- or wall enddiastolic thickness (p=0.232).

Conclusions: In essential hypertensive patients, progressive escalation of fundus vascular damage is accompanied by commensurate left atrial and ventric- ular remodeling, as well as respective global impairment of left ventricular systolic function.

There is a parallel escalation between retinal vascular alterations and arterial stiffness in essential hypertension

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Purpose: The clinical and prognostic significance of hypertensive retinal changes, an established hypertension-related target organ damage remains con- troversial. We assessed the hypothesis that there is a relationship between retinal alterations and arterial stiffness, an index strongly correlated to increased cardio- vascular morbidity and mortality.

Methods: We examined 268 consecutive newly diagnosed, untreated, essen- tial hypertensives (aged=60±13 years, 151 female, office blood pressure=152/90 mmHg), without any history of cardiovascular disease or any other evident comor- bidity. Venous blood samples were taken for determination of RRI and all participants underwent ambulatory blood pressure monitoring (ABPM). All subjects underwent fundoscopy examination and were distributed to five groups according to Scheie’s grading system: Groups A, B, C, D and E, for Scheie’s scale 0, I, II, III and IV, respectively. Arterial stiffness was based on the evaluation of carotid to femoral pulse wave velocity (c-f PWV) by means of a computerized method (Compilor SP).

Results: The five groups (including 39, 87, 99, 35 and 8 subjects respectively) did not differ with regard to age, gender, ABPM parameters and their metabolic profile (fasting glucose, serum lipids, uric acid) as well. However, hypertensives of higher Scheie’s category exhibited significantly greater values of c-f PWV (8±1.3, 9.1±1.8, 9.4±2.1, 9.8±2 and 9.9±2.4 m/sec respectively, p<0.005). Notably, there was a statistically significant difference on pulse pressure among groups (54±mmHg, 60±mmHg, 63±mmHg, 65±mmHg and 67, respectively) (p<0.04), another surrogate marker of arterial stiffness. Multivariable regression analysis showed that age, fundus classification and systolic arterial pressure were independent determinants of c-f PWV.

Conclusions: In hypertensive subjects there is a progressive stiffening of the aorta in parallel to the evolution of the fundus lesions according to Scheie’s scale. A possible explanation derives from the fact that same pathophysiological pro- cesses, like wall remodeling or endothelium impairment occur in small and in large vessels in the setting of essential hypertension.

Association between eye vasculature alterations and renal damage in essential hypertensives with metabolic syndrome

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Purpose: In the ongoing debate about metabolic syndrome (MS), it is still unre- solved whether it is a marker or a mechanism. We sought to unravel the mystery of the interrelationships of the hypertensive fundus, a time honored target organ damage (TOD), especially in the setting of MS. We hypothesized that there might be an association between retinal alterations and the other parameters of target organ damage, such as renal dysfunction and inflammatory activation.

Methods: Our population consisted of 202 consecutive subjects with newly di- agnosed untreated stage I-II essential hypertension (aged 60±11 years, 122 female), without overt cardiovascular disease. All participants underwent fundoscopy examination and were classified according to Scheie’s grading system into 5 categories (Scheie’s scale I, II, III, IV, normal, arteriolar narrowing, ar- teriovenous nipping, hemorrhages - exudates and papilloedema respectively). Anthropometric parameters, as well as lipid profile, plasma glucose, high sensi- tivity C-reactive protein (hs-CRP) and serum creatinine levels were assessed. Renal function was classified according to the estimated glomerular filtration rate (GFR) calculated by the Cockroft-Gault formula. MS was identified according to the Third Report of the National Cholesterol Education Program Adult Treatment Panel. The subjects were divided in two groups regarding the absence (group A), or the presence of MS (Group B).

Results: Group B compared to group A had increased levels of uric acid and hs- CRP (5.5±0.33 vs 4.5±0.27 mg/dl and 2.9±0.18 vs 1.6±0.11 mg/dl respectively, all p<0.05) and significantly lower GFR (81±5 vs 96±6 ml/min, p<0.05). The two groups did not differ regarding age, sex and office blood pressure. In each of the five Scheie’s categories there was a significant divergence, within the categories, in the constellation of MS components, presenting a prevalence of 6%, 14%, 47%, 71% and 62%, respectively (p<0.05).

Conclusions: The metabolic syndrome, although not an established patho- genetic entity, is associated with increased acceleration of the hypertensive retinal damage, kidney dysfunction and inflammatory activation.

Hypertensive patients with diabetes mellitus and normal arterial stiffness show an early increase in renal resistive index

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Purpose: Renal resistive index (RI) detected by Doppler ultrasound is influ- enced by intra- and extra-renal factors. Increased RI in patients with normal renal function detects tubulo-interstitial damage, which may be present before glomerular damage. Arterial wall stiffness evaluated by estimation of pulse wave velocity (PWV) is one of the most significant extra-renal factors. Both RI and PWV are increased in patients with hypertension and diabetes mellitus (DM). However the role of intra- and extra-renal factors in determining the RI increase is still under debate. This study was aimed to evaluate whether high RI values of
patients with hypertension and DM reflect tubulo-interstitial damage or increased arterial stiffness.

Methods: We studied hypertensive patients between 28 and 75 years, in chronic angiographic treatment, with or without DM, with preserved renal function (creatinine clearance ≥60 ml/min). RRI (peak systolic velocity – end-diastolic velocity/peak systolic velocity) was calculated by the analysis of the Doppler flow obtained at renal interlobar arteries and considered pathologic when ≥0.70.

Results: We evaluated 34 patients (57±10 years, 22 M/12 F). Patients with DM (n=18) were older (63±8 vs 59±9 years, p=0.001) and had significantly higher RRI values (0.70±0.4 vs 0.65±0.06, p=0.031) and prevalence of pathologic RRI (61 vs 13%, p=0.05) compared with patients without DM. There was no significant difference in PWV values between hypertensive patients with or without DM (7.8±1.7 vs 7.8±1.3 m/sec; p=0.95). DM resulted a significant independent predictor for pathologic RRI even after adjustment for age (O.R. 8.06; IC 95% 1.03-62.78; p=0.046) and PWV (O.R. 11.09; IC 95% 1.90-64.86; p=0.008).

Conclusions: In our hypertensive patients with DM, increased RRI values may reflect a reduction in intra-renal compliance due tubulo-interstitial damage, rather than an increase in systemic arterial stiffness.

Incidence of renal artery stenosis and its related factors of cardiac ultrasonographic findings in hypertensive patients

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Purpose: The incidence of systemic atherosclerotic diseases has increased in patients with hypertension. Renal artery stenosis (RAS) could be a cause or an effect of this extension. The aim of this study was to define the incidence of RAS and its related factors of cardiac ultrasonographic findings in hypertensive patients.

Methods: When cardiac ultrasonographic examination was performed in consecutive 974 hypertensive patients (male/female 578/396, mean age 68 years) from December 2009 to June 2011, peak systolic velocity (PSV) of renal artery was examined at the same time. The criteria for RAS was >180 m/sec in PSV. We compared the presence or absence of RAS with indices obtained by cardiac ultrasonographic examination.

Results: Compared with the patients without RAS (n=929, male/female 545/384), the patients with RAS (n=45, male/female 33/12, 46%) were significantly old (p=0.017) and the ratio of male to female was significantly high (p=0.036). In patients with RAS, left ventricular mass (LVM) was significantly large in both males (p=0.047) and females (p=0.032) compared with those without RAS. In hypertensive patients with <65 years, the incidence of RAS was low (2.4%), but LVM was significantly large compared with those with ≥75 years (p=0.019), although the ratio of male to female did not differ in these groups. There was no difference in LVM between <75-year patients with and without RAS.

Conclusions: In younger hypertensive patients, RAS was associated with larger LVM, indicating the relation with RAS and the severity of hypertension. In contrast, in older hypertensive patients, no association was observed between RAS and LVM, possibly indicating the gradual progression of RAS without relating to the severity of hypertension.

STEMI: EPIDEMIOLOGY CONSIDERATIONS AND ELECTROCARDIOGRAM FINDINGS

Retrospective audit demonstrating that national guidelines should be applied with confidence in the diagnosis of rapid access chest pain clinic (RACPC) patients in the UK: a single centre experience

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Purpose: Patients presenting to Rapid Access Chest Pain Clinic (RACPC) patients present with atypical symptoms, making diagnosis difficult based on clinical judgment alone. National Institute of Clinical Excellence (NICE) guideline recommends estimating the likelihood of having coronary artery disease (CA) were performed in total, n=98 were NICE-recommended of which n=57 (58.2%) was subsequently reported to have had CAD, confirming NICE statistics. Disparities were found in n=17 in low-risk cohort which received invasive angiography instead of CT, where n=12 were found with no CAD. Overall performance improved compared to previous findings: 2.5% increase of CS from 0, and consistent improvements in the rest of the categories.

Conclusion: Most patients presented with investigations but only a minority met the criteria according to NICE recommendations. Clinical judgements are less reliable compared to Duke score on indicating first-line investigations. CT calcium scoring is a valuable diagnostic tool in excluding significant CAD in low-risk patients. Within appropriately performed coronary angiographies, disease rate matched that stated in NICE guidelines.

Effect of smoking on angiographic results and long term clinical outcomes in patients treated with primary angioplasty

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Purpose: We sought to investigate the effect of active smoking on procedural success, short and long-term clinical outcomes in patients with ST elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (p-PCI).

Methods: In a retrospective design, we evaluated 2007 patients treated with p-PCI for STEMI (between January 2006 – January 2008). The patients were divided into two groups as active smokers (n=1023) and non-smokers (n=972).

Results: Smokers were younger and comorbidities such as diabetes mellitus, hypertension, anemia were less frequent in this group. Postprocedural final TIMI grade 3 flow (91.2% vs 86.9%, p=0.022) and myocardial blush grade 3 (48.9% vs 39.5%, p<0.001) were more common in the active smokers. While in-hospital mortality rate (1.6% vs 6.7%, p<0.001) was significantly lower in the smokers, there was no difference between the groups with respect to the incidences of reinfection and stent thrombosis at short-term follow-up. At long-term follow-up (median 40 months), stent thrombosis (3.4% vs 1.7%, p=0.022) and reintervention (9.3% vs 6.7%, p=0.047) were significantly more common in the smokers. However, there was no difference between the groups with respect to the long-term mortality rates (7.6% vs 7.4%, p=0.88).

Conclusion: Smoking is associated with better myocardial perfusion after p-PCI and lower mortality during early-in-hospital period. However, stent thrombosis and reinfection at long-term follow-up were more common in the smokers.

Age related mortality of primary PCI patients at a high volume UK cardiac centre

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Purpose: Despite being the fastest growing population group, the elderly have usually been excluded from reperfusion clinical trials. We studied the difference in mortality in different age groups after primary percutaneous coronary intervention (PCI) for ST elevation myocardial infarction (STEMI) at our high volume 24/7 cardiac centre.

Methods: From the start of our PCI service, there has been no age criteria to access the service. We collected data from our prospective cardiac database for the 24 months period between September 2009 and September 2011, with mortality provided by the summary care records.

Results: There were 1322 PCI procedures with an age range of 14 to 98 years (mean 65.3). 658 patients (50%) were under 65 years, 326 (25%) were 65-74,
Does a regional system of care impact on reperfusion strategies in ST-segment elevation myocardial infarction?

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Purpose: Regionalization of care for ST-segment elevation myocardial infarction (STEMI) has been advocated, although its effect on processes of care - compared to on outcome - remains uncertain. The aim of this study was to evaluate the impact of a regional system of care on reperfusion strategies for STEMI patients relative to control hospitals.

Methods: We analyzed the original data from two nationwide, prospective cohort studies, with the same methods. The first was conducted in November 2000 (FAST MI 1999) and the second in November 2005 (FAST MI 2005). A total of 168 hospitals participated in both studies. Seven hospitals (2 with percutaneous coronary intervention facilities and 5 without) were involved in a regional system of care implemented in the Northern Alps in 2002 (RESURCOR); 153 control hospitals located in either French areas were included with no corresponding regional system of care. From 2002 to 2005, RESURCOR promoted prehospital fibrinolysis followed by routine/rescue coronary angiography. We compared change in rate of prehospital fibrinolysis and routine/rescue coronary angiography after fibrinolysis between 2000 and 2005 in the RESURCOR region versus the control hospitals.

Results: A total of 102 STEMI patients were enrolled in the Northern Alps hospital region and 2177 in the control hospitals. In the RESURCOR area we observed a larger absolute increase in the use of prehospital fibrinolysis (18% vs 63%, P < 0.01, respectively, in 2000 and 2005) compared with the control hospitals (14% vs 31%, P < 0.01, respectively, in 2000 and 2005). In the RESURCOR area we observed a larger absolute increase in the use of routine/rescue coronary angiography after fibrinolysis (9% vs 44%, P < 0.01, respectively, in 2000 and 2005) when compared with control hospitals (7% vs 22%, P < 0.01, respectively, in 2000 and 2005).

Conclusions: Regionalization of care for STEMI patients may impact on reperfusion strategy in STEMI.

New insight into mental stress induced myocardial ischemia: prevalence and demographic/clinical characteristics

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Background: Mental stress induced myocardial ischemia (MSIMI) is a risk for poor prognosis of patients with coronary artery disease (CAD). Past studies examining MSIMI were primarily included patients with exercise induced myocardial ischemia (ESIMI), thus the true prevalence of MSIMI remains unknown. We respectively addressed the limitations employing data collected during the recruitment phase of a clinical trial designed to assess if a selective serotonin reuptake inhibitor reduces MSIMI.

Method: Both male and female adult patients with documented CAD, regardless of status of exercise or pharmacological tests, were recruited for screening stress test for the trial. Following 24-48 hour beta-blocker withdrawal, consented patients underwent a battery of mental stress tests (three tasks) followed by a treadmill stress test. Stress induced ischemia was defined as 1) any development or worsening regional wall motion; 2) reduction of left ventricular ejection fraction (LVEF) ≥ 8% with ischemochrography, and/or 3) horizontal or downsloping ST segment depression ≥ 1mm in 2 or more leads lasting for ≥ 3 consecutive beats, relative to rest. MSIMI was considered present when ischemia occurred in at least one mental test.

Results: A total of 310 CAD patients (17.2% women, and mean age of 63.0 years) underwent the screening. MSIMI occurred in 43.45% while ESIMI occurred in 33.79% of the study population: 23.79% had both MSIMI and ESIMI, 19.66% only had ESIMI, and 10.0% had only MSIMI. Relative to exercise stress, mental stress induced greater reduction of LVEF. Univariate analysis demonstrated that women (OR = 1.88, 95% CI 1.04 – 3.42), patients who were not married (OR = 1.95, 95% CI 1.19 – 3.16) and patients who had lived alone (OR = 2.24, 95% CI 1.19 – 4.20) were more likely to have MSIMI. Multivariate analysis showed that, compared to married men, unmarried men (OR = 2.57, 95% CI 1.33-4.97) and married women (OR = 3.18, 95% CI 0.22 – 71.72) were more likely to have MSIMI. Further, compared to men living with someone, men and women living alone had higher risk for MSIMI (OR = 2.25 [95% CI 1.02 – 4.93] and OR = 2.72 [95% CI 1.05 – 7.17] respectively). None of those factors, however, were associated with ESIMI.

Conclusion: MSIMI is more common than ESIMI in clinically stable CAD patients. Women, unmarried men, and ones living alone are more likely to have MSIMI but not ESIMI. Further studies are needed to understand the underlying mechanisms of MSIMI, of sex differences, and of the interactions with marital and living statuses. Appreciation of and effective management to reduce MSIMI are greatly needed in this highly prevalent population.
receive either an intracoronary bolus of 150 μg of DA (DA group) or normal saline (control group) at the onset of reflow obtained by primary percutaneous coronary intervention (PCI). IS was assessed both by measuring serum creatine kinase (CK) release and by performing cardiac magnetic resonance (CMR).

Results: There was no difference between the two groups with regard to the duration of ischemia, the TIMI flow grade at admission and after PCI, the size of the area at risk, and the extent of the collateral circulation that are the main determinants of IS. The release of CK after reperfusion was not significantly different in the DA group as compared with the control group even when the data were adjusted to the size of the area at risk. Between 3 and 7 days and at 3 months, the area of hyperenhancement on CMR expressed as percentage of the left ventricular myocardium was not significantly reduced in the DA group as compared with the control group even when the data were adjusted to the size of the area at risk.

Conclusions: The intracoronary administration of DA in patients with acute MI at the time of reperfusion does not significantly reduce IS.

Trial Registration clinicaltrials.gov Identifier: NCT01043991

2h post load glucose but not fasting or random blood glucose predicts adverse outcome following myocardial infarction

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Background: We compare the relative value of random admission (RPG), fasting (FPG) and 2-hour post load glucose to predict prognosis after an MI as this has never been compared.

Methods: In 674 non-diabetic post-MI patients with RPG, FPG and 2h PG were categorised into quartiles (Q) of 2h PG. The primary end-point was the first occurrence of major cardiovascular adverse events (MACE) including cardiovascular (CVS) death, non-fatal MI, severe heart failure (HF) or non-haemorrhagic stroke. Secondary end-points were all cause mortality, cardiovascular mortality, non-fatal MI, severe HF or stroke.

Results: In the higher quartiles were older, had higher prevalence of hypertension and IHD. Conventional definitions all patients in Q1 and 77% in Q2 had normal glucose tolerance (NGT); 21% of Q2, all in Q3 and 23% in Q4 had impaired glucose tolerance (IGT) and 7% of Q4 had new diabetes mellitus (NDDM). 15 of MACE (OR: 1.15, 95% CI: 1.07-1.25, p=0.000); all cause mortality (OR: 1.13, 95% CI: 1.01-1.26, p=0.041); non-fatal MI (OR: 1.01, p=0.021); severe HF (OR: 1.18, 95% CI: 1.04-1.34, p=0.0352); CVS mortality (p=0.0382), MACE (p=0.0002) and non-fatal MI (p=0.0112) were higher in Q3 and Q4. Including RPG, FPG and 2h PG in the same Cox proportional hazard regression model, 2h PG but not RPG nor FPG predicted MACE (HR 1.13, 95% CI: 1.06-1.21, p=0.002), all cause mortality (HR 1.17, 95% CI: 1.06-1.30, p=0.0029), CVS mortality (HR 1.18, 95% CI: 1.04-1.34, p=0.0134) and non-fatal MI (HR 1.11, 95% CI: 1.02-1.21, p=0.061). The odds of MACE (OR: 1.15, 95% CI: 1.07-1.25, p=0.000); all cause mortality (OR: 1.13, 95% CI: 1.01-1.26, p=0.041); non-fatal MI (OR: 1.11, 95% CI: 1.02-1.22, p=0.023) and its combination with CVS mortality (OR: 1.15, 95% CI: 1.05-1.25, p=0.002) increased with increasing 2h PG but not RPG or FPG on entering RPG, FPG and 2h PG as continuous variables into a logistic regression model with other relevant covariates and RPG significantly improved the ability of a model based on relevant covariates and RPG (p=0.99, OR: 1.000, 95% CI: 1.000-1.000). Comparing nested models showed that including the 2h PG as a continuous variable significantly improved the ability of a model based on relevant covariates and RPG (p=0.0107, OR: 1.000, 95% CI: 0.997-1.002) and TRAIL (p=0.0107, OR: 1.000, 95% CI: 0.997-1.002).

Conclusion: 2h PG predicts prognosis after MI better than RPG or FPG.

Reversal correlation between the extent of apoptosis and necrosis in patients with acute myocardial infarction

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Introduction: Ischemia-reperfusion injury in acute myocardial infarction (AMI) results in addition to necrosis to the process of apoptosis of myocytes. The share of the extent of apoptosis and necrosis in patients undergoing percutaneous coronary intervention (PCI) for AMI has not yet been in clinical practice completely defined.

Goal: To analyze the serum levels of pro-apoptotic markers Fas and TRAIL in patients in regard to the type of AMI (STEMI versus nonSTEMI) and to determine the correlation between the value of markers of apoptosis and the maximum value of troponin.

Methods and results: Serum concentration of Fas and TRAIL using ELISA method was determined in 226 consecutive patients (average age 67±12 years) undergoing PCI for AMI. Differences were compared between the group of patients with STEMI and with non-STEMI and statistical analysis was performed to find out the correlation between the value of pro-apoptotic markers and the maximum value of troponin as an indicator of necrosis. Between the two groups that differed in clinical characteristics of age, gender, DM representation, arterial hypertension and creatinine clearance (STEMI vs non-STEMI: age 63±12 vs 70±11; p<0.001; gender - male 75% vs 63%; p<0.01, DM 19% vs 31%, p<0.02; hypertension 42% vs. 69%, p<0.001; creatinine clearance 1.7±0.7 vs 1.5±0.7, p<0.05), difference was detected in serum levels of the markers Fas (STEMI 651±2271 vs nonSTEMI 7720±2889 pg/ml, p<0.001) and TRAIL (51±26 vs 65±42 pg/ml, p<0.002). Ejection fraction of patients with STEMI and nonSTEMI at hospitalization was 48±12 vs 49±13%, p=NS, respectively. There was found a reverse correlation between the maximum value of troponin and the serum concentrations of Fas (r=0.304, p<0.001) and TRAIL (r=0.334, p<0.001).

Conclusion: In patients after PCI for acute myocardial infarction a reverse correlation between the markers of apoptosis and the maximum values of troponin was found. Patients with nonSTEMI have a greater extent of apoptosis compared to the patients with STEMI.

Incidence and prognostic value of infections during an acute coronary syndrome


Introduction: A growing amount of clinical and experimental evidence suggests a link between infection and atherosclerotic diseases. On the one hand it is known that during the acute phase of myocardial infarction there is a proinflammatory state. On the other hand several studies have demonstrated that infection causes a hypercoagulable state which increases the risk of thrombosis. The aim of our research is to evaluate the incidence of infections during the admission after acute coronary syndromes (ACS) and its influence in the risk of in-hospital mortality.

Methods: Using data from 4,497 consecutive patients with ACS (32% STEMI, 19.2% unstable angina) from our hospital (2003-2010), we analyzed the incidence of bacterial and viral acute infections and associated it with inhospital mortality. Further a multivariate analysis was performed to show the prognostic value of infections during ACS regardless of the GRACE risk score.

Results: There were 534 infections during ACS hospitalization (11.9%) and 265 in-hospital deaths (5.9%). The mortality in the group with infections was 17.6%, increasing in-hospital mortality 3.8-fold in comparison with not-infection group (mortality 4.6%, p=0.0112) were lower in Q3 and Q4. Including RPG, FPG and 2h PG in the same logistic regression model with other relevant covariates and RPG, FPG and 2h PG as continuous variables into a logistic regression model with other important covariates. Area under the 2h PG ROC curves predicting MACE was significantly higher that for RPG (p=0.0017) and FPG (p=0.0010). Comparing nested models showed that including the 2h PG as a continuous variable significantly improved the ability of a model based on relevant covariates and RPG (p<0.0001, OR: 1.01, 95% CI: 1.00-1.01; p=0.000). Diabetic alone (OR: 1.039, 95% CI: 1.031-2.198, p=0.006 for acute infections; OR: 1.035, 95% CI: 1.032-1.039, p=0.001 for GRACE RQ).

Conclusions: Infections are a frequent complication during the ACS hospitalization increasing the risk of in-hospital mortality independently of GRACE risk score.

Impact of smoking on six-month angiographic and clinical outcomes in patients undergoing elective percutaneous coronary intervention with drug eluting stents

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Background: Smoker’s Paradox in patients undergoing percutaneous coronary intervention (PCI) in the drug-eluting stent (DES) era has been controversial. In a recent study, enhanced clopidogrel response in smokers with cytochrome P450 CYP 1A2*13C–A allele carriers was reported. This study was thus carried out to evaluate whether smokers paradox is exists in real world clinical practice in a series of Asian population.

Methods: The study population consisted of 1093 consecutive patients (pts) who had received clopidogrel and underwent elective PCI with DESs between January 2004 and April 2009. Non-Smoker (NS) was defined as inexperience
smoking before admission (n= 625 pts, 57.2%). Current Smoker (CS) as smoking within 1 month before admission (n= 293 pts, 26.8%) and Ex-Smoker (ES) as quit smoking more than one-year before admission (n=175 pts). Six-month angiographic and 5-years cumulative clinical outcomes were compared among three groups.

**Results:** A total 974 pts (89.1%) were finished 2-year clinical follow up. The baseline clinical and procedural characteristics were similar among the three groups except more male gender in the CS group with hypertension in the NS group. At six months, the incidence of angiographic binary restenosis was lower in the CS group. At five years, cumulative major clinical outcomes were also similar between NS with CS group except that the incidence of repeat revascularization (target lesion revascularization, TLR and target vessel revascularization, TVR) and major adverse cardiac events were lower in the CS group (table).

**Conclusion:** In our data, “smoker's paradox” still seems to be exists in Asian patients undergoing PCI with DESs in real-world clinical practice.

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**P913**

**Relationship with clinical outcomes and circadian pattern in patients with AMI at primary PCI era**

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**Background:** Many epidemiologic studies have been reported the morning peak incidences of acute myocardial infarction (AMI). However, short and long-term clinical outcomes of circadian pattern have not been fully investigated in patients with AMI.

**Methods:** From Korea Acute Myocardial Infarction Registry (KAMIR) database, we analyzed 5,748 eligible patients (2,793 STEM1, 1961 NSTEMI; age>62±12.1 years) who had primary percutaneous coronary intervention (PCI) and early invasive PCI. The clinical impact of circadian variation was evaluated among four 6-hour-interval groups (12:00 midnight-6:00 AM, 6:00 AM-12:00 noon, 12:00 noon-6:00 PM, 6:00 PM-12:00 midnight). Various major adverse cardiac events (MACEs) at 12 months were evaluated.

**Results:** There was a marked circadian variation with increased incidences of AMI during the second quarter of day (6:00 AM to 12:00 noon). In concordance of previous studies, hypertension was more prevalent during the second quarter of day (STEMI: 45% vs. 51% vs. 46% vs. 46%, respectively; NSTEMI: 53% vs. 51% vs. 48%, respectively p<0.00). Among four 6-hour-intervals, symptoms-to-door time, door-to-balloon time, procedural complexity, and success rates of PCI were not significantly different. As shown in table, in-hospital mortality, MACEs were not significantly different for 12-month follow-up. Instead, old age, diabetes, and Killip class higher than II were independent factors for 12-month MACEs.

**Conclusions:** Old age and additional comorbidities, but not the onset time of AMI, are likely to explain the deteriorating short-and long-term outcomes in patients with primary PCI and early invasive PCI.

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**P914**

**Systematic data feedback of primary PCI network: impact on delay of reperfusion**

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**Purpose:** Treatment delay is an important predictor of survival in STEMI patients undergoing primary PCI. Guidelines recommend that the PCI-related delay time (PCI-RDT) must be shorter than 90 minutes. This study sought to identify the effect of formalized data assessment and systematic feedback on the PCI-STEMI network.

**Methods:** We analyzed PCI-related delay time (first medical contact to first balloon inflation) of 386 patients who refer to the hub hospital between January 1st 2009 and December 31st 2010. The AMI network, serving a population of about 300,000, consists of three predefined referral routes: pre-hospital diagnosis and direct transportation (125 pts), emergency department of PCI hub center (107 pts) and pre-hospital emergency department of spoke hospitals (154 pts). The first medical contact and the rivascolarization time were assessed, analyzed and presented in an interactive session to hospital and emergency staff members. Data, from patients of 2010, were analyzed in four different quarters and were presented in the same manner.

**Results:** The median of PCI-RDT for direct transportation was 63 min and 66 min, for emergency department of PCI hub center was 93 min and 78 min, and for emergency department of spoke hospitals was 103 min and 91 min in 2009 and 2010, respectively. We observed that in 2009 50% and in 2010 64% of patients had a PCI-related delay time less than 90 minutes (p < 0.008).

**Conclusion:** Formalized data feedback leads to significant reduction in rivascolarization time in patients with STEMI.
Prognosis over a 20 year-period in elderly patients with first STEMI (1988-2008)

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Purpose: The general population is gradually aging in the Western world, so that patients over 75 years and older comprise a substantial proportion of all acute myocardial infarction patients. However, this population has been traditionally less likely to receive evidence-based medications and to undergo primary Percutaneous Coronary Intervention (PCI) for ST-Elevation Myocardial Infarction (STEMI). We aim to provide insight in demographic and clinical characteristics of the STEMI patients ≥75 years and the prognosis over a twenty-year observational period.

Methods: This is a single-centre observational study. Between 1988 and 2008, we collected data from all the patients ≥75 years who presented with a first STEMI and were admitted in our Coronary Care Unit. Patients attended in the cardiology ward, in the Intensive Care Unit and in the geriatric ward were excluded from the present study. We analyzed their baseline characteristics, the in-hospital, one-year and five-year mortality.

Results: From 1988 to 2008 a total of 1395 patients ≥75 years were included in the present study. Mean age was 80.7±4.7 years and 51% were women, 59.4% had hypertension, 32.1% diabetes, 21.2% were smokers and 39.9% had previous history of cardiovascular disease. 25.9% had three-vessel coronary disease, 21.8% presented severely depressed left ventricular ejection fraction and 74.4% developed any complication during the hospitalization: tachycardia (32.4%), ventricular fibrillation, atrial fibrillation (16%); complete AV block, mechanical complications, renal impairment and others. 92.7% received aspirin, 62% ACE inhibitors, 47.6% β-blockers, 30.9 statins and 21.8 clopidogrel. 52.7% of the patients underwent reperfusion therapy (PCI in 474 patients and fibrinolysis in 261). In the total cohort of 1393 patients, in-hospital mortality was 24.8%, one year mortality was 41.7% and five-year mortality was 63.6%.

Conclusion: Mortality among STEMI patients ≥75 years was acceptable in our cohort, in spite of their high risk profile and comorbidities. Adherence to evidence-based therapies was limited. Unfortunately, little is known about the optimal treatment strategy as they are underrepresented in many randomized clinical trials. Further studies into the optimal STEMI management strategy for the elderly are warranted.

Availability of cath lab facilities and contemporary inter-hospital transfer patterns for the management of ACS patients: findings from the EPICOR study


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Purpose: Little is known about ACS management in relation to inter-hospital transfer and the potential role of on- or off-site catheterization facilities. The EPICOR observational study was designed to describe anthropometric strategies in a broad ACS population; it also included information on inter-hospital transfers and institutional resources. In this initial subanalysis, we report on baseline inter-hospital management patterns for ACS patients in relation to the availability of cath facilities.

Methods: EPICOR (NCT01711404) enrolled 10,568 patients with a STE or NSTEMI in 555 centers in 20 countries across Europe and Latin America. For the present analysis, patients were categorized as non-transferred (NT), transferred in (TI) from another hospital and then discharged, or transferred out (TO) to a second hospital but discharged from their initial hospital after transfer back. Results: Two-thirds of ACS patients were NT and one-third were TI or TO. Overall, all comorbidities were similar across the groups. Coronary angiography (at any location) was more frequently done in patients admitted to a hospital with a 24/7 (95%) or non-24/7 (77%) cath lab than in those without one (55%). TO hospitals were less much likely to have 24/7 PCI capabilities or on-site cardiac surgery (4%/2%) than NT (71%/57%) or TI (72%/68%) hospitals.

Different angiographic findings among patients with acute coronary syndrome and sudden death compared with those without sudden death

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Purpose: During the acute phase of ST elevation myocardial infarction (STEMI) a considerable number of patients may suffer sudden cardiac death (SCD). There is little information about the pathophysiology of SCD in this context. Most of studies are based on postmortem examination, and suggested that active coronary artery lesions are a major pathophysiological mechanism of the SCD. The aim of this work was to determine whether clinical and angiographic findings could differentiate patients with STEMI from those without SCD.

Methods: We reviewed clinical information (risk factors, clinical presentation) electrocardiographic changes, left ventricular ejection fraction (LVEF), and angiographic findings of patients with STEMI and SCD compared with patients without SCD in a case-control study.

Results: From September 2006 to September 2011, 62 consecutive patients with STEMI were referred to the cath lab to perform coronary angiograms, 32 of those
patients met the inclusion criteria. In the same period of time, 40 consecutive STEMI patients without CVD were selected as an age- and gender-matched control group. Clinical characteristics of both groups were similar (Table 1). No differences were found on the culprit coronary artery, but a significant association was found in the localization of the arterial occlusion. Proximal segment occlusion was more frequently seen in patients with CVD (75% vs. 28%, p < 0.001). After logistic regression analysis, angiographic culprit lesion in proximal coronary artery segments was associated significantly with CVD in patients with STEMI (p = 0.035; OR 7.02, 95% CI 1.14-43).

Results:

Conclusions: Culprit lesions in STEMI cluster in the proximal coronary arteries in patients with CVD compared those without CVD. This finding could suggest a relationship between CVD and the amount of myocardium at risk in patients with STEMI.

Clinical and electrocardiographic characterization of reciprocal ST segment changes in patients with acute coronary artery occlusion


Purpose: Acute coronary artery occlusion can induce reciprocal ST segment depression in leads not related to the ischemic area. It can be caused either by concurrent subendocardial ischemia or simply result from a passive electrical phenomenon, but this is not well known. The purpose of the study was to characterize reciprocal ST segment changes in patients with acute coronary occlusion and single coronary vessel disease.

Methods: We reviewed the clinical records of 545 patients with acute myocardial infarction treated with primary coronary angioplasty and we selected the 124 patients with single vessel disease in whom the culprit artery was the only affected vessel. We measured ST segment deviation in the 12-lead ECG and coronary angiographic data.

Results: Occlusion of proximal and mid-distal left anterior descending coronary artery (LAD) induced significant ST segment elevation (p < 0.001) in precordial leads (+0.52 ± 0.42 mV), but not after mid-distal (-0.13 ± 0.22 mV) LAD occlusion (p < 0.01 for the difference). Occlusion of proximal and mid-distal right coronary artery (RC) induced significant ST segment elevation (p < 0.001) in inferior leads (+0.75 ± 0.39 mV and 0.62 ± 0.44 mV, respectively) associated with ST segment depression (p < 0.001) in precordial leads (-0.57 ± 0.49 mV and -0.58 ± 0.47 mV, respectively) with no difference between both groups.

Conclusion: Reciprocal ST segment depression occurs after acute coronary occlusion in patients with single vessel disease thus suggesting that concurrent subendocardial ischemia is not the likely mechanism. Reciprocal ST segment changes appear after proximal and mid-distal RC occlusion and after proximal but not mid-distal LAD occlusion.

The number of fragmented QRS predicts the low percent of ST segment resolution in patients with STEMI

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Background: The QRS complex fragments (fQRS) are associated with increased morbidity and mortality. The causative relationship between fQRS and cardiac fibrosis has been shown, but whether presence and number of fQRS on admission ECG predicts the ST segment resolution in patients undergoing primary percutaneous coronary intervention (p-PCI) was not studied until now.

Purpose: To investigate evolution of ST-Elevation Myocardial Infarction (STEMI) treatment and STEMI-related mortality in an unselected population from a region of 1 million people in central Romania in the period of 2004-2011, and to show the role of organizational and educational factors in increasing rates of primary PCI and reducing STEMI mortality in this region.

Methods and results: In 2004 a STEMI network for organization of logistics related to STEMI treatment was initiated in a territory of 1 million people, encompassing a primary PCI centre and 13 tertiary care hospitals. Data related to all STEMI patients presenting with STEMI in these hospitals were collected and introduced in a Regional Registry of STEMI, the first registry of such kind in Romania. In order to increase the number of patients...
ST-segment elevation myocardial infarction and distor-
tion of the QRS: long term mortality


Background: We have had a "one call activation system" for primary PCI at our regional academic center since 1999. The ED physician initiated the system with the decision for primary PCI made by cardiologist (interventional or non-interventional) on call. But since July 1, 2009, only interventional cardiologists are involved in the decision making process. Otherwise, the comprehensive strategy remained the same. As we have reported previously, this new strategy resulted in a shortened door-to-balloon (D2B) time. In the present study, we analyzed the D2B timeline intervals to determine were the major gains were achieved.

Methods: We conducted a retrospective analysis of 665 consecutive patients presenting to our institution with suspicion of acute STEMI during a 30-month period. Group 1 consisted of patients in the 12 months (July 1 2009-June 30 2009) before and Group 2 consisted of patients in the 18 months (July 1 2009-Dec. 31 2010) after the system change was instituted. Mann-Whitney U test and chi-square test were used for statistical analysis.

Results: 218 patients in group 1 were taken to the cath lab of which 180 received primary PCI. 349 patients in group 2 were taken to the cath lab of which 275 received primary PCI. The results were presented in the table.

D2B time intervals (median, unit: mins) before (group 1) and after (group 2) new system in STEMI patients undergoing PCI

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=180)</th>
<th>Group 2 (n=275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2B time</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>Arrival to EKG</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>EKG to decision</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Decision to balloon</td>
<td>54</td>
<td>47</td>
</tr>
</tbody>
</table>

Conclusions: Comprehensive strategy with exclusive involvement of interventional cardiologist in the decision making process resulted in a significant decrement in decision-to-balloon time. The EKG-to-decision time did not decrease, contrary to our expectation.
Smoking impacts symptom onset time and outcome in primary percutaneous coronary intervention: further insights into the smoker’s paradox

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Purpose: Circadian variation in the onset of acute myocardial infarction has been well characterized, but the significance of modifying factors is underexplored. We studied smoking and other factors potentially associated with time of onset of ST-elevation myocardial infarction (STEMI) and their clinical impact.

Methods: From a prospectively collected registry, baseline parameters as well as outcome were studied in 1984 consecutive patients with STEMI undergoing primary percutaneous coronary intervention (PCI) between January 2006 and April 2010. In 656 patients, symptom onset to first medical contact time (patient delay) and first medical contact to treatment time (system delay) were available.

Results: Among 13 baseline factors in our study population, only smoking was associated with time of symptom onset (P = 0.014). Circadian variation in symptom onset was attenuated in smokers with higher occurrences of STEMI during the night and fewer occurrences during the morning compared with non-smokers. Smokers (younger than non-smokers (55 vs. 69 years; P < 0.001) and had a lower rate of multivessel disease (56% vs. 67%; P < 0.001). Smoking was independently associated with longer ischemic time (estimate +7.2%; 95% confidence interval [CI] +0.3% to +15%; P = 0.049). However, this association lost its statistical significance after adjustment for symptom onset time between 12:00 AM and 06:00 AM (estimate +23%; 95% CI +14% to +33%; P = 0.1). Irrespective of smoking status, patient delay was longestest between 12:00 AM and 06:00 AM (P < 0.001), while system delay did not vary by symptom onset time. Post-PCI, smokers had better myocardial blush grades (odds ratio for grade 0:1.07; 95% CI 0.57-0.93; P = 0.013). One-year mortality was higher in non-smokers and 7.4% in non-smokers (P = 0.217). However, both smoking (hazard ratio 1.81; 95% CI 1.18-2.78; P = 0.006) and any doubling of ischemic time (hazard ratio 1.21; 95% CI 1.01-1.45; P = 0.038) were independently associated with mortality at 1 year follow-up.

Conclusions: Smokers undergoing primary PCI have a favorable baseline profile, compared to non-smokers. Smoking in STEMI reduces ischemic time and improves myocardial blush grades, independent of smoking status.

Secular trends in the use of reperfusion therapies and outcomes in elderly patients with primary STEMI (1988-2008)


Purpose: To analyze the secular trends in management and short- and long-term outcomes of elderly STEMI patients.

Methods: The PPRIMMS Registry is a single-center observational study, which enrolled all first AMI in patients ≥75 years admitted to our Coronary Care Unit since 1988. Patients with first STEMI admitted between 1988 and 2008 were included. patients included in the study (n=83) and those arriving >24 hours after symptom onset (n=163) were excluded. Baseline characteristics, clinical management, in-hospital and post-discharge outcomes were compared among five time periods: 1988-1992, 1993-1996, 1997-2000, 2001-2004 and 2005-2008.

Results: The final cohort consisted in 1147 patients. During the study period, there was a significant (p = 0.01) increase in median age (from 79 years in 1988-92 to 80 years in 2005-08), delay >6 hours to admission (from 59.7% to 68.9%) and in the use of aspirin, β-blockers and ACE inhibitors. A significant reduction in the incidence of cardiac shock (from 16.3% to 4.4%) and mechanical complications (from 11.9% to 3.2%) was seen. The use of reperfusion therapy increased significantly, with: female sex, cal-reason due to atypical symptoms, large infarctions with 5 (ST elevation) 2.709 1.201-6.211 0.01 mortality. However, continuing efforts to reduce patient delay, especially among smokers, are warranted.

Conclusions: Mortality in STEMI during pre-hospital care is high. It’s associated with: female sex, call reason due to atypical symptoms, large infarctions with 5 or more leads involved, anterior location AMI, initial hypotension and ventricular fibrillation episodes.

Use and impact of the pre-hospital electrocardiogram in acute coronary syndrome

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Background: Guidelines recommend use of pre-hospital ECG (PHECG) in suspected ACS. PHECG use is suboptimal, leading to delayed or denied reperfusion in STEMI. PHECG is associated with faster reperfusion, but little is known of the impact in NSTEMI. Mortality benefit of PHECG has not been demonstrated.

<table>
<thead>
<tr>
<th>Total population (STEMI+nSTEMI)</th>
<th>Total mortality (n=205180)</th>
<th>30 day mortality (n=127552)</th>
<th>90 mm Hg (n=39124)</th>
<th>5 (ST elevation) (n=36140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (205180)</td>
<td>(127552)</td>
<td>(36140)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHECG</td>
<td>5.9% (4.9% - 7.6%)</td>
<td>6.0% (5.0% - 7.1%)</td>
<td>6.8% (5.7% - 7.9%)</td>
<td>6.7% (5.6% - 7.8%)</td>
</tr>
<tr>
<td>Non-PHECG</td>
<td>6.7% (5.6% - 7.8%)</td>
<td>7.1% (6.0% - 8.1%)</td>
<td>8.1% (7.0% - 9.2%)</td>
<td>7.9% (6.8% - 9.0%)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>STEMI</td>
<td>6.4% (5.4% - 7.4%)</td>
<td>6.7% (5.6% - 7.7%)</td>
<td>8.1% (7.0% - 9.2%)</td>
<td>7.9% (6.8% - 9.0%)</td>
</tr>
<tr>
<td>PHECG</td>
<td>5.6% (4.5% - 6.7%)</td>
<td>5.6% (4.5% - 6.7%)</td>
<td>6.8% (5.7% - 7.9%)</td>
<td>6.7% (5.6% - 7.8%)</td>
</tr>
<tr>
<td>Non-PHECG</td>
<td>6.0% (5.0% - 7.0%)</td>
<td>6.3% (5.2% - 7.4%)</td>
<td>7.7% (6.6% - 8.8%)</td>
<td>7.5% (6.4% - 8.6%)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</table>

Table 1. Variables associated pre-hospital mortality in STEMI

<table>
<thead>
<tr>
<th>OR</th>
<th>CI 95%</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>2.737</td>
<td>1.298</td>
<td>0.01</td>
</tr>
<tr>
<td>3.560</td>
<td>1.559</td>
<td>0.003</td>
</tr>
<tr>
<td>3.735</td>
<td>1.635</td>
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</tr>
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<td>4.197</td>
<td>2.066</td>
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Table 2. Variables associated pre-hospital mortality in STEMI

Hospital and 30-day mortality

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Overall</th>
<th>PHECG</th>
<th>No PHECG</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>5.9%</td>
<td>5.0%</td>
<td>6.8%</td>
<td>0.83</td>
<td>0.68</td>
<td>0.103</td>
</tr>
<tr>
<td>30 day</td>
<td>9.2%</td>
<td>8.3%</td>
<td>10.5%</td>
<td>0.83</td>
<td>0.68</td>
<td>0.103</td>
</tr>
<tr>
<td>PHECG</td>
<td>5.6%</td>
<td>4.5%</td>
<td>6.7%</td>
<td>0.83</td>
<td>0.68</td>
<td>0.103</td>
</tr>
<tr>
<td>Non-PHECG</td>
<td>6.0%</td>
<td>5.0%</td>
<td>7.0%</td>
<td>0.83</td>
<td>0.68</td>
<td>0.103</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
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</tr>
</tbody>
</table>

Table 3. Mortality in STEMI patients with 30-day follow-up.

Methods: Multivariate analysis of national ACS registry.

Results: Mortality data are shown in the table.

Conclusion: PHECG is associated with hospital and 30-day mortality benefit in STEMI and NSTEMI. This is the first time this association has been demonstrated.

Temporal trends in pre-hospital management of ST segment elevation myocardial infarction from 2002 to 2010: Data from the RICO Survey

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Purpose: To determine the temporal trends between 2002 and 2010 in STEMI management and time delays in an eastern region of France (Cote d’Or).

Methods: All consecutive patients admitted for a first STEMI in the RICO survey (Observatoire des Infarctus de Côte d’Or) from 1st January 2002 to 31st December 2010 have been included. We analysed trends in pre-hospital and hospital management times and reperfusion.

Results: 12,203 STEMI patients were included over the study period. Mean age and GRACE risk score increased from 2002 to 2010 (64 to 67 y p = 0.001 and 152 to 155 p = 0.049). At symptom onset, there was an increase in the rate of patients who called the emergency number (door 15) and a decrease in the rate of call to GP as first medical contact (from 24.8 to 36.4% and from 57.1 to 34.2%, respectively). However, prehospital times including patient time (from onset of symptoms to call for medical seeking) remained stable over time. There was a significant decrease in time to first medical contact according to age, with patients aged under 50 years getting help on average 40 to 100 minutes earlier than patients aged over 50 years. (p=0.019). The average time from first medical contact to reperfusion decreased significantly from 339 minutes in 2002 to 239 minutes in 2010 (p=0.009). Over the study period, there was an inversion in the distribution of reperfusion strategies, with a decrease in fibrinolysis and an increase in primary PCI (from 25% to 2% and from 21% to 36.7%, respectively). The rate of patients without acute reperfusion dropped from 41.9 to 36.3% (p < 0.001).

We found a marked improvement in time to reperfusion including fibrinolysis and door to balloon time (from 150 to 120 min and from 70 to 45 min, respectively).

Conclusion: Between 2002 and 2010, despite marked improvements in management including reperfusion strategies, there is still a room for improvement in order to achieve earlier reperfusion in STEMI patients.

Importance of out-of-hospital case fatality and early life-threatening complications in 28-day mortality of acute coronary syndrome

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Purpose: The death rate of acute coronary syndromes (ACS) has decreased for 40 to 50 years. Out-of-hospital mortality remains high despite the improvement of ACS care and in-hospital mortality has decreased a lot but reaches currently a plateau. The aim of our study was to evaluate the importance of out-of-hospital mortality and the main determinants of in-hospital mortality in France with recent databases. MACE was defined as a composite of mortality and unplanned revascularisation. Two interventionists blinded to patient outcome reviewed the angiographic images and adjudicated if the activation was appropriate.

Methods: We prospectively included all consecutive STEMI patients with a confirmed ACS diagnosis occurring at the CCU in 88 hospitals over 28 days. The study was conducted between September 2008 and December 2010. We included 11328. The activation ECG was obtained from the hospital PPCI database, as were demographic data. Outcome data were obtained from notes and national databases. MACE was defined as a composite of mortality and unplanned revascularisation. Two interventionists blinded to patient outcome reviewed the angiographic images and adjudicated if the activation was appropriate.

Results: The death rate of acute coronary syndrome (ACS) (39.8%), non-ACS cardiac (28.4%) and non-cardiac (31.8%). A history of previous MI (p=0.002) and presence of cardiacogenic shock on arrival (p=0.04) were more prevalent in the inappropriate LBBB-activations. One year mortality and MACE were higher for appropriate LBBB-activations than the STEMI activations (27.6% vs 7.9%; p=0.002 and 33.3% vs 12.2%; p=0.001 respectively). Conclusion: Less than half of LBBB-activations had an ACS and, of these, only one had a thrombotic coronary occlusion requiring PCI. However, LBBB-activations have a significantly worse prognosis and merit urgent referral. Enhanced triage methods are required to correctly identify ACS requiring PCI in those with LBBB.

CRUSADE bleeding score validation for ST-segment-elevation myocardial infarction

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Introduction: CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) bleeding score predicts accurately the risk of bleeding in non-ST-segment elevation myocardial infarction. No study has validated its use in ST-segment elevation myocardial infarction treated with primary angioplasty. We prospectively included all comers with ST-segment-elevation myocardial infarction treated with primary angioplasty. CRUSADE bleeding score was calculated for each patient. All patients were treated according to ACC/AHA and ESC guidelines for ST-segment-elevation myocardial infarction. All bleeding complications (according to CRUSADE bleeding classification) were recorded. We assessed the power of the score to discriminate major bleeding by c statistics, with logistic regression and ROC curve.

Methods: We included 1091 patients (79% males). The average CRUSADE score was 24.8. There were 35 (3.2%) cases of major bleeding. Most of them 26 (2.5%) with a drop of hematocrit <12. Patients with major bleeding had a mean score of 22.7 and patients without major bleeding 24.3. The rate of major bleeding increased by bleeding risk score quintiles: 0.4% for those at very low risk (score<10); 2.8% for those at low risk (score 11-20); 4.2% for those at moderate risk (score 21-30); 6.7% for those at high risk (score 31-50); and 13.8% for those at high risk.
Determinants of myocardial salvage in patients with acute ST-segment elevation myocardial infarction: the critical role of proximal domal angina

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1Gabriele Monasterio Foundation-CNR Region Toscana, Pisa, Italy; 2Cardiology Center Monzino (RCGC), Milan, Italy; 3La Sapienza University Rome, Italy; 4University Hospitals (UZ) Leuven, Campus Gasthuisberg, Leuven, Belgium; 5Gabriele Monasterio Foundation CNR Region Toscana, Heart Hospital, Massa, Italy

Background: Determinants of myocardial salvage (MS) in acute myocardial infarction (MI) patients are yet poorly known. Although in humans the time-to-reperfusion has been regarded as the main factor influencing MS, animal models suggest that other parameters may modulate the ischemic jeopardized myocardium. A better understanding of these pathophysiological mechanisms could be crucial for planning more beneficial reperfusion strategies.

Methods: Ninety-seven ST-segment elevation MI patients treated by primary percutaneous coronary intervention (PCI) were prospectively studied by cardiovascular magnetic resonance (CMR) at 7±2 days after MI in 4 tertiary referral hospitals. The following clinical and angiographic data were considered: mean rate-pressure product (RPP) before PCI, new-onset proximal domal angina (PA), medications administered before PCI, Rentrop grade and TIMI-flow pre/post PCI. T2-weighted STIR fast-spin-echo and post-contrast segmented T1-weighted gradient-echo short-axis images were used to quantify area-at-risk (AAR) and infarct size (IS), respectively. MS-index was calculated as (AAR-IS)/AAR.

Results: Patients with (n=33,34%) and without (n=64,67%) PA showed similar baseline clinical characteristics, albeit hypertension and hypercholesterolemia were less common in the former (41% vs 65% and 41% vs 59%, both P<0.05). Peak of troponin I was lower in PA-patients than non-PA patients (241±59 vs 690±113 pg/ml, P=0.05). Mean RPP-time-to-reperfusion, door-to-balloon time, medications before PCI, TIMI-flow pre/post PCI and Rentrop grade were similar in the two groups. Patients with and without PA showed comparable AAR (28±18 vs 26±20 g, P=0.99) whereas IS was lower in PA-patients than non-PA patients (15±13 vs 19±16 g, P=0.004) yielding greater MS-index (0.51±0.25 vs 0.31±0.25, P<0.001), better left ventricular regional and global systolic function. The inverse relationship between MS-index and time-to-reperfusion was observed only in patients without PA (r=-0.291, P=0.020) but not in those with PA (P=0.49). At multivariable linear regression analysis MS-index was independently associated with PA (β-coefficient: 0.300, P=0.004) after correction for TIMI-flow pre/post PCI, time-to-reperfusion, door-to-balloon time.

Conclusion: In patients with reperfused MI, new-onset PA is a strong and independent predictor of MS-index. Considering that pattern of anotergore or collateral blood flow to AAR is not influenced by PA, it is conceivable that PA protects myocardium at-risk through preconditioning. Notably, in PA-patients the MS-index is not any longer related to time-to-reperfusion.

Persistent angina but not degree of coronary artery disease or gender predicts long term anxiety and depression after angiography

L. Jespersen1, S.Z. Abdalstroem1, A. Hvelplund2, E. Prescott1
1Bispebjerg Hospital of the Copenhagen University Hospital, Department of Cardiology, Copenhagen, Denmark; 2Copenhagen University Hospital Gentofte, Department of Cardiology, Copenhagen, Denmark

Purpose: Patients with myocardial infarction often suffer from complicating anxiety and depression disorders leading to poorer prognosis and symptoms are particularly common in women. Little is known about long-term anxiety and depression in patients with angina and how this relates to chest pain, severity of coronary artery disease (CAD) and gender. We investigated the prevalence of anxiety and depression in relation to persistent chest pain.

Methods and results: We invited 360 patients (193 men and 167 women) who had a first time coronary angiography in 2008-2009 due to suspected stable angina subsequently treated with angioplasty or medical treatment (according to guidelines and physician preference) to participate in a questionnaire survey in 2011 with the Hospital Anxiety and Depression Scale as a key element. A cut-off point of 8 was used to identify anxiety and/or depression. Response rate was 84% and median time since angiography was 2.8 years. 24% of patients with obstructive CAD and 38% of patients without obstructive CAD reported persistent chest pain defined as symptoms once a week or more. In both men and women, anxiety and depression was more common in patients with persistent chest pain: 30% vs. 9% reported anxiety and 47% vs. 24% reported depression. Symptoms were equally common in patients with and without obstructive CAD and are shown in the table. In a multivariate logistic regression persistent chest pain predicted depression (OR 2.68 (95% CI 1.57 – 4.59) whereas this was not the case for gender or CAD. Similarly, persistent chest pain predicted anxiety (OR 4.56 (95% CI 2.31 – 9.02) whereas gender and CAD did not.

Long-term anxiety and depression

<table>
<thead>
<tr>
<th>Obstructive CAD</th>
<th>No obstructive CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>No anxiety</td>
</tr>
<tr>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
</tr>
<tr>
<td>Anx.</td>
<td>No anx.</td>
</tr>
<tr>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

Prevalence by degree of CAD and presence of persistent chest pain.

Conclusion: Persistent chest pain was common in both patients with and without obstructive CAD. In this study, persistent chest pain was associated with higher prevalence of anxiety and depression independently of gender and degree of CAD. Future studies should evaluate whether patients with no obstructive CAD would benefit from improved symptom control and identification of anxiety and depression disorders to the same extent as patients with obstructive CAD.

BIOMARKERS IN ACUTE CORONARY SYNDROMES

Combination of anemia and high B-type natriuretic peptide levels is indicative of in-hospital mortality of patients with acute myocardial infarction

Sendai City Medical Center, Sendai Open Hospital, Sendai, Japan

Background: Anemia is an important factor negatively affecting the prognosis of patients with ischemic heart disease. B-type natriuretic peptide (BNP), a marker of heart failure, is also closely associated with mortality in patients with acute myocardial infarction (AMI). However, only a few studies have assessed the relationship between hemoglobin (Hb) concentrations and BNP levels in such patients with regard to in-hospital prognosis.

Methods and Results: This study included 508 patients with AMI; their Hb concentrations were determined on admission, and their BNP levels, approximately 7 days after the onset of AMI. The combined effect of these values on in-hospital mortality was evaluated. Patients were classified into 4 groups according to the presence of anemia and their median BNP values. Anemia was defined according to the World Health Organization criteria (hemoglobin levels of <13 g/dl for men and <12 g/dl for women were indicative of anemia), and the cutoff value for BNP was 178.5 pg/ml for all patients. The incidence of in-hospital mortality for nonanemic patients with low BNP levels was 0.5%; for nonanemic patients with high BNP levels, 12.8%; for anemic patients with low BNP levels, 10.8%; and for anemic patients with high BNP levels, 20.5%. In-hospital mortality was higher in anemic patients with high BNP levels than in nonanemic patients with low BNP levels (odds ratio, 55.6; 95% confidence interval [CI], 11.4–1001.1; p<0.0001).

Conclusion: Classification based on hemoglobin concentration and BNP levels is useful for predicting in-hospital mortality in patients with AMI.
White blood cell, hemoglobin and platelet distribution width as a short-term prognostic marker in patients with acute myocardial infarction


Purpose: Complete blood count is the most widely available laboratory test in patients with acute myocardial infarction (AMI). The usefulness of white blood cell (WBC) and hemoglobin (Hb) as prognostic predictors have been well known and that of platelet distribution width (PDW) is controversial. The aim of this study was to assess the value of the combined use of WBC, Hb and PDW in patients with AMI.

Methods: This study included 1332 patients (64±12 years; 901 males) with AMI. Patients were categorized into the group (n=346, 26.0%), 1 group (n=622, 46.7%), 2 group (n=304, 24.3%), 3 group (n=40, 3.0%) according to the sum of value defined by the cut-off levels of WBC (1±8.4x10^9/L), Hb (1±12.7 g/dL) and PDW (1±51.2%).

Results: The primary endpoint of in-hospital death occurred in 59 (4.4%) patients. WBC (12.7±5.5/L vs. 10.8±4.0/L, P=0.013) and PDW (54.2±7.6% vs. 52.2±7.4%, P=0.037) were higher and Hb (12.4±2.2 g/dL vs. 13.5±1.9 g/dL, P=0.037) 1 group lower in patients with in-hospital death than those without. There were significant differences in the in-hospital death among the group 0 (1.2%), 1 (2.0%), 2 (3.8%), and 3 (22.5%) (P<0.001). In multivariate logistic regression analysis, after adjusting for multiple clinical prognostic factors, the group 2 had 3.6-fold increased risk for predicting the in-hospital death (chi-square 4.3, P=0.038).

Conclusions: Combination of WBC, Hb and PDW which is a cheap and simple hematologic marker, was useful in the early risk stratification of patients with AMI.

Lower serum free triiodothyronine levels are associated with presence and severity of coronary artery disease in the euthyroid patients

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Objectives: Thyroid hormones have many effects on the heart and cardiovascular system. The aim of this study was to investigate the relationship between serum thyroid hormone levels, within the normal range, and the presence and severity of CAD in patients referred for coronary angiography.

Methods: We have studied a total of 119 consecutive patients (77 men, mean age 60.7±13.8 years) who underwent coronary angiography. Blood samples were tested for serum thyroid stimulating hormone (TSH) concentrations and for free triiodothyronine (T3) and free thyroxine (T4) concentrations. Additionally, conventional risk factors, clinical characteristics and angiographic results of coronary artery assessment were obtained. The Gensini scores were calculated for determination of the severity of CAD.

Results: T3 levels were significantly lower in subjects with CAD (4.0±0.7 vs. 4.5±0.6, P<0.0001). Moreover, severe CAD was significantly associated with lower T3 levels (3.9±0.7 vs. 4.5±0.6, P<0.0001). Multivariate logistic regression analysis demonstrated that the lower serum T3 levels was associated with presence (OR: 0.266, 95% CI: 0.097-0.731, p=0.01) and severity (OR: 0.238, 95% CI: 0.083-0.685, p=0.008) of CAD. By ROC analysis, a level of T3 < 4.2 predicted the presence of CAD with 69% sensitivity and 71% specificity (ROC area under curve: 0.744, 95% CI: 0.653-0.834, P<0.0001) in euthyroid patients.

Conclusions: Serum T3 levels within the normal range were inversely associated with the presence and severity of CAD in patients referred for coronary angiography. Moreover, lower serum T3 concentrations were correlated with the Gensini score and independently predicted the presence and severity of CAD in euthyroid patients. The T3 levels may be used to indicate increased risk of CAD.

The importance of troponin I release curve in the Myocardial Infarction

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Troponin is a decisive biomarker in the diagnosis of myocardial infarction (MI) and has established prognostic power, differentiating MI from unstable angina. However, the best timing for the blood sample or the cut-off point, of troponin I (T) blood concentration, which has the most prognostic information, is not yet established. We aimed to clarify the prognostic information given by the T release curve.

The subjects admitted with MI (68.9±13.0 years, 62.6 men, 44.9% STEMI), variables: admission T (Tadm), 2nd T measurement (T24h), 2nd T measurement (Tmax), T slope between the 1st and 2nd measurement (Tsp) and the maximum T value at 24 hours from admission (T24h), Tadm and T24h were further divided (percentile50, 50.75). Primary outcomes were in-hospital (IH) and 24-months mortality (24M).
T release curve does not increased prognostic information compared to other validated risk scores. Frequent T measurements, usually done in daily practice, seems not to have any clinical relevance.

### Phosphoglucomutase activity might be a useful diagnostic marker during the acute phase of ST-elevation myocardial infarction

**M. Nishinari**1, N. Ayama2, Z. Ogawa2, S. Yuki2, S. Oka2, Y. Kurosaki2, I. Takeuchi1, R. Inukai3, H. Takehana4, T. Izumi5, 1Kitasato University, School of Medicine, Department of Cardio-Angiology, Sagamihara, Japan; 2Kitasato University, School of Allied Health Sciences, Sagamihara, Japan

**Purpose:** In acute myocardial infarction (AMI) patients, the activity of phosphoglucomutase (PGM), a key enzyme in cellular glucose utilization and energy homeostasis, was previously found to be higher than that in patients with angina pectoris. Since PGM levels increased along with those of myocardial (creatine phosphokinase, aspartate aminotransferase, troponin T, heart type fatty acid-binding protein), thrombosis (total plasminogen-activator inhibitor type 1, D-dimer), and inflammatory biomarkers (C-reactive protein, pentraxin 3), PGM might be a useful diagnostic marker during the acute phase in these patients. However, the relationship between PGM activity and acute thrombosis (AT) in patients with ST-elevation myocardial infarction (STEMI) remains unknown. To clarify this, in this study, PGM activity in patients with STEMI was compared with that in non-STEMI patients.

**Methods:** We evaluated the PGM activity in 290 healthy adults. PGM activity in the range 4.8–29.0 U/l was considered normal. Then, we evaluated the levels of serum PGM activity in 62 patients with AMI (54 with STEMI and 8 with NSTEMI).

**Results:** The levels of PGM activity were increased in AMI, especially in the STEMI group (49.6 U/l) on admission. Peak PGM activity was significantly higher in the STEMI than in the NSTEMI group (STEMI 157.8 U/l, NSTEMI 86.0 U/l, P = 0.0038). Additionally, of all the myocardial markers, the median time from admission to the peak level was shortest for PGM. Moreover, PGM activity in AMI patients with shock was 3-fold higher than that in AMI patients without shock.

**Figure 1. PGM activity in ischemic heart disease**

**Conclusions:** Our findings suggest that PGM activity can increase with the development of AT; moreover, it might be useful as a diagnostic and predictive marker in patients with STEMI.

### Effects of CD31 expression on circulating CD4 T-cells in patients with unstable angina

**P. Tourakis, D. Toussouli, A. Katakis, N. Papageorgiou, C. Mpiri, K. Toulouzas, G. Siasos, C. Antoniades, C. Tsetlouri, C. Stefanadis. Hippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece**

**Purpose:** CD4+CD28null T cells are considered to have a direct involvement in plaque destabilization and in occurrence of acute coronary syndromes. In addition, studies indicate that CD31 signal acts as regulator of T cells activation and proliferation as modulator of T cell migration through vascular wall. Therefore, in the present study we aimed to evaluate CD31 expression on overall CD4+T cells in patients with unstable angina compared to healthy controls.

**Forty one patients with unstable angina and fourteen healthy controls were enrolled. Peripheral venous blood samples were obtained within 24h after admission of patients with unstable angina. Circulating CD4+CD28null T cells and total CD4+CD31- T cells were assessed by flow cytometry and expressed as percentage of CD4+ T cells. At the same time CD4+CD31+ T cells, CD4+CD28+ T cells and CD4+CD28null T cells were analyzed by the same method and expressed as percentage of the whole number of T cells.**

**Results:** The number of circulating CD4+CD28null T cells and total CD4+CD31- T cells was compared between patients with unstable angina and healthy controls. Patients with unstable angina had higher frequencies of CD4+CD28null T cells (18.335±8.990 vs 13.848±9.737, p=0.1199), and total CD4+CD31- T cells (84.166±9.766 vs 76.114±16.173, p=0.1701), but no significant difference was observed. In addition, CD4+CD28+ T cells (35.483±3.029 vs 37.579±11.647, p=0.52) and CD4+CD28null T cells (9.111±5.463 vs 6.338±4.538, p=0.0948) did not differ significantly between the two groups when expressed as percentage of the whole number of T cells. Nevertheless, the frequency of CD4+CD31+ T cells showed a significant increase in healthy controls (6.674±3.895 vs 11.227±7.709, p=0.0057).

**Conclusions:** We have shown that patients with unstable angina have significantly lower frequencies of circulating CD4+CD31+ T cells. However, no significant difference in the percentage of circulating CD4+CD28null T cells and total CD4+CD31- T cells was observed. Our results suggest that the presence of CD31 molecule seems to have a key atheroprotective role.

### Glycated hemoglobin is associated with complexity of coronary artery disease even in non-diabetic patients

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**Purpose:** Glycated hemoglobin (HbA1c) value relates with risks of cardiovascular events. However there is no previous study to evaluate the predictive value of HbA1c for the complexity of coronary lesions. The aim of this study is to evaluate the correlations between HbA1c and complexity of coronary artery disease using the SYNTAX score (SXscore).

**Methods:** Subjects were 577 consecutive patients who underwent first coronary angiography and were measured HbA1c from December 2008 to August 2011. The complexity of the coronary lesions were evaluated by the SXscore.

**Results:** The study patients were divided into quartiles according to HbA1c or demonstrated higher (FG) values. Both higher HbA1c quartiles and higher FG quartiles were significantly associated with higher SXscore (p<0.0001 and p=0.026, respectively). When the study population was limited to the patients with any coronary lesions (n=249), higher HbA1c quartiles still presented association with higher SXscore (p=0.048). However, the association between FG quartiles and the SXscore disappeared. The association between higher HbA1c quartiles and SXscore was present even in non-diabetic subset (n=433, p=0.004).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Sex</td>
<td>2.989 (1.570–5.786)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Age</td>
<td>1.045 (1.019–1.070)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.438 (0.827–2.498)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.407 (0.901–2.200)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.052 (0.583–1.900)</td>
<td>NS</td>
</tr>
<tr>
<td>pCRP</td>
<td>1.000 (0.991–1.008)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.564 (1.202–2.034)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

**Table 1. Adjusted Odds ratios for prediction of intermediate or high SYNTAX score patients**
In addition, higher HbA1c value presented independent predictive value for the patients with intermediate or high SxScore (the SxScore >23) after adjusted for age, sex, hypertension, dyslipidemia, creatinine and GFR values (Odds ratio 1.564, 95% CI 1.202 to 2.034, p=0.0069) Table. 

Conclusions: HbA1c significantly associates with the complexity of coronary lesions. The association is observed even in non-diabetic adults. Higher HbA1c value is an independent predictor for the prevalence of complex coronary lesions.

Predicator 948

Endothelial function and circulating CD4+T cells in acute coronary syndromes

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Purpose: Previous studies support the crucial role of immune responses in the development and progression of atherosclerosis. CD4+CD28null T cells and CD4+CD31- T cells represent two specific subsets of circulating CD4+ T cells that affect endothelium. However, their accurate role on endothelial function remains controversial. Therefore, in the present study we examined the association between the frequencies of these T cells subsets and endothelial function in patients with unstable angina compared to healthy individuals.

Methods: Twenty nine patients with unstable angina (23 males, mean age 61±2 years) and fifteen healthy controls (8 males, mean age 58±2 years) were studied. Endothelium-dependent function was evaluated by estimating the flow mediated dilation (FMD) of the brachial artery. Venous blood samples were taken at the time of the index event for the patients with unstable angina. Circulating total CD4+ T cells, CD4+CD28null T cells, CD4+CD28+ T cells, CD4+CD31+ T cells and CD4+CD31- T cells were analyzed on fresh blood samples by flow cytometry.

Results: We compared the endothelial function and the levels of circulating CD4 T cells between patients with unstable angina and healthy controls. Patients with unstable angina had significantly impaired FMD than healthy controls (5.12±0.47 vs 8.24±0.713, p=0.001) that was correlated with a significant increase in the frequency of circulating CD4+CD31- T cells when these cells were expressed as percentage of CD4+ T cells (83.95±2.049 vs 72.76±4.803, p=0.002) and as percentage of the whole T cells (33.54±5.272 vs 24.49±3.3, p=0.002). However, there was no significant difference in the percentage of total CD4+ T cells between the two groups (57.06±2.542 vs 59.87±3.598, p=0.15), either in the frequency of CD4+CD31+ T cells (5.57±0.632 vs 8.83±1.773, p=0.346), CD4+CD28null T cells (6.1±0.949 vs 6.83±1.55, p=0.241) or CD4+CD28+ T cells (30.22±2.116 vs 25.51±3.652, p=0.157) when expressed as percentage of the whole number of T cells.

Conclusions: The findings of the present study demonstrate that patients with unstable angina have significantly impaired FMD and significantly higher frequencies of CD4+CD31- T cells. These findings suggest that the increased levels of circulating CD4+CD31- T cells may significantly ameliorate endothelial function in patients with unstable angina.

Predicator 949

Obesity and body mass index: how they affect BNP measurements in patients with acute myocardial infarction?


Purpose: Several studies have indicated an inverse relation between obesity and body mass index (BMI) and BNP levels in Heart Failure patients. This pattern is not known in patients with acute myocardial infarction (AMI).

Methods: From 2004 to 2011, 1293 consecutive patients with acute myocardial infarction were enrolled in a prospective registry of a tertiary hospital. We selected 458 patients for whom BNP was drawn. Obesity was defined as BMI ≥ 30 kg/m². The higher level of BNP, clinical and laboratory characteristics were compared between Obese and non-obese patients. Continuous variables are described as means±SD or median with interquartile range. Categorical variables are described as relative frequencies. The t-Student test and Mann-Whitney test were used to compare continuous variables as appropriate and the x² test was used for categorical variables comparison. The multivariable linear regression model was used to identify independent predictors of MVD (odds ratio: 1.378, 95% confidence interval: 1.231 to 1.543, p=0.001).

Results: The higher level of BNP, clinical and laboratory characteristics were compared between Obese and non-Obese patients. Continuous variables are described as means±SD or median with interquartile range. Categorical variables are described as relative frequencies. The t-Student test and Mann-Whitney test were used to compare continuous variables as appropriate and the x² test was used for categorical variables comparison. The multivariable linear regression model was used to identify independent predictors of MVD (odds ratio: 1.378, 95% confidence interval: 1.231 to 1.543, p=0.001).

Conclusions: Our results revealed that the increased proportion of CD4+CD16+ monocytes associated with severity of CAD in patients with SAP. Preferential increase in peripheral CD4+CD16+ monocytes might closely relate to the pathophysiology of CAD progression.

Predicator 950

Circulating CD4+CD16+ monocyte subsets as biomarkers for severity of coronary artery disease in patients with stable angina pectoris

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Purpose: Circulating monocytes can be divided into two subsets typically identified by the expression of CD14 and CD16. Although previous studies have shown that circulating monocytes contribute to the progression of coronary atherosclerotic lesions, the relationship between the severity of coronary artery disease (CAD) and the two distinct monocyte subsets has not previously been evaluated. We investigated the relationship between monocyte subsets and severity of CAD assessed by coronary angiography (CAG) in patients with stable angina pectoris (SAP).

Methods: We enrolled 125 patients who underwent diagnostic CAG. Patients were divided into three groups; those without CAD, those with single- vessel disease (SVD) and those with multiple-vessel disease (MVD), according to diagnostic CAG findings. In addition, severity of CAD was assessed by angiographic score (ASAP). Two monocyte subsets (CD14+CD16- and CD14+CD16+) were measured by flow cytometry.

Results: Circulating CD14+CD16+ monocytes were more frequently observed in patients with MVD (24.4±18.5 to 29.8%) than in those with SVD (vs. 12.0 to 16.2%, p<0.001) or without CAD (vs. 9.7 [6 to 10.2%], p<0.001). High-sensitivity C-reactive protein and soluble CD40 ligand were not significantly different among the three groups. The proportion of CD14+CD16+ monocytes was positively correlated with Gensini score (r=0.618, p<0.001). Multivariate logistic analysis revealed that the preferential increase of CD14+CD16+ monocytes was an independent predictor of MVD (odds ratio: 1.378, 95% confidence interval: 1.231 to 1.543, p=0.001).

Conclusions: Our results revealed that the increased proportion of CD14+CD16+ monocytes associated with severity of CAD in patients with SAP. Preferential increase in peripheral CD14+CD16+ monocytes might closely relate to the pathophysiology of CAD progression.

Predicator 951

Location of ischemia below the stent - intracoronary electrocardiography for identification of mechanisms for periprocedural myocardic infarction

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Background: We studied a new method for detection of ischemia in main vessel territory after stenting using intracoronary guidewire as ECG electrode. Methods: After placement of intracoronary guidewire an uninsulated proximal end of wire was connected to unipolar V lead. Intracoronary unipolar ECGs were recorded before, during and after stent placement and at the end of procedure. The maximal ST-segment elevation during intervention and 5 min after the procedure was recorded. At the end, the coronary wire was placed in every distal vessels with reference caliper “1.5 mm”, “mapping” the distal zones for ischemia presence and distribution. The patient population consists from 42 patients with stable/ unstable angina with troponin I evaluated before and after PCI.

Results: From 42 pts. 71% were males, mean age 67±8, 9 diabetes 29%. Thirty seven percent had previous myocardial infarction, 41% previous PCI. 69% had multivessel disease. The main treated vessel was LAD (75%). After PCI 19 patients had increased troponin values (45%). On cECG the maximal ST-segment elevation was 13.6±8 mm. At the end of procedure 26 patients had residual ST elevation (62%); 10/24 (24%) in distal MB (> 3cm for distal stent length), 8/42 (19%) in 3 cm below the stent and 5/42 (12%) in both locations. In comparison with those without enzyme leak, in troponin (+) patients after PCI, the residual ST-segment elevation was significantly higher (2.9±3.0mm vs. 0.1±1.9mm, p=0.013). The cECG final STE-3mm had sensitivity of 100%, specificity 82% to detect periprocedural myocardic infarction (troponin elevation), with positive predictive value of 75% and negative predictive value 100%.

Conclusions: The intracoronary ECG identified 3 types of residual location of ST-segment elevation at the end of stenting predicting periprocedural myocardic infarction. The proximal type (immediately below the stent) is possibly connected with microvascular dysfunction caused from stent implantation, distal type possibly connected with distal plaque/thrombus embolisation and combined type – combination of both types.
Periprocedural ischemia in coronary bifurcation: staining detected by intracoronary electrocardiography - influence on long-term results

D.I. Vassilev1, A.A.Alexandrova1, H.F. Mateev1, M. Pehlivanova1, P. Pavlova1, E. Kostova1, M. Hazan2, S.L. Golebiowska1, N. Gotcheva1, R.J. Gölz1, 1National Heart Hospital, Sofia, Bulgaria; 2Central Hospital of the Internal Affairs and Administration Ministry, Warsaw, Poland

Background: There is uncertainty about influence of periprocedural ischemia and myocardnecrosis on long-term results of coronary artery bifurcation stenting (PCI). The aim of the study is to explore the influence of end-procedural ischemia (detected with intracoronary electrocardiography [ieECG]) and post-procedural myocardnecrosis (toprofin and creatin-phosphokinase -- MB [CK-MB] elevation) on revascularization rates (TLR) and cumulative MACE (death, myocardial infarction, TLR, rehospitalization) rates at 9-12 months after PCI.

Methods: After placement of intracoronary guidewires in main branch (MB) and side branch (SB) an unintoshed proximal ends of wires were connected to unipolar V leads. Intra coronary unipolar ECGs (ieECG) were recorded before, during and after stent placement and at the end of procedure. The maximal ST-segment elevation during intervention and 5 min after the procedure was recorded in MB and SB. At the end, the coronary wire was placed in every distal vessels with reference caliber >1.0mm, as well as in MB just below the stent, "mapping" the largest fibrocic area was found in OMI (≥50% vs. CONTR), whereas the highest from 60 patients with stable/unstable angina. Procedural T-stenting was a default strategy.

Results: 72% were males, age 66±8, diabetes 34%; 43% had previous myocardial infarction, 41% previous PCI. 58% had multivessel disease. The main treated vessel was LAD (72%). True bifurcation lesions (Medina XX1) were 58%.

On ieECG the maximal ST-segment elevation was 12±9 mV in MB and 8±7 mV in SB (p<0.044). At the end procedure 44 patients had residual ST changes (66%): 7:13% SB only, 11 (21%) MB only, 16 (27%) in both. In 8:12% depression in SB or MB, 1:15% was with SB ST-depression and MB ST-elevation, 1.1% with ST-depression in both branches. Changes on ieECG have 78% sensitivity, 0.97% specificity for detection of post-procedural troponin elevation (32, 48%)

Conclusion: Differentiation of ischemia region, prediction of periprocedural myonecrosis and markers for perifibrosis may be helpful for the stage classification of myocardial infarction.
Left circumflex coronary artery is underdiagnosed as culprit lesion in STEMI and increases both short- and long-term mortality

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**Background:** Left circumflex coronary artery (LCA) occlusion in the setting of acute coronary syndrome (ACS) is often difficult to diagnose and thus primary PCI in this subgroup of patients may be delayed.

**Methods and patients:** Altogether 24 894 patients enrolled into the nationwide Registry of Cardiovascular Interventions (RCI) in the years 2005 and 2006 were classified as having ACS. From this number 12 123 (mean age 65.8 yrs, 4 062 females) were classified as having no ST segment elevation myocardial infarction (NSTE) and 12 771 (mean age 63.9 yrs, 3,967 females) as ST segment elevation myocardial infarction (STEMI). RCI is connected to the official Institute of Health Information and Statistics and updates regularly information about the death of any subject in the RCI.

**Results:** Culprit lesion was identified as left main (LM) in 2.12%, left anterior descending (LAD) in 38.11%, LCA in 28.2%, right (RCA) coronary artery in 28.7%, and aorto-coronary venous graft or left internal mammary graft in 2.89% in NSTE patients and in 1.25%, 42.52%, 15.1%, 40.35% and 0.81% in STEMI patients, respectively. Patients with LCA involvement were significantly more often represented in NSTE group as compared to STEMI patients (p<0.05). Thirty-day survival rate in NSTE with LAD, LCA and RCA and STEMI patients with LAD, LCA and RCA culprit lesion was 97.8%, 96.9%, 97.8%, 91.8%, 86.9% and 96.1%, respectively; p<0.05), five-year survival rates in the respective subgroups were 91.01%, 0.762%, 0.797%, 0.753%, 0.678% and 0.799% (p<0.05) (Fig. 1).

**Conclusion:** Underdiagnosis of LCA involvement in STEMI translates into significantly worse both short- and long-term prognosis in these patients.

Unrestricted use of two new-generation drug-eluting stents in patients with acute myocardial infarction: a propensity score matched analysis

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**Objectives:** This study sought to compare everolimus-eluting stents (EES) with zotarolimus-eluting stents (ZES) in patients with acute myocardial infarction (AMI).

**Background:** A paucity of data has exclusively evaluated the safety and efficacy of second-generation drug-eluting stents (DES) in the setting of AMI.

**Methods:** The present study enrolled 3309 AMI patients treated with ZES (n=1,608) or EES (n=1,701) in a large-scale, prospective, multicenter Korea Acute Myocardial Infarction Registry (KAMIR). Propensity score matching was applied to adjust for differences in baseline clinical and angiographic characteristics, producing a total of 2,646 patients (1,343 receiving ZES, and 1,334 receiving EES). Major outcomes at 1 year were compared between the 2 propensity score matched groups. Target lesion failure (TLF) was defined as the composite of cardiac death, recurrent nonfatal myocardial infarction (Re-MI), or target lesion revascularization (TLR).

**Results:** After propensity score matching, baseline clinical and angiographic characteristics were similar between the 2 groups. Clinical outcomes of the propensity score matched patients showed that despite similar incidences of Re-MI, in-hospital and 1-year mortality, patients in the EES group had significantly lower incidences of TLF (6.5% vs. 8.7%, P<0.029), and probable or definite stent thrombosis (0.3% vs. 1.6%, P<0.001) as compared with those in the ZES group. Furthermore, there were numerically lower incidences of TLR (1.2% vs. 2.2%, P<0.05) in the EES group than in the ZES group.

**Conclusions:** In this propensity-matched comparison, EES appears to be superior to ZES in reducing TLF and stent thrombosis in patients with AMI.

Characteristics of plaque composition which induce slow flow phenomenon during percutaneous coronary intervention: virtual histology-intravascular ultrasound study

**T. Ohwada**, T. Yokokawa, T. Sakamoto, K. Watanabe, Fukusima red cross hospital, Fukushima city, Japan

The aim of this study is to elucidate the characteristic(s) of plaque composition (PC) which induce slow flow phenomenon (SFP) during percutaneous coronary intervention (PCI) using virtual histology-intravascular ultrasound (VH-IUS).

**Methods:** We assessed PC with VH-IUS in 160 consecutive patients (stable coronary disease, n=89; acute coronary syndrome, n=71) before PCI. Fibrotic (Fi), fibro-fatty, necrotic core, and dense calcification (DC) regions were estimated as the culprit lesion area in the minimum lumen diameter frame and as volume in the entire segment. Angiographic slow-flow was defined as TII flow grade 5-2 after PCI. Patients were divided into slow-flow group (SFG, n=28) and normal-flow group (NFG, n=132). Peaklevel of creatine phosphokinase (CPK) was measured after PCI in patients of SFG.

**Results:** Vessel area (16.0±5.7 vs. 13.2±5.7 mm², P=0.0246), FA area (6.3±3.1 vs. 4.6±3.1 mm², P=0.0103), plaque volume (190±140 vs 129±95mm³, P=0.0496) and FI volume (86±72 vs 53±43 mm³, P=0.0279) were significantly greater in SFG compared with NFG. %DC area (4.1±4.6 vs. 6.8±7.0 mm², P=0.0162) and %DC volume (4.6±3.3 vs. 6.9±5.2 mm³, P=0.0051) of SFG were smaller than those of NFG. Multivariatelogistic regression analysis identified FI volume (OR, 1.357; 95%CI; 1.034-1.782, P=0.0278) as a significant predictor of SFP. Interestingly, peak CPK was correlated with FI volume (r=0.559, P=0.047).

**Conclusion:** SFP during PCI depends on the plaque characteristics defined by VH-IUS. Moreover, myocardial damage after SFG could be estimated by FI volume with VH-IUS.
Significance of ST-segment depression in patients with reperfused ST-segment elevation myocardial infarction. Assessment by cardiac magnetic resonance

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Purpose: The aim of our study was to evaluate by cardiac magnetic resonance (CMR), the dynamics of ST segment depression (STD) in patients with a reperfused ST-segment elevation myocardial infarction (STEMI) and its association with the structural impact on the left ventricle (LV). A preliminary analysis of its prognostic significance was performed.

Methods: The study involved 191 consecutive patients admitted for a first STEMI. ECG was recorded at admission, 90 minutes, 24 and 96 hours after reperfusion. The sum of STD (sumSTD) in all leads was calculated. CMR was performed at one-week, and the ejection fraction (EF %), area at risk (% of LV mass with edema in T2 sequences), infarct size (% of LV mass with late gadolinium enhancement) and microvascular obstruction (MVO, % of LV mass with lack of late gadolinium enhancement in the core of the infarct area) were measured. ECG and CMR were quantified by independent observers. Patients were categorized according to sumSTD, higher than the median at admission (1 sumSTD, anterior infarctions: > 2 mm; non-anterior infarctions: > 6 mm).

Results: SumSTD rapidly normalized in comparison with the ECG recorded at admission (0.9 ± 0.2 vs 24 hrs (0.4 ± 1 mm) and 96 hrs after reperfusion (0.3 ± 1 mm), p < 0.001. A patient with an anterior myocardial infarction (n=85) exhibited less sumSTD at admission than those with a non-anterior infarction (4.7 ± 7 vs 7.5 ± 5 mm, p=0.003). SumSTD was not associated with EF, infarct size nor MVO (p > 0.2) in neither anterior nor non-anterior in- farctions. A single STEMI patient (1/sumSTD) did show association with a larger area at risk in both, anterior (42 ± 14% vs 35 ± 15%, p=0.05) and non-anterior infarctions (25±10% vs 17±12%, p=0.02). During a 6-month follow-up, 17 re-infarctions and 17 re-admissions for acute heart failure: 34 patients (17%) had a myocardial infarction and 17 re-admissions for acute heart failure.

Conclusions: SumSTD was not associated with outcomes neither in anterior (23% ± 6%), nor in non-anterior myocardial infarctions (15% ± 10%, p>0.3). Conclusion: In patients with STEMI tends to progressively and rapidly normal- ize after reperfusion. At admission, STD is greater in anterior myocardial infarctions and, regardless of infarct location, it is associated with a greater my- ocardial area at risk but does not predict the magnitude of systolic dysfunction, the size of necrosis nor the microvascular damage. STD is not an accurate predictor of outcomes during a mid-term follow-up.

Coronary artery calcification and the risk of heart failure in the elderly; The Rotterdam Study

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Background: Heart failure is often observed as a first manifestation of coronary atherosclerosis rather than a sequel from overt coronary heart disease (CHD). Although numerous studies have shown that coronary artery calcification (CAC), an established measure of coronary atherosclerosis, is a strong predictor of myo- cardial infarction and mortality in the general population, the association be- tween CAC and future heart failure remains controversial.

Objectives: The purpose of this study was to determine the association of CAC with incident heart failure in the elderly, and examine its independence of overt CHD.

Methods: Within the Rotterdam Study, a prospective population-based cohort, 1,897 asymptomatic participants (mean age 69.9 years, 56% women) underwent CAC scoring and were followed for the occurrence of heart failure and CHD mortality. Case: During a median follow-up of 6.8 years, we registered 12 deaths, 13 re- hospitalizations for acute heart failure, and 287 cases of non-fatal CHD. After adjustment for cardiovascular risk factors, increasing CAC scores were associated with heart failure (P trend < 0.001), with a RR of 4.2 (95%CI of 1.9 to 9.1) for CAC scores above 400. Moreover, adding CAC to cardiovascular risk factors resulted in an optimization-corrected increase in the c-index (95%CI) by 0.030 (0.001 to 0.050) to 0.734 (0.698 to 0.770) and increased the accuracy of risk estimation in one of the three subsources (continuous net reclassification index 34%).

Conclusions: CAC has a clear association with the risk of heart failure, independ- ently of overt CHD. Since heart failure is highly prevalent in the elderly, it might be worthwhile to include heart failure as an outcome in future risk assessment programs incorporating CAC.

Coronary arterial tortuosity: comparison with retinal arteries and carotid intima-media thickness

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Purpose: We conducted a prospective study to investigate the possible relation- ship between tortuosity of coronary arteries (TCA) and carotid intima-media thick- ness and to compare TCA with retinal artery tortuosity.

Methods: 105 participants (aged 37-81 years) with nonsignificant coronary plaque or apparently normal coronary angiogram were included in the study. Group 1 consisted of 58 individuals with TCA and group 2 consisted of 47 individ- uals without TCA. Tortuosity was identified by finding of ≥3 bends. To deter- mine subclinical atherosclerosis, maximum carotid intima-media thickness was measured. Ophthalmic evaluation was performed to determine retinal tortuosity.

Results: From all demographic variables and risk factors only female gender (p < 0.008), retinal artery tortuosity (p = 0.001), and height were significantly associated with TCA (p = 0.001 and p = 0.01 respectively). Retinal artery tortuosity and retinal artery atherosclerosis were more common in patients with TCA than without TCA group (p = 0.001, R = 0.6; p = 0.02, R = 0.4 re- spectively). Carotid intima-media thickness was higher in participants with TCA than without TCA (p = 0.001) and also presence of carotid artery plaque was more common in patients with TCA (p < 0.001). There was significant correlation between presence of subclinical atherosclerosis and TCA (p = 0.085, R = 0.3). Like- wise, significant correlation were found between subclinical atherosclerosis and retinal artery tortuosity (p = 0.02, R = 0.3). Multivariate analysis identified female gender (p = 0.001), retinal artery tortuosity (p = 0.001), and height (p = 0.01) as independent predictors of TCA.

Conclusion: These results indicate that, whatever the mechanism is, 1) TCA is associated with female gender and in addition retinal artery tortuosity only female gender and height were significantly associated with TCA (p = 0.001 and p = 0.01 respectively). Retinal artery tortuosity and retinal artery atherosclerosis were more common in patients with TCA than without TCA group (p = 0.001, R = 0.6; p = 0.02, R = 0.4 re- spectively). Carotid intima-media thickness was higher in participants with TCA than without TCA (p = 0.001) and also presence of carotid artery plaque was more common in patients with TCA (p < 0.001). There was significant correlation between presence of subclinical atherosclerosis and TCA (p = 0.085, R = 0.3). Like- wise, significant correlation were found between subclinical atherosclerosis and retinal artery tortuosity (p = 0.02, R = 0.3). Multivariate analysis identified female gender (p = 0.001), retinal artery tortuosity (p = 0.001), and height (p = 0.01) as independent predictors of TCA.

Comorbidities are the risk factors of cardiogenic shock complicated by acute myocardial infarction in hospitalized patients


Objectives: To determine the risk factors which can increase the risk of cardio-
genic shock complicated by acute myocardial infarction (AMI) and the influence of cardiac shock on the prognosis of AMI.

**Methods:** We conducted a retrospective study on 5523 Chinese patients who were treated with AMI. Clinical information collected from medical records, including age, sex, comorbidity disease, complication and clinical outcome, were statistically analyzed to determine the risk factors for cardiac shock in patients with AMI. Then we evaluated the influence of cardiac shock on the prognosis of AMI.

**Results:** Of 5523 hospitalized AMI patients, 197 (3.56%) progressed to cardiac shock. On the basis of logistic regression analysis with adjustment for confounding factors, age, previous myocardial infarction, previous stroke, chronic renal failure and pneumonia were independently risk factors for cardiac shock complicated by AMI, with an adjusted OR (odds ratio) of 1.02 [95% CI (confidence interval) 1.01 to 1.03].

**Conclusions:** Our research demonstrates that age, previous myocardial infarction, stroke, chronic renal failure and pneumonia are significantly associated with occurrence of cardiac shock of patients with AMI and once AMI patients complicated with cardiac shock, their risk of 30-day mortality is increased. Early verified and managed AMI patients who were prone to cardiac shock may reduce 30-day mortality.

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**Table 1. Comparison of apoptosis levels according to reperfusion time in two groups**

<table>
<thead>
<tr>
<th>Time of reperfusion (hour)</th>
<th>PCI</th>
<th>Thrombolysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>0.83±0.241</td>
<td>0.868±0.245</td>
<td>0.211</td>
</tr>
<tr>
<td>6 h</td>
<td>1.03±0.33</td>
<td>0.971±0.30</td>
<td>0.092</td>
</tr>
<tr>
<td>12 h</td>
<td>1.415±1.04</td>
<td>1.45±0.77</td>
<td>0.715</td>
</tr>
<tr>
<td>24 h</td>
<td>1.415±1.04</td>
<td>1.70±0.91</td>
<td>0.417</td>
</tr>
<tr>
<td>48 h</td>
<td>2.59±1.55</td>
<td>2.64±1.86</td>
<td>0.895</td>
</tr>
<tr>
<td>72 h</td>
<td>3.57±2.03</td>
<td>3.95±2.15</td>
<td>0.665</td>
</tr>
</tbody>
</table>

**Conclusion:** Apoptosis is accelerated by reperfusion and is regardless of reperfusion method either thrombolysis or PCI.

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**P966**

**Comparison of levels of reperfusion induced apoptosis between thrombolytic and primary percutaneous coronary intervention to treat ST-segment elevation myocardial infarction**

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**Objective:** After an acute ST-segment elevation myocardial infarction (STEMI), early and successful myocardial reperfusion is the most effective strategy for reducing the size of myocardial infarct. The process of restoring blood flow to the ischemic myocardium, however, can induce injury. This phenomenon, termed myocardial reperfusion injury, can paradoxically reduce the effects of myocardial reperfusion.

Apoptosis is a specific feature of reperfusion injury in cardiomyocytes leading to late cell death. We aimed to compare the apoptosis levels of patients underwent primary percutaneous coronary intervention (PCI) (Group 1) versus thrombolysis (Group 2) for acute ST-segment elevation myocardial infarction (STEMI).

**Methods:** The total of ninety-two patients with STEMI who were admitted within the first 6 h of onset of symptoms and treated with PCI or thrombolysis were included in the study. Venous blood sampling to measure the levels of apoptosis by using Cell Death Detection ELISA plus kit were obtained before (0 h) and after the reperfusion therapy at the 6th, 12th, 24th, 48th and 72nd hours. Furthermore, Creatine kinase (CK), CK-MB and troponin levels were measured at 0, 6, 12 and 24 hours.

**Results:** Group 1 and Group 2 patients did not differ for main demographic, clinical characteristic and laboratory findings. Reperfusion induced apoptosis developed progressively during the late phase of reperfusion. There was no significant differences between the two groups for the level of apoptosis (Table 1).

**Conclusion:** Apoptosis is accelerated by reperfusion and is regardless of reperfusion method either thrombolysis or PCI.

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**P967**

**Implantation of new echocardiographic techniques for asses in patients with acute myocardial infarction**

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The aim of our study was to investigate the ability of speckle tracking echocardiography (STE) (using vector velocity imaging technique (VVI)) to determine the infarct size 24 hours after early primary percutaneous coronary angioplasty in patients with AMI. The results were compared with intracoronary electrocardiography records (i.e. ECG), as a sensitive method for ischemia detection.

**Methods:** 20 volunteers (31±5) and 36 patients (63±13) with AMI in the first 24 hours after PCI, were enrolled in this study. Standard echocardiography was performed and B-mode gray scale (65±7 frames/s) were acquired in the apical 4, and 3- chamber long axis and in the parasternal short axis at basal, middle and apical levels and strain (%) was analyzing, using a commercial STE tool in infarct, perinfarct and remote regions. The strain curves (LL, LC, RRI) were extracted and derived using VVI software in 18 segments left ventricle model. The i.e. ECG was performed during PCI procedure, making a ‘map’ of residual ischemic region expressed in same 18 segments model. STE segment resolution less than 70% on i.e ECG was accepted as a marker of necrosis in a given segment.

**Results:** After infarct, adverse remodeling (progressive increase in LV size, mass and reduced EF) was found and longitudinal strain was significantly decreased in perinfarct and remote regions early after AMI (r=-0.49, p<0.01, radial strain (r=-0.37, p<0.01) and circumferential strain (r=-0.39, p<0.05).

**Conclusion:** STE enables quantification of regional myocardial function in patients with AMI. The longitudinal strain measured early after mechanical reperfusion may predict infarct size and LV remodeling. Thus, this data suggests that radial and circumferential strain in perinfarct and remote regions early after AMI may contribute to adverse left ventricular remodeling.
Clinical impact of pre and post PCI TIMI 3 flow on myocardial infarction

Methods: Patients admitted with a first diagnosis of STEMI undergoing primary PCI (pPCI) within 12 hours from symptom onset were included in the study. Standard M-mode and 2D-echochardography was performed within 12 hours and repeated daily up to discharge and at 1 month. Diastolic thickness (EDWT) in the infarcted area was measured. Similar measures were taken in a remote area and used as control.

Results: Thirty-four consecutive patients (70% males; average age: 64±3 years old) have been enrolled so far. EDWT in the infarcted area was 11±4 mm early after reperfusion and increased progressively to the fourth day (13±4±1.3 mm; p<0.05), remaining stable thereafter (6±2 mm); no significant change in EDWT was observed in the remote area (10.8±0.9 mm and 11±0.9 mm respectively; p=ns). The variation of EDWT (∆EDWT) was significantly higher in infarcted area vs control (38.1±12% vs 12±3.7%; p<0.001). At 1 month follow-up, ∆EDWT per se does not correlate with LVEF (r² 0.010; p=0.56), while the ∆EDWT correlates with LVEF (r² 0.33; p=0.0004) and EDV (r² 0.74; p<0.0001).

Conclusions: This study confirms a progressive increase in EDWT following pPCI, as documented by pathological reports. Monitoring regional myocardial EDWT and ∆EDWT may provide a simple and reliable method to monitor myocardial recovery in STEMI, expressed as reduced end diastolic LV volume and improvement of LVEF at 1 month.

Background: Imaging techniques for assessment of ST-segment elevation MI patients

Methods: From the Korea Acute Myocardial Infarction Registry, 2,993 patients were enrolled. Cine and late gadolinium enhancement (LGE) CMR images were analysed for both AAR (Area at Risk) and infarct size. CMR early after anterior STEMI treated with primary angioplasty.

Results: The APPROACH jeopardy score was significantly lower in STEMI with TIMI 3 flow (p<0.05). Pa-PCI, as documented by pathological report. Monitoring regional myocardial EDWT and ∆EDWT may provide a simple and reliable method to monitor myocardial recovery in STEMI, expressed as reduced end diastolic LV volume and improvement of LVEF at 1 month.

Conclusions: This study demonstrates that initial TIMI 3 flow significantly decrease 1-year MACE. Also final TIMI 3 flow significantly decrease in-hospital mortality, 1-year mortality, 1-year MACE rate in patients with STEMI in Korea.
P972 Predictive value of 2D/3D deformation parameters and 3D wall motion score to identify transmural myocardial necrosis in STEMI patients: a comparative study against cardiac magnetic resonance


Purpose: To evaluate if 2D/3D deformation parameters can improve the prediction of transmural myocardial necrosis over visual wall motion assessed on 3D LV data sets by experienced reader.

Methods: In 46 patients with recent STEMI (pts, 8±3 days after primary PCI), echo and delayed enhancement cardiac magnetic resonance (DE-CMR) studies were performed <24hrs apart. The relative amount of DE tissue per segment was used to define: no necrosis (0% DE), non-transmural (0-50% DE) and transmural necrosis (51-100% DE). All subjects were selected for good image quality, sinus rhythm and adequate 2D/3D speckle-tracking in at least 14 of 17 LV segments. LV function was assessed from three apical LV 2D views by measuring 2D longitudinal strain (2D-Ls), and from 4-beat LV full-volume data sets, assessing wall motion score (WMS) and measuring 3D longitudinal (Ls), circumferential (Cs) and radial (Rs) strains.

Results: Among all parameters, 3D WMS (AUC= 0.87, 95%CI 0.83-0.90) and 2D-Ls (AUC= 0.83, 95%CI 0.80-0.87) were the best predictors of transmural extent of myocardial necrosis. The predictive value of 3D WMS was significantly higher than that of 3D C (P<0.0001; AUC= 0.76-0.84), Rs (AUC= 0.81, 95%CI 0.77-0.84; P<0.05), Ls (AUC= 0.81, 95%CI 0.77-0.84), and Lc (AUC= 0.73, 95%CI 0.69-0.77). The incremental predictive value of 2D and 3D strain parameters over 3D WMS was significant, but small (Figure). However, the AUC of the predictive model for transmural necrosis at DE-CMR which included 3D WMS, 2D Ls and 3D Cr was 0.91 (95%CI 0.88-0.93; p<0.0001).

Conclusions: Despite a good accuracy for both 3D Cr and 2D Ls, visual wall motion assessment by experienced reader on good-quality 3D data sets was found to be superior than strain quantification to predict transmural necrosis at DE-CMR.

P973 Detection of unstable plaques in STEMI patients

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The aim: Using an optical coherence tomography (OCT) to assess plaque characterisation of culprit lesion of infant related vessel and to detect possible unstable plaques of noninfarcted vessel in patients with ST elevation myocardial infarction (STEMI) treated with primary PCI (pPCI).

Method: 30 consecutive patients with single vessel disease and STEMI were enrolled in the study. OCT study of the culprit lesion of infant related vessel was performed initially after the insertion of intravenous wire either with or without lesion predilation. Final OCT of culprit lesion after stenting/aspiration and also after predilation of culprit lesion was performed after pPCI. A 9 month follow up angiography and OCT study were performed in all patients.

Results: Plaque rupture of culprit lesion was found in 10 (70%) patients. In the infant-related culprit lesion, TCFa and trombus was found in 100% of cases. Plaque rupture was recognized in 70% of lesion. In the OCT findings of non-infarct vessels, the frequency of unstable plaques was 47%. In the majority of cases (37%), only 1 non-infarct related vessel was involved. However, 3 patients (10%) have unstable plaques in both non-infarcted arteries. Moreover, plaque rupture and thrombus formation were found in 23% of cases of non-infarcted related vessels. 30-day, 6-month and 9 month follow-ups were eventful. At 9 month, the number of unstable plaques according to OCT significantly decreased from average 5.9 to 4. Furthermore, both total cholesterol and LDL cholesterol also decreased significantly (from 5.7 to 4.28 mmol/l and from 3.58 to 2.44 mmol/l respectively). Hs-CRP decreased significantly at 9 month to (5.7 to 2.5 mg/l). We found a strong correlation between the number of unstable plaques and smoking. Patients who did not quit smoking, the number of plaques was significantly higher.

Conclusions: Present study demonstrates high frequency of OCT-derived TCFa, plaque rupture and thrombus of both, infant and noninfarct-related coronary vessels in patients with evolving STEMI. Fortunately, at 9 month follow up, the number of unstable plaques significantly decreased.

P974 High intensity interval exercise training program improves quality of life and exercise capacity without significant effect on left ventricular function, in patients with chronic heart failure

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Introduction: Although exercise may have beneficial effects on cardiovascular system, findings from previous studies of the effects of exercise training programs in chronic heart failure are inconsistent. Among other diagnostic methods which determine the severity of heart failure, the six-minute corridor walk test has been revealed as a useful clinical predictor for mortality and morbidity in patients with systolic heart failure and has been used as a noninvasive tool to evaluate the efficacy of new therapies. The purpose of this study was to evaluate the effect of cardiac rehabilitation program including high intensity-interval exercise and calories balanced diet intervention, on left ventricular diastolic function, exercise capacity and QOL, in patients with CHF under optimal medical treatment.

Methods: Of the 47 clinically stable patients with CHF (NYHA II-IV, mean left ventricular ejection fraction 30%), 33 patients (82% males, mean age 55±10, 70% ischemic CHF) and 14 patients (92% males, mean age 65±9, 70% ischemic CHF) were randomly allocated as intervention and control group. The intervention group included exercise training of 30 min/day high-intensity (100% Wpeak) interval exercise on a bicycle ergometer 3 d/wk for 12 consecutive wks. Echocardiographic assessment was performed in all patients before and after rehabilitation. From the apical four-chamber view, a 10 mm sample volume was placed at the lateral mitral annulus, and transmitral E and A velocities were recorded. Quality of life (QOL) was evaluated using the Minnesota Living with Heart Failure questionnaire (range 0-105).

Results: The intervention group improved QOL-score (20% in control-group vs. 88% in intervention-group, p=0.001); increased 6-minutes walk distance (3% in control-group vs. 10% in intervention-group, p=0.025); increase watts in cardiopulmonary exercise capacity (0.5% in control-group vs. 1% in intervention-group, p=0.001); increased VO2max (5% in control-group, vs.11% in intervention-group, p=0.002); while no statistical significant differences were observed on left ventricular ejection fraction, E to A ratio (p=0.09), as compared to control group, after adjustments were made for age, gender, BMI difference.

Conclusion: High-intensity interval exercise training program, seems to improve QOL and cardiopulmonary exercise capacity, although those improvements are not accompanied with significant beneficial modification of left ventricular diastolic properties in patients with chronic heart failure.
followed by a HF trained home nurse (average 10 home visits/year) who monitored simple health indicators that were conveyed by a web-based medical record to primary care physicians and cardiologists who also received automatic alerts generated by the computer system. We used the ICAI lazy information system and national hospitalisation database to conduct the analyses. Two quasi-experimental methods were used to assess HF hospitalisations rates: one individual before-and-after analysis and one time-series trends comparison of the French national to the Lorraine region data using the national hospitalisation database. Results: The median age of the 1222 patient recruited before 2010, was 76 years and 65.5% were male. Upon enrolment, patients essentially presented with NYHA class II (n=537, 48.4%) or class III (n=395, 32.4%) symptoms. One-year mortality rate was 20.3%. The mean number of hospitalisations was significantly lower during the 6-month period after inclusion in the programme than during the 6-month period preceding inclusion (40%). The difference between the number of hospitalisations observed in the Lorraine region and that expected had it been similar to that observed in the whole country was -7.19% in 2010. The annual hospital cost avoided by ICAI was estimated to €1,766 < €2,299 per patient. Conclusions: Disease management of HF based on patient education and HF trained home-nurse patient monitoring with automated feedback to primary care physicians improve outcome cost-effectively in France. Lower rate of HF hospitalisations in patients included in ICAI had a significant population impact and could prevent in Lorraine the concomitant continuous rise of the annual HF hospitalisations rate otherwise observed in France.

**Trends in prevalence of heart failure in Sweden from 1990 to 2007 by age**

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**Purpose:** To examine trends in prevalence of heart failure (HF) leading to hospitalisation in Sweden from 1990 to 2007 in different age groups.

**Methods:** The Swedish hospital discharge register was used to calculate age-specific annual prevalence of HF in surviving patients aged 19-99 from 1990 to 2007. The Swedish population aged 19-99 was 6531984 in 1990 increasing to 7130632 in 2007.

**Results:** Prevalence of HF throughout the study increased with age. In the three oldest age groups prevalence increased from 1990 to 1998 followed by a decrease until 2007. In the two youngest age groups prevalence increased from 1990 to 2007 (Table 1). In absolute numbers HF patients in the age group 85-99 years increased from 16149 in 1990 to 24088 in 2007 (Figure 1).

**Table 1. Prevalence of heart failure in percentage from 1990 to 2007 by age**

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<td>5.0</td>
<td>4.4</td>
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<td>85-99</td>
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<td>11.5</td>
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Fig. 1: Trends in number of HF patients

**Conclusions:** Overall, prevalence of HF peaked in the late 90s and then decreased. In the three oldest age groups, containing most HF patients, prevalence peaked in 1998 followed by a decrease until 2007. Prevalence increased in the two youngest age groups, most markedly among people <55 years. In absolute numbers the age group 85-99 years increased, mainly due to demographic changes.

**Economic burden of patients with various etiologies of chronic systolic heart failure analyzed by resource use and costs**

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**Purpose:** Chronic heart failure is a major cardiac disease, going along with a high economic burden. Diagnostic and therapy differ depending on etiology of chronic heart failure. The present work analyses disease-related resource use and associated costs of systolic chronic heart failure with respect to the etiology of the disease.

**Methods:** From the database of the German Competence Network Heart Failure, 2,710 individuals with systolic chronic heart failure (mean age 62.9 years ± 13.6, 25.2% female, 89.8% NYHA II/III) were included into analyses. Resource use was assessed with regard to outpatient contacts, hospitalisations including rehabilitation, and drug utilization.

**Results:** Overall care costs per patient were 3,150 € per year. Costs of inpatient care were the largest component of direct costs (2,622 €) thus representing 83% of all costs. Costs of medication (290 €) and outpatient physician contacts (238 €) were significantly lower. Over-average costs of heart failure care appeared in patients with hypertrophic cardiomyopathy (4,681 €) and dilated cardiomyopathy (3,596 €). While patients with heart failure due to coronary artery disease (3,066 €) and arterial hypertension (1,039 €) exhibited significantly lower resource use and costs per year.

**Conclusions:** Heart failure is associated with a high economic burden. Patients with non-vascular forms of heart failure require an over-average resource use primarily due to hospital admissions. Efficient treatment strategies have to consider these aspects for optimizing care and to delimitate the economic costs of heart failure care.

**Patients with chronic systolic heart failure require individualised care also for non-cardiac problems**

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**Purpose:** The Interdisciplinary Network for Heart Failure (INH) Study developed a novel nurse-coordinated program, HeartNetCare-HF (HNC), which provides telephone-based structured monitoring and education. HNC uses a standardised 19-item questionnaire addressing indicators of worsening heart failure, symptoms, compliance, state of mood and health care utilisation. Educational modules cover e.g. medication, nutrition and physical activity. Further, patients are invited to raise questions themselves. According to the INH protocol nurses documented all telephone contacts during follow up (FUP, 180 days) were categorised regarding monitoring, education and medical problems addressed by the patients.

**Results:** 411 contacts with a mean duration of 12.5 min took place between nurses and HNC-patients. 85% of the 329 HNC patients received at least one intervention and were thus included into the analysis. Contents of telephone contacts during follow up (FUP, 180 days) were categorised regarding monitoring, education and medical problems addressed by the patients.

**Conclusions:** Our study highlights the importance of outcome-relevant non-cardiologic problems.
cardiac co-morbidities in HF patients. Solely technically based telemedical strategies can obviously not meet resulting patient needs. Individualised risk assessment and tailored integration of appropriate cardiac telemonitoring with comprehensive individualised care is required to improve outcomes in HF.

Heart failure, ventricular dysfunction and risk factor prevalence in a young Aboriginal population: The Heart of the Heart Study

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Purpose: Heart failure (HF) has a grim prognosis, with Indigenous populations having poorer outcomes and HF mortality 2-3 times greater than non-Indigenous counterparts. Despite this there has been little evaluation in this group, thus we sought to document HF, asymptomatic left ventricular dysfunction (ALVD), risk factor prevalence and associations in a young Indigenous population.

Methods: Comprehensive cardiovascular assessments, including clinical examination, echocardiography, biomarkers, ambient air measured, and medical record review were used to determine heart failure status (independently adjudicated), ALVD and underlying risk factors in participants enrolled across 6 Indigenous communities.

Results: Of 436 participants (mean age 44±14 years, 64% women) enrolled, 23 were diagnosed with HF (5.3%; 95% CI: 3.2-7.5%), only 8 had a pre-existing HF diagnosis. ALVD was observed in 53 (syngestic 11, diastolic 42) participants (13%, 95% CI: 9.4-15.7%). HF risk factor prevalence was as follows: hypertension (45% [95% CI: 37-47]), diabetes 34% (95% CI: 30-39%), coronary artery disease (CAD) 7.4% (95% CI: 4.9-9.9%), obesity (BMI >30kg/m2) and history of acute rheumatic fever or rheumatic heart disease 7.3% (95% CI: 4.9-9.8%). The mean HbA1c was 6.9±1.9%, with 37% (95% CI: 33-42%) of subjects having an elevated HbA1c (>5.5%), 18% (95% CI: 15-22%) of these without diabetes diagnosis. Elevated BP (systolic ≥140mmHg and/or diastolic ≥90mmHg) was measured in 34% (95% CI: 29-38%) with 68% (95% CI: 61-70%) without hypertension diagnosis. In logistic regression (adjusted for age and gender), HF was associated with CAD (OR: 10.9; 95% CI: 3.1-37.7), hypertension, and obesity (OR: 1.9, p=0.002; 0.9-3.9; 2.9, p=0.02). All of the above HF risk factors were associated with both systolic and diastolic dysfunction. In multivariate models (adjusted for age, sex, HF risk factors, BNP and creatinine), only CAD (p=0.04) and BNP (p=0.001) remained independently associated with impaired systolic dysfunction (LVEF <50%) and age (p=0.001), diabetes (p=0.006) and BNP (p=0.006) with diastolic dysfunction.

Conclusion: The burden of HF, a large proportion undiagnosed, along with ALVD, and risk factors in this young population were high. Impaired glucose metabolism and high BP were also noted in a significant proportion without a history of diabetes or hypertension. BP was independently associated with both systolic and diastolic dysfunction. These findings may have implications for developing appropriate strategies to improve the high rates of premature morbidity and mortality within Indigenous populations.

A comparative study of exposure to ambient air particles in patients hospitalized for heart failure: preserved versus depressed ejection fraction

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Purpose: Previous studies using administrative data have reported a positive association between short-term increases in ambient air pollution and hospitalization for HF. However, most studies have focused on patients with preserved systolic function and there is limited information on the impact of exposure to ambient air particles in patients with depressed ejection fraction (HF-REF). The aim of this study is to evaluate the impact of short-term increases in ambient particles on the hospitalization rate for HF-PEF and HF-REF.

Methods: We studied 353 consecutive patients admitted into a tertiary care hospital with a diagnosis of HF. Patients with ejection fraction of ≥45% were classified as having HF-PEF and those with an ejection fraction of <45% were classified as having HF-REF. We determined the average concentrations of different sizes of PM and SO2 in ambient air measured within 1 day up to 7 days prior to hospital admission.

Results: According to the pre-established criteria, 124 patients were classified as HF-PEF (Table). The HF-PEF population was exposed to higher nitrogen dioxide concentrations compared to the HF-REF population (12.9±6.22 vs 4.5±3.24 μg/m3, p=0.001). When comparing levels of PM10 between patients with HF-PEF and HF-REF, the first group tended to have lower values of PM10 (2.1±1.30 vs 25.1±7.53 μg/m3, p=0.02). We carried out multivariable binary logistic regression analysis, using a stepwise selection model.

Conclusion: This study has shown that nitrogen dioxide was a significant predictor of HF-PEF (OR ranging from [1.403, CI 95% 1.003-2.007, p=0.04] to [1.669, CI95% 1.043-2.671, p=0.03]).

Clinical variables of 353 consecutive patients with HF.

Conclusions: This is the first study to demonstrate that short-term nitrogen dioxide exposure is independently associated with HF admission in the HF-PEF population.

What is the burden of hospitalizations for Heart Failure in France in 2010?

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Background: Chronic heart failure (HF), common to multiple disease areas (hypertension, hyperlipidemia, diabetes, atrial fibrillation...), has a high medical unmet need (due to its morbidity/mortality) and high economic burden. Despite its severity, there is a lack of data on this disease in France, and particularly on the burden linked to HF-related hospitalizations.

Objective: Our objective was to assess the number of hospitalizations related to HF in France over one year and to estimate its burden.

Methods: Data were extracted from the French national hospital database (PMSI MCO database) covering 96% of all hospitalizations in France. For this study, all hospitalizations with an ICD-10 code related to HF as principal diagnosis for 2010 were included. Over this one-year period, we looked at the number of hospitalizations, hospitalization rate and number of patients, the duration of hospital stay, and patients' age and outcomes.

Results: In 2010, there had been 210,490 hospitalizations in France with a code related to HF as principal diagnosis. 9.1% of them were hospitalizations of less than 2 days. A hospital stay for HF had an average duration of 9.6 days (10.5 after exclusion of hospital stay shorter than 2 days). This number of hospitalizations was linked to 160,002 patients (mean age: 79.9 years), corresponding to a number per patient of hospitalizations of 1.3 and of days spent in the hospital of 12.7 (13.4 after exclusion of hospital stay shorter than 2 days). For 17.5% of the hospitalizations, patients spent on average 4.2 days in an intensive care unit. 92.2% of the patients came to hospital directly from home (via emergency rooms for 58.2% of them). Hospitalization mortality rate was 7.5%, 71.5% of the patients went back home directly after their hospitalization, and 20.6% were discharged to skilled nursing facilities.

Conclusion: In applying the 2009 average cost for hospitalization due to HF (4,458€), the annual cost associated with HF-related hospitalizations in France is close to € 1 billion. Any intervention that would significantly reduce HF-related hospitalization rate will consequently have a major impact on costs related to this disease.

A novel model to increase the rate of cardiac rehabilitation in patients after acute heart failure

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Background: Heart failure (HF) is a major cardiovascular syndrome. Cardiac rehabilitation (CR) was shown to lower the rehospitalization rate, and improve cardiac remodeling and the health-related quality of life. Nevertheless, the rate of patients who undergo CR is low. This study demonstrated a novel design to improve the CR rate.

Methods: In total, 218 patients hospitalized due to acute cardiogenic pulmonary edema were consecutively enrolled. For 60 patients in the beginning, CR was arranged in a traditional way (TW). For the following 158 patients, CR was arranged using integration (INT) of extensive amendments including a CR room design (a glass room incorporated in the cardiovascular ward), coordination with a clinical pathway-based disease manager, exercise prescription according to non-invasive hemodynamic monitoring during cardipulmonary exercise testing (CPET), adoption of arterial interval training (AIT), and change to a community-based system.

Results: There were no significant differences in the demographics between the two groups. In the INT group, compared to the TW group, patients’ knowledge of CR benefits and the motivation to engage in CR significantly improved. Our design provided a chance for patients in the acute stage to interact with those undergoing CR. The physical therapists were fully supported to perform CR since
all events during CR were safely managed by the ward team. Appropriate exercise prescription was individualized for each patient.

Conclusions: The inadequate CR rate in patients with HF can be improved by a novel integration of multidisciplinary soft- and hardware facilities.

INTRODUCTION

Physiologic variables exhibit diurnal variation due to changes in activity, posture and neural activity. HF and other diseases may influence this variation. Quantifying the variation, however, has been difficult due to limited availability of ambulatory data. MultiSENSE, a feasibility study designed to gather data from implanted CRT devices, enables evaluation of diurnal patterns in HF patients.

METHOD

Heart rate (HR, bpm), tidal volume (TV, l), respiration rate (RR, bpm) and RV-can intra-thoracic impedance (Z, Ohm) were collected throughout the day while 3rd heart sound (S3 measured by accelerometer, mg) was collected in at least 40% of patients. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows.

RESULTS

Mean age was 71.2 years, 32% were female, 65% had previous hospitalizations (LEVF = 40%) in Spain. On average, 1.2% of patients had reduced activity and a more supine posture. Mean CVs (%, mean ± SD) are: HR 7.1 ± 6.8, TV 46.4 ± 20.8, RR 7.6 ± 8.8, 2.16 ± 4.3 and S3 24.2 ± 31.7 (all p < 0.001).

CONCLUSION

Simultaneous chronic measurements from an implanted device permit quantification of diurnal variation of multiple physiologic variables. Further evaluation is warranted to determine its clinical value in HF patient management.

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Quantifying circadian variation of multiple physiologic signals in ambulatory heart failure patients

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Introduction: Physiologic variables exhibit diurnal variation due to changes in activity, posture and neural activity. HF and other diseases may influence this variation. Quantifying the variation, however, has been difficult due to limited availability of ambulatory data. MultiSENSE, a feasibility study designed to gather data from implanted CRT devices, enables evaluation of diurnal patterns in HF patients.

Methods: Heart rate (HR, bpm), tidal volume (TV, l), respiration rate (RR, bpm) and RV-can intra-thoracic impedance (Z, Ohm) were collected throughout the day while 3rd heart sound (S3 measured by accelerometer, mg) was collected in at least 40% of patients. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows. Circadian variation of a variable (CV, %) was defined as the difference between the day-time and night-time mean normalized by the least two 4-hour windows.

Results: Mean age was 71.2 years, 32% were female, 65% had previous hospitalizations due to HF and 40% of patients were evaluated within 7 years. NYHA class III/IV was assigned in older patients more than in younger patients (53% vs 37%, p < 0.001). Older patients had more previous admissions for HF (74% vs 55%, p < 0.001), atrial fibrillation (57% vs 45%, p < 0.026), anaemia (26 vs 17%, p < 0.05) and renal failure (31 vs 18%, p < 0.002). Prevalence of risk factors, ischemic heart disease and other comorbidities were similar in both groups. LEVF was 33.6% in both groups. No differences in drug therapy were observed between patients below and above 75 years in Spain.

Conclusion: Circadian variation of multiple physiologic signals was measured in ambulatory HF patients. Results suggest that, despite positive clinical evidence and guidelines recommendations, elderly HF patients may benefit from a more personalized approach.

P986

Hemodynamic optimization of cardiac resynchronization devices: Is an empiric AV delay of 120 ms the solution for any patient?

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Background: Many patients with medically refractory heart failure due to severe left ventricular (LV) systolic dysfunction and interventricular conduction disturbances benefit from cardiac resynchronization therapy (CRT). Yet there is a paucity of data regarding the optimal atrioventricular (AV) and interventricular delay (VVD) during CRT to maximize the hemodynamic response to this treatment and reduce the number of patients who do not respond to CRT. Aim of this study was to compare an empiric 120 ms AV delay to a hemodynamic optimized AV delay via non-invasive measurements via impedance cardiography (IC).

Methods: 92 patients with a CRT-D or CRT-P due to an ischaemic (n=39) or dilated cardiomyopathy (N=53) were evaluated by means of IC. Cardiac index, stroke volume, velocity index and systemic vascular resistance were measured immediately after device implantation and during every follow-up visit for a period of 6 months. After measuring the hemodynamic parameters at an AVD of 120 ms, a hemodynamic optimization via IC was performed using a standard protocol (between 80 and 200 ms were tested in increments of 20 ms) and controlled via TTE by a second physician. In order to avoid impact of the VVD, all measurements were performed at a VVD of 0 ms. Furthermore, a hemodynamic assessment at baseline settings of the device was performed.

Results: In all patients CO increased significantly at optimized AVD and VVD compared to baseline settings. Similar results were achieved for the empiric programmed AVD of 120ms, thus the results for optimized AVDs were significantly higher. Mean cardiac output prior to the optimization was 2.77 l/min/m² ± 0.65 and could be increased to 3.12 l/min/m² ± 0.67 (p < 0.01).

Conclusion: Hemodynamic optimization of the AVD can improve cardiac output significantly. Performing the optimization with IC leads to better results than an empiric programming of 120 ms. Since a large interindividual variability of optimal AVD, every patient requires an individual optimization to maximize the response to this treatment and reduce the rate of non-responders.
Lifting the curtain on takotsubo cardiomyopathy. Revelations from the takotsubo index

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Background: Takotsubo cardiomyopathy (TC) is typically considered reversible, though recent findings with 2D imaging demonstrate persisting late wall motion abnormalities. The pattern, timeframe and completeness of improvement remain to be determined. This study utilises the new parameter - The Takotsubo Index (TTI) = length of level of hypokinesia (cm)/total length of LV apex (cm) and analysis of standard 16 segment wall motion scoring on sequential follow-up of TC patients.

Methods: 69 patients (4 male, 67±12 yrs) with TC were evaluated with transthoracic echocardiography at Day 1 of presentation and follow up (514±74 days). Chest pain was the most common presentation (79%). Complications included arrhythmias (6%), death (1%) and recurrent TC (2%). Causes included emotional stress (38%), acute medical illness (31%), post-operative (13%) and other (18%). Echocardiography included STEMI (59%) and Non-STEMI (41%). Echocardiography showed ejection fraction at diagnosis of 47±3.5% rising to 56±14% at late follow up (1-1422, mean 513 days). The Takotsubo Index increased from 0.52 to 0.61±0.14 LV systolic strain (40±4.1% vs 76±14% s/p = 0.004). A multi-factor analysis moves apically with time. Apical wall motion improvement but did not normalise (see Fig. 1B).

Results: At 1-1423 days follow-up (1-1422, mean 513 days). The Takotsubo Index increased from 0.52 to 0.61±0.14 LV systolic strain (40±4.1% vs 76±14% s/p = 0.004). A multi-factor analysis moves apically with time. Apical wall motion improvement but did not normalise (see Fig. 1B).

P990 Edema index-assisted disease management improves the outcomes of patients with acute heart failure

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The efficacy of heart failure (HF) management programs is compromised by the challenge of early identification of patients at imminent risk. Segmental multi-frequency bioelectrical impedance analysis can generate an “edema index” (EI) as a surrogate for body fluid volume. We tested whether integration of EI-guided management improved the 6-month outcomes of HF patients under multidisciplinary care. In total, 189 patients with acute HF were randomized into control, case management (CM), and EI-guided CM (EI) groups (n=63 in each group). In the EI group, a management algorithm was activated only if based on the measured EI. The analyzed end points included HF, and all cause-related events during the 6-month follow-up period. In the 6 months, there were 13 late (6.9%) deaths in the control group (CM), and 10 (6.2%) in the EI group. HF-related hospitalizations and all-cause-related hospitalizations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. Compared to the control (26.4%) and CM groups (15.1%), the EI group had a lower rate of HF-related death and rehospializations. 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**Relationship of reduced cerebral blood flow and heart failure severity in elderly males**

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*Purpose:* To determine the relationship between cerebral blood flow (CBF) in elderly patients with heart failure (HF) and the severity of HF.

*Methods:* A total of 50 patients with HF were included in the study. CBF was assessed using transcranial Doppler ultrasound. The severity of HF was assessed using the New York Heart Association (NYHA) classification.

*Results:* CBF was reduced in patients with NYHA class III and IV compared to healthy controls. The correlation between CBF and NYHA class was significant (r = -0.67, p < 0.01).

*Conclusion:* Reduced CBF is associated with increased HF severity.

**Acoustic cardiography helps to identify heart failure and its phenotypes**

S. Wang, Y.Y. Lam, F. Fang, M. Liu, Q. Shang, X.X. Luo, J. Wang, J.E. Sanderson, J.P. Sun, C.M. Yu. Division of Card, Dept of M&T, VM, LiHS, SH Ho Cardio Disease & Stroke Ctr, PWH, CUHK, Hong Kong, China.

*Purpose:* To explore the utility of acoustic cardiography in the detection of heart failure and its phenotypes.

*Methods:* Acoustic cardiography was performed on 50 patients with heart failure and 50 healthy controls.

*Results:* Acoustic cardiography parameters, such as S3 score and QRS duration, showed significant differences between patients with heart failure and healthy controls.

*Conclusion:* Acoustic cardiography is a promising tool for the early detection of heart failure.

**Feasibility and validity of chair based exercise in heart failure patients**

N.A. Razab, P.J. Doherty. York St John University, York, United Kingdom

*Purpose:* To evaluate the feasibility and validity of chair based exercise (CBE) in heart failure patients.

*Method:* CBE was performed for 6 to 8 weeks in a randomized controlled trial. The CBE included walking, balance, and strength exercises.

*Results:* The CBE was feasible and well tolerated by the patients. There was a significant improvement in physical function and quality of life.

*Conclusion:* CBE is a feasible and valid exercise intervention in heart failure patients.

**Preoperative prediction of post-operative right ventricular function in patients referred for left ventricular assist device implantation**


*Purpose:* To predict post-operative right ventricular function in patients referred for left ventricular assist device (LVAD) implantation.

*Methods:* A prospective cohort study was conducted on 30 patients referred for LVAD implantation.

*Results:* The preoperative echocardiographic parameters were significantly correlated with post-operative RV function.

*Conclusion:* Preoperative echocardiographic parameters can predict post-operative RV function.

**Lung ultrasound may be useful in predicting cardiac filling pressures and PVR**

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*Purpose:* To assess the utility of lung ultrasound in predicting cardiac filling pressures and pulmonary vascular resistance (PVR).

*Methods:* A prospective study was conducted on 50 patients with heart failure.

*Results:* Lung ultrasound findings were significantly correlated with cardiac filling pressures and PVR.

*Conclusion:* Lung ultrasound may be a useful tool in predicting cardiac filling pressures and PVR.
Importance of lung impedance monitoring in the outpatient clinic for predicting and preventing of hospitalizations patients with Chronic Heart Failure

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Background: Implantable intra-thoracic impedance device has shown that lung fluid accumulation in patients with decompensated chronic heart failure (CHF) begins several days before admission, but predicts hospitalizations with only 50-76% accuracy.

Aim: We evaluated the ability of the new non-invasive method for lung impedance monitoring to predict decompensation in CHF patients and to trigger early therapy in order to prevent hospitalizations.

Methods: Lung impedance (LI) was measured by device based on transverse distribution of electromagnetic energy through the chest. Changes in the clinical status of patients, LI and NT-proBNP levels were concurrently recorded at each outpatient heart failure clinic visit (20±18 days).

Results: 172 CHF patients (72±10 years) at NYHA III/IV (72/70/30) were followed in an outpatient clinic. Patients were treated with diuretics, beta blockers and ACE/ARB/aldosterone. An LI decrease ≥15% from normal baseline was used to initiate early preventive therapy since we have shown previously that clinical decompensation occurred at this level of LI decrease. 250 CHF patients were recruited. 28 patients stopped their participation in the study after less than 3 months of follow up and were excluded, 81 of 172 patients were treated as usual by clinical evaluation (Gr.1) and 91 according to LI (Gr. 2). LVFE and NT-proBNP in groups 1 and 2 were 23±7%, 5820±2434 pg/ml, and 23.6% and 5868±2532 pg/ml respectively (p=NS). 172 episodes of LI decrease ≥15% occurred in Gr. 1 with changes in treatment administered according to clinical signs only. These LI decrease episodes included 144 AHF hospitalizations and 23 deaths. In Gr. 2, 192 episodes of LI decrease ≥15% were recorded. Treatment was immediately intensified. In 161 cases LI increased as the result of treatment intensification of and only 31 AHF hospitalizations were required (p<0.01) and 15 patients died (p<0.045). Time elapsed between LI decrease ≥15% and hospitalization in both groups was 16±6 days. Free time between hospitalizations was longer in LI-guided treated Gr.2 than in Gr. 1 (p<0.01).

Conclusions: Early preventive LI-guided treatment is effective for prevention of hospitalizations and reducing mortality.

The relationship between coronary flow reserve, exercise capacity, metabolic and vascular function in chronic heart failure patients

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Aim: Coronary flow reserve (CFR) is a measure of microvascular function in the absence of coronary artery stenosis and reduced CFR has been shown to be associated with poor outcome in dilated cardiomyopathy. The purpose of the study is to assess the association between CFR and other important prognostic markers in dilated cardiomyopathy as exercise capacity, metabolic and vascular function in chronic heart failure.

Methods and Results: 38 heart failure patients with LVEF ≥35% underwent echocardiography with measurement of CFR. Peak coronary flow velocity (CFV) was measured in the mid-distal part of LAD at rest and during 2 minutes of stress with adenosine using color guided pulsewave Doppler. CFR was calculated as the ratio between CFV at rest and during stress. All patients underwent measurement of maximal peak oxygen uptake (VO2peak), endothelial function, augmentation index and a 2 hr hyperinsulinemic (40 mU/min/m²) isoglycemic clamp. Median duration of follow-up was 31 (interquartile range (IQ) 23-33.6) and 23/38 were of ischemic origin. Median CFR was 1.77 (IQ 1.01-2.62). There was a linear correlation between CFR and VO2peak (r=0.48, p=0.002) and insulin sensitivity (r=0.43, p=0.008), both corrected for fat free mass, but not with endothelial function (r=0.10, p=0.59). In a multivariable adjusted linear regression, CFR remained independently associated with insulin sensitivity (β=0.18 CI 0.06-0.30 p=0.004) and augmentation index (β=0.02 CI -0.03 to -0.004, p=0.01) but not with VO2peak.

Conclusion: CFR was associated to VO2peak, insulin sensitivity and augmentation index, which are known prognostic risk factors for cardiovascular disease. Insulin sensitivity and augmentation index are independently associated with CFR, suggesting that they influence CFR through different mechanisms.
Abstract P999 - Figure 1

P1000 Measuring only septal and lateral wall systolic velocities using tissue doppler velocities is an easy and reproducible method to determine contractile reserve

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Purpose: The average Spectral Tissue Doppler (TDI) from 6 basal myocardial segments on exercise is an established method of determining contractile reserve during exercise stress echocardiography (EXE) in heart failure patients. It can however be challenging to acquire. TDI velocity may be influenced by both cardiac contraction and tethering of non-contracting segments which might render two walls a less accurate measure of global function than six. We sought to establish how closely the mean systolic velocity of the septum and lateral wall was related to the mean of six myocardial segments.

Methods: Patients with heart failure underwent EXE. Spectral TDI peak systolic velocity (s’) measurements were made at rest and peak exertion in six perianal left ventricular locations. The results of the septal and lateral walls were compared to the mean of all six segments.

Results: 70 patients (72±9 years, 65.8% HD; 48 males) underwent EXE. 100% of the septal and lateral walls were determined at exercise. Measuring all 6 walls was possible in 56 patients (73%) at rest and in 30 patients at exercise (39%). At exercise it was not possible to measure 1 wall in 12 patients (16%), 2 walls in 26 (34%) patients, 3 walls in 3 patients (4%) and in 5 patients (7%) 4 walls were not determined. Both septal and lateral s’ correlated highly with the mean of all segments both at rest (r = 0.94; p<0.0001) and exercise (r = 0.92; p<0.0001).

In the subgroup of patients with IHD the results were similar (rest: r = 0.92; p<0.0001; exercise: r = 0.91; p<0.0001).

Conclusion: Septal-lateral TDI is easier to acquire successfully, and is closely related to the mean s’ in all walls, with and without IHD.

P1001 The effects of telemonitoring on heart failure patients’ knowledge, self-care, self-efficacy and adherence: a randomized controlled trial

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Background: Education of heart failure patients by health care professionals is an essential part of the treatment. Perspectives of an increasing number of patients and lack of professionals force health care to explore new strategies in supporting patients.

Methods: Patients with heart failure were randomly recruited in the outpatient clinics of 3 institutions and assigned to the telemonitoring or usual care group. The device used for this study was the Health Buddy® system, without transfer of vital signs. Follow-up time was one year; patients received four postal questionnaires to assess level of knowledge, self-care, self-efficacy and adherence. Analysis was performed by generalized estimating equations analysis to assess effects of telemonitoring during the follow-up of one year.

Results: Of the 382 patients included, 197 were allocated to the intervention group and 185 to the usual-care group. Mean age was 72 (±SD 11.2 years) and 46% were ≥75 years old; 59% were male, 65% lived with a partner; 57% were in functional class II, 40% of the patients was in class III, and 3% in class IV. Patients in the telemonitoring group had a significant improved knowledge level, and increased with 0.9 point on the 15-points Dutch HF knowledge scale (p<0.001). Despite randomization baseline differences in favor of the intervention group were found for self-care (p<0.001) and self-efficacy (p=0.024) for which correction was performed. Self-care abilities improved on the 10-item HF self-care behavior scale with 1.5 point in the intervention group whereas no changes were found in the controls (p=0.001). Self-efficacy, measured with the Barnsow Efficacy Expectation Scale, improved significantly after three and six months, yet was not significantly different after one year. Adherence improved for daily weigh- ing (p=0.001) during whole follow-up; fluid intake results varied from p=0.019 after three months to p=0.086 after twelve months. Adherence for activity recommendations improved (p=0.023) after three months and importance of medication adherence increased after six (p=0.012) and twelve months (p=0.037). No effects were found appointments with caregivers, diet, smoking and use of alcohol. Adherence was measured with the HF compliance questionairr. The overall daily compliance using the telemonitoring system was 95%.

Conclusions: This telemonitoring system improved education and empowers pa- tients, and therefore supported patients and healthcare professionals in their in- teractions.

P1002 Significant improvement in functional status and quality of life in heart failure patients who received EECP

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Purpose: EECP therapy has been studied in refractory ischemic cardiomyopathy and heart failure patients with good results in the past. However, the mechanism and potential indications remain unexplored.

Methods: We did a retrospective analysis of defined end points in 60 heart fail- ure patients; 26 patients who received EECP therapy at our centre. Comparison of EECP therapy was significant diffuse coronary artery disease in patients who were not candidates for any revascularization therapy (95%) and continued to have symptoms despite maximal tolerated medical therapy. Majority of the pa- tients were NYHA class III with mean age 64 years. The EECP therapy included daily sessions of one hour duration for 35 days. The Canadian Cardiovascular So- ciety (CCS) angina class and the Medical Research Council (MRC) breathless- ness scale were used to study improvement in symptoms. Quality of life indicators were (a) reduction in symptoms (b) improvement in activity (c) improvement in psychological parameters. The objective parameters studied were ejection frac- tion and 6 minute walk distance.

Results: There was a significant improvement in all study parameters after EECP therapy (Table-1).

Table: Parameters Pre-EECP Post-EECP Difference Z value P Value

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-EECP</th>
<th>Post-EECP</th>
<th>Difference</th>
<th>Z value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF (%)</td>
<td>24.666</td>
<td>56.666</td>
<td>32</td>
<td>-12.53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.4666</td>
<td>0.4666</td>
<td>-2</td>
<td>15.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCL - Symptoms</td>
<td>7.3803</td>
<td>15.172</td>
<td>-7.8</td>
<td>-24.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCL - Psychological</td>
<td>5.8275</td>
<td>7.6206</td>
<td>1.8</td>
<td>8.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OCL - Activities</td>
<td>3.3620</td>
<td>6.9695</td>
<td>3.6</td>
<td>11.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 Minute Walk Distance</td>
<td>256.16</td>
<td>379.13</td>
<td>123.17</td>
<td>7.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: EECP therapy is an excellent treatment option for heart failure patients who are at the end of the road in terms of medical and interventional therapies. Our hypothesis is that EECP therapy works not only through a mechanism of improved collateral circulation but also improves endothelial function with potential benefit in all vasculopathies. Large randomized trials to validate the hypothe- ses are proposed.
Left cardiac sympathetic denervation for treatment of symptomatic systolic heart failure patients - 3 years follow-up


Objective: To evaluate the feasibility, safety and potential beneficial effects of additional Left Cardiac Sympathetic Denervation (LCSD) in systolic HF patients. Methods: In this prospective randomised pilot study, inclusion criteria were: NYHA functional class II or III, left ventricular ejection fraction (LVEF) <40%, sinus rhythm and resting heart rate ~65 bpm, despite optimal medical therapy (MT). Fifteen patients were randomly assigned either to MT alone or MT plus LCSD. Primary endpoint was safety, measured by mortality in first month follow-up and morbidity according to prespecified criteria. Secondary endpoints: exercise capacity, quality of life, LVEF, LF/HF ratio, 123-methoxydobenzylguanidine scintigraphy (MBG), muscle sympathetic nerve activity (MSNA), BNP levels and 24-Hr Holter mean heart rate before and after 6 months. We studied clinical effects in long term follow-up.

Results: 10 patients underwent ST. There were no adverse events attributable to surgery. No one died in both groups during the first month of follow-up. ST LVEF improved from 25±6.6 to 33±5.2 (p=0.03); ST 6 min walking distance improved 167±35 to 198±47m, (p=0.02). ST MLHFQ score physical dimension tended to improve from 21±5.5 to 15.7±0.0658. The remainder analysed variables were unchanged. During the follow-up of 484±549 days, in MT group most patients either died or underwent CT, while in ST group most were alive without CT.

Conclusions: LCSD was feasible and seemed to be safe in SHF patients. Its beneficial effects warrant the development of a larger randomized trial.

3D echocardiography for predicting response to cardiac resynchronisation therapy in patients with congestive heart failure

D.V. Kirochkin, V.A. Kuznetsov, N.N. Menikhov. Tyumen Cardiology Center, Tyumen, Russian Federation

Purpose: To assess the significance of the real-time 3D echocardiography for predicting response to cardiac resynchronisation therapy (CRT) in patients with congestive heart failure

Materials and methods: 38 patients were examined with 3D echocardiography prior to CRT and in 5-7 days after implantation when the optimization of the device was performed. All the patients with reduction in LV end-systolic volume ≥15% after the implantation (along with improvement in LV systolic function) were considered CRT responders. Cardiac dyssynchrony was evaluated with systolic dyssynchrony index (SDI) which is used as a marker of global LV dyssynchrony.

Results: Right after the implantation in 26 patients (68%) there was found a reduction in LV end-systolic volume ≥15% from baseline which was considered as an acute response to CRT and these patients were assigned to the group of responders. Baseline characteristics of both groups were not different with exception of SDI (p<0.0001). Responders demonstrated a significant reduction in SDI right after the implantation (from 10.3±6.0 to 5.6±3.0, p<0.0001), whereas in non-responders SDI remained unchanged (from 3.6±3.0 to 3.1±0.23, p=NS). To determine an optimal threshold value for SDI as an echocardiographic predictor of CRT acute response, ROC analysis was performed. A threshold value of 5.6% with 98% sensitivity and 95% specificity predicted acute reduction in LV end-systolic volume ≥15% (area under the curve: 0.98, 95% CI 0.87-1.00). Responders demonstrated a significant reduction in SDI to 5.6% ±2.3% vs 11.1% ±2.7% in non-responders (p<0.0001). The use of this threshold value in 26 patients showed a decrease in SDI of 5.6% with 96% sensitivity and 92% specificity predicted acute reduction in LV end-systolic volume ≥15% (area under the curve: 0.90, 95% CI 0.77-1.04, p<0.0001). The use of this threshold value in 26 patients showed a decrease in SDI of 5.6% with 96% sensitivity and 92% specificity predicted acute reduction in LV end-systolic volume ≥15% (area under the curve: 0.90, 95% CI 0.77-1.04, p<0.0001).

Conclusions: LCSD is feasible and seemed to be safe in SHF patients. Its beneficial effects warrant the development of a larger randomized trial.

Peripheral arterial stiffness and reactivity in heart failure

M. Popovici, V. Cobet, N. Cobanu, V. Ivanov, I. Popovici, L. Cobanu, I. Moraru, M. Todras on behalf of Popovici M. Institute of Cardiology. Chisinau, Moldova, Republic of

Aim: Assessment of the arterial stiffness indices and in vitro vascular reactivity in heart failure.

Material and methods: The large (C1) and small artery (C2) elasticity indices were evaluated in patients with systolic (60 men with supported acute myocardial infarction, mean age 57±2 years) or diastolic (26 men with arterial hypertension, mean age 58±2 years) heart failure (HF) using technical diastolic Pressure Wave CR-2000. The obtained outcomes were compared with normal indices accepted for this age and gender (C1>11, and C2<7). The assays in vitro vascular reactivity study included the constricting and relaxing aortic rings response determining in endothelium- intact on various stimuli action (NE, Phe, ET-1, Ang II, Ach, Ang 1-7 concentration of 10-7 M) using Computer TSE Acquisition System.

Results: Arterielyastisitively significantly decreased in HF especially in hyperten-
performed ≤24h apart from the echo study and compared with global strain values. In all pts, global strain values were compared against peak troponin I (TnI), 3D EF and 3D WMSI at predischARGE. 

Results: Among all strain components, global 2D LV and 3D Cx had the closest correlation with 3D EF, 3D WMSI and TnI, while 3D LV showed the weakest correlation with the same parameters. At multivariable analysis, 3D Cx (R2=0.76) and 3D WMSI (R2=0.70) were independently correlated with global LV function in terms of 3D LVEF (p<0.0001 for both). 2D LV and 3D Cx showed the closest correlation with infarct size index at DE-CMR. 

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak TnI</td>
</tr>
<tr>
<td>n=57</td>
</tr>
<tr>
<td>3D longitudinal strain</td>
</tr>
<tr>
<td>3D circumferential strain</td>
</tr>
<tr>
<td>3D radial strain</td>
</tr>
<tr>
<td>3D area strain</td>
</tr>
<tr>
<td>3D longitudinal strain</td>
</tr>
<tr>
<td>p&lt;0.0001 for all, except ^p=0.01.</td>
</tr>
</tbody>
</table>

Conclusions: Global 3D Cx, as well as 2D LV could be used as an objective and accurate estimate of LV damage and overall function at bedside in patients with recent STEMI. Since infarct size is a strong prognostic marker, prospective follow-up studies are warranted in order to verify the ability of 2D and 3D LV to improve risk stratification early after STEMI.
The implication of surgical parameters as predictors of development of perioperative heart failure in patients undergoing non-cardiac surgery


Purpose: Perioperative heart failure is important cause of morbidity in patients undergoing non-cardiac surgery. The role of perioperative echocardiographic biomarker, and clinical risk factors such as Revised Cardiac Risk Index (RCRI) for the risk stratification has been investigated. However surgical data as predictors of development of perioperative heart failure has not been well investigated.

Methods: A total of 734 consecutive patients (64.1±12.7; 415 males) who performed cardiac consultation for elective non-cardiac surgery were studied. We evaluated the clinical risk factors including RCRI, echocardiographic and laboratory findings. Surgical data included types of surgery and anesthetic, surgical times, transfusion, hemoglobin levels before and after surgery. The primary endpoint was a development of heart failure within 30 days after surgery.

Results: There were 58 (7.9%) perioperative heart failures. Age (72.0±11.0 years vs 66.0±12.7 years, P<0.001) was significantly older in patients with perioperative heart failure than those without. Clinical risk factors and comorbidities such as hypertension, diabetes, hyperlipidemia, current smoking, historic of ischemic heart disease and heart failure were not different between the two groups. Among the echocardiographic parameters, E/E' was significantly higher in patients with perioperative heart failure, however left ventricular ejection fraction was not different. ECG parameters except the STT changes were not different. Among the surgical data, surgical times (277±167 min vs 192±112 min, P=0.002), hemoglobin change during surgery (1.4±1.6 g/dl vs 1.0±1.3 g/dl, P=0.017), the proportions of high risk surgery (13.8% vs 6.1%, P=0.047) and transfusion (19.0% vs 4.3%, P<0.001) were significantly different between the two groups. In the multivariate logistic regression analysis, age (odds ratio [OR] 1.070, 95% confidence interval [CI] 1.018-1.124, P=0.007), surgical times ≥240 min (OR 3.321, 95% CI 1.410-7.820, P=0.006), transfusion (OR 4.021, 95% CI 1.491-10.844, P=0.006), and high hemoglobin change during surgery (OR 1.441, 95% CI 1.093-1.900, P=0.010) after adjusting the RCRI, high-risk surgery, E/E' and the STT change were independent predictors for perioperative heart failure.

Conclusions: Surgical parameters, itself such as surgical times, transfusion and hemoglobin change during surgery compared with clinical risk factors, echocardiographic and ECG findings were more strong predictors for development of perioperative heart failure than in patients undergoing non-cardiac surgery.

Role of osteopontin and lipoprotein-associated phospholipase A2 as biomarkers in heart failure patients

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1Medcenter, Bucharest, Romania; 2Victor Babes National Institute, Department of Pathology, Bucharest, Romania; 3University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

Purpose: Both forms of heart failure (HF), with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFrEF) are present in approximately the same proportion between HF patients. We have investigated osteopontin (OPN), a pleiotropic cytokine implicated in vascular remodeling and fibrosis and lipoprotein associated phospholipase A2 (LpPLA2), an enzyme which is now recognized as a marker of vascular inflammation.

Methods: The study included 208 HF patients and 20 healthy controls. Baseline evaluation for patients included clinical examination, 12-lead ECG, estimation of NYHA functional class, transthoracic echocardiography (left ventricular ejection fraction, left atrial and left ventricular end diastolic diameter), and routine laboratory tests. LpPLA2 activity was determined by spectrophotometric method and OPN by ELISA method.

Results: HFrEF patients represented 42.31% from all HF patients. OPN was higher in HFrEF patients (43.9±17.05 ng/ml) than in normal (21.49±4.18 ng/ml) and was higher in HFrEF patients (46.0±15.66 ng/ml) than in HFrEF (42.46±17.92 ng/ml). LpPLA2 activity was higher in HFrEF patients (414.25±106.07) than in normal (225.65±20.8 UL). LpPLA2 activity was higher (442.44±112.65 UL) in HFrEF patients than in HFrEF patients (393.58±96.30 UL).

Conclusion: Elevated plasma levels of LpPLA2 in HFrEF patients are in concordance with elevated levels of OPN and with exacerbated inflammation status existing in these patients, which is confirmed by higher incidence of left ventricular hypertrophy (LHV) within the HFrEF patients compared with HFrEF patients.

Prognostic value of CA-125 circulating levels in stable heart failure patients

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1Hospital de la Santa Creu i Sant Pau, Department of Cardiology, Barcelona, Spain; 2Hospital de la Santa Creu i Sant Pau, Department of Biochemistry, Barcelona, Spain

CA-125 is a high-molecular weight glycoprotein used as tumor marker. Increased levels of CA-125 are associated with the severity of congestion and systemic inflammatory activity in heart failure (HF) patients (Pts). Increased levels of CA-125 have been associated with poor prognosis in acute HF. To assess the prognostic value of increased circulating levels of CA-125 in stable chronic HF, 154 pts were studied. Pts were in stable condition in NYHA functional class II-III and followed in a HF Unit. New hospital admissions for worsening HF and death were evaluated. NT-proBNP values were also assessed on the same day.

Results: Mean age was 72.2±12 years. 62% were men. The etiology of HF was hypertension in 22%, ischemic heart disease in 35%, dilated cardiomyopathy in 8%, valve heart disease 19%, congenital 2% and others 14%. Mean ejection fraction (EF) was 48±17% with 53% of pts having preserved EF. Pts were treated with ACEI, or angiotensin antagonists in 77% of pts, diuretics in 83%, beta-blockers in 58% and aldosterone antagonists in 48%. CA-125 levels correlated with NT-proBNP levels (p<0.001). During follow-up (18.8 months), 105 pts required a hospital admission for worsening HF (68%) and 28 died (18%). New HF episodes and death were associated with higher CA-125 values: 58±85 vs 34±41 KU/L (p<0.05) and 93±123 vs 45±77 KU/L (p<0.001), respectively. While comparison of NT-proBNP values between pts having new HF episodes or died were 343±478 vs 2096±4385 pg/ml (NS) and 6175±1485 vs 2298±2834 pg/ml (p<0.001), respectively. CA-125 circulating levels higher than the 75% percentile (50 KU/L) were identified as the most powerful predictor of death and hospital readmission for worsening HF by multivariate Cox regression analysis (p<0.01). According to Kaplan-Meier survival curves, survival was significantly reduced in Pts with CA-125>50 KU/L, compared to their counterparts (64% vs 82% at 24 months, Long rank test p<0.001).

Conclusions: CA-125 circulating levels are a useful biomarker in chronic stable HF. Pts. 2 CA-125 levels > 50 KU/L identified patients with worsening HF and higher mortality.

Left atrio-ventricular matching in patients with heart failure

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Objectives: Left atrial (LA) systolic function plays an important role in filling of the left ventricle. LA surrogate (surrogate of LA function) is used to evaluate the LA function. We aim to assess the left atrio-ventricular matching in patients with heart failure (HF) using the after load-adjusted left atrial ejection fraction (aLAEJF).

Methods: 55 consecutive patients with HF and 12 age and gender matched normal controls were prospectively recruited and underwent standard echocardiography. The aLAEJF was formulated as 1/3.01*0.06*cm²/m²(mitral annulus area)*D2/D1* and D1 and D2 were measured from apical four-and two-chamber view, A is peak atrial velocity (sample volume at mitral annulus). After load was estimated as septal/E' and aLAEJF was calculated as ratio of LAEJF and septal E'/E'.

Results: LAEJF and septal E'/E' were increased, but aLAEJF decreased in HF patients compared with controls (8.49±6.02 vs 4.12±2.50; 0.38±0.32 kdyne vs 0.56±0.26 kdyne, both p<0.05), as-LAEJF was comparable in diastolic HF compared with normal controls. However, in systolic HF, aLAEJF was significantly decreased compared with diastolic HF patients.

Table 1. The echocardiographic parameters in different groups

<table>
<thead>
<tr>
<th>Normal Controls (n=12)</th>
<th>Diastolic HF (n=53)</th>
<th>Systolic HF (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59±11.12</td>
<td>72±8.96</td>
</tr>
<tr>
<td>BSA</td>
<td>1.70±0.25</td>
<td>1.60±0.34</td>
</tr>
<tr>
<td>Male/Female</td>
<td>83/17</td>
<td>70/35</td>
</tr>
<tr>
<td>Left ventricle ejection fraction (%)</td>
<td>60.50±10.82</td>
<td>58.63±8.32</td>
</tr>
<tr>
<td>LAEJF (kdyne)</td>
<td>4.12±0.20</td>
<td>7.97±5.31</td>
</tr>
<tr>
<td>as-LAEJF (kdyne)</td>
<td>7.30±3.25</td>
<td>16.33±5.25</td>
</tr>
<tr>
<td>p&lt;0.05 compared with normal controls, *p&lt;0.05 compared with diastolic HF group (paired t test).</td>
<td></td>
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</tbody>
</table>

Conclusion: Although left atrial ejection force is increased in HF patients with or without preserved ejection fraction, but after load-adjusted atrial left ejection force...
decreased only in systolic HF patients, which means that the atio-ventricular matching differ substantially. Our data suggests that atio-ventricular matching is preserved in diastolic HF, but the progression in systolic HF is mediated by the manifestation of atio-ventricular mismatching.

**P1017** Increased incidence of heart failure after the great East Japan earthquake and tsunami disaster in iwate M. Homma, M. Nakamura, Y. Koeda, S. Nakajima, F. Tanaka, T. Sakai, H. Endo, M. Kawakami, K. Sakata, T. Onoda on behalf of Northern Iwate Heart Disease Registy Consortium, Iwate Medical University, Iwate, Japan

**Background:** On 11 March 2011, a massive 9.0 magnitude earthquake occurred on the northeastern coast of Japan. Just after the earthquake, a massive tsunami struck the coast area and caused extensive and severe damage. Although several previous studies have shown an increased incidence in cardiovascular disease after natural disasters, the impact of tsunami remains unknown.

**Methods:** We have investigated the incidence and clinical characteristics of hospitalized patients with HF in the coastal area hit by the tsunami (tsunami area) for two months after the disaster (from 11 March 2011 to 10 May 2011). For comparison with the period before the disaster, the incidence of HF was investigated retrospectively in the same area and period for two months during 2009 and 2010. In addition, to elucidate the impact of the tsunami, incidence of HF was also ascertained from a remote area with minimal effect from the tsunami (control area).

To capture HF E/E' as defined by the Framingham criteria, medical charts from all hospitals located in these areas were reviewed. The tsunami area was defined by an officially published tsunami invasive area ratio (tsunami invasive area/town area) greater than 10%.

**Results:** Secular trends in the number of HF cases are shown in the figure. There was a significant increase in the number of HF cases after the disaster within the tsunami area (Z = 7.99, p = 0.018), but not in the control area (Z = 2.94, p = 0.023). No significant difference in the percentage of new onset HF were observed before and after the disaster in either area.

**Conclusion:** After the catastrophic earthquake and tsunami, the incidence of HF in the tsunami area increased significantly compared to the control area.

**P1018** Heart rate does not predict post-discharge events in patients hospitalized for heart failure with reduced ejection fraction in the EVEREST trial J. Wilcox, S.J. Greene, M. Gheorghide, M.E. Harinstein, M.J. Kwansy, A. Fought, M.A. Konstam, F. Zannad, A.P. Maggioni, K. Swedberg, 1Feinberg School of Medicine, Division of Cardiology and Cardiovascular Surgery, Chicago, United States of America; 2Northwestern University, Feinberg School of Medicine, Chicago, United States of America; 3University of Pittsburgh, Cardiovascular Institute, Pittsburgh, United States of America; 4T ufts Medical Center, Division of Cardiology and the CardioVascular Center, Boston, United States of America; 5Inserm, CIC9501, U961, CHU, Nancy, France; 6ANMCO Research Center, Florence, Italy; 7Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

**Purpose:** Elevated resting heart rate (HR) is associated with worse outcomes in patients (pts) with stable chronic heart failure (HF). HR may predict post-discharge outcomes in these patients.

**Methods:** The Effect of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial examined the effects of tolvaptan (TLV), a vasopressin antagonist, in pts with worsening HF and ejection fraction (EF) <40%. We analyzed 1894 pts in sinus rhythm and not pacemaker dependent. Baseline demographic, medication history, physical exam and laboratory findings were compared across quartiles (Q) as well as hazard ratios for (1) all-cause and (2) cardiovascular (CV) mortality, and (3) CV mortality or HR re-hospitalization.

**Results:** Baseline data are shown in Table 1. TLV had no effect on HR. Higher HR was not associated with any endpoint. Adjusted multivariate analysis showed no significant difference by in-hospital HR change or baseline HR.

**Conclusion:** In chronic HF pts hospitalized with worsening HF and reduced EF, baseline HR did not predict mortality or PDI. HR in this unstable situation may reflect different conditions compared with stable phases.

**P1019** Relation between heart rate and quality of life in chronic heart failure patients A. Torrens Oses, C. Enjuanes Grau, J. Comin Colet, G. Gonzalez, M. Cladellas, J.M. Verdu, A. Linas, J. Brugera Cortada, Hospital del Mar, Department of Cardiology, Heart Failure Program, Barcelona, Spain

**Purpose:** Recent data from the SHIFT study suggests that heart rate (HR) is a key determinant of health-related quality of life (HRQoL). After proving the concept in a clinical trial, the relation between heart rate and HRQoL in "real-world" CHF patients from the community with higher age and high prevalence of preserved LVEF has not been explored. The aim of our study was to evaluate the relationship between HR and HRQoL in this "real-world" non-selected patients with CHF.

**Methods:** Up to 684 consecutive stable CHF patients with reduced or preserved LVEF referred to a comprehensive nurse-based heart failure programme were included. At inclusion, relevant clinical and demographic information were obtained. HRQoL was measured using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) (range of scores from 0, best QoL, to 105, worst QoL). HR was evaluated from a resting ECG at inclusion and classified into 4 different groups: <70 beats per minute (bpm), 70 to 90 bpm, and ≥90 bpm.

**Results:** Mean age was 72±11, with a 57% of male patients. Mean LVEF was 43.14±25.41, with a 42% of preserved LVEF. CHF aetiology was ischemic in 42% cases, with a 30% of hypertensive cardiomyopathy. Sinus rhythm was present in 55.5% of patients, and chronic atrial fibrillation in 33%, with a mean HR of 79.9±20.3. Mean overall summary score of the MLWHFQ was 43.4±25.4, and 49.8% of patients were in NYHA class III or IV.

As expected, patients with higher HR had worse HRQoL. The overall summary score of the MLWHFQ for the groups ≤70 bpm, 70-90 bpm, ≥90 bpm were 40.75 ±26, 42.9±25 and 48.2 ±0.05, respectively (p-value <0.05) in the multivariate analysis (multiple linear regression), HR was an independent predictor of worse scores in the HRQoL evaluation (beta standardized = 0.11; p-value = 0.004). When we analyzed the subgroups created according LVIF, HR was an independent predictor of worse HRQoL in the reduced LVEF group (overall MLWHFQ: ≤70 bpm = 40.75 ±26.7, 70-90 bpm = 40.67 ±25.3, ≥90 bpm = 49.3 ±21.6; p-value = 0.002) but this relation didn’t exist in the preserved LVEF group/overall MLWHFQ: ≤70 bpm = 40.75 ±26, 70-90 bpm = 45.9±24.5, ≥90 bpm = 44.6 ±23; p-value = 0.23.

**Conclusion:** As shown in the SHIFT study, higher HR is associated with worse QoL in real-world non-selected CHF patients. However, this association appears to be mostly due to the effects of HR in patients with reduced LVEF. Additional studies are needed to confirm this hypothesis and to establish whether this differential effect according to LVIF is driven by differences in pathophysiological mechanisms between patients with CHF with reduced or preserved LVEF.

**P1020** Urinary acid base imbalance in patients with chronic heart failure Y. Otaki, T. Watanabe, H. Takashashi, T. Narumi, S. Kadowaki, T. Arimoto, T. Shishishod, T. Miyashita, T. Miyamoto, I. Kubota, Yamagata University, Yamagata, Japan

**Purpose:** Renal dysfunction is reported to be associated with poor outcome in patients with chronic heart failure (CHF). A recent study showed that acidic urine is related to chronic kidney disease (CKD), which is a risk factor for the development of CHF. However, it remains to be determined whether urinary acid base imbalance is associated with a poor outcome in patients with CHF.

**Methods and Results:** We measured urine pH using dipsticks in 592 patients with CHF. Patients were prospectively followed and divided into three groups based on their urine pH level: (acidic urine, urine pH ≤ 5.5; normal urine, urine pH >5.5; alkaline urine, urine pH ≥ 6.5).
6.0 to 7.0; alkaline urine, urine pH ≥ 7.5). There were 170 cardiac events during a median follow-up period of 522 days. Patients with acidic urine or alkaline urine had severe New York Heart Association (NYHA) functional class compared to those with normal urine. Prevalence of acidic urine increased with worsening CKD stage. In the univariate analysis, the presence of acidic urine or alkaline urine was significantly associated with cardiac events. Furthermore, age, NYHA functional class, estimated glomerular filtration rate, brain natriuretic peptide, hemoglobin, uric acid, proteinuria, and left ventricular ejection fraction were significantly related to cardiac events. In the multivariate Cox proportional hazard analysis, both acidic urine and alkaline urine were independent predictors of cardiac events. A Kaplan-Meier analysis demonstrated that the rate of cardiac events was higher in patients with acidic urine or alkaline urine than in those with normal urine.

Conclusion: The presence of urinary acid base imbalance can reliably identify patients at high risk of future cardiac events in patients with CHF.

### Table 1. Time intervals in HF patients

<table>
<thead>
<tr>
<th>Group</th>
<th>(n=18)</th>
<th>(n=57)</th>
<th>(n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-sS' (ms)</td>
<td>49.37±8.22</td>
<td>67.47±24.63</td>
<td>19.38±10.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-E' (ms)</td>
<td>460.10±51.69</td>
<td>468.85±42.44</td>
<td>432.71±26.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-lS' (ms)</td>
<td>61.81±26.13</td>
<td>74.89±37.54</td>
<td>19.34±11.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-lE' (ms)</td>
<td>460.54±51.34</td>
<td>464.07±64.48</td>
<td>433.81±23.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-S' (ms)</td>
<td>48.00±22.40</td>
<td>35.62±19.15</td>
<td>23.93±18.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-E' (ms)</td>
<td>432.14±37.11</td>
<td>430.38±53.56</td>
<td>435.21±44.44</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Diastolic and systolic mechanical dyssynchrony in patients with heart failure**

**Objectives:** To evaluate the cardiac mechanical dyssynchrony in patients with heart failure (HF).

**Methods:** 75 patients with HF (mean age: 61.6±10.5y) and 30 healthy controls (mean age: 59.8±6.6y) were involved. Subjects were divided into: group 1 (LV EF = 50%), group 2 (LV EF = 50%) and group 3 (controls). The time intervals of R wave on ECG to the onset of mitral annulus velocities S' and E' at septal (R-sS', R-sE'), lateral (R-lS', R-lE') and tricuspid annulus velocities S' and E' (R-tS', R-tE') were recorded.

**Results:** R-S' of mitral annulus at septal, lateral and tricuspid annulus significantly prolonged in patients with HF in comparison to the normal subjects (58.43±24.30 ms vs 19.38±10.44, 68.55±34.17 ms vs 19.34±11.85, 48.00±22.40 ms vs 23.93±18.08, respectively, p<0.001); R-E' of mitral annulus at septal and lateral severely significantly prolonged in patients with HF in comparison to the controls (464.85±42.44 ms vs 432.71±26.85, 462.34±69.78 vs 433.81±33.03, respectively, p<0.001). Only R-sS' significantly increased in group 2 compared with group 1. In group 1, there was a significantly differences between R-sS' and R-lS' and both R-S' and R-E' of mitral annulus had significantly prolonged compared with of tricuspid annulus (Table 1).

**Conclusions:** There were significant LV electromechanical time delay in both systole and early diastolic in HF patients compared to normals and more severe in patients without HFPEF. In patients with HFPEF, there was a regional systolic mechanical dyssynchrony between septal and lateral mitral annulus, whereas in patients without HFPEF, it occurred in the tricuspid annulus and mitral annulus.

### P1022

**Serum neutrophil gelatinase-associated lipocalin and cystatin-c levels are associated with arterial stiffness in patients with heart failure**

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1. University of Athens Medical School, Hippokration General Hospital, Department of Cardiology, Athens, Greece; 2. University of Athens Medical School, Department of Biochemistry, Athens, Greece.

**Purpose:** Patients with heart failure (HF) have a significant decline of renal function. Measurement of arterial stiffness is well validated in large population studies as strong predictor of adverse cardiovascular outcomes. In the present study we investigate the association between novel biomarkers of renal dysfunction and indices of arterial function in HF.

**Methods:** We enrolled 79 consecutive patients with HF (mean age 65) and 79 healthy subjects (CI) adjusted for age and sex. Both logNGAL levels and serum creatinine levels were positively correlated with serum creatinine levels (r=0.458, p<0.001). Patients with HF compared to CI, had significantly higher PWV (9.5±2.80 m/sec vs. 9.0±1.78 m/sec, p<0.027) and higher AIx (23.53±9.54 vs. 19.82±8.04%, p<0.047). Interestingly, in HF patients, AIx was correlated with logCystatin-C levels (r=0.261, p<0.029) while, PWV was correlated with logBNP levels (r=0.304, p<0.049). Furthermore, in HF patients, regression analysis revealed that logNGAL levels were correlated with MMP-9 levels independently of other confounders such as age, eCcr, ejection fraction, and sex (β=784.95%) (314.125%) p<0.002).

**Conclusions:** Elevated arterial stiffness is correlated with BNP levels in HF patients. Moreover novel biomarkers of renal function are associated with arterial stiffness and biomarkers of cardiac remodeling. These findings highlight a possible common pathogenetic mechanism of arterial, cardiac and renal dysfunction in HF.

### P1023

**First-degree atrioventricular block is a reliable risk factor in patients with chronic heart failure**

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**Background:** First-degree atrioventricular block (AVB) is frequently encountered in clinical practice. Previous studies have proved that first-degree AVB is a benign finding in healthy patients. However, it has been recently reported that first-degree AVB is associated with atrial fibrillation, pacemaker implantation, and all-cause mortality among outpatients in the Framingham heart study. The purpose of this study was to elucidate whether first-degree AVB can predict cardiac events in patients with chronic heart failure (CHF).

**Methods and Results:** We measured the PR interval in 306 CHF patients and divided into 2 groups based on presence of first-degree AVB (PR interval ≥220 ms). Patients were prospectively followed with end points of cardiac death or rehospitalization for worsening CHF. There were 82 cardiac events, including 13 cardiac deaths and 69 re-hospitalization during median follow-up period of 463 days. Patients with cardiac events were older, had more severe NYHA functional class and the prevalence of first-degree AVB compared to those without cardiac events. Furthermore, patients with cardiac events showed more renal dysfunction, and higher levels of brain natriuretic peptide and uric acid compared to those without cardiac events. Kaplan-Meier analysis showed that cardiac event rate was higher in patients with first-degree AVB than in those without. Multiple Cox hazard analysis revealed that first-degree AVB was independently associated with cardiac events.

**Conclusion:** First-degree AVB may be a reliable prognostic factor in CHF patients.
The enormous earthquake hit Japan on March 11 increased acute heart failure -analysis of remote monitoring of intrathoracic impedance-

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Background: The enormous earthquake which hit Japan on March 11, 2011, induced physical and mental stresses to residents in Fukushima Prefecture, Japan. Several studies have revealed that stress in catastrophe/predictors can trigger cardiovascular events such as myocardial infarction and fatal arrhythmia, however, little is known about the association with the occurrence of acute heart failure. Recently, remote monitoring of implantable device allows us earlier detections of clinical problems including pulmonary congestion and arrhythmic events. Objectives: The purpose of this study was to determine whether the March 11 earthquake and subsequent disasters including tsunami and radiation leaks from damaged nuclear power plants increased the incidence of acute decompensated heart failure in patients with chronic heart failure.

Methods: Forty chronic heart failure patients (mean age 62±13 years, mean left ventricular ejection fraction 30.8%) who lived in Fukushima Prefecture on March 11 were enrolled in this study. All subjects received implantable cardioverter defibrillator or cardiac resynchronization therapy with defibrillator which can check ventricular ejection fraction over 60%, defined the existence of pulmonary congestion. We compared the incidence of pulmonary congestion and arrhythmic events between one month before and after March 11. Results: Thirteen patients were excluded because of missing data. No spontaneous myocardial infarction was noted in the one month following March 11.

Conclusions: These results suggest that earthquake-induced stress causes an increased risk of worsening heart failure without changes in fatal arrhythmia. In addition, remote monitoring of intrathoracic impedance may be a useful tool for the management of chronic heart failure patients in catastrophic disasters, but have some limitation of network system during evacuation.

Omega-3 supplementation modulated beneficially the adverse effect of depressive symptomatology on 1-year prognosis in patients with chronic heart failure


In the clinical course of chronic heart failure severe short term depressive symptoms have been recognised to confer to adverse outcome through various mechanisms. Many studies have shown long-chain Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are a potential treatment of depressive disorders. The purpose of this study was to evaluate the role of n3-PUFA supplementation on the clinical course of patients with chronic heart failure and depressive symptomatology.

Methods: We enrolled 256 consecutive patients (mean age 61±13 years old) with chronic compensated heart failure, due to ischemic or dilated cardiomyopathy, NYHA classification II-III, under optimal medical treatment. They were randomly assigned to 1000 mg n-PUFA supplementation. Detailed information regarding their medical records, anthropometric data, physical activity, nutrition and smoking habits, and adverse cardiovascular events (death or re-hospitalization due to cardiovascular disease) were recorded; while depression was assessed with the Zung’s Depression scale (ZDS) range 20-80.

Results: Thirty five percent of patients experienced an adverse event during the one year of follow up. Logistic Regression analysis revealed that depressive symptomatology increased the risk by 2.8% (95% CI 1.1-6.05, p=0.05), after taking into account several confounders. A significant interaction was observed between omega-3 intervention and depression (p<0.001). Thus the analysis was performed by intervention group. Depression symptomatology was associated with increased risk of adverse events only in patients who did not receive omega-3 supplementation (OR=1.074, 95% CI=1.051-1.1.137); while depression did not influence outcome in patients in the omega-3 intervention group (p=0.54).

Conclusion: Omega n-PUFA supplementation seems to mediate the adverse effect of depression on the 1-year clinical course of patients with chronic heart failure under optimal medical treatment. This finding may illustrate another potent effect of omega-3 supplementation in patients with heart failure.

Extent of myocardial scar and edema is related to left ventricular longitudinal strain and torsion but not with diastolic function in reperfused acute myocardial infarction

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Background: Hemodynamics on infarct or non-infarct myocardium are related to left ventricular (LV) remodeling in patients with acute myocardial infarction. However, influence of myocardial tissue characteristics after myocardial infarction on regional or global myocardial mechanics has not been fully investigated.

Methods: Consecutive twenty-six reperfused acute myocardial infarction patients (55±12 years, 22 men) underwent cardiac magnetic resonance (CMR) imaging with cine, T2 weighted imaging (T2WI), resting 1st pass perfusion and delayed enhancement (DE) imaging 2 or 3 days after percutaneous coronary revascularization. Extent of edema, scar, presence of microvascular obstruction, perfusion defect were measured based on 17 myocardial segment model and degree of transmurality. At the same day with CMR, echocardiography was also done. Using 2D speckle tracking analysis, longitudinal, circumferential strain and torsion were measured. Serial blood cardiac biomarkers and electrocardiography were done until discharge.

Results: Twelve patients had left anterior descending culprit lesion, 11 had right coronary and 3 had circumflex artery culprit lesions. Extent of myocardial scar and edema measured by DE-CMR and T2WI was significantly correlated with peak level of CK-MB (r=0.755, p<0.001) and 12-lead ECG-derived extent of Q wave (r=0.677, p<0.001). Extent of edema significantly correlated with global longitudinal strain (r=0.627, p=0.001) and torsion (r=0.429, p=0.029). But extent of myocardial scar or edema did not correlate with diastolic function as represented by E/e' and early diastolic longitudinal strain rate. E/e' is correlated with average non-infarct circumferential myocardial wall strain (r=0.452, p=0.001).

Conclusions: Extent of myocardial scar and edema is correlated with LV longitudinal strain and torsion but not with diastolic function in reperfused acute myocardial infarction. Diastolic function in acute myocardial infarction is determined not only by infarct extent but also noninfect myocardial tissue characteristics.

Predictors of worsening left ventricular hypertrophy in 509 patients with aortic stenosis

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Background: Left ventricular hypertrophy (LVH) is a maladaptive effect of aortic stenosis (AS) and portends worse outcomes. We aim to determine predictors and course of LVH progression.

Methods: We analysed 509 consecutive patients with AS who underwent paired echocardiographic studies >180 days apart. One hundred and eighty-eight patients (37%) had significant increase (>20%) in left ventricular mass index (LVMI). We compare their baseline echocardiographic parameters to the group without progression.

Results: The mean time interval between the paired studies, LV ejection fraction and aortic valve area (AVA) were 1252±910 days, 60.1±2 and 1.29±0.4cm² respectively and were not significantly different between the two groups. One hundred and forty patients (28.8%) had mild AS (AVA<1.5cm²), 217 (44.7%) had moderate AS (AVA=1.5-2.0cm²) and 129 (26.5%) had severe AS (AVA<1.0cm²); there was significant difference in the degree of progression of LVH between the 3 groups (8.3% vs. 9.9% vs. 9.6%, P<NS). Despite similar LV systolic function and aortic valve parameters, progression of LVH was noted in the group with smaller baseline LV mass index and volumes but increase end-systolic wall stress (ESWS) (EWSS).

Table 1

<table>
<thead>
<tr>
<th>Echocardiographic parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20% increase in LVMI</td>
<td>(n=188)</td>
<td>(n=321)</td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>Subsequent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVMI (g/m2)</td>
<td>99.0±89.5</td>
<td>114.7±953</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic valve dimensions</td>
<td>60.3±12.8</td>
<td>55.8±16.1</td>
<td>0.001</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>1.28±0.43</td>
<td>0.99±0.40</td>
<td>0.130 ±0.44</td>
</tr>
<tr>
<td>Peak transaortic valve</td>
<td>291.4±75.3</td>
<td>333.7±144</td>
<td>0.284 ±175</td>
</tr>
<tr>
<td>gradient (mmHg)</td>
<td>20.7±13.6</td>
<td>28.8±17.6</td>
<td>0.260±20</td>
</tr>
<tr>
<td>Aortic valve resistance</td>
<td>122.2±92.7</td>
<td>189.5±137.1</td>
<td>125.1±126</td>
</tr>
</tbody>
</table>

*Comparison between initial and subsequent parameters.
P1028 Incidence and clinical outcome of Prosthesis patient mismatch after transcatheter aortic valve implantation with the CoreValve prosthesis

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Prosthesis-patient mismatch (P-PM) is an important determinant of morbidity and mortality after aortic valve replacement. The aims of this study were to report the frequency of P-PM and its relation to the clinical outcome after transcatheter aortic valve implantation (TAVI). Between April 2008 and December 2011, 166 patients with symptomatic severe aortic stenosis, who had undergone successful transcatheter aortic valve implantation with the CoreValve prosthesis, the indexed effective orifice area (EOA) at baseline and discharge were measured. P-PM was defined as severe (indexed EOA < 0.65 cm²/m²) or moderate P-PM was defined as indexed aortic valve effective orifice area EAO ≥ 0.65 cm²/m². Clinical, echocardiographic, and procedural factors relating to P-PM were studied.

Mean age was 79.3 ± 6.2 years and 59.6% were female. The indexed EOA increased from 0.35 ± 0.1 to 0.94 ± 0.2 cm²/m² P < 0.001 after TAVI. Moderate and severe P-PM occurred in 74 (44.6%) and 15 (9%) of 201 patients, respectively. Mortality beyond 30 days was more in patients with severe P-PM than those with moderate or no P-PM (35.5% vs. 8.8%, P = 0.003) but was no significant different with mortality at 30 days. In the multivariate analysis the occurrence of severe P-PM was predictor mortality HR 6.28 (1.84-21.42) p = 0.003. P-PM was related with age, body surface, weight, LVEF, ratio p/annulus.

Conclusions: Prosthesis-patient mismatch is frequent (in this series) after transcatheter aortic valve implantation, and only severe P-PM was associated with the clinical outcome at follow-up.

P1029 Small hemodynamically non-compromising pericardial effusion is associated with increased mortality in patients with heart failure

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Introduction: The prognostic relevance of a small, hemodynamically non-compromising pericardial effusion in patients with reduced ejection fraction has not been investigated. However, in patients with pulmonary hypertension, the presence of a minor pericardial effusion has a negative effect on prognosis. Therefore, this study assessed the impact of a small pericardial effusion on mortality in a heart failure population.

Methods: All patients who were diagnosed with a decreased ejection fraction (<50%) by echocardiography and had follow-up examinations in our heart failure clinic from years 1995 until 2010 were eligible for inclusion. Patients with a hemodynamically relevant pericardial effusion were excluded, as well as patients with myocardial infarction, post-myocardial infarction or congenital heart disease. A total of 901 patients (control: 826 patients; pericardial effusion: 75 patients) were included. The groups were comparable with regard to age (median 56 years [IR 46-65] vs. 54 years [IR 36-63]; P=0.07), male gender (82% vs. 73%; P=0.09), LV-EF (median 31% [IR 25-43] vs. 31% [IR 19-42]; P=0.002), BMI (median 28.8 [IR 23-35] vs. 27.3 [IR 21-33]; P=0.10), creatinine (median 1.2 [IR 0.9-1.7] vs. 1.1 [IR 0.9-1.5]; P=0.21), and left ventricular hypertrophy (56% vs. 40%; P=0.001). Cox regression analysis identified the following independent risk factors for death: a) the presence of a pericardial effusion (P=0.02, HR 1.98), b) advanced age (P=0.03, HR 1.02), c) reduced LV-EF (P=0.005, HR 0.98).

Conclusions: Small pericardial effusion is associated with an accentuated hazard for death in a population with reduced ejection fraction.

YOUNG INVESTIGATORS AWARDS SESSION: BASIC SCIENCE

P1031 Dual benefits of caloric restriction on chronic heart failure; caloric restriction augments cardiac angiogenesis and mitophagy via cyclic AMP elevation

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Purpose: Caloric restriction (CR) promotes beneficial cardiovascular effects; however, the effects of CR on the cardiac remodeling in chronic heart failure remain unclear. CR increases intracellular cyclic AMP levels leading to protein kinase A (PKA) activation and maintains cellular viability by modulating selective mitochondrial autophagy in cells (Nat Cell Bio2011) and activates AMP-dependent kinase (AMPK) pathway in mice (JBC2010). We examined the effects of CR on the cardiac remodeling using chronic heart failure models induced by diabetes and by pressure overload.

Methods and Results: Eighteen-week-old diet-induced obesity (DIO) mice were allocated to 4-week CR (DIO-CR) and ad libitum (DIO-AL) group. Pressure overload (load 4 weeks) was generated by transaortic constriction (TAC) in mice, which were randomly allocated to a 4-week CR (TAC-CR) and AL (TAC-AL) group and analyzed at 18-week-old. Echocardiography revealed that systolic and diastolic function and left ventricular hypertrophy were improved in both DIO-CR and TAC-CR compared to each AL group and significant different in both CR groups (0.5±0.10 fold for DIO-CR and 0.3±0.10 fold versus each AL counterpart). Capillary density was increased both in DIO-CR (2.1±0.3 fold) and TAC-CR (1.5±0.4 fold) in the AMPK-GDS dependent manner. Cardiomyocyte surface area was decreased in both CR groups (0.7±0.1 fold for DIO-CR, 0.8±0.1 fold for TAC-CR). Abnormal accumulation of PINK1 and Parkin (the cooperative surrogates indicating mitochondrial damages) were observed in the mitochondrial fraction obtained from DIO-AL and TAC-AL heart extracts, which were reversed in both CR groups. Myocardial cyclic AMP concentration and autophagic activity were elevated in both CR groups. In vitro analysis revealed that glucose deprivation increased the autophagic activity and the AMPK phosphorylation in a cyclic AMP-PKA dependent manner both in cultured neonatal rat cardiomyocytes (NRVMs) and microvascular endothelial cells (ECs). Forskolin (10 μM) and 8-bromo-cyclic AMP (1 mM) increased autophagy of the NRVMs and ECs, which was abrogated by RNA interference to ablate the catalytic subunits of PKA and H-89 (10 μM).

Conclusions: CR ameliorates not only metabolic cardiac dysfunction but also pressure overload-induced heart failure. The increase in cyclic AMP level induced by CR promoted the activation of PKA/AMPK axis, which was essential for the reverse remodeling of heart via enhanced angiogenesis and mitophagy independent of pathological causes.

P1032 Deficiency of mitogen-activated protein kinase activated protein kinase 2 (MK2) prevents maladaptive vascular remodeling and promotes endothelial regeneration after injury of the carotid artery

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Background: Maladaptive vascular remodeling after mechanical injury of the arterial wall (e.g. angioplasty) is characterized by neointima formation and media hypertrophy causing narrowing of the affected artery. Moreover, mechanical injury of the arterial wall results in a loss of the vessel protecting endothelial cell layer. The MAP kinase-activated protein kinase-2 (MK2) regulates expression of inflammatory mediators, cell migration, and cell proliferation; processes known to be important for vascular remodeling and endothelial regeneration after vascular injury. Therefore, we hypothesized an important role of MK2 in vascular remodelling and endothelial regeneration after injury of the arterial wall.

Methods & Results: The functional role of MK2 in arterial remodeling after vascular injury was investigated in hypercholesterolemic low-density-lipoprotein receptor deficient mice (LDLKO) subjected to wire injury of the common carotid artery (CCA). MK2-deficiency (LDL/R0/MK2KO) almost completely protected LDLKO against neointima formation, media hypertrophy and luminal stenosis (n=8, P<0.01, histomorphometry, day 28 post-injury). To elucidate potentially underlying mechanisms cell proliferation (BrdU-assay), expression of RhoA (Westernblot) was analyzed in cultured smooth muscle cells (SMC) isolated from aortas of wildtype (WT) and MK2-deficient mice (MK2KO). MK2-deficiency significantly reduced cell proliferation as expression of RhoA was induced by FCS or PDGF in SMC (n=6-9, P<0.01). Furthermore, MK2-deficiency decreased migration of SMC (wound scratch assay) induced by PDGF and FCS (n=9-13).

Conclusion: MK2 is essential for vascular remodeling and endothelial regeneration after vascular injury. MK2-deficiency significantly reduced cell proliferation and migration as expression of RhoA was induced by FCS or PDGF in SMC (n=6-9, P<0.01). Moreover, we investigated the functional relevance of MK2 for vascular regeneration in the model of re-endothelialization after electric injury of the CCA in WT and MK2KO mice (Evan's blue staining of denuded area). MK2-deficiency enhanced re-endothelialization of the denuded area after injury of the CCA (n=6-8, P<0.05, WT vs. MK2KO). Consistently, MK2-deficiency significantly increased endothelial cell proliferation in vivo (EdU-staining 3 days post-injury, confocal microscopy) across the denuded area of the CCA (n=3-4, P<0.001, WT vs. MK2KO). Fur-
thermore, employing endothelial cells isolated from WT and MK2KO mice MK2-deficiency increased cell proliferation, expression of p-Rb and cyclinD1 as well as cell migration induced by endothelial growth medium (EGM) or FCS (n=3–5, p<0.001). Conclusion: Deficiency of mitogen-activated protein kinase activated protein kinase C (p66Shc) prevents maladaptive vascular remodeling and promotes vascular regeneration after vascular injury.

Secretome of apoptotic peripheral blood cells (APOSEC) attenuates microvascular obstruction in a porcine acute myocardial infarction model: role of platelet aggregation and vasodilatation

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Early reperfusion of the culprit coronary artery within a narrow time window has significantly improved early mortality after acute myocardial infarction (AMI). However, a lack of adequate reperfusion at the microvascular level is often a limiting prognostic factor. Our group has recently found that paracrine factors secreted from apoptotic peripheral blood mononuclear cells (APOSEC) attenuate the size of AMI. The aim of this study was to determine the influence of APOSEC on microvascular obstruction (MVO) in a porcine AMI model. Cell culture supernatants derived from irradiated apoptotic peripheral blood mononuclear cells (APOSEC) were collected and injected intravenously after induction of AMI. MVO was determined by magnetic resonance imaging and cardiac catheterization. Platelet function and platelet-associated parameters were monitored in vitro and in vivo by means of ELISA, flow cytometry, aggregometry, and western blots. Effects of APOSEC on pathophysiology and coronary vascular tone were determined by ELISA, western blot and myographic experiments, respectively.

Treatment of AMI with APOSEC resulted in a significantly improved microvascular perfusion (Myocardial blush grade 1.3±0.3 vs. 2.5±0.3; p<0.003). Platelet activation markers (P-selectin, CD40L, PF-4, TSP-1) were reduced in plasma samples, suggesting an anti-aggregatory capacity of APOSEC. This finding was confirmed by in vitro studies showing that activation and aggregation of both porcine and human platelets were significantly impaired by co-incubation with APOSEC, paralleled by vasodilator-stimulated phosphoprotein (VASP)-mediated inhibition of platelets. In addition, APOSEC evidenced a significant vasodilatory capacity of coronary arteries. HUV-ECs co-incubated with the compound significantly upregulated iNOS expression. Treatment of isolated coronary arterial segments with APOSEC resulted in a dilation of the vessels in a dose dependent manner (APOSEC from 5×10⁶ to 5×10⁷ cells: 23% dilation; 1×10⁶: 26%; 5×10⁶: 34%). These findings were corroborated by in vivo data showing heightened vasodilatory mediations 40min after administration of APOSEC in the porcine AMI model (NO, VIP, PGII).

Our data give first evidence that APOSEC reduces the extent of MVO during AMI. This explains the improved long-term outcome after APOSEC treatment in AMI as previously described.

Vascular hyperglycemic memory is driven by p66Shc via epigenetic changes and post-translational modifications: insights for the progression of vascular complications despite intensive glycemic control

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Purpose: Hyperglycemic memory may explain why intensive glucose control has failed to improve cardiovascular outcomes in patients with diabetes. Indeed, hyperglycemia promotes vascular dysfunction even after glucose normalization. Reactive oxygen species (ROS) may be involved in this phenomenon. The present study investigates the p66Shc role in this setting.

Methods: Human aortic endothelial cells (HAECs) were exposed for 6 days either to normal (NG, 5 mmol/L) or high glucose (HG, 25 mmol/L) as well as to HG for 3 days followed by NG for the remaining 3 days. Diabetes was induced in 129sv mice (aged 4-6 months) by streptozocin. After 3 weeks, diabetic animals were randomized to receive either insulin alone or insulin in combination with pharmacological scrambled siRNA for the following 3 weeks (n=6-8/group). Protein expression was assessed by immunoblotting. We investigated p66Shc promoter methylation by standard quantitative PCR using a predesigned primer. Superoxide anion and nitric oxide (NO) levels were determined by ESR spectroscopy. Endothelium-dependent vasorelaxation to acetylcholine (Ach) was measured in mice aorta. Annexin V and TUNEL staining as well as caspase 3 activity were used for detection of apoptosis.

Results: In HAECs exposed to HG and aortas of diabetic mice activation of p66Shc by protein kinase C (PKC)III persisted after returning to normoglycemia. Sustained p66Shc upregulation and mitochondrial translocation were associated with continued ROS production, reduced NO bioavailability and apoptosis. We found that p66Shc gene expression was epigenetically regulated by promoter CpG hypomethylation and increased histone 3 (H3) acetylation. Indeed, pharmacological inhibition of H3 acetytransferase restored basal expression levels of p66Shc. Furthermore, p66Shc-derived ROS production maintained PKC-III-dependent inhibitory phosphorylation of eNOS at Thr-495, leading to a detrimental vicious cycle despite restoration of normoglycemia. In vitro and in vivo silencing of p66Shc, performed at the time of glucose normalization, blunted ROS production and restored Ach-induced relaxation. Vascular apoptosis persisted even after intensive glycemic control with insulin whereas concomitant i.v administration of p66Shc siRNA abolished this event by limiting mitochondrial cytochrome c release and caspase 3 activation.

Conclusions: p66Shc is the key effector driving vascular hyperglycemic memory in diabetes. Our study provides molecular insights for the progression of diabetic vascular complications despite intensive glycemic control.

YOUNG INVESTIGATORS AWARDS SESSION: POPULATION SCIENCES

Obesity is associated with improved survival in patients with atherosclerotic heart disease

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Purpose: We examined the influence of obesity on survival in patients with proven atherothrombotic heart disease to further examine the paradox that obesity may appear protective in patients with established cardiovascular disease.

Methods: A cohort study based on registry data from the Western Denmark Heart Registry (WDHR). We included all patients in WDHR with coronary atherosclerosis confirmed by coronary angiography from February 2000 to August 2011. Patients were divided into eight groups according to body mass index (BMI): Group1: BMI<18.5 kg/m², group 2: 18.5 ≤ BMI < 23 kg/m², group 3 (reference group) 23 ≤ BMI < 25 kg/m², group 4: 25 ≤ BMI < 27.5 kg/m², group 5: 27.5 ≤ BMI < 30 kg/m², group 6: 30 ≤ BMI < 35 kg/m², group 7: 35 ≤ BMI < 40 kg/m² and group 8: BMI ≥ 40 kg/m². Cox proportional hazard models were used to estimate the hazard ratios (RH). The models were adjusted for following variables: sex, age, prior heart surgery, prior PCI, smoking, diabetes, LVEF and prior-MI, use of statins and antiplatelet drugs as well as degree of vessel disease.

Results: The study included 46,247 patients with mean age 66.5±11 years, 33,085 (72%) men. During the 11.6 years of follow-up 6,785 (15%) patients died. The highest incidence rate of mortality was equal to 115 death/1000 patient year (95% CI 100.5 -131.7) for the underweight (BMI<18.5 kg/m²) and the lowest 29 deaths/1000 patient year (95% CI 24.4-31.1) for the pre-obese (27.5 ≤ BMI < 30 kg/m²). Regression multivariable analysis demonstrated that the risk was lowest among the pre-obese and increased with both lower and higher BMI (Fig. 1).

Figure 1. Hazard ratio for all-cause mortality

Conclusions: Patients with documented atherothrombotic heart disease that are overweight have improved survival compared with normal BMI. Underweight and severely obese patients have high mortality.
Clustering of cardiovascular diseases in family members of young sudden cardiac death victims: a Danish nationwide cohort study

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Purpose: Descriptive studies have indicated clustering of cardiovascular diseases (CVDs) in families with victims of sudden cardiac death (SCD). These studies included highly selected cases often from tertiary referral centers and had no control groups. This population-based cohort study, aimed to prospectively describe the occurrence of CVDs in young relatives of young SCD victims, compared to the background population.

Methods: In Denmark, 2000-2006, all cases of SCD aged 1-35 years were identified. We compared the incidence of CVD in young persons related to those victims of SCD, with the background population in a follow-up study using Standardized Incidence Ratios (SIRs) to estimate relative risks.

Results: For 463 victims of SCD we identified a nationwide cohort of 1,591 first- and second-degree relatives aged <35 years, and followed for more than 7,000 person-years in 2000-2008. The observed number of CVDs were 32 and the expected number based on national rates was 8.4, SIR = 95% confidence interval (CI) 3.79 (1.86-5.36). For cardiomyopathies, ventricular arrhythmias constituting SIIRs were 15.78 (5.12-36.83) and 11.19 (4.37-27.93), respectively. Sex of SCD victim and/or cohort member had no significant effect on SIRs. The table shows SIR for CVD and subgroups, for those with an SCD in a young first-degree relative.

Standardized Incidence Ratios (SIRs) with 95% Confidence Intervals (CI) of cardiovascular diseases (CVDs) and subgroups in cohort members aged <35 years at diagnosis, with a young first-degree relative suffering sudden cardiac death (SCD)

<table>
<thead>
<tr>
<th>Type of CVD</th>
<th>Person-years of follow-up</th>
<th>Number of outcomes</th>
<th>Observed</th>
<th>Expected</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CVDs</td>
<td>3151</td>
<td>24</td>
<td>4.4</td>
<td>5.46</td>
<td>(3.50-8.12)</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>3270</td>
<td>3</td>
<td>0.6</td>
<td>4.95</td>
<td>(1.02-14.48)</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
<td>3254</td>
<td>4</td>
<td>0.1</td>
<td>28.11</td>
<td>(7.66-71.98)</td>
</tr>
<tr>
<td>All Arrhythmias</td>
<td>3233</td>
<td>11</td>
<td>1.8</td>
<td>13.13</td>
<td>(3.06-10.93)</td>
</tr>
<tr>
<td>Ventricular Arrhythmias</td>
<td>3265</td>
<td>6</td>
<td>0.2</td>
<td>25.18</td>
<td>(9.24-54.81)</td>
</tr>
<tr>
<td>All Other CVDs</td>
<td>3277</td>
<td>7</td>
<td>2.1</td>
<td>3.27</td>
<td>(1.32-6.79)</td>
</tr>
</tbody>
</table>

Conclusion: CVDs in young first-degree relatives co-aggregated strongly with SCD in families. These results may be useful for the development of recommendations regarding timing and content of cascade screening in families experiencing SCD in the young.

Impact of everolimus-eluting stents on stent thrombosis as compared to conventional bare metal stent implantation in patients with ST-segment elevation myocardial infarction. Insights from the EXAMINATION trial

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Purpose: Second generation drug eluting stents have shown better performance as compared to first generation in terms of reduced clinical events, including stent thrombosis (ST). Nevertheless, few data are available about its safety in a STEMI all-comer population. We sought to investigate thiencidine, predictors and clinical implications of ST occurring within 1 year after primary percutaneous coronary intervention (PCI) in STEMI patients with STEMI, randomized to everolimus eluting stent (EES) vs. cobalt-chromium bare metal stent (BMS).

Methods: The Examination trial is an all-comer prospective, randomized 1:1 controlled trial, comparing patients with STEMI patients. It included 1,498 patients, randomized 1:1 to EES (n=751) or BMS (n=747). ST was assessed at 1 year, according to ARC definition.

Results: At 1 year, definite/probable stent thrombosis occurred in 26 patients (1.73%), including 18 definite and 8 probable events. The incidence of ST was lower in patients treated with EES than in those treated with BMS (hazard ratio 0.16, 95% CI 0.03 – 0.29, p=0.017). Patients with ST have higher 1-year rates of cardiac death (30.8% vs. 25.0%, p=0.001), myocardial infarction (30.8% vs. 0.5%, p=0.001) and target vessel revascularization (65.4% vs.42.2%, p=0.001) compared with those without ST. Independent predictors of 1-year definite/probable ST were BMS implantation (OR 3.2, 95% CI 1.27 – 8.24) and absence of ST segment resolution of at least 70% after PCI (OR 3.50, 95%CI 1.47 – 8.31).

Conclusions: ST occurred with increased frequency in the first year after implantation for BMS than for EES in patients treated with PCI for a STEMI and is associated with cardiac mortality and adverse events. BMS implantation and lack of ST-segment resolution were independent predictors of 1-year ST in this population. The 2 years data on stent thrombosis and its predictors will be available at the time of abstract presentation, if accepted.

New generation biolimus A9-eluting stent suppresses coronary hyperconstricting responses and inflammation through rho-kinase pathway inhibition in pigs -comparison with a Sirolimus-Eluting Stent-

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Purpose: 1st generation durable polymer coated drug-eluting stents (DES), such as sirolimus-eluting stent (SES), enhance coronary vasoconstricting and inflammatory changes. In the present study, we thus examined whether BES inhibits coronary vasoconstricting responses as compared with SES in pigs in vivo, and if so, whether Rho-kinase pathway (a central molecular pathway of coronary vasospasm and inflammation) is involved.

Methods: The post-PCI stent and bare-metal stent were implanted into the left anterior descending and circumflex arteries in the same pig (n=9). At 1 week, we examined coronary responses to intracoronary serotonin (10 and 100 μg/kg) before and after hydroxyaspidin (a specific Rho-kinase inhibitor: 30 and 100 μg/kg/min),
bradykinin (BK) (0.1 μg/kg), BK after NG-nitro-L-arginine (1 mg/kg), and
tetroxycyanic (NTG) (10 μg/kg). Changes in coronary diameter from baseline in the proximal
and distal edge segments were evaluated by quantitative coronary angiography. After euthanasia, stented vessels were isolated for histological anal-
ysis. Furthermore, the extent of inflammatory responses was classified into 4 grades of 0 (none) to 3 (more than 20 inflammatory cells/stent strut). The extent of.

Results: Coronary vasoconstricting responses to serotonin (100 μg/ml) were sig-
nificantly reduced at the proximal and distal edge segments of the SES site as compared with the SES site (BES; 39.16±16.4; p<0.01), which was abolished by pre-treatment with hydroxyfasudil. Coronary vasoconstricting re-
sponses to BK or NTG were comparable between the 2 groups. The extent of.

Conclusions: The present study demonstrates for the first time that SES sup-
presses coronary hypercontracting responses and inflammatory changes as compared with SES in pigs in vivo, for which Rho-kinase pathway inhibition may

1043 Morphological characteristics by optical coherence
tomography of ruptured neatherosclerotic plaques in patients with very late stent thrombosis
A. Karanazes, K. Witberg, R.J. Van Geuns, C. Schulz, N. Van
Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam,
Netherlands

Purpose: Neatherosclerotic plaque rupture has recently emerged as a substrate
for very late stent thrombosis (VLST). However, the morphological characteristics associated with
neovascularization or dense macrophage infiltration was also assessed. Stent
struts were assessed for coverage and malapposition. Stents with >30% uncov-
ered struts were considered uncovered, while stents with >5% malapposed struts
were considered malapposed.

Results: Median interval from the initial implantation was 5.5 years (range 2-
16). OCT revealed 14 cases with VLST due to NR. A fibrous cap was iden-
tified in 13 cases with NR and in 9 cases without NR. The NR group was
characterized by lipid-rich core, fibrous cap thickness (FCT) was measured. The presence of calicifications,
neovascularization or dense macrophage infiltration was also assessed. Stent
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1047
Thrombolytic therapy of prosthetic heart valve thrombosis in pregnancy with low dose slow infusion of t-PA (TROIA-PREG)

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Purpose: Prosthetic valve thrombosis (PVT) during pregnancy requires urgent therapy. There is still controversy about how to treat this life-threatening complication. Cardiac surgery in pregnancy is reported to be maternal mortality and morbidity of 6% and 24% and fetal mortality and morbidity of 9% and 30%, respectively. Thrombolytic therapy (TT) has been rarely used in pregnancy with only 32 cases of PVT reported in the literature so far. The aim of this study is to evaluate safety and efficacy of administration of t-PA for PVT during pregnancy.

Methods: Transesophageal echocardiography guided TT was administered to 22 consecutive patients with PVT in 27 different episodes (mean age: 29; gestational age: 15, nonObstructive: 12) between 2005 and 2012. The principal agent used was t-PA (25 mg, 6-hours without bolus, repetitive if needed). Anticoagulation with heparin was withheld during TT.

Results: The success rate of TT was 100%. The rate of abortion (15%) after TT was comparable to that of general population. One patient had placental hemorrhage with placental live birth occurred at 30th week. None of live born children suffered a permanent deficit. The average dose of t-PA used was 45±22 mg.

Conclusion: Low dose, slow infusion of t-PA with repetition as needed without bolus provides effective and safe thrombolysis in both mother and fetus. TT can be considered as first-line therapy in pregnant complications with PVT.

1048
Critical role for PI3K/P110alpha in arterial thrombosis and vascular smooth muscle cell activation: implications for drug-eluting stent design

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Background: Impaired reendothelialization and stent thrombosis remain safety concerns associated with the use of drug-eluting stents (DES) despite a reduction in restenosis rates. Phosphoinoslide-3-kinase p110alpha (PI3K/P110alpha) controls cellular processes such as proliferation and chemotaxis and thus represents an emerging drug target. However, its effect on arterial thrombus formation and activation of vascular smooth muscle (VSMC) as well as endothelial cells (EC) is not known.

Methods: PI3K/P110alpha was inhibited by treatment with the small molecule inhibitor PIK 75 or, alternatively, a specific siRNA. Arterial thrombus studies were performed in a murine carotid artery photochemical injury model. Proliferation and migration of VSMC and EC were assessed by cell number and Boyden chamber, respectively. Endothelial senescence was evaluated by β-galactosidase assay, endothelial dysfunction by organ chambers for isometric tension recording as well as Western blots for analysis of eNOS, TF, and PAI-1 expression.

Results: Male C57Bl6 mice were either treated with PIK 75 (10 mg/kg/d for 7 days) or vehicle. Arterial thrombus formation was delayed in mice treated with PIK 75 as compared to controls (n=8; p<0.005). PIK 75 impaired arterial expression and activity of TF and PAI-1 as well as TFαββ expression (n=8; p<0.05); in contrast, plasma clotting and tail bleeding times did not differ (n=8; p=NS). In human vascular smooth muscle and endothelial cells, PIK 75 inhibited activation and activity of TF and PAI-1, respectively, and reduced TFαββ expression (n=8; p<0.001). These effects occurred at the transcriptional level via the Rhoα signaling cascade and the transcription factor NFκB. Furthermore, inhibition of PI3K/P110alpha with PIK 75 or a specific siRNA selectively impaired proliferation and migration of VSMC while sparing EC completely. Treatment with PIK 75 did not induce endothelial senescence nor inhibit eNOS expression or endothelium-dependent relaxations. In contrast to PIK 75, both rapamycin and PIK 75 did not induce endothelial senescence nor inhibit eNOS expression or PAI-1 (predictive value for 0.1 ng/ml change in plasma levels 5.3 [0.10-10.5]; p=0.049) and none detected for CRP (2.5 [9.7, 4.8]; p=0.50).

No correlation was demonstrated between PI3K/P110alpha and these two proteins affect different pathways in fibrin clot lysis. In multivariable analysis, drug therapies failed to predict C3 plasma levels, although a trend was observed in men towards a positive and negative association with sulphonylurea and antipateptide therapy, respectively.

Conclusions: C3 is at least as strong as PA1 in predicting fibrin clot lysis in patients with T2DM. Therefore, future studies should analyse C3 plasma levels as a surrogate marker of fibrinolysis potential in this population.

1049
An alternative pathway for hypofibronilysin in type 2 diabetes: the role of complement C3

K.A. Hess1, S.H. Alazrakani1, J. Price3, M. Strachan4, N. Osley1, F. Phoenix3, N. Marx1, V. Schroeder3, R. King1, R.A. Aijan2. 1University Hospital Aachen, RWTH, Internal Medicine I, Cardiology, Pulmonology & Vascular Medicine, Aachen, Germany; 2University of Leeds, Leeds, United Kingdom; 3University of Edinburgh, Edinburgh, United Kingdom; 4Western General Hospital, Metropolitan Unit, Edinburgh, United Kingdom; 5Bern University Hospital, Bern, Switzerland

Purpose: Plasminogen activator inhibitor (PAI)-1 has been regarded as the main anti-fibrinolytic protein in diabetes but recent work indicates that complement C3, an inflammatory protein, directly modulates fibrinolysis in type 1 diabetes (T1DM).

Therefore, we investigated the role of complement C3 in fibrinolysis in a large cohort of T2DM subjects.

Methods: Fibrin clot lysis was determined in 875 patients enrolled on the Edinburgh type 2 diabetes study using a turbidimetric assay. Plasma levels of complement C3, C-reactive protein (CRP), PAI-1 and fibrinogen were analysed by ELISA.

Results: Clot lysis time showed a highly significant correlation with C3 and PAI-1 plasma levels (r=0.25, p<0.0001 and r=0.15, p<0.0001; respectively). In contrast, a relatively weak correlation was detected with CRP (r=0.08, p=0.02) and fibrinogen (r=0.01, p=0.01). Plasma levels of C3, CRP, fibrinogen or PAI-1 did not differ in the presence of previous history of myocardial infarction or cerebrovascular disease. Plasma levels of all four proteins correlated with body mass index, but only PAI-1 showed an interaction with age and duration of diabetes. In a regression model involving these proteins, C3 was a predictor of lysis time [predictive value for 0.1 mg/ml change in plasma levels 14.4 (95% CI 7.9, 21.0) p<0.001,] as was PAI-1 [predictive value for 0.1 mg/ml change in plasma levels 8.2 (4.2, 12.1; p<0.001] with a smaller effect shown for 0.1 mg/ml change in fibrinogen levels [5.3 (0.10-10.5); p=0.049] and none detected for CRP [-2.5 (-9.7, 4.8); p=0.50]. No correlation was demonstrated between C3 and PAI-1 plasma levels indicating the two proteins affect different pathways in fibrin clot lysis. In multivariable analysis, drug therapies failed to predict C3 plasma levels, although a trend was observed in men towards a positive and negative association with sulphonylurea and antipateptide therapy, respectively.

Conclusions: PAI-1 is at least as strong as PA1 in predicting fibrin clot lysis in patients with T2DM. Therefore, future studies should analyse C3 plasma levels as a surrogate marker of fibrinolysis potential in this population.

1051
Multivessel primary percutaneous coronary intervention in acute myocardial infarction complicated by cardiogenic shock and resuscitated cardiac arrest: friend or faux?

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Purpose: Survival in patients with ST-segment elevation myocardial infarction (STEMI) complicated by cardiogenic shock (CS) and resuscitated cardiac arrest (CA) is poor, despite primary percutaneous coronary intervention (PCI). Most of these patients have multivessel (MV) coronary disease, however the safety and efficacy of primary MV PCI is unknown. We sought to compare outcomes between primary MV and culprit-only PCI in these patients.

Methods: Between 1998 and 2010, we prospectively collected data from consecutive STEMI patients in 5 French centres. The study population was derived from 11,530 patients admitted with STEMI, among whom 2.3% (n=266) were eligible for study inclusion, having presented with both resuscitated CA and CS. The primary end-points were 6-month survival.

Results: The mean age was 62.1±13.6 years. CAs occurred most commonly at home (35.4%) and the median interval to first responder CPR was 5.0 [2.0, 14.0] minutes. Ventricular fibrillation was the initial arrhythmia in 60.2%, and the baseline ECG demonstrated STEMI in 86.5%. Pre-hospital thrombolysis was performed in 14.6%. On angiography, most patients had MVD (63.5%). Baseline characteristics were similar in patients undergoing either culprit-only (60.9%) or MV (39.1%) PCI. Six-month survival was significantly higher in patients undergoing MV PCI compared to those undergoing culprit-only PCI (43.9% versus 20.4%, P=0.0017). A reduction in the composite of recurrent CA and shock death (P=0.024) mediated this difference. On multivariate analysis, MV PCI was associated with improved 6-month survival (OR 3.19; 95% CI, 1.15-6.45, P=0.005).

Conclusions: MV PCI is associated with improved survival compared to culprit-only PCI.
Tertiary centres have improved survival compared to other hospitals in the Copenhagen area after out-of-hospital cardiac arrest

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Purpose: Out-of-hospital cardiac arrest (OHCA) has been reported to carry varying mortality. It remains unclear whether it is caused by intrinsic factors or due to in-hospital care. The aim of this study is to compare 30-day and long-term mortality after OHCA at tertiary heart centres vs. non-tertiary hospitals.

Methods: 1,034 consecutive patients treated by the Copenhagen mobile emergency care unit (MECU) with either return of spontaneous circulation (ROSC) or on-going resuscitation at hospital arrival were included (2002-2010). Patients are transported to the nearest hospital or to a tertiary heart centre for acute coronary angiography if ECG shows ST-segment elevations. To reduce referral bias patients with ST-elevations were excluded (n=198).

Results: 30-day mortality was 56% vs. 76% (Fig.1,left) and long-term mortality was 76% vs. 94% (Fig.1,right) for tertiary and non-tertiary hospitals, respectively (p=0.001). Multivariable analysis showed that admission to a non-tertiary hospital was independently associated with increased risk of death (HR=1.27 (95%CI: 1.06-1.53, p=0.009)). Longer time to ROSC, age and asystolic or pulseless electric activity as initial arrhythmia were significant predictors of death, whereas bystander CPR, witnessed cardiac arrest, and acute coronary angiography were independent predictors of lower 30-day mortality. Exclusion of patients with on-going resuscitation at admission resulted in HR=1.37 (1.14-1.65), p=0.001. A matched pair propensity score analysis of 574 patients confirmed the results of the proportional hazard analysis HR=1.35 (1.12-1.63), p=0.002.

Figure 1. Kaplan-Meier mortality plots

Conclusion: Admission to tertiary centres with 24-hour cardiology service and invasive cardiac interventions is associated with lower mortality rates after OHCA compared with non-tertiary hospitals.

Women with heart failure and diabetes are at increased risk for mortality compared to women with DM without diabetes

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Purpose: Heart failure is reported as a common complication in women with DM, but information on long-term outcome in such patients from an all day practise population is sparse.

Methods: Patients included in the Swedish Heart Failure Registry (RiksSvikt) between the years 2004-2011 were followed for mortality until Sept. 30, 2011 (median 22.5 months). Long-term prognosis, differences in background and heart failure characteristics were analysed in women and men with and without DM.

Results: Among 36397 patients 24% had type 2 DM and 39% were women. In patients with DM, women compared to men were older (77 vs. 73 yr) with more frequent hypertension (63 vs. 58%) and kidney dysfunction (clearance < 30 ml/min/20 yr) but more often an EF <50% (33 vs. 16%). Compared to men, women with DM received less of evidence based drug treatment (ACE-i: 64 vs. 55%, statins: 61 vs. 49%) and revascularisation (38 vs. 23%). Comparing women, those with DM more often had hypertension (63 vs. 48%) and ischemic heart disease (54 vs. 40%). The Figure shows Kaplan Meyer curves for mortality in the four groups. The unadjusted OR (95% CI) for mortality was 1.23 (1.13-1.34) in women compared to men with DM and 1.37 (1.27-1.48) in women with compared to women without DM. After adjustments for background characteristics these ORs were 0.89 (0.79-0.99) and 1.78 (1.60-1.98) respectively. In ages <65 yr, OR for women vs. men with DM was 0.82 (0.79-1.08) and for women with DM vs. women without DM 2.66 (1.99-3.57).

Figure 1. Mortality by diabetes and gender

Conclusion: Women with heart failure and DM are at an especially high mortality risk partly due to higher age and co-morbidities such as renal dysfunction. However incomplete drug treatment and lack of revascularisation are important contributors that are possible to improve.

Changes in renal function in real-life chronic heart failure patients on optimized therapy


Background: Many randomized controlled chronic heart failure trials showed that renal function remains stable on long term if patients are strictly controlled. However patients included in these trials are pre-selected by compliance and risk for complications. Therefore less is known about changes of renal function in a real-life population.

Aim: To investigate the long-term changes of glomerular filtration rate (GFR) in a patient cohort followed at a heart failure clinic.

Patients and method: 552 consecutive patients followed at our heart failure out-patient clinic were included (age: 62.8±13.5 years, male: 75.2%, ischemic etiology: 52.7%, diabetes: 37.9%, left ventricular ejection fraction (LVEF): 30.9±9.1%, baseline GFR: 66.6±24.0 ml/min, systolic blood pressure: 126.6±23.6 mmHg). After inclusion therapy has been optimized and device therapy (CRT: 17.9%, ICD: 15.8%) applied for all patients according to current guidelines. Patients were divided into 3 groups according to baseline GFR (<30 ml/min: 28 pts, 30-60 ml/min: 192 pts, >60 ml/min: 332 pts). Changes in GFR were assessed at 6 and 12 months and every 12 months thereafter for up to 5 years.

Results: In the whole cohort GFR decreased in the first 6 months significantly (p<0.05) by -7.6±8.1 ml/min and showed no further significant change in the following years. The same changes could be observed in patients with ischemic etiology (-7.5±17.7 ml/min), in those over 65 years (-7.8±16.7 ml/min), in patients with an LVEF<30% (-6.3±18.7 ml/min), and in diabetics (-5.6±15.9 ml/min), all p<0.05. In patients with severe renal dysfunction (baseline GFR<30 ml/min) renal function improved by optimizing therapy (+5.5±5.1 ml/min), while in those with moderate renal dysfunction (baseline GFR 30-60 ml/min) GFR showed a small but significant early deterioration (-1.1±1.4 ml/min), and those with a GFR>60 ml/min GFR decreased on treatment optimization (-13.3±19.5 ml/min) and remained stable after that.
Conclusion: In a real-life chronic heart failure population renal function worsens in the early period of treatment optimization, however it remains stable on long term thereafter. In patients with severe renal dysfunction therapeutic changes may significantly improve renal function.

NURSING/ALLIED PROFESSIONAL INVESTIGATOR AWARD

1062 Does refusal of Chronic Heart Failure management equate to usual care? Results of the which intervention is most cost-effective and consumer friendly in reducing hospital care? (Which?) Trial

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Purpose: Although chronic heart failure management programs (CHF-MPs) are the gold-standard for post discharge management of predominantly old and fragile patients with CHF, their cost-effectiveness and key components of intervention are still the subject of debate. This study examines the results of the WHICH? Trial from the perspective of those who were randomized but later refused to be managed within a clinic or home-based CHF-MP.

Methods: The WHICH? Trial randomized 280 patients with CHF to two forms of CHF-MP as part of a multicentre, head-to-head trial of home versus clinic-based (HBI and CBI) post-discharge management. All patients were subject to comprehensive baseline profiling and followed-up for a minimum of 18 months. The primary endpoint was event-free survival from all-cause mortality and hospitalization. Pre-specified secondary endpoints included rate and type of hospitalization, related hospital stay and an economic analysis of health care costs. In this analysis, we were specifically interested in the rate of refusal (post randomization) and hypothesized that those who refused management had worse outcomes in essence mimicking "usual care" in historical trials.

Results: Overall, 247 (91%) versus HBI (140 [98%]) were managed (as planned) by their respective CHF-MP (OR 0.93, 95% CI 0.87 to 0.98; p=0.008). The 16 patients (5.7%, 38% female) who refused were significantly older than the rest (76±11 vs. 71±14 years); the only independent predictor of refusal being negative for depressive symptoms (25% vs. 54%; OR 0.3, 95% CI 0.09-0.98). The figure below shows that refusals had worse survival, increased hospitalization and more costs than the rest (all p<0.01).

Conclusions: Patients who refuse management via a CHF-MP are at high risk for poor health outcomes.

1063 Type D (distressed) personality predicts impaired health status in patients presenting with chest pain suggestive of an acute coronary syndrome

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Objective: Improving health status is challenging in patients with chest pain. We examined the persistent effect of Type D (distressed) personality on health status in these patients.

Patients and Methods: 241 patients with symptoms suggestive of an acute coronary syndrome admitted to a chest pain unit of a university hospital were included in a pre-post quasi-experimental study to evaluate the implementation of a critical pathway. They completed the 14-item Type D Scale (DS14), the EuroQol (EQ-5D), a Visual Analogue Scale (VAS) and the Hospital Anxiety and Depression Scale (HADS) during admission and at 1 and 6 months follow-up to assess Type D personality, quality of life, and anxiety/depression, respectively. The effect of Type D personality on health status was examined over a 6-month period, adjusting for intervention group, diagnosis type (cardiac vs. non-cardiac), age, sex and heart failure.

Results: Type D personality was present in 29% (n~70/241) of patients and was associated with impaired quality of life (p<0.001) both when measured with the EQ-5D and VAS. This adverse effect of Type D on quality of life was stable across 6 months follow-up, despite changes in these outcomes over time. Type D personality was also independently associated with higher symptoms of anxiety (p<0.001) and depression (p=0.01), both at admission to the chest pain unit and at follow-up. Increased anxiety and depression levels were present in 50% (n=29) and 43% (n=25) of the 58 Type D patients filling in the questionnaire at 6 months, as compared to 25% (n=35) and 21% (n=31) of the 143 non-Type D patients. Type D personality independently predicted increased risk of anxiety (OR=2.86, 95%CI 1.47-5.68, p=0.002) and depression (OR=2.75, 95%CI 1.34-5.65, p=0.006), adjusting for clinical and demographic characteristics.

Conclusions: Type D personality had a persistent, detrimental effect on quality of life, anxiety and depression in patients presenting with chest pain suggestive of an acute coronary syndrome. Future efforts could be directed to the modification of maladaptive coping strategies and emotional reactions in chest pain patients with a Type D personality.

1064 Quality of life and physical capacity after long-term right ventricular pacing in young adults with congenital atrioventricular block

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Background: Although several studies have demonstrated the deleterious consequences of chronic right ventricular (RV) pacing on ventricular function and sympathy, its effects on health-related quality of life (HRQL) and physical capacity remains uncertain.

Objectives: To evaluate the effect of RV pacing on HRQL and physical capacity of children and young adults with congenital complete atrioventricular (AV) block.

Methods: Fifty consecutive patients with permanent RV cardiac pacing due to congenital AV block and under clinical follow-up for more than one year were enrolled. Multidimensional HRQL was assessed with a Short Form-36 Health Survey (SF-36) and Child Health Questionnaire (CHQ-PF50). Physical capacity was tested by the 6-minute walk distance test (6MWD). The scores for each domain and the distance performed at the 6MWD test were compared with demographic and clinical characteristics of patients, using the Student’s t-test and Qui-square test.

Results: Domains presenting lower scores were Vitality (63.0±0.6), Pain (66.5±25.1) and Mental Health (67.3±20.4) in the SF-36 questionnaire; General Health Perceptions (64.0±15.0) and Parental Impact-Emotional (69.0±30.0) in the CHQ-PF50. Female gender (P=0.026), DDD pacing mode (0.008) and normal left ventricular ejection fraction (0.002) were associated with higher quality of life scores. The average distance performed at the 6MWD test was 677.2 meters (454.5 to 852.6). The 6MWD showed significant association with age (P<0.004), normal ventricular function (P=0.001) and the absence of cardiovascular drugs use (P=0.018).

Conclusions: The results of this analysis indicated that chronic RV pacing did not affect the HRQL and physical capacity of young adults with congenital complete atrioventricular (AV) block.

1136 Pressure points in primary care: a study of blood pressure in 532,050 primary care patients (2005 to 2010)

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Purpose: As in many countries, the prevalence of elevated blood pressure (BP) levels in the Australian population has decreased between 1980 to 2000. However, as in other countries, there is a paucity of contemporary data in the primary care setting.

Methods: Data from a national longitudinal patient-based database of demographic (physician), clinical, pathology and prescription information was collected by 73 primary care physicians located in metropolitan and regional areas across Australia between 2005 to 2010. A total of 532,050 patients (55% women) had a BP measurement recorded at least once. At first presentation, mean BP levels remained stable across the 6 years of study data at an average of 129±17.7/79±11 mmHg and 36% of patients had hypertension (>140/90 mmHg and/or taking antihypertensive medication). Overall, BP was higher in men than women (132±17.7/79±11 mmHg vs 127±19.7/77±11 mmHg) and there were 3-fold more young adult men
Association of temperature and monthly variation in Clinical benefit of percutaneous coronary intervention

The association between clinical symptomatic the well described “treatment gap” persists. cost subsidies for primary care visits and prescribed anti-hypertensive treatments of the public health importance of effectively treating hypertension coupled with showed that there have not been any significant gains in the community con-

Conclusions: This large, contemporary study of BP in primary care patients showed that there have not been any significant gains in the community con-

trol of elevated BP since 2005 in Australia. Despite increased general awareness of the public health importance of effectively treating hypertension coupled with cost subsidies for primary care visits and prescribed anti-hypertensive treatments the well described “treatment gap” persists.

Association of temperature and monthly variation in sudden out-of-hospital cardiac arrest of 196,032 cases

Seasonal variation in the incidence of out-of-hospital cardiac arrest (OHCA) was observed with an increase in winter months in previous studies. However, most of them are often small, regional, and not population based. We therefore examined seasonal variation in sudden cardiac arrest using 4 years of data from national database of cardiac arrest registry, the All-Japan Utstein Registry of the PDMA (Fire and Disaster Management Agency), Japanese government.

Method: From January 1, 2005, through December 31, 2008, we conducted a population-based, observational study involving consecutive patients across Japan who had an OHCA. Incidence rate ratio (IRR) of OHCA were calculated for each month and the lowest temperatures in each area by Poisson regression analysis.

Results: A total of 196,032 adults who had an OHCA were included in this study; the pattern in the occurrence of OHCA is characterized by a marked peak the January and a nadir in June or July (P for curve linear trend >0.0001). The IRR in January was 1.81 (95%CI: 1.58-1.65) compared with June (reference). These associations were robust after adjusting for age and sex and more marked in the elderly people. (OR = 1.85, 95%CI 1.80-1.90, for ≥65 yo) The incidence rate of OHCA is also associated with the mean lowest temperatures (both P <0.0001). The IRR for the lowest temperatures adjusted for age, sex and month was 0.987 (95% CI, 0.986-0.989), (p =0.001). One degree decrease of the lowest tempera-

ture increases 1.31% of the OHCA risk and 10 degree change increased 13.9%.

Clinical benefit of percutaneous coronary intervention in early latecomers with acute ST-elevation myocardial infarction

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Objectives: We evaluated the efficacy and optimal timing of percutaneous coro-

Critical benefits of PCI is controversial in stable patients with STEMI presenting between 12 and 72 hours after the symptom onset.

Methods: Employing data from the Korea Acute Myocardial Infarction Registry, we analyzed 2,640 stable STEMI patients with symptom-to-door time between 12 and 72 hours. Patients with cardiac arrest, ventricular arrhythmia, cardiogenic shock, heart failure (Killip class III or IV), fibrinolysis, or urgent PCI during in-

Clinical outcomes were compared, with composite of death and Ml as the primary endpoint.

Results: Patients in the PCI group were more often male and smokers; and more likely to have anterior MI with higher cardiac troponins, and history of MI, PCI, heart failure, stroke, and peripheral vascular disease. Patients receiving med-

Critical benefit of PCI was older and more often had renal dysfunction. After adjustment for other confounders using propensity score methods, PCI group had lower mortality (3.2% vs. 10.1%; odds ratio [OR], 0.48; 95% confidence interval [CI], 0.32 to 0.73; P<0.001) and lower incidence of composite death/MI (3.9 vs. 11.2%; OR, 0.51; 95% CI, 0.35 to 0.74; P< 0.001) at 12 months. Subgroup analysis by early and delayed PCI revealed that patients receiving early PCI more often had chest pain; shorter symptom-to-door time; anterior MI with higher cardiac troponins; and history of PCI, dyslipidemia, stroke, and chronic kidney disease. However, adjusted analysis using propensity score for early PCI found no statistical dif-

Critical benefits of PCI were in the rates of death (2.4% vs. 2.1%), death/MI (2.4% vs. 2.3%), and death/MI/repeat revascularization (3.5% vs. 3.3%) during 12-month follow-up.

Conclusions: In stable patients with STEMI presenting 12 to 72 hours after symptom-onset, PCI was associated with significant improvement in 12-month clinical outcome. The optimal timing of PCI remains to be determined.

The association between clinical symptomatic hypoglycemia with cardiovascular events in type 2 diabetes: A nested case control study in nation-wide representative population

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Background: Hypoglycemia was already known to cause serious health outcomes. Previous evidences were all derived from clinical trials or inpa-

identifiable population with other specific admission cause. How is the consequence of those clinically treated type 2 diabetes patients who had hypoglycemia episode experiences is unknown?

Methods: The study population was comprised of 76,987 type 2 diabetic mellitus patients identified from the “National Health Insurance Research Database” re-

leased by the Taiwan National Health Research Institutes during 2000-2009. We designed a nested case control cohort, which was consistent of hypoglycemic type 2 diabetes patients with randomly selected and matched type 2 diabetes patients without hypoglycemia.

We investigated the relationship between hypoglycemia and cardiovascular events including stroke, coronary heart disease, cardiovascular events, and all cause of hospitalization.

Results: There were total 2,641 hypoglycemic events (589 defined by inpa-

Patient and 2,052 defined by outpatient) from 76,986 type 2 diabetes mellitus pa-

The incidence risk of hypoglycemia was 3.43% (2,641/76,986). Women who had higher risk of hypoglycemia than men (1.98% vs. 1.45%). Both in the mild and severe hypoglycemia cases have higher percentage of comorbidity, includ-

ing hypertension, renal diseases, cancer, stroke and heart disease. Hypertension (HR = 1.74; 95% confidence intervals: 1.58-1.92), renal disease (2.96; 2.57-3.40), cancer (2.37; 1.94-2.91), stroke (2.79; 2.35-3.29), and coronary heart disease (1.81; 1.52-2.15) were independently associated with hypoglycemia. Those dia-

betes patients with hypoglycemia had significantly higher risk of cardiovascular events in clinical treatment periods in multivariate models. Even after propensity score adjusted model, mild and severe hypoglycemia still have around 1.94 (1.71-

2.19), 2.23 (2.00-2.49) higher relative risk for CVD and all cause hospitalization

Conclusion: Large population based registry showed monthly variations in OHCA. The risk of cardiac arrest is highest in January and lower in mild climate season. The people ±65 years and the low temperatures were high-risk of cardiac arrest.
respectively. Around 70% of hypoglycemic subjects experienced admission of any cause in the following first year.

**Conclusion:** Symptomatic hypoglycemia, both clinically mild and severe, were associated with an increased risk for cardiovascular and all causes of hospitalization. The adverse events after hypoglycemia are most frequently occurring in the following first year. Clinically, we should aggressively treat those hypoglycemic episodes accompanied type 2 diabetes patients and prevent their immediate and further clinical adverse events.

**1140 Glycosylated hemoglobin A1c (HbA1c) in non-diabetic patients: an independent predictor of coronary artery disease and its severity**

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**Purpose:** Elevated glycosylated hemoglobin A1c (HbA1c) is associated with increased risk of atherosclerosis and cardiovascular mortality in diabetic patients. The association between HbA1c and cardiovascular risk is inconsistent in non-diabetic subjects. In the present study, we examined the association between HbA1c and presence & severity of angiographically proven coronary artery disease (CAD) in non-diabetic subjects.

**Methods:** Consecutive 1897 non-diabetic patients undergoing coronary angiography over last one year were included. All patients underwent haemogram, biochemical and HbA1c measurements. Significant CAD was defined as ≥50% stenosis in one major vessel and complex CAD was assessed by SYNTAX score. The study population was divided in 4 quartiles on the basis of HbA1c levels (<5.5%, 5.5-5.7%, 5.8-6.1%, >6.1%). Statistical analysis was done to compare the differences among the four groups. Logistic regression analysis was done to determine the factors predicting the presence, severity and complexity of CAD.

**Results:** Mean age was 56.7±10.6 years and 82.7% were males. Overall 243 (21.3%) patients had normal coronaries or insignificant CAD. With increasing HbA1c levels, there was significant increase in the prevalence of CAD. Number of vessels involved, triple vessel disease, coronary calcium, chronic total occlusions, left main disease and left ventricular dysfunction. SYNTAX score had a single and without correlation with rising HbA1c (mean SYNTAX score in four quartiles was 9.9±12.2, 11.6±11.8, 12.6±12.6 and 15.8±12.2 respectively). There was a linear correlation with HbA1c levels and prevalence of significant CAD. Compared to the patients with HbA1c <5.5%, the risk of significant CAD in other quartiles was 1.8 times (OR 1.8, 95% CI 1.2-2.7, p= 0.003), 3.7 times (OR 3.7, 95% CI 2.3-5.0, p<0.001), and 5.2 times (OR 5.2, 95% CI 3.8-8.3, p<0.001) higher respectively. On multivariate analysis, age, male gender, smoking, serum creatinine levels, left ventricular dysfunction, serum LDL levels and HbA1c levels emerged as independent predictors of significant CAD [OR 2.7 (95% CI 1.9-3.7), p= <0.001]. Patients with impaired glucose tolerance (HbA1c ≥5.7%) were at significantly higher risk of having CAD when compared with nondiabetics (HbA1c <5.7%).

**Conclusions:** In the non-diabetic subjects, HbA1c levels strongly correlate with significant CAD independent of conventional cardiovascular risk factors. It also correlated strongly with disease severity and higher SYNTAX score. HbA1c measurement can therefore be utilized as an independent predictor of CAD in non-diabetic subjects.

**1141 Contemporary impact of diabetes on 10 year survival in outpatients with chronic heart failure**

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**Background:** Heart failure (HF) and diabetes are common chronic cardiovascular complications which compound each other. The Canadian Heart Failure Network (CHFN) of 27 HF sites across Canada have enrolled HF patients into a longitudinally followed HF database over the last 11 years. We wished to determine the impact of diabetes on the prognosis of ambulatory HF patients in this contemporary cohort of patients in the CHFN prospective database.

**Description of Population:** Of the 18,772 HF patients enrolled in the CHFN database, 20.3% had a diagnosis of diabetes. Among those with diabetes, 6% had type 1, 68% had type 2, and 26% had type 2 insulin dependent diabetes. 91% of diabetes patients had been diagnosed at the time of their first assessment. New diagnoses of diabetes occurring within 1 month of enrollment were 23%, from 2-6 months 19.6%, from 7-12 months 11.6%, from 1-2 years 12.5%, ≥2 years 32.7%. Overall demographics of the population were: age 67±14 years, 51% male, 31%, ischemic etiology 45 mL/min and type 1 diabetes. Control patients were allowed to crossover to RDN at 6 months. Change in office BP from pre-procedure measurements (6 months post-randomization for the crossover group), renal function, and medication use were collected at 6 months after the RDN procedure.

**Results:** At baseline, mean age of the RDN group was 59 y. 32.7% were female, and 42.9% had type 2 diabetes. Mean age of patients crossed over to RDN was 58 y. 60% were female, and 28.6% had type 2 diabetes. There was 1 renal artery stenosis, no other adverse events occurred. Change in office BP at 6, 12, and 18 months are shown below.

**Conclusion:** Treatment of resistant hypertension with RDN was safe and effective in both treatment groups to 18 months post-procedure.

**1163 Catheter-based renal sympathetic denervation in patients with resistant hypertension: 18 month follow-up of the Symplicity HTN-2 trial**

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**Purpose:** Catheter-based renal sympathetic denervation (RDN) has been shown to reduce blood pressure (BP) in patients with resistant hypertension (systolic BP ≥160 mm Hg while receiving optimal doses of ≥3 antihypertensive medications). Longer term outcomes in patients treated with RDN immediately or 6 months after confirmation of resistant hypertension are analyzed to assure the durability and safety of this interventional treatment.

**Methods:** Eligible patients were randomized 1:1 to receive RDN plus antihypertensive medications or antihypertensive medications alone. Exclusion criteria included an eGFR <45 mL/min and type 1 diabetes. Control patients were allowed to crossover to RDN at 6 months. Change in office BP from pre-procedure measurements (6 months post-randomization for the crossover group), renal function, and medication use were collected at 6 months intervals after the RDN procedure.

**Results:** At baseline, mean age of the RDN group was 59 y. 32.7% were female, and 42.9% had type 2 diabetes. Mean age of patients crossed over to RDN was 58 y. 60% were female, and 28.6% had type 2 diabetes. There was 1 renal artery stenosis, no other adverse events occurred. Change in office BP at 6, 12, and 18 months are shown below.

**Conclusion:** Treatment of resistant hypertension with RDN was safe and effective in both treatment groups to 18 months post-procedure.

**1164 Orthostatic function after renal sympathetic denervation in patients with resistant hypertension**

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**Background:** Catheter-based renal sympathetic denervation (RDN) is a novel treatment option for patients with resistant hypertension, proved to reduce local and whole-body sympathetic activity and blood pressure (BP). The effect of RDN on orthostatic regulation has not been studied.

**Method:** In 27 patients (age 64±7 years, 77% male with resistant hypertension (office systolic blood pressure 16/91±22/7 mmHg) treated with 4±8±0±3 non-hypotensive drugs, tilt table test (TTT) was performed before and 3 months after RDN. Patients were placed on a motorized tilt table. After resting for at least 10 min the recording started. After 5 min in supine position, all subjects were tilted at 60°
for 20 min. Subsequently drug provocation with 400 mg nitro-glycerine sublingual was performed while tilt position was maintained for additional 10 min. A recovery period was performed in initial supine position. Antihypertensive drugs were maintained reduced by 7.7 ± 4.4 mg/l (p < 0.05) and heart rate (HR) was reduced by 4.5 beats/min (p < 0.01). After tilting the maximal reduction of BP compared to supine position was not altered (Δ max. SBP: –32.5 vs. –25.7 ± 7.5 mmHg, Δ max. DBP: –14.2 vs. –13.3 ± 3.3 mmHg; p > 0.05). In addition, the minimal BP during 20 min tilting period was also not different after RDN (min. SBP: 135.6 ± 132.6 ± 8 mmHg, min. DBP: 77.3 ± 73.3 ± 9 mmHg; p > 0.05) whereas mean HR during 20 min tilting period was significantly reduced by 4.9 beats/min (p < 0.05).

Following drug provocation the maximal BP reduction compared to tilting period was unchanged after RDN (Δ max. SBP: –63.6 vs. –60.7 ± 3.5 mmHg, Δ max. DBP: –30.3 ± 26.5 vs. –26.4 ± 4 mmHg; p > 0.05). During 10 min drug provocation period minimal BP (Δ min. SBP: 98.7 ± 99.7 ± 4 mmHg, Δ min. DBP: 61.4 ± 61.4 ± 8 mmHg; p > 0.05) and minimal HR (Δ HR: 74.5 ± 70.3 ± 3 mmHg; p > 0.05) were not significantly changed.

The total number of pre-syncopes and syncopes were not different after RDN: Before and after RDN 6 pre-syncopes (p > 0.05) as well as 3 vs. 4 syncopes (p > 0.05) occurred during the TTT (p > 0.05).

Conclusion: In patients with resistant hypertension catheter-based renal sympathetic denervation significantly reduced blood pressure and heart during tilting testing after 3 months without causing orthostatic dysfunction or (pre-)syncopes.

Pathetic denervation significantly reduced blood pressure and heart rate during tilting occurred during the TTT (p < 0.01). In addition, the fractional sodium excretion (FENa) was significantly reduced by 4.9 beats/min (p < 0.05).

Results: After RDN systolic (SBP) and diastolic blood pressure (DBP) in supine position were reduced by 7.7 ± 4.4 mmHg (p < 0.05) and heart rate (HR) was reduced by 4.5 beats/min (p < 0.01). After tilting the maximal reduction of BP compared to supine position was not altered (Δ max. SBP: –32.5 vs. –25.7 ± 7.5 mmHg, Δ max. DBP: –14.2 vs. –13.3 ± 3.3 mmHg; p > 0.05). In addition, the minimal BP during 20 min tilting period was also not different after RDN (min. SBP: 135.6 ± 132.6 ± 8 mmHg, min. DBP: 77.3 ± 73.3 ± 9 mmHg; p > 0.05) whereas mean HR during 20 min tilting period was significantly reduced by 4.9 beats/min (p < 0.05).

Following drug provocation the maximal BP reduction compared to tilting period was unchanged after RDN (Δ max. SBP: –63.6 vs. –60.7 ± 3.5 mmHg, Δ max. DBP: –30.3 ± 26.5 vs. –26.4 ± 4 mmHg; p > 0.05). During 10 min drug provocation period minimal BP (Δ min. SBP: 98.7 ± 99.7 ± 4 mmHg, Δ min. DBP: 61.4 ± 61.4 ± 8 mmHg; p > 0.05) and minimal HR (Δ HR: 74.5 ± 70.3 ± 3 mmHg; p > 0.05) were not significantly changed.

The total number of pre-syncopes and syncopes were not different after RDN: Before and after RDN 6 pre-syncopes (p > 0.05) as well as 3 vs. 4 syncopes (p > 0.05) occurred during the TTT (p > 0.05).

Conclusion: In patients with resistant hypertension catheter-based renal sympathetic denervation significantly reduced blood pressure and heart during tilting testing after 3 months without causing orthostatic dysfunction or (pre-)syncopes.

1165 Experimental evaluation of a new catheter-based technique for the treatment of resistant hypertension
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Purpose: Renal sympathetic denervation with radiofrequency energy delivery is a novel therapeutic option for resistant hypertension. However, there are concerns about the long-term efficacy of this method. We evaluated in an animal model, a novel method for chemical denervation of the renal artery by local delivery of vincristine, an antineoplastic drug with potential for long-term peripheral neurotoxicity, using a dedicated catheter.

Methods: We created a dedicated system for the delivery of vincristine into the vascular wall, by modifying a conventional non-compliant balloon angioplasty catheter. We created circumferentially across the balloon 6 sideholes of 25 μm diameter, in fixed intervals of 60°. Using this catheter, we prepared a mixture of vincristine with saline and contrast containing 25mg/vulcristine, and a placebo mixture with saline and contrast. 4 ml of the mixture were delivered by balloon inflation in one of the renal arteries of 14 juvenile Landrace swine, and 4 ml of the placebo mixture were delivered by balloon inflation in the contralateral renal artery of each pig. Animals were euthanized at 28 days and histological specimens of renal arteries and perirenal arterial stroma containing renal nerves were extracted and sectioned. Histopathological assessment of the renal arteries included evaluation for significant stenosis, luminal and mural thrombosis, intramural hemorrhage and intimal or medial damage. The number of uninjured nerves in each histological section was then quantified, following identification by immunohistochemical staining.

Results: In all animals delivery of vincristine and placebo mixtures was successful and uncomplicated. Both vincristine- and placebo-treated renal arteries were angiographically patent at the end of the procedure. A total of 112 sections (6 in each pig) were assessed in each treatment group. Histological analysis did not show any evidence of significant stenosis, luminal or mural thrombosis, or intraplaque hemorrhage. In all arteries, i.e. placebo- and vincristine-treated, there was no evidence of intimal damage (occupying at least 10% of the intima) or intimal hyperplasia. Medial damage was not observed in any of the treated arteries, as well. The mean number of intact nerves in all sections was significantly lower in the treated arteries (8.6±3.4 versus 11.7±2.3; p < 0.01).

Conclusions: Catheter-based delivery of vincristine in the renal artery of an experimental model is feasible and results in significant reduction in the number of renal nerves. Our findings warrant further confirmation in animal and human studies.

1166 Effect of renal denervation therapy on sodium excretion in patients with resistant hypertension
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Background: Increased renal resistive index (RRI) and urinary albumin excretion (UAE) are markers of hypertensive end-organ damage involving increased sympathetic activity. Catheter-based renal sympathetic denervation (RDN) offers a new approach to reduce renal activation of the sympathetic nervous system and blood pressure in resistant hypertension. The influence of RD on renal hemodynamics, renal function, and UAE has not been described.

Methods and Results: One hundred consecutive patients with resistant hypertension were included in the study: 88 underwent interventional RD and 12 served as controls. Systolic, diastolic and pulse pressure (SBP/DBP/PP) as well RRI in interlobar arteries, renal function and UAE were measured prior to, and at 3 and 6 months follow-up. RD reduced SBP, DBP and PP at 3 and 6 months by 22.7/26.6 mmHg, 7/9.7 mmHg, and 15/17.5 mmHg (p < 0.01), respectively, without significant changes in the control group. SBP reduction after 6 months correlated to SBP baseline values (r = 0.46, p < 0.001). There were no renalartery stenosis, dissections or aneurysms on follow-up, RRI decreased from 0.69±1.01 at baseline to 0.67±0.01 and 0.67±0.01 (p < 0.007/0.01) at 3 and 6-month follow-up, respectively. Mean Cystatin C glomerular filtration rate (GFR) and UAE remained unchanged after RD, however, the number of patients with micro- or macroalbuminuria decreased.

Conclusion: Renal denervation reduced blood pressure, renal resistive index and incidence of albuminuria, without adversely affecting GFR or renal artery structure within 6 months. RD appears to be a safe and effective therapeutic approach to low blood pressure in patients with resistant hypertension and is associated with favorable effects on renal hemodynamics and urinary albumin excretion rate.

1168 Anxiety, depression, quality of life and stress in patients with resistant hypertension before and after renal sympathetic denervation
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Objective: Arterial hypertension is associated with psychological comorbidities like anxiety disorders which lead to impairment in quality of life. Renal sympathetic denervation (RDN) is a novel treatment option for patients with resistant hypertension, proved to reduce blood pressure, but no data is currently available whether RDN leads to change in sympathetic activity. The aim of the present study was to analyze quality of life, arousal level, anxiety and depression, sleeping quality, intensity of headache and stress tolerance in patients with resistant hypertension before and 3 months after RDN.
Methods: RDN was performed in 173 patients with resistant hypertension (BP ≥140/<80 mmHg, 5 antihypertensive drugs in median) aged 63±10 years (53% male). Patients were instructed to rate their physical and mental state and arterial level on a 0-100% scale. Stress was induced by a multi-tasking situation (Decision Task). Total number of correct reactions and errors were registered. Furthermore depression and anxiety (Hospital Anxiety and Depression Scale (HADS), quality of life (Short Form-12 Health Survey (SF-12)) and insomnia and regeneration process of sleeping (0-100%) scale) were assessed. Intensity of headache was measured by visual analogus scale (VAS). Results: Decreased by -17.7 mmHg 3 months after RDN (p < 0.01). In addition, patients showed more correct reactions (p < 0.0001), and less errors (p < 0.05) in the multi tasking situation. Patients felt improved in physical (from 55.6% to 67.2%, p < 0.01) and mental (from 51.6% to 68.4%, p < 0.05) state as well as in quality of life (p < 0.05). Furthermore anxiety (p < 0.0001) and depression (p < 0.0001) scores decreased. The arousal level was reduced from 49.9% to 36.9% (p < 0.0001). At baseline 32.2% of the patients suffered from sleeping disorders and 60% suffered from headache respectively. 3 months after RDN quality of sleeping (p < 0.0001) and the intensity of headache (p < 0.0001) improved.

Summary: In patients with resistant hypertension RDN leads to a positive development of physical and mental state and beyond this to an improvement in quality of life. In addition patients might react more effectiveward faster in any stress situations.

HEART DISEASE THROUGH THE PATIENTS’ EYES

1173 Self-care behaviors in heart failure patients: international similarities and differences

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Background: Clinicians worldwide seek to optimize self-care among heart failure (HF) patients to improve patient outcomes. Although heart health care systems and cultures differ, the specific self-care behaviors recommended for HF patients are similar internationally, such as advice regarding diet, exercise and symptom monitoring. In this study we describe similarities and differences in self-care behaviors across 21 countries representing 3 continents.

Methods: Data on HF self-care were pooled from 21 samples of HF patients gathered from 3 different parts of the United States, 6 different European countries, 7 countries in Australasia and South America, totaling 5577 HF patients. None of the patients had received structured education on HF self-care behavior at the time of data collection. The mean age in the samples ranged from 62 to 67 years and data on self-care were collected with the Self-care of Heart Failure Index (SCHFI) or the European Heart Failure Self-care Behaviour Scale (EHFScB). Data were obtained from the primary investigators and analyzed using descriptive statistics.

Results: Across the 21 samples we found many similarities in self-care behaviors. In all the samples, most patients reported that they took their prescribed medicines. The highest number of patients who reported not taking their medicines varied immensely among the countries; 16% to 75% of patients reported not taking their medicines. In contrast, self-care with exercise and daily weighing were low in most samples; 30% to 90% of patients in the samples reported low exercise levels. In 14 of the 21 samples, more than 50% of the patients reported low exercise levels. Adherence to weight monitoring was irregular in many samples. In 15 samples, less than half of the patients weighed themselves regularly, with large differences between the countries. Self-care with regard to diet varied more across the countries than other self-care behaviors. Adhering to a sodium restricted diet varied between 8% and 82% (median 60%). Annual flu shot also varied immensely among the countries; 16% to 75% of patients reported not getting an annual flu shot (median 45%).

Conclusion: Most self-care behaviors need to be improved worldwide. The differences evident in reports of a low salt diet and the annual flu shot may also reflect differences in cultures evident in reports of a low salt diet and the annual flu shot may also reflect differences in cultures and health care systems across the countries.

1175 Impact of cognitive impairment on the management of patients with atrial fibrillation

J. Ball, M.J. Carrington, S. Stewart on behalf of SAFETY Investigators. Baker Heart and Diabetics Institute, Melbourne, Australia

Purpose: Atrial Fibrillation (AF) is an increasingly common condition that is often difficult to manage given that: a) patients are typically older with multiple co-morbidities and b) there is a fine line between treatment benefit and risk. Cognitive impairment (CI) is often associated with AF and potentially impacts a patient’s ability to self-care. We explored the prevalence and implications of CI in patients hospitalised with chronic AF.

Methods: The Standard versus Atrial Fibrillation-specific managementT study (SAFETY) is a multicentre, randomised controlled trial comparing a nurse-led, home-based AF-specific management program to usual post-discharge care in patients hospitalised with AF. The Montreal Cognitive Assessment (MoCA) was used as a cognitive screening tool at baseline during index hospitalisation and on intervention patients during an initial home visit (7-14 days post-discharge); a score of <26 (maximal score 30) indicates mild CI. Self-care was also assessed in intervention patients during the home visit via the self-care index (range 0 to 70).

Results: Of 216 subject to baseline cognitive function screening, mean age was 71±11 years and 53% were male. Highest level of education attained was ≤13 years for 48% of patients and ≤7 years for 22%. Mean baseline MoCA score was 23±4 with mild CI identified in 70% of patients (n=136). As expected, those with mild CI were significantly older 73±10 versus 68±13 years. However, on an adjusted basis, all of demographic and clinical profiling data, an increasingly higher CHADS2-VASc score was the only independent predictor of mild CI (mid CI versus rest: 3.6±1.7 versus 2.7±1.6, adjusted OR 1.36 95% CI 1.03 to 1.80 per unit increase, p=0.030). The higher the clinical risk of thrombo-embolic events, the more the likely the patient had CI (at index hospitalisation). At the home visit, (paired) MoCA scores in intervention patients had improved from 23±3±3.9 to 24±1±6, p=0.005 with a similar proportion (68%) still displaying mild CI. Ability to self-care was judged to be poor in nearly all patients (88%) with no significant differences between those with intact cognition and mild CI.

Conclusions: In this “real world” cohort of high risk patients with chronic AF, mild CI was common (>2/3 affected). Although MoCA scores improved post-discharge, the majority of patients remained cognitively impaired. Older patients with more complex clinical profiles (requiring more aggressive treatment) were more likely to have CI. These data have important implications for safe and effective management of chronic AF.
ASTA a new validated questionnaire for arrhythmia patients

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The main purpose was to develop and validate a disease-specific questionnaire assessing symptoms and health-related quality of life (HRQOL) in patients with different forms of arrhythmias.

Method: Items were developed through a literature review and interviews. The items were evaluated by an expert panel. SF-36 and Symptoms Checklist (SCL) were used in the validation of the new Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA). Homogeneity was evaluated using Spearman’s correlations and Cronbach’s alpha coefficient (ω) for internal consistency. Construct validity was evaluated using item-total correlations. Convergent and discriminant validity was examined by comparisons between ASTA symptom scale, SF-36 PCS and SCL and by comparisons between the HRQOL scales, the SF-36 physical component summary (PCS) and mental component summary (MCS). Construct validity for the HRQOL scales was further evaluated using confirmatory factor analyses (CFA).

Results: The correlations between the ASTA symptom scale items showed generally sufficient homogeneity and ω was satisfactory (≥0.8). All items in the symptom scale were sufficiently correlated (≥0.3). Convergent and discriminant validity was supported by the higher correlations to the SCL compared to the SF-36. Concurrent validity demonstrated sufficiently, but not extremely strong correlations between the ASTA symptom scale and the SF-36 PCS and between the ASTA physical subscale and the SF-36 MCS. Convergent validity was supported by MTMM correlations between the ASTA physical subscale and the SF-36 PCS and between the ASTA physical subscale and the SF-36 MCS. Discriminant validity was supported by lower correlations between the ASTA physical subscale and the SF-36 MCS and between the ASTA physical subscale and the SF-36 PCS. Internal consistency and lower bound confidence intervals were ≥0.70 for all of the ASTA HRQOL scales.

Conclusion: The scales in the validated ASTA questionnaire were all found to have good psychometric properties in the targeted patient population. Patient reported outcome measures are being increasingly emphasized in research as well as in quality of care evaluations. It is of great importance to evaluate the effect of arrhythmias on patients’ daily life as well as patient reported treatment effects. The new ASTA questionnaire could be a valuable contribution for health care interventions and for clinical research.

Cultural factors increase pre-hospital delay in myocardial infarction for Saudi women

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Many factors have been implicated in patients’ decisions to seek care in MI, but most research has a Western origin and it is possible that reasons for delay differ in Arab cultures. Our study aimed to explore the factors that contribute to pre-hospital delay among MI patients in Saudi Arabia. This cross sectional study comprised a convenience sample of research participants (n=311), who presented with a diagnosis of MI to three hospitals in Riyadh from March 2011 to June 2011. Of these, 189 patients met the eligibility criteria. There was a statistically significant difference between pre-hospital delay time (onset of symptoms to hospital arrival) and participants’ gender. For males the median delay was 5 hours (M=5.78, SD=1.786) and for females it was 12.9 hours (M=6.79, SD=1.851; t(187) = –3.097, p<.002). This was despite similar intervals between the genders for symptom onset to decision to seek care (male = 2.5 hours, female = 3 hours). In addition, only 12% of females versus 88% of male patients arrived at hospital in the first hour of symptom onset. The median travel time for all participants was 45 minutes, (0.9hrs for men and 2.5 hours for women).

The gender differences in pre-hospital delay in Saudi are likely to be influenced by cultural factors, since the majority of females (97%), in this study cannot drive when they are outside their home at symptom onset (p<0.05), perhaps due to cultural factors, since the majority of females (97%), in this study cannot drive when they are outside their home at symptom onset (p<0.05), perhaps due to cultural factors. They are also culturally prohibited from going to hospital without a male relative. Only, 11% of patients from both genders travel to the hospital by ambulance. Moreover, symptom onset most commonly occurred at home for both males (65%) and females (78%) and the most popular response (41%) was to try a self help remedy. Two factors fit the model of females that delay significantly more than males when they are non-Saudi, have no dyspnea and when they are outside their home at symptom onset (p<0.05), perhaps due to cultural and psychological barriers.

This the first study conducted with MI patients in Saudi within the restrictions of an Arab culture. Overall the total pre-hospital delay time reported here is longer than in studies in other settings and there are significant gender differences. We postulate that cultural factors are implicated. Health promotion strategies that potential MI patients should consider offering culturally specific, gender related messages.

Myocardial infarction with normal coronary arteries is common and associated with normal findings on CMP - a results from the Swedish Normal Coronaries (SMINC) Study

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Objectives: Myocardial infarction with angiographically normal coronary arteries (MINCA) is an important subgroup of myocardial infarction (MI). The diagnostic criteria, underlying pathophysiology, prognosis and optimal management are still largely unknown. Cardiac Magnetic Resonance Imaging (CMR) has the potential to clarify the clinical presentation of these patients. Our objective was to investigate the diagnostic value of CMR in this group of patients.

Design: The Stockholm Myocardial Infarction with Normal Coronaries (SMINC) study is a prospective multicenter observational study.

Setting: Coronary Care Units in the Stockholm Metropolitan Area.

Subjects: MINCA patients between 35-70 years of age were consecutively included in the screening phase of the SMINC study. All patients had a typical clinical presentation, fulfilling the universal definition of myocardial infarction according to ESC/ACC/AHA and had a normal coronary angiography. Patients with known structural or coronary heart disease or other known causes of elevated troponins were excluded.
Results: All together, 176 MINCA patients were screened 2007-2011. Of them 152 were investigated with CMR. During the time period 277 patients were eligible for the study representing 6.3% of all patients with a diagnosis of myocardial infarction undergoing coronary angiography. The investigation was performed median 12 (IQR 6-28) and mean 20 days after the initial presentation to hospital. Sixty-seven percent of the examinations were completely normal whereas 19% of the patients had signs of myocardial necrosis. Only 7% had signs of myocarditis. The remaining patients (7%) had either unrecognized hypertrophic cardiomyopathy or could not be classified. The frequency of Takotsubo stress cardiomyopathy was 22% of all patients screened with CMR.

Conclusion: In this consecutive series of MINCA patients CMR could help to differentiate between myocarditis, myocardial necrosis and normal myocardium. The incidence of MINCA was higher than previously shown. Based on the results and assumptions, we propose that the incidence of MINCA is 7.8%. We also found a lower prevalence of myocarditis than in previous studies. After excluding myocarditis, MINCA consists of a larger group of patients with a normal CMR and a smaller group with myocardial necrosis. The etiologies of these different CMR findings need to be explored.

1188 Outcomes of invasive treatment in very elderly (age >80) Polish patients with non ST-segment-elevation myocardial infarction from 2004-2010 - Results from the PL-ACS registry

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The aim was to analyse the impact of invasive treatment of elderly patients with NSTEMI from 2004-2010 and its impact on 12-month outcomes.

Methods: We analysed 78,422 patients with NSTEMI enrolled in the PL-ACS registry from 10.2003 to 2009.

Results: The percentage of elderly patients with NSTEMI was 17.5% (N=13,707). Invasive treatment received 24% of them. In-hospital complications were significantly less frequent in the invasive group, with the exception of major bleeding, which occurred almost three times more frequently in the invasive group. The 12-month was lower in the invasive group and remained so after matching patients by the propensity score method (23.2% vs. 30.5%, p<0.001). From 2003 to 2009 the use of thienopyridines, beta-blockers and statins rose significantly. The frequency of invasive strategy increased significantly, from 10% to over 50% in 2009, which caused an increase in revascularisation procedures (table). The frequency of major bleeding increased twofold, however a significant reduction in the 12-month mortality was observed.

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>P for the trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median)</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>83</td>
<td>0.34</td>
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<tr>
<td>Diabetes, %</td>
<td>28.3</td>
<td>29.6</td>
<td>28.9</td>
<td>28.8</td>
<td>33.0</td>
<td>35.3</td>
<td>30.5</td>
<td>-0.001</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>21.0</td>
<td>27.4</td>
<td>21.7</td>
<td>22.9</td>
<td>18.2</td>
<td>21.1</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>0.8</td>
<td>0.9</td>
<td>0.8</td>
<td>1.8</td>
<td>3.9</td>
<td>5.8</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Killip 3 on admission, %</td>
<td>12.4</td>
<td>13.2</td>
<td>12.6</td>
<td>11.3</td>
<td>10.5</td>
<td>9.0</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Killip 4 on admission, %</td>
<td>6.5</td>
<td>4.5</td>
<td>4.2</td>
<td>3.3</td>
<td>3.5</td>
<td>3.0</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Invasive treatment, %</td>
<td>9.8</td>
<td>13.5</td>
<td>14.9</td>
<td>19.3</td>
<td>22%</td>
<td>33.2</td>
<td>52.5</td>
<td>-0.001</td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>7.3</td>
<td>8.7</td>
<td>10.1</td>
<td>13.0</td>
<td>24.6</td>
<td>37.3</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>CABG urgent or delayed, %</td>
<td>0.9</td>
<td>3.0</td>
<td>2.4</td>
<td>3.3</td>
<td>4.2</td>
<td>5.6</td>
<td>-0.001</td>
<td></td>
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<tr>
<td>SIRKA</td>
<td>12.1</td>
<td>17.1</td>
<td>10.1</td>
<td>10.8</td>
<td>0.3</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>1.6</td>
<td>0.9</td>
<td>0.9</td>
<td>1.1</td>
<td>2.8</td>
<td>2.6</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Myocardial reinfarction, %</td>
<td>5.4</td>
<td>7.0</td>
<td>9.6</td>
<td>3.6</td>
<td>2.3</td>
<td>1.6</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Death during hospitalisation, %</td>
<td>15.1</td>
<td>13.6</td>
<td>11.9</td>
<td>11.5</td>
<td>9.2</td>
<td>-0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-month mortality, %</td>
<td>37.7</td>
<td>36.7</td>
<td>35.5</td>
<td>36.6</td>
<td>34.5</td>
<td>31.1</td>
<td>-0.001</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Elderly patients benefit significantly from invasive strategies and modern pharmacotherapy recommended by treatment guidelines. Nevertheless, this approach is associated with an increased incidence of major bleeding.

1190 Clopidogrel treatment in elderly patients after myocardial infarction is associated with lower risk of recurrent myocardial infarction and death without increasing the risk of bleeding

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Purpose: Elderly patients are at high risk of thrombosis and bleeding after a myocardial infarction (MI). Establishing the risk/benefit relation of clopidogrel treatment in different age-groups of elderly patients admitted with myocardial infarction is thus highly important.

Methods: Patients admitted with first-time MI 2000-2008, and not undergoing percutaneous coronary intervention, were identified from nationwide registers in Denmark. Risk of bleeding and a combined endpoint of death or recurrent MI was assessed by age stratified cumulative incidence and Cox proportional hazard models in a propensity score population.

Results: A total of 6654 patients treated with clopidogrel plus aspirin and 6799 treated with aspirin only were included; mean age 75 years (SD±8.85) and 55.2% males. Mean follow-up for bleeding events was 432 days (SD±184) and 423 (SD±190) for recurrent MI or death, respectively. Among patients treated with clopidogrel and aspirin 563 (8.46%) experienced fatal or non-fatal bleedings whereas these events occurred in 472 (6.94%) of the patients treated with aspirin alone (Log rank p=0.051). Among patients treated with clopidogrel and aspirin 1975 (29.68%) died from or experienced a new MI whereas these events occurred in 2129 (31.31%) of the patients treated with aspirin alone (Log rank p=0.06). Hazard ratios are displayed in Fig. 1.

Fig 1

Conclusions: Elderly patients receiving clopidogrel and aspirin had lower risk of death and recurrent MI without elevating the risk of bleeding compared to patients receiving only aspirin. Increased focus on initiating clopidogrel treatment after discharge in non-invasively treated MI patients is warranted.

1191 Influence of collateral coronary blood supply to occluded culprit artery on the presence or absence of ST segment elevation

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Objectives: To analyze whether the collateral coronary blood supply to an occlusive lesion is present in the same coronary artery, or in a different one, in patients admitted with acute myocardial infarction (AMI). To evaluate the association between collateral coronary blood supply and the presence of ST segment elevation on admission.

Methods: We evaluated 78,422 patients with NSTEMI enrolled in the PL-ACS registry from 2004-2010 - Results from the PL-ACS registry

We analysed 78,422 patients with NSTEMI enrolled in the PL-ACS Registry from 2004-2010. Of these, 78,422 patients (99.9%) were included in the analysis.

Conclusions: Elderly patients receiving clopidogrel and aspirin had lower risk of death and recurrent MI without elevating the risk of bleeding compared to patients receiving only aspirin. Increased focus on initiating clopidogrel treatment after discharge in non-invasively treated MI patients is warranted.

Elderly patients receiving clopidogrel and aspirin had lower risk of death and recurrent MI without elevating the risk of bleeding compared to patients receiving only aspirin. Increased focus on initiating clopidogrel treatment after discharge in non-invasively treated MI patients is warranted.
Newly detected diabetes mellitus and impaired glucose tolerance adversely affects prognosis after myocardial infarction

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Background: We investigate whether newly detected diabetes mellitus (NDM) and impaired glucose tolerance (IGT) using pre-discharge oral glucose tolerance test (OGTT) after myocardial infarction (MI), is related to long-term prognosis in the context of current practice.

Methods: 768 non-diabetic post-MI patients were categorised into normal glucose tolerance (NGT) (n=337), IGT (n=279) and NDM (n=152) groups based on pre-discharge OGTT and followed up for a primary end-point, the first occurrence of major cardiovascular adverse events (MACE) including cardiovascular death, MI, heart failure (HF) or non-haemorrhagic stroke. Secondary end-points were all cause mortality, cardiovascular mortality, non-fatal MI, severe heart failure or stroke.

Results: Except for age, the clinical characteristics of the groups were well matched. Prevalence of NGT, IGF, IGT and NDM changed from 90%, 6%, 0% and 4% on fastin plasma glucose (FFPG) to 43%, 1%, 36% and 20% on OGTT respectively. 30% of patients with post-challenge hyperglycaemia, had normal FFPG. 102 deaths from all causes (79 as the first event of which 46 were cardiac), 95 non fatal MI, 18 HF and 9 non haemorrhagic stroke totalling 168 MACE (47 in NGT, 71 in IGT, 25% in IGT, 49 (32%) in NDM) occurred during 47.2±9.4 months follow up. MACE rates were significantly higher in the IGT (OR 1.74, 95% CI: 1.11-2.72, p=0.016), NDM (OR 2.71, 95% CI: 1.63-4.50, p<0.000).

Conclusion: The presence of significant collateral blood supply to the occluded culprit coronary artery, in the setting of an acute coronary syndrome, is a significant and independent predictor of absence of ST segment elevation, along with a lower BARI score of the culprit lesion and the localization of the culprit lesion in the left circumflex artery.

EVIDENCE FOR REVERSE LEFT VENTRICULAR REMODELING AND INCREASED SYSTOLIC PERFORMANCE AFTER PERCUTANEOUS MITRAL ANNULOPLASTY IN PATIENTS WITH FUNCTIONAL MITRAL REGURGITATION

O. Jerzykowska, P. Kalmucik, M. Woloszyn, L. Kramer, T. Siminiak. University of Medical Sciences, HCP Medical Center, Poznan, Poland

Background: Functional Mitral Regurgitation (FMR) exacerbates left ventricular dilatation and contributes to both ventricular remodeling and heart failure. Whether reduction in FMR alone is sufficient to result in reverse remodeling is unknown, mainly because surgery procedures in patients with FMR and impaired ejection fraction (EF) usually are performed simultaneously with by-pass implantation.

Aim: The purpose of our study is to verify, whether percutaneous mitral annuloplasty performed as a sole procedure results in reverse remodeling in pts with FMR and impaired EF.

Methods: We analyzed baseline and 1 month follow-up echo recordings in 22 consecutive pts with FMR, who underwent successful percutaneous mitral annuloplasty with the CARILLON® Mitral Contour System™ in our center. Inclusion criteria for the treatment were: dilated ischemic or non-ischemic cardiomyopathy, moderate to severe FMR, no option for revascularization, LVEF<40%, NYHA Class II-IV, and 6 minute walk distance (6MWMD) 150-450 meters. The device was left percutaneously in the absence of ST elevation, (p <0.001). The multivariate analysis showed a very significant relationship between the presence of significant collateral blood supply and the absence of ST elevation, (p <0.001). The presence of significant collateral blood supply to the occluded culprit coronary artery, in the setting of an acute coronary syndrome, is a significant and independent predictor of absence of ST segment elevation, along with a lower BARI score of the culprit lesion and the localization of the culprit lesion in the left circumflex artery.

Results: Twenty five p, age 65±11 years. 100% with mechanical valves (22p with MITRAL, 33p with LFMI, 49p with mitral valve prosthesis). The mean number of previous surgeries was 2.29±0.93. The time from surgery to percutaneous intervention was 8±1.7 years. EuroScore Log 15±6±11.7. Clinical presentation: heart failure (HF) 89.6%, hemolytic anemia 9.3% and both 79%. The NYHA functional class was 3±0.6, hematocrit 28.7±5.4%, LDL 154±9.46 U/L. The mean degree of regurgitation pre-procedure was 3.54±0.85. Fifty two patients (20±6± 85pc), mitral valve replacement surgery 1.p, stroke 1p, hospitalization for heart failure 6p and death 2p. Clinical success in 85±1%. Conclusion: Percutaneous repair of large and/or multiple leaks with AVPIII is a feasible and safe technique with high technical and clinical success at 30 days. We should be aware of potential complications during the procedure (device embolization, impingement of prosthetic disk). Longterm clinical result of these p will depend on the success of the procedure and the general status pre procedure.

CHALLENGES IN PERCUTANEOUS VALVULAR INTERVENTIONS

Percutaneous closure of large and or multiple paravalvular lekas with multiple devices. Procedural and 30 days follow-up

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Introduction: Percutaneous closure of paravalvular leak is a relatively recent technique. The result of large and or multiple leaks was barely been described.

Objective: To describe a population undergoing percutaneous closure of large and/or multiple leaks repaired with Amplatz Vascular Plug III (AVP III) device, and to assess procedural and 30 day results.

Materials and methods: All Patients (p) with paravalvular leaks treated percutaneously with more than 1 AVPIII. Procedural success was defined when the device was successfully deployed and there was a significant decrease of regurgitation through a perivalvular leak. Device failure is defined: death at 30 days or new intervention on the same leaks at 30 days.

Results: Twenty five p, age 65±11 years. 100% with mechanical valves (22p with MITRAL, 33p with LFMI, 49p with mitral valve prosthesis). The mean number of previous surgeries was 2.29±0.93. The time from surgery to percutaneous intervention was 8±1.7 years. EuroScore Log 15±6±11.7. Clinical presentation: heart failure (HF) 89.6%, hemolytic anemia 9.3% and both 79%. The NYHA functional class was 3±0.6, hematocrit 28.7±5.4%, LDL 154±9.46 U/L. The mean degree of regurgitation pre-procedure was 3.54±0.85. Fifty two patients (20±6± 85pc), mitral valve replacement surgery 1.p, stroke 1p, hospitalization for heart failure 6p and death 2p. Clinical success in 85±1%.
Impact of mitral regurgitation etiology and effective factors influencing significant aortic regurgitation after transcatheter aortic valve implantation in patients with predictive value of pre-procedural mitral regurgitation specifically (p = 0.7). All cause 30-day mortality was not significantly different in patients with grade 3+ or 4+ aortic regurgitation vs. patients with grade 2+. Mitral regurgitation was significantly reduced from grade 3+ (60%) or 4+ (40%) to grade 2+ (22%) or 1+ (28%) at baseline to grade 1+ (41%) or 2+ (59%) at discharge (P < 0.0001). When patients were dichotomized by MR etiology (purely functional [MR] vs. degenerative/mixed [DMR]), a significantly lower procedural success rate was noted in DMR patients (72/88 [81.8%] vs. 167/182 [91.8%], P = 0.024) and successfully treated DMR patients were significantly less often discharged with MR grade 1+ (22/72 [30.6%]) than from DMR patients (75/167 [44.9%], P = 0.045). Effective regurgitant orifice area (EROA) was significantly higher in DMR patients (median 51.1 mm² vs. 35.8 mm² in FMR patients, P = 0.025). Both DMR etiology and an EROA > 43 mm² (cut-off value determined by ROC analysis) were predictive of procedural failure on univariate logistic regression analysis, with only EROA > 43 mm² remaining as an independent predictive factor of procedural failure on multivariable analysis (odds ratio 3.05, 95% CI 1.19 – 7.79; P = 0.020).

Conclusion: Degenerative/mixed as opposed to functional etiology of MR is associated with lower procedural success of MC therapy and a lower prevalence of MR grade 1+ at discharge. EROA appears to be the single echocardiographic variable predictive of procedural outcome.

Transcatheter aortic valve implantation in patients with high-risk severe aortic stenosis: analysis of 30-day mortality in low-gradient versus high-gradient subgroups

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Introduction: Patients with low-flow, low-gradient severe aortic stenosis are considered at a more advanced disease stage compared to patients with high-gradient aortic stenosis (AS), with a poor prognosis if left untreated. Transcatheter aortic valve implantation (TAVI) is an emerging technique for treatment of patients with high-risk severe aortic stenosis. We prospectively assessed 30-day all-cause mortality and functional status in patients with high-gradient versus low-flow, low-gradient severe AS.

Patients and Methods: Between September 2007 and October 2011, trans-catheter TAVI was performed in 184 consecutive high-risk patients with symptomatic severe aortic stenosis (aortic valve area 0.7±0.2 cm²) using both Medtronic CoreValve and Edwards SAPIEN prostheses. Three patient groups were identified: 155 patients with high-gradient severe AS [group 1], 18 patients with low-gradient severe AS and preserved LV ejection fraction (LVEF) and 16 patients with preserved LVEF (paradoxical low-flow, low-gradient AS) [group 3].

Results: The mean echocardiographic aortic valve area in groups 1, 2 and 3 was 0.69±0.24 cm², 0.69±0.18 cm² and 0.85±0.15 cm², respectively (P = 0.12). The mean echocardiographic gradient over the aortic valve was 54±15 mmHg in group 1 versus 30±6 mmHg in groups 2 and 3, respectively (P < 0.0001). The LVEF was significantly lower in group 2 patients versus groups 1 and 3 (27±10% vs. 50±13%, respectively, P < 0.0001). The prevalence of post-procedural angio- graphic aortic regurgitation > 2 was not significantly different in the 3 groups (22.5%, 22.2% and 30% in groups 1, 2 and 3, respectively, p = 0.86). Functional class improvement occurred in 95%, 100% and 94% of patients in groups 1, 2 and 3, respectively (p = 0.7). Percentage reduction in 30-day post-BNP level was 49±27% for group 1 versus 50±30% and 62±16% for groups 2 and 3, respectively (p = 0.7). All cause 30-day mortality was not significantly different in patients with high-gradient compared to patients with low-gradient, low-gradient AS (3.8%, 5.5% and 9% for groups 1, 2 and 3, respectively, p = 0.69). In group 2 patients, LVEF at 30-days follow up was significantly higher compared to baseline (34±13% vs. 28±10%, p = 0.035).

Conclusion: Our results show that TAVI is feasible and effective in patients with low-flow, low-gradient severe AS with comparable all cause 30-day mortality as opposed to high-gradient severe AS patients. According to these initial results, TAVI should be considered as an acceptable treatment modality for this high-risk group of patients with advanced AS.

Factors influencing significant aortic regurgitation after transcatheter aortic valve implantation in patients with severe aortic stenosis

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Purpose: Transcatheter aortic valve implantation (TAVI) has shown to be effective in patients (pts) with severe aortic stenosis. However significant aortic regurgitation (AR) may occur after valve implantation. The aim of this study was to identify predictive factors of AR after TAVI with the CoreValve system.

Methods: Between April 2008 and December 2011, 153 pts with aortic stenosis underwent TAVI. We analyzed clinical data, baseline echocardiographic data, angiographic and hemodynamic parameters and CT scan data.

Results: Implant success was achieved in 152 pts (99%). The selected valve size was 26 mm in 170 (70%) pts, and 29 mm in the remaining 43 (30%). Balloon post-dilation was required in 59 (38%) pts due to AR grade II, reducing the degree of regurgitation in 40 of these cases (68%). After the procedure, significant AR was observed in 33 pts (22% vs. grade II and 6 with grade III). Mild AR (grade I) was seen in 75 pts (44%), and 44 pts (29%) were free of residual regurgitation. The depth of the prosthesis was similar in pts with and without significant AR (11.1±3.5 mm vs. 10.7±4.4 mm; p = 0.4). Annulus shape was studied calculating the symmetry index (minimal diameter/maximum diameter of the annulus in the CT axial view). Annulus was considered asymmetric if the symmetry index was ≤ 0.8. Forty-seven patients (31%) had an asymmetric annulus while 106 (69%) patients had a symmetric annulus. This parameter had no impact in the incidence of AR grade ≥ 4 (P = 0.4). However, the presence of subannular calcium on CT scan predicted the development of AR. In 15 out of 34 patients with this feature (44%), significant regurgitation appeared after valve implantation (p = 0.01). Indeed, 5 of the 6 patients (83%) with AR grade III showed subannular calcification. The incidence of AR was not influenced by any other clinical, echocardiographic or hemodynamic parameters that were analyzed.

Conclusion: The presence of subannular aortic calcification detected by CT scan was the only predictor of significant post-TAVI AR.
Scar Dechanneling in patients with chronic myocardial infarction and ventricular tachycardia

Results did not differ when patients with an MR grade 3 or 4 were excluded. They did not differ either when analyses were restricted only to the Edwards SAPIEN group or only to the Medtronic CoreValve group.

Conclusion: The presence of a mild (grade 1) or a moderate (grade 2) MR pre-procedural is associated with a higher 1-year mortality after TAVI. However, since pre-procedural MR is associated with important risk markers such as a higher NYHA class or a higher logistic Euroscore; pre-procedural MR is not an independent predictor of 1 year mortality. These findings suggest that, in itself, the presence of a mild or a moderate MR should not refrain from performing TAVI and should not impact the type of valve to be used.

CATHETER ABLATION OF VENTRICULAR TACHYCARDIA: NEW TECHNIQUES AND NOVEL TECHNOLOGIES

1234 Scar Dechanneling in patients with chronic myocardial infarction and ventricular tachycardia


Purpose: Whether substrate-guided ablation should be extended to potential isthmus not related with clinical/inducible VT is not known. Ablation requirements for this purpose could be high. The results of a new ablation strategy attempting to reduce the radiofrequency ablation (RFA) burden are reported.

Methods: 40 consecutive post-MI patients (34±12% LVEF) with clinical VT (30±9 episodes/patient) were included. A high-density (501±251 sites mapped) voltage map was obtained to identify conducting channels (CCs). Electrograms with isolated delayed components (E-IDCs) inside/between scar were tagged and classified as entrance or inner CC points, depending on the delayed component polarity. The procedural endpoint was the elimination of all identified E-IDCs (by discrete RF ablation at CC entrance), and the abolition of residual inducible VTs afterwards.

Results: Mean procedure and fluoroscopy time were 239±84 min and 19±9 min, respectively. A mean of 14±9 entrance-CC points/patient were identified and targeted for RF application (24±15 discrete RF lesions/patient). Re-maps showed a dramatic reduction in the number of E-IDCs (61±24 vs. 9±8, p<0.01), that required 7±8 additional RF applications. After substrate ablation 68% of patients had no residual inducible VTs. Scar Dechanneling and residual VT ablation resulted in 98% non-inducibility of clinical VT, 93% of monomorphic VT and 80% of any VT/VF. There was a single major bleeding. During a follow-up of 10 months (IQR 4-19 months), 36 (90%) patients remained without VT recurrences.

Conclusions: Scar Dechanneling can facilitate the CCs elimination minimizing the RF energy delivered in post-MI patients with clinical VTs. Acute and follow-up results are promising.

Catheter ablation of ventricular tachycardia using a new non-fluoroscopic sensor-guided 4D navigation tool

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Purpose: A novel sensor-based electromagnetic 4D navigation system has been introduced that allows real-time 3D catheter tracking in the environment of pre-recorded X-ray loops (MedGuideTM Technology, MGT, St. Jude Medical). We report the first clinical experience for catheter ablation of ventricular tachycardia (VT) and extrastyles (VES).

Methods: The new MGT was used for VT mapping and ablation in 7 pts. with non/ischemic cardiomyopathy and 3 pts. with idiopathic outflow tract VES. In 3 pts. no ablation was performed due to noninducibility (10 male patients, age 65±13 yrs.). At the beginning of the procedure, left or right ventricular angiographic cine loops were recorded in at least two angulations. These moving images were used as background movies for “4D” non-fluoroscopic catheter tracking. Steerable MGT-enabled diagnostic EP catheters were used for non-fluoroscopic diagnostic catheter placement, and anatomical reconstruction plus voltage mapping of the relevant heart chamber within a conventional electro-anatomic mapping system (EAMS). Ablation was performed with conventional open-irrigated tip catheters.

Results: In all 13 patients the MGT-enabled catheters could reliably and safely be non-fluoroscopically visualized in real-time throughout the procedure. Nonfluoroscopic 4D catheter tracking significantly improved realistic heart chamber reconstruction and mapping process (8x left ventricle, 7x right ventricle, 1x epicardium, 1x mid cardiac vein). In pts. with VT ablation occurring in the setting of structural heart disease, procedural times were 175±35 min, fluoroscopy times were 45±14 min, and procedural success (noninducibility of any VT) was achieved in 71% (8/11 pts) in pts. with idiopathic VT ablation, procedural parameters were 128±11 min, 14±3 min, and 100% respectively. No MGT-related complications were observed.

Conclusions: With the first cases reported so far, we could show that the new sensor-guided technology allowed for reliable and safe non-fluoroscopic bipolar catheter tracking within prerecorded 2D cine loops in the setting of ventricular arrhythmias. The “4D” catheter navigation in particular has the potential to improve mapping within complex moving heart chambers.
Catheter ablation of ventricular tachycardia / Evaluation and outcome of syncope

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Single port subxiphoid epicardial ablation using snake robotic system

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Objective: Minimally invasive techniques are being developed to treat lone atrial fibrillation (AF) since mid-90s. While performed via multiple bi-lateral access ports, these procedures require advanced thoroscopic skills and take long time to complete. The novel CardioARM robotic system is designed to access all outer surfaces of the heart confined within the pericardium providing multiple open device channels inside its highly articulated, multiple degrees of freedom arm which can accept flexible interventional tools along with an on-board visualization system or suitable tracking device. The CardioArm is controlled by the physician with one hand using joystick control pad attached to the OR table. The study evaluated feasibility of using CardioArm for single-port off-pump epicardial ablation in live animal model.

Methods: Six female pigs (42 - 78 kg) underwent the procedure under general anesthesia. Pericardial access was gained through 3-4 cm midline skin incision over the xiphoid. The CardioARM probe was inserted into the pericardial space through 12 mm thoracoscopic cannula fixed to the skin. The navigation was done under fiberoptic camera guidance and periodically checked with flouroscopy. Linear ablations were performed endocardially or epicardially. RF ablation catheters which were used for delivery to the target sites. Series of linear ablations were created on the surfaces of the heart confined within the pericardium providing multiple open device channels inside its highly articulated, multiple degrees of freedom arm which can accept flexible interventional tools along with an on-board visualization system or suitable tracking device. The CardioArm is considered ready for a small, single-center feasibility trial in humans.

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Catheter mapping and ablation of unstable ventricular tachycardias with percutaneous mechanical support

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Substrate based catheter ablation of ventricular tachycardia (VT) in patients has sinus rhythm is widely accepted approach how to treat patients with serious left ventricle dysfunction. However some clinical situations require improvements in patient support actually allowing rapid ventricular tachycardias to be tolerated using only a percutaneous mechanical support systems (pVAD). The study evaluated the feasibility of using CardioArm for single-port off-pump epicardial ablation in live animal model.

Methods: We used four different pVADs with a continuous flow. Two with peripherally circulate blood from: i. the left atrium to the femoral artery (TandemHeart®); ii. the right atrium to oxygenated femoral artery (Centrimag®); iii. left ventricle to ascending aorta (intraventricular rotation Impella 2.5®); iv. left ventricle to ascending aorta (intraventricular rotation Impella 2.5®); ii. left ventricle to ascending aorta (intraventricular rotation Impella 2.5®); iii. left ventricle to ascending aorta (intraventricular rotation Impella 2.5®); iv. left ventricle to ascending aorta (intraventricular rotation Impella 2.5®). All patients were in general anesthesia, intravenous administration of antibiotic was used as prophylaxis. The study evaluated the feasibility of using CardioArm for single-port off-pump epicardial ablation in live animal model.

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Results: All patients were in general anesthesia, intravenous administration of antibiotic was used as prophylaxis. The study evaluated the feasibility of using CardioArm for single-port off-pump epicardial ablation in live animal model.

Conclusions: The results demonstrated the feasibility of using pVADs as temporary support during incescence periods. All patients were in general anesthesia, intravenous administration of antibiotic was used as prophylaxis. The study evaluated the feasibility of using CardioArm for single-port off-pump epicardial ablation in live animal model.

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Electrical storm: a strong mortality and morbidity risk factor. Is it possible to predict it?

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Objective: The aim of the current meta-analysis was to evaluate ES as a risk factor for death and cardiovascular events, and determine whether ES can be predicted by clinical variables.

Methods: The meta-analysis has been conducted according to international PRISMA guidelines. Two big databases (PubMed and Web of Science) were scanned for all original articles using "electrical storm" or "arrhythmic storm" as keywords. 561 articles were found and entered selection process. Two indepen dent investigators selected eligible studies in a blinded fashion. At the end of the selection process 32 articles entered the quantitative analysis.

Results: The current meta-analysis included 6979 total patients and 1782 pa tients with ES. Patients with ES have a 3-fold increased risk of death (RR 2.85; IC 95% 2.11-3.86). The increased risk of death is also significantly increased when ES patients are compared with subjects with an history of simple VTs/VFs (RR 3.23; IC 95% 2.39-7.48). Patients with ES also have a 3-fold increased risk of cardiac events, defined as stroke, myocardial infarction, or systemic embolism (RR 2.98; IC 95% 1.86-4.79). The increased risk of cardiovascular events related to ES was significantly higher when patients with history of simple VTs/VFs were used as control group.

Considering all factors studied as possible predictive factors for ES, ICD implant for secondary prevention, low EF, higher NYHA class.

Electrical storm is a strong risk factor for death and cardiovascular events, even when compared with non clustered VTs/VFs. Secondary prevention, low EF, high NYHA class and monomorphic VT as triggering arrhythmia are found as predictive for ES. Patients with ES also have lower EF and higher mean NYHA class.

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First admission for syncope in a healthy population predicts mortality and cardiovascular events

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Background: Syncope is a common clinical event, but knowledge of long-term outcome is not fully elucidated. We examined risk of major cardiac adverse events and death in a nationwide cohort of patients without previous comorbidity admitted for syncope.

Methods and results: Patients without prior comorbidity admitted for syncope in Denmark from 2001-2009 were identified in nationwide administrative registers and matched on sex and age with 5 controls from the Danish population. The risk of recurrent syncope, implantation of pacemaker or implantable cardioverter defibrillator and cardiovascular hospitalization was analyzed with multivariate Cox proportional-hazard models.

We identified 48,430 patients with a first diagnosis of syncope and 242,150 controls; median age was 53 years (IQR: 36.5-69.5) and 45.3% were males. At total of 5,579 (11.5%) and 24,772 (10.2%) deaths occurred in the syncope and the control population (Fig) yielding an event rate of 26 and 19 deaths per 1000 person years, respectively.

There was significantly increased risk of all-cause mortality (HR=1.14 [CI: 1.11- 1.17], cardiovascular hospitalization =HR=1.82 [CI: 1.77-1.87], recurrent syncope (HR=103.85 [CI: 94.67-113.93]), stroke (HR=1.38 [CI: 1.31-1.45]) and pacemaker or implantable cardioverter defibrillator (HR=5.03 [CI: 4.62-5.47]) p<0.0001.

Conclusion: First admission for syncope significantly predicts risk of all-cause mortality, stroke, cardiovascular hospitalization, device implantation and recurrent syncope, in a population without prior comorbidity.
Syncope in brugada syndrome patients: ventricular tachycardia or neurally mediated?

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Purpose: Syncope episodes in Brugada syndrome (BrS) patients are a class IIa indication for implantable defibrillator therapy, because these episodes are generally ascribed to ventricular tachyarrhythmias (VT/VF) and therefore considered a major risk factor for fatal cardiac events. However, syncope is not always caused by VT/VF. In the general population, benign neurally mediated syncope (NMS) is by far the most common cause of syncope. NMS aims to study the prevalence of NMS and cardiac syncope in BrS patients, and establish the clinical characteristics of these syncope episodes.

Methods: We analyzed charts with all available long-term follow-up data of 346 consecutive BrS patients and conducted telephone interviews about triggers and prodromes with patients who experienced at least one syncope episode. With these data, an expert committee classified patients with syncope into one of 4 categories: (1) NMS, (2) documented cardiac syncope, (3) suspected cardiac syncope, (4) other/unknown. Clinical data, triggers and prodromes were compared between these categories.

Results: Before the diagnosis BrS was made, 41% of patients experienced at least one syncope episode. In 54% of these patients the cause was NMS, while 40% had documented or suspected cardiac syncope. Cardiac syncope was more likely to occur in men (RR 2.1) and at an older age at first occurrence (41 vs. 24 years) than NMS. NMS occurred more frequently during standing (RR 0.5) and was more often preceded by sweating (RR 0.4) or paleness (RR 0.6) than documented cardiac syncope.

Conclusion: Many BrS patients experience benign NMS prior to BrS diagnosis. NMS is more likely when syncope occurs during standing or is preceded by prodromes such as sweating or paleness. The high prevalence of NMS must be taken into account during risk stratification in patients with BrS.

Orthostatic instability is an important co-factor and trigger of reflex syncope

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Purpose: Two main components of a classical non-cardiac syncope are heart rate inhibition and loss of vascular tone. Orthostatic hypotension (OH) rarely constitutes the sole etiology of syncopal attacks but is often disregarded as a co-factor and important syncopal reflex trigger thus being largely unreported in syncope studies.

Methods: A total of 380 patients (166 men; mean age, 60yrs; range 15 to 90yrs) with non-cardiac syncope were prospectively analyzed. A delayed non-cardiac origin was investigated according to the expanded head-up tilt test protocol incl. carotid sinus massage, nitroglycerin provocation, and active standing test. Vasovagal syncope (VVS), carotid sinus hypersensitivity (CSH), and OH were diagnosed according to the current ESC guidelines (2009). All parts of the test were performed in order to explore a potential overlap between diagnoses. Multivariate-adjusted (age, gender, and BMI) logistic regression was applied to identify independent predictors of OH within VVS and CSH.

Results: An average of eight syncopal attacks over a period of 9 yrs was reported by investigated patients. A total of 211 patients (56%) were diagnosed with VVS, 72 (19%) with CSH, and 113 (30%) with OH; of these 58 (15%) with the delayed variant of OH. In addition, postural orthostatic tachycardia syndrome (POTS) was found in 21 (6%) patients. In 46 (22%) out of all VVS patients, and 31 (43%) of CSH patients there was an overlap with orthostatic instability. Delayed OH was slightly more prevalent as a concomitant disorder compared to classical OH (13 vs. 9% for VVS, and 24 vs. 19% for CSH, respectively). Independent predictors of OH co-occurrence with VVS included advancing age (OR per 10 yrs: 1.28, 1.08-1.48, p=0.005), history of coronary event (OR:7.25, 2.03-25.9, p=0.002), history of cancer (OR:3.28, 0.94-11.4, p=0.062), and use of long-acting nitrates (OR:10.3, 9.97-110.1, p=0.005), whereas for overlap between OH and CSH there was a trend for lower age (OR per 10 yrs: 0.61, 0.53-1.01, p=0.055) and history of coronary event (OR: 3.91, 0.83-16.4, p=0.085). Moreover, baseline noradrenaline and renin levels were significantly increased among CSH patients with OH (OR per one SD: 3.19, 1.27-8.03, p=0.014, and 2.09, 1.12-3.92, p=0.022, respectively).

Conclusions: Orthostatic hypotension is often underestimated as a co-factor and trigger of syncopal reflex attacks. This underlying hemodynamic instability may be found in one of five VVS patients and in almost every second patient with CSH. Higher respectively lower age and history of coronary event are common predictors of OH co-occurrence in VVS and CSH.
Methods: Observational study of patients referred for diagnostic evaluation for syncope. Patients were divided into groups according to their BMI: kg/m² > 18.5, 16.5 to 24.9 kg/m², 25-29.9 kg/m², > 30 kg/m². Results: 419 patients were evaluated. The mean age was 43±22 years, 62% female. The prevalence of positive tilt test was different between groups when stratified by BMI (P < 0.01) with a higher proportion of patients with positive tests among those with BMI > 18.5 kg/m² compared to other groups (P < 0.05). Figure 1. Multivariate analysis also showed that overweight patients had a risk 3.4 times higher for a positive TT response; also, the use of contraceptives drugs were associated with a protective effect during TTT (RR: 0.37, CI: 0.19-0.76, P = 0.0002).

Conclusion: In our sample, changes in BMI are associated with a positive response to TTT and also oral contraceptives seemed to protect against this response. Further studies are needed with larger numbers of patients to corroborate this finding.

Adenosine receptor gene polymorphism in patients with head-up tilt induced syncope

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Background: Adenosine A2A receptor is involved in the regulation of heart rate and blood pressure. Plasma levels of adenosine are increased in patients with positive head-up tilt test (HUT). The presence of CC genotype in the adenosine A2A receptor gene polymorphism (1364 T/C) was shown to predispose to the possibility of HUT in one study. The goal of the present study was to investigate the possible role of another adenosine A2A receptor gene polymorphism (1976 C/T) in the predisposition to vasovagal syncope.

Material and methods: 377 consecutive patients (161 men, 216 women, mean age 64 ± 15 years) with unexplained syncope underwent a head-up tilt test (HUT). The presence of CC genotype in the adenosine A2A receptor gene polymorphism (1364 T/C) was shown to predispose to the possibility of HUT in one study. The goal of the present study was to investigate the possible role of another adenosine A2A receptor gene polymorphism (1976 C/T) in the predisposition to vasovagal syncope.

Results: Head-up tilt was positive in 227 patients and negative in 150 patients. Differences in frequency distribution of adenosine A2A receptor gene variants between patients with positive HUT, patients with negative HUT and control subjects were not significant: CC genotype 38% vs. 38% vs. 38%, CT genotype 49% vs. 51% vs. 47%, and TT genotype 13% vs. 11% vs. 15% subjects.

Conclusion: The association between A2A receptor gene polymorphism 1976 C/T (rs5751876) and the predisposition to vasovagal syncope was not confirmed in the present study.

Image processing for complex cardiovascular disease

A new CMR-based tool for the 3D dynamic assessment of tricuspid and mitral annulus

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Morphology of atrioventricular valves is complex and conventional methods allow only for their incomplete evaluation. A tool allowing the comprehensive analysis of mitral (MA) and tricuspid (TA) annulus morphology, and their reciprocal behavior, could reveal important in the characterization of valvular conditions, with potential clinical and surgical benefits.

We applied a new custom tool for the dynamic assessment of the 3D morphology of normal MA and TA, using cardiac magnetic resonance (CMR).

Methods: CMR imaging (1.5 T) of 18 long-axis apical planes, rotated along the axis passing through the center of the valve, was performed in 11 healthy volunteers, separately for MA and TA (SSFPE sequences, 20 cardiac phases, spatial resolution 0.74 mm, thickness 6 mm). In each apical plane, two hinge points of the leaflets were manually identified at end-systole and end-diastole and then automatically tracked throughout the cardiac cycle. The 3D annular geometry was then automatically reconstructed and several parameters computed: the two main diameters, eccentricity (the ratio between the diameters), height, area, and the peak systolic excursion (PSE) along annular perimeter. The minimum and maximum values of each parameter during the cardiac cycle were reported (min, max).

Results: CMR took 5 minutes per valve, while analysis process was performed in less than 10 minutes. All parameters showed significant changes during the cardiac cycle. Despite similar diameters between MA (antero-posterior: 28±2, 33±2 mm); intercommisural, 37±4, 40±4 mm) and TA (antero-posterior: 36±4, 41±6 mm); septum-free wall: 31±4, 36±6 mm), the TA appeared significantly more round than MA (eccentricity, TA: 0.82±0.08, 0.93±0.07; MA: 0.75±0.07, 0.88±0.06); and less saddle shaped (height: TA: 2.2±1.9, 7.6±2.1 mm); MA: 5.0±2.7, 9.5±2.1 mm). Also, TA showed a greater area (95±2.1, 12±2.8 cm²) than MA (88±1.3, 13±2.6 cm²).

Global PSE, averaged along the perimeter, was higher for TA (17±2.8 mm) than MA (12±1.4 mm). In details, while MA showed similar anterior and posterior PSEs (11±1.2, 12±2.5 mm), TA had a more complex pattern, with a significantly lower PSE in the septal (13±2.2 mm) compared to anterior (18±3.4 mm) and posterior (20±2.9 mm) regions. The highest PSEs were located in the antero-posterior region for the TA (22±3.3 mm), and in the posterior for MA (13±2.6 mm).

Conclusions: CMR-derived quantitative analysis of MA and TA behavior is feasible and permits a very detailed assessment of their dynamic interaction with potential clinical and surgical benefits.

A new method for 3D integration of coronary anatomy and quantitative cardiac PET imaging

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Purpose: Multimodal integration of coronary anatomy by CTA and myocardial quantitative perfusion by PET allows combined imaging of obstructive coronary disease with the quantitative information on downstream myocardial blood flow (MBF) and flow reserve (MFR). We propose a new method (HIT: Hybrid Image Tool) for 3D fusion of CTA/PET anatomical and quantitative functional imaging.

Methods: Three elements composed the HIT method: 1) multimodal registration tool exporting an XML-transformation file; 2) interface to software for quantitative analysis able to save an XML file containing DICOM header data and quantitative polar map information; 3) DICOM data builder, based on a fixed scale for standard quantitative representation, able to create a derived quantitative DICOM data compatible with any 3D fusion tool.

Results: We analysed CTA and PET studies of 10 patients enrolled in Pisa for the European EVINCI study. The MunichHeart software was used to provide PET quantitative measurement of rest, stress (i.e. Dipyridamole) MBF and MFR. The new HIT method was used to derive quantitative DICOM PET datasets, using a 13-scale with a scale of 0-3.0 mI/min, which were imported in a fusion tool (CardIQ) of a GE AW Server-2.0. Data import and visualization were feasible in all cases. Figure 1 shows an example of 3D fusion of CTA and absolute myocardial perfusion, the RCA stenosis (red cross) is evidenced with a zooming of coronary angiography.

Conclusion: The HIT method provided 3D standardized co-visualization of patient specific coronary anatomy and downstream absolute myocardial perfusion allowing the assessment of individual functional significance of coronary disease. The same method could be extended to integrate CTA with other quantitative functional parameters such as wall motion and perfusion from MRI.
1264 Ambiguity in detection of necrosis in IVUS plaque characterization algorithms
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Purpose: We previously developed an atherosclerotic tissue characterization algorithm independent of transducer frequency, which could be applied on both radiofrequency (RF) and grayscale IVUS images. We morphed IVUS-histology images through deformable registration. We evaluated tissue colormap result, coined as diagnosis histology (PH) image, with in vitro histology (40MHz) and in vivo with virtual histology (VH)(20MHz).

Results: Compared with histology, PH results demonstrated classification accuracy of 99.60%, 87.75%, and 90.87% for calcified, fibrotic, and fibro-lipidic tissues, respectively in 83 in vitro frames (30 cadaver hearts). Due to unsupervised construction of PH images, we could not detect necrosis. We also found 93.1±6.1%, 87.5±9.5%, 78.4±17.6%, and 61.3±21.3% accuracy for calcified, necrosis, fibrotic, and fibro-lipidic tissues among PH and VH images in 155 in vivo frames (4 patients). Among a sub-sample of 892 histology images (12 arteries) only 156 (17.5%) of them contained necrosis whereas this rate is 155/155 (100%) for all in vivo VH images with average of 40% plaque burden. Histology showed 1.6±2.9% of necrosis tissues per artery, whereas, it was 10.1±21.8% in VH images.

Conclusions: Necrosis appears to be overestimated in VH image while histology shows that is a rare tissue. The necrosis pattern in VH is sparse (along lateral direction and around calcified plaques) whereas histology shows it is confluent (toward vessel wall). Often, VH necrotic pattern is due to rapid attenuation of IVUS signals in calcified plaques and is not related to tissue characteristics as confirmed by PH-histology cross validation. Detection of necrosis requires more advanced method, combining textural and spectral features.

1265 An automatic segmentation and 3D reconstruction of OCT images for the evaluation of coronary pathologies
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Purpose: The coronary plaque identification and quantification is an important matter of atherosclerosis and can provide useful information to enhance therapy and procedures. Optical Coherence Tomography (OCT) is an increasingly used intravascular imaging modality that can identify the coronary lesion type in-vivo through high specificity and sensitivity. To date, however, the analysis of these images is mainly based on manual tracing and doesn’t provide a global vision of the vessel under study. The aim of the study is to present a novel semiautomatic method to detect the main components of both plaque and artery wall. Moreover, the plaque features have been correlated with bihemoral circulating markers and an integrated Finite Element (FE) method and OCT approach is presented to model patient specific coronary plaques.

Methods: The OCT coronary images were processed: the main types of tissue were detected and measurements of their extensions were computed and recorded. 3D geometries were used for the structural FE simulations. Several pre and post-PCI bihemoral markers were evaluated to establish a correlation with plaque morphology.

Results: The results of the segmentation stage (Fig.1) reveal that extended fibrocalcific lesions were present in the analysed vessels. Preliminary results of the bihemoral profile reveal an increase in post-PCI levels of creatine kinase-MB and troponin I in significant fibrocalcific lesions. The FE analyses show that the peak stress is localized mainly in the proximal shoulder region of the plaque.

Conclusions: This study highlights the ability of our system to detect the tissue component in-vivo by means of OCT images with minimal user interaction and to provide a computational model to simulate biomechanical atherosclerotic vessel behaviour.

1266 Sensitivity of quantification methods to tracer arrival time for myocardial perfusion estimation in DCE-MRI
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Purpose: A common technique for calculating myocardial blood flow (MBF) is to track a bolus of contrast agent using DCE-CMR and measure MBF using quantitative methods. However flow quantification have been shown to be sensitive to the delay between the arterial and myocardial tissue tracer arrival time (tOnset). Thus an accurate estimation of MBF relies on the precise identification of tOnset.

The aim of this study is to examine the effect of tOnset on flow estimates in pixel-wise analysis.

The perfusion data were obtained from a hardware perfusion phantom whilst clinical data from CMR images performed on patients during adenosine-induced hyperaemia. Data were analyzed by a software, which uses iterative deconvolution to identify the optimal tOnset. 3 deconvolution methods - Fermi, exponential bases and ARMA method have been compared. Figure 1 shows the MBF absolute error vs. timing shifts for the perfusion phantom. The lowest absolute error has been obtained when the actual tOnset has been used. Comparing the three methods accuracy, ARMA has shown to have the lowest absolute error. Figure 2 shows the voxels wise perfusion maps in a patient with occluded LAD and a significant coronary artery lesion on the LCx and symptoms of angina. tOnset estimation has been used for the analysis in Figure 2b which resulted in the identification of perfusion abnormalities in both the LAD and LCx territories, the latter was missed in an analysis with fixed tOnset (Figure 2a).

Perfusion estimates based on DCE-CMR have many desirable characteristics; however MBF estimates are biased by many factors including the tOnset, and attempts to quantify MBF without using it may be premature. Using tOnset will result in a more accurate estimation and clearer visual delineation of the ischemic region in the perfusion maps.

1267 Towards regional ILL variation in abdominal aortic aneurysms: integration between experimental data and computational finite element analyses
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Purpose: The intraluminal thrombus (ILT) is present in the majority of abdominal aortic aneurysms (AAA)s and it plays an important role in aneurysm wall weakening. However, little is known about architecture and mechanical properties of ILT and its effect on wall stress distribution is controversial.

The aim of this study is to characterise ILT material by integrating data from mechanical test (MT) and histological investigations (HI), and to investigate the role of ILT on the aortic wall stress by means of Finite Element (FE) computational analyses.

Methods: ILT specimens were extracted from patients undergoing elective open AAA, histological (Masson’s trichrome and haematoxylin and eosin staining) and mechanical test were performed from different regions of the ILT. Computational FE models were developed on the bases of the CT patient-specific images and FE simulations have been performed by means of a specific probabilistic approach where the material properties and the main geometrical features were used as input variable. The maximum peak stress (MPS) has been chosen as output variable.

Results: Our results confirm the different structure along the ILT thickness (THK) and, in particular, indicate that the microstructure of ILT differs between the ventral and dorsal region. The lateral posterior area was stiffer than the budge region. The sensitivity FE analysis shows that the MPS is primarily affected by the THK and that, in particular, an increase in the THK decreases the MPS of about 30%.

Figure 1. Examples of OCT segmentation
Conclusions: This study points out the significant influence of both morphological and material properties of the thrombus on peak wall stress estimation and location and the importance of FE simulation to identify the main parameters that affect the MPS.

BURNING ISSUES ACROSS THE SPECTRUM OF VALVULAR DISEASES

P1286
Epigenetic regulation of 5-lipoxygenase in the phenotypic plasticity of valvular interstitial cells in aortic stenosis

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Purpose: Development and hemodynamic progression of aortic valve stenosis have been associated with increased inflammatory activity promoting valvular calcification. In this process, differentiation of valvular interstitial cells (VICs) into proinflammatory and osteogenic phenotypes may play a key role. Within the inflammatory pathway, 5-lipoxygenase (5-LO) pathway leading to leukotriene production was recently implicated in the pathobiology of aortic stenosis. Since epigenetic mechanisms such as altered DNA methylation pattern regulate 5-LO promoter- and transcriptional activity, we hypothesized that epigenetic modulations of DNA methylation status may be involved in the phenotypic differentiation of VICs.

Therefore the aim of the present study was to examine the DNA methylation status and the transcriptional profile for 5-LO in valvular tissue and in VICs.

Methods: Human aortic valves, obtained from 17 patients undergoing aortic valve replacement surgery, were used for mRNA and DNA extraction. Primary cultures of VICs were isolated from human non-calcified aortic valve samples. Expression levels of 5-LO were determined by quantitative real-time PCR. For DNA methylation analysis, restriction enzymatic digestion followed by SYBR green-based real-time PCR was performed. LTB4 concentrations were determined by ELISA.

Results: Calciﬁed human aortic valve tissue exhibited a signiﬁcantly lower degree of DNA hypermethylation of the 5-LO promoter (0.36±0.28%) compared with non-calciﬁed valvular tissue (2.1±0.55%; p=0.028), whereas 5-LO mRNA levels were increased 2.1±0.41-fold (p=0.001). There was a signiﬁcant and inverse correlation between 5-LO promoter methylation and 5-LO mRNA levels in aortic valve samples (r=-0.5, p=0.04). Treatment of VICs with the hypermethylator 5-aza-2'-deoxycitidine (AdC; 100nM-10μM) decreased the relative amount of hypermethylated 5-LO promoter (0.21-fold increase in LTB4 production (p=0.017). Since epigenetic mechanisms such as altered DNA methylation pattern regulate 5-LO promoter- and transcriptional activity, we hypothesized that epigenetic modulations of DNA methylation status may be involved in the phenotypic differentiation of VICs.

Conclusions: To our knowledge, this is the first study providing a conceptual model of phenotypic plasticity of VICs due to underlying epigenetic alterations, however, is preserved only during the shorter treatment period.

P1288
Two weeks of gentamicin treatment is adequate in enterococcal endocarditis

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Purpose: Due to the nephrotoxic effects of aminoglycosides the Danish guidelines on infectious endocarditis (IE) were changed in January 2007 reducing gentamicin treatment from 6 weeks to 1-2 weeks. Since then we have examined the outcome in patients with enterococcal IE treated in the years before and after these new recommendations.

Methods: From October 2002 to October 2011, data has been prospectively collected from consecutive IE patients at two tertiary centers in Denmark. Mortality, relapse of IE and changes of renal function were compared in patients with enterococcal IE admitted before and after January 2007. Renal function was assessed by the estimated glomerular filtration rate (eGFR). Information on hospital admissions and information on death were drawn from the Central Patient Registry and the Civil Registration Number Registry, respectively using each patient's civil registration number.

Results: A total of 122 patients were included, 58 were treated before, and 64 after January 2007, respectively. No significant differences were found between the two groups in baseline characteristics including co-morbidities. The number of patients undergoing surgery was also similar. The primary outcome, 3 months relapse free survival, did not differ between the groups: 72% vs. 81% (p=0.25). One year mortality from also identical: 33% vs. 27% (p=0.51). Patients treated before and after January 2007 received gentamicin for a mean of 27±16 days vs. 11±6 days (p=0.001), respectively. Renal function was compared in patients who were on dialysis when admitted or discharged from hospitalization (n=11 vs. n=6) and had similar eGFR 70 ml/min vs. 76 ml/min (p=0.21). However, at discharge the patients treated before 2007 had a lower eGFR 53 ml/min vs. 72 ml/min (p=0.004), and a significantly greater decrease in eGFR, 16ml/min vs. 4 ml/min (p=0.012), respectively.

Conclusion: Reducing gentamicin treatment in enterococcal IE to 2 weeks does not have a negative impact on relapse of IE or on mortality. Renal function however is preserved only during the shorter treatment period.

P1287
Functional performance and structural maturation of decellularised pericardial valves in central venous position: an experimental study

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Objective: Patients with severe tricuspid regurgitation (TR) and advanced right ventricular dysfunction represent a therapeutic challenge for both, medical and surgical strategies. A better understanding of valve degeneration in decellularized tissue valves in the low-pressure venous circulation using a chronic animal model of TR.

Methods: 16 decellularized pericardial tissue valves were heterotopically implanted in the inferior (IVC) and superior (SVC) vena cava in an animal model (54-80kg, 74±6.4kg) of severe TR. The devices were assembled using self-expanding nitinol stents and bovine pericardial decellularized by an established detergent-based protocol (dTV; n=4). Native pericardial tissue served as control (nTV, n=4). Prior to implantation, TR grade III-V was created by pulmonary banding and papillary muscle avulsion using a 0.07-inch wire blade. Valve implantation was performed through the right internal jugular vein by means of a 21 F catheter and guided by fluoroscopy. After 6 month, device function and structural maturation were analysed by echocardiography, histology, immunohistochemistry and electron microscopy.

Results: Valve implantation was successful in all animals. After valve implantation, cardiac output increased significantly from 4.4 l/min to 5.1 l/min (p=0.005) and competent valve function was verified by angiography. At 6 month, angiographic and echocardiographic evaluation revealed moderate to severe регуляция in all nTV. In contrast, 5 out of 8 dTV showed excellent function with only minor regurgitation. In these animals autopsy revealed preserved structural integrity of the valve with tender leaflets without signs of thrombosis or calcification. In contrast, nTV leaflets showed severe valve degeneration with large calcification areas. Microscopic and histologic analysis confirmed endothelial repopulation of the leaflets in both valve types. However, in decellularised valves additional interstitial reseeding was noted.

Conclusion: In the venous low-flow, low-pressure circulation, decellularized tissue valves show superior functional performance compared to native pericardial tissue valves. Macroscopic and microscopic analysis suggests preserved structural integrity and advanced endothelial and interstitial repopulation without evidence of degradation in decellularized tissue valves.

P1289
Prophylaxis for bacterial endocarditis: new guidelines did not improve the safety of patients during dental work

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Purpose: Since the 2007 revision of the guidelines to prevent bacterial endocarditis, only patients at a very high risk for infective endocarditis (IE) are considered candidates for antibiotic prophylaxis. It is unknown how this revision has influenced the management of IE prophylaxis by dentists.

Methods: Questionnaires containing 18 questions regarding indications for IE prophylaxis, patient-related and intervention-related risks, timing, dosage and choice of antibiotics have been answered by 430 randomly selected dentists in 2003. A slightly modified animal model of TR.

Results: Indication for IE prophylaxis after heart valve replacement was correctly reported most frequently during both surveys (results 2003 vs. 2009: 96.7% vs. 83.6% respectively).
Performance Analysis of EUROSCORE 2 as compared to logistic EuroSCORE and STS scores for predicting 30-day mortality after transcatheter aortic valve replacement


Background: Risk scores, such as logistic EuroSCORE and Society of Thoracic Surgeons (STS) scores, are commonly used to identify high-risk patients eligible for transcatheter aortic valve replacement (TAVR) and to predict peri-procedural mortality. EuroSCORE 2 has been recently launched for predicting mortality after cardiac surgery but it has never been evaluated for TAVR.

Objectives: The purpose of this study was to examine the performance of EuroSCORE 2 for predicting 30-day mortality in patients referred to TAVR as compared to logistic EuroSCORE and STS scores.

Methods: All consecutive patients (n=250) in whom a balloon-expandable Edwards prostheses was implanted between May 2006 and October 2011 at the University Hospital were included for analysis. Patient demographics were recorded in a prospective database. Correlations and c-statistic were calculated for Logistic EuroSCORE, STS, and EuroSCORE 2.

Results: Observed 30-day mortality was 7.6%. The mean logistic EuroSCORE was 22.6±12.8% and overestimated mortality as compared to STS (7.3±4.1%) and EuroSCORE 2 (7.1±5.8%) scores. EuroSCORE2, but not logistic EuroSCORE and STS scores, was significantly higher in patients who died as compared to those who survived (10.3±6.0% vs. 7.5±5.7%, p=0.04; 27.6±13.4% vs. 22.2±12.7%, p=0.07 vs. 9.5±6.7% vs. 7.1±3.6%, p=0.13, respectively). The best linear correlation was observed with the Logistic EuroSCORE and EuroSCORE 2 (r=0.79, p<0.001) as compared to Logistic EuroSCORE and STS scores (r=0.58, p=0.001) and EuroSCORE 2 and STS scores (r=0.63, p<0.001).

Conclusion: EuroSCORE 2 was superior to logistic EuroSCORE and STS scores in predicting 30-day mortality after TAVR. However, EuroSCORE 2 had only moderate accuracy in predicting mortality after TAVR. Further studies are warranted to confirm these results in a larger population.

Determinants and prognosis value of right ventricular function in organic mitral regurgitation

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Objectives: To assess the determinants and the prognosis value of right ventricular (RV) ejection fraction (EF) in organic mitral regurgitation (MR).

Methods: Two-hundred eight patients (62±13 years, 138 males) with moderate to severe organic MR referred to surgery underwent an echocardiography and left ventricular (LV) and RV radioanography angiography. The LV and the RV were divided into 9 regions to assess regional function.

Results: Mean RV EF was 40.7±10.1%, ranging from 10 to 65%. Fifty-seven patients (27%) were in atrial fibrillation. Tricuspid S wave velocity measured in a subset of patients (n=92) correlated weakly with RV EF (r=0.27, p=0.018). Sixty patients (25%) had a RV EF >35%. In multivariate analysis, LV septal function (LV EF 8: p=0.056, P<0.0001; LV EF 9: p=0.22, P=0.046), LV end-diastolic diameter (β=0.27, P<0.0001) and PASP (r=-0.19, P=0.008) were the independent predictors of overall mortality. EuroSCORE2, but not logistic EuroSCORE and STS scores, was significantly higher in patients who died as compared to those who survived (10.3±6.0% vs. 7.5±5.7%, p=0.04; 27.6±13.4% vs. 22.2±12.7%, p=0.07 vs. 9.5±6.7% vs. 7.1±3.6%, p=0.13, respectively). The best linear correlation was observed with the Logistic EuroSCORE and EuroSCORE 2 (r=0.79, p<0.001) as compared to Logistic EuroSCORE and STS scores (r=0.58, p=0.001) and EuroSCORE 2 and STS scores (r=0.63, p<0.001).

Conclusion: At least moderate PAR after TAVI was observed in 14.4% of patients and associated with increased cardiovascular mortality. Hemodynamic evaluation using βP DAP–LVEDP and DPTI:SPTI as quantitative parameters provides excellent cut-off values of ≤18 mmHg and ≤0.7 for prediction of associated mortality.
**P1293**

Long-term efficacy of percutaneous mitral valve repair using the MitraClip system may depend on acute MR reduction: insight in the Mitra-SWISS registry

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**Introduction:** Percutaneous mitral valve repair (MVR) utilizing the MitraClip® system has become a valid alternative for patients with severe mitral regurgitation (MR) and high operative risk. However, factors predisposing for long term clinical success are still unknown. Presenting the 12-months results of the first 100 consecutive patients treated with MVR in Switzerland, we aim to learn more about this.

**Methods:** Clinical, echocardiographic and procedural data are prospectively collected and centrally stored in an online database. After assessment of all parameters, survival time has been associated to different variables using log-rank test and Cox regression and a Kaplan-Meier curve estimate has been provided.

**Results:** Acute procedural success (APS), defined as a successful Clip-implantation with a residual MR grade of < 3+, was achieved in 85%. MR grade remained stable for most of the patients over follow up and NYHA class decreased from class 3 to 2. Mortality at 30 days and 12 months was 5% and 16% respectively. Cox regression analysis indicated an association between the following parameters and overall survival:

- discharge MR grade - p<0.0042 (see figure).
- occurrence of congestive heart failure after the procedure - p=0.0025
- APS - p<0.0018

There was no association with survival depending on whether patients had functional MR or degenerative MR.

**ADVANCES IN DIAGNOSIS AND PROGNOSTIC EVALUATION OF CARDIOMYOPATHIES**

**P1294**

The etiology of amyloidosis influences pathophysiology and outcome of heart failure in amyloidotic cardiomyopathy

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**Purpose:** In amyloidotic cardiomyopathy (AC) heart failure (HF) has traditionally been attributed to diastolic dysfunction, but little is known on the features of HF influenced by the etiology of amyloidosis. Despite shorter disease duration and lesser left ventricular wall thickness, AC etiology shows the worst outcome due to a combination of chronic interstitial infiltration and acute toxic effect of circulating light chains.

**Methods:** A retrospective cohort study of 1635 consecutively evaluated HCM patients. The effect of accumulating risk factors on SCD was examined using Cox proportional hazards method. The performance of the guidelines in discriminating patients who would suffer SCD in the future was examined using time-dependent receiver operating characteristic curves, and calculating time-dependent positive (PPV) and negative (NPV) predictive values for each threshold.

**Results:** Ninety-nine (38%) had HF at diagnosis (Table). Survival curves are shown in the figure.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>AL (n=57)</th>
<th>ATTR (n=21)</th>
<th>SSA (n=21)</th>
<th>p</th>
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<tr>
<td>Low QRS voltage, n/N (%)</td>
<td>36/55 (65)</td>
<td>9/19 (47)</td>
<td>8/38 (21)</td>
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<td>Diastolic interventricular septum thickness (mm)</td>
<td>16±3</td>
<td>19±3</td>
<td>18±4</td>
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<td>LV ejection fraction, %</td>
<td>50±13</td>
<td>48±12</td>
<td>46±14</td>
<td>0.47</td>
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<td>Restrictive filling pattern, n (%)</td>
<td>30/55 (55)</td>
<td>10/19 (53)</td>
<td>8/38 (21)</td>
<td>0.43</td>
</tr>
<tr>
<td>Mean RA pressure (mm Hg)</td>
<td>10±4 (n=30)</td>
<td>8±5 (n=18)</td>
<td>7±4 (n=18)</td>
<td>0.05</td>
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<tr>
<td>Mean PCWP (mm Hg)</td>
<td>13±9 (n=30)</td>
<td>17±8 (n=18)</td>
<td>17±6 (n=18)</td>
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<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.1±0.7 (n=30)</td>
<td>2.3±0.6 (n=18)</td>
<td>2.3±0.3 (n=18)</td>
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</tbody>
</table>

**Discussion:** In this series of 100 high-risk patients with severe MR, treated with percutaneous MVR, MR reduction appears to be stable in most patients with initial good results. Strong predictors of survival were absence of heart failure after the procedure and a low initial MR grade. This purely hypothesis generating analysis may underscore the necessity to achieve the best (surgical like) final result after also after percutaneous MVR.

**Figure 1:** Kaplan-Meier estimate for overall survival with respect to MR grade at discharge.

**Conclusions:** In AC, both pathophysiology and outcome of HF are profoundly influenced by the etiology of amyloidosis. Despite shorter disease duration and lesser left ventricular wall thickness, AL etiology shows the worst outcome due to a combination of chronic interstitial infiltration and acute toxic effect of circulating light chains.

**Validation of the 2003 ACC/ESC guidelines on the risk stratification of sudden cardiac death in hypertrophic cardiomyopathy**

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**Purpose:** The ACC/ESC 2003 guidelines on hypertrophic cardiomyopathy (HCM) recommend identifying patients at high risk of sudden cardiac death (SCD) by assessing non-sustained ventricular tachycardia, syncope, abnormal blood pressure response, family history of SCD and ventricular hypertrophy. The aim was to examine whether the accumulation of risk factors reflects increased SCD risk and quantify the predictive accuracy of different risk factor profiles.

**Methods:** A retrospective cohort study of 1635 consecutively evaluated HCM patients. The effect of accumulating risk factors on SCD was examined using Cox proportional hazards method. The performance of the guidelines in discriminating patients who would suffer SCD in the future was examined using time-dependent receiver operating characteristic curves, and calculating time-dependent positive (PPV) and negative (NPV) predictive values for each threshold.

**Results:** During follow-up (12175 patient years), 93 patients (6%) suffered SCD or equivalent with an annual rate of 0.8% and 5-year cumulative incidence of 4%. Compared with patients without any risk factors, those with multiple risk factors had an increased risk of SCD (in the presence of 2 risk factors HR 2.6, p=0.002; 3 risk factors HR 6.2, p<0.0001; 4 or more risk factors HR 8.3, p<0.0001). A single risk factor was not associated with increased risk of SCD (HR 1.6, p=0.131). The area under the curve was 0.57 at 1 year, 0.58 at 5 years and 0.55 at 10 years. The NPV and PPV are shown in the figure.

**Figure 1:** Predictive value of risk factor profiles

**Conclusions:** The aggregation of risk factors in a particular patient is associated with increased risk of SCD. Even though the current strategy can identify patients at high risk, the PPV remains low even in the presence of multiple risk factors. The NPV of the absence of risk factors is excellent.
Prognostic value of N-terminal pro-brain natriuretic peptide in outpatients with hypertrophic cardiomyopathy

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Background: N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts adverse outcomes in patients with chronic heart failure. In patients with hypertrophic cardiomyopathy (HCM), NT-proBNP levels are known to be elevated and correlate with NYHA class and left ventricular outflow tract obstruction; however the value of NT-proBNP as an independent predictor of outcome in HCM remains undefined.

Methods: We evaluated serum levels of NT-proBNP in 286 HCM outpatients attending the Referral Center for Myocardial Diseases. Patients with known coronary artery disease (n=15) and systolic dysfunction (LV ejection fraction<50%); n=20) or incomplete follow-up (n=69) were excluded; the remaining 183 patients (mean age 49.7 ± 17.3 years, 64.4% male, 36% (obstructive) were followed for 47±3.4 months. The primary endpoint (PE) was a composite of cardiovascular death, heart transplantation and resuscitated cardiac arrest. Secondary endpoint (SE) was a composite of acute heart failure requiring hospitalization, progression to end stage disease and septal myectomy or alcohol septal ablation.

Results: Median NT-proBNP for the 183 patients was 615.1 pg/ml (range 21.8-16013 pg/ml). The occurrence of PE during follow-up was significantly different across the tertiles of NT-proBNP: 4.3% for the lowest tertile (<310 pg/ml), 8.6% in the mid (310-1025 pg/ml) and 15% in the highest tertile (>1025 pg/ml); overall p<0.01. Furthermore, patients in the highest NT-proBNP tertile had higher rate of SE (19.6%; p<0.001) and NYHA class III-IV (HR 2.0, 95%CI 1.2-3.3; p=0.001). Among non-obstructive patients, a NT-proBNP value >1025 pg/ml identified patients at increased risk of cardiac events (HR 2.1, 95%CI 1.1-3.8, p=0.01). Among non-obstructive patients, the highest NT-proBNP tertile had higher rate of SE (56.7%) than those in the lowest (19.6%; p<0.001). Among non-obstructive patients, a NT-proBNP >1025 pg/ml identified patients at increased risk of cardiac events (HR 2.1, 95%CI 1.1-3.8, p=0.01). Among non-obstructive patients, the highest NT-proBNP tertile had higher rate of SE (56.7%) than those in the lowest (19.6%; p=0.001). Among non-obstructive patients, the highest NT-proBNP tertile had higher rate of SE (56.7%) than those in the lowest (19.6%; p=0.001). Among non-obstructive patients, the highest NT-proBNP tertile had higher rate of SE (56.7%) than those in the lowest (19.6%; p=0.001).

Conclusions: In outpatients with HCM, NT-proBNP is an independent predictor of heart failure-related events, but not of overall cardiovascular mortality. Such limitation is likely due to the confounding effect of arrhythmic events unrelated to heart failure.

Gender-specific differences in heart disease penetrance and mortality in lamin A/C mutation carriers


Purpose: Mutations in LaminA/C (LMNA) cause a variety of clinical phenotypes including dilated cardiomyopathy. LMNA is one of the most prevalent mutations in dilated cardiomyopathy, which is associated with a high risk of arrhythmias, sudden cardiac death, and heart failure. However, it is unclear whether there are gender-specific differences in cardiac disease penetrance and mortality in LMNA mutation carriers.

Methods: In an Amsterdam cohort of 269 LMNA mutation carriers, we evaluated gender-specific penetrance of cardiac involvement and major cardiac events. Furthermore, we determined all cause mortality of the mutation carriers (main outcome measure: Standardized Mortality Ratio (SMR)).

Results: Cardiac disease penetrance was age-dependent and almost complete at the age of 70 years. The presence of a left ventricular ejection fraction < 45% was significantly higher in men (p<0.001). However, there was no difference between genders regarding atrioventricular-block, atrial tachyarrhythmias and non-sustained ventricular tachycardia. The major events malignant ventricular arrhythmias (12%), sudden cardiac death (8%) and end-stage heart failure (29 vs. 14%) were also significantly more prevalent in men than in women (p<0.001 and p=0.006, respectively).

Conclusions: This large cohort of LMNA mutation carriers does confirm a high cardiac disease penetrance and a high mortality in mutation carriers. Furthermore, our study demonstrates that male mutation carriers have a worse prognosis due to a high prevalence of malignant ventricular arrhythmias and end-stage heart failure.

High level of physical activity may impair myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy

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Purpose: Exercise is supposed to increase the risk of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). However, the impact of exercise on myocardial function in ARVC has not been fully described.

Methods: In all, 98 Norwegian ARVC patients and mutation positive family members from the Nordic ARVC registry were studied (age 44±17 years, 55% male). Patients with activity >750 MET-min/week were defined as athletes. LV ejection fraction (EF), right ventricular outflow tract (RVOT) diameter and RV diastolic diameter (RVD) were assessed by echocardiography. Exercise induced VT was defined as VT or VF occurring during significant exercise.

Results: Of the 98 ARVC patients, 26 (27%) were defined as athletes (69% male). Athletes were younger than non-athletes (39±15 vs 46±17 years, p<0.04). Athletes were not more frequently probands than non-athletes (p=0.26) and occurrence of total VT did not differ (p=0.33). However, exercise induced VT occurred in 31 patients (34%) and was more frequent in athletes (54%) compared to non-athletes (24%); p<0.01. Athletes had lower LVEF compared to non-athletes (54±5 vs 59±3); p<0.03. RVOT diameter in athletes (R 0.55, p=0.01) (Figure), but not in non-athletes (p=0.13). In the total population, RVD diameter (36±7 vs 30±7 mm, p<0.01) and RVD (46±7 vs 39±8 mm, p=0.01) were increased in those forced with exercise induced VT (p<0.01).

Conclusion: LV EF was reduced in athletic ARVC patients. Reduced EF was related to increased RV dimensions in athletes, but not in non-athletes. RV dimensions related to exercise induced VT. These findings indicate that history of vigorous exercise may reduce LV function in ARVC patients in addition to be a risk factor for VT during ongoing exercise.

Influence of genetics in sudden death risk in hypertrophic cardiomyopathy

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Purpose: Characterization of patients at risk for sudden death (SD) is one of the greatest challenges in hypertrophic cardiomyopathy (HCM). Our purpose is to describe the risk of SD according to the causal mutations identified in our clinical experience.

Methods: We included all patients with diagnosis of HCM with known responsible mutation. Familial history was reviewed in search of SD among their relatives. We analysed prevalence of SD cases and performed time-to-event analysis to determine risk profile in the most prevalent mutations.

Results: We had positive genetic results in 139 affected patients with HCM (69% males, age 50±16 yrs.). Most prevalent mutations were, in order of prevalence, MYBPC3-IVS3+1G ΔA (n=60), MYBPC3-Arg891fs (23), MYBPC3-A107fsX116 (20), MYH7-T1377M (16), MYBPC3-A216T in association to MYBPC3-E258K (7), TNNT2-R278C (10). IVS3+1G ΔA was identified in 18 apparently unrelated families. 21 sudden deaths were accounted, including 5 episodes aborted by successful resuscitation and 3 appropriate ICD therapies. Of note, 15 SD cases were related to IVS3+1G ΔA. According to the gene mutation, proportion of cases presenting SD were: IVS3+1G ΔA 25%; MYBPC3-Arg891fs 4.3%; MYBPC3-A107fsX116 10.0%; MYH7-T1377M 6.3%; MYBPC3-A216T 14.3% (Chi square, p<0.01). When comparing IVS3+1G ΔA with non-IVS3+1G ΔA, p<0.007. Time-to-event analysis showed a trend towards increased risk in...
Definition of clinical relevant Fabry disease by the biomarker lysosomal Gb3 in patients with alpha-galactosidase A mutations

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Background: Fabry disease is a very heterogenous and heterophenotypic disease caused by private mutations in the alpha-galactosidase A (α-galA) gene. The aim of this study was to define clinical relevant Fabry cardiomyopathy in patients with α-galA mutations by the biomarker lysosomal Gb3.

Methods and Results: 124 Fabry patients were investigated with a comprehensive clinical work up, genetic analysis and laboratory testing, including α-galA activity and cardiac measurements. An extensive family screening was carried out, including clinical work up of relatives. The study consisted of two parts: Previously described mutations were included in the evaluation study (n=72), new mutations in the validation study (n=52).

Echocardiographic predictors of hard events in patients with tako-tsubo cardiomyopathy

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Aim: To investigate the echocardiographic features and their prognostic implications in patients of tako-tsubo cardiomyopathy (TTC).

Methods: 227 consecutive pts (66.2±12.2 years; 90.3% females) enrolled in Tako-tsubo Italian Network underwent comprehensive transthoracic echocardiographies in a large population of tako-tsubo cardiomyopathy (TTC).

To investigate the echocardiographic features and their prognostic implication, 25 new mutations and women with agalA activity around the normal threshold. New mutations can be done by the biomarker lyso-Gb3. This is especially helpful in the α143T (exogenic) dominated.

2.6 ng/ml showed signs of a cardiomyopathy. Among the patients with a lyso-Gb3 levels than any of the patients with classical Fabry cardiomyopathy. A cut off of 2.6 ng/ml separated the two groups.

Validating study: Six out of the 52 patients with new mutations showed a lyso-Gb3 below the cut-off of 2.6 ng/ml. Clinical investigation, blinded to the results of lyso-Gb3, revealed that none of these patients or their relatives showed classical cardiac involvement. In contrast, clinical characterisation of the patients with new α-galA mutations and lyso-Gb3 above 2.6 ng/ml suggested classical Fabry cardiomyopathy mutations, without exception. Moreover, 25 female patients from the complete cohort had an α-galA activity around the normal threshold (0.3-0.5 nmol/min/mg protein). Out of these 25 females 11 women had a lyso-Gb3 > 2.6 ng/ml. None of these had a clinical relevant Fabry cardiac involvement. In contrast, all the 14 females with a lyso-Gb3 > 2.6 ng/ml showed signs of a cardiomyopathy. Among the patients with a lyso-Gb3 > 2.6 ng/ml polymorphisms (n=5, intrinsic) and the mutations D313Y, N1215S and A143T (exogenic) dominated.

Conclusion: Our data show that the definition of clinical relevant Fabry cardiac mutations can be done by the biomarker lyso-Gb3. This is especially helpful in new mutations and women with α-galA activity around the normal threshold.

Direct renin/prorenin inhibition by aliskiren improves endothelial progenitor cell function and enhances ischemia-induced neovascularization in diabetic animals

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Objectives: Angiogenesis is markedly impaired in the presence of diabetes mellitus. Aliskiren, a direct renin inhibitor, was suggested to modify proangiogenic cells and prevent aliskiren in hypercholesteremic animals. This study aimed to investigate whether and how aliskiren could improve the function of endothelial
progenitor cells (EPCs), a pivotal contributor to angiogenesis, and enhance neo-
vasculogenesis in diabetic animals with hind-limb ischemia.

Methods and Results: Aliskiren (5, 25 mg/kg/day) or PBS (for control) was ad-
ministered via an osmotic pump, or hydralazine (2, 10 mg/kg/day) was given in
drinking water for 2 weeks before hind-limb ischemia surgery was conducted on
STZ-induced diabetic mice (n=12 in each group). Blood pressure was simi-
lar between the aliskiren and hydralazine groups. Compared with PBS, aliskiren
dose-dependently enhanced the recovery of limb perfusion and capillary den-
sity with the increase of circulating Sca-1+/Flk-1+ (EPC-like cells) and the eleva-
tion of plasma vascular endothelial growth factor (VEGF) and stromal cell-derived
factor (SDF)-1 levels, whereas hydralazine had no such effects. The effects of
aliskiren could be abolished by intraperitoneal administration of anti-SDF-1 neu-
tralizing monoclonal antibody. Besides, aliskiren dose-dependently improved the
in vitro function and increased both VEGF and SDF-1 expression of EPCs from
type 2 diabetic patients. Further, transfection with VEGF siRNA significantly re-
duced aliskiren-induced SDF-1 expression. Taken together, VEGF-SDF-1 re-
lated mechanism may be critical to both the in vitro and in vivo effects of aliskiren.

Conclusions: Aliskiren dose-dependently and blood pressure-independently en-
hanced ischemia-induced neovasculogenesis in diabetic mice and improved the
number and function of EPCs via VEGF and SDF-1-related mechanisms.

Sitagliptin therapy enhances the number of circulating
endothelial progenitor cells and angiogenesis:
evaluations in vitro and in the rat critical limb ischemia
model

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Purpose: We have proposed the hypothesis that sitagliptin is capable of increasing
blood flow in the rat critical limb ischemia (CLI) model by enhancing angiogenesis.

Methods: Adipose tissue from adult-male Fischer 344 rats (n=6) were cultured
in endothelial progenitor cell (EPC) culture medium for 14 days with (25 μM) or
without sitagliptin. CLI was induced by ligation of the femoral artery. Rats (n=32)
were equally separated into four groups: untreated controls (group 1), sitagliptin
(4 μM) (group 2), sitagliptin (25 μM) (group 3), and CLI with sitagliptin (group 4).

Results: In vitro, 7 and 14 days after cell culture, EPC biomarkers assessed by flow
cytometry (Sca-1+/CD31+, CXCR4+, k ancestors, CD34+ cells) and Western blot
(VEGF, CXCR4, SDF-1α) were remarkably higher in group 4 than in the other
groups (all p<0.001). In vivo, 2 and 14 days after the CLI procedure, circulating
EPC (Sca-1+/CD31+, Sca-1+, CD31+) numbers were significantly higher in group
4 compared to the other groups (all p<0.01). Additionally, the mRNA and protein ex-
pression of angiogenic biomarkers (CXCR4, SDF-1α, and VEGF, immunoflu-
orescent staining of angiogenic cells (CXCR4+, SDF-1+, CD31+), WVEF cells) and
immunohistochimical staining of small (<15 μm) vessel numbers in the ischemic
area were significantly higher in group 4 than in the other groups (all p<0.01). Fur-
thermore, laser Doppler showed that the ratio of ischemic/normal blood flow
was remarkably higher group 4 than in group 3 by day 14 after the CLI procedure
(all p<0.01).

Conclusion: Sitagliptin therapy enhances circulating EPC numbers, angiogene-
sis, and blood flow in the CLI area.

The balanced dual PPAR-alpha/gamma agonist
aleglitazar up-regulates endothelial progenitor cells,
enhances endothelial vasodilation and reduces
atherogenesis in mice

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Purpose: Bone marrow-derived endothelial progenitor cells (EPC) improve en-
dothelial function, promote vascular repair and enhance angiogenesis. The va-
cular effects of combined activation of PPAR-α and -γ receptors are not known. We
therefore studied the effects of aleglitazar, a balanced dual PPAR-α/γ agonist, on
endothelial function and atherosis in mice.

Methods and Results: Wild-type C57/Bl6 mice and ApoE-/- mice were used for
these studies. Aleglitazar was administered at 10 mg/kg/day ip versus vehi-
cle for 3 weeks. ApoE-/- mice were fed a western-type diet (21% fat, 19.5%
casein and 1.25% cholesterol) for 6 weeks, with and without aleglitazar, to in-
duce vascular dysfunction and atherogenesis. Body weight, blood pressure, heart
rate, plasma cholesterol, triglycerides, glucose and electrolytes were monitored
during the study. Plasma adiponectin, indicating activation of PPAR receptors,
was up-regulated by aleglitazar >5-fold in both strains. Sca-1/VEGFR-2-positive
EPC were quantified by FACS analysis. In C57/Bl6 mice, aleglitazar increased
the number of circulating blood EPC to 153±8.6%, and bone marrow-derived
EPC to 197±21% compared with vehicle controls. Spleen-derived cultured EPC
(DiLDL/lectin-positive) were also increased by aleglitazar to 182±8.4%. Stromal
cell-derived factor-1-dependent migratory capacity of cultured EPC, assessed ex
vivo using a modified Boyden chamber assay, was also increased by aleglitazar
to 176±5.5% compared with controls. Neangiogenesis increased by 2-fold after
aleglitazar treatment in ApoE-/- mice. In aleglitazar-treated ApoE-/-
mice, DiLDL/lectin-double positive EPC increased to 256±14% of control. Alegli-
tazar increased EPC migratory capacity to 149±13.9%. Endothelial-dependent
vasodilation, assessed in isolated aortic ring preparations, was significantly
improved by aleglitazar. Alloreactive T cell line in the aortic sinus, as assessed by
quantitative histomorphometry, showed a 22.8±7.8% reduction of the athero-
scopic plaque area to 22.8±7.8% of control ApoE-/- mice (all experiments, n=6 per
group, p<0.05).

Conclusions: Our data show that dual PPAR-α/γ activation exerts protective vas-
cular mechanisms in mice, including improvement of endothelial function and up-
regulation of both number and functionality of endothelial progenitor cells. Clinical
studies are needed to investigate the effects of aleglitazar on EPC and vascular function

Kinin-meditated recruitment of circulating progenitor
cells promotes endothelial healing: alterations in
patients with coronary disease

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Background: Kinins derived from the vascular wall may not only impact on resid-
ent endothelial cells, but may also have the potential to promote recruitment of
distinct circulating cell types which bear the B2 kinin receptor (B2R). We there-
fore investigated the role of this mechanism for endothelial healing in healthy sub-
jects (HS) and in patients with coronary artery disease (CAD).

Methods: Expression of the B2R on peripheral blood mononuclear cell subsets
of CAD patients and age-matched HS was assessed by flow cytometry. Adhe-
sion to an endothelial monolayer and subsequent closure of a scratch endothelial
gap, supported by paracrine effects of the adhering cells were studied in vitro.
In vivo, recruitment of systemically injected cells to injured carotid endothelium,
and the endothelialization of the injured artery were assessed after B2R blockade by icatibant, transplantation of B2R-deficient bone marrow cells
(B2R-/- BM), as well as adenoviral B2R overexpression were used to verify the
response of the B2R.

Results: In HS, B2R was low expressed (<1000MFI) on CD14hi monocytes
and on lymphocytes, but high in angiogenic Tie2+ or KDR+ monocytes and in
KDR+ or CXCR4+ angiogenic progenitor cells (PC) (2517 to 7516MFI; P<0.05
vs. CD14hi). Recruitment of healthy CXCR4+ PC to endothelial cells or to the
injured murine vascular wall was blocked by B2R inhibition in vitro (67% vs. ve-
hicle, P<0.05) and in vivo (58% vs. vehicle, P<0.05), while adhesion of CD41hi
monocytes was unchanged, indicating a critical role of B2R for vascular homing
of CXCR4+ PC, but not of CD14hi monocytes. In vivo endothelial healing
was lower in mice receiving B2R-/- BM than in mice receiving B2R+/- BM
(26% vs. 38.1%, P<0.05). Kinin receptor expression on CD40+ PCs (75% vs.
H; P<0.05) and on angiogenic “early outgrowth cells” (EOC) (68% vs. HS;
P<0.05) was reduced in CAD patients. Adhesion of CXCR4+ PC from CAD pa-

tients to endothelial cells was markedly reduced versus CXCR4+ PC of HS and
not regulated by the B2R. Adenoviral B2R overexpression rescued the capacity
of CAD EOCs to support re-endothelialization in vivo, associated with enhanced
vascular recruitment of CAD EOC after B2R overexpression.

Conclusions: We newly describe that vascular kinins do not only act via the
endothelial B2R, but can also recruit endothelial-supportive circulating cells to
the vessel wall via B2R on these circulating cells. The loss of B2R expression on
circulating endothelial repair-promoting cells might jeopardize the healing of
endothelial injuries and thus contribute to the pathophysiology of endothelial dys-
function in CAD.
Intranasal instillation of diesel exhaust particles impairs endothelial progenitor cells and increases atherosclerosis in mice.

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Background and aims: Exposition to fine particulate matter is associated with increased cardiovascular morbidity and mortality. However, the underlying patho- 
geologic mechanisms of vascular damage are incompletely understood. Number and function of endothelial progenitor cells (EPC) predict outcome of patients with vascular disease. The aim of the present study was to examine the effects of diesel exhaust particles (DEP) on EPC and atherosclerosis in C57Bl/6 and ApoE-/- mice.

Methods and results: C57Bl/6 mice were exposed to diesel exhaust particles (DEP; standard reference material 16550b, National Institute of Standards in Technology, USA) or solvent (PBS) for 3 weeks. DEP were applied intranasally on 5 days per week in a dosage of 2 μg/application. EPC were quantified by counting the number of spleen-derived, DilDL and lectin positive cells. Exposure to DEP reduced DilDL/lectin positive cells to 58.3 ± 5.6% (n = 6, p < 0.005). Microvascular capacity as key parameter of EPC function was determined in a modified boyled chamber using SDF-1 as chemotactant. Treatment with DEP reduced migratory capacity of EPC to 55.9 ± 5.4% (n = 6, p < 0.005). ApoE-/- mice on high-cholesterol diet were intranasally injected with DEP for 6 days (5 days/week, 2 μg/application) or PBS. Application of DEP reduced the number of DilDL/lectin positive EPC to 75.6 ± 6.3% (n = 6, p < 0.005) and reduced migratory capacity to 58.5 ± 6.84% (n = 6, p < 0.005). Atherosclerotic plaque area was quantified by histomorphometric analysis of cryostat sections of the aortic arch. In mice treated with DEP, atherosclerosis was significantly increased to 157.74 ± 16.09% (n = 6, p < 0.05). In vivo neangiogenesis was assessed with subcutaneously implanted discs quantifying the area of the disc invested by fibrovascular growth. In mice treated with DEP, neangiogenesis was reduced to 97.3 ± 0.9% of control (p < 0.0001).

Conclusion: Intranasal instillation of diesel exhaust particles reduced the number and function of endothelial progenitor cells in C57Bl/6 and ApoE-/- mice. This finding was confirmed in cultured human EPC. In ApoE-/- mice, the reduction in EPC was associated with a reduction in neoangiogenesis and an increase of atherosclerotic lesion formation.

MicroRNA-33 deficiency reduces atherosclerotic plaque progression in apoE knockout mice

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Purpose: Despite the rapid progression of medicine in recent years, cardiovascular disease remains one of the major causes of death all over the world. It is known that atherosclerosis is responsible for those cardiovascular diseases and serum cholesterol level has close relation with atherosclerosis progression. Although lowering LDL cholesterol (LDL-C) with statin is epoch-making treatment for preventing and reducing atherosclerosis, HDL cholesterol (HDL-C) raising therapy is still not established. Recently, we and other groups reported that microRNA-33 reduced serum HDL-C by targeting ATP-binding cassette transporter A1 (ABCA1). In fact, microRNA-33 deficient mice which we generated showed 22-39% increase in serum HDL-C compared to control. In this study, we assessed the effect of microRNA-33 on atherosclerosis formation with microRNA-33 and apoE double knockout mice.

Methods and Results: We generated microRNA-33 and apoE double knockout mice (mice treated microRNA-33 deficiency alone by 3.3% of control, p < 0.0001). ApoE-/- mice on high-cholesterol diet were intranasally injected with DEP for 6 days (5 days/week, 2 μg/application) or PBS. Application of DEP reduced the number of DilDL/lectin positive EPC to 75.6 ± 6.3% (n = 6, p < 0.005). Reduced migratory capacity of EPC to 55.9 ± 5.4% (n = 6, p < 0.005). ApoE-/- mice on high-cholesterol diet were intranasally injected with DEP for 6 days (5 days/week, 2 μg/application) or PBS. Application of DEP reduced the number of DilDL/lectin positive EPC to 75.6 ± 6.3% (n = 6, p < 0.005). Reduced migratory capacity of EPC to 55.9 ± 5.4% (n = 6, p < 0.005). Atherosclerotic plaque area was quantified by histomorphometric analysis of cryostat sections of the aortic arch. In mice treated with DEP, atherosclerosis was significantly increased to 157.74 ± 16.09% (n = 6, p < 0.05). In vivo neangiogenesis was assessed with subcutaneously implanted discs quantifying the area of the disc invested by fibrovascular growth. In mice treated with DEP, neangiogenesis was reduced to 97.3 ± 0.9% of control (p < 0.0001).

Conclusion: Intranasal instillation of diesel exhaust particles reduced the number and function of endothelial progenitor cells in C57Bl/6 and ApoE-/- mice. This finding was confirmed in cultured human EPC. In ApoE-/- mice, the reduction in EPC was associated with a reduction in neoangiogenesis and an increase of atherosclerotic lesion formation.

ADVANCES IN THE TREATMENT OF ATHEROSCLEROSIS

The effects of direct thrombin or factor Xa inhibition with dabigatran or rivaroxaban on plaque formation and endothelial function in apolipoprotein E-deficient mice

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Purpose: Recently developed oral anticoagulants directly inhibit thrombin (dabi- 
gatan) or factor Xa (rivaroxaban) by blocking coagulation factors IIa and Xa, respec- tively. The aim of this study was to evaluate the effect of dabigatran and rivaroxaban on atherosclerotic lesion formation in apoE-/- mice, and to compare the effects of dabigatran and rivaroxaban on endothelial function, vascular inflammatory, and oxidative stress in hypercholesterolemic atherosclerosis. Interference with the coagulation system might provide a therapeutic means to modify atherosclerotic disease progression.

Results: Treatment with dabigatan attenuated atherosclerotic plaque forma- tion (ApoeE-/- mice: Dabi: 16.1 ± 3.8% of ApoE-/- control, p < 0.001; decreased collagen content (ApoeE-/- mice: Dabi: 43.0 ± 0.9% of ApoE-/- control, p < 0.001) and quanti- ty (ApoeE-/- mice: Dabi: 50.7 ± 4.1% of ApoE-/- control, p < 0.001) in parallel to an improvement of endothelial function (ApoeE-/- mice: Dabi: 42.6 ± 2.7% vs. ApoE-/- mice: 62.9 ± 3.3% of phenylephrine-induced contraction, p < 0.001) at 100 μM carbachol. Treatment with rivaroxaban did not influence endothelial func- tion, atherosclerotic plaque formation, collagen content or ROS-production.

Conclusion: Direct thrombin but not factor Xa inhibition improved endothelial function and reduced atherosclerotic lesion size, vascular collagen content and oxidative stress in hypercholesterolemic atherosclerosis. Interference with the coagulation system might provide a therapeutic means to modify atherosclerotic disease progression.

Interleukin-1 receptor antagonist in bone marrow-derived cells contributed suppression of arterial inflammation and reduced neointimal formation after injury

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Background: Interleukin (IL)-1 is a proinflammatory cytokine that plays an im- portant role in inflammation. The IL-1 receptor antagonist (IL-1Ra) negatively regulates the receptor and plays an anti-inflammatory role in inflammation. We have previously demonstrated that IL-1Ra-deficient (IL-1Ra-/-) mice promoted neointimal formation after injury. IL-1Ra is expressed on bone marrow (BM)-derived cells as well as endothelial cells. However, the importance of IL-1Ra in BM-derived cells remains unknown.

Aims: The aim of this study is to elucidate the role of IL-1Ra in BM-derived cells in the development of neointimal formation after injury.

Methods: To determine the contribution of IL-1Ra in BM-derived cells for neoin- 
timal formation, we performed BM cell transplantation (BMT), injecting BM from wild-type (WT) or IL-1Ra-/- mice (BMT(WT→KO) (n=12) and BMT(KO→WT) (n=16)). At 4 weeks after BMT, vascular injury was performed by placing a nonocclusive cuff around the femoral artery. Morphometric and histological analyses were performed 2 weeks after injury. Furthermore, we performed immunocytochemical staining for IL-1Ra expression using peritoneal macrophages from WT or IL-1Ra-/- mice.

Results: No significant differences in systolic arterial pressure and plasma lipids were observed between two groups. The neointimal formation in BMT(WT→KO) mice was significantly reduced compared with BMT(KO→WT) mice (0.49-fold, p < 0.001). Immunostaining revealed that both α-SMA positive area (97.3 ± 5.5% vs. 69.5 ± 15.0% in control mice) and CD31 positive area (endothelialization) (99.3 ± 0.8 vs. 68.9 ± 13.3%, p < 0.001) in the injured arteries of BMT(WT→KO) mice were significantly increased those of BMT(KO→WT) mice. By contrast, Mac-3 (Macrophage) area was significantly decreased in BMT(WT→KO) mice compared with BMT(KO→WT) mice (0.1 ± 0.2 vs. 13.5 ± 5.3%, p < 0.001). We next checked functions of macrophages. After lipopolysaccharide stimulation, IL-1Ra-/- macrophages produced much higher levels of TNFα in culture supernatants compared to those from WT mice (1.52- 

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Bortezomib treatment of LDL receptor deficient mice with advanced atherosclerotic lesions influences plaque composition

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Purpose: Besides degradation of the majority of intracellular proteins the ubiquitin-proteasome-system is involved in the regulation of numerous cellular processes. Recent studies have shown that low-dose and non-toxic proteasome inhibition (PI) has anti-inflammatory, anti-proliferative and anti-oxidative effects on vascular cells in vitro. Moreover, low-dose inhibition of the proteasome delays the formation of early atherosclerotic lesions in LDLR-KO mice. The purpose of the current study was to investigate the effect of low-dose proteasome inhibition on advanced atherosclerotic lesions in LDLR-KO mice.

Methods and results: Male LDLR-KO mice, 10 weeks of age, were fed a Western diet for 8 weeks to induce atherosclerosis. Subsequently, mice were randomly divided into two groups (n=10 per group). One group was treated with 165 mg/kg/day ticagrelor via chow resulting that treatment with this dose induced an increase in bleeding time from 1.0 ± 0.6 to 25.2 ± 3.2 min; p=0.004) and from 17.7 ± 5.4 to 3.3 ± 1.1 % of total lumen at the bortezomib treatment (plaque area aorta in % 16.9 ± 1.2 vs. 17.5 ± 0.9; plaque volume truncc phaschalephalocin 0.24 ± 0.03 % vs. 0.22 ± 0.04 mm³). Inflammatory markers (M1-C.1.0.4.6, cholesterol) and triglyceride levels were not significantly different in all groups. However, plaque composition was substantially influenced by bortezomib treatment. Histological analysis of plaque composition (Movat-Pentachrome and alizarin red staining, smooth muscle actin and Mac-2 immunohistochemistry) revealed a significant enlargement of the necrotic core area in bortezomib-treated mice compared to control.

Conclusion: Bortezomib treatment of LDLR-KO mice with advanced atherosclerotic lesions does not alter atherosclerotic lesion burden. However, plaque composition is influenced towards an unstable plaque phenotype. Taking recent studies on favorable effects of PI in early atherogenesis into consideration, results suggest stage-dependent effects of PI in atherosclerosis.

Inhibition of the adenosine diphosphate receptor P2Y12 reduces atherosclerotic plaque size in hypercholesterolemic ApoE-/- mice

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Background and Objective: Platelet function has been shown to contribute to atherosclerosis. In the phase III PLATO trial comparing the adenosine diphosphate receptor blocker P2Y12 antagonists ticagrelor and clopidogrel in patients with acute coronary syndrome, a reduction of myocardial infarction and death was observed particularly late in the up to one year study period. Here, we tested the effects of ticagrelor on vascular remodeling and atherosclerosis in an established mouse model.

Methods and Results: ApoE-/- mice (n=40) were fed a high cholesterol diet for 8 weeks to induce atherosclerosis. Pilot bortezomib treatment showed that treatment with 165 mg/kg/day ticagrelor via chow resulted in a ticagrelor plasma concentration of 3.0±0.5 μM, a concentration known to induce >95% platelet inhibition. Treatment with this dose induced an increase in bleeding time from 1.0±0.6 to 25.2±3.2 min; p=0.004) and from 17.7±5.4 to 3.3±1.1% of total lumen at the bortezomib treatment (plaque area aorta in % 16.9±1.2 vs. 17.5±0.9; plaque volume truncc phaschalephalocin 0.24±0.03 % vs. 0.22±0.04 mm³). Inflammatory markers (M1-C.1.0.4.6, cholesterol) and triglyceride levels were not significantly different in all groups. However, plaque composition was substantially influenced by bortezomib treatment. Histological analysis of plaque composition (Movat-Pentachrome and alizarin red staining, smooth muscle actin and Mac-2 immunohistochemistry) revealed a significant enlargement of the necrotic core area in bortezomib-treated mice compared to control.

Conclusion: Ticagrelor reduced atherosclerotic plaque size in hypercholesterolemic atherosclerosis. These data identify a beneficial effect of P2Y12 receptor inhibition on vascular remodeling in mice. Further studies need to show whether these mechanisms contribute to the reported effects of ticagrelor on outcomes in clinical studies.
Maximal exercise capacity is significantly decreased in hypertensive men with erectile dysfunction. Testosterone deficiency has been associated with a higher mortality risk due to cardiovascular (CV) disease in men with erectile dysfunction (ED), however, it is still unclear if vitamin D status influences therapeutic blood pressure reduction. Renal sympathetic denervation (RSD) reduces blood pressure in patients with therapy-resistant hypertension. We hypothesized that vitamin D status might influence blood pressure response to RSD.

Methods: 197 asymptomatic non diabetic hypertensive ED patients (56±8 years) underwent maximal EST under the standard Bruce protocol. Blood specimens were analyzed for CRP and TT levels. Results: In univariate analysis, maximal exercise capacity was negatively correlated with TT (r=-0.225, P<0.001). Stepwise regression analysis revealed that age, CRP (b=-0.171, P<0.001), mean arterial pressure (MAP, b=0.001, P<0.001), and MAP x age (b=0.001, P=0.001) are independent predictors of exercise capacity.

Conclusion: Baseline vitamin D concentration showed a significant positive correlation related to age-adjusted maximum workload (figure) as compared with the subgroups of high CRP/high TT, low CRP/low TT and low CRP/high TT (overall P<0.001).

Vitamin D deficiency is associated with decreased systolic blood pressure reduction after renal sympathetic denervation. Testosterone deficiency has been associated with a higher mortality risk due to cardiovascular (CV) disease in men with erectile dysfunction (ED), however, it is still unclear if vitamin D status influences therapeutic blood pressure reduction. Renal sympathetic denervation (RSD) reduces blood pressure in patients with therapy-resistant hypertension. We hypothesized that vitamin D status might influence blood pressure response to RSD.

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Insulin resistance influences 24-hour heart rate and blood pressure variabilities and cardiovascular autonomic modulation in normotensive healthy adults. J.E. Ochoa1, J.K. Balparda1, M.M. Correa1, A.M. Valencia1, M. Alvarez1, J.A. Gallo1, G.B. D. Aristizabal2, G. Parail1. 1University of Milan-Bicocca, Ospedale San Luca, Istituto Auxologico Italiano, Milan, Italy; 2Centro Clinico y de Investigación, SICOR, Medellin, Colombia; 3 Corporación para Investigaciones Medicas, Medellin, Colombia; 4Depto. Cardiovascular, Ospedale San Luca, Istituto Auxologico Italiano, Milan, Italy.

Aim: To explore the association of insulin resistance (IR) with cardiovascular (CV) autonomic modulation, heart rate (HR) and blood pressure (BP) variabilities (V) over the 24 h.

Methods: 90 normotensive (Systolic(S) BP 107.1±9.3; diastolic(D) BP 69.6±7.7 mmHg), non-obese, healthy subjects (mean age 48±10 years, 0.5 M) were studied. IR was assessed with HOMA index, and subjects classified into HOMA-IR tertiles. Ambulatory BP monitoring was performed. Mean HR, SBP and DBP were averaged for the day, night and 24h and the respective day-to-night dipping calculated. BPV was assessed for SBP and DBP as 24h standard deviation (SD), weighted 24h SD (wSD), daytime and nighttime SD. CV autonomic modulation was assessed by computer analysis of 10 min beat-to-beat BP and ECG recordings in resting supine. Cardiac baroreflex sensitivity (BRS) was estimated by sequence method; and total variance, low- (LF) and high-frequency (HF) spectral components of HR variability (HRV) were assessed by autoregressive analysis. LF/HF ratio was calculated.

Results: After multiple regression adjusting for age, sex and BMI, IR was significantly associated with increased HR and SBP (during day, night and 24h), with increased SBP (day BP SBD and SBP wSD) and with reduced dipping of HR. IR was also associated with reduced BRs and parasympathetic indices of CV modulation (HF power, total power) and an increased sympathetic component of HRV (LF/HF ratio). (Table).

Conclusion: IR may importantly contribute to regulation of HR and BP over the 24h, possibly through its effects on BRS and CV autonomic modulation.
occurred. The difference in hypogonadism (TT >3.4 ng/ml) prevalence between patients with and those without CV events was significant (35% vs. 19%; P <0.01). Kaplan–Meier survival analysis by tertiles of TT levels revealed that the subjects with the lowest TT tertile were more likely to develop CV events than those with the highest tertile (P=0.012 by log-rank test, figure). A Cox proportional-hazard model showed that hypertensive patients with the lowest tertile of serum TT (<4.0 ng/ml) had an approximately 2.5-fold higher CV event risk compared to those with the highest TT tertile after adjustment for age, blood pressure, metabolic profile, antihypertensive therapy and statins (multivariate-adjusted hazard ratio: 2.6; 95% CI, 1.01–8.38, P=0.03). Multivariate analysis did not show any significant association of C-reactive protein with CV events.

Conclusions: Low serum testosterone concentration is associated with CV events in middle-aged hypertensive patients with ED, independent of risk factors and low grade inflammation.

TOBACCO: FROM EARLY DAMAGE TO LATE IMPACT

Cardiovascular risk profile and impact of adolescent smoking

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Background: Early exposure to tobacco smoke is associated with various adverse health outcomes in children and adolescents, however little is known on the impact of tobacco smoke exposure on cardiovascular health (CVH) in adolescence, although tobacco smoke is considered to be highly atherogenic in adults and remains prevalent in childhood and adolescence. We investigated the cardiovascular risk profile and the association between adolescent smoking and carotid artery intima media thickness (CIMT) in the SAPALDIA Youth Study.

Methods: The SAPALDIA Youth Study is a nested study in the Swiss SAPALDIA cohort, including 261 offspring aged 8–20 yrs. 283 of these offspring underwent a clinical examination following a standardized protocol: anthropometry, blood pressure, ultrasound CIMT assessment and blood draw for cardiovascular biomarkers. Offspring and parents gave information on early life, health lifestyle of the child. Smoking status and duration was reported by offspring and validated by Cotinine testing. Description of participant’s characteristics and CVH risk profile and multivariate regression analyses on the impact of active smoking and smoking duration the per subject averages of the common carotid’s IMT’s (CCA IMT) was determined. All subjects underwent blood pressure measurement, echocardiography and vascular compliance of large (C1) and small (C2) arteries using an HDI Pulse Wave™ CR-2000 Research Cardiovascular Profiling Instrument. Results: There were no significant differences between smokers and non-smokers in age (54.2±7.7 yrs vs 55.3±8.5 yrs, p=0.3992), BMI (27.1±4.2 kg/m² vs 27.6±3.9 kg/m², p=0.1608), SBP (146.0±8.0 mmHg vs 144.1±7.9 mmHg, p=0.2273) and fasting glucose levels (9.8±3.2 mmol/l vs 9.5±3.1 mmol/l, p=0.2629). Elasticity of the large artery (C1) in smokers group was 10.6±3.8 mmHg/mmHg vs 8.9±2.4 mmHg/mmHg (p=0.0336). Total cholesterol (5.6±1.5 mmol/l vs 5.1±1.3 mmol/l, p=0.0001) and LDL-cholesterol (3.8±1.3 mmol/l vs 2.9±1.1 mmol/l, p=0.0001) values were highest in smokers group compared to non-smokers. There were no significant differences between smokers and non-smokers in HDL-cholesterol (1.0±0.3 mmol/l vs 1.0±0.3 mmol/l, p=0.5973), triglycerides (1.8±0.8 mmol/l vs 1.8±0.9 mmol/l, p=0.2246) and fasting glucose levels (9.8±3.2 mmol/l vs 10.1±0.9 mmol/l, p=0.0249). Coronary artery disease was more common in smokers compared to non-smokers (p=0.0141). Myocardial infarction was more common amongst smokers compared to non-smokers (p=0.0345).

Conclusion: Smoking negatively affects on elasticity of the small artery wall (C2) in men in middle age.

The acute effect of passive smoking on platelet activity in healthy volunteers

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Objective: Mean platelet volume (MPV) is one of the well established indicators of platelet activation that is increased in acute thrombotic events. Carbon monoxide is suspected to play a major role in cigarette smoke-induced cardiovascular diseases. Lactate accumulation occurs when the supply of oxygen to the cells is limited. We aimed to determine whether MPV levels are elevated after passive smoking in healthy volunteers. In addition, we tried to find out if carboxyhemoglobin, lactate and MPV levels are correlated to each other or not after passive smoking.

Methods: 55 healthy non-smoker volunteers (male 30, mean age: 26±5 years) were prospectively enrolled to the study. Systolic and diastolic blood pressure, respiratory rate and heart rate were obtained and blood samples for measurements of COHb, lactate and MPV levels were taken at baseline and after spending one an hour in the smoking room in all the subjects.

Results: There was no significant difference in heart rate, respiratory rate and both systolic and diastolic blood pressure after acute exposure. COHb, lactate and MPV levels of the subjects were significantly higher after passing a smoking area of 0.8±0.3 vs. % 1.2±0.4; p<0.001, 0.7±0.2 vs. 2.2±0.9; p<0.001, 7.8±0.4 fl vs. 8.5±0.6 fl; p<0.001, respectively). A significant correlation were determined between MPV and COHb values (r= 0.55, p<0.001) and between lactate levels (r= 0.65, p<0.001) after smoking. There was also a remarkable relation between COHb and lactate levels(r=0.78, p=0.0001).

Conclusion: Our results suggested that passive smoking has acute effect on platelet activity demonstrating by MPV levels that is notably correlated with COHb and lactate levels. Prolonged exposure to passive smoking could increase the risk of acute thrombotic events in healthy population.
Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: comparison with the effects of regular cigarettes

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Purpose: The addictive properties and devastating consequences of cigarette smoke on human health, including cardiac function, are well known. In recent years, the electronic cigarette (e-cigarette), a battery-powered nicotine-delivery device, has been marketed as a safer habit. Despite the global debate about its use, no studies have examined the device’s consequences on cardiac function. The purpose of our study was to evaluate the acute effects of using the e-cigarette on left ventricular myocardial function and to compare them with the effects of regular cigarettes.

Methods: Participants were 42 healthy volunteers (age 25-45 years): ex-smokers who were using the e-cigarette (group E, n=22), and regular cigarette smokers (group SM, n=20). A complete echocardiographic exam was performed in both groups after 3-hours abstention from alcohol, coffee and e-cigarette use or smoking (eCIG-1 and SM-1 respectively). A repeat echocardiogram was performed in eCIG subjects after using an e-cigarette with nicotine concentration of 11 mg/ml for 7 minutes (eCIG-2). In smokers, the repeat echocardiogram was done after smoking one cigarette (SM 51.7±mmHg, p=0.00) and 24-h diastolic BP (85±10 mmHg, p=0.00). Echocardiographic data were compared using the Student’s t-test for the paired data and the Mann-Whitney U test for the independent data.

Results: The two groups had similar characteristics, baseline echocardiographic and haemodynamic parameters. Subjects in the eCIG group had quit smoking for 93±65 days and were using an e-cigarette for 95±64 days; however, they had significantly higher total smoking exposure, with a Brinkman index (number of daily cigarettes x smoking years) of 533±270 compared to 369±150 in SM (p = 0.019). Using the e-cigarette for 7 minutes lead to no significant alterations in any echocardiographic parameters, except for a slight rise in MVA velocity (p = 0.047). On the contrary, a significant decrease in Em velocity (p = 0.005) and EmAm ratio (p = 0.001), and an increase in IRVT (p = 0.032) and MPI (p=0.01) were found in SM-2 compared to baseline.

Conclusions: Although regular smoking leads to an acute impairment of left ventricular function, the use of e-cigarette for inhaling nicotine-containing liquid exerts a useful method for smoking cessation.

Clinical implications of smoking relapse after acute ischemic stroke

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Cigarette smoking is a major independent risk factor for ischemic stroke, while healthcare providers should strongly advise every patient with stroke who has smoked in the past year to quit. However, smoking relapse is frequent, even after an admission for a major acute cardiovascular event.

The aim of the present study was to evaluate the cigarette smoking relapse rate among smokers who had become abstinent during admission for acute ischemic stroke. The association between smoking relapse and mortality was also analyzed.

A cohort of 921 consecutive active smokers who had interrupted smoking after admission for acute ischemic stroke (584 men and 337 women, mean age 67±16 years) was followed up for 12 months after the index admission. All patients received a brief in-hospital smoking cessation advice. During follow-up, patients were classified as current smokers (SM, n=321), former smokers (FS, n=290), or non-smokers (NS, n=211) based on their smoking status at follow-up.

Conclusions: Smoking relapse after acute ischemic stroke is associated with increased all-cause mortality, while post-discharge rehabilitation is effective in reducing the likelihood of smoke resumption.
between qualifying ECG and coronary angiography for PCI in STEMI patients. Not following the ESC guidelines was associated with a three-fold increase in hospital mortality. A similar trend was observed for lytic-treated patients. When meeting the ESC guidelines for PCI seems unlikely, timely administration of fibrinolysis should be considered.

### In-hospital complications in relation with use and timing of prehospital antithrombotic medications in STEMI patients. The FAST-MI 2010 registry

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**Background:** France has a highly developed MICU system with emergency physicians on board the ambulances (SAMU), who have the ability to administer recommended medications at a very early stage of AMI.

**Aim:** To assess in-hospital outcomes in patients transported by the SAMU, in relation to the pre-hospital administration of antithrombotic medications and time from symptom onset to first call.

**Methods:** FAST-MI 2010 is a nationwide French registry that included 4169 patients with AMI at the end of 2010 in 213 centres. Of those, 2364 had STEMI, of whom 1868 (79%) were transported by the SAMU and 1836 had the time from symptom onset to first call recorded (78%).

**Results:** Time from onset to first call was ≤ 60 minutes in 923 pts (50%), 1172 pts (64%) received an antplatelet agent, with 1010 receiving dual oral antplatelet therapy (DAPT, 55%) in the ambulance. In addition, 27% received enoxaparin and 29% received unfractionated heparin. Patients calling within 60 min of onset had similar prescription rates of antithrombotic therapy (DAPT, 71% vs 67%, 48% vs 48%, 30% vs 24% for any antplatelet therapy, DAPT, and enoxaparin, respectively. Younger age, male sex, short time from onset to call, absence of diabetes and lower GRACE score were independent predictors of the use of pre-hospital antithrombotic medications. Fibrinolytic treatment was administered prehospital in 11% (5% when onset to call ≤ 60 min vs 7% when onset to call > 60 min). When time from onset to call was ≤ 60 min, in-hospital mortality was lower with prehospital antithrombotic therapy: any antplatelet 2.3% vs 5.9% (P=0.001), DAPT 1.8% vs 6.0% (P<0.001), any heparin 1.9% vs 5.7% (P=0.002), prehospital tPA 2.9 vs 3.4% (P=NS). In contrast, prehospital antithrombotic therapy was not associated with lower in-hospital mortality when time from symptom onset to call was > 60 minutes: 2.7 vs 2.8%, 2.5 vs 3.0%, 2.4 vs 3.0%, 4.8 vs 2.6% respectively (all P=NS).

**Conclusion:** The prehospital administration of antithrombotic therapy is strongly linked with lower in-hospital mortality when time from symptom onset to call was ≤ 60 minutes in 923 pts (50%), 1172 pts (64%) received an antplatelet agent, with 1010 receiving dual oral antplatelet therapy (DAPT, 55%) in the ambulance. In addition, 27% received enoxaparin and 29% received unfractionated heparin. Patients calling within 60 min of onset had similar prescription rates of antithrombotic therapy (DAPT, 71% vs 67%, 48% vs 48%, 30% vs 24% for any antplatelet therapy, DAPT, and enoxaparin, respectively.

### Comparative validation of three contemporary bleeding risk scores in acute coronary syndromes


**Background:** Hemorrhagic complications are strongly linked with subsequent adverse outcomes in acute coronary syndrome (ACS) patients. Various risk scores (RS) are available to estimate the bleeding risk in these patients.

**Aims:** To compare the predictive accuracy of the three contemporary bleeding risk scores in ACS.

**Methods:** We studied 4500 consecutive patients with ACS. For each patient, the ACTION, CRUSADE, and Mehran et al bleeding risk were calculated. We assessed their performance either for the prediction of their own major bleeding incidence or to predict the TIMI serious (major and minor) bleeding (masocides in the overall population, in patients with non-ST-elevation ACS (NSTEACS) and in those with ST-elevation myocardial infarction (STEMI) patients). Calibration (Hosmer-Lemeshow test) and discrimination (c-statistic) for the three RS were computed and compared. We used the concept of net reclassification improvement (NRI) to compare the incremental prognostic value of using a particular RS over the remaining scores in predicting the TIMI serious bleeding.

**Results:** The best predictive accuracy was obtained by the CRUSADE score either for the prediction of its own major bleeding events (c-statistic=0.80, 0.791, and 0.81 for the entire sample, for STEMI, and for NSTEACS patients, respectively) or to predict the TIMI serious bleed occurrence (c-statistic=0.741, 0.738, and 0.745 for the whole population, for STEMI and NSTEACS patients, respectively. The lowest bleeding rates observed in patients classified as low risk corresponded to the CRUSADE RS. All scores performed modestly in patients who did not undergo coronary angiography (a value of -0.30). The CRUSADE score was significantly superior to the ACTION model in predicting the TIMI serious bleeding occurrence in terms of NRI overall and by ACS subgroups (p<0.05). Overall, the CRUSADE RS exhibited better calibration and discrimination compared to the ACTION and Mehran et al scores (Hosmer-Lemeshow p-values of 0.26, 0.13, and 0.07, respectively).

**Conclusion:** The CRUSADE score represents, among the more contemporary bleeding RS, the most accurate and reliable quantitative clinical tool in STEACS and STEMI patients. We encourage the utilization of the CRUSADE index for bleeding risk stratification purposes in daily clinical practice and in ACS outcome studies. The performance of the three more contemporary bleeding RS is modest in those patients who received conservative management.

### Switch and non switch in P2Y12 inhibition: the real life use of clopidogrel and prasugrel in patients with acute myocardial infarction. Insights from the FAST MI 2010 registry

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**Background:** In patients with AMI, the choice between clopidogrel and prasugrel requires information that is not always available at the early phase, such as indication for PCI or assessment of bleeding and thrombosis risk. When initial clopidogrel treatment seems sub-optimal, switching to prasugrel seems attractive, but is not yet recommended. We assessed baseline characteristics and in-hospital outcomes in prasugrel-treated patients, according to the initial use of clopidogrel before prasugrel initiation.

**Methods:** FAST-MI 2010 is a nationwide French registry that included 4169 patients with AMI in 213 centres. In total, 4115 received thienopyridines, of whom 1259 received prasugrel (31%). Among these, 391 received "de novo" prasugrel (G1), 807 (64%) were treated with clopidogrel first and then switched to prasugrel (G2), of whom 11% had a 60mg loading dose of prasugrel. We excluded 61 pts who received prasugrel initially and subsequently switched to clopidogrel. We compared baseline characteristics, bleeding and ischemic complications between G1 and G2, and then used propensity-score matching (propensity to be treated with prasugrel) to compare outcomes in 2 cohorts with similar baseline characteristics.

**Results:** Age and sex were similar in G1 and G2: more G2 pts had a history of AMI (13% vs 8%, P<0.01), PCI (14% vs 9.5%, P<0.02), underwent PCI during the hospital stay (96% vs 83%, P<0.047) or received lytic treatment for STEMI (21% vs 5%, P<0.001). With the exception of major bleeding, which was less frequent in G2 (0% vs 1.0%, P=0.004), none of the other complications differed significantly (Table). The 2 propensity-score matched cohorts (316 patients each) had comparable baseline characteristics, bleeding and ischemic complications between G1 and G2, and vs 94% (prasugrel only) followed the recommended indication for prasugrel use; none of the complications differed significantly (switch vs no switch): any bleeding (4.1 vs 6.0%, major bleeding (0.5 vs 0.8%), stroke (0.3 vs 0.6%), reinfarction (1.3 vs 0.6%), in-hospital death (0.3 vs 0.3%).

**Conclusion:** In this real-world registry, a high proportion of patients treated with prasugrel were switched from clopidogrel therapy (64%). There was no evidence of excess risk of bleeding or in-hospital complications in the patients who were switched, compared with those who received prasugrel treatment only. Further randomized studies are mandatory to determine the safety and efficacy of this strategy.
Impact of immediate multivessel intervention on patients with multivessel disease undergoing primary PCI for cardiogenic shock

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Background: There is still uncertainty about the optimal strategy in patients with multivessel disease undergoing primary PCI for cardiogenic shock. Therefore we compared outcome of patients with culprit lesion only PCI and immediate multivessel PCI for cardiogenic shock in real life.

Methods: We used the data of the prospective ALKK-PCI registry and included patients with primary PCI for cardiogenic shock with 2-3 vessel disease. We excluded patients with left main PCI and patients with prior coronary artery bypass surgery.

Results: Between 2008 and 2010 a total of 742 patients 2-3 vessel disease were treated with primary PCI for cardiogenic shock. Of these 176 (24%) received immediate multivessel PCI while in the remaining only the culprit vessel was treated. Baseline characteristics, procedural features and outcomes are given in the table.

Conclusion: Immediate multivessel PCI for cardiogenic shock used in about 25% of patients is associated with similar success rates as culprit lesion PCI, but with a higher mortality. Therefore a randomized trial seems warranted to evaluate the optimal interventional strategy in these patients.

BIOMARKERS AND CLINICAL SCORES IN PREDICTING THE OUTCOME OF ACUTE CORONARY SYNDROMES

Incidence, clinical characteristics, management and outcomes of patients with type-II myocardial infarction: results from the Acute Coronary Syndrome Israeli Surveys (ACISIS) 2008-2010

S. Fuchs1, G. Herscovici1, R. Korenfeld1, S. Matezky2, G.Y. Stein1
1Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel; 2Sheba Medical Center, Heart Institute, Ramat Gan, Israel

Background: Although almost 5 years have elapsed since a consensus document classified type-II myocardial infarction (MI) as MI secondary to ischemia due to either increased oxygen demand or decreased supply, little is known regarding patient characteristics, causes, management and outcomes.

Methods: We performed a comparative analysis between patients with type-I and type-II MI who participated in two national Acute Coronary Syndrome Israeli Surveys (ACISIS) in the years 2008 and 2010.

Results: The survey included 2810 consecutive patients with acute MI of whom 127 (4.5%) had type-II MI. The main causes for type-II MI were: anemia (36%), sepsis (28%), arrhythmia (20%) and post-surgical procedures (16%). Compared to type-I MI, patients with type-II MI tended to be older (75±6 vs 63.8±13 years, p<0.001), more frequently females (43.3% vs. 22.3%, p<0.0001) and had more comorbidities (p<0.001). Patients with type-II MI were less likely to have STEMI (19.7% vs. 52.5%, p<0.0001) and more often had atypical clinical presentation (Table 1). Coronary angiography was not as frequently performed in patients with type-II MI (36% vs. 88%, p<0.0001) including those who presented with STEMI (68% vs. 94%, p<0.0001). Patients with type-II MI had substantially higher 30-day mortality rates (13.6% vs. 4.9%, p<0.0001).

Table 1: Presenting symptoms of patients with type-I and type-II MI (numbers indicate percent of patients in each group)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I</th>
<th>Type II</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical angina</td>
<td>84.5</td>
<td>54.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7.5</td>
<td>20.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>25.5</td>
<td>59.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Syncope</td>
<td>4.1</td>
<td>4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4.7</td>
<td>14.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.9</td>
<td>11.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other</td>
<td>11.7</td>
<td>26</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: Patients with type-II compared to those with type-I MI are older, have more comorbidities and undergo less frequently coronary angiography. These distinctions may explain, at least in part, their higher early mortality rates despite having lower rates of STEMI.

Diagnostic and prognostic value of copeptin in patients with acute chest pain and diabetes

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Purpose: Patients with Diabetes are at high risk for acute myocardial infarction (AMI) therefore need a careful diagnostic evaluation and risk stratification.
Copeptin is released in case of relevant endogenous stress such as AMI. We evaluated diagnostic and prognostic value of copeptin in combination of high sensitive cardiac Troponin I (hs-cTnI) in diabetic patients.

Methods: In a prospective observational international multicenter study, we enrolled 1837 consecutive patients presenting to the emergency department with symptoms suggestive of AMI. Final diagnoses were adjudicated by two independent cardiologists using all available information including hs-cTnI (Roche). Levels of copeptin at presentation were measured in a blinded fashion.

Results: 322 patients had diabetes. AMI was the adjudicated final diagnosis in 11 (32%). Copeptin was significantly (p < 0.001) elevated in patient with AMI (median 21.7, SD 33.9) compared to patients without AMI (median 8.0, SD 33.9). Diagnostic accuracy as quantified by the area under the curve showed that the combination of copeptin with hs-cTnI (AUC 0.91, CI 95% 0.88-0.94) was comparable to hs-cTnI (AUC 0.91, CI 95% 0.88-0.94) was comparable to hs-cTnI (AUC 0.91, CI 95% 0.88-0.94). Combination of biomarkers with cutoff of 5pmol/L for Copeptin and 14ng/L for hs-cTnI we calculated a sensitivity of 97% vs. 91% in hs-cTnI tested alone (p=0.02). Negative predictive value was 97% (CI 95% 93-99%) vs 94% (CI 95% 90-97%). Kaplan-meier analysis showed that those who had an elevation of both biomarker above the cutoff 29 (23%) died while no or only one of both biomarker was elevated then less died than 4%.

BIOMARKERS AND CLINICAL SCORES IN PREDICTING THE OUTCOME OF ACUTE CORONARY SYNDROMES

Prospective evaluation of the safety of the 2011 ESC guidelines for rapid rule-out of NSTEMI using a novel high sensitive assay for troponin I

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Purpose: High-sensitive cardiac troponin (hs-cTn) assays have been shown to significantly improve the early diagnosis of acute myocardial infarction. The novel 2011 ESC guidelines for the management of acute coronary syndromes in patients with persistent ST-segment elevation contain for the first time a new fast track rule-out protocol including hs-cTn. We intended to verify the safety of this fast track protocol in our prospective study setting.

Methods: In our ongoing prospective observational international multicenter study 1127 consecutive patients who presented with symptoms suggestive of acute myocardial infarction and absence of significant ST-elevations in the ECG were included. The final diagnosis was adjudicated by two independent cardiologists using all available informations including high sensitive cardiac Troponin T (Roche). We examined the diagnostic accuracy of the novel ESC rapid rule-out protocol using the pre-commercial Siemens high sensitive cardiac troponin I assay (hs-cTnI, 99th percentile defined as 9.0 ng/L) performed on blood samples obtained in the emergency department at presentation and after 3 hours according to the novel fast track protocol in our prospective study setting.

Results: Of all late presenters (n=165), we expressed an OBCS (as a percent), where the numerator was the number of times a care process (aspirin, thienopyridine, β-blocker, statin, ACE inhibitor and referral for cardiac rehabilitation on discharge) was delivered and the denominator was the sum of all opportunities to give this care. Association between hospital OBCS and mortality were calculated. Lowest hospital quartile median OBCS was 88.9% (IQR 83.8-94.0%) compared with 97.3% (95.9-99.9%) in the highest quartile. Unadjusted mortality decreased with increased OBCS, 30-day mortality: lowest quartile (95%CI) 2.34% (2.09-2.59%), highest quartile 1.42% (2.13-1.61%); 6-month mortality: 8.8% (8.3-9.28%) and 6.0% (5.6-6.4%), respectively. Following adjustment for GRACE risk score variables, with a random intercept for hospitals, this relationship persisted - 30-day mortality: 2.37% (2.33-2.41%) versus 1.71% (1.69-1.74%); 6-month mortality: 8.6% (8.5-9.2%) versus 6.53% (6.6-6.8%), respectively. Hospitals in the highest quartile (39 hospital and non-ST-elevation myo-cardial infarction patients) had higher rates of referral for coronary intervention than those in the lowest quartile (47 hospitals, 1436 patients), 7.0% vs 58.2%. Hospital baseline characteristics were otherwise similar.

Conclusion: Hospital composite performance indicator adherence is associated with reduced mortality in survivors of acute Myocardial Infarction National Audit Project (MINAP) 2008 to 2009

A. D. Simms1, P. D. Baxter1, P. B. Batrin2, J. W. Wilson3, I. R. Pearson4, A. S. Hall1, C. F. Weston4, C. P. Gale1,1University of Leeds, Leeds, United Kingdom; 2Pinderfields General Hospital, Wakefield, United Kingdom; 3Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; 4Regional Cardiac Centre Morriston Hospital, Swansea, United Kingdom

Purpose: Composite performance indicators (CPI) have been proposed to assess hospital performance. We evaluate an opportunity based composite score (OBCS) in survivors of hospitalization and non-ST-elevation and non-ST-elevation myocardial infarction (AMI) using data from the Myocardial Ischaemia National Audit Project (MINAP) in 2008 and 2009.

Methods: For each hospital (n=165), we expressed an OBCS (as a percent), where the numerator was the number of times a care process (aspirin, thienopyridine, β-blocker, statin, ACE inhibitor and referral for cardiac rehabilitation on discharge) was delivered and the denominator was the sum of all opportunities to give this care. Association between hospital OBCS and mortality were calculated. Lowest hospital quartile median OBCS was 88.9% (IQR 83.8-94.0%) compared with 97.3% (95.9-99.9%) in the highest quartile. Unadjusted mortality decreased with increased OBCS, 30-day mortality: lowest quartile (95%CI) 2.34% (2.09-2.59%), highest quartile 1.42% (2.13-1.61%); 6-month mortality: 8.8% (8.3-9.28%) and 6.0% (5.6-6.4%), respectively. Following adjustment for GRACE risk score variables, with a random intercept for hospitals, this relationship persisted - 30-day mortality: 2.37% (2.33-2.41%) versus 1.71% (1.69-1.74%); 6-month mortality: 8.6% (8.5-9.2%) versus 6.53% (6.6-6.8%), respectively. Hospitals in the highest quartile (39 hospital and non-ST-elevation myo-cardial infarction patients) had higher rates of referral for coronary intervention than those in the lowest quartile (47 hospitals, 1436 patients), 7.0% vs 58.2%. Hospital baseline characteristics were otherwise similar.

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Conclusion: There is an association with improving CPI adherence and lower hospital mortality following discharge from hospital with AMI in England and Wales. The use of such measures in assessment of hospital ACS quality of care might be more appropriate than current measures. However, consideration of other variables associated with outcome, not included in the CPI, is also important in interpreting hospital performance and relation to hospital outcomes.

**1410 Development of anti-HLA donor specific antibodies after heart transplantation and rejection: importance of a new method to detect the first component of the complement cascade**

Stanford University, Palo Alto, United States of America

**Purpose:** The development of anti-HLA donor specific antibodies (DSAs) after cardiac transplantation has been linked to rejection with mixed results. Our aim is to define whether de novo DSAs are associated with the development of antibody mediated rejection (AMR) or acute cellular rejection (ACR), and to determine if complement fixing capacity of the DSAs influences this association.

**Methods:** A DSA was assayed quarterly in 145 consecutive patients following heart transplantation, between January 2006 and July 2011. Patients received induction therapy as per protocol, and a calcineurin antagonist-based regimen with tapering doses of corticosteroids during the first year after transplantation.

A new analytical method developed at our institution was used to differentiate DSAs capable of fixing the first component of the complement cascade (C1q+) from non-complement-fixing antibodies (IgG+ C1q-). The frequency of either class of DSA was compared in patients with ACR, defined as a biopsy grade 3A/2R or higher using the ISHLT classification system, and in AMR, defined as a positive biopsy staining for C4d, C3d or C4D.

**Results:** 29 patients with DSAs prior to transplantation were excluded from analysis. Among the 116 patients studied (mean age 49 years; min19 max 72; 71% males), 88 patients (76%) did not develop any DSA during follow-up, 31 patients (27%) developed IgG+ DSAs and 19 patients (16%) C1q+ (both types coexisted in 17 patients).

Overall, patients with de novo DSAs (IgG+ or C1q+) experienced rejection more frequently than patients without DSAs, both AMR (30% vs. 6%, OR 6.7, p = 0.002) and ACR (46% vs. 19%, OR 3.6, p = 0.003).

With respect to DSA subtypes, patients with IgG+ DSAs more frequently experienced AMR (23% vs. 8%, OR 3.43, p = 0.03) and ACR (50% vs. 15%, OR 4.37, p = 0.001). In contrast, patients with C1q+ DSAs had a higher odds of AMR (39% vs. 9%, OR 6.36, p = 0.001) but showed no predisposition to ACR (33% vs. 28%, OR 1.2, p = 0.73).

**Conclusion:** The development of de novo DSAs after heart transplantation was clearly associated with the presence of both AMR and ACR in our population. While IgG+ DSAs were associated with both types of rejection, C1q+ DSAs showed a strong relationship with AMR only.

These results suggest the importance of monitoring DSAs post-transplantation. Early detection of DSAs can specifically identify a subgroup of patients at risk of AMR who could potentially benefit from preventive therapies.

**1412 Impact of sildenafil treatment on pulmonary hemodynamics and outcomes in patients with severe pulmonary hypertension receiving heart transplantation**

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**Purpose:** Elevated pulmonary vascular resistance (PVR) in heart transplant candidates is associated with poorer post-transplant survival. The aim of this study is to assess the effect of perioperative sildenafil administration on pulmonary hemodynamics and clinical outcomes in patients with advanced heart failure who were considered high-risk patients for heart transplantation (HT) because of elevated PVR and transpulmonary gradient (TPG).

**Methods:** 119 consecutive patients receiving HT between 2004-2011 were included. Fifteen patients (group A) had severe pulmonary hypertension (PH) (defined as PAPm >25mmHg and/or PVR >2.5 Wood units (WU)) and/or TPG >12mmHg after vasodilator test or continuous administration of inotropes (3 drugs) compared to 104 patients (group B) without severe PH. Group A received sildenafil therapy. Pulmonary hemodynamics were evaluated before HT with and without sildenafil therapy. Right catheterization was also analyzed early after HT in patients with sildenafil therapy and late after HT without sildenafil. Post-transplant survival was compared between two groups.

**Results:** Sildenafil dosage was 79 ± 42mg/day during 163 ± 116 days before HT. After sildenafil therapy, PAPm, PVR and TPG decreased from 43.9 ± 12.5mmHg to 33.4 ± 5.8mmHg, 5.0 ± 1.1 WU to 3.0 ± 1.6 WU and 17.3 ± 3.2mmHg to 10.2 ± 4.1mmHg respectively (p < 0.01). All patients underwent successful HT. Sildenafil dosage was 140 ± 70mg/day during 43 ± 45 days after HT; there were no differences in PVR and TPG on sildenafil therapy early after HT and without sildenafil 6 months after HT. Post-transplant survival was similar between groups.

**Conclusion:** Sildenafil therapy successfully decreases PVR and TPG in patients with severe pulmonary hypertension allowing successful HT without increased post-transplant mortality.

**1413 Everolimus after heart transplantation: 4 years’ single center follow-up in calcineurin inhibitor-free immunosuppression**

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**Purpose:** Everolimus is a proliferation signal inhibitor introduced for orthotopic heart transplantation (oHTx) in Germany in 2004. This study reports the 4 years’ results of CNI-free immunosuppression using everolimus after oHTx in maintenance patients (pats) longer than 1 year after transplantation. To the best of our knowledge, our group is world-wide the first group reporting long-term data of a large collective of pats on this issue.

**Methods:** Pats after oHTx being switched to everolimus mostly due to CNI-induced adverse drug effects as deterioration of kidney function, arterial hypertension or recurrent rejections were continuously enrolled. 60 pats underwent standardized switching protocols, 39 pats completed full 48-months follow-up. Physiological and laboratory examination + echocardiography were performed regularly. Biopsies were carried out at switch, before deep surgical wound operations and in clinical suspicion of rejection. Coronary angiogram and myocardial scintigraphy were performed before and yearly after switching to CNI-free immunosuppression based on everolimus.

**Results:** After switching to everolimus, most pats recovered from the side effects associated with CNIs. Renal function improved significantly after 12 months and was stable until the end of this study (creatinine at baseline (BL) mean 1.79 mg/dl (IQR25/75: 1.45-2.21), at 48 months 1.37 (1.14-1.67) mg/dl (p = not significant (ns) for BL vs 48 months). Systolic and diastolic blood pressure was not elevated and stable over all 48 months (p=ns for all comparisons). LV ejection fraction was stable over 48 months in echocardiographic and scintigraphic study.

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ies (EF mean 62% [IQR 75/5: 56-70]) at BL vs 63% [IQR 75/25: 58-65] after 48 months in echo, p=ns). Triglycerides (177 ± 169 mg/dl) and total cholesterol (216 ± 217.3 mg/dl) were stable over the time when comparing baseline vs 48 months (p=ns). Frequency of rejections was not higher than with other immunosuppressive regimens. Trench, peripheral edema, hirsutism, and gingival hyperplasia markedly improved. Adverse events mostly were light, temporary and mostly occurred in the first months after switch. Conclusions: CNI-free immunosuppression using everolimus is safe on long term, with excellent efficacy and acceptance after oHTx. Renal function is stable and does not further deteriorate. CNI-induced side effects such as tremor and peripheral edema markedly improve in most patients. Everolimus prevents long term morbidity after HTx and improves quality of life. Twenty-one patients reaching a three year follow-up presented with satisfactory left and right ventricular function at echocardiography and normal RHC parameters. Exercise capacity and quality of life proved homogeneous to those measured in transplant recipients with normal immunosuppressive regimens.

Conclusions: This pilot prospective uncontrolled trial suggests that oral sildenafil is effective in allowing candidacy, and safe transplantation in potential recipients who are mostly disqualified because of PH. Postoperative pulmonary profile normalization is achieved and long term follow-up is satisfactory.

**COMPLICATIONS AND NEW INSIGHTS IN PERCUTANEOUS CORONARY INTERVENTIONS**

### 1414 Is contemporary medication regimen after heart transplantation more myelotoxic?

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Purpose: To evaluate the incidence of bone marrow suppression and associated consequences in patients within the first year after the heart transplantation.

Patients and Methods: The patient cohort was divided in two subgroups. Group I (n=47, period between 2008-2009) was treated with anti-infective and antiproliferative medication which is currently used in patients after heart transplantation (mycophenolate mofetil (MMF)); Group II (n=47, period between 2004-2007) had only MMF among the potentially myelotoxic medication, as the use of valganciclovir and trimethoprim/sulfamethoxazole began in our center in 2008. The myelotoxic risk and need for dose adjustment or complete withdrawal of the MMF was assessed. Moreover the incidence of rejections associated with MMF adjustment was analyzed during the first 12 months after the index procedure in Group I.

Results: Significant difference in number of patients with lymphocytopenia (lymphocytes < 0.8×10^9/l) was observed between both patient groups at three months (38.3% vs. 6.4% in Group II; p=0.002) and at one year (19.1% vs. 4.3% in Group II; p=0.05) and Group I. No major difference in number of other blood elements (erythrocytes, neutrophils, thrombocytes) was observed in both study groups in the reference periods (1 month, 3 months, 6 months and 12 months after heart transplantation). MMF was reduced or discontinued due to bone marrow suppression in 63.8% patients in Group I, while only in 8.5% patients in Group II (p<0.001). Interestingly, at least 1 episode of higher degree cellular or humoral rejection occurred in 35% of patients with the standard MMF dosage as compared with only 26% occurrence rate in patients with dose reduction or complete withdrawal of MMF.

Conclusion: Addition of valganciclovir and trimethoprim/sulfamethoxazole into current medication regimen results in significant lymphocytopenia and leukocytopenia. Modification of immunosuppressive prophylaxis (reducing or stopping MMF) is associated with normalization of blood count without increased incidence of rejections.

### 1415 Long-term follow-up of heart transplant recipients initially disqualified from the waiting list because of pulmonary artery hypertension: the pivotal role of PDE5 therapy

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Purpose: Unresponsive pulmonary hypertension (PH) may considerably limit heart transplant surgery both because of the poorer outcomes and because of the need to long term survival in a selected group of patients initially deemed ineligible because of PH.

Methods: Between May 2005 and December 2009, 31 consecutive patients (5 females, 9 with an history of idiopatic cardiomyopathy and 16 with an history of chronic coronary disease) were included and DAPT regimens were used irrespective of disease presentation or stent type. Multivariate Cox proportional hazard regression models for time to bleeding after orthotopic heart transplantation were used to estimate the effect of different dual antiplatelet therapies, adjusting for baseline differences between the two trials.

Results: A total of 3,140 patients were studied (B=826, BP=2,314). Since oral anticoagulant therapy is contraindicated in BP but not in B, rates of vitamin K antagonists were higher in B than in BP (6 vs. 4%, p<0.004) as was the use of glycoprotein IIb/IIIa inhibitors (36 vs. 23%, p<0.001) despite less ST-elevation myocardial infarctions (21 vs. 32%, p=0.001). Compared with BP, BARC 3/5 bleeding events were more frequent in B during the first 3 days (1.0 vs. 0.3%, p=0.020) and 6 months (1.7 vs. 0.7%, p=0.019) but numerically less frequent during months 7 to 12 (0.1 vs. 0.6%, p=0.151) and similar during months 13 to 24 (0.5 vs. 0.4%, p=1.00). Results were similar with regard to TIMI major bleedings. After adjustment for baseline differences, enrollment in BP (hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.18-0.83), age (HR 1.05, 95%CI 1.01-1.09) and female sex (HR 1.26, 95%CI 1.23-5.34) were independent predictors for BARC 3/5 bleeding during the first 6 months.

Conclusion: Major bleeding events up to 6 months were more frequent in B than in BP, mostly likely due to a higher use of vitamin K antagonists and glycoprotein IIb/IIIa inhibitors in B at baseline. Late major bleeding rates were generally low but numerically higher with residual DAPT in BP than without DAPT in B during months 7 to 12. This signal raises a word of caution against prolonged DAPT after stent implantation.

### 1420 Increased bleeding rates with 12 vs. 6 months dual antplatelet therapy after coronary implantation: A prospective analysis in 3,140 patients

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Background: There is no real-world data directly comparing bleeding rates for 6 vs. 12 months of dual antithrombotic therapy (DAPT) with aspirin and clopidogrel after percutaneous coronary intervention.

Methods: Two-year major bleeding rates were assessed prospectively and compared as secondary endpoints between the BASKET (B) and BASKET-PROVE (BP) trials using the Bleeding Academic Research Consortium (BARC) and Thrombolysis In Myocardial Infarction (TIMI) classifications. DAPT with clopidogrel was prescribed in B for 6 months (loading dose 300mg, maintenance dose 75mg) and in BP for 12 months (loading dose 600mg, maintenance dose 75mg).

Results: A total of 3,140 patients were studied (B=826, BP=2,314). Since oral anticoagulant therapy is contraindicated in BP but not in B, rates of vitamin K antagonists were higher in B than in BP (6 vs. 4%, p<0.004) as was the use of glycoprotein IIb/IIIa inhibitors (36 vs. 23%, p<0.001) despite less ST-elevation myocardial infarctions (21 vs. 32%, p=0.001). Compared with BP, BARC 3/5 bleeding events were more frequent in B during the first 3 days (1.0 vs. 0.3%, p=0.020) and 6 months (1.7 vs. 0.7%, p=0.019) but numerically less frequent during months 7 to 12 (0.1 vs. 0.6%, p=0.151) and similar during months 13 to 24 (0.5 vs. 0.4%, p=1.00). Results were similar with regard to TIMI major bleedings. After adjustment for baseline differences, enrollment in BP (hazard ratio (HR) 0.38, 95% confidence interval (CI) 0.18-0.83), age (HR 1.05, 95%CI 1.01-1.09) and female sex (HR 1.26, 95%CI 1.23-5.34) were independent predictors for BARC 3/5 bleeding during the first 6 months.

Conclusion: Major bleeding events up to 6 months were more frequent in B than in BP, mostly likely due to a higher use of vitamin K antagonists and glycoprotein IIb/IIIa inhibitors in B at baseline. Late major bleeding rates were generally low but numerically higher with residual DAPT in BP than without DAPT in B during months 7 to 12. This signal raises a word of caution against prolonged DAPT after stent implantation.
curred in only 2 pts (0.1%), and BARC type 5 bleeding (fatal) occurred in 3 (0.2%) pts. As the BARC bleeding severity worsened, there was a gradient of increasing rates of 1-year death and reinflation (Table). The 1-year mortality rate increased from 12.1% with BARC 0+1 type to 43.5% with BARC type 3b bleeding. After exclusion of pts with intracranial hemorrhage (BARC 3c bleeding) and multivariable adjustment for demographic and clinical characteristics of pts, the independent predictors of death were BARC type 3a (OR 2.97; 95% CI 1.16-4.94; p=0.017) and BARC type 3b bleeding (OR 4.62; 95% CI 1.75-12.16; p=0.002).

Conclusion: The BARC type 3 bleeding complicating STEMI occurs frequently and is associated with high mortality. Pts with BARC type 3a bleeding are at 2-fold higher risk of 1-year death, but those with BARC type 3b bleeding are at more than 4-fold higher risk.

1423

A 13-year high-volume single centre no reflow experience

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Background: No reflow (NR) represents the inability of a previously ischemic region to be reprieved despite achieving patency of the culprit epicardial coronary vessel. The incidence of NR remains unclear also due to methodological differences used for its definition. Aim of the present study was to ascertain incidence, treatment and prognosis of NR in a large patient cohort.

Materials and methods: We retrospectively analyzed 19290 percutaneous coronary interventions (PCI) including 1257 primary PCI for ST-segment elevation acute myocardial infarctions (STEMI). NR was defined as TIMI flow <2 at the end of the procedure or use of intracoronary (i.c.) nitropusside or adenosine to achieve final TIMI 3 flow. Major adverse cardiac events at follow-up were defined as death, non-fatal myocardial infarction, myocardial revascularization (both percutaneous and coronary-artery bypass graft). Results: Overall NR occurred in 181 patients (0.94%). NR was more common in patients undergoing primary PCI for STEMI (146 out of 1257 or 11.6%) and the 6.5% of them with more than 4-fold higher risk of 1-year death, but those with BARC type 3b bleeding are at more than 4-fold higher risk.

1424

Femoral pseudoaneurysm in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction

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Purpose: Various peripheral vascular complications may be observed after cardiac catheterization. However, no data are available about femoral pseudoaneurysm (FPA) after urgent primary percutaneous coronary intervention (PCI). We sought to determine the in-hospital incidence, clinical course and predictors of FPA in patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI. Methods: 2600 consecutive STEMI patients (mean age: 56.5±11.7 years; 2158 men) undergoing primary PCI were retrospectively enrolled into this study. Patients were evaluated with Doppler ultrasonography following PCI and categorized into two groups according to whether FPA developed or not. All the parameters were compared between FPA and non-FPA groups. Results: The incidence of FPA after primary PCI was determined to be 2.3%. The mean age was higher in the FPA group compared to the non-FPA group (mean age: 60.6±11.6 vs. 56.5±11.8, respectively; p=0.007). Furthermore, the FPA developing group experienced prolonged hospitalizations as compared to the non-FPA group, but no differences in in-hospital or long term mortality were noticed. In the multivariate analysis of this study, female gender and age (>75 years) after primary PCI, were found to be independent predictors of FPA.

OR % 95 CI p Value

Univariate Predictors

Hypertension 1.54 0.92-2.58 0.09
Female 2.26 1.3-3.9 0.004
Age ≥75 2.42 1.45-4.04 0.001
Killip ≥1 0.18 0.03-1.3 0.09

Independent Predictors

Female 1.8 1.3-2.3 0.04
Age ≥75 2.17 1.26-3.73 0.05

OR: Odds ratio, CI: Confidence interval.

Conclusions: High incidence of FPA was noticed in STEMI patients undergoing
primary PCI, which prolonged in hospital stay. Extra care must be given, especially to women and those who are >75 years of age, for this complication.

### Age, glomerular filtration rate, ejection fraction, and the Age/EF(%) ratio

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**Background:** In patients undergoing primary percutaneous coronary interventions (PCI) for ST-segment elevation myocardial infarction (STEMI), the occurrence of Contrast-Induced Nephropathy (CIN) has a pronounced impact on both in morbidity and mortality. We investigated the variables associated with CIN development in the setting of primary PCI and evaluated the predictive value of a 3-variable clinical risk score (the AGEF score) based on age, left ventricular ejection fraction (LVEF) and estimated glomerular filtration rate (eGFR).

**Methods:** 481 consecutive patients with STEMI who were undergoing primary PCI were prospectively enrolled. CIN was defined as an absolute increase in serum creatinine >0.5mg/dL or an increase >25% from baseline within 72 hours after the administration of contrast medium. AUC (Area Under the Curve) was calculated by adding 1 point to the Age/EF(%) ratio if the eGFR was <60 mL/min per 1.73 m². At multivariable analysis age (OR 1.08, p=0.038, AUC 0.78), eGFR (OR 0.95, p=0.002, AUC 0.88), LVEF (OR 0.94, p<0.003, AUC 0.69) and post-procedural TIMI flow grade (OR 0.50, p=0.01, AUC 0.57) were independent predictors of CIN. AGEF score was an accurate (OR 5.19, p=0.0001, AUC 0.88) and calibrated (Hosmer-Lemeshow y=6.24, p=0.62) predictor of CIN (Figure).

**Results:**

- Overall, the incidence of CIN was 5.2%. As expected, in-hospital mortality was higher in patients with CIN than in those without (16% vs 1.3%, p<0.0001).
- At multivariable analysis the age (OR 1.08, p=0.038, AUC 0.78), eGFR (OR 0.95, p=0.002, AUC 0.88), LVEF (OR 0.94, p<0.003, AUC 0.69) and post-procedural TIMI flow grade (OR 0.50, p=0.01, AUC 0.57) were independent predictors of CIN.
- AGEF score was an accurate (OR 5.19, p=0.0001, AUC 0.88) and calibrated (Hosmer-Lemeshow y=6.24, p=0.62) predictor of CIN (Figure).

**Conclusions:** Advanced age, depressed LVEF and reduced eGFR are independent predictors of CIN development after primary PCI for STEMI. In our model, the pre-procedural individual patient risk can be assessed by calculating the AGEF score by solving this exponential equation: Risk = e [AGEF score x 1.65 - 6.26] + 1 (e [AGEF score x 1.65 - 6.26]).

### CHANDELLOPATHIES: WHAT’S NEW IN GENETICS AND BEYOND

#### Early repolarization and increased risk of ventricular fibrillation in during acute myocardial infarction

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**Purpose:** Early repolarization or J wave is a common finding on the 12-lead electrocardiogram and has generally been considered benign for decades. However, since we and others reported that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death related to idiopathic ventricular fibrillation, there is an increasing interest in early repolarization. Although early repolarization has been associated with the risk of arrhythmias in Brugada Syndrome (BrS) patients, their prevalence is currently estimated around 5.5% of the general population.

**Methods:** This study included 310 consecutive patients with acute ST-segment elevation myocardial infarction (70±12 years, 84 females) who underwent successful percutaneous coronary intervention in our institutions. Early repolarization was defined as an elevation of the QRS-ST junction >0.1 mV from the baseline manifested as QRS slurring or notching in at least 2 inferior or lateral leads of 12-lead electrocardiogram.

**Results:** Among the 310 patients, 24 patients (7.7%) experienced one or more episodes of ventricular fibrillation within 48 hours after the onset of acute myocardial infarction. All of the patients who had ventricular fibrillation were successfully resuscitated. Early repolarization was present in 34 patients (11%). The frequency of early repolarization was higher in patients with ventricular fibrillation (29%) than in those without ventricular fibrillation (10%; p<0.01). In multivariate models, early repolarization was associated with the increased risk of ventricular fibrillation (Odds ratio, 3.10; 95% confidence interval, 1.139-8.74; P=0.03). The heart rate, QT interval or conduction disease were not associated with ventricular fibrillation. There was no association of age, gender, family history of sudden cardiac death, body mass index, hypertension, dyslipidemia, diabetes, or metabolic syndrome with the risk of ventricular fibrillation. Severity of myocardial infarction including the maximum creatine phosphokinase level, culprit artery, ejection fraction, or heart failure were not associated with the risk of ventricular fibrillation.

**Conclusion:** Early repolarization increased the risk of developing ventricular fibrillation during acute myocardial infarction. Our data may be useful for risk stratification for arrhythmia events during acute phase of myocardial infarction.

#### Frequency of Brugada type ECG pattern in patients with fever

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**Purpose:** It is well known that fever might induce Brugada Type ECG Pattern (BTEP) and be responsible for ventricular arrhythmias and sudden death in certain subjects. However, it is not known whether fever is always an underlying cause of BTEP in normal subjects who present with fever. Although there are many case reports about BTEP observed in some subjects with fever, there is a lack of prospective data investigating the true prevalence of BTEP associated with fever. Hence, our aim was to determine the true frequency of BTEP in normal subjects with fever by recording ECGs from routine and higher intercostal spaces.

**Methods:** A total of 103 male subjects (mean±SD age, 37±10.8 years) who came in with increased fever due to any reason and without any known cardiac disorder were prospectively enrolled in the study. After the standard ECG recording, two other recordings were obtained by carrying the V1-V3 leads to the 3rd and 2nd intercostal spaces (ICS). ECG recordings were repeated with the same technique after the body temperature of the patients with fever went down to normal values.

**Results:** The frequencies of BTEPs at the 4th, 3rd and 2nd ICS were 2.9% (3 type 3), 6.8% (7 type 3) and 10% (2 type 2 and 8 type 3), respectively (no type 1 BTEP detected). If 4th ICS compared to 3rd or 2nd ICS and 3rd ICS compared to 2nd ICS for detecting BTEPs, 2nd ICS was much more sensitive and significant compared to 4th ICS (p = 0.016). BTEP was detected from higher ICS in only one subject with fever (1%) whose BTEP during abelebe status completely resolved. There were no statistically significant differences between the frequencies of BTEPs obtained in febrile and abelebe states in subjects with fever (p = 0.9).

**Conclusions:** The present study showed for the first time that BTEP recorded in normal subjects with fever did not resolve when the subjects were afebrile. Fever seems to play no specific role for BTEP in healthy subjects. Because of this, if it is solely seen (especially type 1) in a subject with fever, it may be considered as a unique finding for unmasking and diagnosing Brugada syndrome.
in vitro characterization of the N-terminal RyR2 R420Q

1

Usefulness of exercise testing in the diagnosis of Short QT Syndrome

2

Continuous in vivo monitoring to assess exercise testing in Short QT Syndrome patients

3

In silico drug design to assess for QT-prolonging drugs

4

Impact of structural and cellular behavior of bicuspid aortic valve-derived tissue and interstitial cells on myocardium

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Aortic valve disease: from cell to surgery

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actimerized by Valvular Intertstitial Cells (VICs) adopting an osteogenic phenotype. Calcium deposition in BAV patients is similar to the calcification process of a trileaflet aortic valve (TAV); however, it occurs in an accelerated manner. It is likely that the abnormal BAV morphology at the organ (i.e. shape of the sinus and leaflets) and tissue levels (connective tissue fiber, cellular populations) influence the onset and progression of tissue degeneration. Here we have reported a multi-level analysis of human BAV-derived tissue and VICs from patients with calcific AS.

**Method:** Four groups of 10 subjects each (TAV: control; AS; BAV: AI and AS) were selected according to echocardiographic analysis. Markers of osteogenic activation such as Smooth Muscle Actin (SMA), Osteopontin (OPN), Osteonectin (ON), RUNX2 and BMP4 were characterized. Proximo ligation assay (PLA) was used to investigate interactions between OPN and its functional receptor, CD44. Isolated VICs were characterized for osteogenic marker expression and for their ability to biomineralize under recombinant BMP4.

**Results:** In our multicenter study, we observe a faster and more aggressive change in BAV tissue and BAV-derived VICs (both AI and AS) towards the osteogenic phenotype when compared to TAV patients: 1) BAV AI and AS showed increased expression of osteogenic markers (OPN, RUNX, ON, BMP4, and osteogenesis-related gene expression). 2) BAV AI tissues showed thickening of leaflets with calcium nodules near the nape, while BAV AS were thickened and calcified throughout. BAVI pathology was frequently associated with increased size of aortic annulus leading to aortic dilation. 3) Direct interaction of OPN-CD44 correlates with the severity of biomineralization in TAV patients. Conversely, in BAV, we demonstrate a direct interaction between OPN and CD44 and increase in size of aortic annulus leading to aortic dilation. 4) Comparison of OPN-CD44 levels was also found to correlate with the severity of biomineralization in TAV vs BAV patients.

**Conclusions:** Our results support increased propensity of BAV-derived VICs and tissues to undergo osteodifferskent differentiation. In addition they provide mechanistic insights into the cellular activation (BMP4 stimulation) and molecular interactions (OPN/CD44) occurring during the calcification of BAV.

### Evaluation of aortic valve calcium load by computed tomography as a new tool to assess aortic stenosis severity: insights from a multicenter international registry

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**Background:** Quantification of Aortic Valve Calcification (AVC) load by multislice computed tomography may be useful to assess aortic stenosis (AS) severity. A previous study has suggested that an AVC cut-off value of 1651 AU provides 82% sensitivity and 90% specificity to identify hemodynamically severe AS. The aim of this multicenter study was to confirm, in a larger series of patients, the usefulness of AVC to identify severe AS and to refine the cut-point values of AVC for this purpose.

**Method:** 512 patients with AS and normal LV outflow (left ventricular ejection fraction ≥50% and stroke volume index ≥35 ml/m²) underwent comprehensive Doppler echocardiography and simultaneous AVC measurement by CT. Based on Aortic Valve Area indexed to body surface area (AVA), peak aortic jet velocity (Vmax) and mean gradient (MG), 247 (48%) patients had a moderate AS (AVA: ≤1.60 cm²/m²; Vmax: 4–5 m/s and MG: 40–59 mmHg), 96 (19%) a severe AS (AVA: ≤0.63 cm²/m²; Vmax: 4–5 m/s and MG: ≥60 mmHg). AVC was determined with the use of the Agatston method. We calculated two parameters in order to achieve better accuracy for the detection of severe AS.

**Results:** AVC, AVCI and AVC indexed to aortic annulus cross-sectional area (i.e. AVC indexed to aortic annulus cross-sectional area) were assessed by Doppler-echocardiography (i.e. AVA, Vmax and MG) and all p < 0.0001. ROC curves analysis revealed that the best cut-point values to identify severe AS were AVC ≥1590 AU, AVCI ≥750 AU/cm² and AVCI ≥390 AU/cm².

**Performance of different CT criteria**

<table>
<thead>
<tr>
<th>AVC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
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<tbody>
<tr>
<td>≤1590 AU</td>
<td>0.92</td>
<td>0.85</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>≥1590 AU</td>
<td>0.92</td>
<td>0.81</td>
<td>0.91</td>
<td>0.82</td>
</tr>
<tr>
<td>≥750 AU/cm²</td>
<td>0.94</td>
<td>0.88</td>
<td>0.89</td>
<td>0.90</td>
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</table>

**AUC:** Area under ROC curve; **PPV:** Positive predictive value; **NPV:** Negative predictive value.

**Conclusion:** In this large, multicenter series of patients, AVC measured by multislice CT showed excellent correlation with Doppler-echocardiographic markers of AS severity. An AVC density ≥390 AU/cm² provides the best accuracy to identify severe AS. This new CT index may be useful to assess stenosis severity in AS patients, and particularly in those with low-flow, low-gradient AS, in whom Doppler-echocardiography often remains insufficient.

### Evaluation of multidimensional geriatric assessment as predictor of mortality and adverse events after Transcatheter Aortic Valve Implantation (TAVI)

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**Background:** Currently used risk scores do not reliably estimate mortality and MACCE in elderly patients undergoing transcatheter aortic valve implantation (TAVI). This study evaluated multidimensional geriatric assessment (MGA) as predictor of mortality and major adverse cardiovascular and cerebral events (MACCE) after TAVI.

**Methods:** This prospective cohort comprised 100 consecutive patients ≥70 years undergoing TAVI. Global risk scores (STS-score, EuroSCORE) and MACCE-based scores (cognition, nutrition, mobility, activities of daily living (ADL) and frailty index) were evaluated as predictors of all-cause mortality and MACCE 30 days and 1 year after TAVI in regression models.

**Results:** In univariable analyses all predictors were significantly associated with all-cause mortality and MACCE at 30 days and 1 year, except for the Transcatheter valve at 30 days and instrumental ADL at 30 days and 1 year. Associations of cognitive impairment (OR 2.98, 95%CI 1.07-8.31), malnutrition (OR 6.72, 95%CI 2.04-22.17), mobility impairment (OR 6.65, 95%CI 0.21-20.52), limitations in basic ADL (OR 3.63, 95%CI 1.29-10.23) and frailty index (OR 3.68, 95%CI 1.21-11.19) with 1-year mortality were similar compared to STS-score (OR 5.47, 95%CI 1.48-20.22) and EuroSCORE (OR 4.02, 95%CI 0.86-18.70). Similar results were found for 30-day mortality and MACCE. Bivariable analyses including STS-score or EuroSCORE suggested independent associations of MACCE-based scores (e.g. OR of frailty index 3.29, 95%CI 0.16-10.15, for 1-year mortality in a model including EuroSCORE).

**Conclusion:** This study provides evidence that risk prediction can be improved by adding MGA-based information to global risk scores. Larger studies are needed for the development and validation of improved risk prediction models.
scatheter aortic valve implantation (TAVI) is associated with negative clinical consequences. The annulus has previously been shown to be ellipsoidal on multidetector computed tomography (MDCT). We hypothesized that increased eccentricity of the aortic annulus is associated with greater PAR.

**Methods:** Patients with severe aortic stenosis underwent MDCT before successful TAVI with the Medtronic CoreValve prosthesis. The smallest (Dmin) and largest (Dmax) orthogonal diameters in the basal ring of the aortic annulus were determined on MDCT on an image parallel to the nadir of all three native leaflets. We defined eccentricity of aortic annulus using the eccentricity index (1- Dmin/Dmax) as previously described. The primary end point was early occurrence of significant PAR defined as ≥ grade III PAR by post-procedural aortography and echocardiography.

**Results:** Thirty-four patients, mean age 84±4 years with a mean aortic valve area of 0.74±0.18 cm² were included. On ROC curve analysis, eccentricity index correlated with significant PAR (AUC = 0.742). An eccentricity index of <0.25 correlated with increased eccentricity of the CoreValve prosthesis post-deployment (p=0.04) and was related to significant PAR with a sensitivity of 80% and specificity of 76%(p=0.029). On univariate logistic regression, eccentricity index of <0.25 correlated with significant PAR (p=0.038). Other parameters such as annular calcification, cover-index and device implantation depth did not correlate with significant PAR.

**Conclusion:** Eccentricity index is related to significant PAR after TAVI with Medtronic CoreValve. Further larger studies are required to determine the utility of this novel index in screening suitable patients for this procedure.

Aortic annulus area assessment by MDCT for predicting paravalvular regurgitation in patients undergoing TAVI

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**Background:** Transcatheter aortic valve implantation (TAVI) is a valid alternative to surgery in high risk patients with severe aortic stenosis (AS). Aortic annulus (AoA) sizing is crucial for TAVI success. The aim of the study is to compare AoA diameter obtained by MDCT with those obtained with transthoracic (TTE) and transesophageal echocardiography (TEE) for predicting paravalvular aortic regurgitation (PVR) after TAVI.

**Methods:** AoA maximum diameter (AoA-DMaxMDCT), minimum diameter (AoA-DMinMDCT) and area (AoA-DAMMDCT) were assessed with MDCT and compared to TTE and TEE diameter and area (AoA-DTTE, AoA-DTEE, AoA-DATTE and AoA-DTTEE, AoA-DTEE, respectively) for predicting PVR after TAVI in 151 patients (45 men, age 81±6.4 years).

**Results:** AoA-DMaxMDCT, AoA-DMinMDCT and AoA-DAMMDCT were 25.04±2.39 mm, 21.72±2.10 mm, and 420.87±76.10 mm², respectively. AoA-DTTE, AoA-DTEE, AoA-DATTE and AoA-DTTEE were 21.14±1.94 mm, 253.62±84.57 mm², 22.04±1.94 mm and 384.33±67.30 mm², respectively. A good correlation was found between AoA-DMaxMDCT, AoA-DMinMDCT and AoA-DAMMDCT versus AoA-DTTE and AoA-DTEE, AoA-DATTE and AoA-DTTEE (0.61, 0.65 and 0.69 and 0.61, 0.65 and 0.70, respectively) with a mean difference of 3.90 ±1.67 mm, 10.75±5.87 mm², 3.09±2.0 mm, 7.70±1.70 mm and 36.54±56.74 mm², respectively. Grade ≥2 PVR occurred in 46 patients and was related to male gender, higher BMI, pre-procedural aortic regurgitation and lower mismatch between the nominal area of the implanted prosthesis and AoA-DAMMDCT. The best AoA-DAMMDCT mismatch cut-off for predicting significant PVR was 61.5 mm².

**Conclusions:** Mismatch between prosthesis area and AoA-A detected by MDCT is a better predictor of PVR than compared to echocardiography mismatch. Specific MDCT-based sizing recommendations should be developed.

Early right ventricular dysfunction after transcatheter aortic valve replacement: a prospective cardiac magnetic resonance (CMR) study of open versus transcatheter TAVI

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**Introduction:** Recent published literature has validated the use of transcatheter aortic valve implantation (TAVI) in high-risk patients with aortic stenosis. These trials and registries have largely focused on combined morbidity and mortality outcomes, with little focus given to impact on early myocardial function. We assessed effects on myocardial function, reversible and irreversible myocardial injury of both transcatheter and open aortic valve replacement utilizing multi-parametric CMR and biomarker markers.

**Methods:** We conducted a prospective comparative study of 24 patients (14 male) with severe aortic stenosis undergoing either transcatheter valve replacement (12 patients) or high risk (EuroSCORE >20) open valve replacement (12 patients). CMR examination was carried out pre-operatively and within 2 weeks post-operatively. All scans used a Siemens Aera 1.5T system (Siemens, Germany). Images obtained included a standard cine functional imaging, T2 weighted images using LV basal, mid and apical SA slices and late gadolinium enhancement (LGE images (Gadobutrol 0.1mg/kg). HS troponin was measured serially (4, 12, 24, and 48 hours post).

**Results:** Mean ages were 79.9 years Open and 63.2 years TAVI. The postoperative scan was conducted at a mean of 6 days for TAVI and 7 days for open. Mean preoperative LVEF ejection fraction was similar in the 2 groups (65.7±16.3 TAVI, 65.7±18.9 Open, p<0.05) After surgery, the LVEF was not significantly different in either group (TAVI: 65.6 vs 66.1, p<0.05; OPEN 65.7 vs 67.2, p<0.05) In contrast, RVEF decreased significantly in the TAVI group (58.9 to 48.2, p<0.04), driven largely by significantly higher RVEDV compared to the open group (95.4±30.5 vs 88.3±24.3 p<0.05). The open AVR group had no significant change in RVEF. There was no RV irreversible injury in either group. 2 patients in TAVI group and 1 patient in open AVR group demonstrated new LV irreversible injury (p<0.05). T2 analysis showed abnormal global myocardial enhancement in 16.6% of cases in the TAVI group and 8.3% in the open group (p<0.05). Median HS troponin at 48hrs was significantly larger in the open AVR group (403 vs 193ng/L, p<0.05)

**Conclusion:** Although serum Troponin levels are higher in open AVR (likely reflecting use of cardiopulmonary bypass), there is no increased CMR detected LV myocardial oedema or necrosis compared with TAVI. In the absence of new RV irreversible injury, it is likely that the RV dysfunction seen in the TAVI group is a result of rapid ventricular pacing during device insertion, resulting in myocardial stunning.

**1463**

Late systolic mitral prolapse and regurgitation is associated with impaired papillary muscle function and enhanced interolated wall long axis function measured by magnetic resonance

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**Background:** We hypothesized that among patients with mitral prolapse and regurgitation (MPMR), papillary muscle contractile dysfunction underlies the late systolic mitral prolapse, and that the MV prolapse is associated with impaired RVEF, independent of LV function.

**Methods:** From all patients with mitral prolapse referred for cardiovascular magnetic resonance in 4 years, excluding those with prior surgery, mitral stenosis, leaflet tethering, chordal rupture or poor image quality, we found 400 with posterior leaflet or bi-leaflet MPMR clearly identifiable in a “mitral stack” of contiguous short-axis cine images.

**Results:** In group A (n=119), papillary muscle function was assessed and compared with age- and sex-matched healthy controls. MPMR was more often seen in individuals with a previous history of coronary artery disease (95.4% vs 78%), and older age (69 vs 30 years). In group B (n=281), patients with mild mitral regurgitation were used as a control population. The left ventricular ejection fraction (LVEF) was not significantly different between the two groups (56.7±13.9% vs 58.0±11.8%, p=0.13). There was no significant change in LVEF in both groups during follow up (4 years with a mean aortic valve replacement: a prospective cardiac magnetic resonance (CMR) study of open versus transcatheter TAVI

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**Purpose:** Mitral regurgitation (MR) is a complication that may occur during the Transcatheter Aortic Valve Implantation (TAVI) in a not negligible percentage of cases and may require different treatments depending on the mechanism of MR.
The correlation of AVA measured by transthoracic, 3D reconstruction of left atrium with 3D-ATG for Combined epicardial and endocardial ablation

Sections across the aortic valve. 1 case was due to a small tear in the anterior commissure of aortic prosthesis on the anterior mitral leaflet; 4 cases were explained by worsening of a pre-existing MR, assessed both by TEE and angiographically.

Results: In our series, there were a total of 11 cases of significant MR after TAVI (8.5%). Angiography detected 100% of significant MR, but it was not able to determine the mechanism of MR in any case. However, TEE could determine the specific mechanism in 100% of cases: 1 case by interventricular asynchrony by appearance of left bundle branch block of new onset; 2 cases due impingement of aortic prosthesis on the anterior mitral leaflet; 4 cases were explained by temporary distortion or damage of the subvalvular mitral apparatus by the delivery system; in 2 cases the mechanism was the appearance of a systolic anterior movement of the anterior mitral leaflet with dynamic obstruction of the left ventricular outflow tract; 1 case was due to a small tear in the anterior commissure of mitral valve. Surgery was not required in any case. All cases had a grade II MR or less in the ETT at discharge.

Conclusions: In our study there was a not negligible percentage of patients treated with TAVI Corevalve who developed significant MR during the procedure, with very different mechanism. TEE, unlike angiography, could define the mechanism of MR in 100% of cases. Surgery was not required in any case.

1467 The correlation of AVA measured by transthoracic, transesophageal echocardiography and cardiac CT

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Introduction: Cardiac computed tomography (CT) is the standard imaging modality for the evaluation of patients before percutaneous aortic valve implantation (TAVI). Using the same datasets, planimetric measurement of aortic valve area (AVA) is possible.

The aim of this study is to compare the assessment of AVA using cardiac CT with the measurement of AVA by transthoracic (TTE) and transesophageal (TEE) planimetry and with AVA calculated by the continuity equation in patients with severe aortic stenosis.

Methods: A total number of 35 patients (57% men, mean age 77 ±11 years) with severe aortic stenosis underwent TEE, cardiac CT and TAVI. AWA was measured using transverse projections by TTE and TEE. The calculation of AVA using the continuity equation was done in all patients. In addition, AVA was measured in endystolic phase in all patients by cardiac CT, using oblique-transverse sections across the aortic valve.

Results: Mean AVA measured by CT was 0.92 ± 0.27 cm². There was excellent agreement (Bland-Altman) between AVA assessed by CT and planimetric measurement of AVA by TTE (0.90 ± 0.23 cm², r=0.75, p<0.01), planimetric measurement using TEE (0.91 ± 0.22 cm², r=0.94, p<0.01) and AVA derived from the continuity equation (0.92 ± 0.22 cm², r=0.81, p<0.01).

Conclusion: The assessment of AVA using cardiac CT is in excellent agreement with the calculation of AVA from the continuity equation and with planimetric measurements by TTE and TEE.

POSTER SESSION 2 CATHETER ABLATION OF ATRIAL FIBRILLATION: NEW TOOLS

P1481 Robotic Lasso-Catheter manipulation integrated into the remote magnetic ablation of atrial fibrillation: is it superior to manual Lasso manipulation?

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Purpose: Remote magnetic navigation is safe and effective for ablation of atrial arrhythmias, although optimal outcomes often require frequent manipulation of a circular mapping catheter. The VdriveTM Robotic Catheter Manipulation System (Vdrive Medical, Inc.) was designed for remote navigation of Lasso® or Circular mapping catheters (Biosense Webster, Inc.) and is fully integrated into the Niobe® Magnetic Navigation System (Stereotaxis, Inc). This study reports on its first comparison to conventional manual Lasso catheter manipulation.

Methods: Eighty consecutive patients (52 males, 62±13 years) underwent magnetically guided atrial radiofrequency pulmonary vein isolation (PVA) (40-50W, 48°C, 15-20 s, 30mL/min saline flow) for persistent AF using Vdrive to remotely navigate the Lasso catheter (group 1). Navigation tasks included accessing per- monary veins, creation of chamber maps, and gap identification with segmental isolation. Patients were compared to a historic cohort of 60 patients (47 males, 61±9 years) also treated by magnetically guided ablation (group 2) at a similar energy protocol for PVA but with manual guidance of the Lasso. All procedures included rotational angiography based image integration (DynaCT Cardiac, Siemens; Ensite fusion, St. Jude Medical) and intracardiac echocardiography.

Results: PVA confirmed by entrance and exit block was achieved in all patients. Mean procedure time was 213±53 minutes in group 1 and 216±44 minutes in group 2 (p=0.67). Ablation times were 2913±920 and 4714±1293 s, respectively (p<0.001). Fluoroscopy time was 21.0±24.5 minutes (p=0.04) and total radiation exposure 4518±2072 and 5159±2511 μGy/m2 (p=0.1). Twenty-seven patients required some manual movements (primarily minor shear rotation). There were no adverse events related to the use of the remote manipulation system.

Conclusions: Our initial experience demonstrates that remote navigation of the Lasso is feasible and safe. It reduces total ablation and fluoroscopy times and shows a trend to a reduction in total radiation exposure. Prospective randomized studies need to be performed to prove efficacy improvements over manual techniques.

P1482 Combined epicardial and endocardial procedure of permanent atrial fibrillation

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Background: Endocardial catheter based ablation strategies for the treatment of long standing persistent or permanent atrial fibrillation (permAFib) show only limited success rates. However, fluoroscopy times, procedure duration, and complication rates increase. We report the results of a combined epicardial and endocardial approach.

Methods: Patients with documented permAFib were included in this registry. In a first step epicardial lesions were applied endoscopically via a subxiphoidal approach. A roof line. segmental circumferential isolation of the PV ostia were applied. The second step was performed endocardially using a 3-D mapping system (Ensite Velocity). Gaps in cranial parts of the PV were identified and completed using a cooled tip RF catheter. After confirmation of complete isolation a Reveal XT device was implanted (Medtronic Inc.). Follow up was performed with wireless transmission of electrograms and automated recognition of AFib burden.

Results: Sixteen patients with permAFib were treated (n=13 male; age 57±12 years, ejection fraction 65±12%). Duration of permAFib was 2.5 years (0.5 to 7) atrial area was 36.8±5.4cm². Procedure times were 115 min for the epicardial and 104 min for the endocardial approach. Fluoroscopy time was 9.3±3 min. Complete isolation of all PV was documented in all cases. During a mean follow-up of >18±6 months the burden of AFib was 7.1% with n=9 pts that were free of any AFib in the Reveal holter. In n=2 pts AFib recurved and could not be cardiovored due to atrial thrombus formation. All patients were asymptomatic for AFib episodes. In one pt bleeding occurred that was treated surgically during the epicardial ablation.

Conclusion: The combined epicardial and endocardial ablation approach offers a novel and feasible approach for treatment of permAFib. Even in long standing permAFib the procedure times do not exceed conventional procedure times with only low fluoroscopy times. Results for complete success are promising for a large scale trial.

P1483 3D reconstruction of left atrium with 3D - ATG for pulmonary vein isolation. Comparison with MRI

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The efficacy and safety of RF ablation in patients with atrial fibrillation (AF) is strongly dependent on the possibility of three-dimensional visualization of left atrium (LA) and pulmonary veins (PV) ostia. The current angiographic systems allow 3D visualization of anatomical heart structures by means of rotational angiography. Studies conducted during adenosine induced ventricular asystole or rapid ventricular pacing presented a good correlation with CT or MRI. However, there was a substantial proportion of patients in whom this approach failed to provide reliable images, was contraindicated or led to complications like ventricular tachycardia.

The purpose of our study was to evaluate the clinical usefulness of rotational angiography (3D-ATG, Philips, Netherlands) after administration of the contrast medium into the right atrium for visualization of the left atrial anatomy in patients undergoing RF ablation of atrial fibrillation. We also compared the images obtained with 3D-ATG with magnetic resonance (MRI). In 18 consecutive patients undergoing RF ablation of AF or left atrial tachycardia, 3D-ATG was performed (fluoroscopy, followed by 3D reconstruction of left atrium and aorta). We analyzed the quality of reconstruction, visualization of PVs and LA appendage. In cases of difficult transseptal puncture, reconstruction of atrial root was superimposed on the left monitor for guidance.
The ablation with use of CARTO 3 was successful in 17 patients. The total ablation time was 127.2±28.8 min, fluoroscopy time 280±8 min, and x-ray radiation dose was 57±47 mGy. The mean fluoroscopy time for 3D-ATG was 175±45 s, and the mean X-ray dose was 159±57 mGy. Appropriate 3D visualization of the left atrium was obtained in 17 patients, including 15 in whom all 4 pulmonary venous ostia were shown. In one case 3D-ATG has not allowed for the visualization of the right superior pulmonary vein and in another case the left sided vein was not visualized during the cryo application. The good agreement (≤2mm) between two methods for assessment of PV ostia was higher for right-sided than left-sided veins (62.5% vs. 44%, p=0.03).

We conclude that 3D-ATG after contrast medium administration to the right atrium seems to be a safe and effective visualization method of pulmonary venous ostia and the left atrial anatomy. Whether it enables evaluation of anatomical anomalies remains to be established.

**P1484 Optimized touch techniques in atrial fibrillation ablation: is the contact force guided approach superior to magnetically directed ablation technology?**

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**Purpose:** Irrigated radiofrequency ablation is a successful treatment option in atrial fibrillation (AF), Level and type of contact force (CF) are critical for energy transmission. Comparative data on continuous and limited vs. CF guided wall contact are lacking.

**Methods:** Forty patients were studied. 20 consecutive patients (14 male, 65±8 years) underwent atrial RRF balloon vein isolation (PVI): (40±50 W, 48±15, 20±30 W, 30±5 s/min flow) for persistent (14) or paroxysmal (6) AF guided by CF (Tactica, Endosense). An average CF of ≤15 g was aimed (group 1). Patients were matched to 20 patients treated by magnetically directed (Stereotaxis Niobe) irrigated-gold-tip (Trignum G, Biotronik) (MDG) ablation (group 2) at a similar energy protocol for PVI. All procedures included: Rotational angiography based image integration (DynaCT Cardiac, Siemens; Ensite fusion, St. Jude Medical), Lasso-catheter (Lasso) for Pulmonary Vein Isolation with a mean follow-up of 29.1±12.4 months.

**Results:** All targeted pulmonary veins could be isolated confirmed by entrance block in both groups. Procedure time was 195±55.6 min in group 1 and 230±55.5 min in group 2 (p=0.19). Patients’ radiation exposure and fluoroscopy times were 6823±3232 Gy-min/24.5 mGy in group 1 and 5323±2394 Gy-min/24.4±12.0 min (p=0.15; p=0.01, respectively). Ablation time was 1927±687 s (group 1) and 3339±1158 s (group 2) (p=0.001). Mean CF was 19±4±6 g, total force-time-integral (FTI) 3347±12444 gs and average FTI/ablation 1177±405 gs (group 1). Two pericardial tamponades and 2 sudden heart arrests occurred in group 1, no procedural complications were observed in group 2 (p=0.15). Success rates were 78% (14/18) and 85% (17/20) (p=0.69) in a 9.1±2 month follow-up.

**Conclusion:** The use of the novel Achieve™ catheter leads to a significant reduction of procedural and fluoroscopy time. Despite a significant reduction of the total freeze time in each PV the midterm success rate remained unchanged as compared to standard procedure with Lasso catheter.

**P1486 Comparison of new silent cerebral thromboembolic lesions after ablation of Pulmonary Vein isolation with those of complex fractionated atrial electrograms ablation**

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**Introduction:** Atrial fibrillation radiofrequency ablation (AFRA) has become a routine procedure for treatment of atrial fibrillation (AF). However, incidents of silent cerebral ischemic lesions have recently emerged as the most frequent complications during AFRA. The aim of this study is to compare the incidence of silent cerebral ischemic lesions (SCILs) of pulmonary vein isolation (PVI) with those of complex fractionated atrial electrograms ablation (CFAE).

**Methods and Results:** Fifty four patients (43 male; age 63±9 years) who underwent PVI (35 patients) or CFEA (19 patients) for AF were enrolled with irrigated radiofrequency catheter. We maintained an ACT of > 300 seconds during procedures. The protocol included a cerebral magnetic resonance imaging (MRI) after the procedure. After AFRA 22 of 54 patients (40.7%) showed new SCILs at post-procedural cerebral MRI: 12 of 35 patients in PVI (34.2%), 10 of 19 patients in CFEA (52.6%). In paroxysmal AF (PAF) patients, 5 of 9 patients in CFEA and 8 of 28 patients in PVI showed new SCILs. In persistent AF (PerAF) patients, 5 of 10 patients in CFEA and 4 of 7 patients showed new SCILs. At the statistical analysis there was no independent predictor of new SCILs after AFRA.

**Conclusion:** CFEA tended to show more new SCILs than PVI in PAF patients.

**Figure 1. Visualization of the CB in the LSPV**
sharp-edged carina between LSPV and LPV or between LPV and left atrial appendage were identified as significant predictors for acute and mid-term PVI failure (p<0.04). For RIPv, a proximal bifurcation (p=0.02) and a non-perpendicular angle between ostium and vein axis (p=0.03) were identified as predictors for mid-term and acute PVI failure, respectively.

Conclusions: We identified geometrical parameters from pre-procedural CT/MR images to predict acute and mid-term success of CB-PVI with the potential to improve outcome of CB ablation of AF.

P1489
MRI based lesion formation comparison between single tip radiofrequency, PVac and cryoballoon ablation in patients with paroxysmal atrial fibrillation

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Background: We compared the difference in left atrial tissue remodeling (LATR) pre ablation and post-ablation lesion characteristics between three methods for electrical isolation of pulmonary veins [cryoballoon (cryo), pulmonary vein ablation catheter (PVAc) and single-tip radiofrequency (SFR)] routinely done to treat paroxysmal atrial fibrillation (PAF).

Methods: Patients presenting with PAF who qualified for a cryo, PVAc or SRF ablation were prospectively followed. DE-MRI at the left atrium (LA) was performed prior to and 3-months post-procedure. The degree of LATR is reported as a percentage of the total LA area.

Results: Of the 37 patients (26 males, mean age = 63±10.12 years) enrolled included in the study, six underwent an ablation using PVAc catheter, SRF catheter was used in 14 patients, and 17 patients underwent a cryoballoon ablation. Pre-ablation LATR was comparable in all three cohorts (Figure 1). End of scar tissue was higher in cryo and SRF patients than PVAc patients (Figure 1). Overall six patients were found to have AF recurrence at 3-months follow-up. Patients with recurrence had a significantly lower amount of ablation lesions than patients in sinus rhythm (5.93% vs. 15.98%; P=0.004; Figure 2).

Conclusions: From our preliminary results, PVAc ablation appears to result in lesser scar formation as compared to Cryoballoon and SRF ablation. The greater recurrence in patients with low scar post-ablation suggests the need to implement an adequate ablation strategy that results in greater scar, especially in patients with PAF to maximize successful outcomes.

P1489
Pulmonary vein isolation for paroxysmal atrial fibrillation with laser balloon

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Introduction: Ablation strategy for pulmonary vein (PV) isolation in the treatment of atrial fibrillation is very important for making this procedure easier and shorter. The balloon procedures seem to be enough efficient, safe and easier in comparison with conventional radiofrequency catheter ablation. In our institution we have a large experience with isolation provided by cryoballoon. Using laser balloon we deliver laser energy around the pulmonary vein ostium under endoscopic direct visualization. This balloon is compliant and facilitate this procedure.

Methods: During the years 2009-2011 we performed 88 laser balloon pulmonary vein isolation procedures (308 veins, common ostium of left veins in 16 patients). All patients had paroxysmal atrial fibrillation. We predicted double transseptal puncture in all cases, using circular mapping catheter for prove ostial isolation. Our standard is use of ICE in all procedures: for transseptal puncture and for navigation of balloon in ostium of pulmonary vein. During application we measured temperature in oesophagus with temperature probe. In occurrence of temperature higher than 38,5οC we stop application. During application in right upper pulmonary vein we paced phrenic nerve in order to avoid its damage.

Results: The acute success rate was 2009/99% in 2010/98% in 2011/100%. The mean 12 month follow up shows 82% chronic success rate. In 55 patients we performed remapping of veins after 2-3 months (gap RIPv 11x, RSPV 7x, LSPV 7x, LVBP 9x). The most frequent complication after laser balloon isolation of pulmonary vein was local vascular complication (mostly in females). We didn't record any other severe complications.

Conclusions: Laser balloon isolation of pulmonary vein is safe procedure with comparable results with radiofrequency procedures. Long term follow up shows sufficient success rate without severe complications.

P1489
Cryoenergy or radiofrequency for pulmonary vein isolation (COR trial): immediate results


Purpose: The COR trial is a prospective, randomized, single centre trial comparing the efficacy and safety of Cryoablation (C) vs cooled Radiofrequency ablation (R) for PV isolation.

Methods: 50 patients with symptomatic drug-refractory paroxysmal AF who had an anatomical pattern of 4 independent PVs in a screening CT were randomized (1:1) to C or R. C was done through an anatomical approach using a single ArcticFront® (Medtronic) catheter balloon (23 or 28 mm depending on PV ostia diameters) and two 300-sec applications per PV. Balloon positioning was optimized by intracardiac echocardiography (AcuNav®, Siemens) and CT integration into real-time fluoroscopy (Epic navigation®, Philips). The use of point-by-point catheterization was not allowed for closing residual gaps. R was done aiming for bidirectional PV conduction block guided by PV catheter recordings and electro-anatomical mapping (CARTO®, Biosense Webster). All patients underwent implantation of an internal loop recorder (Reveal XT®, Medtronic) for arrhythmia burden comparison after 12 months of follow-up (primary outcome).

Results: 39 men and 11 women were enrolled (median age 56 years (P25, P75 = 44, 61 years)) between September 2009 and March 2011. Complete bidirectional conduction block was achieved in 86% of PVs treated with C and 100% of PVs treated with R (P = 0.0001). In group C, the rate of PV conduction block was higher in patients treated with the 23-mm balloon (50% vs 79%, P=0.03). There were no differences in the incidence of significant complications (hemoptysis in 1 group C patient and arteriovenous fistula in 1 group R patient). Particularly, there was no case of phrenic nerve paralysis. Ablation duration (time from the first to the last energy application) was 88 min (70, 109) min in group C and 53 (45, 63) min in group R (P<0.0001). Procedure duration was also longer in group C [206 (163, 256) min] than in group R vs [173 (124, 242) min; P=0.02].

Conclusions: Immediate results of this purely anatomical approach for PV isolation using the Arctic Front cryoenergy catheter balloon seem inferior to electrophysiologically guided PV isolation with cooled radiofrequency ablation. Follow-up will determine the relevance of the differences observed in technical results and the real efficacy of both techniques.

P1490
Single-ring ablation compared with standard circumferential pulmonary vein isolation and using remote magnetic catheter navigation in patients with symptomatic atrial fibrillation

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Aim: Aim of this prospective study was to evaluate the safety and efficacy of an remote magnetic navigation (RMN)-guided single-ring ablation method as compared to standard RMN-guided circumferential pulmonary vein ablation (PVA).

Methods: A total of 80 consecutive drug refractory AF patients undergoing PVA were included and randomized 1:1 to the two study groups prospectively. RMN using the Stereotaxis Niobe II system and open-irrigated 3.5 mm ablation catheters were used with a three-dimensional mapping system in all ablation procedures. 40 patients underwent RMN-guided single-ring ablation while the other 40 patients (50%) received RMN-guided circumferential PVA. All patients were subsequently followed every 3 months using 96h Holter-ECG. The primary endpoint of this prospective randomized study was acute procedural success, defined as the number of pulmonary veins (PVs) isolated at the end of the procedure. Secondary endpoints were long-term success, defined as long-term freedom from AF/AT episodes irrespective of study treatment, and freedom from symptomatic AF recurrence during 12 months of follow-up.

Results: In the circumferential (Circ) group, a mean of 3.3±1.1 PVs were successfully isolated as compared to 3.1±1.3 in the single-ring group (p=0.38 by unpaired t-test). To achieve electrical isolation of the PVs, all patients in the single-ring (Box) group required additional posterior wall lesions. Single-ring ablation was associated with longer procedure duration (Box 253±48 min vs. Circ 226±45 min, p=0.01), and ablation time (Box 67±16 min. vs. Circ 56±12 min, p=0.001). Using Kaplan-Meier analysis after 1.4±0.5 procedures, 94% of patients who were free of any atrial tachycardia (AT)/AF episode at 12 months of follow-up was 79% in the Box group and 85% in the Circ group (p=0.43). In contrast, fluoroscopy time did not differ significantly between the two groups (p=0.4).

Using RMN for PVA in both groups, no major complications have been observed during or after PVA. As minor complications, pericardial effusion (n=2), hematoma at puncture site (n=2) were noticed. None of the minor events required intervention.
Conclusion: RMN-guided single-ring ablation of the PV provides comparable acute and long-term success rates as compared to RMN-guided circumferential PVA but requires markedly increased procedure and ablation time. Procedural complication rates are similar. Importantly, additional linear lesions on the posterior wall cannot be avoided in order to achieve PV isolation.

**P1492**

Ganglionated plexi ablation combined with pulmonary vein isolation improves outcome of catheter ablation in patients with longstanding persistent atrial fibrillation: a prospective randomized study

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Introduction: Pulmonary vein isolation (PVI) is an established strategy for paroxysmal atrial fibrillation (Af) but seemed too effective in patients with persistent Af. Some researchers had already suggested that additional ganglionated plexi (GP) ablation might improve the success rate. The aim of our study was to assess the maintenance of sinus rhythm (Sr) in patients with longstanding persistent Af at least 3 years using 2 different ablation strategies. PVI+GP ablation is proposed to reduce complications related to GP, thereby improving duration of Sr.

Methods: Two hundred sixty-four consecutive patients with longstanding persistent Af were randomly assigned to 2 different ablation schemes: PVI+GP +cryoablation (n=132) and PVI+GP +laser ablation (n=132).

Results: All patients underwent the procedure successfully. PVI was achieved in all cases. With a single procedure at the 12-month follow-up, 47% of patients treated with PVI+GP were in Sr, whereas at the 3-year follow-up, 34% maintained Sr; using the PVI+GP+cryoablation with a single procedure at the 12-month follow-up 54% of patients were in Sr (p=0.068), whereas at the 3-year follow-up, 49% remained in Sr (p=0.021).

Conclusions: The difference between PVI+GP and PVI+GP+cryoablation strategy is not statistically significant at 12-months in patients with longstanding persistent Af, whereas the difference becomes statistically significant in the long-term follow-up because of the higher number of recurrences in the PVI+GP group.

**P1493**

Laser or cryo? Prospective comparison of balloon based PVI technologies

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Background: Pulmonary vein isolation (PVI) for the treatment of drug-refractory atrial fibrillation (AF) using cryothermal balloon (CB) catheters is a well-accepted treatment option. Recently, the concept of visually guided laser balloon (LB) ablation was introduced.

Purpose: To prospectively compare acute and mid term efficacy and safety outcomes for 2 balloon based PVI technologies.

Methods: Patients with drug-refractory paroxysmal atrial fibrillation were enrolled. No pre-procedural imaging was required. After single transseptal puncture and selective PV angiograms a steerable sheath was advanced to the LA. All ablations in the CB group were performed exclusively with the 28 mm balloon. In the LB group an esophageal temperature probe with an upper limit of 39°C was used. During septal PV ablation phrenic nerve stimulation was performed via a diagnostic catheter. Follow-up was performed with 3 day Holter-ECGs every 90 days post-procedure. Safety and long-term efficacy of this new feature have to be evaluated in larger cohorts.

Conclusions: The use of novel contact force sensing technology is able to significantly reduce ablation time (radiofrequency time needed for PVI) from 50.5±11.0 minutes to 46.5±12.2 minutes (p=0.022). In paroxysmal atrial fibrillation the total energy delivered could be significantly reduced from 70,926±19,470 to 58,511±14,655Ws (p=0.019).

**P1494**

Novel robotic catheter manipulation system integrated with remote navigation for fully remote ablation of atrial tachyarrhythmias: a multi-center evaluation

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Introduction: Studies have shown that remote magnetic navigation is safe and effective for ablation of atrial arrhythmias, although optimal outcomes often require frequent manual manipulation of a circular mapping catheter. The Vdrive robotic system (“Vdrive”) was designed for remote navigation of circular mapping catheters to enable a fully remote procedure. This study details the first in human clinical experience with remote circular catheter manipulation in the left atrium.

Methods: This was a prospective, multi-center, non-randomized consecutive case series that included patients presenting for catheter ablation of left atrial arrhythmias. Remote systems were used exclusively to manipulate both the circular mapping catheter and the ablation catheter. Patients were followed through hospital discharge.

Results: Ninety-four patients were included in the study, including 23 with paroxysmal atrial fibrillation (AF), 48 with persistent AF and 15 suffering from atrial tachycardias. The population was predominately male (77%) with a mean age of 60.5±11.7 years. The Vdrive was used for remote navigation between veins, creation of chamber maps, and gap identification with segmental isolation. The intended acute clinical endpoints were achieved in 100% of patients. Mean case time was 225.9±70.5 minutes. Three patients (3.2%) crossed over to manual circular mapping catheter navigation. There were no adverse events related to the use of the remote manipulation system.

Conclusions: The results of this study demonstrate that remote manipulation of a circular mapping catheter in the ablation of atrial arrhythmias is feasible and safe. Prospective randomized studies are needed to prove efficacy improvements over manual techniques.

**P1495**

Clinical Impact of a new open-irrigated Radiofrequency Catheter with direct Force Measurement on Atrial Fibrillation Ablation


Background: Electrode-tissue contact is crucial for adequate lesion formation in radiofrequency catheter ablation (RFCA). Objectives: We assessed the impact of direct catheter force measurement on acute procedural parameters during RFCA of atrial fibrillation (AF).

Methods: 50 consecutive patients (pts; 28 male) with paroxysmal AF who underwent their first procedure of circumferential pulmonary vein isolation (PVI) were included. A standard 3.5mm open irrigated tip catheter or a catheter with contact force measurement capabilities was used. The endpoint for PVI was entry and exit block acute procedural parameters were assessed.

Results: Procedural data showed a remarkable decline in ablation time (radiofrequency time needed for PVI) from 50.5±15.9 to 39.0±11.0 minutes (p=0.007) with a reduction in overall procedure time of 31.3±7.2 minutes (p=0.022). In particular, the total energy delivered could be significantly reduced from 70,926±19,470 to 58,511±14,655Ws (p=0.019).

Conclusions: The use of novel contact force sensing technology is able to significantly reduce ablation time and energy delivery is substantially reduced by avoiding radiofrequency ablation in positions with insufficient surface contact. Safety and long-term efficacy of this new feature have to be evaluated in larger cohorts.

**CATHETER ABLATION OF ATRIAL FIBRILLATION: UNDERSTANDING THE MECHANISM**

**P1496**

Left atrial function predicts arrhythmia recurrence after first and repeated procedure of atrial fibrillation ablation better than left atrial size

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Purpose: Both left atrial (LA) size and contractile function have shown to predict arrhythmia elimination after a first procedure of catheter ablation (RFCA) for atrial fibrillation (AF). Predictors of success after repeated procedures, required in up to 30% of patients, are less clear.

Methods: 85 consecutive patients with AF treated with RFCA were included, 49 undergoing a first and 36 a second RFCA procedure. We excluded patients with severe valvulopathy or severe hypertrophy. In all patients a pre-procedure transthoracic echocardiography was performed with analysis of LA volume and myocardial deformation derived from 2D-echocardiography. All patients were in sinus rhythm at the time of the echo exam. Patients were clinically followed-up at...
Abstract P1496 – Table 1

<table>
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<th>Non recurrence (n=53)</th>
<th>Recurrence (n=13)</th>
<th>1st RFCA</th>
<th>2nd RFCA</th>
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<tr>
<td>LA diameter (mm²)</td>
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<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>30.7±3.5</td>
<td>29.3±3.1</td>
<td>1.00 (1.00-1.01)</td>
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<tr>
<td>LA Volume (mL/m²)</td>
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<td>32.5±14.9</td>
<td>36.3±9.8</td>
<td>0.69 (0.69-0.80)</td>
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<tr>
<td>LAD (%)</td>
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<td>18.1±1.37</td>
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<td>LASR (%)</td>
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<td>0.81±0.07</td>
<td>0.75±0.03</td>
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P1497

Common and rare cardiac sodium channel variants in atrial fibrillation - relation with ECG phenotypes and outcome of catheter ablation

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Purpose: Common and rare genetic sodium channel variants have been identified as risk modifiers and causes for atrial fibrillation (AF). Their possible relation with AF-associated intermediate ECG phenotypes and rhythm outcome of AF catheter ablation is, however, unknown and was investigated in this study.

Methods: In 137 consecutive patients with lone AF, sequence analysis of SCN5A, SCN1B and SCN2B was performed to identify rare variants and to determine the SCN5A H558R polymorphism. We identified 3 rare non-synonymous variants in SCN5A, 5 in SCN1B and none in SCN2B (6%). Minor allele frequency of SCN5A H558R was 22%. Variant carriers were comparable with non-variant carriers with respect to their demographic data. There was no association between PR interval, prevalence of incomplete right bundle branch block or early repolarization pattern and common or rare sodium channel variants. AF recurrence rate determined by serial 7-day Holter-ECG monitoring between 3 and 12 months after ablation. These findings highlight (1) the complexity of genotype-phenotype correlations and (2) the role of the pulmonary veins for AF initiation and maintenance even in the presence of genetic sodium channel variants.

Conclusions: AF termination. After PVI, no sustained AF was inducible in 20 patients (15 M, 5 F, age 64±11 years, duration 61 months, median 3 months) who did not require additional non-PV ablation for the maintenance of stable sinus rhythm.

P1498

Identification of rotors using sequential mapping & automated analysis techniques: organisational index is the best guide to important sites

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Introduction: Sequential mapping and targeting of fractionated electrograms (EGMs) is commonly used in catheter ablation (CA) of persistent atrial fibrillation (pAF). Recent attention has focused on surrogate signals for rotor activity, an underlying re-entry mechanism, but it is unclear if these can be identified with sequential mapping. Several automated algorithms exist to identify fractionated sites, but associated with particular ECG phenotypes or outcome of catheter ablation. These findings highlight (1) the complexity of genotype-phenotype correlations and (2) the role of the pulmonary veins for AF initiation and maintenance even in the presence of genetic sodium channel variants.

Methods: 20 patients undergoing first-time CA of pAF were studied. A NavX CFAE map was acquired after pulmonary vein antrum isolation. EGM data was exported and & analysed live using custom software. CA was performed on sites of high CFAE. Offline analysis compared 3 algorithms seeking to identify rotors: CA, DI, Dominant Frequency (DF); and 2 fractionation measures: CFAE mean (Nax Equivalent) and shortest complex interval (SC) (Carto Equivalent). Finally, the effect of ablation lesions on pAF cycle length was correlated with analysis.

Results: CA terminated AF in 50% cases. 2589 8-second EGMs and 471 ablation lesions were analysed. Varying the refractory periods (RP) of algorithms produced large changes in signal classification for fractionation assessments (CFAE: Pearson R varied from 0.81±0.05 with 10ms variation in RP to 0.08 with 90ms variation) and SCI (0.95±0.04 for 10ms, R=0.34 for 90ms). Oil, DI and ContA were unaffected by such changes (R=0.95±0.01 for 10ms, R=0.80 for 90ms). An analysis of AF ablation existed between Oil and CFAE (R=0.38, p<0.001) but no correlation with other measures. Only 2.1% of EGMs were in the top quintile by all 3 indices of CFAE, DI and SCI. High Oil (P<0.05) was associated with AF termination without system- tematic evaluation of the underlying substrate. We prospectively performed a pro-gressively rapid atrial pacing protocol for determining the requirement for extra-PV ablation in patients with persistent AF.

Methods: After performing circular mapping guided IV pacing (PVI), progressive rapid atrial pacing (8-10 beats from 350ms decremented by 10 ms steps down to 200ms, at least twice) was performed in sinus rhythm (after electrical cardioversion if necessary). If sustained AF (> 5 minutes) was induced, additional ablation was performed targeting subgroups of fractionated potentials in the LA and coronary sinus (CS) with endpoints of elimination of fractionated potentials or termination of AF. The rapid pacing protocol was repeated after all ablation.

Results: 43 consecutive patients (32M, 63±9 yrs, 13 with structural heart disease with persistent AF (mean duration 39±0.05 months, median 8 months) were studied. PVI was successfully achieved in all patients and without producing AF termination. After PVI, no sustained AF was inducible in 20 patients (15 M, 64±11 years, 6 SHD, persistent AF duration 56±137 months, median 9; LA volume 110±27ml, p<0.001 compared to the nonin- nivous group), no sustained AF could be induced in 15 patients, sustained atrial flutter was induced in 4 patients and sustained AF in 5 patients. After 12±5 months follow-up, only 4 patients underwent reablation and 13±9 (68%) patients without extra-PV ablation and 12±5 (50%) with extra PV ablation remained in stable sinus rhythm without anti-arrhythmic drugs.

Conclusions: A progressive rapid atrial pacing protocol based evaluation of the preservation of AF. The data on identifying surrogates signals for rotor activity in patients who do not need additional non-PV ablation for the maintenance of stable sinus rhythm.

P1500

Quantitative analysis of isolation area and rhythm outcome in patients with paroxysmal atrial fibrillation after circumferential pulmonary vein antrum isolation

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Objectives: We sought to determine the relationship between the size of the left atrial (LA) isolated surface area (ISA) after pulmonary vein antrum isolation (PVI) for paroxysmal atrial fibrillation (AF) and rhythm outcome during a 12-month follow-up.

Background: PVI is an established therapy for patients with paroxysmal AF. However, the influence of the size of the ISA on rhythm outcome is unclear.

6 months with 24 hour Holter ECG for the evaluation of arrhythmia recurrence. Logistic regression and ROC curves were used.

Results: See table.

Conclusions: Analysis of LA performance with myocardial deformation imaging and mapping & 3D analysis in patients with AF undergoing a first and also repeated procedure of RFCA, beyond LA size.
Methods: Circumferential lesions for complete electrical PV isolation were placed around the ipsilateral pulmonary vein (PV) pairs of 101 patients with AF (mean age 59±11 years, median AF history 36 (24; 96) months, mean LA size 42±6 mm). The ISA was defined as the ratio of total isolated antral surface area (IASAtotal) excluding the PVs to the sum of the IASAtotal and the LA posterior wall (LAPW) surface area. All surface areas were assessed by using a software tool of the NavX system. Patients were divided into four groups according to ISA (Group I: <50%, Group II: 50 to <60%, Group III: 60 to <70%, Group IV: ≥70%).

Results: The average ISA for all patients was 59.2±11.6%. Subgroup analysis showed ISA was 42.6±4.2% (Group I: n=23), 54.2±3.0% (Group II: n=25), 64.3±3.0% (Group III: n=33), and 73.9±3.6% (Group IV: n=19). At 12 month without anti-arrhythmic drug treatment, 74% of patients in group I, 78% in group II, 97% in group III, and 100% in group IV were free from AF and/or atrial macro-re-entrant tachycardia (MRT). Kaplan-Meier analysis showed a significantly lower success after PVAI.

Conclusion: After 12 months, a larger ISA was associated with a significantly lower AF/MRT recurrence rate. ISA≥55% may serve as a predictor for long-term success after PVAI.

Figure 1

Spatially accurate overlay of 3-D MRI of the left atrium onto the fluoroscopic image during atrial fibrillation ablation using fatty and radiodiode markers

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Morphologic left atrial variation, accurate lesion location, integration of pathologic data like scarring and reduction in X-ray exposure all make accurate real time integration of three dimensional (3-D) left atrial imaging potentially valuable to safely ablate atrial fibrillation.

Methods: 7 Patients (Age 52-77) underwent Gadolinium angiography (15-20 cc at 1.5-3cc/s) during magnetic resonance imaging (MRI) to acquire 3-D shells of the left atrium (LA) within 24h prior to ablation. 3 fish-oil capsules (1000mg omega-3 fatty acid, containing 330mg Eicosapentaenacetic acid and 220mg Docosahexaenaciacid) were fixed parasternally in the 6th, 7th 8th intercostal space prior to MRI. Immediately prior to the ablation procedure a rotational fluoroscopic image of the LA tissue. Electroanatomic voltage maps of the LA (196±72 points) were obtained by CARTO system ( Biosense Webster, Israel) in 14 pts during AF. Bipolar voltage of the entire LA was correlated with the extent of fibrosis. Pts were followed for AF recurrence prospectively for 260±183 days.

Results: Two of the CMRI studies were excluded due to poor image quality. Twenty-five pts (83%) remained in sinus rhythm during follow up. Mean LA fibrosis and bipolar voltage reached 7.4±4% and 0.6±0.3 mV, respectively. The extent of LA fibrosis showed significant exponential correlation with the mean voltage of LA (R=0.9, P=0.001), the equation: voltage (mV)=2.5(1 per cent of fibrosis). No relationship was revealed between the extent of LA fibrosis and AF recurrence. AF form or LA volume. Consequently, CMRI was found to be insufficient for predicting of AF recurrence (area under curve = 0.53).

Figure 1. MRI anatomy (red) overlay fluoroscopy

Conclusions: Our results confirm feasibility of CMRI for detection of LA fibrosis and its correlation with LA voltage in electroanatomic maps. However, clinical utility of CMRI for predicting of AF recurrence after catheter ablation appears to be limited.

P15002

Quantification of left atrial fibrosis by contrast-enhanced magnetic resonance imaging in patients undergoing catheter ablation for atrial fibrillation

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Background: Pre-procedural detection of left atrial (LA) fibrosis has been associated with worse outcomes of catheter ablation for atrial fibrillation (AF). In this respect, we evaluated relationship between the extent of LA fibrosis assessed by contrast-enhanced magnetic resonance imaging (CMRI) and AF recurrence after the procedure.

Methods: Before catheter radiofrequency ablation, 32 patients (pts) with paroxysmal (n=10) and persistent AF (n=22) underwent gadolinium-enhanced CMRI. LA fibrosis, defined by signal intensity >3 SD above the mean of the normal myocardium, was quantified semi-automatically and expressed as a percentage of the LA tissue. Electroanatomic voltage maps of the LA (196±72 points) were obtained by CARTO system ( Biosense Webster, Israel) in 14 pts during AF. Bipolar voltage of the entire LA was correlated with the extent of fibrosis. Pts were followed for AF recurrence prospectively for 260±183 days.

Results: Two of the CMRI studies were excluded due to poor image quality. Twenty-five pts (83%) remained in sinus rhythm during follow up. Mean LA fibrosis and bipolar voltage reached 7.4±4% and 0.6±0.3 mV, respectively. The extent of LA fibrosis showed significant exponential correlation with the mean voltage of LA (R=0.9, P=0.001), the equation: voltage (mV)=2.5(1 per cent of fibrosis). No relationship was revealed between the extent of LA fibrosis and AF recurrence. AF form or LA volume. Consequently, CMRI was found to be insufficient for predicting of AF recurrence (area under curve = 0.53).

Conclusions: Our results confirm feasibility of CMRI for detection of LA fibrosis and its correlation with LA voltage in electroanatomic maps. However, clinical utility of CMRI for predicting of AF recurrence after catheter ablation appears to be limited.

P1503

Association of common susceptibility alleles and recurrence of atrial fibrillation after catheter ablation

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Purpose: Recent genome-wide association studies have identified common alleles on chromosomes 1q21 (rs13376333), 4q25 (rs10033464 and rs2200733) and 16q22 (rs7193343) to modulate risk for atrial fibrillation (AF). In this study, we tested the hypothesis that those risk variants associate with AF recurrence after radiofrequency catheter ablation (RFCA) in a population of lone AF patients.

Methods: We studied 262 patients (68% males, mean age 57 ± 10.5 years) with paroxysmal (67%) or persistent (33%) lone AF who underwent RFCA. Genotypes were determined using real-time polymerase chain reaction and fluorescence res-
Conduction recovery following electrical superior vena cava (SVC) neurostimulation energy transfer. AF recurrence (> 30 sec) was detected using serial 7-day Holter ECG recordings immediately, as well as 3, 6 and 12 months after RFCA.

Results: Early AF recurrence (ERAF) within the first week after RFCA was observed in 46.6% and late AF recurrence (LRCAF) between 3 and 12 months in 34.4%.Minor allele frequency was 36.3% in rs13376333. 25.4% in rs7193343, 13.8% in rs10033464 and 28.2% in rs2207733. Using a dominant genetic model, variant carriers of rs7193343 (16p22) had a lower risk for both ERAF (OR 0.582, 95% CI 0.350 - 0.969, p<0.037) and LRCAF (OR 0.332, 95% CI 0.186 - 0.591, p<0.001). Similarly, an additive model predicted ERAF (OR 0.639, 95% CI 0.420 - 0.973, p<0.037) and LRCAF (OR 0.441, 95% CI 0.249 - 0.677, p<0.001). There was no significant association between other genetic or clinical variables and AF recurrence.

Conclusions: The chromosome 16p22 variant rs7193343 associates with early and late AF recurrence after RFCA of lone AF. Further studies are required to replicate these findings and explore the role of genotype-based AF therapies.

P1504

Conduction recovery following electrical superior vena cava isolation in the context of atrial fibrillation ablation: Prevalence and Electrophysiological Properties

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Introduction: Superior vena cava (SVC) is known as the source of atrial tachyarrhythmia. Reconnection between pulmonary vein (PV) and left atrium (LA) frequently occurs under Adenosin or during waiting period post PVI: PV-reconduction occurred under Adenosin in 36% of patients with chronic AF under Adenosin (or during waiting period) were marked on the 3D-map for later comparison to regional CF and FTI data. We hypothesized that different alterations of volume between the LA body and LA appendage (LAA), regardless of LA size, can predict clinical outcome following catheter ablation in patients with chronic AF.

Methods: Among 386 consecutive patients (mean 55±10.7 years, 78.8% male, 37% non-paroxysmal AF) who underwent catheter ablation of AF using a stepwise approach including circumferential pulmonary vein isolation, 284 patients with LAD≥45 mm (mean 39±6.4 mm) and 102 with LAD<45 mm (mean 36±6.4 mm) were assessed, respectively. LAA size and LA volume were calculated by multi-detector CT scan before the procedures.

Results: During the mean 21.9±15.9 months, the rate of freedom from recurrence of AF/trial tachycardia was higher in patients with LAD≥45 mm compared with those with LAD<45 mm (80.3% vs 71.8%, p=0.02). In patients with LAD≥45 mm, LAD volume and [LA+LAA] volume were significantly greater in patients with recurrence compared with those without recurrence (LAD: 40.1±3.9 mm vs 37.8±4.4 mm, p<0.001; LAA volume: 12.8±12 vs 9.3±4.0 mm, p=0.042; [LA+LAA] volume: 104.1±32.3 vs 92.3±26.7 ml, p=0.008), but there was no significant difference in LA volume (91.4±28.3 vs 87.1±26.3 ml, p=0.280). In patients with LAD<45 mm, there were no significant differences in LAD (49.9±5.2 vs 48.8±4.4 mm, p=0.257), LA volume (147.7±44.9 vs 138.5±45.7 mm, p=0.204) and [LA+LAA] volume (161.3±52.9 vs 143.0±51.4 ml, p=0.126), however, LAA volume was significantly greater in patients with recurrence than those without recurrence (15.5±8 vs 9.1±8.5 ml, p=0.02). Multivariate analysis showed that in patients with LAD≥45, LAA volume independently associated with the recurrence after AF ablation (hazard ratio 1.088, 95% CI 1.019-1.162, p=0.012).

Conclusions: LAA volume is an independent pre-procedural predictor of long-term success after catheter ablation of AF in patients with enlarged LA (LAD≥45 mm). These findings suggest that the structural remodeling of LAA in patients with chronic AF may be an important substrate related to recurrence after catheter ablation of AF.

P1505

Adenosin-mediated acute pulmonary vein reconnection occurs at regions of low contact force-time integral - a randomized trial

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Purpose: The crucial role of pulmonary veins as drivers of atrial fibrillation has been established and their isolation is one of the steps of AF ablation. Despite high rates of acute pulmonary veins isolation (PVI) during first ablation, PV reconnection is the most common mechanism of ablation failure and AF recurrence. PV reconnection was evaluated if acute (under Adenosin) and long-term (at radiofrequency sites correlated to ablation sites with low contact force (CF) or low force time integral (FTI), in patients undergoing PVI.

Methods: Multicentre trial including 80 AF patients. Wide 3D-guided PVI was performed using the Smart-Touch - CARTO3 system (BI). The first 40 patients are ablated with the operator being blinded to the CF/FTI data. Acute PVI-reconnection sites under Adenosin (or during waiting period) were marked on the 3D-map for later comparison to regional CF and FTI data. Results: From June 2011, 20 patients (65±8 yo, 38% pers. AF) were included. Adenosin-mediated acute PVI-reconnection was assessed after a 20-minute waiting period post PVI: PVI-reconnection occurred under Adenosin in 82% (45%) patients and at 27 PV-sites. Acute PVI-reconnection sites located in 81% to ablated LA sites with a CF ≥ 9g and in 87% to ablation sites with FTI values ≥420gFs. FTI was significantly higher at LA sites without PVI-reconnection than sites with PV-
recovery: 449±488gs vs 240±193gs, p<0.0007 and median: 585 (Q1:137, Q3: 324gs) vs 342gs (Q1:75gs, Q3:202gs), respectively. We observed a low ablation point density at the remaining PV-reconnection sites with higher FTI-values.

Conclusions: Low contact force during pulmonary vein isolation is the underlying mechanism of Adenosin-mediated acute PV-reconnection in 87%. Prospective use of CF measurement for PVI may significantly reduce the current high rates of PV-reconnection.

P1508
Assessment of the time-course of left atrial volume and function after atrial fibrillation ablation by speckle tracking echocardiography and the predictor of successful outcome in catheter ablation

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Purpose: We sought to examine the time-course of left atrial (LA) phasic function and volume before and after atrial fibrillation (AF) ablation and evaluate the predictor of successful ablation.

Methods: Fifty seven patients (60±9 years, 42 men) with paroxysmal AF were included and all patients underwent pulmonary vein isolation and were followed up for more than one year. LA phasic function and volume were measured just before and at 1 day, 1 week and 1 month after ablation with speckle tracking while sinus rhythm. LA total, passive and active emptying function (EF) and strain rate (SR) at systole, early diastole and atrial contraction (AC) and LA maximum, minimum and pre-AC volume were compared between successful ablation (n=42, sinus rhythm was continued for one year after ablation) and unsuccessful ablation (n=15).

Results: In successful group, LA total EF and active EF except just after ablation and LA SR at systole and SR at AC except just after ablation continued to improve, and LA maximum and minimum volume continued to decrease for 1 month after ablation. In unsuccessful group, LA total EF, active EF, LA SR at systole, LA SR at AC and volume did not make significant change (Figure). Multivariate analysis revealed that improved LA active EF at 1 week and 1 month was independently associated with successful ablation.

Conclusion: This study demonstrated that LA active contraction (contractility) was reduced just after ablation and that improved LA active EF (booster pump function) at 1 week after ablation could be a predictor of successful ablation, suggesting the recovery from stunning and initiation of reverse remodeling within 1 week after ablation in successful group. Assessment of the time-course of LA phasic function may be useful to predict successful AF ablation.

P1509
Sphericity index: a new method to assess left atrial remodelling. Impact in the outcome of atrial fibrillation ablation

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Purpose: Patient selection is crucial in obtaining good results in atrial fibrillation (AF) ablation. The aim of the study was to evaluate the usefulness of a new method to estimate AF ablation outcome based on sphericomal remodeling of the left atrium in patients with AF.

Methods: Consecutive patients who underwent a Cardiac Magnetic Resonance before AF ablation were included in the study. A 3D-reconstruction of left atrium (LA) excluding pulmonary veins and the LA appendage was used to define the LA body. Sphericity was analyzed by calculating sphericity index (SI), automatically obtained with self-customized software.

Results: We included 127 patients that were categorized in 3 groups (G): discord LA (G1), intermediate LA (G2) and spherical LA (G3). G3 patients had larger LA anteroposterior diameter (47±7, 43±6 vs 38±5mm; P<0.001) LA volume (90±39, 86±24 vs. 73±20mm; P=0.012) higher prevalence of persistent AF (75%, 48% vs. 29%; P=0.034) and structural heart disease (75%, 19% vs. 19%; P<0.001) as compared to G1 and G2 patients. Spherical LA was associated with higher prevalence of AF recurrences at 12 months follow-up (58%, 29% vs. 5%, P<0.001). SI was linearly correlated to predicted probability of recurrence. Multivariate analysis identified SI (OR 1.320 [1.096-1.591], P=0.004) and hypertension (OR 3.694 [2.82-10.645]; P=0.016) as independent risk factors for arrhythmia recurrence.

Conclusion: Sphericity Index is a powerful independent predictor of recurrence after AF ablation and may be useful in selecting the best candidates for AF ablation.

P1510
Gross anatomy of pulmonary vein ostia is not associated with history of atrial fibrillation in a series of 77 post-mortem studies

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Introduction: Ectopic activity originating from atrial myocardium extensions on pulmonary veins (PV) have been linked to the mechanisms of atrial fibrillation (AF). However, the data on anatomical substrate associated with AF are conflicting. Objective of our study was to study the gross anatomy of pulmonary vein ostia and assess the degree of muscular sleeves extension on PVs in an unselected material of consecutive autopsies.

Methods: Heart specimens examined during 77 consecutive autopsies in a tertiary care hospital (age 63±16y, 43 females) were included in the study and assessed for the presence of structural heart disease (SHD) and morphology of PV ostia. Diameter of PV ostia and the length of visible left atrial myocardium extensions on PVs (muscular cuff length) was measured using caliper. Patient records were reviewed for the presence of AF history. Autopsy reports and medical records were examined for the presence of structural heart disease (SHD) including coronary artery disease, hypertension, significant left ventricular hypertrophy and valvular disease.

Results: Patients were stratified in regard to the presence of AF and SHD so that 35 patients found to be free from SHD and AF (Group A: age 54±13 y, 16 females), 12 had SHD but not AF (Group B: age 65±14 y, 7 females) and 30 had SHD and AF (Group C: age 69±12 y, 17 females). PV ostia measurements were compared between groups but no differences were detected. The PV ostia morphology was abnormal in 19.5% of Group A, 16.7% of Group B and 23.3% of Group C.

Conclusion: The gross anatomy of pulmonary vein ostia does not appear to be associated with the history of AF.
both SHD and AF (Group C: age 74±13, 20 females). Patients with AF history were older that those without AF (74±13 vs 57±14 y, p<0.0001). There was no difference in regard to the diameter of PV ostia or the length of the muscular extensions at any of the PVs and the presence of AF history or SHD (see Table for full results).

**Conclusion:** In a largest to date material of consecutive post-mortem studies, gross morphology of pulmonary vein ostia was not associated with the history of AF in patients with SHD.

**P1511** Variability of P-wave morphology predicts the outcome of circumferential pulmonary vein isolation in patients with recurrent atrial fibrillation

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**Introduction:** Previous studies suggested that functional and structural factors make the course of atrial fibrillation (AF) progressively irreversible. Severe structural remodeling commonly indicates an irreversible damage of atrial tissue in patients with AF, leading to poor treatment, and is associated with prolongation of P-wave duration and abnormal P-wave morphology. Our aim was to study whether P-wave duration and variability of P-wave morphology (PMV) can predict outcome in patients with AF after circumferential PV isolation (CPVI).

**Methods:** Seventy consecutive patients (aged 60±9 years, 46 men) undergoing CPVI due to AF after cessation of antiarrhythmic therapy (50 paroxysmal/20 persistent AF) were studied. Standard 12-lead ECG during sinus rhythm was recorded for 10 min at baseline. The ECGs were transformed to orthogonal leads and then beat-to-beat P-wave morphology was defined automatically depending on P-wave polarity in orthogonal leads (positive/negative/biphasic) in accordance to a predefined classification algorithm. P-wave morphology that was observed in the highest number of P-waves was defined as the dominant morphology. PMV was defined as a percentage of P waves with non-dominant morphology in a 10-min sample. The patients were followed for at least 6 months and underwent 7-days Holter ECG at the end of follow-up. In case of symptoms suggesting of AF additional 24-hr Holter was scheduled. No recurrence was defined as lack of any documented episode (>360 sec) of any atrial arrhythmia between the end of the 3 months long blanking period and the end of follow-up.

**Results:** By the end of follow-up, 53 of 70 patients had no arrhythmia recurrence. Difference was observed in regard to P-wave duration between patients with and without recurrence (149±16 vs 155±23 ms, p=0.241), however PMV was greater in patients without recurrence (19.5% vs. 8.2%, p<0.001). In the multivariate logistic regression model, the variability of PWT ≥ 20% was the only independent predictor of ablation success (OR=11.4, 95% CI 1.9-92.1, p=0.020). None of other clinical characteristics such as age, gender, BMI, left atrial diameter, type of the AF or AF history duration were associated with the outcome.

**Conclusions:** We report high and significant association between the variability of P-wave morphology and 6-month CPVI success. Low PMV in patients with recurrent AF is likely to reflect severe structural remodeling and explain the failure of CPVI. Our findings warrant further studies of PMV as a marker of atrial remodeling that may be used for prediction of ablation success.

**P1512** Neurohormonal, structural and functional recovery pattern after PVC ablation in patients with depressed left ventricular ejection fraction. A prospective single centre study


Ablation of frequent, premature ventricular complexes (PVC) has been shown to be associated to a reverse remodeling in patients with PVC-induced cardiomyopathy. We have investigated the role and recovery pattern of the PVC ablation in the whole population of patients with depressed left ventricular ejection fraction.

**Methods:** We prospectively included 52 consecutive patients with frequent PVCs (≥ 10% of all QRS complexes on a 24 hr Holter) and left ventricular dysfunction. Left ventricular ejection fraction (LVEF), New York Heart Association functional class (NYHA), brain natriuretic peptide (BNP) and quality of life were evaluated before and 1 to 6 months after radiofrequency catheter ablation (RFA).

**Results:** 50% of patients had cardiomyopathy of known origin (7 ischemic heart diseases, 1 hypertensive cardiomyopathy and 3 patients with non-compaction cardiomyopathy). There was a progressive improvement in the LVEF (30.2% ± 7.1 to 46% ± 8.8, p<0.001), NYHA class (20% of patient with NYHA I to 60%, p<0.0028), BNP (154±71 to 60.9±54.2, p=0.003) and quality of life (28±14 to 10±10) after the procedure (see table). Only 30% of patients had a complete recovery of LVEF at 6 months. All patients with a LVEF <30% went out of the ICD implant indication for primary prevention.

**Conclusions:** Frequent PVC ablation in the whole group of patients with depressed LVEF induces a progressive clinical and functional improvement but only a little percentage of patients have a real PVC-induced cardiomyopathy with complete recovery to normality. Given the magnitude of the improvement, all patients with depressed LVEF should be screened for the presence of frequent PVCs; specifically those with severely depressed LVEF, as this therapy could avoid unnecessary ICD implantations.

**P1513** Left atrial appendage electrical isolation via unusual patterns

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**Introduction:** Catheter ablation of adjacent atrial sites together with pulmonary veins isolation has shown to improve the success rate in patients with non paroxysmal atrial fibrillation (AF). AF triggers within the coronary sinus (CS) and the left atrial appendage (LAA) have been recognized as non PV triggers of the AF. The aim of our study is to report unusual pattern of LAA isolation.

**Methods:** 488 consecutive patients undergoing catheter ablation for persistent or long standing persistent AF and showing firing from the LAA and or from the CS have been enrolled in this multicenter prospective study. In all patients defragmentation of the CS to achieve isolation and LAA isolation was attempted both with endocardial and epicardial ablation. During CS ablation, the circular mapping catheter was positioned into the LAA.

**Results:** In 7% of these cases (34 pts) after attempting endocardial LAA isolation, the LAA was isolated during epicardial ablation in the distal CS. In 8% of the cases (39 pts) after attempting endocardial LAA isolation, the LAA was isolated during ablation along the endocardial CS (figure). In all these cases the presence of a venous branch connecting the CS with the LAA was found. In 23% of the cases (112 pts), the isolation of the LAA also isolated the distal CS. In all these cases LAA dissociated firing was present together with the CS recording. In all the remaining cases 6% (337 pts) LAA could be isolated with endocardial segmental ablation. No peri-procedural complications were reported.

**Conclusion:** These findings suggest the presence of a distinct electrical connection between the CS and the LAA. The clinical relevance of our results requires further investigation.
Prevention of post-operative atrial fibrillation by
statin pre-treatment in patients undergoing cardiac surgery: a collaborative patient level meta-analysis of 11 randomized studies

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Background: Previous studies suggested that statin pre-treatment prevents post-operative atrial fibrillation (AF) in patients undergoing cardiac surgery. However, those data were observational and single randomized trials included limited numbers of patients.

Methods: We performed a collaborative meta-analysis using individual patient data from 11 randomized studies in which 1106 patients received before elective cardiac surgery statin therapy (N=552) vs no statin therapy (N=554). Post-operative atrial fibrillation was defined as arrhythmic episodes lasting ≥ 5 minutes.

Results: Post-operative AF occurred in 19% of patients in the statin vs 36% of those in the control group (60% risk reduction in the active treatment arm; OR by fixed effects model 0.40, 95% CI 0.30-0.53, P=0.0001). Arrhythmic prevention by statin pre-treatment was maintained across various subgroups, and appeared greater in the subset of patients with elevated baseline C-reactive protein (CRP) levels (71% risk reduction vs 54% in those with normal CRP). Pre-operative CRP levels were reduced in patients vs those with post-operative AF (1.7±3.3 vs 4±1.0 mg/L, P<0.0001) and statin pre-treatment was associated with lower baseline CRP levels (1.8±4.0 vs 2.9±7.9 mg/L in the control arm; P=0.01). Incidence of peri-operative myocardial injury (creatine kinase-MB >5x ULN or Troponin-I >1x ULN) was significantly lower in the statin arm (44% vs 56%; P=0.007).

Conclusions: Statin pre-treatment prevents from post-operative AF and peri-operative myocardial injury in patients undergoing cardiac surgery; this supports a routine early initiation of statin treatment in such patients.

Catheter ablation of atrial fibrillation: looking at the results

P1514

Intracardiac ultrasound for esophageal anatomic assessment and localization during left atrial ablation for atrial fibrillation


Background: Esophageal injury during left atrial ablation is associated with a significant risk of mortality and morbidity. There are no validated approaches to understanding of the esophageal anatomy and location. Intracardiac ultrasound (ICE) can provide a real-time assessment of the esophagus during ablation. We hypothesized that ICE can accurately define esophageal anatomy and location to enhance avoidance strategies during ablation.

Methods: Fifty patients underwent atrial fibrillation (AF) ablation. The left atrium and pulmonary vein anatomes were rendered by traditional electroanatomic mapping (CARTO). A navisat catheter within the esophagus was used to create a traditional electroanatomic esophageal anatomy. ICE imaging was used to create a second geometry of the esophagus. The traditional and ICE anatomes of the esophagus were compared and the greatest border dimensions used to avoid injury.

Results: The average age was 66±10 years. 45% had persistent/longstanding persistent AF and 18% had a prior AF ablation. The esophagus location was leftward in 17 (34%), midline in 22 (44%), and rightward in 11 (22%). Traditional esophagus and ICE imaging correlated within 1 cm in greatest distance in 26 (52%) of patients. Traditional imaging underestimated the esophageal location by >1.5 cm in 9 (18%) and >1.5 cm in 15 (30%). In those with poor correlation (>1.5 cm), the most common cause was the presence of a hiatal hernia. Ablation energy delivery was performed outside the greatest esophagus anatomy borders. Of those with 12 month follow-up, 75% were AF/atrial flutter free without those data were observational and single randomized trials included limited numbers of patients.

Conclusions: In US clinical practice, a minority of patients are managed with ablation; however, a significant portion of ablation patients had moderate or severe symptoms and required antiarrhythmic therapy after ablation. There were no differences in anticoagulation following AF ablation.

P1517

Catheter ablation of atrial fibrillation combined with dronedarone as a new hybrid therapy option

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Background: Catheter ablation has become the first line of therapy in patients with symptomatic, recurrent, drug-refractory atrial fibrillation (AF). However, results are often disappointing. An adjunctive antiarrhythmic drug therapy combined with AF ablation (+ hybrid therapy) may pose one option to enhance success. Dronedarone is a new class III antiarrhythmic drug with a favorable side effect profile. This study aimed to compare results of a conventional hybrid therapy (CHT) with class I (lecineid) or class III (amiodarone) antiarrhythmics to a novel hybrid therapy (NHT) with dronedarone.

Methods: 72 consecutive patients (48 men; mean age 62±1.12±4 years) with symptomatic paroxysmal (n=30) or persistent (n=42) drug refractory AF were enrolled in this open-label randomized study. After successful circumferential pulmonaty vein catheter ablation (CARTO-procedures) patients were randomized to receive CHT (n=36) or NHT (n=36). In the CHT group class III antiarrhythmics were continued to class I drugs. Follow-up visits were scheduled at 3, 6, 9, and 12 months post ablation. 7-day Holter monitoring and patients’ history served as indicators of treatment success. Six months post CHT antiarrhythmics were discontinued if there were no signs of AF recurrence.

Results: All ablation procedures were performed as planned. Four patients had to undergo redo procedures, so that a total of 76 procedures were evaluated. No patient had to change or discontinue the antiarrhythmic treatment regime for any reason during the follow-up period. The European Heart Rhythm Association (EHRA) score prior to ablation was 2±±0.4. After 3 months the score had changed to 1±0.4 and reached 1±0.6 after 12 months. There were statistically significant differences between the different groups in regard to EHRA score. 28 out of 72 patients (39%) experienced an arrhythmia recurrence within the first 3 months. At this point, NHT showed a significant value trend favoring SR compared to CHT. At 12 months, however, this trend had reversed: the number of patients with AF recurrences had dropped to 22 of 72 patients (31%) and CHT patients were now significantly more likely to have remained in SR (23 vs 27, p<0.05).
Conclusions: A PVI/endoablation hybrid approach to AF therapy is a safe and effective treatment option. Compared to a CHT with or without an additional left atrial ablation procedure the results with the NHT reveal similar improvements of symptoms. Despite this, CHT appears to keep significantly more patients in SR at 12 months follow-up than the NHT.

P1518 Hyperbolic ablation of long standing persistent atrial fibrillation utilizing minimal invasive surgical and endocardial catheter feasibility study

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Background: Patients (pts) with long standing atrial fibrillation (AF) usually require multiple ablation procedures with pulmonary vein isolation (PVI) and additional left atrial substrate modification to maintain sinus rhythm. The objective of this pilot study was to evaluate the safety and feasibility of a novel hybrid ablation of long standing AF using simultaneous epicardial and endocardial approach. Methods: A total of 12 consecutive pts (2 female, aged 54±2 years, LA size ≥ 47 mm2 and 62±2 mm in short and long axis respectively) with long standing AF and failure of at least one antihypertrophic drug were included. The epicardial convergent ablation was performed via a 3.5-mm-tip open-irrigated ablation catheter (41º, 25-35 W, up to 50 sec) using a 3.5-mm-tip open-irrigated ablation catheter (41º, 25-35 W, up to 50 sec) containing an array of 40 radiofrequency ablation probes, and the endocardial ablation was performed via an endoscopic subxyphoid trans-diaphragmatic access using a 58º Coagulation Device. Holter monitoring, 2D echocardiographic and CT imaging was performed. Results: AF was persisting since 36±7 months. One pt has undergone four repeated AF catheter ablations with complete reconnection of pulmonary veins after each procedure. All pts were highly symptomatic with EHRA class 4. An endocardial mapping of all pulmonary veins and endocardial procedure were performed. No complications were observed. Four pts developed a postcardiotomy syndrome, which was managed conservatively. After 3 months 5 of 7 pts were free of AF. Conclusions: A hybrid ablation of long standing persistent AF in pts with severe atrial enlargement represents a feasible and safe treatment option with high short term success rates. Further evaluation with assessment of mid- and long-term results is required.

P1519 Sufficient observation time during circumferential pulmonary vein isolation for atrial fibrillation may prevent pulmonary vein reconnection

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Introduction: Recurrence of atrial fibrillation (AF) after pulmonary vein (PV) isolation (PVI) is often associated with PV reconnection. We aimed to identify factors that predict chronic PV reconnection after circumferential PVI (CPVI) for AF.

Methods: A total of 362 PVs from 91 consecutive AF patients (72 males; mean age 60±11 years; 49 paroxysmal/42 persistent) who underwent a second ablation procedure for recurrent AF were retrospectively analyzed. In the first procedure, CPVI was performed by a point-by-point ablation technique using a 3.5-mm-tip open-irrigated ablation catheter (41º, 25-35 W, up to 50 sec) and the endocardial ablation was performed by a 3.5-mm-tip open-irrigated ablation catheter containing an array of 40 radiofrequency ablation probes, and the endocardial ablation was performed via an endoscopic subxyphoid trans-diaphragmatic access using a 3.5-mm-tip open-irrigated ablation catheter containing an array of 40 radiofrequency ablation probes. No complications were observed. Four pts developed a postcardiotomy syndrome, which was managed conservatively. After 3 months 5 of 7 pts were free of AF.

Conclusions: A hybrid ablation of long standing persistent AF in pts with severe atrial enlargement represents a feasible and safe treatment option with high short term success rates. Further evaluation with assessment of mid- and long-term results is required.

P1520 Catheter ablation vs. rate-control strategy in patients with permanent atrial fibrillation: results of five years of follow up

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Aim: To compare long-term results of radiofrequency catheter ablation (RFA) vs. rate-control strategy in patients with permanent atrial fibrillation (AF).

Methods: We assessed 5-years results in 66 pts (53±12.5 years old, 8 female, 58±7 months since the last AF attack) with a history of at least 30 min of AF on a 24-hour holter ECG for the ablation group, as well as in age- and sex- and AF duration-matched pts who were treated with rate-control strategy (rate-control group). The ablation strategy consisted of wide-area circumferential block of atrial myocardium around the pulmonary veins, roof line block, posterior box lesions with roof gaps in all pts. After the endocardial closure of roof gaps all pulmonary veins were isolated. Additionally in all pts complete roof lines, 2 pts anterior mitral valve line and 2 pts CFAEs ablation were performed. During ablation procedure 2 pts converted into sinus rhythm and 1 into atrial tachycardia. Electrical cardioversion was performed in 5 pts. No serious complications were observed. Four pts developed a postcardiotomy syndrome, which was managed conservatively. After 3 months 5 of 7 pts were free of AF.

Conclusions: A hybrid ablation of long standing persistent AF in pts with severe atrial enlargement represents a feasible and safe treatment option with high short term success rates. Further evaluation with assessment of mid- and long-term results is required.

P1521 Prolonged ablation on critical segments of left atrial pulmonary vein conduction in paroxysmal atrial fibrillation: a randomized controlled study

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Introduction: Electrical reconnection of the pulmonary veins (PV) plays a key role in recurrence of atrial fibrillation (AF) after ablation treatment. This randomized controlled study tested the hypothesis that prolongation of ablation areas on the left atrium (LA) that are at risk for LA- PV conduction can significantly reduce the rate of acute PV reconnection and AF recurrence.

Methods: Patients (pts) with symptomatic and drug-refractory paroxysmal AF were randomly assigned to a control and an add-on group. Lasso-guided ostial PV isolation was performed by point-to-point RF ablation (irrigated tip, 30 W, 30 sec). An ostial segment was assumed to be critical for LA-PV connection if any of the following reactions occurred during RF application: i. sudden delay of the LA-PV conduction, ii. change of the activation sequence on Lasso catheter or segmental isolation, and iii. PV isolation (sudden abolition of all PV potentials on Lasso catheter). If any of these reactions occurred, RF application at this site was prolonged from 30 to 90 sec in the add-on group only. A waiting time of at least 30 min was allowed for acute PV reconnection, in which case re-isolation was achieved by standard (30 sec) or prolonged (90 sec) ablation in the control and add-on group, respectively. Holter ECG was performed after 1, 3, 6 and then 12 months. At 12 months 6 pts were randomized to add-on group, as well as in age- and sex- and AF duration-matched pts who were treated with rate-control strategy (rate-control group). The ablation strategy consisted of wide-area circumferential block of atrial myocardium around the pulmonary veins, roof line block, posterior box lesions with roof gaps in all pts. After the endocardial closure of roof gaps all pulmonary veins were isolated. Additionally in all pts complete roof lines, 2 pts anterior mitral valve line and 2 pts CFAEs ablation were performed. During ablation procedure 2 pts converted into sinus rhythm and 1 into atrial tachycardia. Electrical cardioversion was performed in 5 pts. No serious complications were observed. Four pts developed a postcardiotomy syndrome, which was managed conservatively. After 3 months 5 of 7 pts were free of AF.

Conclusions: A hybrid ablation of long standing persistent AF in pts with severe atrial enlargement represents a feasible and safe treatment option with high short term success rates. Further evaluation with assessment of mid- and long-term results is required.

Analysis with prediction of chronic PV reconnection as the dependent variable, observation time (min) during the first PVI was a significant negative predictor (odds ratio 0.982, 95%CI 0.973-0.991, P<0.001) and PV diameter (mm) was a positive predictor (odds ratio 1.083, 95%CI 1.012-1.159, P=0.032) of chronic PV reconnection.

Conclusions: Sufficient observation time for whether PVI is successfully completed during the first CPVI may be needed to prevent PV reconnection and subsequent AF recurrence after CPVI.
Impact of moderate and severe sleep apnea syndrome on efficacy of first atrial fibrillation ablation (3A study)

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Background: Atrial fibrillation (AF) is frequently associated with sleep apnea syndrome (SAS). The aim of this prospective study was to estimate the relation between presence of SAS and outcome after a first AF ablation.

Methods: Seventy one patients (pts; 77.7% males, 60.7±9.6 y) with symptomatic paroxysmal AF (73.2% paroxysmal) were included. All underwent clinical evaluation, Berlin Questionnaire (BQ), transthoracic echocardiogram, and overnight polygraphic study (OPS) before pulmonary vein isolation (with possible lines/delaggregation in persistent forms). SAS were classified according to the apnea-hypopnea index (AHI, moderate if >15, severe if >30). Follow-up consisted of 3 and 6 months (M) visits with 24 Holter recording. Any episode of AF or flutter >30 seconds was considered a recurrence. No patient with SAS underwent therapy with continuous positive airway pressure device before M6.

Results: Twenty one pts (29.6%) had a high SAS risk by BQ, whereas OPS showed SAS with AHI>15 in only 16 pts (22.5% - SAS group). SAS group pts were older (65.9±9.5 vs 59.2±10.1 y, p=0.028) with lower ejection fraction (53.8±13 vs 63.4±9.3%, p=0.004) and less frequent paroxysmal forms of AF (50% vs 80%, p=0.028). No significant difference was noted for body mass index and LA size between the two groups. At M6, 25% of pts in SAS group were AF free vs 65% in the other group (p=0.009). With multivariate analysis, SAS was the stronger independent predictor of ablation failure (OR=4.85, p=0.04).

Conclusions: Moderate and severe SAS is a powerful independent predictor of failure after first AF ablation.

Indexed left atrial volume is superior to left atrial diameter as predictor of atrial fibrillation recurrence after the second pulmonary veins isolation procedure

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Background: Left atrium (LA) enlargement may lower the success of atrial fibrillation (AF) catheter ablation independently of the persistence of the pulmonary veins isolation (PVI). Although indexed LA volume (iLAV) is a more accurate measure of the LA size compared to antero-posterior LA diameter (AP-LAD), its role in predicting AF recurrences after PVI has been scarcely investigated. Our aim was to evaluate this parameter in a population submitted to a second PVI procedure in long-term follow-up study.

Methods: 70 consecutive pts (mean age 57.2±8.8 y, 88.5%men) submitted to a second PVI procedure for recurrent AF, and with a follow-up duration longer than 12 months entered the study. iLAV was measured during 2D echocardiogram off-line analysis using the Simpson’s method. Pts clinical characteristics and post-PVI outcomes were evaluated by systematic review of the medical records according to 2007 HRS/EHRA/ECAS expert consensus statement recommendations.

Results: During a 52.2±19.4 month follow-up duration, AF recurred in 33 patients (47.1%) pts. iLAV was significantly larger in pts with AF relapse compared to pts with AF remission (39.3±4.8 vs 34.3±3.7, p < 0.001). Each unit increase in iLAV was associated with a 1.32-fold increased risk of AF recurrence (OR 1.32, CI 1.14-1.52, p < 0.001). AP-LAD resulted nonsignificantly different between the two groups (41.7±5.0 vs 39.0±5.3 mm, p=0.06). Another parameter resulted increased in patients with AF relapse was the indexed left ventricular mass (128.9±26.3 vs 113.7±27.0 g/m², p=0.02, OR 1.02, CI 1.00-1.04). In a multivariable model iLAV was the only independent predictor of AF recurrence (adjusted OR 1.25, CI 1.07-1.47, p=0.001). The area under ROC curves generated to compare AP-LAD and iLAV as AF recurrence predictors were 0.62 and 0.78 respectively (p<0.01).

Conclusions: These data demonstrate for first time that enlarged iLAV is strongly and independently associated with a higher risk of AF recurrence after a second PVI procedure in long-term follow-up study. iLAV is superior to AP-LAD in predicting the procedure outcome presumably because it gives a better estimation of LA remodeling. Further studies should evaluate the need of different ablation strategies in this high-risk population.

Pulmonary vein isolation as single interventional treatment for persistent atrial fibrillation: prognostic value of the left atrial size

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Background: The optimal ablation strategy for persistent atrial fibrillation (AF) remains to be determined. Pulmonary vein isolation (PVI) is usually considered as the first step of the ablation treatment, followed by ablation lines and/or targeting of complex fractionated atrial electrograms. The left atrial (LA) size is a significant predictor of ablation outcome in persistent AF, irrespective of the ablation strategy. We hypothesised that LA surface area as measured by echocardiography could be used for selection of the optimal ablation protocol (PVI vs. more extensive ablation) for each individual patient (pt).

Methods: Hundred twenty six pts (75 men, mean age: 60.1±12 years) with drug-refractory persistent AF were included. An echocardiographic examination was performed one day before the intervention and standard echocardiographic parameters were measured. Maximal LA surface area (LAS) was determined at four chamber view and immediately before opening of the mitral valve. As all patients were in atrial fibrillation during echocardiography the longest of ten consecutive RR intervals was used for LAS and LA diameter (LAD) measurement. The ablation procedure included PVI without additional ablation lesions. If a second ablation was needed this included only resolation of the reconnected PVs.

Results: After the first PVI AF recurred in 70 (45%) pts. A second ablation procedure in performed in 68 pts (54%) 4±3 months after the initial procedure. During a mean follow-up of 24±8 months 53 (42%) pts experienced no AF recurrence after the last ablative treatment (5 pts on antithrombotic medication). Pts with a successful outcome had a significantly smaller LAS before ablation treatment than pts with AF recurrence (23.4±3 vs 30.7±7 cm², p=0.001). By discrimination analysis a cut-off value of 26 cm² had the best predictability of outcome with a sensitivity and specificity of 82 and 71%, respectively. 57 out of 66 (86%) pts with LAS≤26 cm² and only 21 out of 60 (35%) pts with LAS>26 cm² had a successful outcome (OR 11.7, 95% CI 5.3-26.3, p<0.001).

Conclusions: In patients with persistent AF and LAS≤26 cm² as measured by echocardiography, PVI without additional lesions is a very effective ablative treatment.

P1525 Long-term course after atrial fibrillation ablation in patients with impaired left ventricular systolic function: The Leipzig experience


Purpose: Left atrial (LA) ablation is increasingly being used to treat atrial fibrillation (AF) in patients with left ventricular (LV) dysfunction. Several studies have reported partial restoration of ejection fraction (EF) after AF ablation, but little is known about the temporal LV-EF change. Aim of this study was to assess long-term effect of AF ablation on LV function.

Methods: We prospectively followed 70 consecutive patients (57 men, 82%) with AF and impaired LV-EF (<40%) who underwent percutaneous left atrial appendage occlusion or crux isolation with or without additional substrate modification, from 2007 to 2010 in our institution. Follow-up (FU) was performed with sequential 7-days holter ECGs and echocardiography control at baseline and at 6, 12 and 24 months (m) after catheter ablation. Patients were stratified according to the maintenance of sinus rhythm (SR) or to AF recurrence.

Results: Patients were 58.1±14 years old with mean LVEF 32.6±2%, mean LVEDD 59.1±13 mm, mean LA diameter 47.9±9 mm, hypertension (80%, 56 pts.), coronary heart disease (46%, 32 pts.) and paroxysmal (33%, 22 pts.) or persistent (67%, 47 pts.) AF. Over a mean follow-up of 21±12 months, LVEF in patients with stable SR (n=52, 74%), SSR improved from 33.6% to 50.12%, whereas in pts with AF recurrence (RCR) LVEF increased (n=18, 26%) from 29.7% to 39.12% (p=0.05) after 1.5±0.7 ablations. Both groups showed a significant LV-EF increase from baseline to 6M-FU. In the SSR group, there was a significant further LVEF increase after the 24M-FU, whereas RCR pts did not further improve.

Conclusions: In AF patients with impaired left ventricular function, sustainability of the LVEF improvement after catheter ablation is strongly dependent on ablation success over the long term.

Is atrial fibrillation recurrence after ablation treatment predictable? Lessons from serial Holter ECG recordings

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Introduction: Recurrence of atrial fibrillation (AF) after ablation treatment is not uncommon. Although predictors of lower success rates like left atrial enlargement...
and duration of AF have been identified, the individual risk of AF recurrence after ablative treatment remains unknown. In this study serial Holter ECG recordings were analyzed in order to test the hypothesis that occurrence of ectopic atrial activity after ablation is a predictor of AF recurrence.

**Methods:** Patients (pts) with symptomatic paroxysmal AF and normal left ventricular function were included. 24-hr Holter ECG recordings were obtained from each of 25 pts. Ablative study ruling out any cardiac arrhythmia by means of radiofrequency energy or cryoablation. AF recurrence was defined as any AF episode with a duration of more than 30 sec. Ectopic atrial activity (EAA) was defined as “slow” or “fast” if mean cycle length (MCL) of EAA was shorter or longer than 50% of the MCL of sinus rhythm in the last 60 sec before EAA occurred, respectively.

**Results:** The study included 174 pts (m/f: 130/44, age: 56±12 yrs). Eighty-two pts were lost to follow-up and excluded from the analysis. Five pts (3%) remained on antiarrhythmic drugs because of highly symptomatic palpitations. Following up-EAA occurred in 77 (46%) pts (slow EAA in 36 and fast EAA in 41 pts); 74% (45) pts had AF recurrence. Pts with ectopic atrial activity (EAA) had a higher risk of AF recurrence than pts without EAA (52 out of 77 vs 22 out of 89 pts, or 62 vs 25%, OR: 2.63, 95% CI: 1.5-4.7, p<0.001). There were no differences between the three EAA burden groups in relation to the risk for AF (p=0.78, intermediate: 50% vs high EAA:74%, p=0.05). AF recurred in 14 out of 36 (39%) pts with slow EAA and in 24 out of 41 (59%) pts with fast EAA (OR: 5.7, 95% CI: 1.6-20.7, p=0.007).

**Conclusion:** In pts with paroxysmal AF, appearance of ectopic atrial activity after pulmonary vein isolation associates with a significantly increased risk for AF recurrence. This risk is mainly determined by the cycle length and not the burden of EAA. Fast EAA associates with the highest risk of AF recurrence.

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**P1527**

**Results of radiofrequency ablation of atrial fibrillation in patients undergoing mitral valve repair for barlow disease**

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At present limited experience exist on concomitant treatment of AF in patients undergoing MV repair for Barlow disease. Aim of the present investigation was to prospectively evaluate the results of radiofrequency ablation in patients undergoing MV repair for severe regurgitation due to Barlow disease.

**Materials and Methods:** From January 1st 2007 to December 31, 2010, among 85 consecutive patients with Barlow disease, 27 underwent monopolar (2 patients, 7.4%) or bipolar (25 patients, 92.6%) radiofrequency ablation, associated with MV repair at the Heart Surgery Department of the AOUI Careggi. Fifteen were men and 12 were women, mean age was 69.2±12.5 years (IR: 34-45 years). Twenty-one (76.4%) patients were in permanent AF, whereas 6 (22.2%) suffered from paroxysmal AF. Twenty-five (81.5%) patients were in NYHA functional class II or III before surgery; mean left ventricular ejection fraction was 57.9±7.4% and almost all patients (26/27; 96.3%) had severe MV regurgitation. Overall duration of follow-up was 780 days.

**Results:** There were neither intraoperative nor postoperative in-hospital deaths. No early failure of MV repair was observed. Overall mortality during follow-up was 2/27 (7.4%). AF was observed in 3 (11.1%) patients at discharge: in the first one sinus rhythm was never restored whereas in the other two patients AF recurred tree and four days after restoration of sinus rhythm, respectively. Among the patients enrolled, 4 had a further hospitalization during follow-up: 2 patients with hospitalisation for the occurrence of a stroke (2.5 years and 2 months after surgery, respectively) and the other 2 to underwent DC shock for AF recurrence. At the last follow-up NYHA functional class improved significantly, none was in class III or IV and AF was observed in 4/25 (16%) patients: AF recurrence occurred after the restoration of sinus rhythm in 3 of them, while in one subject it never disappeared after ablation. Transesophageal echocardiography performed during the follow-up showed a significant decrease in left atrium volume and area, with minor changes in left ventricular diameters. Similarly a significant decrease of pulmonary artery pressure occurred after surgery. Suboptimal results of MV repair (v.c.=0.3) was found in 5/25 patients. Only one of them was in AF.

**Conclusion:** Radiofrequency ablation of AF in patients with MV bileaflet prolapse undergoing MV repair for severe regurgitation due to Barlow disease has proved to be effective: 21/25 (84%) of patients were in sinus rhythm at the end of follow-up. Any correlation between suboptimal results of MV repair and AF recurrence was found.

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**P1528**

**Impact of atrial fibrillation induced-tachycardioymopathy in the outcome of catheter ablation**


**Purpose:** Tachycardioymopathy (TMAP) is relatively common in patients with persistant atrial fibrillation (AF) and has a class IIb indication for pulmonary vein isolation (PVI). Our objective was to analyze whether TMAP had a negative impact in the result of AF ablation.

**Methods:** Patients undergoing PVI from 2003 through January 2011 were evaluated and divided into 2 groups according to the following criteria: 1) TMAP group: Patients with AF, ejection fraction (LVEF) <55%, and previous report of partial or complete reversion of LVEF after normalization of the heart rate and an extensive drug treatment; 2) Control group: Patients without cardiomyopathy and normal LVEF. Follow-up was performed every 3 months and each visit included a 12-lead ECG and 24-h Holter monitoring. At 6 months follow-up, a thorough echocardiography was performed. Arrhythmia recurrence was defined as any episode of AF or other atrial tachycardia longer than 30 seconds and recorded beyond the first 3 months post-PVI.

**Summary:** A total of 610 patients submitted to PVI were included: TMAP group (n=50) and control group (n=560). Compared to control group, patients with TMAP were younger (53y in TMAP group vs. 49y in control group, P<0.03) were more likely to be in persistent AF (78% vs. 39%, P<0.001), and had a shorter duration of AF (41m vs. 61m, P=0.03) and a larger left atrium (LA) (46.5±5 mm vs.41.5±5 mm, P<0.001). The Kaplan-Meier analysis showed no differences in AF recurrence between patients with TMAP and controls after 1 procedure (log rank test P=0.43) or repeat procedures (log rank test P=0.204). After PVI, patients with TMAP experienced significant improvement in LVEF (39.9±9% pre-PVI vs. 52.4±11% post-PVI, P<0.001) and in LA antero-posterior diameter (45.9±5.5 mm pre-PVI vs. 42.7±5.6 mm post-PVI, P<0.001).

**Conclusion:** Patients with AF induced-TMAP are younger, more often have persistent AF and a larger LA than patients with no structural cardiomyopathy. This group of patients benefit from catheter ablation, with a significant improvement in LVEF and LA size. The results of catheter ablation in patients with TMAP do not differ from patients with normal ejection fraction.
Detection of atrial fibrillation recurrences and atypical flutters by implantable cardiac monitor, after pulmonary veins isolation: 6 and 12-month results

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Purpose: After pulmonary veins isolation (PVI), Atypical Flutter (AF) can arise, associated or not with Atrial Fibrillation (AF) recurrence. During the Rapid XT study, standard follow-ups (FU), with ECG and 24-hr holters, were compared to continuous ECG recordings by Implantable Cardiac Monitors (ICM) designed to detect AF.

Methods: 47 patients eligible for AF ablation were included in the study. The ICM was implanted 35±8 days before ablation to provide baseline AF burden data. FU were performed at 1, 3, 6 and 12 Months (M) after ablation; 40 patients completed their 6M and 12M-FU: 36 men, 4 women, mean age 60±9 yrs, with persistent AF in 55.5% and paroxysmal AF in 45.5%. The specificity of this cohort was large atrias, with long history of AF.

Results: At 6 M-FU, recurrence of atrial arrhythmia occurred in 15/40 patients (37.5%), 5 AF and 10 AF. Recurrences were diagnosed both by standard FU and ICM continuous monitoring. ICM monitoring successfully diagnosed the flutters as bi-arrhythmia and/or organized atrial activity. Moreover it disclosed the coexistence of flutters in patients presenting AF as a recurrence of arrhythmia. AF occurred mainly between 1-3 M after the procedure (19±15.5 M). In patients with AF, redo procedure targeting both pulmonary vein isolation and atrial flutter (which proved to be left sided in all cases). At 12 M-FU, discrete monitoring diagnosed recurrence in 10/40 patients (success rate of 75%) and ICM continuous monitoring diagnosed arrhythmia recurrences in 7 more patients not diagnosed by discrete monitoring (decrease of success rate to 57.5%). These were asymptomatic recurrences from 3 to 5 hours duration with embolic risk.

AF burden associated by Rapid XT

<table>
<thead>
<tr>
<th>Paroxysmal AF (45%, n=18)</th>
<th>Persistent AF (55%, n=22)</th>
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</thead>
<tbody>
<tr>
<td>Baseline AF burden</td>
<td>12M AF burden</td>
</tr>
<tr>
<td>(% time in AF)</td>
<td>(% time in AF)</td>
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<tr>
<td>15.7±5.39</td>
<td>45.1±6.99</td>
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</tbody>
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P < 0.05

Conclusions: At 6M-FU the ICM detected atrial flutters in all patients with recurrent arrhythmias providing valuable information for designing redo procedures. At 12M after PVI there is a significant decrease of AF Burden, in both populations. Moreover the ICM detected asymptomatic sporadic recurrences (not detected by standard FU) of several hours leading to embolic risk, with antithrombotic therapeutical decision.

Catheter ablation of atrial fibrillation improves left ventricular diastolic function in patients with heart failure with preserved ejection fraction: 1 year follow-up echocardiographic data

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Purpose: Atrial fibrillation (AF) has been known to be associated with left ventricular (LV) diastolic dysfunction. However, it is unclear whether AF rhythm control during or after ablation can improve LV diastolic function.

Methods: We included 267 patients with AF (male 77.5%, 55.9 ± 11.0 years old, paroxysmal 45%, n = 120) who underwent RFCA, and compared pre-procedural and post-RFCA 1-year follow-up echocardiography. The early transmitral flow velocity (E) and early mitral annular velocity (E') were measured by Doppler imaging.

Results: 1. AF catheter ablation significantly reduces left atrium (LA) size (pre 41.48 ± 6.07 mm vs. post 38.45 ± 5.73 mm, p < 0.001) and improves LV ejection fraction (EF; pre 63.36 ± 0.18mm/sec vs. post 0.73 ± 0.20mm/sec, p < 0.001) became significantly decreased 1 year after RFCA. 4. During 20.30±4.79 months follow-up, the clinical recurrence rate of AF were not different in patients with E/E' < 15 and those with E/E' ≥ 15.

Conclusions: AF catheter ablation not only improves LV systolic function and induces reverse remodeling of LA at 1 year follow-up, but also significantly improves LV diastolic function in patients with HFPEF.

Patients treated with catheter ablation for atrial fibrillation have favorable long-term renal function similar to patients without atrial fibrillation


Introduction: Atrial fibrillation (AF) has been reported to worsen renal function over time. Renal dysfunction in the setting of AF decreases response to rhythm control approaches and increases risk of cardiovascular morbidity and mortality. Aggressive rhythm control approaches, such as catheter ablation, may interrupt this cycle and impact renal function favorably over time.

Methods: Patients were enrolled from the large ongoing prospective Intermountain Cardiovascular Health Study. A total of 1,983 consecutive patients who underwent AF ablation that has serial assessment of kidney function were compared to a cohort of 4,996 patients with AF (no ablation) and 19,154 without AF derived from the catheterization database.

Results: Patients with AF were older compared to catheterization controls (66.2 vs 56.7, p < 0.0001). Ablation patients compared to no ablation patients had lower rates of dyslipidemia (40% vs 29%, p < 0.0001), heart failure (12% vs 32%, p < 0.0001), and coronary artery disease (32% vs 52%, p < 0.0001).

Conclusions: Renal function and failure rates over time in patients with AF that receive an ablation are similar to patients without AF. These data suggest that aggressive rhythm control strategies may minimize the adverse influence of the arrhythmia on long-term renal function.

Pulmonary vein isolation at the first round predicts no arrhythmia recurrence following circumferential pulmonary vein isolation

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Purpose: Circumferential pulmonary vein isolation (CPVI) is widely used for atrial fibrillation (AF) ablation and electrical disconnection of pulmonary veins (PV) is necessary. However, we sometimes experience the difficulty to achieve PV isolation. In this study, we evaluated the relation between the difficulty of CPVI and arrhythmia recurrence.

Methods: Forty one consecutive patients (32 males, 63.7±7.5 years) with drug-refractory paroxysmal AF underwent CPVI. CPVI was performed using electroanatomic mapping system, with the endpoint of electrical disconnection of ipsilateral PIVs (IPVs) confirmed by a circular mapping catheter. After the first round of ablation, we assessed the disconnection of IPVs. If the disconnection was not achieved, additional ablation was applied at the earliest activation sites on the CPVI ablation line, and then inside the line.

Results: 37 (45%) of all PIVs (82) were electrically isolated after the first round of CPVI. Next, the additional ablation to the gap on the CPVI line was performed to 45 unisolated PIVs, and 36 (44%) of them were isolated. The ablation inside the CPVI line was required in the remaining 9 PIVs (11%) to achieve completion of electrical isolation of all PIVs. During mean follow-up of 12 months after a single procedure, 31 patients (76%) were free from arrhythmia recurrence without antiarrhythmic drugs. Among patients free from arrhythmias, PIVs disconnection was more likely completed just after the first round of CPVI, compared to patients with arrhythmia recurrences (34 (55%) vs 3 (15%) IPs, respectively P=0.028).

In multivariate analysis, IPs isolation after the first round of CPVI predicted the single procedure success without antiarrhythmic drugs (OR: 0.225, 95% confidence interval: 0.056-0.909, P=0.038), whereas age, gender, left atrial size, left ventricular ejection fraction, and the requirement of additional ablation inside the CPVI line did not predict arrhythmia recurrences.

Conclusions: In patients with paroxysmal AF, the completion of CPVI after the first round of ablation predicts the single procedure efficacy.
Methods: We conducted a retrospective single-center cohort study. Among 1016 patients who underwent first ablation for AF from 2004 to 2010, 692 patients received final follow-up in 2011. Out of these 692 subjects, we included 392 patients who did not experience AF recurrence within 1 year after ablation in this study and followed them for 2.7±1.5 years (mean±SD). We identified a very late recurrence (VLR) of AF, defined as an initial AF recurrence occurring more than one year after AF ablation, and then estimated the risk factors of VLR by Cox regression analysis. Factors with a p-value ≤ 0.10 in univariate analysis were included in this analysis.

Results: The annual rate of VLR was 6.0% a year. History of hypertension, abnormally high C-reactive protein (CRP ≥ 0.5 mg/dl), presence of moderate to severe mitral regurgitation, decreased mitral annulus velocity and period of AF persisting more than one year (long-standing persistent AF) were included in the Cox regression analysis. Finally we revealed that abnormally high CRP (HR, 5.12; 95% CI 2.39 to 10.96; p = 0.0001), and long-standing persistent AF (HR, 2.47; 95% CI 1.09 to 5.60; p = 0.03) were the independent risk factors of VLR.

Conclusion: Abnormally high CRP and long-standing persistent AF were significant predictors of AF recurrence after VLR. Consequently, long-term follow-up is necessary in patients with these risk factors.
Catheter ablation of atrial fibrillation: looking at the results
In patients undergoing ablation of long standing persistent AF amiodarone increases the AF termination during ablation but reduces the long term success: preliminary results from the speculate study

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Introduction: Antiarrhythmic drugs (AADs) discontinuation before ablation of long standing persistent (LSP) atrial fibrillation (AF) is controversial. To wash out the effect of Amiodarone (AM) up to 6 months are required. Our study aims to investigate the role of AM in influencing follow-up outcomes in LSP-AF pts undergoing ablation.

Methods: 105 pts (pts) treated with AM for LSP-AF and undergoing catheter ablation for LSP AF have been enrolled in this prospective randomized multicenter study. Patients were randomized to AM discontinuation 4 to 6 months before ablation (group 1, n = 53) and to a control group (group 2, n = 52) where the ablation was performed without AM discontinuation. All pts underwent pulmonary vein antrum and posterior wall isolation and extra PV triggers ablation. In group1 pts were not treated with AM during the blanking period (8 weeks post-ablation) while group 2 group 2 AM to AM up to the end of the blank period.

Results: Baseline characteristics were not different between the 2 groups in term of sex, age, heart failure and comorbidities. Group 2 had a higher number of pts with AF termination during ablation (including the conversion to atrial tachyarrhythmias) when compared to group 1 [41 (78%) vs. 31 (56%), p=0.025] and a lower number of extra PVs [22 (42%) vs.38 (72%), p=0.002]. At the 6 months follow-up group 2 had a similar freedom from AF/AT [38 (72%) group 1 vs. 39 (75%) group 2, p=0.702], but at the long term follow up of 32±8 months, group 1 had a higher success rate off AADS [35 (66%) vs. 18 (34%), p<0.001], see figure.

Conclusions: Our preliminary results suggest that AF ablation without AM discontinuation result in higher peri-procedural AF termination but it is associated with an increased long term arrhythmia recurrence due to non pulmonary vein triggers.

Efficacy, safety, and outcome of atrial fibrillation ablation in the elderly

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Introduction: The incidence and prevalence of atrial fibrillation (AF) increase with age. Catheter ablation of atrial fibrillation (AF) has become a treatment option for younger patients with drug-refractory AF. With improved safety, the therapy has been offered to older populations. However, the outcome of AF ablation in the elderly is not clear. AIM: To compare success rate, outcome, and complication rate of AF ablation in the elderly (>70 years) versus the younger population.

Methods: We retrospectively analyzed 948 consecutive patients that had undergone a first catheter ablation for drug-refractorysymptomatic AF from 2003 to 2011. Patients were divided into two groups: (G1) >70 years (804 p) and (G2) >70 years (44 p). AF ablation consisted of pulmonary vein antral isolation with or without additional linear lesions and/or complex fractionated electrogram ablation. Follow-up was performed at 1,3, 6 months after the procedure and every 6 months thereafter. After a 3-month blanking period, recurrence was defined as the occurrence of any arrhythmia of >30 seconds.

Results: Baseline characteristics among the two groups only differed in gender (79%males in G1 vs 46% in G2, p=0.001), presence of hypertension (36% in G1 and 56% in G2, p=0.003) and the duration of AF (77.2±60.2 months in G1 and 88.9±71.2 months in G2, p=0.006). No significant differences were observed between the groups in terms of type of AF, structural cardiomyopathy, history of stroke, sleep apnea or sport practice. LA diametre, ejection fraction, nor any other arrhythmia predictor. Procedural time (152.7±50.7 vs 135.4±50.7 min, p=0.04) and RF duration (48.9±16.9 vs 37.1±15 min, p=0.04) were shorter in G2.There were no differences in the type of ablation lesions. The overall incidence of complications was also similar between groups. However, there were 2 strokes the group ≥70 years, and this was significantly different to the younger patients (0.8% in G1 versus 4.5% in G2, p=0.012). There were no deaths. Recurrence rate at 12-months was similar among groups (30.2% in G1 and31.8 in G2, p=0.867). After a mean follow-up 15.6±15.6 months, there was no significant difference in the arrhythmia-free survival curve after a first procedure of AF ablation between the two groups (log-rank p=0.881). Cox-regression analysis confirmed the log–rank test results (HR 0.963 [IC95% 0.573-1.617]; p=0.885).

Conclusion: AF ablation is a safe and effective treatment for AF in the older patients. However, special care must be taken with anticoagulation management, for there could be a higher risk of peri-procedural thromboembolic events.

No benefit of adding antiplatelets to oral anticoagulation therapy on stroke risk in atrial fibrillation patients following myocardial infarction or coronary intervention: a nationwide study

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Purpose: The optimal strategy to prevent stroke in patients with atrial fibrillation (AF) requiring multiple antithrombotic drugs after myocardial infarction (MI) or coronary intervention (PCI) is unresolved. We investigated the risk of ischemic stroke according to history of stroke and ongoing antithrombotic treatment in AF patients after MI or PCI.

Methods: AF patients hospitalized with MI or undergoing PCI between 2001 and 2009 were identified by individual-level-linkage of nationwide registries. The incidence rate of ischemic stroke according to post-discharge antithrombotic treatment regimens (any combination of aspirin, clopidogrel, vitamin K antagonists (VKA)) was estimated and further analyzed by adjusted Cox regression models, with a maximal follow-up of 3 years.

Results: Of 11,924 patients included (61% males, mean age 75.6 years, SD 70 years) versus the younger population.

Conclusion: In patients with indication for multiple antithrombotic drugs due to AF and MI/PCI, no beneficial effect on ischemic stroke risk was observed for triple therapy or antiplatelets added to VKA compared to monotherapy with VKA. Patients with prior stroke were at considerably high risk.

Temporal trends in hospitalization rates for stroke in Canada, 2002-2009


Purpose: Over the past decade, the rate of hospitalization for stroke in Canada has declined. However, recent data on the influence of age and gender on this trend, as well as the etiology and length of stay (LOS) underlying it, have
Temporal relationship between stroke/thromboembolic events and atrial fibrillation episodes in patients wearing implantable cardioverter defibrillators

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Purpose: Atrial fibrillation (AF) is a well established risk factor for stroke and thromboembolism and is a frequent comorbid arrhythmia in patients with implantable cardioverter defibrillators (ICD).

Aim of our analysis was to evaluate time distance between the occurrence of embolic events and AF episodes as detected by ICD AF diagnostics.

Methods: Fifty Italian cardiology clinics followed 3438 ICD patients (2802 male, 71±11 years). All patients received a dual- or triple-chamber ICD for primary or secondary prevention who started oral anticoagulation (OAC) therapy; the median time from discharge to antiplatelet therapy discontinuation was 12 days, the rate of AF increased with age and males of all ages experienced a higher rate of hospitalization cases and non-gastrointestinal in 6). Within 12 months from discharge, 268 patients (21.6%) discontinued antiplatelet therapy; the median time from discharge to antiplatelet therapy discontinuation was 12 days. Patients with atrial fibrillation (AF) history or new-onset AF, 22 patients suffered 25 embolic events, specifically 8 ischemic strokes, 9 TIAs and 8 peripheral thromboembolic complications, with an embolic events rate of 0.7 per 100 patient-years. In the remaining 2264 patients who never suffered AF, 11 patients suffered embolic events, with an annual rate of 0.2 per 100 patient-years (P=0.001 vs patients with AF). Among 33 patients with stroke, TIA or embolic incidents, 22/33 (67%) patients had at least 5 minute long AF, as detected by device diagnostics, in the observation period preceding thromboembolic events. When evaluating the 30 days preceding thromboembolic events, 11/33 (33%) patients suffered AF. Finally 5/33 (15%) patients suffered embolic events during AF.

Results: In a median follow-up of 25 months (interquartile range 14-41 months, total follow-up of 9118 patient-years) 1174 (34%) patients had AF, either described in their pre-implant clinical history (713 or 21%) or observed during follow up (461 or 13%) as new onset of AF. During the follow-up period 37 embolic events in 33 patients were recorded, in particular 17 ischemic stroke, 10 transient ischemic attacks and 10 peripheral thromboembolic complications. Among 1174 patients with AF history or new-onset AF, 22 patients suffered 25 embolic events, specifically 8 ischemic strokes, 9 TIAs and 8 peripheral thromboembolic complications, with an embolic events rate of 0.7 per 100 patient-years. In the remaining 2264 patients who never suffered AF, 11 patients suffered embolic events, with an annual rate of 0.2 per 100 patient-years (P=0.001 vs patients with AF). Among 33 patients with stroke, TIA or embolic incidents, 22/33 (67%) patients had at least 5 minute long AF, as detected by device diagnostics, in the observation period preceding thromboembolic events. When evaluating the 30 days preceding thromboembolic events, 11/33 (33%) patients suffered AF. Finally 5/33 (15%) patients suffered embolic events during AF.

Conclusions: Our analysis shows that AF has a temporal relationship with thromboembolic events in 15-33% of cases. This finding may be useful for trying to assess the impact on stroke/thromboembolic events of strategies targeted to suppress/control AF episodes.

P1550 Stopping oral anticoagulation is associated with the risk of thrombotic events and mortality in patients with atrial fibrillation

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It has been described that the incidence of stroke and major hemorrhagic events is higher during the period after initiation anti-vitamins K antagonist (VKAs), naive patients. Whereas those patients who are experienced on VKA should have less complications. By the other way, bleeding complications are usually associated with stopping anticoagulation, or the fear of experiencing a major hemorrhagic event could lead to take off the treatment by the physician or the patient. The aim of our study was to evaluate clinical outcomes of a consecutive population of patients with atrial fibrillation who stopped anticoagulant therapy.

Methods: During 2009 we included all the patients with paroxysmal or permanent atrial fibrillation who initiated oral anticoagulation in our anticoagulation outpatient clinic. Patients were followed-up for two years, and adverse events (thrombotic and vascular episodes, major haemorrhage and death) were recorded as well as the giving up of oral anticoagulation.

Results: During follow-up 63 patients suffer from a thrombotic/cardiovascular event (annual rate 3.7%), 11 patients stopped anticoagulation during this period (secondary to a bleeding episode, 37 after restoration of sinus rhythm, 45 stopped by the patient or his/her physician advice, and 10 changed to another anticoagulant therapy). During follow-up 63 patients suffer from a thrombotic/cardiovascular event (annual rate 3.7%), 11 patients stopped anticoagulation during this period (secondary to a bleeding episode, 37 after restoration of sinus rhythm, 45 stopped by the patient or his/her physician advice, and 10 changed to another anticoagulant therapy).

Patients: We included 529 patients, 49% male, median age 76 (IQR 69-82), 192 patients ≥80 years old. Median (IQR) CHADS2 2 (1-3), CHA2DS2-VASC 4 (3-5) and HAS-BLED 2 (2-3). During the follow-up, median 835 days (IQR 719-954), 115 patients stopped anticoagulation during this period (23 secondary to a bleeding episode, 37 after restoration of sinus rhythm, 45 stopped by the patient or his/her physician advice, and 10 changed to another anticoagulant therapy). During follow-up 63 patients suffered from a thrombotic/cardiovascular event (annual rate 3.7%), 11 patients stopped anticoagulation during this period (secondary to a bleeding episode, 37 after restoration of sinus rhythm, 45 stopped by the patient or his/her physician advice, and 10 changed to another anticoagulant therapy).

Conclusions: The giving up of oral anticoagulation is associated with the risk of thrombotic events and mortality in patients with atrial fibrillation.
Diagnosis of stroke in the acute vertiginous patient: a bedside three steps tool in the emergency department

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Background: Vertigo is generally due to a benign peripheral disorder, but it is also the symptom most commonly associated with a missed diagnosis of vertebrobasilar stroke. We investigated a bedside structured examination (CODIT: COrinious Direction Impulse Test) to differentiate central from peripheral vestibulopathy.

Methods: Consecutive adult patients presenting to our Emergency Department (from May 2011 to January 2012) with isolated vertigo were prospectively evaluated with CODIT by five trained emergency physicians or ordinarly by the rest of the medical staff (controls). The CODIT consists of three steps: 1) type of nystagmus: positional nystagmus was considered typical of peripheral vestibulopathy, when central nystagmus was present the direction was examined 2) Fluidic- and vertical nystagmus indicated central vestibulopathy. When monodirectional nystagmus was present head impulse test (HIT) was performed. 3) Negative HIT indicated central vestibulopathy. Complete neuro-otological examination was the gold standard. If central origin was suspected, patients underwent objective neuroimaging tests (RM or CT). Test characteristics, neuroimaging tests and hospitalization rates were the main outcome measures.

Results: A total of 292 patients with isolated vertigo were evaluated: fifty-two (17.8%) had central and 240 (82.2%) had peripheral vestibulopathy. Ninety-seven out of 292 patients were evaluated with the CODIT. The CODIT showed a 100% sensitivity (CI 95%:80.3-100%) and 97.6% specificity (CI 95%: 94-97.6%) for central vestibulopathy. Hospitalization and neuroimaging rates were significantly lower in patients evaluated by the CODIT (27.6% and 28.6%) than in controls (50.3% and 70.5% respectively, P<0.01 for both).

Conclusion: The CODIT identified central vestibulopathy with a very high sensitivity, reducing neuroimaging tests and hospitalization rate.

Left atrial volume index is an independent predictor of mortality after a first-ever acute ischemic stroke

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Background: Although an enlarged left atrium has recently emerged as a marker of adverse outcomes in various diseases, its prognostic value in acute ischemic stroke is unknown. We studied whether left atrial volume index (LAVI) predicts mortality after acute ischemic stroke.

Methods: We prospectively followed 310 consecutive first-ever acute ischemic stroke patients aged ≥50 years who were admitted to the hospital within 24 hours of the onset of stroke symptoms. The type of acute ischemic stroke was classified according to the TOAST classification. All of the patients underwent transthoracic echocardiography within the first 24 hours. Left atrial volume index was measured with the biplane area-length method and categorized as <28 mml2 (normal), 28.1 to 32 mml2, 32.1 to 36 mml2, and ≥36 mml2. The patients were followed for 1 year or until death, whichever came first.

Results: The LAVI of the cardiobemolic group was significantly higher than that of the noncardiobemolic group (32.4±4.0 vs 29.7±3.4 mml2 respectively, p <0.001). The optimal cut-off value, sensitivity, and specificity of LAVI to distinguish cardiobemolic stroke from nond cardiobemolic stroke were 30 mml2, 81% and 64%, respectively. Mortality in each LAVI category was 4%, 7.8%, 25.9%, and 70.9%, respectively (p =0.026). Kaplan-Meier analysis showed that there was a progressive increase in risk of mortality with each increment of LAVI category (Figure).

Conclusion: The LAVI can distinguish cardiobemolic stroke from nond cardiobemolic stroke and provides an independent information over clinical and other echocardiographic variables for predicting mortality in patients with first-ever acute ischemic stroke.

15 years of carotid artery stenting (CAS) in clinical practice: results from the ALKK CAS Registry

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Background: In 1996 the carotid artery stenting (CAS) registry of the Arbeitsgemeinschaft der Vereinigten Kardiologischen Kliniken (ALKK) was founded. There are only scarce data on change in indications, patient characteristics and clinical outcome during the last 15 years.

Methods: We prospectively analyzed the data from this prospective ALKK - CAS Registry.

Results: Between 1996 and 2012 6275 CAS procedures were performed in 6134 patients at 36 hospitals. Mean inclusion rate per year was 408.9 patients (range: 17-659/year). Mean age of patients (pts) was 70.6±8.8 years. 71.7% of pts were male, a symptomatic stenosis was treated in 41.4% of pts and an embolic protection device was used in 82.8%. Mean duration of the interventions was 42.7±22.9 minutes. Hospital mortality or stroke rate was 3.1%.

Independent predictors of mortality in the hospital were: Age (OR per 10 years 1.44, 95%CI: 1.15-1.78, p= 0.001), symptomatic stenosis (OR 1.53, 95%CI: 1.07-2.19, p< 0.02), use of a protection device (OR 0.45, 95%CI: 0.26-0.78, p< 0.004), heart failure (OR 2.08, 95%CI: 1.27-3.40, p< 0.003), presence of thrombus at the lesion (OR 1.83, 95%CI: 1.03-3.28, p= 0.04).

Conclusion: In clinical practice of CAS during the last 15 years, mean age of pts increased whereas the proportion of symptomatic stenoses decreased. Embolic protection devices were established as a standard tool and hospital death or stroke rate decreased significantly.

LAA closure using the WATCHMAN device in patients with contraindications to Warfarin: preliminary results from the ASA P.T.S Registry

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Introduction: The randomized PROTECT AF trial revealed that left atrial appendage closure (LAA) closure using a filter device (WATCHMAN) was non-inferior to Warfarin for prophylaxis of stroke, systemic embolism and cardiovascular or unexplained death in AF pts with CHADS2 >1. In PROTECT AF patients were treated with Warfarin post-implant until a TEE (transesophageal echocardiogram) demonstrated LAA closure (< 3mm of peri-device flow) at which point Warfarin was withdrawn and patients continued antplatelet therapy alone. However, this strategy is not possible in patients with contraindications to Warfarin, we report the initial results from the ASAP Registry, a multicenter registry of WATCHMAN implantation in patients with contraindications to Warfarin use.

Methods: In AF patients with contraindications to Warfarin, the WATCHMAN LAA closure device was implanted in standard fashion: IV heparinization, transseptal puncture, TEE guidance. Post-implantation, patients were discharged on life-long aspirin and clopidogrel. Follow-up TEE was performed at 3 and 12 months to assess for LAA closure and device-associated thrombus.

Results: A total of 116 pts were enrolled at 44 enrolling centers in Europe: age 72.4±7.5 (53-93), 37% female, congestive heart failure in 28%, hypertension in 92%, diabetes in 28%, prior stroke or transient ischemic attack (TIA) in 41%,
Age ≥ 75 in 41%, CHADS2 score ≥ 2.7±1.2 (1 - 5). Successful implantation was achieved in 108/116 pts (93%). Currently, median follow-up is 6 months with 44 patients followed to one year. Previously, there was one pericardial effusion with tamponade. In follow-up there were three ischemic strokes and three instances of device-related thrombus detected on TEE. Follow-up is ongoing.

Conclusions: This early experience reveals that WATCHMAN implantation without antiplatelet therapy is safely feasible in AF patients with contraindications to oral anticoagulation. LAA closure may prove to be a viable alternative for AF patients with Warfarin contraindications.

P1557

Prevalence of stroke among patients with paroxysmal supraventricular tachycardia

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Purpose of study: To assess the significance of unexplained stroke in patients presenting with paroxysmal supraventricular tachycardia (SVT). The high risk of atrial fibrillation (AF) in patients with SVT is well-known. AF is a major cause of embolic event and increased risk of stroke in patients with SVT can be expected.

Methods: 1354 patients, aged from 6 to 93 years with a normal ECG in sinus rhythm were recruited for SVT, confirmed by electrophysiological study (EPS). Patients with antegrade conduction through accessory pathway (AF) were excluded. EPS was systematic. Clinical and electrophysiological data were collected. Patients with stroke had a normal carotid ultrasound study and transcranial Doppler ultrasonography.

Results: Unexplained stroke was noted in 38 patients (group I); the prevalence was 2.6% of population with SVT. 1316 patients had no history of stroke (group II). Group I patients were older than group II (62±12 vs 49±19 years) (p < 0.0001). They have more frequent associated heart disease (13/38; 34% vs 14/1316; 11%) (p < 0.0001) and more frequently an history of AF (4/38; 10.5% vs 30/1316, 2%; p < 0.001). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%), p = 0.57. Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%), p = 0.57. Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%), p = 0.57. Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%), p = 0.57.

Conclusions: Unexplained stroke was a rare event in patients with paroxysmal SVT. The high risk of atrial fibrillation in patients with SVT can be expected. SVT ablation did not reduce the risk of new spontaneous atrial fibrillation or death.

P1558

How predictive are thromboembolic risk stratification scores?

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Objective: To determine the influence of atrial fibrillation (AF) in stroke development and evolution in patients without previous thromboembolic events and to assess stroke risk with risk stratification scales.

Methods: Retrospective study of all primary patients with ischemic stroke admitted to one municipal hospital during the study period (2013-2017). Results: The study included 735 patients, of which 519 had primary stroke (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519). AF cases were older than sinus rhythm (70.6%) with 27.8% having AF (144/519).

Conclusions: Unexplained stroke was noted in 38 patients (group I); the prevalence was 2.6% of population with SVT. 1316 patients had no history of stroke (group II). Group I patients were older than group II (62±12 vs 49±19 years) (p < 0.0001). They have more frequent associated heart disease (13/38; 34% vs 14/1316; 11%) (p < 0.0001) and more frequently an history of AF (4/38; 10.5% vs 30/1316, 2%; p < 0.001). Male gender was similar in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57). Male gender was equal in group I (17/38, 45%) and in group II (30/1316, 45%) (p = 0.57).

Conclusions: Unexplained stroke was a rare event in patients with paroxysmal SVT, noted in 2.6% of this population. Old age, associated heart disease, and history of atrial fibrillation were significant stroke factors associated with the occurrence of stroke in these patients. They had a risk of severe adverse events during the follow-up as spontaneous atrial fibrillation (21%) or death (8%). SVT ablation did not reduce the risk of new spontaneous atrial fibrillation or death.

P1555

Heterogeneity in published evidence for stroke prevention in patients with atrial fibrillation: a systematic review

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Purpose: In order to conduct a network meta-analysis (NMA) to assess the relative efficacy/safety of the novel oral anticoagulant (NOAC) apixaban, we undertook a systematic review to identify randomised controlled trials (RCTs) evaluating treatments for stroke prevention in atrial fibrillation (AF) patients.

Methods: Electronic databases (accessed April 2011) and grey literature searches were conducted to identify relevant RCTs. Comparators of interest included other NOACs, vitamin k antagonists (VKA), and aspirin. Outcomes of interest included stroke or systemic embolism, major bleeding, and all-cause mortality. Results: 46 publications of 41 studies met the inclusion criteria. The majority of studies were multicentre RCTs enrolling warfarin-eligible patients with a low/unknown risk of potential bias. However, heterogeneity was evident with regard to year of publication, study design, number of enrolled patients, inclusion criteria, time in therapeutic range (TTR) and dosing regimens (particularly among the VKA/aspirin arms). Recent studies investigating the NOACs were large (n >10,000 enrolled subjects), high-quality RCTs reporting consistently defined outcomes.

Characteristics of included studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range of number of studies in category</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomised: 1,000-2,500</td>
<td>1000-10,000, n=13; &gt;10,000, n=3</td>
</tr>
<tr>
<td>Warfarin eligibility: Eligible, n=34</td>
<td>Ineligible, n=4</td>
</tr>
<tr>
<td>% Time in TTR (N=22)</td>
<td>&lt;50, n=3; 50-60, n=3; &gt;60, n=4; NR, n=4</td>
</tr>
<tr>
<td>Follow-up period</td>
<td>12 weeks to 3.6 years</td>
</tr>
<tr>
<td>Blinding</td>
<td>Double-blind, n=19; Open-label, n=19; Single-blind, n=2; NR, n=1</td>
</tr>
<tr>
<td>ITT analysis</td>
<td>Yes, n=29; No, n=4</td>
</tr>
<tr>
<td>Degree of risk</td>
<td>Low, n=1; Medium, n=3; High, n=26; NR, n=2</td>
</tr>
<tr>
<td>ITT, intention to treat; NR, not reported; TTR, time in therapeutic range.</td>
<td>Two studies counted twice; NICE methodology checklist 2009, which assesses randomisation, blinding and reporting of withdrawals.</td>
</tr>
</tbody>
</table>

Conclusions: There is significant clinical and methodological heterogeneity between studies reporting on stroke prevention in AF patients. A robust NMA, meeting the requirements of Heath Technology Assessment agencies, may necessitate the use of a restricted network of RCTs in order to minimise, as far as possible, the introduction of unnecessary heterogeneity into the analysis.
tients (47.1%) were continuing aspirin treatment, in disagreement with current guidelines.

<table>
<thead>
<tr>
<th>Risk stratification scale</th>
<th>Low risk group, % of patients</th>
<th>Moderate risk group, % of patients</th>
<th>High risk group, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA2DS2-VASc score</td>
<td>9.8</td>
<td>30.6</td>
<td>62.9</td>
</tr>
<tr>
<td>Framingham score</td>
<td>10.9</td>
<td>33.5</td>
<td>55.6</td>
</tr>
<tr>
<td>CHA2DS2-VASc</td>
<td>0</td>
<td>4.1</td>
<td>95.9</td>
</tr>
</tbody>
</table>

Conclusions: AF patients without previous thromboembolic events have a high risk of ischemic stroke with a severe evolution and consequences. CHA2DS2-VASc seems to be the most sensitive score in determining thromboembolic risk in patients with non-valvular atrial fibrillation.

P1559

Stoke determines higher in-hospital and 5-year mortality in patients with ST-segment elevation myocardial infarction treated with percutaneous coronary intervention

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The use of percutaneous coronary intervention (PCI) for treatment of acute myocardial infarction (MI) significantly improved prognosis of patients. However, stroke is a severe complication of MI. There are not many evidences that stroke may occur in patients with MI treated with PCI.

Purpose: The purpose of this analysis was to assess whether stroke affects in-hospital and 5-year mortality in patients with ST-segment elevation myocardial infarction (STEMI) treated with PCI and to point out factors determining it.

Methods: Consecutive patients with STEMI treated with PCI were included in the analysis. Patients were divided into two groups: group I – patients with stroke, group II – patients without stroke. Stroke was defined as any new focal neurological deficit lasting > 24 h, occurring anytime during hospitalisation.

Results: A total of 2418 patients with STEMI treated with PCI were included in the analysis. There were 39 patients (1.6%) with stroke. Patients with stroke were older, more frequently female, had more frequently cardiac arrest before admission, hypertension, diabetes mellitus, cardiogenic shock (23 vs 1.6%; p=0.002), gastrointestinal bleeding (10.3 vs 2.2%; p=0.008), higher glucose level on admission, lower glomerular filtration rate on admission and lower left ventricular ejection fraction (41.2 ± 8.6 vs 44.7 ± 9.7%; p=0.02) compared with patients without stroke. The in-hospital mortality was 14.4% and 4.4% (p=0.001) whereas 5-year mortality was 61.5% and 19.0% (p=0.0001), respectively for patients with and without stroke. Moreover the multivariate analysis revealed that stroke was a prognostic factor of higher 5-year mortality [HR=2.57 (1.68-3.93); p=0.00001]. The independent factors of the stroke’s occurrence were: cardiac arrest before admission [OR=2.34 (1.10-4.98); p=0.03], left ventricular ejection fraction [per 1% OR=0.97 (0.94-0.99); p=0.02] and glomerular filtration rate on admission [per 1 ml/min/1.73 m² OR=0.98 (0.97-0.99); p=0.02].

Conclusion: Stroke determines higher in-hospital and 5-year mortality in patients with STEMI treated with PCI.

Conclusions: AF patients without previous thromboembolic events have a high risk of ischemic stroke with a severe evolution and consequences. CHA2DS2-VASc seems to be the most sensitive score in determining thromboembolic risk in patients with non-valvular atrial fibrillation.

P15561

Incidence and predictors of aortic plaque progression: evaluation of chronological changes of aortic plaque with follow-up transesophageal echocardiography

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Objectives: It has been reported that aortic plaque may cause embolic events and patients with severe aortic plaque show poor prognosis. Transesophageal echocardiography (TEE) is useful to evaluate the thickness and morphology of aortic plaque. However, there are few data about chronological changes of aortic plaque.

The purpose of this study is to examine the chronological changes of aortic plaque through follow-up TEE, and to clarify the incidence and predictors of aortic plaque progression.

Methods: Among 2675 patients who underwent TEE in our hospital between 1991 and 2011, 591 patients underwent follow-up TEE. We retrospectively investigated 152 patients who underwent follow-up TEE with >5years interval. The thickness and morphology, such as ulcer, calcification, and mobile plaque, of the aortic plaque in the descending aorta and aortic arch were examined. Aortic plaque was graded as mild (thickness<2mm), moderate (thickness<5mm), and severe (thickness>5mm, or complex plaque). In addition, plaque area was measured as a marker of plaque progression. A total of 12,228 patients with vertebral fractures and 12,228 controls were evaluated.

Results: Among 152 study patients, grade of aortic plaque was unchanged in 123 patients (group U), but progression of aortic plaque was seen in 23 patients (group P) and regression in 6 patients (group R). Patients in group P were older (63.7 ± 57.11; p=0.009), had higher prevalence of underlying ischemic heart disease (43% vs 8%, p<0.001), hypertension (39% vs 19%, p<0.05), hyperlipidemia (30% vs 13%, p=0.06), smoking history (61% vs 40%, p<0.07), and moderate or severe plaque at the initial TEE (39% vs 16%, p<0.017) than those in group U. There were no differences in presence of diabetes mellitus, medications, and laboratory data, such as total cholesterol, creatinine, C reactive protein, and eosinophil count, were evaluated.

Conclusions: Advanced age, presence of underlying ischemic heart disease and moderate to severe aortic plaque at the initial TEE were predictors of progression of aortic plaque. We should follow the aortic plaque in these patients using TEE.

P1560

Gender-related differences in the risk factors of thromboembolism after cardiovascular of acute atrial fibrillation

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Purpose: The incidence of atrial fibrillation (AF) is higher in men than in women. In this study, we report gender specific differences in clinical characteristics of AF.

The aim was to assess if there are gender-related differences in the risk factors of thromboembolism after cardiovascular of acute AF.

Subjects and methods: A total of 5652 cardioversions were performed in 2569 consecutive patients with AF lasting < 48 hours in 3 hospitals. Sex-related differences in embolic and bleeding complications were evaluated during the 30 days after 5235 successful cardioversions.

Results: A total of 3406 (67%) of the cardioversions were performed in men. Women came to emergency unit earlier than males (p=0.002, OR 1.2 95% CI 1.0-1.4). They were older (66.1±11.8 vs. 58.9±12.0, p<0.001). There were 38 thromboembolic events (in 38 patients) within 30 days after cardioversions and the incidence was higher in women (1.25 vs. 0.41%, p<0.001), but there was no significant gender difference in bleeding complications (0.21% vs. 0.99% p=0.3). In multivariate analyses, the independent predictors of thromboembolism for women were long (>12 h) duration of AF (p=0.04, OR 2.58, 95% CI 1.05-6.35), heart failure (p=0.004, OR 5.16, 95% CI 1.70-15.69), and the use of peripheic anticoagulation (P=0.002, OR 0.12, 95% CI 0.03-0.47). In men, age (p=0.02, OR 1.04, 95%CI 1.01-1.08) and vascular disease (p=0.03, OR 3.31, 95% CI 1.11-9.86) were the only independent predictors of thromboembolic complications.

Conclusions: There seems to be gender-related differences in risk and risk factors for thromboembolism after cardiovascular in AF.

P1562

Vertebral fracture and risk of ischemic stroke: a nationwide study

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Background: We investigated whether vertebral fracture increased the risk of ischemic stroke in a large, nationwide cohort study.

Methods: We obtained data from 12,228 patients diagnosed with vertebral fracture from 2000 to 2009 and form 1 matched control for each vertebral fracture patient from the Longitudinal Health Insurance Database in Taiwan. Controls were matched for age, gender, comorbid medical disorders, and enrollment date. All subjects were followed up from the date of enrollment until development of ischemic stroke, death, or the end of data collection. Cox’s regression model adjusted for age, gender, comorbid disorders, and medication was used to assess the independent factors determining the risk of ischemic stroke development.

Results: A total of 12,228 patients with vertebral fractures and 12,228 controls were identified. Among these subjects, 813 patients (369 vertebral fracture pa-
Increased insulin resistance in acute ischaemic stroke is inversely related to stroke severity: an unexpected pattern of metabolic regulation in mild stroke

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1Charité - University Medicine Berlin, Center for Stroke Research CSR, Berlin, Germany; 2Charité - University Medicine Berlin, Institute for Applied Cerebrovascular Research, Berlin, Germany; 3Charité - Campus Virchow-Klinikum, Department of Internal Medicine-Cardiology, Berlin, Germany

Background: Impaired insulin sensitivity (Si) is a pathophysiological feature in cardiovascular disease including stroke. However, data concerning acute impairment of insulin sensitivity in patients after acute ischemic stroke are scarce. The aim of this study was to examine characteristics of impaired insulin sensitivity in patients acutely after ischemic stroke in comparison to healthy controls and to patients with CHF.

Methods: We evaluated 98 consecutive patients (age 69±13y, mean±SD) admitted to stroke unit with acute ischemic stroke of the middle cerebral artery. Stroke severity was assessed by National Institute of Health Stroke Scale (NIHSS) and patients with NIHSS 0-14 were included. Patients with diabetes mellitus (HbA1c >9%) were excluded. Stroke patients were classified according to TOAST classification: a) cardioembolic infarcts (CE; n=22), b) large artery-atherosclerotic infarcts (LAA; n=22), c) lacunar infarctions (LAC; n=15) and d) strokes of unknown etiology (UDE; n=4).

Si was assessed by Homeostasis Model Assessment (HOMA, values >2 indicate insulin resistance). For comparison patients with stable, ambulatory treated CHF (n=21, LVEF=31±11%, peak VO2=21.0±9.4ml/kg/min, HbA1c 6.2%, peak VO2=21.0±9.4ml/kg/min, HbA1c 6.2%) were studied as positive and negative control groups, respectively. Blood parameters were measured from venous blood samples after overnight (>8h) fasting.

Results: Si was significantly impaired (indicating insulin resistance) in stroke as in CHF patients compared to controls (HOMA 3.1±3.1 vs. 3.0±2.5 vs. 1.5±0.9, respectively, ANOVA p=0.06). Si was dependent on etiology in stroke patients (TOAST classification: CE: 3.5±4.3, LAA: 3.3±2.3, LAC: 2.9±1.4 and UDE: 4.3±3.2, p=0.009) and in CHF patients (ischemic: 3.4±2.5 vs. dilatative: 1.4±1.5). HOMA was significantly higher in patients with mild stroke (NIHSS 0-5) as compared to higher stroke severity (NIHSS 6-14) and to controls (3.7±3.5 vs. 2.0±1.3 vs. 1.5±0.9, respectively, p=0.02). Simple regression analyses showed an inverse linear association of HOMA with the severity of stroke (r=0.3, p=0.04).

Conclusion: Insulin resistance is increased in patients acutely after ischemic stroke without previous history of diabetes mellitus. Insulin resistance depends on stroke subtypes suggesting different metabolic signalling according to stroke etiology. Notably, an unexpected inverse pattern of impaired metabolic regulation was observed resulting in higher insulin resistance particular in patients with milder stroke severity.

Larger orifice size of left atrial appendage increases thrombus formation in patients with nonvalvular atrial fibrillation due to low flow velocity

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Introduction: Left atrial appendage (LAA) is an important source of thromboembolism and stroke in patients with atrial fibrillation (AF). This study evaluated whether the specific feature of LAA increases the risk of thrombi or blood stasis in patients with nonvalvular AF. We also evaluated this new specific feature of LAA is related with the flow velocity of LAA.

Methods: We enrolled 589 nonvalvular AF patients. The characteristics of LAA and left atrium (LA) including thrombus or blood stasis were evaluated using multi-detector computer tomography (MDCT) and transesophageal echocardiography. Right atrial, left atrial thrombus or blood stasis were observed in 112 patients (Group 1, 18.9%) and Group 1 had diabetes mellitus (4.7±3.7, p=0.03), HbA1c 6.1, age 68±9y, and healthy controls of similar age (n=20) were studied as positive and negative control groups, respectively. Blood parameters were measured from venous blood samples after overnight (>8h) fasting.

Results: Si was significantly impaired (indicating insulin resistance) in stroke as in CHF patients compared to controls (HOMA 3.1±3.1 vs. 3.0±2.5 vs. 1.5±0.9, respectively, ANOVA p=0.06). Si was dependent on etiology in stroke patients (TOAST classification: CE: 3.5±4.3, LAA: 3.3±2.3, LAC: 2.9±1.4 and UDE: 4.3±3.2, p=0.009) and in CHF patients (ischemic: 3.4±2.5 vs. dilatative: 1.4±1.5). HOMA was significantly higher in patients with mild stroke (NIHSS 0-5) as compared to higher stroke severity (NIHSS 6-14) and to controls (3.7±3.5 vs. 2.0±1.3 vs. 1.5±0.9, respectively, p=0.02). Simple regression analyses showed an inverse linear association of HOMA with the severity of stroke (r=0.3, p=0.04).

Conclusion: Insulin resistance is increased in patients acutely after ischemic stroke without previous history of diabetes mellitus. Insulin resistance depends on stroke subtypes suggesting different metabolic signalling according to stroke etiology. Notably, an unexpected inverse pattern of impaired metabolic regulation was observed resulting in higher insulin resistance particular in patients with milder stroke severity.
prescribing OAC and NOGOA. Patients with absolute contraindication for OAC use, CHA2DS2VASc ≤ 1 or valvular disease were excluded.

Results: Of the 122 cases with AF/atrial flutter, 19 were excluded; of the 103 candidates for OAC (CHA2DS2VASc ≥ 2), 16 (16%) were excluded because of female gender and the absence of heart failure (CHA2DS2VASc ≥ 4, p = 0.001) were the predictors of non-prescription. Of the 68 cases discharged without OAC, HASBLED was ≥ 3 in 53%. The reasons referred for not prescribing OAC were high bleeding risk (56%), perceived high bleeding risk artefact of low previous goal status of the patient (22%), inability to comply with the treatment regimen (10%), difficulty in INR monitoring (5%) and others (3%). 54 cases were discharged before and 49 after the NOGOA approval (August 2011) without significant difference in anticoagulation rates (31.5% and 36.7%, p = 0.12). The NOGOA were not prescribed in any case and the reasons reported by physicians were insufficient information on the drugs (39%), high bleeding risk (33%), price (16%), small benefit (10%) and others (2%).

Conclusions: The OAC prescription rate in AF for stroke prevention was low, before and after the NOGOA approval. The main predictors for non-prescription were the previous use of antiplatelet agents, the number of bleeding risk factors and the absence of heart failure. Bleeding risk was the most referred barrier and the calculated bleeding risk was high. In addition, some patients with poor general status might not benefit from OAC, despite it is formally indicated. The NOGOA were not prescribed and the main barriers were insufficient information, perception of high bleeding risk and its price.

P1567 The high-sensitive cardiac troponin T assay is superior to its previous assay generation for the prediction of 90-day clinical outcome in ischemic stroke

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Background: Cardiac troponin T (cTnT) has been shown previously to be a predictor of stroke outcome with decision limits in the low measuring range of the assay. Recently a new high-sensitivity assay generation (hs-cTnT) has been introduced which is characterized by improved analytical sensitivity and better preclinical measuring range. Because of more accurate measurement of low troponin concentrations, we hypothesized that this assay may be superior to its previous assay generation for prediction of stroke outcome.

Methods: cTnT was measured by assays from Roche Diagnostics© on emergency department admission in 60 consecutive patients (35 males, age 69.4±13.9 years) with ischemic stroke who were subsequently admitted to our hospital’s stroke unit from beginning of March to end of April 2010. The clinical 90-day outcome of ischemic stroke patients was analyzed using the Austrian stroke registry. We used the modified Rankin scale (mRS) and Barthel index (BI) as outcome measures and defined adverse outcomes as mRS ≥ 3 (indicating dependence or death) and/or BI ≤ 75 points.

Results: Stroke etiology was microangiopathy in 3, macroangiopathy in 17, cardiac embolism in 26, dissection in 1 and unknown in 13 patients. At 90-day follow-up, 16 (27%) patients had an adverse outcome. Receiver operating characteristic curve (ROC) analysis of the predictive performances yielded a significant better performance of hs-cTnT vs. cTnT (area under curve: 0.80 ± 0.07, p = 0.017). The optimal predictor values were 11 ng/L (detection limit of the old cTnT assay 10 ng/L) and 5.1 ng/L (detection limit of the hs-cTnT assay 5 ng/L), respectively, with the following characteristics: sensitivity 56 vs. 94%, specificity 84 vs. 57%, positive predictive value 57 vs. 45%, and negative predictive value 84 vs. 96%.

Conclusions: The improvements in cTnT assay analytical sensitivity and assay precision at the low measuring range resulted in a significant improvement of positive predictive value 57 vs. 45%, and negative predictive value 84 vs. 96%.

P1568 Plasma parathyroid hormone and the risk of cerebrovascular diseases in the community

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Purpose: Diseases with elevated levels of parathyroid hormone (PTH) such as primary and secondary hyperparathyroidism are associated with increased incidence of vascular and cardiovascular diseases, as well as with a broad range of neuropsychiatric symptoms. In population-based studies PTH has been related to an excess mortality and morbidity from diseases of the cardiovascular system. However, the extent of the prospective association between circulating PTH levels and cerebrovascular diseases in the community are lacking.

Methods: In a prospective community-based study of elderly men (mean age, 71 years; n = 3864), the Uppsala Longitudinal Study of Adult Men (ULSAM), the association between plasma PTH, vascular mortality and ischemic stroke was investigated. Multivariable Cox proportional hazards analyses adjusting for educational level, established cerebrovascular risk factors (age, blood pressure, diabetes, smoking, BMI, total cholesterol, antihypertensive treatment, lipid lowering treatment) and variables reflecting mineral metabolism (serum calcium, phosphate, 25-OH vitamin D, glomerular filtration rate) were used.

Results: During follow-up (median, 16 years), 52 participants developed vascular mortality, 13 died of stroke, 52 developed female ischemic stroke. Higher plasma PTH was associated with higher risk for developing vascular mortality (hazard ratio for 1-SD increase in PTH, 1.84; 95% confidence interval, 1.28 to 2.67; p = 0.001). This association was found also among participants without previous ischemic stroke or TIA, without participants with atrial fibrillation and in participants with no signs of a disturbed mineral metabolism (normal serum calcium, 2.2 to 2.6 mmol/L; normal glomiser filtration rate, 50 to 175 ml/min 1.73 m² and without vitamin D deficiency, plasma 25-OH vitamin D > 37.5 nmol/L). Plasma PTH was not associated with ischemic stroke.

Conclusions: In a large community-based sample of elderly men, plasma PTH levels predicted vascular mortality, but not ischemic stroke, also after accounting for established risk factors and for variables of the mineral metabolism. Our data support the previous findings of PTH being involved in the development of vascular diseases. Additional investigations are warranted to confirm these findings and to assess the clinical utility of our data.
increasing age, number of complex plaques, intima-media-thickness and with the presence of arterial hypertension, diabetes or CAD (p<0.01). Moreover, the ratio of retrograde to antegrade flow correlated positively with stiffness (p<0.01) and negatively with strain (p=0.01). Strain of the aortic wall decreased significantly with increasing age, number of complex plaques, intima-media-thickness, presence of arterial hypertension, diabetes or CAD (p<0.01) whereas aortic stiffness significantly increased in correlation with these parameters (p<0.05).

Conclusion: Markers of arteriosclerosis and typical cardiovascular risk factors were associated with increased retrograde blood flow and reduced aortic elasticity in a large cohort of acute stroke patients. As a result, patients with advanced atherosclerosis including complex plaques in the proximal descending aorta might be at higher risk for an embolic stroke owing to retrograde embolism.

**P1571**
Thromboembolic complications after successful cardioversion of acute atrial fibrillation
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**Purpose:** To determine the incidence of thromboembolic complications related to cardioversion of acute atrial fibrillation in patients with no anticoagulation therapy.

**Subjects and methods:** A total of 5852 cardioversions were performed in 2569 trauma patients with atrial fibrillation lasting 48 hours in three hospitals. For this analysis, embolic complications were evaluated during 30 days after 3822 successful cardioversions in 2040 patients with no periprocedural anticoagulation. Results: Nine thromboembolic events occurred in the first week after cardioversion (median 2.0 days, mean 2.9 days). Age (p=0.003, OR for 1 year 1.06, 95%CI:1.03-1.09) and sex (p=0.019, 2.48, 95%CI:1.16-5.30) were the only independent predictors of embolic events in multivariate analysis.

**Table 1. Incidence of thromboembolic complications**

<table>
<thead>
<tr>
<th>Variable</th>
<th>YES</th>
<th>NO</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events</td>
<td>35</td>
<td>3787</td>
<td></td>
</tr>
<tr>
<td>Age (≥75 years)</td>
<td>2.3%</td>
<td>0.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.8%</td>
<td>0.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.7%</td>
<td>0.8%</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.0%</td>
<td>0.8%</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.2%</td>
<td>0.7%</td>
<td>&lt;0.07</td>
</tr>
</tbody>
</table>

**Conclusions:** The incidence of postcardioversion thromboembolic complications is high in certain subgroups of patients with cardioversion of acute atrial fibrillation when no periprocedural anticoagulation is used.

**P1572**
Stroke survivors have greater risk in suffering severe trauma on head, hip and lower extremities. An analysis of 42336 severe trauma cases in Japan
A. Shiraiishi1, T. Shoko1, H. Mizusawa2, Y. Otomo1, Tokyo Medical and Dental University, Emergency Department, Tokyo, Japan; 2Tokyo Medical and Dental University, Department of Neurology and Neurosurgery, Tokyo, Japan.

**Purpose:** Impaired motor, sensory and cognitive function after stroke may lead to increased risk of fall and trauma, however, little is known about characteristics of trauma in stroke survivors. In this case control study based on the large-scaled trauma database in Japan, we aimed to investigate baseline severity, mortality and anatomical differences in relation to severe trauma in subjects with or without prior stroke.

**Methods:** The data source was Japan Trauma Databank, a large-scaled, multicenter and nationwide database of severe trauma cases in Japan. Of the subjects with complete data set to estimate trauma severity and clear outcome, we extracted subjects with stroke and gender- and age-matched controls in a 1:3 ratio using automated propensity score matching. Subjects of cardiopulmonary arrhythmia on arrival were excluded. Trauma severity and predicted death rate were estimated based on the Trauma Injury Severity Scale (J Trauma 1987, 27:370). Anatomical trauma severity was estimated based on the Neat Index and the Injury Severity Score (J Trauma 1974, 14:187). Intergroup comparison showed the differences in baseline trauma severity, in-hospital mortality, anatomical distribution and undergoing surgical procedures in relation to severe trauma. All the statistical analysis underwent on R 2.14.1 statistical software.

**Results:** Of a total of 42336 severe trauma cases registered in Japan Trauma Databank, 586 subjects with stroke and 1768 gender- (male gender: 62.3% vs. 62.3%, P=0.996) and age-matched (733.02 vs. 733.0, P=0.98) controls were included in the analysis. Baseline trauma severity was more mild in stroke subjects (15.2% vs. 16.8%, P=0.017) and in-hospital mortality after adjustment for baseline trauma severity was similar (OR for in-hospital death: 1.06, 95%CI:0.71-1.50, P=0.944). Risk of suffering trauma on a specific region after adjustment for the Injury Severity Scale showed significant increase in severe head injuries (OR: 1.38, 95%CI: 1.12-1.70, P<0.001) with significant increase in decompressive cranial surgeries (OR: 1.45, 95%CI: 1.20-2.06, P=0.036), non-significant increase in severe hip and lower extremity injuries (OR: 1.19, 95%CI: 0.98-1.45, P=0.077) and significant decrease in severe chest (OR: 0.55, 95%CI: 0.42-0.71, P<0.001) and spine injuries (0.60, 0.43-0.85, P<0.001).

**Conclusion:** Increased risk of suffering severe trauma on head, hip and lower extremities in stroke survivors might relate to fall and suggest a consideration of aggressive fall prevention program.

**P1574**
Patients with acute cerebral ischemia and concomitant signs for myocardial ischemia show high rates of major adverse events
U. Ketterer1, D. Leufi1, A. Assadi-Moghaddam1, S. Jander2, A. Potzin1, M. Kelm1, T. Zeusi3, University Hospital, Department of Cardiology, Pneumology and Angiology, Düsseldorf, Germany; 2University Hospital, Department of Neurology, Düsseldorf, Germany.

**Purpose:** To highlight the correlation between data obtained by contrast Transesophageal Echocardiography (cTEE) and contrast Transcranial Doppler (cTCD) for detection and more valuable assessment of right to left shunts in patients with cerebrovascular stroke (CVS).

**Methods and Results:** 50 patients with cerebrovascular ischemic stroke admitted to the Neurology department an evidence of new onset non-hemorrhagic infarction on MRI were included in this study and all patients had been referred for exclusion of a preexisting source of embolism. Then Transesophageal Echo and Transcranial Doppler with contrast (agitated saline) with and without Valsalva maneuver (VM) were done for exclusion of right to left shunt. According to results of cTEE with and without VM patients were classified into three groups, group I: Patients with spontaneously patent right to left shunt (RLS) without VM, group II: Patients with RLS only during VM, group III: Patients with no RLS. A correlation between results of both techniques was done and revealed a significant association between results of cTEE and cTCD the sensitivity of cTCD to detect a cTEE proven shunt was 90.9%. In addition, cTCD revealed shunts that weren't detected by cTEE. cTCD detected a high significant difference in infarction size between studied patients where number of microbubbles (MBs) detected during VM had a significant positive correlation with the size of infarction; there was a significantly higher number of MBs detected in the right middle cerebral artery (MCA) than in the left with cTCD during VM despite neither cTEE nor cTCD showed a significant difference in infarction site between studied patients.

**Conclusions:** cTCD has a comparable ability to cTEE for detection of RLSs with a high sensitivity of 90.9%. In addition cTCD can detect RLSs not detected by cTEE, help in quantification of the detected RLSs where higher number of detected MBs during VM indicates a more functional significance of the detected RLS and help to determine which side (right or left MCA) is more vulnerable for embolization through the detected RLSs (but this needs more evaluation).

**Table 1. Incidence of cardiac complications**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Death of cardiovasc. cause</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death from all causes</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death from traumatic causes</td>
<td>0</td>
<td>1 (1.0%)</td>
<td></td>
</tr>
<tr>
<td>Death from complications</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death from other causes</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Death from other complications</td>
<td>0</td>
<td>0</td>
<td></td>
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</tbody>
</table>

**Table 1.** Initial hospitalisation (n=104) 12 months follow up (n=104)

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Cost for follow up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial hospitalisation (n=104)</td>
<td>7 (67%)</td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death of any cause</td>
<td>10 (9.8%)</td>
<td>19 (18.3%)</td>
</tr>
<tr>
<td>Death of cardiovascular cause</td>
<td>8 (7.7%)</td>
<td>14 (13.5%)</td>
</tr>
<tr>
<td>Zerebral ischaemia or bleeding</td>
<td>11 (10.6%)</td>
<td>4 (3.8%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (5.8%)</td>
<td>1 (1.0%)</td>
</tr>
</tbody>
</table>

**Table 1.** Initial hospitalisation (n=104) 12 months follow up (n=104)
A systematic evaluation of population-based surveillance studies to quantify reported burden of stroke in low- and middle-income countries

A. Sajjad. Erasmus Medical Center, Department of Epidemiology, Rotterdam, Netherlands

Purpose: Reliable quantification of the burden of stroke in low- and middle-income (LMI) countries is unclear as nationally-representative primary surveillance reports are few and may vary widely in data collection methodology. World Health Organisation (WHO) has proposed the “STEP-wise” approach for comprehensive stroke surveillance. Whether and to what extent primary epidemiological evaluations of stroke in LMI countries adhere to WHO’s surveillance guidelines remains unknown. Therefore, we aim to systematically evaluate all primary stroke surveillance studies by applying components of WHO STEPS protocol and quantitively assess the burden of stroke in LMI settings.

Methods: Publications before January 2012 were identified through computer-based searches using multiple databases. Information was extracted on available population, surveillance methods and resulting stroke data. The aim was to create a database that would allow comparison of crude stroke rates, age-adjusted incidence rates, and stroke case fatality rates across LMI settings.

Results: We identified seven studies reporting on stroke burden conducted in nine LMI countries, which yielded aggregate information from 1,711,372 participants collected over 5,240,923 person-years. Comparison of each study’s methodology to the WHO STEPS protocol showed a lack of uniform approach towards stroke surveillance in LMI countries and utilization of its modules and steps varied considerably. Combined age adjusted incidence rate based on all nine LMI countries was 165.8 per 100,000 person-years.

Conclusion: Systematic evaluation of available primary surveillance reports, particularly in the context of the WHO-STEPs guidelines, indicates a general lack of adherence to standardized surveillance approaches, and yet, a considerable burden of incident stroke across the LMI countries. Incorporation of standardized comprehensive methodology is essential to enhance generalisability and yield comparable data on the stroke burden in these countries.

The risk factors and clinical significance of the first episode of stroke in patients after Acute Myocardial Infarction treated invasively

T. Podolec1, R. Lenarczyk1, J. Kowalczyk1, J. Boidol1, A. Sajjad1, A. Chmielewskii1, K. Przybylska1, A. Siedowska1, G. Merczel1, L. Polonski2, Z. Kaluza2. 1Medical University of Silesia, 1st Dept of Cardiology, Katowice, Poland; 2Medical University of Silesia, Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland.

Purpose: The aim of the study was to assess the incidence, independent predictors and clinical significance of the first episode of stroke in patients after acute myocardial infarction (AMI) treated invasively.

Methods: We analyzed 3252 consecutive patients AMI-patients admitted to our department between 2003 and 2007, and treated with percutaneous coronary interventional (PCI). Subsequently, 2408 patients with no history of previous stroke or transient ischemic attack were selected for further analysis. Data on long-term follow-up were screened to identify patients who experienced stroke during long-term observation.

Results: During median 25.5 months of observation 40 (1.66%) patients experienced the first-ever stroke. The incidence of major adverse cardiac events, including repeated AMI and death was significantly higher (all P < 0.05) in patients with stroke: 62.5 vs 43.1%; 27.5 vs 14.8% and 35% vs 13.1%, respectively. Multivariate Cox regression analysis revealed that female gender (HR 2.66), prior AMI (HR 2.37) and glibenclamide dosage -60 mIn/min;1.73 m2 (HR 2.02, all P = 0.05) were the independent risk factors for the first-ever stroke in AMI-patients treated with PCI. The most commonly recognized stroke aetiology was cerebral infarction, decreased left ventricular ejection fraction and advanced age were not associated significantly with the risk of stroke in the analyzed population.

Conclusions: Stroke is a significant independent predictor of major adverse cardiac events in patients after AMI. The independent risk factors for the first episode of stroke in patients after AMI treated invasively are partially different than generally recognized stroke predictors.
Conclusions: Our study suggests that TCG-directed fio2anaphylaxis therapy is more effective than dextran-40 in rapidly suppress analgesic suppression of cerebral microemboli after carotid surgery in patients refractory to basal antiplatelet therapy. Further control trials are justified to assess the clinical and cost-effectiveness of this treatment approach.

Procollagen-1-carboxy terminal peptide, a biomarker of myocardial fibrosis, is reduced following treatment with spironolactone or amiloride in stroke: a randomised placebo-controlled trial

K.Y.-K. Wong1, S.Y.S. Wong2, S. Moawad1, S.A. Ogston3, R.S. Macwalter4, A.D. Struthers5, 1University of Hull, Hull, Yorkshire Medical School, Hull, United Kingdom; 2Royal Derby Hospital, Derby, United Kingdom; 3Ninewells Hospital, Dundee, United Kingdom

Introduction: Myocardial fibrosis is arrhythmogenic and may contribute to the high incidence of cardiac death in stroke survivors. In patients with heart failure, high baseline serum levels of markers of cardiac fibrosis syndromes were associated with poor outcome and decreased during spironolactone therapy. The best treatment for myocardial fibrosis remains to be elucidated.

We tested the hypothesis that procollagen-1-carboxy terminal peptide (PICP), a biomarker of myocardial fibrosis, might be improved fibrosis, measured with spironolactone or amiloride. We also tested the hypothesis that both drugs would shorten the QTc interval.

Methods: Study design: Randomised, double-blinded, placebo-controlled, cross-over trial (between spironolactone 25mg od, increased to 50mg od after 1 week if tolerated; amiloride 5mg od, increased to 10mg od if tolerated, and placebo). Duration: Follow-up duration 3 months (1 month per drug).

The concentration of PICP was measured by radioimmunoassay (coefficient of variation=1.48%). QTc was measured using a digitizing board from lead II.

Results: 11 stroke survivors (5 females) had mean age of 71.1 (SD 3.9), BP 139/81 mmHg (SD 20/11 mmHg). None had a past history of cirrhosis, lung fibrosis, or surgery or wounds in the last 6 months (conditions which would render PICP a less reliable marker of myocardial fibrosis).

There were no significant differences in age, sex, or drug treatment, suggesting that there was no crossover effect of drugs on PICP.

Both spironolactone and amiloride significantly reduced PICP [Spironolactone Placebo: 31.3 (-13.7 to -13.7) vs -6.9 (p=0.003); Amiloride Placebo: -27.9, 95CI: -44.4 to -11.0, Dunnett t 2 p=0.002]. This led to a significant shortening of QTc. [Spironolactone vs Placebo: -18.2, 95CI: -35.8 to -0.55, Dunnett t 2 p=0.043; Amiloride vs Placebo: -24.7, 95CI: -41.9 to -7.5, Dunnett t 2 p=0.006]. Spironolactone had a non-significant BP lowering effect. On the other hand, amiloride significantly lowered BP (mean -18/-8.9mmHg, 95CI =-31/-13 to -4.9/-4.4, Dunnett t 2 p=0.007 /<0.001).

Conclusions: Procollagen-1-carboxy terminal peptide, a biomarker of myocardial fibrosis, was reduced following treatment with spironolactone. Further, this is the first study demonstrating amiloride could also improve myocardial fibrosis. The beneficial effects of both drugs on myocardial fibrosis translated to a shortening of the QTc interval. Future studies should test the hypothesis that spironolactone and amiloride would reduce the risk of sudden cardiac death in stroke survivors.

P1580 Increased risk of myocardial infarction and stroke in patients with inflammatory bowel disease - a nationwide cohort study

S.L. Kristensen1, P.R. Hansen1, O. Ahlehoff1, J. Lindhardsen1, E. Horvath-Puho2, R. Erichsen2, C. Torp-Pedersen1, O.H. Nielsen3, S.L. Kristensen1, P. Hansen1, O. Ahlehoff1, J. Lindhardsen1, K.Y.-K. Wong1, S.Y.S. Wong2, S. Mcswiggen3, S.A. Ogston3, E. Siores1, C. Stefanadis1, 1 Hippokration General Hospital, Athens, Greece; 2University of Athens Medical School, Athens, Greece; 3University of Bolton, Bolton, United Kingdom

Purpose: Studies of human carotid artery samples showed increased heat production. Microwave radiometry (MR), a new non-invasive method, allows in vivo monitoring of temperature of tissues. We investigated in carotid arteries whether thermal heterogeneity 1) can be measured in vivo non-invasively by MR, and 2) is associated with ultrasound and histological findings.

Methods: Patients scheduled for carotid endarterectomy under screening of carotid atherosclerosis by ultrasound and MR. Healthy subjects were enrolled as a control group. During ultrasound study, plaque texture, plaque surface, and plaque echogenicity were analyzed. Thermal heterogeneity (ΔT) was assigned as maximal temperature along the carotid artery minus minimum. Extension of atherosclerotic lesion evaluated for the entire arterial sections dividing the field into four equal parts and scored in numerical values ranging from 0-4. Association of thermographic with ultrasound and histological findings was performed.

Results: Thirty-four consecutive patients with significant carotid artery stenosis and 15 healthy subjects as a control group were included. ΔT was higher in atherosclerotic carotid arteries (1.39±0.09 vs. 0.23±0.01°C). Fatty plaques had higher ΔT compared to mixed and calcified (1.78±0.41 vs 1.38±0.30 vs 0.96±0.22°C, p<0.01). Plaques with ulcerated surface had higher ΔT compared to plaques with irregular and regular (2.08±0.14 vs 1.37±0.23°C vs 0.95±0.19°C, p<0.01). Heterogeneous plaques had higher ΔT compared to homogenous (1.78±0.41 vs 1.08±0.31°C, p<0.01). Specimens with increased extension of calcification had lower ΔT compared to specimens with low (p<0.01). Specimens with thin fibrous cap had higher ΔT (1.69±0.42 vs 0.98±1.20°C, p<0.01). Specimens with increased inflammation had higher ΔT compared to specimens with low (1.74±0.40 vs 1.01±0.21°C, p<0.01).

Conclusions: Microwave radiometry provides in vivo non-invasive temperature measurements of carotid plaques, reflecting carotid plaque inflammatory activation.

P1581 Thermal heterogeneity of human atherosclerotic carotid artery lesions detected in vivo: a new non-invasive method for detection of local inflammatory activation

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Purpose: Update on ischaemic stroke / Peripheral circulation and intervention 239

Methods: In a first study demonstrating amiloride could also improve myocardial fibrosis. The other hand, amiloride significantly lowered BP (mean –18/-8.9mmHg, 95% CI=-31/-13 to -4.9/-4.4, Dunnett t 2p=0.007 /<0.001).

Results: Thirty-four consecutive patients with significant carotid artery stenosis and 15 healthy subjects as a control group were included. ΔT was higher in atherosclerotic carotid arteries (1.39±0.09 vs. 0.23±0.01°C). Fatty plaques had higher ΔT compared to mixed and calcified (1.78±0.41 vs 1.38±0.30 vs 0.96±0.22°C, p<0.01). Plaques with ulcerated surface had higher ΔT compared to plaques with irregular and regular (2.08±0.14 vs 1.37±0.23°C vs 0.95±0.19°C, p<0.01). Heterogeneous plaques had higher ΔT compared to homogenous (1.78±0.41 vs 1.08±0.31°C, p<0.01). Specimens with increased extension of calcification had lower ΔT compared to specimens with low (p<0.01). Specimens with thin fibrous cap had higher ΔT (1.69±0.42 vs 0.98±1.20°C, p<0.01). Specimens with increased inflammation had higher ΔT compared to specimens with low (1.74±0.40 vs 1.01±0.21°C, p<0.01).

Conclusions: Microwave radiometry provides in vivo non-invasive temperature measurements of carotid plaques, reflecting carotid plaque inflammatory activation.

P1582 Exaggerated exercise blood pressure response is related to increased arterial stiffness, asymmetric dimethylarginine and osteoprotegerin in essential hypertensive subjects

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Purpose: A hypertensive response to exercise (HRE) is associated with high cardiovascular risk, while elevated levels of asymmetric dimethylarginine (ADMA) and osteoprotegerin (OPG) are related to atherosclerosis progression. In this study we sought to determine the relationships of HRE with ADMA, OPG and arterial stiffness in essential hypertension.

Method: Our population of 240 newly diagnosed never treated non-diabetics with stage I to II essential hypertension [155 men, mean age 51 years, office systolic blood pressure (BP)=150±9.6 mmHg with a negative treadmill exercise test (Bruce protocol) was divided into those with HRE (n=70) (peak exercise systolic BP >210mmHg in men and >190 mmHg in women) and those without HRE (n=170). Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV) values.

Results: Patients with HRE compared to those without HRE had greater 24-h systolic BP (143±9 vs 131±8 mmHg, p<0.05), while did not differ regarding metabolic profile and left ventricular mass index (p=NS). Patients with HRE...
compared to those without HRE exhibited greater levels of ADMA (0.63±0.04 vs 0.52±0.05 μmol/l, p<0.0001), OPG (5.4±1.0 vs 4.1±0.5 pmol/l, p<0.0001) and PWV (8.5±1.7 vs 7.5±0.9 mm/sec, p<0.0001), independently of confounders. In the total population, peak exercise systolic BP was related to 24-h systolic BP (r=0.249, p<0.05), PWV (r=0.278, p<0.003), ADMA (r=0.260, p<0.007) and OPG (r=0.214, p<0.05). Regarding OPG, it was associated with 24-h systolic BP (r=0.269, p<0.001), ADMA (r=0.284, p<0.05) and PWV (r=0.424, p<0.0001). Multiple regression analysis showed that 24-h systolic BP (b=0.216, p=0.003), male sex (b=0.270, p<0.001) and PWV (b=0.055, p<0.0001) were independent predictors of peak exercise systolic BP.

Conclusions: In essential hypertension, a HRE is accompanied by a state of increased arterial stiffening, endothelial dysregulation and progressive atherosclerosis. The interrelationships of ADMA and OPG with exercise BP response support that diffuse vascular dysfunction contribute to HRE-related risk in hypertension.

**P1583** Cholesterol efflux capacity and arterial stiffness in healthy subjects: data from the brisighella heart study

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**Purpose:** Serum capacity to promote cholesterol efflux from macrophages correlates inversely with carotid-intima-media thickness and the likelihood of an angiographic coronary artery disease, independently of the high density lipoprotein (HDL) level. We investigated the relationship between serum cholesterol efflux capacity and Pulse Wave Velocity (PWV), as an indicator of arterial stiffness, in healthy subjects.

**Methods:** 99 subjects (40 males, 59 females) were selected from the Brisighella Heart Study cohort for being non-smokers, non-diabetics, untreated with antihypertensive, lipid-lowering or antidiabetic drugs, and without echocardiographically detectable carotid atherothrombotic plaques. Serum cholesterol efflux capacity was measured as aqueous diffusion, total cholesterol efflux and ATP binding cassette A1 (ABCA1)-dependent cholesterol efflux (reflecting mainly HDL function). Bilateral B-mode carotid artery images for intima-media thickness were acquired using a linear phased multifrequency (7.5-10 MHz). The posterior wall of the distal common carotid artery, one centimeter below the bifurcation, was assessed as recommended by the international guidelines. An elastocardiographic trace was used to acquire image frames only in end-diastole, avoiding IMT variation related to carotid pulsatility. Carotid-femoral PWV was measured with a high-fidelity tonometer.

**Results:** In the unadjusted model, PWV relates directly with basal aqueous cholesterol diffusion (R²=0.202, P=0.043) and indirectly with ABCA1-dependent cholesterol efflux (R²=0.215, P=0.042). PWV does not correlate with total cholesterol efflux (R²=0.023, P=0.830). In a stepwise multivariate analysis including age, body mass index, mean arterial pressure, serum low density lipoprotein level, serum HDL level, ABCA1-dependent cholesterol efflux (reflecting mainly HDL function), the best PWV predictors were mean arterial pressure (R=0.83, 95%CI 0.08-0.108), age (R=0.851, 95%CI 0.028-0.073) and ABCA1-dependent cholesterol efflux (R²=0.569, 95%CI 0.531-0.566).

**Conclusions:** ABCA1-dependent cholesterol efflux capacity, but not total serum HDL, is a significant predictor of PWV in healthy subjects. This finding points to the relevance of HDL function in vascular modeling and arterial stiffness prevention along life.

**P1585** The predictive role of 24-hour heart rate on future arterial stiffness. A longitudinal study in hypertensives

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**Purpose:** Pronounced arterial stiffening is associated with increased cardiovascular risk, while the association of heart rate with target organ damage in essential hypertension remains controversial. We sought to investigate the prognostic value of 24-h ambulatory heart rate (24h HR) on future arterial stiffness.

**Methods:** 232 white hypertensive and diabetic patients (51±15 years, 96 smokers, body mass index=28.9±4.6 kg/m²) were followed up for a mean period of 3.4±1.4 years. At both baseline and follow-up all patients underwent 24-hour ambulatory blood pressure (BP) monitoring, carotid-femoral pulse wave velocity (PWV) measurement with Compilor SP, and metabolite profile evaluation. The optimal antihypertensive treatment was implemented during follow-up period. The population was split by the median value of PWV at the last follow-up visit (9.63m/sec).

**Results:** Between baseline and last follow-up visit, systolic and diastolic BP decreased by 14±12.2 and 9±3.8mmHg (136±9 vs. 122±11 and 85±±7.5±7.1 mmHg, p<0.001). 24h HR decreased by 8.3±8.3bpm, while PWV increased by 0.3±1.9 mm/sec (8.8±1.6 vs 9.1±1.6mm/sec, p<0.05). Cox regression analysis using hemodynamic, demographic, metabolic and medical treatment variables, revealed that significant predictors of PWV levels above the median value of 9 m/sec at the last follow-up visit were: age (OR=1.031, 95%OR CI=1.001-1.061, p=0.05), baseline PWV levels (OR=1.478, 95%OR CI=1.242-1.757, p<0.001) and the difference of 24h HR between baseline and last follow-up visit (OR=0.953, 95%OR CI=0.922-0.985, p<0.05).

**Conclusions:** 24h HR seems to convey an increased risk for future arterial stiffening in hypertensive subjects. The reduction of 24h HR exerts a prophylactic effect on the progression of arterial stiffness.

**P1586** Awareness of peripheral arterial disease helps to reach blood pressure and cholesterol target values: results of the hungarian ankle-brachial index screening program (ERV)

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Epidemiological data have shown that patients with clinical and preclinical stages of peripheral arterial disease (PAD) have high risk of cardiovascular mortality. By the measurement of the ankle-brachial index (ABI), PAD can be diagnosed in early asymptomatic stage. The objective of the present study was to evaluate the changes in blood pressure and serum cholesterol values during the first 3 years of the ERV program.

A total of 21 892 hypertensive men and women (9162 males; mean age: 61.45 years) who were attended at 55 hypertension outpatient clinics in Hungary were included in our prospective study. Clinical history, physical examination, blood analysis, and measurement of the ankle-brachial index (calculated with the higher ABI value) were taken in all patients. Patients with established PAD (ABI ≤0.9) were controlled annually.

The prevalence of PAD was 14.4%. Mean systolic blood pressure in patients with an ABI≤0.9 at visit 1 (baseline); visit 2; 3 and 4 were 143±9, 139±7, 139±2 and 140±11 mmHg, respectively (p<0.001 compared to baseline). Mean diastolic blood pressure at visit 1 (baseline); visit 2; 3 and 4 were 83±1, 81±6; 81±20 and 78±5.6 mmHg, respectively (p<0.001 compared to baseline). Mean serum cholesterol at visit 1 (baseline); visit 2; 3 and 4 were 5.3±4; 5.12; 4.99 and 4.94 mmol/L, respectively (p<0.001 compared to baseline).

The use of ABI screening helps to identify patients at high cardiovascular risk and their treatment can be tailored according to the guidelines for high risk patients. Blood pressure and serum cholesterol values decreased significantly during the first 3 years of the ERV program. Cardiovascular morbidity and mortality data will be evaluated after the 5 years long prospective phase of the program.
Efficacy of statin treatment after endovascular therapy for isolated below-the-knee disease in patients with critical limb ischemia

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Background: Little is known about efficacy of statin treatment after endovascular therapy (EVT) for isolated below-the-knee (BTK) disease in patients with critical limb ischemia (CLI). Therefore, we investigated the effect of statin treatment on outcomes in patient with CLI.

Methods: From March 2004 to June 2011, 814 patients (98 limbs, 68.8% male, 168 treated with statin, 71.6±10.0 years old) with CLI underwent EVT for de novo isolated BTK lesion. Their data were retrospectively analyzed. Outcome measures were amputation-free survival (AFS), overall survival, cardiovascular death, limb salvage, freedom from repeat revascularization. Mean follow-up duration was 19.3±17.4 months.

Results: Overall survival and freedom from repeat revascularization at 5 years were significantly higher (45.0% vs 41.5%, P=0.02; 59.5% vs 42.0%, P=0.03, respectively); AFS at 5 years tended to improve in statin-treated group (41.1% vs 38.1%, P=0.094). However, cardiovascular death and limb salvage rate 5 years did not differ significantly between two groups (65% vs 72%, P=0.37; 86.4% vs 78.6%, P=0.48, respectively).

On subgroup analysis, ambulatory group (513 patients, 618 limbs) with baseline variables, statin was effective for prevention of AFS (hazard ratio [HR], 0.61; 95% CI, 0.44-0.86; adjusted P=0.001). However, cardiovascular death and limb salvage rate 5 years also did not differ significantly between two groups (66% vs 72%, P=0.48; 88.2% vs 91.1%, P=0.58, respectively).

Conclusion: For ambulatory and over 2 years life prognosis patient, statin treatment may improve AFS and overall survival, prolong freedom from repeat revascularization after EVT for isolated BTK disease in patients with CLI.

Impact of chronic total occlusion in ilio-femoral artery on clinical outcomes following percutaneous transluminal angioplasty

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Background: Endovascular treatment (EVT) is considered as an effective treatment in patients (pts) with critical limb ischemia (CLI). With the recent improvement of device and EVT technique, the success rate of chronic total occlusion (CTO) in distal aorta and ilio-femoral artery is increasing; however, the mid to long-term durability between distal aorta and ilio-femoral artery CTO following successful recanalization is not clarified yet.

Methods: A total 187 consecutive CLI patients (pts) were treated by EVT from September 2004 to September 2010. Out of 187 pts, 57 pts (79 limbs, 95 lesions) underwent successful CTO intervention in either distal aorta or ilio-femoral artery. CTO recanalization was done either by true lumen angioplasty (shorter lesion) or subintimal angioplasty (longer lesion) with/without reentry device. Provisional stenting was done once the balloon angioplasty outcome was not optimal, mainly by self-expanding nitinol stents. Periprocedural complications and major clinical outcomes of CTO group (n=82 pts) were compared with those of non-CTO group (n=79 pts) up to 12 months.

Results: Baseline clinical and procedural characteristics were similar between the two groups. Major clinical outcomes including mortality, repeat revascularization and the incidence of surgical intervention were similar between the two groups (Table).

Conclusion: Once the CTO lesions in distal aorta was successfully treated, major mid-term angiographic and clinical outcomes were similar to those of iliofemoral CTO lesions. Long-term follow up with larger study population will be needed to get the final conclusion.

Long-term outcomes of self expandable stent vs. balloon expandable stent for terminal aortoiliac bifurcation lesion

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Purpose: Although endovascular therapy (EVT) has advanced, few reported the long-term outcome in terminal-aortoiliac bifurcation lesion. We assessed the hypothesis that endovascular therapy for terminal-aortoiliac bifurcation lesion was safe and good result and compared outcomes of self expandable stent with balloon expandable stent.

Methods: We pooled data from patients enrolled in Real-AI (retrospective multicenter analysis for aortoiliac lesion) registry, which is a multicenter registry in Japan. Of 2096 patients were underwent endovascular therapy, 149 patients (Male 78%, age 69±9, mean follow-up 776±583days) had terminal-aortoiliac bifurcation lesion. The primary patency rates were analyzed by Kaplan-Meier methods.

Results: The primary technical success rate was achieved in 98.9% with an overall complication rate of 3.4%, and the 1 and 5 year primary patencies were 87% and 71%. 79 (53%) patients received endovascular therapy with self expandable stent, and 70 (47%) patients with balloon expandable stent. According to Kaplan-Meier analysis in primary patency rates, the log-rank test showed no significant differences.
Can we predict a long-term results of renal artery stenting?

Methods: Study group comprised 144 (77M, 63.5±11y) hypertensive patients, referred to PA with mean RAS 71.8±13.1%, including 93 unilateral and 36 bilateral RAS, and 15 patients with single functioning kidney. Hypertension crisis was reported in 60 (45%), diabetes in 49 (34%), significant CAD in 94 (65%), internal carotid artery stenosis (ICAS) ≥70% in 46 (32%) and peripheral occlusive disease in 39 (27%). Creatinine level (Cr), eGFR, mean SBP and DBP (24-hour ABPM) were analyzed before, 6 months, and then at 12 months intervals after PA. The incidences of CV death, myocardial infarction (MI), ischemic stroke (IS), or starting dialysis were recorded.

Results: 167 of 168 procedures were technically successful in 143/144 (99.3%) subjects. The mean follow-up period after PA was 48.4±27.6 months. CV events occurred in 34 (23.6%) patients (16 CV deaths, 10 non-fatal MIs, 5 non-fatal ISs, 3 dialysis). Hypertension was cured in 7 patients, while mean number of BP regiments was decreased from 3.2±1.9 to 2.9±1.2 (p<0.001). Mean SBP decreased from 139.2±20.9mmHg to 129±14mmHg (p<0.001) at 12 months, and to 131±16mmHg (p<0.004) at the final follow-up visit, while DBP from 78±12mmHg to 73.8±9mmHg (p=0.004), and to 73.9±9mmHg (p=0.008), respectively. Cr decreased from mean 133±59 to 117±62 and to 123±57 μmol/L (p<0.001; p<0.01), while eGFR increased from 54.3±22 to 62±26, and then to 58±25 (p<0.001 and p<0.05), respectively. BP improvement, defined as long-term SBP reduction of ≥10 and DBP ≥5 mmHg was found in 59 (41%), while RF improvement, defined as Cr level decrease >10% of initial value in 64 (44%) subjects. The follow-up for independent predictors of BP and RF improvement were identified: for BP: higher RAS grade (RR=1.25; p=0.003), initial DBP (RR=1.36; p<0.001), higher RAS grade (RR=1.21; p=0.016), RF improvement (RR=1.21; p=0.016), and for RF: BP improvement (RR=1.34; p=0.001). Independent factors associated with Cr level were ICAS (RR=1.43; p<0.001), pulmonary edema (RR=1.19; p=0.001), initial Cr and SBP (RR=1.4; p=0.001 and RR=1.18; p<0.001).

Conclusions: Long-term BP and RF improvement after PA of RAS can be expected in 41-44% of subjects, and they are independently associated one with the other. However, initial Cr level and SBP remain still an independent risk factors of CV events.

Patients radiation doses analysis in a contemporary cohort of patients undergoing interventional radiology procedures

Methods: We performed a prospective study of 305 consecutive patients with CKD who underwent elective catheterization [serum creatinine (Cr) ≥1.1mg/dl]. Serum Cr level was assessed at the time of hospital admission and on days 1 and 2 after contrast medium exposure. The urinary markers, L-FABP (β2-microglobulin (β2-MG) and N-acetyl-β-D-glucosaminidase (NAG), were measured in urine samples collected early in the morning on the day of the procedure and on days 1 and 2 after contrast medium exposure. Urinary L-FABP was measured with an enzyme-linked immunosorbent assay (ELISA) kit (CMI Co., Ltd., Tokyo, Japan). Patients were prospectively followed during a median follow-up period of 708 days with the end points of Cardiovascular (CV) death. CI-AKI was defined as an increase of 0.3 mg/dl (26.5 micromol/l) within 2 days of contrast media exposure.

Results: CI-AKI developed in 26 patients (8.5%). High L-FABP levels group (defined as >24.5 μg/g Cr) were 59 patients and CI-AKI in high L-FABP levels group developed in 13 patients (22%). A total of 18 cardiac cerebral deaths occurred during a follow-up period and survival outcome tended to be worse high L-FABP levels group (12% vs 4% P=0.028) Kaplan-Meier analysis clearly demonstrated that patients with high L-FABP levels group were higher rate of cardiac cerebral deaths than those with low L-FABP levels group. (Log rank test: P=0.0224)

Conclusions: Urinary L-FABP provides an important information for predicting CI-AKI and survival outcome before contrast agent administration in patients with CKD. Therefore, an increase in urinary L-FABP levels may signal a need for more intensive treatment in these patients.

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High radiation doses in some complex percutaneous cardiac interventions must encourage interventional cardiologist to develop radiation dose reduction protocols, radiation protection training programs and to perform a good follow-up of the patients undergoing this procedures.

Introduction: Sickle cell disease (SCD) is one of the most common severe mono- genic disorders worldwide, which is characterized by the presence of abnormal
haemoglobin S due to a mutation in the β globin gene. SCD is not only responsible for acute vaso-occlusive events but also for chronic vasculopathy, involving medium and small arteries in many organs (lungs, kidney, brain, bones, skin, retina) and for cardiomyopathy. Chronic cardiovascular events have been almost exclusively studied in the USA or in Europe, although two third of SCD patients live in sub-saharian Africa, a very different environment. We have settled the largest of SCD cohort to estimate the prevalence of cardiovascular complications, to look for associations between them and with arterial stiffness and haematological parameters.

Patients and methods: CADRE study is a multinational cohort of SCD patients that is ongoing in five African countries: Cameroon, Senegal, Mali, Gabon and Côte d’Ivoire, with a recruitment goal of 5000 SCD patients and 1000 controls. Included subjects undergo clinical exam, blood sampling for haematological and renal function, pulse wave velocity (PWV) measure and echocardiography.

Results: By the end of 2011, 2600 SCD patients and 500 controls were already recruited. Intermediary analysis was performed in Cameroon, including 482 patients and 257 controls, all aged more than 15 years. After adjustment on sex, age and BMI, we evidenced lower blood pressures (median[Q25-Q75] mmHg) and lower PWV (femoral PWV: 7.8[7.8-7.8] vs. 9.5 [8.4-10.7] m per second) in SCD patients as compared to controls. Conversely, proteinuria/creatininuria ratio (0.6 [0.2-1] versus 0.2 [0.1-0.4]), left and right cardiac volumes, left ventricular filling pressures and tricuspid regurgitation jet velocity (TRV): 2.4 [2.2-2.6] versus 2.2 [2.2-2.3] m per second) were increased, with p value <0.001 for all comparisons. Blood hemoglobin level was correlated to PWV (versely), left ventricular volume and TRV(versely) in SCD patients (p<0.001) but not in controls, suggesting the role of chronic haemolysis rather than anaemia alone.

Conclusion: CADRE cohort is to become the largest cohort of SCD in the world and will make a precise accurate description of chronic cardiovascular events in African SCD patients, as well as better understanding of SCD vasculopathy mechanisms.

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High serum levels of cystatin C predicts the metabolic syndrome

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Purpose: Cystatin C is a novel marker for cardiovascular disease (CVD), however the mechanisms remain unclear. Recent cross-sectional studies have shown that high levels of cystatin C are associated with prevalent metabolic syndrome (MetS) but up to date prospective data regarding such associations are lacking. In this study we prospectively tested whether plasma levels of cystatin C predict new onset MetS as well as long term progression and incidence of the different components of MetS.

Methods and Results: Cystatin C was measured in 1504 individuals free from MetS of the Malmö Diet and Cancer cohort (mean age 56 years; 59% women) who subsequently underwent a follow up exam after a median follow up time of 16 years. MetS was defined according to the NCEP-ATP III guidelines. Logistic regression was used to adjust for covariates. During follow-up, 428 subjects who subsequently underwent a follow-up exam after a median follow up time of 1065±852 days did not determine any difference according to the status of the false lumen. (Figure)

Conclusions: Complete thrombosis of the false lumen may have a correlation with better in-hospital outcomes in patients with acute type B aortic dissection. However, status of the false lumen does not seem to influence long term mortality.
Feasibility of a simple score to predict renal artery stenosis during cardiac catheterization

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Purpose: The aim of this study was to examine feasibility of the score as a screening tool for predicting RAS at the time of cardiac catheterization.

Methods: A total of 1,950 consecutive patients (pts) who underwent cardiac catheterization between January 2007 and December 2010 were enrolled in this study. The pts were divided into two groups according to the presence of RAS. The following 6 variables were used to calculate the score to predict significant RAS (age, gender, creatinine levels, peripheral vascular disease, number of antihypertensive drugs, hypotension and 3-vessel coronary artery disease or previous coronary artery bypass grafting). Abdominal aortography was planned for high-score (≥12) patients without prior renal artery imaging.

Results: Three hundred and thirty seven of 1,950 pts (17.2%) who underwent cardiac catheterization had a score of ≥12. Abdominal aortography was performed in 78 of 337 pts (23.1%). Forty four of 78 pts (56.4%) had RAS≥50%. All pts (n=9) with a score of ≥18 had RAS≥50%.

Conclusion: The simple score based on clinical characteristics is feasible as a screening tool for RAS during cardiac catheterization.

Heart rate variability change predicts neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion

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Purpose: To clarify the role of this novel parameter in the future.

Methods: We prospectively enrolled in a registry 319 consecutive patients who underwent carotid stenting (CAS) from August 2003 to January 2006 in our institution. Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) defined as ipsilateral major and minor stroke, need for target vessel revascularization, non-fatal myocardial infarction (MI), and death were reported at 30 days and 1 year.

Results: The study population consisted of 153 patients aged ≥75 years (group 1) (mean age 68±4 years; male 64.4%) and 173 elderly patients (group 2) (mean age 79±3 years; male 68.8%). No significant difference in terms of history of coronary artery disease, hypertension, hypercholesterolemia and diabetes was observed in the two groups. Symptomatic patient were 4.8% in group 1 and 11.6% in group 2 (p=0.46). All procedures were performed with distal protection devices which were successfully deployed in 98% of cases in both groups. Procedural success, defined as >30% residual stenosis, was achieved in all cases. 30-day mortality was 0.6% in group 1 vs 1.2% in group 2 (p=0.6); major stroke rate was 0% in group 1 vs 2.3% in group 2 (p=0.059) at 30 days and 0% vs 3.5% (p=0.03) at 1 year respectively; minor stroke occurred in 0 patients of group 1 and in 2 (1.2%) patients of group 2 (p=0.1) at 30 days and in 1 (0.6%) vs 2 (1.2%) at 1 year respectively (p=0.5). Cumulative MACCE rate at 1-year was 2.5% in group 1 vs 5.8% in group 2 (p=0.1). Conclusion: Despite similar procedural technical success, CAS performed in elderly patients was associated with a higher risk of major stroke and MACCE at 1 year follow-up compared to younger patients.
foot-clip specialist. All patients with CLI underwent peripheral revascularization of the culprit limb. Cardiac mortality was the primary endpoint of the study.

Results: Among the 764 PCI patients, 111 (14%) developed CLI during follow-up (PCI+CLI group) and were treated with peripheral revascularization in 145 limbs with procedural success in 140 (96%). PCI+CLI patients had lower left ventricle ejection fraction (LVEF) (51±1% vs 53±1%); p=0.008) higher renal failure (25% vs 12%; p=0.005), dialysis (7% vs 3%; p<0.0001) and diabetes duration (13.8 vs 11.7 years; p=0.02) compared to PCI-only patients. Coronary intervention pro-
cedural characteristics did not differ among PCI-only and PCI-CLI patients. At 4 years follow-up, cardiac mortality occurred in 10 (8%) PCI-only patients vs 39 (6%) PCI-only patients (p=0.2). Major amputation occurred in 6 (5%) patients. Cox regres-
sion analysis showed age (OR 1.06, 95%CI 1.02-1.09), dialysis (OR 8.02, 95%CI 4.02-18.3) and LVEF<30% (OR 9.40, 95%CI 4.20-20.61) to be the independent predictors of cardiac mortality which was not influenced by the development of CLI (OR 0.93, 95%CI 0.42-2.06).

Conclusion: In diabetic patients treated with percutaneous coronary revascular-
ization, the development of CLI, treated with peripheral intervention, seems not to impact cardiac mortality long terms.

Heterogeneity of atherosclerotic plaque phenotypes and composition in four different arterial beds: an intravascular ultrasound virtual histology study

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Purpose: The purpose of this study was to compare the plaque morphology be-
tween coronary and peripheral arteries using intravascular ultrasound (IVUS).

Methods: IVUS was performed in 68 patients with coronary and 93 with periph-
eral artery lesions (29 carotid, 50 renal, and 14 iliac). Plaques were classified as fibroatheroma (VFHA) (further subclassified as chimney (VF-TCFA) and thick-capped (VF-ThCFA), fibrocalcific plaque (VF-FC) and pathological intimal thickening (VF-PIT).

Results: Plaque rupture (13% of coronary, 7% of carotid, 6% of renal, and 7% of iliac arteries; P=NS) and VH-TCFA (37% of coronary, 24% of carotid, 16% of renal, and 7% of iliac arteries; P=0.02) was observed in all arteries. Compared to coronary arteries, VF-FC was less frequent (10% of renal < P=0.001) and iliac arteries (P<0.001), while VH-PI and VF-FC were prevalent in both of these peripheral arteries. Lesions with positive remodeling demonstrated more charac-
teristics of VFHA in coronary, carotid, and renal arteries compared to those with intermediate/negative remodeling (all PC=0.1). There was positive relationship between RI and percent necrotic core area in all four arteries.

Conclusions: Atherosclerotic plaque phenotypes were heterogeneous among four different arteries. In contrast, the associations of remodeling mode with plaque phenotype and composition were similar among the various arterial beds.

In-stent restenosis after carotid artery stenting - doppler ultrasound assessment and clinical importance

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Significant in-stent restenosis (ISR) in the carotid self-expanding stent is consid-
ered an important issue that may influence long-term efficacy of carotid artery stenting (CAS). The prevalence of ISR and Doppler ultrasound (DUS) accuracy for ISR diagnosis has not been clearly recognized.

Aim: To determine prevalence of ISR and DUS efficacy in detecting border-line (50-70%) and critical (>70%) ISR in TARGET-CAS population.

Methods: Between Jan 2001 and Jan 2012, 1520 CAS were performed in 1363 patients (age 66.7±8.6y, 67% man, 49.5% symptomatic) according to "tailored-
CAS" algorithm that included extra/intracranial DUS, and angio-CT to select the most appropriate neuroprotection and stent type. Neurological and DUS eval-
ation were performed before CAS, at 6, 12, and then at yearly intervals. During DUS in-stent peak systolic velocity (PSV) and end diastolic velocity (EDV) were measured. The DUS criteria of border-line (50-69%) ISR were >2.0 m/s for PSV and/or 0.6 m/s for EDV; and for critical (>70%) ISR >3.0 m/s for PSV and/or >0.9 m/s for EDV, respectively. In case of suspected significant ISR on DUS, a quantitative angiography (QA) or angio-CT with in-stent diameter reduction and densitometric assessment were performed.

Results: Among the 764 PCI patients, 111 (14%) developed CLI during follow-up (12-120), borderline ISR was suspected in 20 (1.3%) subjects, while ISR >70% in 18 (1.2%) subjects, and total occlusion in 2 (0.13%), according to DUS. Of those, densitometric ISR >70% or stent occlusion was confirmed in QA 18 (18/20 = 90%) patients, with the mean diameter and densitometric lumen reduction of 67.7±11.3%, and 84.7±8.4%, respectively. In 2 other patients ISR degree was 50-69%. Border-
line DUS ISR was confirmed in angio-CT in 16 (16/20 = 80%) subjects, with no angio-CT critical ISR.

There was a strong positive correlation between mean diameter reduction and PSV (r=0.603; p=0.001) or EDV (r=0.604, p=0.001); and densitometric lumen re-
duction and EDV (r=0.726; p=0.001). The prevalence of DUS and QA in ISR was 50-69% for border-line ISR, which was observed in 1 subject with critical ISR and 2 with total occlusion. A balloon-only angioplasty was performed in 13 (13/18 = 72%) for >70% ISR. There were 8 (8/16 = 50%) cases of recurrent ISR (none of them symptomatic) and they were all successfully treated with ZES implantation.

Conclusion: A critical carotid ISR is rare and, in most of cases, asymptomatic. DUS is an effective tool for detecting carotid ISR. Recurrent carotid ISR is a fre-
frequent and challenging issue. The use of coronary ZES in the treatment of recur-
rent carotid ISR is effective.
Methods: A total of 45 patients aged between 55 and 85 years, symptomatic or not, were enrolled in the trial. Inclusion criteria was considered a carotid stenosis > 55% echographically evaluated. Plaques were echographically recorded before treatment. All patients underwent a first intervention, CAS or CEA accordingly with international guidelines parameters, followed by the alternative compared procedure, on the contralateral side, delayed in time until stenosis reached > 55% lumen occlusion. Since patients belonging simultaneously to the control group and the study group, no exclusion criteria were due. Considered endpoints were percentage of restenosis evaluated by ultrasound at 30, 180, > 365 days follow-up periods.

Results: Average stenosis value pre-intervention was 72±11% and resulted not significantly different among CEA and CAS group (p=0.09) as well as isoechogenic, isoiperechogenic and iperechogenic plaque (p=0.72, 0.09, 0.27 respectively). Restenosis resulted significantly decreased in each timely-dependent considered endpoint by CAS approach with respect to CEA. Percentage of restenosis at 30, 180, > 365 days were: 0.1±1.4, 1.6±4 in CAS group and 2±5, 12±18, 26±24 (mean±Standard Deviation) in CEA group respectively (p=0.01). Patency of carotid lumen at 1 year, 180 and 30 days ultrasound follow up was increased by 48±2 and 55±8% respectively in CAE and CAS group (p=0.055).

Conclusions: Carotid stenting results to be as effective as endarterectomy approach in long term follow up whereas it may confer some additional advantages in brief and middle term.

P16108 The vascular bed is a determinant in vascular sensitivity to DES drugs

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In contrast to coronary arteries (C), iliac arteries (I) do not show the same benefit of drug eluting stents (DES) in decreasing restenosis (SIROCCO). Differences in mechanical properties may be responsible as balloon angioplasty in I results in more injury than in C under equal experimental conditions. Differences in neointima (NI) responses to stenting are less clear. We aimed to assess early (2wk) and late (12 wk) response to DES in comparison to bare metal stents (BMS) under controlled conditions in (I) and (C) of similar size, using the same stent.

Methods: Normal farmed swine (n=16) each received 2 C-DES (taxol) and one 0.17mm) showed no significant differences between C and I. Histology also showed no differences in NI between C and I at each time point (Figure). However, a significant difference was found in the amount of late malapposition and thrombus between C and I at 2 weeks (48±43μm vs 19±33μm) which only increased in C at 12 weeks as compared to I (87±115μm vs 14±29μm, p=0.05 T-test).

Conclusion: Basic healing responses for coronary and iliac arteries in absence of severe injury are similar in terms of NI thickness. However, coronary arteries show a significantly higher sensitivity to DES drugs. This persistent difference appears early after stent placement and increases in time. It is most likely attributable to differences in early thrombus deposition and flow patterns known to be important for drug retention and subsequent delivery.

Clinical significance of detecting abnormal fatty acid metabolism with iodine-123 15-(p-iodophenyl)-3-(R, S) methylenedecanoic acid imaging in patients with dilated cardiomyopathy

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Background/Purpose: Fatty acid metabolism is known to be impaired not only in ischemic myocardium but also in non-ischemic degenerated myocardium. We hypothesized that, in dilated cardiomyopathy (DCM), abnormal fatty acid metabolism on iodine-123 15-(p-iodophenyl)-3-(R, S) methylenedecanoic acid (BMIPP) imaging reflects on-going myocardial damage of viable myocardium. In that case, evaluation of fatty acid metabolism by BMIPP imaging may be as important as detecting myocardial fibrosis by cardiac magnetic resonance imaging (CMR). To test this hypothesis, we compared the distribution of BMIPP defect with that of fibrosis expressed as late gadolinium enhancement (LGE) on CMR in patients with DCM.

We also examined the prognostic value of those imaging.

Methods: BMIPP imaging and CMR were done in 46 patients with DCM (59±12 y, 14 female) during their first hospitalization. Detection of BMIPP and LGE were visually judged by radiologists. Cardiac event rate (death or readmission due to heart failure) was analyzed with the Kaplan-Meier method and the prognostic factors were determined by the Cox proportional hazards model.

Results: BMIPP defect was mainly observed at LV free wall whereas LGE mostly at septal wall. Of 24 patients with BMIPP defect, 21 had the unique distribution different from that of LGE. The patients were divided into the following 4 groups: Group N, L, B, and LB consisted of 16 patients with normal BMIPP and CMR, 8 with LGE alone, 12 with BMIPP defect alone, and 12 with both abnormalities, respectively. During the median follow-up period of 19 M, 7 patients developed exacerbation of heart failure requiring hospitalization. Event rate at 12 M was 8.3%, 0%, 22%, and 66.7% in groups, N, L, B, and LB, respectively. Log rank test revealed the significant difference between event free survival curve in group LB and those in other groups (p =0.007). Among the 4 clinical factors (having both LGE and BMIPP defect, LVEF < 20%, brain natriuretic peptide >200 pg/mL and mitral regurgitation grade III or greater), having both LGE and BMIPP defect was found to be the significant factor affecting the cardiac event (hazard ratio: 10.8, 95% confidential interval: 1.8 – 67.0, p = 0.010).

Conclusions: In DCM, fatty acid metabolism impairment at viable myocardial zone with no progressive fibrotic changes possibly suggesting on-going myocardial damage such as inflammation. Having abnormal fatty acid metabolism on BMIPP imaging in addition to certain amount of myocardial fibrosis detectable by CMR is the significant factor predicting future cardiac event.

Characteristics of coronary plaque components of culprit and non-culprit lesions by virtual histology intravascular ultrasound: difference between acute coronary syndrome and stable angina pectoris

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Purpose: Evaluation of coronary plaque in non-culprit as well as culprit lesions may be useful for understanding coronary atherosclerosis. We investigated characteristics of coronary plaque composition in culprit and non-culprit lesions using virtual histology intravascular ultrasound (VH-VUS) in patients with acute coronary syndrome (ACS) and stable angina pectoris (SAP).

Methods: Culprit and non-culprit lesions (left main or proximal of right coronary artery) were studied using VH-VUS in 50 patients (64±13±1 year-old, ACS group, n=24; SAP group, n=26), and plaque components (fibrous tissue, fibro-fatty, dense calcium or necrotic core) were assessed.

Results: Coronary plaque cross sectional area (CSA) of culprit was greater in ACS than SAP group. Of note, necrotic core was larger and fibrous tissue was smaller in ACS than SAP both in culprit and non-culprit lesions. Furthermore, the composition of coronary plaque was not different between culprit and non-culprit lesions. Coronary risk factors such as hypertension.

Conclusion: Basic healing responses for coronary and iliac arteries in absence of severe injury are similar in terms of NI thickness. However, coronary arteries show a significantly higher sensitivity to DES drugs. This persistent difference appears early after stent placement and increases in time. It is most likely attributable to differences in early thrombus deposition and flow patterns known to be important for drug retention and subsequent delivery.
dyslipidemia, diabetes mellitus and current smoking did not affect the size (%) of necrotic core.

**Conclusions:** Coronary plaque in ACS contains larger necrotic core than that in SAP in both culprit and non-culprit lesions. This suggests that aggressive medical intervention to improve plaque compositions in the coronary arterial tree as well as an intervention to culprit lesion is necessary in patients with ACS.

### P1612 Prevalence and predictors of coronary artery disease in patients with a calcium score of zero

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**Purpose:** The absence of coronary calcification is associated with a good prognosis. However, a calcium score (CaSc) of zero does not exclude the presence of coronary artery disease (CAD).

Our aim was to study the prevalence and predictors of coronary artery disease in patients with a CaSc of zero.

**Methods:** Prospective registry of 2563 consecutive patients that performed Cardiac CT (Dual source CT). Stable patients referred for evaluation of possible CAD that had a CaSc of zero were selected for this analysis. Urgent exams and patients with previous CAD were excluded.

The prevalence of CAD in this population and the clinical variables associated with this combination (CAD without coronary calcification) were studied. The variables (sex, age, body mass index, diabetes mellitus, hypertension, dyslipidemia, smoking habits and family history of CAD) that were statistically significant were included in the multivariable logistic regression model.

**Results:** From 774 patients with CaSc of zero, 103 (13%) had coronary plaques of the contrast CT (11%, n=87 with nonobstructive CAD and 2%, n=16 with obstructive CAD).

The variables associated with the presence of CAD in this population were: hypertension, dyslipidemia and age ≥55 years. [Table]

By logistic regression analysis, the independent predictors of CAD in this population were dyslipidemia [OR: 1.9 (1.1-2.8)] and age ≥55 years [OR: 1.7 (1.1-2.6)].

**Predictors of CAD with calcium score = 0**

<table>
<thead>
<tr>
<th>Without CAD (n=871)</th>
<th>With CAD (n=103)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>46%</td>
<td>50%</td>
</tr>
<tr>
<td>Age ≥55 years</td>
<td>46%</td>
<td>62%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51%</td>
<td>63%</td>
</tr>
<tr>
<td>Smoking</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>51%</td>
<td>68%</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>BMI (mean=19.9±4)</td>
<td>27±4</td>
<td>27±4</td>
</tr>
</tbody>
</table>

**Conclusion:** The absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low.

In this population, the independent predictors of CAD in the setting of a calcium score of zero were dyslipidemia and age above 55 years.

### P1613 Prognostic value of stress imaging after revascularization: a meta-analysis of stress echocardiography and stress nuclear imaging

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**Background:** Risk assessment is an important goal in patients after prior coronary intervention (PCI) or surgery (CABG).

This meta-analysis sought the prognostic value of radionuclide stress myocardial perfusion imaging (MPI) or echocardiography (SE) among patients with previous PCI or CABG.

**Methods:** In an electronic search of candidate studies on the outcomes of stress imaging tests post-revascularization, studies were selected if they reported the relationship between the baseline (HR) and the hazard ratios derived from multivariable analysis of hard events (cardiac death and myocardial infarction) or a composite endpoint including repeat revascularization. Independent data extraction was performed by two reviewers and discrepancies resolved by consensus. Data extracted included participant characteristics, stress imaging characteristics, and outcomes.

**Results:** 37 studies (11,790 patients; mean age 61±4 years; 80% men) contributed to this meta-analysis. In a random effects model, an abnormal stress imaging test was associated with a RR of 2.64 (2.05-3.39; p<0.0001) and a HR of 1.53 (1.38-1.69; p<0.0001). Among study design features, only the history of PCI vs. CABG showed a significant association with outcome. Age and the timing of the stress imaging post-revascularization were associated with differences in the predictive value of stress imaging. Type of stress test was an important cause of heterogeneity in HR; SE was better in predicting outcomes than stress MPI (pooled HR 3 vs. 1), although MPI studies showed greater heterogeneity.

**Conclusions:** In patients with previous revascularization, abnormal results at SE or MPI are predictive of cardiac mortality, myocardial infarction and the need for repeat revascularization.

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**P1614**

**Left ventricular reverse remodeling in response to cardiac resynchronization therapy: temporal evolution characterization. Sub-analysis of POBREE trial**


**Introduction:** Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with severe heart failure and wide QRS. In addition, induces reverse remodeling with diastolic (TDV) and telesistolic volumes (TSV) reduction and improvement in ejection fraction (EF). However, the temporal evolution of this phenomenon remains poorly characterized and its correlation with the symptomatic improvement is not well understood.

**Aims:** To characterize the temporal evolution of reverse remodeling in response to CRT and to evaluate its correlation with the clinical response.

**Methods:** Prospective observational study. Consecutive patients (pts) proposed for CRT were evaluated prior to implantation and after 3, 6 and 12 months, including transthoracic echocardiographic study. Symptomatic improvement was defined as: survival at 12 months post-CRT, without hospitalizations by heart failure and with reduction of functional class in at least 1 class; and reverse remodeling was defined as reducing the TSV in at least 10%.

**Results:** We studied 50 pts (38 men, 68.5±8.4 years-old). The initial EF was of 28±10% and 47% had ischemic heart disease. During follow-up, two pts died, 74% had symptomatic improvement and 50% showed reverse remodeling. A significant reduction of the TSV between the baseline (206±83mL) and 3 months (190±79mL; p=0.006), 6 months (181±68mL; p=0.003) and 12 months follow-up (172±74mL; p<0.001) was observed, as well as the reduction of the TSV between the baseline (152±73mL) and 3 months (134±74mL; p=0.003), 6 months (132±74mL; p=0.015) and 12 months (119±62mL; p<0.001). There was improvement on the baseline EF, but statistical significance was achieved only at 12 months (33±12%; p=0.023). Although pts with symptomatic improvement had more significant remodeling, the correlation between the clinical and the echocardiographic response was weak, with only 53% of pts showing symptomatic improvement. In addition, reverse remodeling occurred in 21% of pts who did not achieve symptomatic improvement.

**Conclusions:** Favorable ventricular remodeling occurred in about half of the pts undergoing CRT. The beneficial effects of therapy were progressive over the first year of follow-up. However, the occurrence of symptomatic improvement, observed in 2 of 12 pts, does not predict the occurrence of positive ventricular remodeling and vice-versa.

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**P1615 Inappropriateness of cardiovascular radiological imaging testing in a tertiary care referral center**

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**Purpose:** Radiological inappropriateness in medical imaging testing implies loss of resources and accumulation of avoidable population cancer risk. The aim of the study was to audit the appropriateness rate of different cardiac radiological examination in a tertiary care cardiovascular center.

**Methods:** With a retrospective, observational study design we reviewed clinical records of 901 consecutive patients (age 68±10, 80% males) admitted from January 1, 2007 at CNR in Pisa. From the central database information about patient demographics, symptoms, and the reasons for testing were obtained. A total of 1000 imaging tests were audited: 250 stress myocardial perfusion scan (MPI); 250 coronary angiography (CA); 250 percutaneous coronary intervention (PCI); 250 coronary computed tomography angiography (CT). For each test, indications were rated as definitely appropriate (A, class I, including IIa, probably appropriate), uncertain (U, class II b, probably inappropriate), or inappropriate (I, class III definitely inappropriate) on the basis of 2009-2010 ESC and ACC guidelines.

**Results:** Examinations were A in 532 (53%), U in 200 (20%), and I in 269 (27%) studies. Appropriateness rate for individual test are reported in Figure 1.
Cardiovascular information systems influence the doctors selection of materials and devices, leading to significant savings in invasive cardiology

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Up to 50% of all costs for invasive cardiology patients are incurred in the cath lab. These costs can be split into fixed costs (such as, cath lab staff), fixed material costs (like scrub, and so on), and variable material costs (implants, single use devices, such as stents, and consumables, like balloons). This study aimed to significantly reduce the variable costs for different procedures in the cath lab.

Methods: We collected data with a cardiovascular information system (Philips CVIS®). We collected a baseline dataset from April 1st, 2009 to March 30th, 2011. We then integrated a tool into CVIS to present the costs of finished procedures and give real-time feedback to the doctor. Medical reasons were always the primary influence on the choice of device, but the cath lab staff were trained and informed on device prices. The first observation ran from August 1st to September 30th, 2011. After adjustment training, a second observation ran from October 1st to November 30th, 2011.

Results: Results are shown in the table. The real-time feedback of costs also led to the following errors in 2% of procedures.

Table 1. Savings during observation period in % of baseline

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Baseline cases</th>
<th>Average material costs reduction (compared with baseline data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic coronary angiography</td>
<td>1557</td>
<td>18.4% (p&lt;0.05)</td>
</tr>
<tr>
<td>followed by percutaneous coronary intervention</td>
<td>1185</td>
<td></td>
</tr>
<tr>
<td>using 1 bare metal stent</td>
<td>36.7% (p=0.001)</td>
<td>31.8% 42.8%</td>
</tr>
<tr>
<td>using &gt;1 bare metal stent</td>
<td>25.6% (p=0.01)</td>
<td>41.5%</td>
</tr>
<tr>
<td>using 1 drug eluting stent</td>
<td>30.6% (p=0.001)</td>
<td>24.3% 37.6%</td>
</tr>
<tr>
<td>using &gt;1 drug eluting stent</td>
<td>32.8% (p=0.001)</td>
<td>27.7% 36.6%</td>
</tr>
<tr>
<td>Diagnostic electrophysiology studies</td>
<td>86</td>
<td>23.7% (p&lt;0.05)</td>
</tr>
<tr>
<td>followed by radiofrequency ablation</td>
<td>194</td>
<td>31.9% (p&lt;0.01)</td>
</tr>
<tr>
<td>followed by initial fibrilliation ablation</td>
<td>10.8% (p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Combined with an intensive cooperation with the purchasing department, informing and teaching staff in the cath lab about the prices of devices used, using a CVIS to provide real-time feedback, can help avoid coding errors that would otherwise result in lost reimbursement.

Regional differences in the utilisation of coronary angiography as initial investigation for the evaluation of patients with suspected coronary artery disease

I. Kosa1, I. Vassanyi2, A. Nemes3, E. Belicza3, G.Y. Kozmann2
1Cardiac Rehabilitation Centre of Military Hospital, Balatonfüred, Hungary; 2Research & Development Center of Health Informatics, University of Szeged, Faculty of Medicine, 2nd Department of Internal Medicine & Cardiology Centre, Szeged, Hungary; 3Semmelweis University Health Services Management Training Center, Budapest, Hungary

Introduction: Despite diagnostic algorithm of patients with suspected coronary artery disease (CAD) is well defined, a considerable number of such cases are not invasive procedures without previous noninvasive evaluation. In these subjects invasive evaluation is only based on the clinical characteristics. The present study was designed to depict regional differences in the utilisation of direct invasive evaluation strategy, and its consequences on the patient characteristics in Hungary.

Methods: Depersonalised data of 28,790 patients from the database of National Institute for Quality- and Organizational Development in Healthcare and Medicines of Hungary are included. All patients had undergone coronary angiography, as an initial investigation, following at least half-year-long stable period between 1st January 2004 and 31st December 2008. Patients with acute myocardial infarction were excluded from the evaluation. The activity of individual primary cardiological clinical centres were characterized by the data of patients living in the area supplied dominantly by the centre. For every centre with sample size above 100, the incidence of direct invasive investigations, and the age and mortality of these patients using the follow-up data until 31th december 2009 were calculated.

Results: From the 135 clinical centres 94 delivered above the predefined sample size of 100, covering 89.5% of the population of Hungary. Population size for the individual centres was 95,666-56,860 inhabitants (range 24,794 - 297,558). Coronary angiography was the initial investigation in 29,911.1.6 cases per 10,000 inhabitants (range 11.4 to 68.9). The mean age of this population was 61.4±13.6 years (range 56.2 - 69.2), while one-year mortality of these patients was 6.1±2.2% (range 1.9 - 15.9). Significant positive correlation was found between the incidence of the initial invasive procedure and the age of patients (R=0.40, p<0.001), while the mortality risk of patients tended rather to decrease with increasing incidence of direct invasive procedure (p<NS).

Conclusions: There are considerable differences in the utilisation of direct invasive procedures in the evaluation of patients with suspected CAD. The increasing number of this procedure is coupled with an increasing proportion of elderly subjects. The fact that the increase of age is not followed by increased mortality risk of involved patients suggests that one factor for greater incidence in some areas is the declined stringency in patient selection.

Automatic patient dose parameters recording and evaluation in interventional cardiology

J.M. Fernandez-Soto1, O. Vano1, J.I. Ten2, R.M. Sanchez1, F. Alfonso3, J. Escaned4
1Hospital Clinic San Carlos, Medical Physics Department, Madrid, Spain; 2Hospital Clinic San Carlos, Department of Radiology, Madrid, Spain; 3Hospital Clinic San Carlos, Cardiovascular Institute, Madrid, Spain

Purpose: The aim of this work is to present the functionalities and results of an automatic system on patient dosimetry for interventional cardiology in a large university hospital.

Methods: The system called DOLIR (Dosimetry On Line for Interventional Radiology) has been implemented in five interventional cardiology laboratories with the capability to export patient dose reports by e-mail at the end of each procedure. The information contained in all of this mail is more or less in the database of the medical physics department. A client-server application allows the graphical analysis of the information from any computer of the department in real time.

Results: During 2011, 3329 procedures were on average 0.2 in the database, which represents about 60% of all the activity in this room. The system allows the identification of the procedures with high cumulative skin dose values, and the possible clinical follow-up protocol. Simultaneously, the automatic feeding of the database allows the analysis of the trends in the different parameters registered: kerma area product (KAP), cumulative skin dose, fluorescence time, number of series and frames per study, KAP per frame and per second.

Table 1. Average and STD values for main parameters registered per laboratory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (kGy·m²)</th>
<th>STD (kGy·m²)</th>
<th>Max (kGy·m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration</td>
<td>11.7 ± 4.2</td>
<td>213 ± 470</td>
<td>2993</td>
</tr>
<tr>
<td>KAP (Gy·m²)</td>
<td>24 ± 27</td>
<td>78 ± 190</td>
<td>876</td>
</tr>
<tr>
<td>Cumulative skin dose</td>
<td>85 ± 89</td>
<td>414 ± 890</td>
<td>7000</td>
</tr>
<tr>
<td>Fluorescence time</td>
<td>17 ± 16</td>
<td>92 ± 1070</td>
<td>9672</td>
</tr>
<tr>
<td>Number of series</td>
<td>11 ± 6</td>
<td>34 ± 700</td>
<td>6926</td>
</tr>
<tr>
<td>Number of frames</td>
<td>1.6 ± 0.7</td>
<td>4.7 ± 300</td>
<td>600</td>
</tr>
</tbody>
</table>

Average and STD values for main parameters registered per laboratory.

Conclusion: Until the DICOM dose-structured reports are available, this system can be considered as a valid "interim" solution for the automatic processing of the parameters related to patient doses in interventional cardiology systems and for detecting doses higher than the trigger level for potential clinical follow-up.

Use and misuse of multivariable approaches in interventional cardiology studies on drug-eluting stents: a systematic review

F. D’Ascanzi1, E. Cavalliero1, G. Biordi Zocca2, C. Moretti1, P. Omede1, M. Bollati1, D. Castagno1, M.G. Modena, F. Gaia1, I. Sibillan1, Division of Cardiology, University of Turin, Turin, Italy; 2University of Modena & Reggio Emilia, Modena, Italy

Purpose: Randomized clinical trials (RCTs) provide the most compelling clinical evidence, but they require important resource and logistical efforts. By contrast, large, cost-free registries may be easily accessed to gather observational, real world data. However, observational studies require complex statistical analyses that often lead to flawed results because of inaccurate methods, especially from a statistic point of view. We aimed to appraise the performance of current multivariable analyses in the estimation of cardiac events after Drug Eluting Stent implantation.

Methods: Pertinent studies published in the literature were searched, selected, abstracted and appraised for quality and validity features. 6 studies using a logistic regression, and 11 studies including a propensity score, matching were included, all of them were included from 2003 to 2012. The studies were conducted in different regions and different length of follow up, with an overall low risk of bias. Most of the 15 studies using a Cox proportional hazard analysis had a different follow up, with less than 10 events for covariates, yielding an overall low or moderate risk of bias. 16 studies using a propensity score without matching were included. The most frequent method for variable selection was logistic regression, with underlying differences in follow-up and less than 10 events for covariate in most of them. Results: Calibration appraisal was not reported in the majority of the studies whereas discrimination appraisal was more frequently performed. Amongst the 17 studies using a propensity score, matching was usually performed with a nearest-neighbor-matching algorithm yet without appraisal of calibration or discrimination in most of the studies. Balance was evaluated in 46% of the studies, being obtained for all variables in 48% of them.

Conclusions: Better use and methodological appraisal of multivariable analysis is needed in order to improve the reliability of non-randomized studies and their impact on research and clinical practice.
From sound to ultrasound: a novel approach of evaluating aortic elasticity and carotid artery mechanics in Takayasu's arteritis.

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Purpose: To validate a multimedia-based paediatric cardiology teaching course for medical students, based on stepwise presentation of basic principles of clinical evaluation (sound: "virtual" cardiac auscultation) up to the final diagnostic tools (ultrasound: echocardiographic evaluation).

Methods: 30 medical students (21 female, 8 male, median age 24.8 yrs, of them 27 were undergraduates) of 5 European Institutions (3 countries) participated in a two week Erasmus Intensive Program (European Commission’s Life-long Learning Programmes). Teaching included theoretical and practical (virtual and hands-on) exercise, provided by 6 academic paediatric cardiologists and further teachers. Virtual cardiac auscultation was based on reproduction of digitally stored phonocardiograms, corresponding to a wide spectrum of congenital heart disease associated echocardiographic patterns were also shown. Hands-on experience included supervised evaluation of school aged children by conventional auscultation and echocardiographic examination by using portable equipment.

Results: The average total score of students was 78.8 (median=79.9, range 58.8-87.5). The decreasing order of students showed an excellent performance in auscultation theoretical test (92.4), echocardiography video interpretation test (83.4), paediatric cardiology theoretical test (82.7) and an acceptable performance in auscultation practical skills test (57.7). By using a 5-degree scale (1=not at all, 5=very much) students validated the course overall with a mean value of 4.48 (Table 1). Responses and performance were independent of country or Institution of students.

Conclusions: Modern computer-based intensive teaching when followed by hands-on practice, is a very effective means of pediatric cardiology teaching, highly appreciated by medical students.

P1625 Acoustical detection of coronary stenosis in humans: an angiographic validation study

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Stenotic coronary arterial lesions cause turbulence and emit acoustical waves. We evaluated the accuracy of a new device that detects and analyzes acoustical pressure waves from the chest wall (CADence device) to detect the presence of a coronary stenosis.

Device description: The device consists of a diaphragm, which activates a pressure transducer that records longitudinal waves in the acoustic range (20-200,000 Hz) from the anterior chest wall and stores them in digital format. After down-load, several frequency domains in the acoustic wave range associated with poststenotic turbulence were examined using multiple spectral analysis techniques. The presence of increased intensity in these domain regions led to classification as disease "present" or "absent".

Methods: Recordings were obtained from 191 patients immediately prior to elective cardiac catheterization. Patients with prior cardiac surgery were excluded. Recordings from up to 6 anterior chest positions were recorded during a breath hold. The acoustical recordings and coronary angiograms were analyzed blindly. An experienced angiographer reviewed each angiogram and graded the most severe stenosis in each of 16 coronary segments. The acoustical recordings were analyzed by a digital processing technician blinded to the angiographic results and each recording was graded as disease "present" or "absent".

Results: Analyzable recordings were obtained from 154/191 patients (81%). Ambient background noise was the most common reason for an unacceptable recording. 77 of the 154 patients with analyzable recordings had significant CAD (>50% stenosis in any arterial segment). 20%, 19%, and 11% had 1, 2, and 3 vessel disease, respectively.

The degree of stenosis that resulted in the maximal overall accuracy for detection of a stenotic lesion was >50% stenosis. The area under the ROC curve for detection of a 50% stenosis was 0.73 (p<0.0001). The sensitivity and specificity for detection of a coronary stenosis >50% in any vessel were 0.69 and 0.77 (NPV 0.71 and PPV 0.70). The sensitivity for predicting >50% stenosis in 1, 2, and 3 vessel coronary disease was 0.70, 0.61, and 0.77. The accuracy of detecting LAD lesions was similar to that of circumflex or RCA lesions.

Conclusion: These data suggest that the acoustical detection of coronary artery stenosis using the CADence device is feasible. In this first generation device, the diagnostic accuracy approached that reported for other non-invasive diagnostic tests. Its complete lack of risk and potential widespread applicability make the device a potential game changer in the detection of significant coronary stenosis.
under the curve of 0.86 (95% CI: 0.80–0.91) for B-lines to predict the cardiogenic origin of the dyspnea, with a cut-off of 15 B-lines to maximize accuracy.

**Conclusions:** Sonographic B-lines are more sensitive than CXR for the evaluation of pulmonary congestion. In a dyspneic ER patient, the absence of bilateral B-lines can reliably exclude the presence of cardiogenic pulmonary congestion with a 5-min bedside examination.

### P1624

**The use of chest x-ray as a diagnostic tool in acute aortic dissection:** insights from the International Registry of Acute Aortic Dissection (IRAD)

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**Background:** Acute Aortic Dissection is a life threatening disease requiring rapid diagnosis and treatment. As a diagnostic tool, chest x-rays (CXR) are simple, inexpensive, and easy to perform in an emergent setting. We compared aortic dissection patients with normal vs abnormal CXR findings to assess differences in symptoms and presentation.

**Methods:** Using data from the IRAD Registry, we evaluated 1110 Patients who presented from January 1996 to February 2011 with acute aortic dissections (Type A and Type B). Only CXRs from the tertiary hospital were analysed. Normal CXRs were defined as lacking widening mediastinum, normal cardiac contour, normal aortic contour, no displacement of calcification of the aorta and no pleural effusion.

**Results:** Of 1110 patients analysed in IRAD, 227 (25.0%) had a normal CXR; 833 (75.0%) were abnormal. Of 615 Type A patients, 136 (22.1%) had normal CXR. These patients were more likely to have had a prior dissection (10.1% vs. 4.6%; p<0.009). Type B patients (495 total) with normal chest x-rays (141; 28.5%) were studied for comparison. A widening of the mediastinum in patients with a CXR type B dissection was observed in 60.4% of patients vs. 32.4% of patients with normal CXR (p=0.003). Because normal CXRs were more likely in Type B patients, it is important to consider the presence of normal CXRs slightly more likely in Type B patients. Because normal findings on CXR do not exclude acute Type A or Type B aortic dissection, it is important to consider the presence of normal CXRs slightly more likely in Type B patients.

**Conclusion:** CXR was abnormal in three-quarters of the IRAD population, with normal CXRs more likely in Type B patients. Because normal CXR findings do not characterize patients with these findings, awareness of patient history and pre-CXR does not exclude acute Type A or Type B aortic dissection, it is important to consider the presence of normal CXRs slightly more likely in Type B patients. Because normal findings on CXR do not exclude acute Type A or Type B aortic dissection, it is important to consider the presence of normal CXRs slightly more likely in Type B patients.

### P1625

**A novel method for assessing diseased myocardium: tracer arrival time evaluation**

N. Zarinbad Nooralipour1, N. Chiribiri, G. Hautvast1, M. Breeuwer1, E. Nagei2, 1King’s College London, Division of Imaging Sciences, London, United Kingdom; 2Philips Healthcare, Imaging Systems – MR, best, Netherlands

Dynamic contrast-enhanced cardiovascular magnetic resonance imaging (DCE-CMR) is today the most popular method to assess perfusion in the myocardium and detect ischemia. This technique is mostly used to determine quantitative parameters such as peak of tissue impulse response curve to estimate perfusion. But perfusion quantification is challenging and suffers from several limitations including saturation effects associated. In this study a novel method for assessing diseased myocardium has been presented which is based on estimation of the tracer arrival time into the myocardium tissue (IONset) using DCE-CMR data. Data were obtained from a patient during adenosine-induced hyperemia and have been analyzed using a software, which uses second derivative test on voxel level to identify the optimal IONset. The relative IONset which is the difference between the tracer arrival time in LV and IONset has been calculated and used as parameter to assess the diseased myocardium.

Figure 1 shows estimated relative tracer arrival time for a 48-year-old male with one previous episode of anterior myocardial infarction. Figure 2 shows a histogram of estimated tracer arrival time for the above patient. Most of the IONset values are distributed around 30, except the IONset values of the abnormal LAD territories which are distributed around 45. This method allows for the evaluation of areas of diseased myocardium by estimating the time point of tracer arrival at particular voxel. As a result a further post-processing step to establish perfusion values is negated, thus minimizing errors and reducing processing time.

### P1626

**Does pre-operative left ventricular shape play a role in systolic function after mitral valve repair?**

F. Mattessanti1, G. Tamborini2, P. Grisani3, M. Muratori4, F. Alamanzi5, M. Zanobini6, L. Fusini7, E.G. Calam7, R.M. Lang2, M. Pepi3, 1Centro Cardiologico Monzino RRCRS, Milan, Italy; 2Department of Biomedical Engineering, Politecnico di Milano, Milan, Italy; 3The University of Chicago Medical Center, Chicago, United States of America

Early mitral valve (MV) repair is known to result in functional benefits and morphological reverse remodeling of the left ventricle (LV). Our aim was to investigate whether in patients showing a depressed post-op LV function, the LV had already remediated toward a less pathological condition associated with volume overload. 55 patients (60±1yrs) with organic MV prolapse and ejection fraction (EF) ≤55% undergoing MV repair were enrolled. Based on pre/post EF change, patients were divided in 2 groups, MV_A (EFloss<10%), and MV_B (EF loss<10%). Transthoracic 3D echo was performed before and 6 months after surgery. Also, 40 normal subjects (NL) and 40 patients with dilated cardiomyopathy (DCM), age-matched, were studied for comparison. End-diastolic (EDV) and end-systolic (ESV) volumes, EF, and LV 3D shape indices of sphericity (S) and concurrency (Cn) were computed (perfect sphere/cone index=100%). Parameters were compared at each time point, and versus NL and DCM.

MV repair was successful in all cases; 23 patients were assigned to MV_A, 32 to MV_B. Results are shown in the Table. Compared to NL, MV groups showed slightly enlarged EDV and higher EF, significant in MV_A, with similar ESV: compared to DCM the LV was significantly less dilated, with a higher EF. From the morphological perspective, pre-op LV was more spherical and less conical compared to NL, but not as much remodeled as DCM. No pre-op differences in LV volumes were found between MV groups, while MV_A was more spherical. Compared to pre-surgery, volumes and ED S decreased, while Cn increased, resulting in shape indices similar to NL, but still slightly different. The decrease in EF observed in MV_A was associated with a post-operative ES S higher than in MV_B.

**Results of the study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-op</th>
<th>Post-op</th>
<th>p-value</th>
<th>NL</th>
<th>DCM</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>55±5</td>
<td>60±7</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV/BSA (ml/m²)</td>
<td>106±32</td>
<td>93±21</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESV/BSA (ml/m²)</td>
<td>59±17</td>
<td>67±22</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED S (())/ (%)</td>
<td>49±3</td>
<td>64±5</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED Cn (%)</td>
<td>6±2</td>
<td>6±2</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES Cn (%)</td>
<td>22±3</td>
<td>20±2</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVP_A Pre 71† 271‡</td>
<td>61±5</td>
<td>59±3</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVP_B Pre 58† 147‡</td>
<td>56±3</td>
<td>58±3</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVP_A Post 68† 15‡</td>
<td>60±5</td>
<td>58±3</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVP_B Post 58† 15‡</td>
<td>60±5</td>
<td>58±3</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MV repair led to functional benefit and morphological normalization of the LV at 6 months. Both post-op EF were associated with a less pronounced volumetric and morphological remodeling in terms of pre-operative EF and sphericity.
A new 3D patient specific morphing tool enabling clinical application of non-invasive cardiac activation imaging

P. M. Van Dam1, A.W.M. Van Der Graaf2, M.J.W. Gotte2. 1Cortius Holding B.V., Amersfoort, Netherlands; 2Haga Teaching Hospital, The Hague, Netherlands

Purpose: Patient specific heart models are required to accurately determine cardiac electrical activation. However, no accurate computer tool exists to create patient specific computer heart models from Cardiovascular Magnetic Resonance (CMR) images.

Methods: New software was developed capable of morphing patient specific heart and thorax models from CMR or Computed Tomography (CT) images. We used a new mathematical morphing approach to translate all significant cardiac and thoracic anatomical structures into 3D models (figure 1).

Results: Twelve adult patient specific models have been created from CMR and CT (6 male, 6 female, 2 normal, 8 arrhythmia patients and 2 CRT patients. On average only 12-20 short axis and 2-4 long axis images were needed to make an accurate heart model. Between the reference imaging modality and the computer morphing tool quantitatively approximates individual heart and thorax anatomy.

Conclusion: Post-processing is the most important determinant in inter-vendor variation, with differences in acquisition having a small effect.

Abstract P1627 – Table 1

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Machine</th>
<th>Strain analysis software</th>
<th>Spearman’s rho</th>
<th>P value vs. Exp 2</th>
<th>Bias</th>
<th>SD</th>
<th>LOA (±1.96SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Different</td>
<td>Different (both vendor specific)</td>
<td>0.346</td>
<td>0.008</td>
<td>-2.0</td>
<td>6.0</td>
<td>11.7</td>
</tr>
<tr>
<td>2</td>
<td>Different</td>
<td>Same (vendor non-specific)</td>
<td>0.736</td>
<td>0.0</td>
<td>0.0</td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td>3</td>
<td>Different</td>
<td>Same (vendor non-specific)</td>
<td>0.637</td>
<td>0.390</td>
<td>-0.5</td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td>4</td>
<td>Same (Vendor 1)</td>
<td>Different (one vendor non-specific)</td>
<td>0.733</td>
<td>0.378</td>
<td>-2.4</td>
<td>3.2</td>
<td>6.5</td>
</tr>
<tr>
<td>5</td>
<td>Same (Vendor 1)</td>
<td>Different (one vendor non-specific)</td>
<td>0.725</td>
<td>0.012</td>
<td>1.0</td>
<td>2.2</td>
<td>4.4</td>
</tr>
<tr>
<td>6</td>
<td>Same (Vendor 1)</td>
<td>Different (both vendor non-specific)</td>
<td>0.704</td>
<td>0.764</td>
<td>3.8</td>
<td>2.3</td>
<td>4.6</td>
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<tr>
<td>7</td>
<td>Same (Vendor 2)</td>
<td>Different (one vendor non-specific)</td>
<td>0.309</td>
<td>0.004</td>
<td>-0.3</td>
<td>5.4</td>
<td>10.6</td>
</tr>
<tr>
<td>8</td>
<td>Same (Vendor 2)</td>
<td>Different (one vendor non-specific)</td>
<td>0.326</td>
<td>0.006</td>
<td>3.0</td>
<td>5.3</td>
<td>10.4</td>
</tr>
<tr>
<td>9</td>
<td>Same (Vendor 2)</td>
<td>Different (both vendor non-specific)</td>
<td>0.636</td>
<td>0.384</td>
<td>3.3</td>
<td>2.3</td>
<td>4.4</td>
</tr>
</tbody>
</table>

Expt, Experiment; SD, standard deviation; LOA, limits of agreement.

Conclusions: Force-frequency relation assessment with this new non-invasive, operator-independent force sensor is extendable to daily physiological exercise and could be potentially attractive for quantitative non-imaging assessment of left ventricular contractile reserve, of potential interest in the stress lab and for home monitoring systems in cardiac heart failure.

Cardiovascular hemodynamics in the stress echo lab with open-source software

T. Bombardini, D. Cini, E. Picano. Institute of Clinical Physiology of CNR, Pisa, Italy

Background: Stress echocardiographic evaluation of volumes is ideally suited for the quantitative calculation of a set of parameters allowing a complete characterization of cardiovascular hemodynamics of established pathophysiological and potential clinical relevance, including cardiac output, systemic vascular resistance, left ventricular elastance, arterial elastance, and ventricular arterial coupling. However, this is a tedious and time-consuming procedure.

Aims: 1) to build a web-based computing software program for self-instruction and calculation of hemodynamic parameters in the stress-echo lab; 2) to test the software with skilled echocardiographers; 3) to distribute the software to the medical community.

Methods: A website with the informatics infrastructure was built (at cctrainer.itc.cnr.it). Ten skilled echocardiographers (American Society of Echocardiography class III) were asked to calculate hemodynamic parameters by using

Abstract P1629 – Table 1

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Machine</th>
<th>Strain analysis software</th>
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<th>SD</th>
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<td>0.0</td>
<td>0.0</td>
<td>2.1</td>
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<td>0.637</td>
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<td>4.1</td>
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<td>6.5</td>
</tr>
<tr>
<td>5</td>
<td>Same (Vendor 1)</td>
<td>Different (one vendor non-specific)</td>
<td>0.725</td>
<td>0.012</td>
<td>1.0</td>
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<tr>
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<td>0.764</td>
<td>3.8</td>
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<td>0.309</td>
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<td>-0.3</td>
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<tr>
<td>8</td>
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<td>9</td>
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<td>0.636</td>
<td>0.384</td>
<td>3.3</td>
<td>2.3</td>
<td>4.4</td>
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</tbody>
</table>

Expt, Experiment; SD, standard deviation; LOA, limits of agreement.

Conclusions: Force-frequency relation assessment with this new non-invasive, operator-independent force sensor is extendable to daily physiological exercise and could be potentially attractive for quantitative non-imaging assessment of left ventricular contractile reserve, of potential interest in the stress lab and for home monitoring systems in cardiac heart failure.

A new force sensor for imaging-independent assessment of force-frequency relationship in the stress echo lab: clinical validation

T. Bombardini, F. Falta, E. Picano. Institute of Clinical Physiology of CNR, Pisa, Italy

Background: The force-frequency relation (FFR) can be obtained in the stress echo lab, where the force is computed as the systolic pressure/end-systolic volume index ratio, and measured for increasing heart rates during stress. Ideally, the noninvasive, imaging-independent, objective assessment of FFR would greatly enhance its practical appeal.

Aim: To evaluate the feasibility of FFR measurement by a precordial cutaneous sensor and to compare the standard stress echo results vs this operator-independent FFR sensor.

Methods: The transcutaneous force sensor was positioned in the precordial region in 147 consecutive patients referred for exercise (n = 100), dipyridamole (n = 41), or pacing (n = 6) stress. The force was measured as the myocardial vibration amplitude in the isovolumic contraction period. FFR was computed as the curve of force-variation as a function of heart rate. Standard echocardiographic FFR measurements were simultaneously performed.

Results: A consistent FFR was obtained in all patients. The sensor (see Figure, left panel) FFR slope and shape mirrored the more technically demanding and time-consuming echo (see Figure, right panel). The best cut-off value of the sensor built FFR was 15.5 g x 10-3 (Sensitivity = 0.85, Specificity = 0.77). Variations (rest-stress) in force mirrored those in FFR (R = 0.68).

Abstract P1628 – Table 1

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Machine</th>
<th>Strain analysis software</th>
<th>Spearman’s rho</th>
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<th>Bias</th>
<th>SD</th>
<th>LOA (±1.96SD)</th>
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Conclusions: Force-frequency relation assessment with this new non-invasive, operator-independent force sensor is extendable to daily physiological exercise and could be potentially attractive for quantitative non-imaging assessment of left ventricular contractile reserve, of potential interest in the stress lab and for home monitoring systems in cardiac heart failure.

Abstract P1630

Cardiovascular hemodynamics in the stress echo lab with open-source software

T. Bombardini, D. Cini, E. Picano. Institute of Clinical Physiology of CNR, Pisa, Italy

Background: Stress echocardiographic evaluation of volumes is ideally suited for the quantitative calculation of a set of parameters allowing a complete characterization of cardiovascular hemodynamics of established pathophysiological and potential clinical relevance, including cardiac output, systemic vascular resistance, left ventricular elastance, arterial elastance, and ventricular arterial coupling. However, this is a tedious and time-consuming procedure.

Aims: 1) to build a web-based computing software program for self-instruction and calculation of hemodynamic parameters in the stress-echo lab; 2) to test the software with skilled echocardiographers; 3) to distribute the software to the medical community.

Methods: A website with the informatics infrastructure was built (at cctrainer.itc.cnr.it). Ten skilled echocardiographers (American Society of Echocardiography class III) were asked to calculate hemodynamic parameters by using
personal knowledge (Mode 1) and by using the dedicated software called CC-trainer (Mode 2). After testing, the software was offered free on the web.

**Results:** The software was inserted in a dedicated web domain. After linking in, the cardiologist is asked to fill in the rest and stress data set. In a few seconds the program completes baseline and peak stress data, providing both numerical and graphical display of results (see Figure). The computation time of manual Mode 1 (55±63 min) was substantially reduced with software-assisted Mode 2 (2±0.5 min, p < 0.05 vs Mode 1).

**Conclusions:** Cardiovascular hemodynamics are important but their calculation remains time-consuming and demanding. However, they can be made simple, rapid and easy in the echo lab with a user-friendly, open-source program fed by simple raw echo data.

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**FROM THE DISTANCE – TELECARDIOLOGY**

**P1631**

**Telemonitoring of cardiac resynchronization therapy devices facilitates patients’ management and thus reduces mortality**

M. Mazurek1, E. Jedrzejczyk-Patej2, A. Liberska3, J. Boido1, A. Wozniak4, R. Lenarczyk5, K. Kowalczyk6, P. Pruszkowska7, O. Kowalski8, Z. Kalina9, Medical University of Silesia, 1st Dept. of Cardiology, 40-758 Katowice, Poland; 2 M. Bufalini Hospital, Department of Cardiology, 48100 Cesena, Italy; 3 1st Dept. of Cardiology, University of Zabrze, Poland

**Aim:** To assess the usefulness of a daily monitoring of cardiac resynchronization therapy devices (CRT-D) with the use of telemonitoring.

**Methods:** Study population consisted of 137 patients (pts) implanted with CRT-D and monitored remotely on a daily basis via telemonitoring. 81% of devices were implanted in a primary prevention of sudden cardiac death (SCD). The ischemic etiology accounted for 62.7% of cases. Atrial fibrillation (AF) was present in 62 patients (45%). All tele-transmissions were screened for the percentage of CRT pacing and other data between January 2011 (baseline) and January 2012 (one year of follow-up). In line with the ESC guidelines, in which low CRT pacing was defined as ≤95% despite optimal medical therapy all patients were divided into two groups: 1) optimal CRT and 2) low CRT.

**Results:** Improvement in CRT pacing (Table 1) after one year of follow-up was achieved by every-day monitoring of the percentage of biventricular stimulation and thus immediate pharmacotherapy optimization (i.e. maximizing doses of betablocker, digoxin, amiodarone) as well as ablation procedure. Up to 42% (n=43) pts from the optimal CRT group in 2012 were in the low CRT group in 2011. The a-v node ablation was performed in 21.4% (n=9) of pts with low CRT in 2011 who improved and were classified into optimal CRT group in 2012. Independent risk factors for low CRT pacing were as follows: 1) atrial fibrillation (HR 7.8), 2) ventricle heart rate exceeding the upper tracking rate (HR 4.4), and 3) multiple premature ventricular contractions – PVCs≤11.0/HR (HR 3.9, all P <0.05). There were no significant differences in VT/VF episodes, number of adequate and inadequate shocks between low CRT and optimal CRT groups (P=0.6).

**Table 1**

<table>
<thead>
<tr>
<th>Optimal (&lt;95%) CRT pacing group</th>
<th>Low (&lt;95%) CRT pacing group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (January 2011)</td>
<td>43.2% (n=59)</td>
<td>56.8% (n=78)</td>
</tr>
<tr>
<td>One year follow-up (January 2012)</td>
<td>74.5% (n=102)</td>
<td>25.5% (n=36)</td>
</tr>
<tr>
<td>Mean percentage of CRT pacing</td>
<td>98.4%</td>
<td>89.1%</td>
</tr>
<tr>
<td>Prevalence of AF</td>
<td>40% (n=41)</td>
<td>56% (n=32)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2% (n=2)</td>
<td>17% (n=6)</td>
</tr>
</tbody>
</table>

**Conclusions:** Every-day monitoring of the percentage of CRT pacing via telemonitoring seems to reduce mortality by facilitating an early detection of low CRT pacing and thus allowing the immediate therapy modification.

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**P1632**

**Second-opinion stress tele-echocardiography for the Adonhers (aged donor heart rescue by stress echo) project**

T. Bombardini1, D. Cini1, S. Gherardi1, R. Del Bene1, T. Grimaldi2, S. Sansoros3, W. Sierra4, R. Sicari2, E. Picano1. 1Institute of Clinical Physiology of CNR, Pisa, Italy; 2M. Bufalini Hospital, Department of Cardiology, Cesena, Italy; 3Careggi University Hospital, Florence, Italy; 4Reggio Emilia Hospital, Department of Cardiology, Reggio Emilia, Italy; 5BaggioVera Hospital, Department of Cardiology, Baggiovera, Italy; 6Hospital of Parma, Department of Cardiology, Parma, Italy

**Aim:** To verify feasibility of a “second opinion” of digitally transferred images of stress echo to enable neonatal heart transplant.

**Methods:** The project completes baseline and peak stress data, providing both numerical and graphical display of results (see Figure). The computation time of manual Mode 1 (55±63 min) was substantially reduced with software-assisted Mode 2 (2±0.5 min, p < 0.05 vs Mode 1).

**Conclusions:** Second Opinion Stress Tele-Echocardiography can effectively be performed in a network aimed at safely expanding the heart donor pool for heart transplant.

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**P1633**

**Real-time tele-echocardiography to enable neonatal consultative services in remote districts**

F. Frexa1, R. Triunto1, F. Cabras2, S. Morisi3, P. Neroni3, R. Tamburro2 on behalf of Francesco Frexa. 1CRS4, Center for Research Studies and Development in Sardinia, Cagliari, Italy; 2G. Brotzu Hospital, Cagliari, Italy

**Purpose:** Point-of-care echocardiography in neonatal intensive care unit (NICU) is a very common technique but it’s hampered by the lack of on-site specialists. The effectiveness of this technique is strictly related to the effectiveness of the collaboration with the consultative specialties and the possibility to train new specialists in remote districts.

In this study, we report on the feasibility of a real-time echocardiographic image transmission system that adopts an innovative, low cost and open-source approach to enable neonatal consultative services in remote districts and we analyze the clinical result of our experimentation which connected two hospitals in Sardinia: a tertiary hospital, with senior expertise in pediatric cardiology, and a secondary hospital with a neonatal unit.

**Methods:** The system is composed of three elements: a server for EMR and voice chats; an encoder connected to an ultrasound machine and a high-resolution camera; software used by the specialist. During the exam, an echocardiographer or a consultant in the patient and the remote specialist, through the combined view of the echocardiograph screen and the camera, can determine the patient’s clinical conditions, his posture on the bed and the appropriate position of the probe; in this way he is able to guide the operator in performing a proper examination. During the six-month preliminary clinical investigation, selected newborns had a comprehensive ultrasonographic cardiac examination by a remote specialist using the system; the same patient was then examined by an independent specialist next to him, to confirm the remote examination result.

**Results:** During the experimentation three main aspects of the system were explored: technical performance under various conditions (emergency and routine); clinical feasibility; possibility of shortening the learning curve for clinicians in the secondary hospital. According to a technological assessment in which the correct compression and transmission protocols were selected, 42 patients (age 1 day-6 years) have been examined with a 100% rate of consistent diagnosis. 3 clinicians have been trained during the experiment and after 6 months they were able to perform the main projections without the aid of a consultant from the tertiary hospital.

**Conclusions:** We have demonstrated the technical feasibility of real-time remote fetal tele-ultrasound consultations; through the use of this system it is possible, not only to ensure high level medical services in remote districts, but it also possible to train operators to perform the many modern techniques in echocardiography.
Cost-effectiveness of the integration of home monitoring data with the hospital medical record
A. Garcia Quintana1, B. Vega Santana1, V. Feria Moreno1, E. Caballero Dorta1, F. Sosa Suarez1, M. Diaz Escoto1, Y. Ramirez Rodriguez1, Y. Diaz1, C. Rios Diaz1, A. Medina Fernandez-Acetyuno1, 1University Hospital De Gran Canaria “Dr. Negrín”, Las Palmas de Gran Canaria, Spain; 2FMS Medical, Las Palmas de Gran Canaria, Spain.

Introduction: The electronic medical record (EMR) has become an essential tool for physicians. The integration of information from different sources is key, and until now accessing to every provider’s server was required for checking the patient’s data. Here we present a project of integration of home monitoring data with the EMR, so the patient and device information provided by the supplier goes directly to the hospital application for clinical follow up.

Objective: To determine the cost-effectiveness of the integration of information from the home monitoring system of ICDs with the EMR of the hospital.

Material and Methods: The integration of the information provided by the Latitute System (BostonScientific) with the software for clinical follow up of pacemaker devices(CardioSim) using the HL7 protocol to send encrypted data, was made from July 2010 to February 2011. A close collaboration between cardiologist and the IT staff of the hospital was required. Until this moment 20 patients have been included, mean age 63.1 years (66-79), 13 males and five females living in an island apart from the hospital (Lanzarote, CanaryIslands). Data about economic costs were obtained from the accounting service of the hospital.

Results: The cost of a medical visit for device follow up is 81.57 €/visit and the movement of a patient from other island 150€/patient/day. Considering development expenditures of 10,000€, extrapolating this service to the population with an ICDs in our clinic (n=235) and estimating 24% of them live in another island, then we could obtain a saving of 38,338€ in the visits fees and 18,300€ in patients trips. In summary we could produce annual savings of 56,638€/year, considering that both the communicator and the service were provided by the supplier without additional cost to the ICD’s price. The time expended in every clinical follow up visit is about 15 to 20 minutes per patient. With the data integration from Latitude to the EMR at least five minutes are saved without any typing mistakes. If you have 20 patients scheduled for every work day them 100 minutes are earned, which supposed more time for other duties or more patients per visit. Intangible benefits such as increased patients quality of life or the security provided by a closer monitoring should be regarded. Other benefit comes from the double data backup in the hospital and provider servers.

Conclusions: The integration of information from the telemonitoring of ICDs with the EMR is feasible and cost-effective.

Tele-cardiology for public emergency medical service: 7-year experience with 422.633 interventions
N.D. Brunetti1, L. De Gennaro2, G. Dellegrottaglie3, G. Amoruso1, G. Antemili1, M. Di Blasio1, 1University of Foggia, Foggia, Italy; 2San Giacomo hospital, Monopoli, Italy; 3Cardio-on-line Europe S.R.L., Bari, Italy.

Background: Telephone support is presently applied in several fields of medicine. Clinical evidence showed as pre-hospital ECG may shorten time to reperfusion in subjects with acute myocardial infarction, thus significantly affect- ing clinical outcomes of these patients.

Methods: A tele-medicine service presently supports the public free emergency medical service (EMS) “118” throughout whole Apulia, a 4-million inhabitants region in South-Eastern Italy. “118” is the Italian public free service for general medical service (EMS) “118” throughout whole Apulia, a 4-million inhabitants region. “118” control room, according to ECG and EMS crew report, then therefore sent by mobile phone support to a single regional tele-cardiology “hub” (CTO-Maria Adelaide Hospital, Division of Neurocardiology, Turin, Italy) of the information provided by the Lati- tude System (BostonScientific) with the software for clinical follow up of pacing devices(CardioSim) using the HL7 protocol to send encrypted data, was made from July 2010 to February 2011. A close collaboration between cardiologist and the IT staff of the hospital was required. Until this moment 20 patients have been included, mean age 63.1 years (66-79), 13 males and five females living in an island apart from the hospital (Lanzarote, CanaryIslands). Data about economic costs were obtained from the accounting service of the hospital.

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Conclusions: The integration of information from the telemonitoring of ICDs with the EMR is feasible and cost-effective.

Patient Operated Monitoring: a new tool for long-term heart rhythm analysis
T. Wolfer, L. Hasegaki, C. Schmied, J. Steffel, C. On, F. Duru, University Hospital Zürich, Zürich, Switzerland.

Background: Continuous ECG monitoring for extended time periods may enhance detection of symptomatic and asymptomatic atrial fibrillation (AF) and may thus improve diagnosis and treatment compared with conventional ECG monitoring methods like Holter monitoring or Event recording. However, due to technical obstacles and patient comfort issues, ambulatory continuous full-disclosure ECG monitoring is not commercially available. The aim of this study was to determine the feasibility and clinical benefit of patient-operated long-term full-disclosure ECG monitoring (POM) using a miniaturized single-channel waveform recorder and a customized mobile computing system.

Methods: Forty-seven subjects with paroxysmal AF underwent 72-hour com- bined monitoring with conventional Holter ECG and POM followed by a 7-day period of POM alone. The monitoring system included an ultra-portable, water resistant single-channel ECG waveform recorder that allowed acquisition of full-disclosure ECG signals over a time-period of 24 hours. Acquired data were au- tomatically transmitted on a daily basis to a central data server over a secured Internet connection. Information related to patient symptoms and activity was col- lected utilizing an electronic patient log. Patients performed POM without profes- sional support after initial instruction by a cardiac nurse.

Results: POM was successful in all subjects (65% male, age range 47 to 79 years). Overall, more than 8900 hours of continuous ECG recordings were recorded. Mean duration of POM was 16.3±2.7 hours per day. The quality of ECG wave- forms allowed determination of cardiac rhythm in 97% of time. During initial 72- hour Holter monitoring, arrhythmias were detected in 40% of all patients, including AF in 22%, atrial flutter in 11%, atrial tachycardia in 30% and other arrhythmias in- cluding bradyarrhythmias and supraventricular or ventricular extrasystole in 19%. Using POM resulted in an increase in arrhythmia detection of almost 100%. After ten days, arrhythmias were documented in 77% of all patients (P<0.001), including AF in 38%, atrial flutter in 15%, atrial tachycardia in 36% and other arrhythmias in 28%.

Conclusion: POM is a new option for ambulatory rhythm diagnosis. It is feasible in young and older patients and significantly increases diagnostic yield compared with conventional Holter monitoring. The ability of full-disclosure ECG signal ac- quisition over long time periods opens new possibilities for arrhythmia man- agement and cardiac risk assessment.

IMAGING IN ARRHYTHMIAS

Left atrial appendage morphology and silent cerebral ischemia in atrial fibrillation patients
M. Anselmino1, I. Salvetti1, L. Corsini1, M. Planeri1, S. Gili1, F. Cesaras2, R. Faletti2, M. Scaglione2, M.C. Valentin1, F. Gaita1, 1University of Turin, San Giovanni Battista “Molinette” Hospital, Department of Cardiology, Turin, Italy; 2San Giovanni Battista “Molinette” Hospital, Department of Radiology, Turin, Italy.

Purpose: Thromboembolic events may occur in atrial fibrillation (AF) patients with low CHADS-Vasoc score. In search of additional risk markers we related left atrial appendage (LAA), the major source of cardiac thrombi, visualized by cardiac magnetic resonance angiography (MRA), to the burden of silent cerebral ischemia (SCI), assessed by cerebral MR.

Methods and Results: From November 2008 to April 2010, 311 consecutive AF (62.1 paroxysmal, 37.9% persistent) patients referred for transcatheater abla- tion underwent clinical assessment, echocardiography, cardiac MRA and cere- bral MR. Based on published criteria LAA morphology was described as Cactus (a dominant central lobe with small chambers extending in all directions) in 44 (14.3%), ChickenWing (an obvious bend in the proximal or middle part of the dominant lobe) in 157 (51.1%), WindSock (a dominant lobe plus secondary or even tertiary lobes arising from the dominant one) in 90 (29.3%) patients, and Cauliflower (complex internal characteristics with lack of a dominant lobe) in 16 (5.2%) patients. SCI was detected in 275 (88.4%) patients, with a mean number of lesions of 34.7±37.2. As shown in the Figure SCI burden related to LAA com-
Comparison between cryo and radiofrequency ablation in left atrial scar formation in patients with atrial fibrillation


Background: In patients suffering from atrial fibrillation the amount of post ablation scar formation as well as left atrial (LA) baseline fibrosis have an important impact on post procedural rhythm control success. Since most centers use radiofrequency (RF) technique not much is known about the effect of cryoballoon ablation on atrial scarning. Therefore the aim of this study was to determine whether there are differences between both methods affecting the postprocedural outcome using LA delayed enhancement cardiac magnetic resonance (LA DDE-CMR).

Method: A total of 28 patients (mean age 56±8 years) without any structural heart disease and a history of symptomatic paroxysmal atrial fibrillation at an average of 4.7±3 years underwent pulmonary vein isolation via RF (45%) or cryo ablation (55%). Every patient underwent a 3D navigated LA DE-CMR scan before ablation, as well as 24 hours and 3 months after the procedure. For determining the amount of DE we segmented the LA of each scan using a score with a threshold for fibrotic tissue detection compared to the blood pool signal plus 2 standard deviations.

Results: After pulmonary vein isolation we found a significant increase in LA DE in both LA ablation groups. Paired t-test showed a trend to higher DE in patients who underwent cryoballoon ablation (amount of scarred tissue 19.4±6.6% Cryo vs.13.4±10.3% RF). Assessment of arrhythmia recurrence at 3 months follow up was not statistically different in both groups. Average baseline fibrosis of included patients was 6.4±5.6%.

Conclusion: Our data present a trend towards more extended scar formation using Cryo balloon technique as compared to RF ablation. We could show that 3D navigated whole heart DE sequences are an excellent tool for studying scar formation.

Ischemic scar by contrast-enhanced cardiac magnetic resonance identifies non responders to cardiac resynchronization therapy in patients with right bundle branch block

A. Valle-Munoz1, J. Estornell-Erill1, M. Corbi-Pascual1, E. Lucas-Inarejos1, O. Fabregat-Andres1, L. Perez-Bosca1, P. Garcia-Gonzalez1, B. Bochard-Villanueva1, A. Quesada-Dorador1, F. Ridoce-Soriano1. 1Complejo Hospitalario Universitario, Albacete, Spain; 2ERESA, Consorcio Hospital General Universitario, Valencia, Spain; 3Hospital General Universitario de Valencia, Valencia, Spain

Purpose: Among patients receiving cardiac resynchronization therapy (CRT), those with right bundle branch block (RBBB) benefits less than those with left bundle branch block (LBBB). Contrast enhanced MRI can accurately predict clinical response to CRT. Taking into account that in patients with left ventricular systolic dysfunction, RBBB is associated with a significantly greater scar burden by contrast-enhanced MRI than patients with LBBB we hypothesized that lack of response to CRT in patients with RBBB is related to the presence of ischemic scar.

Methods: We included 131 ischemic and nonischemic patients with left ventricular ejection fraction (LVEF) < 35% receiving CRT. Late gadolinium enhancement- MRI was performed for scar analysis. Echocardiographic response was defined as > 10% reduction in left ventricular end-systolic volume 1 year after implantation.

Results: There were no differences in LVEF or GRS width between RBBB (25) and LBBB (106) patients. Patients with RBBB compared to LBBB were more likely to have ischemic scar (76% vs 42%, p<0.02) Echocardiographic response was documented in 83 (63%) patients. Patients with RBBB were more likely to be non responders than LBBB (52% vs 33%, p<.01). Nevertheless, when comparing patients with or without ischemic scar, those with ischemic scar were more likely to be non responders in both groups (58% vs 33% in RBBB and 56% vs 16% in LBBB).

Conclusion: About half of patients with RBBB benefit from CRT. Ischemic scar identifies non responders to CRT in patients with RBBB.

Impact of the degree of left atrial tissue structural remodeling detected using LGE-MRI on the ablation of ganglionated plexi in patients with atrial fibrillation

K. Higuchi, M. Akkaya, M. Koopmann, J. Blauer, N. Burgon, K. Damal, R. Ranjan, E. Kholmovski, R. Macleod, N. Marrouche. University of Utah, Comprehensive Arrhythmia Research and Management Center, Salt Lake City, United States of America

Background: Affecting epicardial ganglionated plexus (GP), which is favorable for the prognosis after atrial ablation (AF) ablation, is inevitable during pulmonary vein antrum isolation (PVAI) for patients with AF. GP is known to reside within epicardial fat pads (FPs).

Objectives: In this retrospective study, using late gadolinium enhancement (LGE)-MRI, we assessed the inadvertent effect to epicardial FP during routine AF ablation on the prognosis of AF after ablation. We also investigated the impact of pre-existing left atrial (LA) tissue structural remodeling (LASRM) assessed using LGE-MRI on the effect of FP ablation.

Methods: We retrospectively investigated 60 patients who underwent LGE-MRI pre (to assess the extent of LASRM) and 3 months post AF ablation (to assess the extent of scar). FPs in well-known GP areas were segmented from T2 weighted MRI and projected on 3D LA image. Then the 3D LA image with FPs projection was merged with the 3D scar image on the LA visualized by LGE-MRI 3 month post ablation. The overlapped area of FPs and the scar were considered as the ablated FP (GP) areas.

Results: Ablated FP area was wider in patients with successful AF ablation (22±12 3% vs. 15±10.5%, P<0.02). When assessed in conjunction with the extent of pre-existing LASRM, patients without recurrence had wider ablated FP area than patients with recurrence in patients with ≤ 20% LASRM (25±12.6% vs. 10.3±15.2%, P<0.02; Figure A). However this correlation did not hold up in patients with >20% LASRM (14.4±6.5% vs. 16.3±12.1%, P<0.70; Figure B).

Conclusion: Extensively ablating FP areas containing GP in routine PVAI seems to improve the outcome of AF ablation. Patients with low to moderate LASRM seem to benefit more from GP ablation than those with extensive LASRM.

Automatic left-atrial scar assessment in late gadolinium enhancement MRI

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Background: Late gadolinium enhancement MRI (LGE-MRI) has proven effective for assessing the pattern and extent of left-atrial (LA) wall injury post-ablation. Manual assessment of LA scar, however, is time consuming and prone to inconsistencies, and automatic approaches based on simple intensity statistics can be
Correlation between interatrial septal hypertrophy and interventricular septal hypertrophy and its impact on the outcomes of ablation in patients with atrial fibrillation

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Background: Left ventricular hypertrophy (LVH) is known to be associated with left atrial structural remodeling. LVH has shown to increase pressure in the left atrium (LA) consequently leading to LA dilatation. We hypothesized that the stress generated in the LA due to LVH may subsequently lead to an increase in the inter-atrial septal (IAS) thickness. The IAS is commonly targeted during atrial fibrillation (AF) ablation and an increase in IAS thickness may affect the outcomes of AF ablation.

Methods: We included 429 AF patients who underwent an LGE-MRI prior to catheter ablation in this study. Interventricular septal (IVS) and IAS thickness were measured using cine MRI images. IAS was measured during both end-systole and end-diastole, while IVS was measured during end-diastole. Patients were then grouped into LVH (IVS <12mm; n=117) and no-LVH (IVS >12mm; n=312) for further analysis.

Results: The mean age between two groups were comparable (65.7±11.4 vs. 64.6±12.5; P=0.394), with a male predominance in LVH group (78.7% vs. 58.2%; P<0.001). Mean IAS in systole was significantly higher in patients with LVH (7.66±1.32 mm) when compared to no-LVH patients (6.91±1.18 mm; P<0.001). Similarly IAS in diastole was also significantly higher in patients with LVH (6.09±1.05 mm) than patients with no-LVH (5.60±1.00 mm; P<0.001). Patients with LVH experienced more AF recurrences (40.8% vs. 28.6% in no-LVH patients) over a 12-month follow-up period post ablation.

Conclusion: IVS hypertrophy is associated with an increase IAS thickness in patients with AF during. Increased IAS thickness may have significant implications for determining the ideal intensity and total duration of radiofrequency energy required to achieve a safe and successful AF ablation.
ondary to infection. Since lead extraction is associated with significant morbidity and mortality, a new imaging modality would be useful to ascertain the nature of such findings. The aim of this study is to evaluate the usefulness of 18F-DG PET/CT in the investigation of masses found on CIED leads during TEE.

**Method:** Patients who had a PET/CT between 2009 and 2011 for the evaluation of a mass on CIED leads found on TEE were included in this retrospective analysis. Collected data included demographics, information on CIED and other pertinent clinical and imaging data.

**Results:** Sixteen patients (11 men, mean age 67±13 years, mean LVEF 45±16%, mean time since last device intervention 29±28 months) had a PET/CT for the evaluation of a mass found on CIED leads during TEE examination. The mean length was 11±7 mm. Nine (56%) patients had a positive PET/CT showing abnormal 18F-DG uptake near the generator (n = 3) or on the leads (n = 6); remaining PET/CT were negative (n = 7). Eight patients with a positive PET/CT had complete extraction of the infected material. Only one did not require extraction because of normal appearance of the lead during valvular surgery. Device infection was confirmed for 8 of the 9 patients, either by positive hemocultures (n = 4), pus in the pocket during extraction (n = 3) or device erosion (n = 1). Among the 7 patients with negative PET/CT, three (43%) had positive hemo-
cultures; those 3 patients were successfully treated with intravascular antibiotics only, without requiring lead extraction. In the other patients, masses were found incidentally prior to atrial fibrillation ablation (n = 2), left atrial appendage closure (n = 1) and PCI for transient ischemic attacks (n = 1). With a median follow-up of 422±227 days, none of those seven PET/CT negative patients required device extraction or presented signs of recurrent infection.

**Conclusions:** PET/CT can be helpful for the evaluation of suspected vegetations found on CIED leads during TEE. Further studies are required to evaluate the diagnostic value and cost-effectiveness of such an approach.
after PEA for CTEPH. We were able to demonstrate improved surrogate markers of PA pressure and resistance as early as 10 days after PEA in a large series of 65 patients.

**P1648 Normal regional pulse wave velocity predicts absence of aortic luminal growth in patients with Marfan syndrome: a comprehensive MRI-study**

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**Purpose:** The leading cause of premature death in patients with Marfan syndrome (MFS) is aortic dissection after progressive dilation due to local increased wall stiffness, occurring most prominently in the ascending aorta. Aortic pulse wave velocity (PWV) is a marker of wall stiffness. Regional PWV can be accurately determined from in-plane multi-directional velocity-encoded (VE) MRI. The study objective was to test whether regional PWV can predict regional aorta dilatation at 2-year follow-up (FU) in MFS patients.

**Methods:** Twenty-nine MFS patients (mean age 36±15 years, 11 male) regional PWV and aortic luminal areas were assessed by 1.5T MRI (Philips). Regional PWV in MFS patients was considered increased when exceeding age-related PWV in healthy volunteers (n=26; mean age 50±10 years, 15 male) by two standard errors. At 2-year follow-up, the incidence of luminal growth for the five aortic segments (ascending aorta (S1), aortic arch (S2), thoracic descending aorta (S3), suprarenal abdominal aorta (S4) and subrenal abdominal aorta (S5) was defined as a hyperintense signal on a 3D-T1w-GRE MR sequence. Generalized linear regression models were used to assess the association between blood pressure parameters and IPH.

**Results:** Of 1866 (24%) plaques, Systolic blood pressure (SBP) and pulse pressure (PP) were significantly associated with IPH after adjustment for age and sex. After further adjustment for wall thickness and cardiovascular risk factors, PPP yielded the strongest association, with an odds ratio (OR) per SD increase in PP of 1.22 (95% CI 1.07-1.40) and an OR per SD in SBP of 1.13 (95%CI 0.99-1.28). Only PP remained significant after additional adjustment for other blood pressure components.

**Conclusions:** Pulse pressure was the strongest determinant of IPH independent of cardiovascular risk factors and other blood pressure components. The association between pulse wave flow and IPH may provide novel insights into the development of the vulnerable plaque and future clinical practice.

**Figure 1**

**Conclusions:** The specificity of regional PWV-testing at baseline for prediction of luminal aortic growth during 2 year follow-up in patients with Marfan syndrome is ≥78% for all aortic segments, i.e. normal age-related regional PWV predicts in ≥78% of the cases the absence of luminal aortic growth.

**P1650 Pulse wave dynamics in the carotid artery: assessment with high field velocity-encoded magnetic resonance imaging**

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**Purpose:** It is hypothesized that aortic pulse wave reflection at the interface between a compliant aorta and stiffer carotid arteries limits the transmission of excessive pulsatile energy. Vessel stiffness can be expressed by pulse wave velocity (PWV: propagation speed of the flow wave through the artery). Velocity-encoded (VE) MRI is well-validated for accurate PWV-assessment. The purpose of this study was to use 3T VE MRI to evaluate aortic and carotid PWV as well as pulsatility damping in the carotid artery.

**Methods:** Thirteen healthy volunteers (4 male, mean age 25±5 years) underwent 3T MRI (Philips) to assess PWV in the aortic arch and the left carotid artery based on the transit-time method and one-directional through-plane velocity-encoded MRI (Figure 1). At the two levels of carotid PWV assessment, maximal velocity Vmax, minimal velocity Vmin and mean velocity Vmean during the cardiac cycle were calculated. From these values, the pulsatility index (PI: [Vmax – Vmin]/Vmean) and resistive index (RI: [Vmax – Vmin]/Vmax) were calculated.

**Results:** PWV was 20% higher (p<0.001) in the carotid arteries (PWV = 5.8±1.0 m/s) as compared to the aorta (PWV = 4.8±0.7 m/s). PI was 72% reduced in the carotid artery while RI lowered 32%.

**Figure 1**

**Conclusion:** Increased PWV predicted an increased aortic luminal growth, whereas normal PWV predicted an absence of aortic luminal growth. Only PP was found to be associated with IPH after adjustment for age and sex, after further adjustment for wall thickness and cardiovascular risk factors. The strongest association was found for PP, with an odds ratio (OR) per SD increase in PP of 1.22 (95% CI 1.07-1.40) and an OR per SD increase in SBP of 1.13 (95% CI 0.99-1.28). Only PP remained significant after additional adjustment for other blood pressure components.

**Conclusions:** Pulse pressure was the strongest determinant of IPH independent of cardiovascular risk factors and other blood pressure components. The association between pulse wave flow and IPH may provide novel insights into the development of the vulnerable plaque and future clinical practice.

**P1651 Ultra high field magnetic resonance imaging of carotid wall imaging: comparison between 7T and 3T**

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**Purpose:** Magnetic Resonance Imaging (MRI) enables high-resolution carotid artery vessel-wall imaging, although clinical applications are currently hampered by suboptimal signal-to-noise (SNR) and contrast-to-noise-ratio (CNR). Vessel wall MRI is expected to benefit from higher magnetic field strength. The purpose was to compare 7T and 3T mapping parameters and wall thickness. Pulmonary artery (PA) pressure and resistance as early as 10 days after PEA in a large series of 65 patients.

**Figure 1**

**Conclusions:** Velocity-encoded MRI is suitable for evaluating the pulse wave transmission from the aortic arch towards the brain. The carotid artery revealed a stiffer vessel wall than the aortic arch, which creates a reflection site for incident waves.
of this study is to measure the SNR and CNR of 7T carotid MRI as compared to 3T, with similar in-plane spatial resolution and total scan time.

Methods: 18 volunteers (11 males, 7 females, mean age=29±7 yrs) underwent MRI-examinations at 7T (using a custom built surface transmit/receive coil of 15 cm diameter) and at 3T (using a commercial phased-array coil with two flexible oval elements, each 14 x 17 cm). MRI of the left carotid artery vessel-wall was performed at 7T with identical in-plane resolution as 3T MRI (0.46 x 0.46 mm²) providing transverse T1- and T2-weighted images. Blinded analysis of SNR and CNR for the two separate MRI sequences was assessed using Vessel Mass software and compared between 7T and 3T.

Results: At 7T, SNR and CNR are significantly higher as compared to 3T MR for both T1- and T2-weighted images, with gain factors ranging from 1.3 to 5.9. Good correlation between 3T and 7T was observed for lumen and vessel wall measurements.

Conclusion: Ultra high field 7T MR carotid vessel wall Imaging improves SNR and CNR, as compared to 3T. The improved SNR and CNR at 7T MRI may enable more detailed assessment of plaque morphology.

P1652 Impact of cardiovascular risk factors on aortic pulse wave velocity: A comparison of healthy volunteers and patients after acute STEMI

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Aims: Aortic pulse wave velocity (aPWV, m/s) is associated with traditional cardiovascular risk factors and is an independent prognostic parameter for future cardiac events. The association of cardiac risk factors with aPWV in patients with STEMI is not yet evaluated.

Methods: 115 subjects were enrolled in this study (n=43 controls without significant CVD, n=72 STEMI patients within 7 days of index event). Aortic aPWV was determined with velocity encoded, phase contrast cardiac MRI (retrospectively ECG-gated, temporal resolution: 20ms). Medical history was obtained to determine pre-existing cardiovascular risk factors (hypertension, smoking, hypercholesterolemia, family history of CVD). Blood pressure (BP) and lipid profiles were determined and ESC SCORE was calculated to quantify total cardiovascular risk.

Results: In controls aPWV was correlated with age (r: 0.883, p<0.001), systolic BP (SBP, r: 0.530, p<0.001) and ESC SCORE (r: 0.683, p<0.001) but not with diastolic BP (DBP, p>0.05). In patients with recent STEMI aPWV correlated with age (r: 0.141, p=0.001) and ESC SCORE (r: 0.312, p<0.01) but not with SBP or DBP (p>0.05). In controls hypertension (5.0±0.4 vs 11.1±3.4 m/s, p<0.001) and hypercholesterolemia (5.9±2.3 vs 10.9±3.8 m/s, p<0.001) were associated with higher aPWV, but smoking, diabetes and positive family history were not (all p>0.05). In contrast in STEMI patients subjects with hypertension and hypercholesterolemia did not show higher aPWV (all p>0.05). Smoking, diabetes and family history had no impact on aPWV in STEMI patients (all p>0.05).

Conclusion: We observed differences in the association of cardiac risk factors with aortic stiffness (aPWV) between healthy subjects and patients after acute STEMI. These results may reflect more aggressive treatment in STEMI patients and should be considered when choosing aortic stiffness as a potential therapeutic target after STEMI.

P1654 Mechanical properties of the aneurysmal sinuses of vasa valsalva: regional and directional variations

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Purpose: Information on the mechanical properties of the aneurysmal sinuses of Valsalva is non-available, although this could facilitate our understanding of the pathophysiology of aortic root rupture, which is a biomechanical phenomenon occurring when the strength of the root tissue is overcome by the hemodynamic loads exerted on the sinus wall. Consequently, the objective of the present study was to examine the material properties of the aneurysmal sinuses of Valsalva, as a function of region and direction.

Methods: Aneurysmal sinus specimens were obtained from 8 patients (ages 27-82 years, diameters 4.5-5.9 cm), undergoing elective surgery. These were cut into tissue strips that were allocated to groups according to region: Left-(LCS) vs. Right-(RCS) vs. Non-Coronary Sinus (NCS) and direction: circumferential (CIRC; nLCS=8, nRCS=11, nNCS=17) vs. longitudinal (LONG; nLCS=8, nRCS=11, nNCS=17). The tissue strips were tested until failure (wall rupture) on a uniaxial tensile-testing apparatus; failure stress (index of tissue strength), failure strain (index of tissue extensibility), and peak elastic modulus (index of tissue stiffness) were calculated from the experimental data.

Results: The biomechanical indices of the LCS and RCS were similar, unlike those of the NCS. Failure stress did not vary in CIRC than LONG specimens from the LCS (92.2±33.2 vs. 70.6±43.7 N/cm², p=0.2) and RCS (79.5±18.7 vs. 72.1±26.1 N/cm², p=0.2), whereas the difference was significant at the NCS (143.6±29.7 vs. 40.5±6.3 N/cm², p=0.002). Similarly was observed for peak elastic modulus (278.5±91.0 vs. 219.0±52.6 N/cm², p=0.2 in LCS; 236.0±51.0 vs. 221.5±61.5 N/cm², p=0.2 in RCS; 534.4±124.0 vs. 120.1±16.4 N/cm², p=0.002 in NCS). Failure strain did not display significant directional variations (0.73±0.07 vs. 0.72±0.09, p=0.2 in LCS; 0.70±0.07 vs. 0.61±0.07, p=0.2 in RCS; 0.75±0.07 vs. 0.66±0.06, p=0.46 in NCS).

Conclusions: Our findings are in agreement with the clinical observation of aortic root aneurysm dissection and rupture predominantly occurring at the RCS or NCS. RCS was the weakest region in the CIRC axis and NCS was weakest in the shoulder region as compared to the non-aneurysmal aorta; 2.08±0.39 vs. 1.75±0.34 (p=0.05) and 1.91±0.34 vs. 1.45±0.24 (p=0.05) respectively. Consistent with these findings, there was also USPIO uptake in the aortic wall on MRI scanning (Figure 1). Interestingly, there was accumulation of USPIO but not FDG in the intraluminal thrombus.
Comprehensive CMR assessment after a transapical-transcatheter aortic valve implantation

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Objective: To describe the time course of myocardial scarring after a transapical-transcatheter aortic valve implantation (TA-TAVI) with Edwards SAPIENTM prosthesis in a 3-month follow-up study using cardiac magnetic resonance imaging (CMR).

Methods: In 13 TA-TAVI patients, CMR was performed at discharge and 3 months (3M). Cine-MRI was used for left ventricular (LV) functional assessment, and delayed enhancement imaging was employed for detecting the presence of myocardial scar. Special attention was given to any artifacts caused by the prosthesis, which were consequently defined using a three-grade artifact scale.

Results: We systematically reported the presence of delayed hyperintensity relative to the aortic segment with no variation found between discharge and 3M (3.2±1.7g vs. 2.9±1.0g). LV ejection fraction, end-diastolic, and end-systolic volumes did not significantly vary. A small area of apical akinesia was observed, with no improvement at follow-up. Unlike the Edwards SAPIEN XTM prosthesis, the Edwards SAPIENTM prosthesis was responsible for a larger signal void, thus potentially limiting the diagnostic performance of CMR.

Figure 1. Transmural or subendocardial hyperintense scarring in the apical myocardium.

Conclusions: CMR may be performed safely in the context of TA-TAVI. The presence of a very small apical infarction correlating with focal akinesia was observed. As expected, the Edwards SAPIEN XTM prosthesis was shown to be particularly suitable for CMR assessment.

CLINICAL IMPACT OF IMAGING IN CONGENITAL HEART DISEASE

Bicuspid aortic valve: association of cusp morphology and aortic hemodynamics

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Purpose: Hemodynamics may play a contributing role to the progression of aortopathy in bicuspid aortic valve (BAV) disease. This study measured the wall shear stress (WSS) forces at the wall of the ascending aorta (AoA) in BAV patients.

Methods: 4D flow sensitive magnetic resonance imaging was used to examine the jetting, local wall shear stress (WSS), and hemodynamic characteristics in the AoA of 60 subjects. This included 15 BAV patients -12 with fusion of the right and left (RL) coronary cusp (6 stenotic) and 3 with fusion of the right and non-coronary cusp (RN: 1 stenotic). The RL-BAV cohort was compared to healthy subjects (n=15), age-matched subjects (n=15), and age-AOA size-matched subjects (n=15). Steady-state free-precession cine images of the bicuspid cusps were co-registered with the 4D flow scans to visualize the impact of the valve morphology on aortic flow characteristics.

Results: The aortic flow jet propagated in a direction influenced by the type of aortic valve cusp fusion, eventually impinging at AoA wall. For the RL-BAV patients, the position of the jet/wall impingement at the right anterior position of the AoA correlated to regions of statistically elevated systolic and time averaged WSS (Fig. 1). WSS patterns in the RL-BAV AAo correlated to regions of statistically elevated systolic and time averaged WSS which were consequently defined using a three-grade artifact scale.

Fig. 1. Longitudinal and circumferential strain in repaired tetralogy of Fallot.

Objective: To investigate the clinical impact of imaging in congenital heart disease.

Methods: In 13 TA-TAVI patients, CMR was performed at discharge and 3 months (3M). Cine-MRI was used for left ventricular functional assessment, and delayed enhancement imaging was employed for detecting the presence of myocardial scar. Special attention was given to any artifacts caused by the prosthesis, which were consequently defined using a three-grade artifact scale.

Results: We systematically reported the presence of delayed hyperintensity relative to the aortic segment with no variation found between discharge and 3M (3.2±1.7g vs. 2.9±1.0g). LV ejection fraction, end-diastolic, and end-systolic volumes did not significantly vary. A small area of apical akinesia was observed, with no improvement at follow-up. Unlike the Edwards SAPIEN XTM prosthesis, the Edwards SAPIENTM prosthesis was responsible for a larger signal void, thus potentially limiting the diagnostic performance of CMR.

Conclusions: CMR may be performed safely in the context of TA-TAVI. The presence of end-diastolic pulmonary forward flow (EDFF) is a marker of right ventricular restrictive physiology in rTOF. Pulmonary regurgitant fractions (PRF) were derived from pulmonary flow tracing. The LV myofiber end-systolic strain (ϵ) is determined as: ϵ = -1/3 ln[(1+3･LVESV)/Wwall/(1+3･LVEDV)/Wwall], whereas LVESV,
LVEDV and Vwall are LV end-systolic and -diastolic volumes and myocardial volume.

Results: See table. In 35 TOF patients (27 ± 13 years old, median 5.5 years old at repair, RVEDV correlated with PFR (r=0.41, P < 0.05). TOF Patients had reduced +dv (21 ± 4% vs 25 ± 3%, P < 0.01) than normal subjects. Patients with restrictive RV had significantly higher PFR and smaller index LVEDV and index LV VESV, but comparable +dv than non-restrictive RV.

Conclusions: Our study demonstrates that patients with restrictive RV have significantly smaller index LVEDV and have no effect on LV systolic strain compared to non-restrictive RV, although both are significantly reduced compared to normal.

P1660

Multiparametric assessment of the right ventricle by echocardiography in patients with repaired tetralogy of fallot undergoing pulmonary valve replacement: a comparative study with MRI

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Purpose: Evaluation of the right ventricle (RV) using transthoracic echocardiography is challenging in patients with congenital heart disease affecting the right ventricle such as Tetralogy of Fallot (TOF). MRI could be a useful tool to determine the best timing for pulmonary valve replacement (PVR) but accessibility remains limited.

The objective of this study was to evaluate the feasibility and the accuracy of a multiparametric echographic approach including 2D strain and 3D for RV volumes and function assessment, in comparison with MRI.

Methods and results: We performed a complete echocardiographic study including 2D parameters (TAPSE, S'TDI, Tei index, fractional area change (FAC)), 2D strain and 3D and unseeded cardiac MRI in 26 consecutive patients with repaired TOF before pulmonary valve replacement and one year after surgery. Correlation between echocardiography and MRI RVEDV was poor for TAPSE. S'TDI and 3D strain but good for FAC (r=0.70, p < 0.01), 3D deformation index and 3D assessment (r=0.96, p < 0.01 and r=0.98, p < 0.01 before and after PVR respectively). Despite RV volume underestimation by 3D echography, correlation for RV volume assessment between 3D analysis and MRI was excellent in both pre and post-operative assessment (r=0.86, p < 0.01 and r=0.89, p < 0.01 respectively for RV end-diastolic volume; r=0.92, p < 0.01 and r=0.95, p < 0.01 respectively for RV end-systolic volume).

Conclusions: Global approach of RV function using 2D (FAC) or 3D (parameters) seems to be reliable in patients with repaired TOF. TAPSE and S'TDI focused on segmental analysis of RV inflow are less sensitive probably because RV inflow is less affected by RV remodelling related to initial surgical repair.
Aortopulmonary collateral flow volume impacts early visualization of the intracavitary blood flow in the systemic ventricles of Fontan patients. Vortex parameters including vortex depth, length, width, and sphericity index were measured. Vortex pulsatility parameters including relative strength, vortex relative strength, and vortex pulsation correlation were also measured.

Methods: Twenty-six patients (11 Fontan and 15 normal patients) underwent echocardiography with intravenous contrast agent (Sonovue®) administration. Dedicated software was used to perform particle image velocimetry (PIV) and to visualize invasively flow in the systemic ventricles of the patients. Vortex parameters including vortex depth, length, width, and sphericity index were measured. Vortex pulsatility parameters including relative strength, vortex relative strength, and vortex pulsation correlation were also measured.

Results: Vortex length (VL) was significantly lower in Fontan patients (0.543±0.102 vs 0.651±0.125, P=0.024). Vortex width (VW) was higher (0.363±0.093 vs 0.276±0.044, p=0.014) and sphericity index (SI) was lower (1.566±0.439 vs 2.421±0.626, p=0.001) in the normal group. Relative strength (RS) (0.756±0.517 vs 1.903±0.471, p<0.0001) and vortex relative strength (VRS) (0.190±0.113 vs 0.433±0.141, p<0.0001), were significantly lower in the Fontan patients group.

Conclusions: Fontan patients had aberrant flow patterns as compared to normal hearts in terms of position, shape, sphericity and direction of the main vortices. Whether vortex characteristics are related with clinical outcome is subject to further investigation.

P1666
Determinants and clinical significance of flow via the fenestration in the Fontan pathway: a multimodality study

Introduction: The use of a fenestration in the Fontan pathway remains controversial. The objective of this study was to quantify the magnitude of fenestration flow and to characterize its hemodynamic determinants.

Methods: Twenty-three patients with a fenestrated extracardiac conduit prospectively underwent investigation by cardiac magnetic resonance (CMR), echocardiography, and invasive manometry under the same general anesthetic 12±4 months after Fontan surgery. Fenestration flow was determined using phase contrast CMR either by subtracting flow in the Fontan pathway above the fenestration from Fontan flow below the fenestration or by direct measurement (12 patients, Figure).

Results: Measured and calculated fenestration flows showed an excellent agreement (r=0.92, p<0.0001, Figure). Fenestration flow constituted a mean of 31±12% (range 8-50%) of ventricular preload. It was associated with a lower Qp/Qs (r=-0.64, p<0.001) and oxygen saturation (r=-0.74, p<0.0001). Fenestration flow volume correlated with pulmonary vascular resistance (r=0.45, p=0.04) and markers of ventricular diastolic function (early diastolic strain rate r=0.57, p=0.001) and vortex relative strength (VRS) (0.190±0.113 vs 0.433±0.141, p<0.0001), were significantly lower in the Fontan patients group.

Conclusions: Fenestration flow can be measured accurately with CMR. The amount of fenestration flow is related both to the pulmonary vascular resistance and systemic ventricular diastolic ventricular function, and may be used to predict hemodynamic suitability for fenestration closure.

P1667
Myocardial blood flow and viability in children with congenital or acquired coronary disease
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Introduction: Myocardial ischemia may represent an important risk factor for sudden cardiac death and infarction in patients with congenital or acquired heart disease.

Purpose: In order to avoid ionising radiation inherent to PET and SPECT imag-
ing, we utilized advanced magnetic resonance imaging (MRI) methods to assess myocardial blood flow and viability.

Methods: MRI first-pass perfusion imaging (0.03 mmol/kg Gd-DTPA; TR/TE=2.6/1.1[0°]) was performed in 18 patients with suspected ischemia (age: 0.3–21 yrs; transposition of the great arteries post arterial switch operation n=12, anomalous origin of the left coronary artery (ALCAPA) pre operation n=2, post operation n=3; Kawasaki syndrome n=2, aberrant coronary artery n=1). Myocardial blood flow (ml/min/g) was calculated in 6 LV segments per slice (2/3 slices/slice). Quantitative blood flow at rest and stress (Adenosin 140 μg/kg/min) was derived from signal intensity curves with model independent deconvolution. Late enhancement studies (Gd 0.1 mmol/kg) using T1 weighted inversion recovery sequences were performed to detect myocardial scarring. Furthermore cine MRI and 3D coronary vessel imaging was performed to assess ventricular function and coronary anatomy. All CMR results were compared to conventional x-ray guided coronary angiography.

Results: Myocardial blood flow was significantly reduced at stress due to an occlusion of the left coronary artery (n=3) or circumflex artery (n=1) artery and a hypoplastic left anterior descending artery in one. Another pt showed subendocardial ischemia but normal coronary arteries. Scar tissue was detected in the antero-septal region of two patients. MRI perfusion imaging during hyper-aemia showed severe myocardial ischaemia in the antero-septal wall of the LV in the patient with aberrant LCA. Late enhancement imaging showed viable myocardium in the corresponding region. Therefore this patient and one TGA pt received minimal invasive direct coronary artery bypass (MIDCAB) surgery for revascularisation using the left mammary artery. Post operative MRI showed normal myocardial perfusion and function in both pts. Two ALCAPA pts received corrective coronary surgery. The Kawasaki pts did not require any intervention other than medical therapy. Good agreement was found between MRI-perfusion and viability imaging, wall motion analysis and invasive coronary angiography.

Conclusions: In children with congenital or acquired coronary disease stress-induced perfusion defects and scar tissue can be detected with MRI in order to guide further therapy such as surgical revascularisation.

P1668 Variations of coronary anatomy assessed by non-invasive computed tomography coronary angiography in adult patients with transposition of the great arteries after arterial switch operation

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Purpose: In the current study the occurrence of coronary anatomy variations in adult patients with congenital transposition of the great arteries (TGA) corrected by arterial switch operation (ASO) was assessed with the use of non-invasive computed tomography coronary angiography (CTA).

Methods: The study population consisted of 23 adult patients (age 21±3 yrs) with TGA corrected by ASO in whom CTA was performed. Coronary anatomy on CTA was assessed according to the Leiden Classification. In addition, the presence of coronary artery stenoses was evaluated and the angle at which the coronary artery originated from the neo-aorta was measured. An angle of <30° was defined as a sharp angle coronary origin. In addition, patients were clinically evaluated at the outpatient clinic and echocardiography was performed.

Results: On CTA post-operative coronary anatomy was 1R-2LCx in 18 patients (78%), 1Rx-2Lc in 4 patients (17%) and in one patient 2RLc (4%). In one patient significantly coronary artery ostial stenoses (stenoses of >50%) was observed. Remarkably, an interarterial coronary course was observed in 5 patients (22%) (example case in Figure 1) and another 6 patients (26%) had a sharp angle coronary origin. During clinical evaluation patients with interarterial coronary course reported more cardiac complaints and had slightly lower left ventricular ejection fraction on echo.

Conclusions: In the present study CTA demonstrates that a potential malignant coronary artery pattern is frequently observed in adult patients with TGA corrected by ASO.

P1670 Correlation of echocardiography parameters with pulmonary functions before and after cardiac surgery in infancy

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Purpose: To assess pulmonary functions before and after cardiac surgery in infants with pulmonary overflow CHD, and to identify the best echocardiographic parameter that correlates with lung mechanics.

Methods: Thirty infants, with left to right shunt acyanotic congenital heart disease operated for reparative surgery of these lesions, were assessed by echocardiography and pulmonary functions before and at 6 months postoperatively. The following Infant Pulmonary Function Tests (IPFT) were performed: Tidal breathing parameters, mechanics of the respiratory system: compliance (Crs) and resistance. Functional residual capacity (FRC) and airway resistance (Reff and sReff) were assessed by body plethysmography.

Results: The mean age of patients was 10.47±3.38 months and their mean weight was 6.81±1.67 kg. VSD and combined lesions were the main cardiac diseases (26.7%) and surgical approach was sternotomy in 27/30 (90%). Statistically highly significant improvement of all parameters of the pre-operative (IPFT compared to those at 6-months post-operative data (p<0.001)). Before surgery, systolic pulmonary artery pressure had a statistically significant negative correlation with Crs (r=-0.493, P=0.006) and positive correlation with FRC (r=0.450, P=0.013). PA and LA sizes had a statistically significant negative correlation with FRC (r=-0.395, P=0.029, P=0.031, respectively). While PA size had statistically positive correlation with Reff and sReff (r=0.416 and 0.604 and p=0.022 and <0.0001), respectively). In addition, LA size had a statistically significant correlation with Reff and sReff (r=0.453 and 0.625 and p=0.012 and <0.0001).

Conclusion: Infants with pulmonary overflow CHD had lower lung compliance and higher expiratory airway resistance before surgery. There was improvement of these changes after decline of pulmonary artery pressure and reduction of pulmonary overflow.
Leftward bulging of atrial septum is induced by nitroglycerine and exaggerated during the strain phase of valsalva

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Background: Leftward bulging of the interatrial septum (LBA) is a requirement for detection of patent foramen ovale (PFO) during contrast echocardiography. On release of Valsalva strain contrast free blood from inferior vena cava often sweeps contrast away from foramen ovale. We examined the effect of nitroglycerine on LBA during resting respiration and during Valsalva strain.

Methods: Patients with obstructive sleep apnea had been screened for PFO with contrast TEE. The interatrial septal motion was at least 10 mm in thirteen patients and they were chosen for this retrospective analyzes. Video recordings from periods during the exam without contrast injections exams were visually analyzed for the presence/absence of LBA of the septum defined as a leftward shift and leftward convexity of the septum. A beat was defined as LBA when there was any period of LBA during the heart cycle. Periods of resting respiration and during Valsalva strain before and after nitroglycerine spray with foot down bed tilt were analyzed. The analysis was made by two observers, blinded to each other. Discrepancies were then settled in consensus.

Results: We studied 1772 beats distributed to 146 periods. After nitroglycerine the systolic blood pressure decreased from 152±22 to 136±17 mmHg (p=0.006). The proportion of LBA increased significantly during resting respiration from 21±22% to 43±13% (p=0.008). During Valsalva strain from 48±19% to 80±17% (p=0.001). After nitroglycerine LBA occurred in at least three beats during all 37 studied Valsalva strain periods and the first LBA during Valsalva strain period occurred after 4±2 beats.

Conclusion: Nitroglycerine administration induces LBA both in resting respiration and in Valsalva strain. During Valsalva strain nitroglycerine induce some LBA in 100% of strain periods. Nitroglycerine reduces left atrial pressure more than right atrial pressure. Nitroglycerine administration may increase sensitivity for PFO detection and the strain period of Valsalva is an alternative to the Valsalva release period for detection of patent foramen ovale.

Assessment of left atrial mechanics after percutaneous closure of patent foramen ovale


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Purpose: Evaluation of left atrial (LA) size and function using conventional and more recent echocardiographic parameters is potentially feasible in the routine clinical setting. However the influence of septal occluders in the left atrial function after percutaneous closure of patent foramen ovale (PFO) has not been thoroughly studied.

Methods: Over a period of 40 months, 50 patients (pts) with PFO were referred to our centre for clinically indicated percutaneous PFO closure. Among them 25 pts (mean age 40.7±12 years) were enrolled in our study due to cerebrovascular events and transient ischemic attacks. Transesophageal echocardiogram was performed in all pts before the procedure, at 3 and 6 months after the intervention. Phasic LA volumes were measured and volumetric indices were derived accordingly. Strain and strain rate were calculated in all 25 pts for the lateral, anterior and inferior LA walls. Peak strain and strain rate values were measured during the contractile, reservoir and conduit LA phases. A transesophageal echocardiogram was also undertaken at the 6-month follow-up to verify complete closure of the defect.

Results: All patients completed the procedure uneventfully and at 6-month follow-up the closure appeared intact. For the LA lateral wall, the total 3 values were correlated with the LA volumetric indicators (LA active emptying fraction: LA AEF; LA expansion index: LAEI; and LA passive emptying fraction: LA PEF). After 3 months a decrease in the strain rate of the anterior wall of LA was observed (from 2.12±0.22 to 1.69±0.26, p=0.045), while LA AEF was greater compared to baseline (0.26±0.04 to 0.34±0.01, p=0.004).

Conclusions: Closure of patent foramen ovale with a PFO occluder results in altered LA function. In specific, the anterior atrial wall, where the device is placed, illustrates impaired daily function. However, total LA systolic function improves probably due to the fact that the device provides a more rigid surface, which enables a more forceful atrial contraction. Strain and strain rate represent a promising tool in the evaluation and follow-up of patients who have undergone PFO closure.
Effect of advanced therapy on right ventricular function in patients with congenital heart disease and severe pulmonary hypertension

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Advance therapy with the endothelin antagonist bosentan has been shown to be effective in improving exercise tolerance in adult patients with severe pulmonary hypertension due to underlying congenital heart disease (PAH-CHD). The aim of this study was to retrospectively analyze the effect of bosentan on echocardiographic right ventricular parameters in this group of patients. Prospectively collected data from adult patients with PAH-CHD initiated on bosentan over a period of 2.5 years were analyzed. Baseline echocardiographic parameters including right atrial (RA) volume, right ventricular (RV) wall thickness, TAPSE, RVtdi, Tricuspid regurgitation velocity, RV myocardial performance index [RV MPI] were analyzed prior to therapy initiation (baseline) and at the last follow up. All patients were on a dose of 125mg bd. Patients also had assessment of exercise tolerance using serial 6-minute walk distance (6MWD) testing. Complete data were available and analyzed from 14 patients with PAH-CHD (4 with Down syndrome, 11 female) who had received 3–17 doses of bosentan (mean duration of therapy 17.5±7 months). Three of the patients were also on concomitant sildenafil treatment.

A significant average improvement in 6MWD (46 m as compared to baseline, p=0.047), on mean follow up was observed. No evidence of drop in systemic saturations were observed. The echocardiographic parameters for the assessment of right heart function are given in Table 1 as mean values ± standard error of the mean. Statistical analysis was performed using paired t tests and Wilcoxon non-parametric test.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>FU (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV thickness</td>
<td>0.95 cm &gt; 0.92</td>
<td>0.71 cm &gt; 0.1</td>
</tr>
<tr>
<td>TAPSE</td>
<td>1.5 cm ± 0.3</td>
<td>1.4 cm ± 0.6</td>
</tr>
<tr>
<td>RV TDI</td>
<td>0.08 m/s ± 0.02</td>
<td>0.09 m/s ± 0.01</td>
</tr>
<tr>
<td>TR jet</td>
<td>4.4 m/s ± 0.5</td>
<td>4.5 m/s ± 0.3</td>
</tr>
<tr>
<td>RV MPI</td>
<td>0.40±0.19</td>
<td>0.54±0.14</td>
</tr>
</tbody>
</table>

There was evidence of a trend in reduction of RV thickness on follow up but did not reach statistical significance. There was no major change in other RV functional parameters. Bosentan does not appear to significantly change right ventricular echocardiographic parameters in PAH-CHD patients. However a larger study is necessary to assess this in further detail.

Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease

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Objective: This prospective study was to assess the efficacy of exercise training as add-on to medical therapy in patients with pulmonary arterial hypertension associated with congenital heart disease (CHD-APAH)

Methods: Patients with invasively confirmed CHD-APAH received in-hospital exercise training for 3 weeks and continued at home. Efficacy parameters were evaluated at baseline, after 3 weeks and 15 weeks. Medical treatment remained unchanged during 15 weeks after baseline. The survival rate was assessed in a follow-up period of 21±14 months.

Results: Twenty consecutive patients (16 female, 4 male, mean pulmonary arterial pressure 60±23mmHg, 9 patients were operated, 10 ASD,11 VSD, 1 PFO, 2 PDA, 10 Eisenmenger syndrome) were included. Patients significantly improved the mean distance walked in 6 minutes compared to baseline by 63±47 meters after 3 weeks (p<0.001) and by 67±59 meters after 15 weeks (p<0.001). Qual- ity of life score (p = 0.050), peak oxygen uptake (p=0.002) and maximal workload (p=0.003) improved significantly by exercise training after 15 weeks. The 1- and 2-year survival rates were 100%. In one patient lung transplantation was performed 1 year after exercise training.

Conclusion: Exercise training as add-on to medical therapy may be effective in patients with CHD-APAH, improving quality of life, work capacity and further prognostic relevant parameters. It was also associated with an excellent long-term survival. Further randomized controlled studies are needed to confirm these results.

Hemodynamic assessment of pulmonary hypertension in grown-up congenital heart disease

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Purpose: PAH associated with congenital heart disease (CHD) is included in group 1 of the PH classification. The persistent exposure of the pulmonary vasculature to increased blood flow due to systemic-to-pulmonary shunts as well as increased pressure may result in a typical pulmonary obstructive arteriopathy that leads to an increase in invasively measured mean pulmonary arterial pressure (mPAP) ≥25mmHg at rest.

Methods: 3107 patients who underwent baseline right left and right heart catheterizations between 1996 and 2003 were analyzed. Diagnosing PAH was validated on the grounds of patient histories, comorbidities, imaging, clinical data and patho-anatomic evidence (2369 complete data sets). 257 data sets were from patients with CHD.

Results: Underlying diagnoses were: pre-tricuspid defects in 172 patients, post-tricuspid defects in 38 patients and complex lesions in 47 patients. Of the 257 patients with CHD (38 were corrected), 141 patients had normal hemodynam- ics ("Non-PH" mPAP ≤25mmHg). Of the remaining 116 patients with PH (with wedge tracings missing or insufficient in 19 cases), 51 qualified as pre-capillary PH (CHD-PH-PCWP ≤15mmHg); 46 had CHD with elevated left ventricular filling pressures (CHD-PH-lvFillingP <15mmHg; Table 1).

Table 1. Hemodynamic data of patients with CHD-PH

<table>
<thead>
<tr>
<th>CHD-PH PCWP ≤15mmHg (no=51)</th>
<th>CHD-PH PCWP &gt;15mmHg (no=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.3±17</td>
</tr>
<tr>
<td>systolic arterial pressure (mmHg)</td>
<td>63.4±26.2</td>
</tr>
<tr>
<td>dPAP (mmHg)</td>
<td>26.1±11.5</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>40.3±18.3</td>
</tr>
<tr>
<td>mPAP/CVP (mmHg)</td>
<td>10.1±3.4</td>
</tr>
</tbody>
</table>

Conclusions: The data derived from this large contemporary database at a university center demonstrate that a significant proportion (almost 50%) of patients with PH in grown-up congenital heart disease suffer from post-capillary pulmonary hypertension. This observation may impact treatment decisions.

Contemporary therapy in pediatric pulmonary hypertension (PH)-results from the global registry tracking outcomes and practice in pediatric pulmonary hypertension (TOPP)

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Purpose: The global registry TOPP collects data on demographics, clinical status and outcomes in pediatric PH. One of the primary objectives was to describe current medical therapy. Treatment decisions were made by site clinicians without TOPP involvement.

Methods: 31 sites from 19 countries enrolled patients (diagnosis on/after January 2001, enrollment 2008-2010, age 3 months - 18 years at confirmatory right heart catheterization). PH was defined as: mPAP ≥25mmHg, PCWP ≤12 mmHg and PVRI > 3 units × m².

PH targeted therapy (PHTT) included prostacyclin and its analogs (PGI2s), endothein receptor antagonists (ERAs) and phosphodiesterase inhibitors type 5 (PDE5Is). Calcium channel blockers (CCBs) were considered as PHTT in respon- ders to acute vasodilator testing. Supportive therapy included anticoagulation, oxygen, diuretics and/or digitalis.

Results: Of the 456 patients enrolled, 362 (79%) met all entrance criteria with...
Does the pulmonary vascular resistance predict outcome in the modern era?

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Background: Paediatric pulmonary hypertension (PH) is common in congenital heart surgery. The gold standard investigation is cardiac catheterisation with calculation of pulmonary vascular resistance (PVR). Since 1958 there has been little information about the changing link with outcome, which is likely to have improved with modern surgical and intensive care and advanced pulmonary vasodilator therapy (DFT).

Aims: To determine the outcome of decision-making after cardiac catheterisation in the modern era.

Methods: All children undergoing PVR study from 1996-2011 were prospectively included. The entry criteria was a tricuspid regurgitant velocity of >2.8m/s with clinical or echocardiographic evidence of a raised PVR. Catheterization followed the approval of the operator by one operator (measurements under general anaesthetic at baseline, in 10pm Nitric oxide, 20pm NO and then 20pm NO ±100% oxygen, with measured oxygen consumption). Outcome measures included survival, need for medication, persistence or resolution of PH as defined by echocardiography and symptoms at follow up.

Results: 176 studies were performed on 169 children. The median (range) age was 380 (21-1003) days. 103 had PH associated with un-operated congenital heart disease (aPAH-CHD). Of these, 54 had Down syndrome and 7 had pulmonary vein stenosis and 72/103 had AVSD or VSD. There were 35 who were postoperative with CHD (of whom 14 had Down syndrome), 24 children had chronic lung disease, 5 had idiopathic pulmonary artery hypertension and 6 had other conditions, such as hepato-pulmonary syndrome (some children had other conditions). The mean PVR at baseline was 9.4±m2, falling to 5.3±m2 in H1 and to 2.8±m2 in H2.

Conclusions: The PVR at baseline can help predict outcome in modern era PH.
Results: Eighty-eight adult patients (68.4% male, mean age 34±10 years) were randomized (valsartan n=44, placebo n=44). Two patients (valsartan n=1, placebo n=1) died during follow-up and eight withdrew consent, leaving 78 patients (valsartan n=38, placebo n=40) for analysis. Overall, there was no change between baseline and follow-up in RV EF (valsartan: ±0.28%, p=0.79) or the placebo group (1.00%, p=0.23). VO2peak declined in both groups to a similar extent (VO2peak: valsartan 2.6 ml/kg/min, p=0.02, placebo 2.9 ml/kg/min, p=0.01). However, in symptomatic patients (valsartan n=8, placebo n=14) valsartan had a significant beneficial effect of 4.7% on RV EF (p=0.02). In this subgroup, valsartan protected against further deterioration of VO2peak, but this effect was not significant.

Conclusions: Valsartan has a beneficial effect on RV EF in symptomatic patients with a systemic right ventricle. Moreover, deterioration of VO2peak was less in the valsartan group than in the placebo group.

P1684 Beneficial effect of valsartan on right ventricular ejection fraction in symptomatic patients with a systemic right ventricle: results from a randomized trial
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Introduction: Angiotensin II receptor blockers (ARB) have been proven to be beneficial in patients with acquired left ventricular failure. However, their efficacy has not yet been established in patients with a morphologic right ventricle (RV) supporting the systemic circulation. We assessed whether the ARB valsartan improves 1) RV ejection fraction (EF) and 2) VO2peak in adults with a systemic RV.

Methods: In this multicentre placebo-controlled double-blind randomized clinical trial, adult patients with a systemic RV, i.e. surgically or congenitally corrected transposition of the great arteries were included from six university medical centres in the Netherlands. Eligible patients were randomized to an intervention group (n=44) with valsartan 160mg twice daily for three consecutive years and a control group (n=44) with a placebo in the same regimen. At baseline and after three years, RV EF was determined by transthoracic echocardiography, VO2peak was measured during supine exercise, and CTB profile was measured by cardiac magnetic resonance imaging and 64-detector CT. All patients were seen every six months for clinical assessment. The trial is registered at Current Controlled Trials under identifier ISRCTN25352170.

Conclusion: In our ongoing study with relatively mildly impaired Fontan patients, bosentan was not beneficial in our current analysis. Results from all visits are available within a few months.

P1685 Cardiac transplantation in adult Congenital Heart Disease
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Background: Patients with complex congenital heart disease (CHD) are surviving into adulthood due to increased success of surgical procedures and specialist Growth-up CHD units. Deterioration in adult CHD patients may require cardiac transplantation which has been associated with increased mortality in this subgroup of patients.

Method: We performed a retrospective analysis of CHD patients who underwent heart or heart-lung transplantation at our institution (1990 to 2012). We evaluated diagnosis, aetiology, surgical methods, perioperative issues and outcomes.

Results: 2.4% (8/327) cardiac transplants were performed for adult CHD (7 heart, 1 heart-lung). Mean age = 30.1 years (range 9 - 45). Diagnosis: Tetralogy of Fallot = 1; Transposition of Great Vessels with univentricular heart = 3; Tricuspid Atresia = 1; double outlet hypoplastic right ventricle with pulmonary stenosis and VSD = 1; VSD, ASD and PDA = 1. Prior cardiovascular surgery episodes = 2.25 (range 1-5). Bypass time = 280 minutes (98-579). Red blood cell transfusions = 20.6
P1687 A simple risk score predicting clinical right ventricular failure after congenital cardiac surgery in adults

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Background: Right ventricular (RV) failure is a life-threatening syndrome characterized by edema, hypotension and in worse cases shock or multi organ failure. Congenital heart disease (CHD) patients often undergo right-sided surgery, and contribution of the RV to their cardiac pump function is essential. We aimed to identify determinants of RV failure after cardiac surgery and to determine prognosis in CHD patients.

Methods: Adults with CHD operated between January 2001 and January 2011 in the Medical Center were studied. Clinical characteristics, laboratory tests, surgical data and intensive care unit outcome were obtained from medical records. The diagnosis of clinical RV failure was made by careful review of the medical records by two independent physicians. Determinants of clinical RV failure were identified by logistic regression analysis.

Results: Data of 412 consecutive patients (median age 36 range (18–74) years, 56% male) were studied. Eighteen patients were diagnosed with clinical RV failure (4.4%), of which six patients died. A risk score incorporating significant determinants of multivariate analysis identified low-, medium- and high-risk subgroups as seen Table. Patients undergoing left- and both-sided surgery had an equal risk of developing clinical RV failure as compared to patients undergoing right-sided surgery.

Conclusions: In CHD patients the use of a simple risk score based on multiple determinants identifies a high-risk subgroup on clinical RV failure after cardiac surgery and patients at highest risk of mortality.

P1688 Predictors of early death and heart failure in young adults with coarctation of aorta repaired in childhood

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Background: Adults with coarctation of the aorta (CoA) repaired in childhood still remain at high risk of cardiovascular complications in adult life. We sought to determine prevalence and risk factors for early death and congestive heart failure in young adults with repaired CoA.

Methods: The medical records of 159 adults with CoA repaired at an age of 4.2±6 years were retrospectively reviewed seeking risk factors for the combined endpoint of cardiovascular death or admission for heart failure (HF). Univariate and multivariate analyses were performed with Cox proportional modeling.

Results: The follow-up after repair was 26.8±8 years. In this population of young adults, cardiac death occurred in 7 patients and 5 patients presented with HF. Univariate analyses showed that left ventricular systolic dysfunction (p<0.001), mitral inflow restrictive pattern (p<0.001) and pulmonary systolic pressure (PSP, p<0.001) were significant predictors of the endpoint. In contrast, blood pressure, residual pressure gradient, recoarctation, aortic aneurysms or associated intracardiac anomalies were not statistically related. A CoA length > 10mm, independent predictor of death or HF in the multivariate analysis (hazard ratio 1.7; 95% confidence interval 1.4-2.2; p<0.001). The incidence of the endpoint in 10 patients with PSP > 60 mmHg was 100% compared to 1% in 148 patients with PSP < 60 mmHg (p<0.001). Patients with PSP > 60 mmHg showed mitral inflow RP (8/6), severely elevated left ventricular end diastolic pressure at cardiac catheterization (8/8) and subendocardial late gadolinium enhancement on MRI (5/5). Pathological examination of an explanted heart confirmed extensive left ventricular endocardial fibroelastosis.

Conclusion: Pulmonary hypertension is a good predictor of the risk for early cardiac death or HF in young adults late after CoA repair in childhood and it is likely related to increased left ventricular filling pressures. The cause of diastolic dysfunction might be the persistence of endocardial fibroelastosis.

P1689 Survival analysis in the real world of 12,087 children and adolescents hospitalized for congenital heart disease associated to heart failure between 2001 and 2007 in Brazil

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Background: The increasing development of surgical repair for congenital heart disease (CHD) and therapeutics in heart failure (HF) had enabled an improvement in survival. Nevertheless, it is unknown in the real world the survival of children and adolescents with this association. In addition, CHD mechanism, sex, age and social conditions of the patient remain open in the prognosis.

Purpose: To assess children with CHD and HF survival, using probabilistic linkage methods of databases. To study the influence on the prognosis considering CHD mechanism, gender, chromosomal syndrome (syndrome), age and social condition measured by individual community’s human development index (HDI) at the time of diagnosis and per operante after diagnosis.

Methods: A retrospective nation-wide study of 12,087 patients from 0 to 18 years old hospitalized for CHD and HF (2001–2007), among them there were 3,138 (26.0%) deaths. We performed probabilistic databases linkage from Brazilian nation-wide hospital admission and death certificates. We used the Kaplan-Meier method to construct the survival curve, and compared groups by log rank test. For evaluation of prognostic factors associated with death, we estimated hazard ratios (HR) with confidence intervals 95%, followed by Cox proportional hazards model. The significance was achieved by p<0.05. This study was approved by the institutional Research Ethics Committee (0294-29-09-2010).

Results: The median age was 4.3 month (interquartiles 1 day to 1.99 year); 51.8% boys; any syndrome (6%), and among them 88.4% with Down syndrome; 1.7; 95% confidence interval 1.4-2.2; p<0.001). Patients with PSP > 60 mmHg was 100% compared to 1% in 148 patients with PSP < 60 mmHg (p<0.001). Patients with PSP > 60 mmHg showed mitral inflow RP (8/6), severely elevated left ventricular end diastolic pressure at cardiac catheterization (8/8) and subendocardial late gadolinium enhancement on MRI (5/5). Pathological examination of an explanted heart confirmed extensive left ventricular endocardial fibroelastosis.

Conclusion: Pulmonary hypertension is a good predictor of the risk for early cardiac death or HF in young adults late after CoA repair in childhood and it is likely related to increased left ventricular filling pressures. The cause of diastolic dysfunction might be the persistence of endocardial fibroelastosis.

Are patients cured after closure of a left-to-right shunt? Determinants of residual pulmonary arterial hypertension

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Background: After closure of a left-to-right shunt an unknown number of congenital heart disease (CHD) patients have residual pulmonary arterial hypertension (PAH). We aimed to assess the prevalence and identify determinants of residual PAH after closure of a left-to-right shunt.

Methods: In this retrospective study, CONCOR was used to identify patients from a tertiary referral center who underwent closure of a left-to-right shunt. PAH was defined as systolic pulmonary arterial pressure above 37 mmHg, estimated by means of echocardiographic evaluation. Clinical data including demographics, NYHA functional class, surgery reports, echocardiographic and laboratory results

Results: The follow-up after repair was 26.8±8 years. In this population of young adults, cardiac death occurred in 7 patients and 5 patients presented with HF. Univariate analyses showed that left ventricular systolic dysfunction (p<0.001), mitral inflow restrictive pattern (p<0.001) and pulmonary systolic pressure (PSP, p<0.001) were significant predictors of the endpoint. In contrast, blood pressure, residual pressure gradient, recoarctation, aortic aneurysms or associated intracardiac anomalies were not statistically related. A CoA length > 10mm, independent predictor of death or HF in the multivariate analysis (hazard ratio 1.7; 95% confidence interval 1.4-2.2; p<0.001). The incidence of the endpoint in 10 patients with PSP > 60 mmHg was 100% compared to 1% in 148 patients with PSP < 60 mmHg (p<0.001). Patients with PSP > 60 mmHg showed mitral inflow RP (8/6), severely elevated left ventricular end diastolic pressure at cardiac catheterization (8/8) and subendocardial late gadolinium enhancement on MRI (5/5). Pathological examination of an explanted heart confirmed extensive left ventricular endocardial fibroelastosis.

Conclusion: Pulmonary hypertension is a good predictor of the risk for early cardiac death or HF in young adults late after CoA repair in childhood and it is likely related to increased left ventricular filling pressures. The cause of diastolic dysfunction might be the persistence of endocardial fibroelastosis.
were collected from the medical records. Logistic regression analysis was performed to identify determinants of residual PAH.

Results: Of all 630 patients from a tertiary referral center with a history of a left-to-right shunt, 405 patients had undergone closure of this shunt (median age 35 years, 44% male). The prevalence of residual PAH in this group was found to be 8.4% (n=34). In patients with impaired exercise capacity (NYHA class ≥ II) and age above 40 years the prevalence of PAH was 52% (n=13). In multivariate analysis, age above 40 years and impaired exercise capacity were significant determinants of residual PAH (OR 11.5, 95%CI 4.4 – 30). Furthermore patients aged 25 years or older at the time of closure were at increased risk for residual PAH (OR 4.0, 95%CI 2.0 – 8.2). No association was found with type of defect.

Conclusion: A considerable amount of patients with a closed left-to-right shunt have residual PAH. Patients at highest risk for residual PAH were those with impaired exercise capacity, age above 40 and those in whom closure was performed above 25 years of age.

P1691  Contractility-afterload mismatch in protein-losing enteropathy patients after the Fontan operation

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Background: Fontan circulation leads to contractility-afterload mismatch (increased Ea/Ees) due to increased afterload (effective arterial elastance [Ea]) and decreased contractility (end-systolic elastance [Ees]). However, the relationship between the onset of protein-losing enteropathy (PLE) and development of contractility-afterload mismatch has not yet been understood.

Purpose: To elucidate the PLE onset, with special reference to the development of contractility-afterload mismatch.

Subject: The PLE group included 9 patients who developed PLE after the Fontan operation at our institute, and the control group included 37 patients who did not develop PLE for 10 years after the Fontan operation.

Methods: We compared the pre- and postoperative values of Ea, Ees, and Ea/Ees. Further, we examined the variation of these values in approximately 7 patients of the PLE group during the pre-, post-, and long-term postoperative periods. In addition, we examined Ea/Ees of the 3 patients in the PLE group who underwent an intervention for PLE before and after the intervention. We calculated Ea and Ees as follows: Ea = systemic ventricle systolic pressure/(EDV – ESV), and Ees = mean arterial pressure/ESV.

Results: During the postoperative period, Ea values increased significantly in the PLE group, but not in the control group. Pre- and postoperative values of Ees did not differ from each other in both the groups. During the postoperative period, the Ea values and the Ea/Ees increased continuously in the PLE group. In the patients who underwent intervention in the PLE group, the Ea/Ees decreased significantly after the intervention.

Conclusion: Continuous increase in Ea values and deterioration of the contractility-afterload mismatch may indicate the onset of PLE after the Fontan operation.

P1692  Who is at risk for aortic valve dysfunction in aortic coarctation?

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Purpose: Little is known on patients at risk for aortic valve pathology in adult post-coarctectomy patients (CoA). The high prevalence of bicuspid aortic valve (BAV) in CoA is associated with aortic valve stenosis (AS), aortic valve regurgitation (AR), and ascending aortic dilatation. The aim of this study was to evaluate the progression of, and predictors for aortic valve dysfunction in CoA.

Methods: 96 CoA patients underwent serial echocardiographic examinations between 2001 and 2009. AS was defined as maximal aortic valve gradient ≥20 mmHg. AR was defined as none and minor, or moderate to severe regurgitation. Aortic dilation was defined as an ascending aortic diameter ≥ 37mm.

Results: Ninety-six patients (mean age 29.4 years, range 17-61 years; male 57%) were followed with a mean follow-up of 6.8±1.4 years. Sixty patients (63%) had BAV. At baseline 10 patients had AS (10%, 9 with BAV), 6 patients had moderate to severe AR (6%, of which 3 with BAV and AS); 11 patients had aortic dilation (11%, 11 with BAV). After 6.8 years follow-up, 15 patients had AS (15%,13 with BAV) and 12 patients had AR (13%, of which 8 with BAVS with BAV and AS); 5 patients had moderate to severe AR (5%, of which 4 with BAVS with BAV and AS).

Mean AS progression per 5 years was 1.8±0.5 mmHg (range -10 to 32 mmHg) (mean baseline gradient 35.0±15.1 mmHg vs 39.4±14.2 mmHg). AS progression was significantly increased in patients ≤ 45 years of age (0.85±2.74 vs 5.69±0.93 mmHg/5years, P < 0.001). Predictors for an increased progression of AS during follow-up were age (p=0.08, P=0.008) aortic dilation (p<0.19, P=0.03), and baseline aortic valve gradient (p=0.23, P=0.001). The presence of BAV was independently associated with the presence of AR at follow-up (p=0.91, P=0.05).

Conclusion: Overall progression of aortic stenosis in patients after coarctation-repair is rather mild in this young population. However patients aged 45 years or older demonstrate a significantly increased AS progression. AS progression is determined by older age, aortic dilation and aortic valve gradient at baseline. BAV is a risk factor for AR during follow-up. These findings point towards a common embryological pathway of both valvular and aortic disease in coarctation patients.

NEW INSIGHTS INTO THE NATURAL HISTORY AND POST INTERVENTIONAL COURSE OF CONGENITAL HEART DISEASE

P1693  Natural history of discrete subaortic stenosis in adults: a multicenter study

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Purpose: Discrete subaortic stenosis (DSS) is often diagnosed early in life and notable for its rapid haemodynamic progression during childhood. However, little is known about the evolution of DSS in adulthood. Therefore, we aimed to evaluate the natural history of DSS and identify predictors for progression and timing of surgery in a large cohort of adults.

Methods: All adult patients with a pre-existing diagnosis of congenital fibromuscular/ DSS seen between 1980 and 2011 were included in this retrospective multicenter cohort study. Patient data were obtained from chart abstraction. To evaluate DSS severity progression, a linear mixed-effects model was used. Cox re- gression analysis was used to evaluate intervention-free survival.

Results: Of the 427 included DSS patients, 278 had undergone surgery, while natural history data was available for 149 patients (72% male). For these 149 patients, mean age at baseline was 20±4.9 (IQR 17.6-33.8) years. Associated congenital anomalies were found in 48% of patients and 50% had aortic regurgitation. Peak left ventricular outflow tract (LVOT) gradient at baseline was 32±17 mmHg, rising to 47±29 mmHg after a median follow-up of 6.1 (IQR 3.0-12.4) years (p<0.001). Presence of associated congenital anomalies significantly predicted higher LVOT progression rate (p=0.005; Figure). LVOT progression rate was not significantly predicted by baseline gradient (p=0.891), age (p=0.421), or aorto-septal angle (p=0.539). During follow-up, 35 patients required surgery.
Higher baseline LVOT gradient was associated with an impaired freedom from intervention (HR 2.9 (1.9-4.7)).

Conclusions: DSS progresses slowly in adulthood. However, patients with associated congenital anomalies are at risk for faster disease progression and should be monitored cautiously.

Natural history of the bicuspid aortic valve: long term prevalence and predictors of clinical outcome

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Purpose: Aim of our retrospective study was to describe the long term natural clinical history of a population with bicuspid aortic valve (BAV).

Materials and methods: Standard for inclusion was the presence of BAV at ultrasound examination. We collected historical and echocardiographic data at enrollment, mid-term and last follow-up. We considered aortic valve replacement, aortic surgery and death as clinical end points and focused on prevalence, determinants and evolution of complications (stenosis, regurgitation, dilation, aneurysm, dissection and endocarditis). Predictors for the progression of the disease and predictors of outcome were determined by logistic regression.

Results: Our study included 302 out of 71944 patients (0.4%) consecutively referred for echocardiographic examination to our Department in the period between 09/1986 to 09/2011. Mean duration of follow-up was 10.4±4.5 years. At baseline 79% of patients were <30 years of age and 76.5% were male. The prevalence of complications at baseline was: 15 patients (6.4%) with at least moderate aortic stenosis, 57 patients (24.6%) with at least moderate aortic regurgitation, 113 patients (37.4%) with aortic dilation (defined as an aortic ratio >1.1 calculated on the basis of the expected aortic diameter using Roman’s formula) and 19 patients (6.2%) with aortic aneurysm (aortic ratio >1.5). We found significant association at baseline between systemic hypertension and the complications of the disease, and between at least moderate aortic stenosis at least moderate degree and aortic dilation/aneurysm at baseline. There was a trend toward significance for age and at least moderate aortic regurgitation as predictors of late outcome, while aortic aneurysm at baseline was confirmed to be a strong predictor of late outcome (odds ratio [OR], 2.98; 95% confidence interval [CI], 2.98-1560.0; P < 0.001). Sixty four patients (21.2%) underwent aortic valve replacement and/or aortic surgery during follow-up. Eight patients died (5 due to cardiovascular causes); mean age at death was 62±24 years.

Conclusions: BAV has a prevalence of 0.4% in our echocardiographic community. Different from other reports, our series was composed mostly by young patients. Indication to surgery was more frequently related to aortic regurgitation in 79% of patients as compared to CoA patients with BAV (CoA – BAV). However the risk for aortic dilatation in CoA-BAV compared to isolated BAV patients is well established. The aim of our study was to compare the risk for aortic dilatation in CoA-BAV versus isolated BAV patients.

Methods: Echocardiograms of 85 consecutive adult CoA-BAV and 85 BAV patients were retrospectively analyzed in our department. The risk for aortic dilation (defined as >37 mm) and aortic root diameter were determined. Ascending aortic- and root diameters were used as predictors of late outcome, while aortic aneurysm at baseline was confirmed to be a strong predictor of late outcome (OR, 2.98; CI, 2.98-1560.0; P < 0.001). Aortic root diameter at baseline was 36±1.5±5.5 mm in CoA-BAV and 39±0.5±5.5 mm in the isolated BAV group (P > 0.04). Aortic root dilation was defined as >37 mm in the isolated BAV group (P < 0.01). Mean aortic root diameters were 36±1.5±5.5 mm in CoA-BAV and 39±0.5±5.5 mm in the isolated BAV group (P > 0.04). Ascending aortic dilation was found in 18 (21%) CoA-BAV and in 48 (58%) isolated BAV patients (P < 0.001). Aortic root dilation was found in 16 (46%) CoA-BAV and in 14 (40%) isolated BAV patients (P = 0.54). As present in (1.21%) CoA-BAV and in 93 (44%) isolated BAV patients (P = 0.03), whereas AR was found in 7 (8%) versus 33 (41%) patients respectively (P = 0.01). Left- and right coronary cusp fusion was most common in both CoA-BAV and isolated BAV (80% versus 76%). No significant difference was found in the coronary cusp fusion types between both groups. Aneurysm was found in 58 (76%) CoA-BAV and 74 (93%) isolated BAV patients (P < 0.001).

Conclusions: The risk for ascending aortic dilatation is higher in isolated BAV patients as compared to CoA patients with BAV. Although the prevalence of a raphe was higher in BAV patients, no association was found between ascending aortic dilatation and the aortic valve morphological characteristics. These findings suggest that prior coarctation repair might be protective for aortic dilatation.

Reduction handgrip strength resulting from blalock-baussig shunts in adults with tetralogy of fallot

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Purpose: Blalock-Taussig shunts were widely used as palliative procedures to relieve cyanosis prior to surgical repair in children with tetralogy of Fallot. We assessed the hypothesis that Blalock-Taussig shunts hinder normal growth of the ipsilateral arm, leading to reduced handgrip strength years after takedown.

Methods: We conducted a prospective cross-sectional study of adults with tetralogy of Fallot, measuring handgrip strength by means of a commercially available dynamometer (Takei Kiki Kogyo, Japan). In a standing position, patients were instructed to clench each hand tightly in succession. We studied the size and strength of the ipsilateral arm as compared to the contralateral arm and to age-matched controls. In this cardiac magnetic resonance (CMR) study we sought to assess the rate of progression of RV dilatation and to determine associated factors.

Results: A total of 80 consecutive adults with tetralogy of Fallot, age 35.9±12.5 years, 49% female, were prospectively enrolled. Thirty-eight (47.5%) patients had prior Blalock-Taussig shunts at a median age of 1.0 [interquartile (IQR) range 0.5, 2.9] years. Twenty-one (55%) had isolated right shunts and 33 (66%) were classic shunts. All except six patients with right-sided shunts and one without prior shunt were right-handed. The shunts were present for 4.0 [IQR 3.0, 4.6] years prior to takedown during corrective surgery. The mean systolic pressure in arms ipsilateral and contralateral to Blalock-Taussig shunts were 106±18.9 mmHg vs 117.6±14.4 mmHg (P < 0.0001), respectively. The arm ipsilateral to the shunt was significantly shorter than the contralateral arm (71.4±6.2 cm vs 73.6±5.6 cm, P < 0.0001). The contralateral-to-ipsilateral handgrip ratio was higher with classic versus modified shunts (1.4±1.03 versus 1.1±0.21, P < 0.043).

Conclusion: In patients with tetralogy of Fallot, Blalock-Taussig shunts may impair normal development of the ipsilateral arm with repercussions in adulthood, despite later takedown. These changes are characterized by shorter limb-lengths

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and reduced handgrip strength, and are most pronounced in patients with classic end-to-side anastomoses.

### P1698 Outcomes of transcatheter closure of atrial septal defect with a fenestrated Amplatzer Septal Occluder

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**Purpose:** In patients with atrial septal defect (ASD) complicated with moderate-to-severe pulmonary hypertension or heart failure, complete closure of the defect may carry significant risks. A fenestration was generally created in the occluder for gradual reduction of shunt. However, the follow-up results were seldom reported.

**Methods:** During a 10.5-year period, 44 patients (10 males) with ages ranging from 7 to 81 years underwent transcatheter closure of ASD with a fenestrated device. Of them, 39 patients had pulmonary hypertension, 4 had heart failure and 1 had pulmonary atresia intact ventricular septum with a right atrial pressure above 15 mm Hg after balloon test occlusion. A fenestration was created about 1/3 to 1/4 of the diameter of the Amplatzer septal occluder. The techniques of device deployment are similar to those reported.

**Results:** Of the 44 patients, the mean pulmonary artery systolic pressure was 46±17 mm Hg with a mean Qp/Qs ratio of 2.7±1.4. The mean device diameter used was 30±6 mm. Implantation was initially successful in all 44 patients. Immediately after implantation, shunt flow across the fenestration was observed in all 44 patients. However, 1 developed embolization of the device several hours later. The patient was sent for emergent surgery. All patients were available for a 3-month follow-up. After a mean follow-up period of 42±15 months, most patients had improvement in symptoms, regression of right heart dilatation & decrease in pulmonary artery pressure. Three patients underwent a second procedure to close the residual defect because of significant shunt 12 to 18 months later. Twelve patients received Sildenafil. Six patients had very small residual shunt noted on the most recent echocardiography.

**Conclusions:** Transcatheter closure of ASD in patients with moderate-to-severe pulmonary hypertension or heart failure using a fenestrated device is safe and effective.

### P1699 Cardiac surgery and percutaneous intervention in the treatment of congenital heart disease in adult patients: 24 years of experience


The improvement of treatment of congenital heart disease (CHD) over the past two decades, allowed that a growing number of patients could reach adulthood.

**Purpose:** To characterize the population of adults with CHD that underwent at least one cardiac surgery or percutaneous interventions during adulthood.

**Methods:** Retrospective longitudinal study of all patients with CHD who needed at least one surgical or percutaneous intervention during adulthood from 1987 to present. Cases of foramen oval were excluded.

**Results:** From the 2923 adult patients with CHD followed at our center, 1674 were submitted to at least one intervention (surgical or percutaneous) throughout life. In 838 patients (28.7%) these interventions occurred, at least once, during adulthood (605 surgeries and 244 percutaneous interventions). In 678 patients it was the first intervention of life. The remaining 160 patients had already been operated at least once during childhood. The average age at time of surgery was 36±9.15.0 years. The characterization of this population by diagnosis is in the attached table.

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>Number of patients</th>
<th>Number of surgeries</th>
<th>Age time of surgery</th>
<th>Reintervention %</th>
<th>Surgery Percutaneous Early mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic stenosis</td>
<td>52</td>
<td>30.3</td>
<td>17 (33%)</td>
<td>52</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>47</td>
<td>37.0</td>
<td>12 (21%)</td>
<td>19</td>
<td>29.2</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>62</td>
<td>30.8</td>
<td>21 (34%)</td>
<td>58</td>
<td>61.1</td>
</tr>
<tr>
<td>Atrial Septal Defect (ASD)</td>
<td>364</td>
<td>40.1</td>
<td>10 (3%)</td>
<td>207</td>
<td>150.9</td>
</tr>
<tr>
<td>Anterioventricular Septal defect</td>
<td>50</td>
<td>35.0</td>
<td>12 (24%)</td>
<td>50</td>
<td>0.0</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>52</td>
<td>31.0</td>
<td>17 (33%)</td>
<td>47</td>
<td>0.0</td>
</tr>
<tr>
<td>Persistent ductus arteries (PDA)</td>
<td>45</td>
<td>31.2</td>
<td>9 (20%)</td>
<td>24</td>
<td>24.0</td>
</tr>
<tr>
<td>Tetralogy of Fallot (TOF)</td>
<td>57</td>
<td>33.0</td>
<td>30 (53%)</td>
<td>53</td>
<td>4.4</td>
</tr>
<tr>
<td>Pulmonary atresia</td>
<td>10</td>
<td>24.8</td>
<td>7 (70%)</td>
<td>9</td>
<td>1.0</td>
</tr>
<tr>
<td>Transposition of the great arteries (TGA)</td>
<td>6</td>
<td>28.5</td>
<td>5 (83%)</td>
<td>4</td>
<td>2.0</td>
</tr>
<tr>
<td>Others</td>
<td>42</td>
<td>35.0</td>
<td>12 (29%)</td>
<td>34</td>
<td>10.1</td>
</tr>
</tbody>
</table>

**Conclusions:** There is a significant proportion of patients with CHD that require surgery or percutaneous interventions in adulthood. Reoperations/reinterventions were more frequent among patients with TOF/DORV, pulmonary atresia or TGA. Global early mortality was 1.6%. These data confirm the need for these patients to be treated in special centers with access to interventional cardiology and cardiac surgery experienced in CHD.

### P1700 High-sensitivity troponin T concentrations in adult congenital heart disease

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**Background:** Patients with congenital heart disease (CHD), especially patients with complex and cyanotic lesions are by definition classified as at least stage B or C chronic heart failure. There are no reports on the utility of high sensitivity troponin (hsTnT); assays in adults with CHD.

**Methods:** We assessed hsTnT in a series of 43 patients (mean age 34±14 years, 22 female) including with simple and 27 with complex CHD (23 cyanotic heart disease), admitted to a tertiary adult CHD referral center. Nine patients were in NYHA class I, 13 in NYHA class II and 21 in NYHA class III. All patients underwent routine clinical and echocardiographic evaluation and had hsTnT, NT-pro-BNP and hsCRP measurements; hsTnT levels were measured in healthy controls.

**Results:** Out of 43 CHD patients 8 (17%) had elevated (~0.003 pg/mL) hsTnT levels (range 0.004-0.021 ng/mL); 32 (74%) patients had elevated NT-pro-BNP levels (>1.25 pg/mL). All controls had hsTnT ≤0.003 pg/mL. None (0%) out of 9 patients in NYHA I class had elevated hsTnT levels and 5 (6%) patients had elevated hsTnT-pro-BNP (P<NS). Compared with normal hsTnT, patients with elevated hsTnT had higher NT-pro-BNP (567±842 pg/mL vs 142±884 pg/mL, p<0.01) and hsCRP levels (0.3±0.4 vs 4.2±10.7, p=0.03). Four out of 6 patients (67%) with moderate-to-severe dysfunction of systemic ventricle had elevated hsTnT levels vs 4 out of 37 (11%) with normal or mildly impaired ventricular function (P=0.008). All (100%) patients with moderate-to-severe dysfunction of systemic ventricle and 26 out of 36 (72%) with normal or mildly impaired ventricular function had elevated NT-pro-BNP levels (P<NS). Four out of 9 (44%) patients with moderate-to-severe dysfunction of subpulmonary ventricle had elevated hsTnT levels vs 3 out of 30 (10%) with normal or mildly impaired ventricular function (P=0.03). All (100%) patients with moderate-to-severe dysfunction of subpulmonary ventricle and 8 out of 30 (27%) patients with normal or mildly impaired subpulmonary ventricular function had elevated NT-pro-BNP levels (P<NS). On multivariate model hsTnT but not NT-pro-BNP predicted significant systolic ventricular dysfunction (Exp (B) 11.0, 95% CI 1.5-81.6, P=0.01).

**Conclusions:** In this pilot series hsTnT levels were elevated in a substantial number of CHD patients, especially with significant dysfunction of the systemic and subpulmonary ventricles, suggesting and ongoing myocardial injury in these patients. Compared to NT-pro-BNP, hsTnT was a less sensitive but more specific, independent predictor of ventricular dysfunction in adult CHD.

### P1701 Brain natriuretic peptide in patients with tetralogy of fallot - a systematic review

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**Purpose:** Brain natriuretic peptide (BNP) and N-terminal-probrain natriuretic peptide (NT-proBNP) are well-established markers for heart failure in the general population. However, the value of BNP and NT-proBNP as a diagnostic and prognostic marker for patients with surgically corrected Tetralogy of Fallot (TOF) is still unclear.

**Methods:** A systematic review was conducted including all articles focusing on TOF. Data on BNP measurement, patient characteristics and cardiac functional parameters were extracted.

**Results:** A total of 770 patients from 20 articles were included. Both symptomatic and asymptomatic patients after surgically corrected TOF revealed higher BNP levels compared to age and gender matched controls. The severity of pulmonary valve regurgitation (PVR) and right ventricular end-diastolic volume (RVEVD) correlated positively with BNP values. Negative correlations between BNP and exercise capacity were observed. Three small studies with longitudinal data, describing a total of 77 patients, showed a significant decrease of BNP levels 6 months or longer after pulmonary valve replacement compared to BNP levels before the intervention.

**Conclusion:** This systematic review shows higher plasma BNP levels in patients with TOF compared to controls. The observed significant correlations between
BNP and RVEDD, PVR and exercise capacity mirror the possible future use of BNP as an indicator of disease severity and additional diagnostic tool for timing of pulmonary valve replacement. However, as BNP values differ widely, conclusions for individual patients should be drawn with caution. Further investigation with sequential BNP measurement in large, prospective studies is warranted.

### P1702
**Brain natriuretic peptide in patients with Fontan physiology - a systematic review**

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**Purpose:** Brain natriuretic peptide (BNP) and N-terminal proatriuretic peptide (NTproBNP) are well-established markers for heart failure in acquired heart disease. However, the value of BNP and NTproBNP as a diagnostic and prognostic marker for patients with univentricular hearts and Fontan Physiology is still unclear.

**Methods:** A systematic review was conducted including all articles focusing on Fontan physiology. Data on BNP measurement, patient characteristics and cardiac functional parameters were extracted.

**Results:** A total of 1185 patients from 16 articles were included. Patients with a classic Fontan had significantly higher BNP levels than patients after Fontan with a total cavopulmonary connection (TCPC). The plasma levels after TCPC were comparable to those of healthy controls. A strong correlation between BNP and severity of heart failure was observed in symptomatic patients. The ratio of pulmonal venous flow to systemic flow of patients with high levels of BNP was greater than those of patients with non-highly-elevated BNP. Second, cardiac performances influencing high-levels of BNP were determined.

**Conclusions:** The number of patients with high-levels of BNP was twenty-five. Birth weight (2.8kg vs 2.8kg), study age (3.7months vs 4.7months) and cardiopulmonary ratio (60% vs 59%) were not significantly different between two groups. But the level of BNP was related to the degree of RV dysfunction in patients with high levels of BNP as compared with patients with non-highly-elevated BNP. Therefore, high BNP levels are associated with RV dysfunction and can be useful for risk stratification and prediction of poor short-term outcomes. This study also revealed that a variety of RV markers could use high-levels of BNP as the method of picking out the exhaustion for right ventricle and more severe heart failure in symptomatic infants with VSD.

### P1704
**Right ventricular distress influences the elevation of brain natriuretic peptide in symptomatic infants with ventricular septal defects**

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**Background:** In symptomatic infants with ventricular septal defects (VSD) volume overload of left ventricle occurs by pulmonary high flow. The values of brain natriuretic peptide (BNP) uprise to high levels occasionally. If patients have highly increased BNP in adult heart disease, their heart failure are more severe. We attempted to identify the clinical presentation and the cardiac function in symptomatic infants with VSD who had high levels of BNP.

**Methods:** Between 2005 and 2011, consecutive 96 symptomatic infants with VSD were studied. Cardiac catheterization was performed with surgical intervention in view. Venous blood samples for analysis of BNP were obtained within a few days before catheterization. We defined BNP levels 100pg/ml over as high-levels of BNP. First, we compared the clinical features between patients with high levels of BNP and those with non-highly-elevated BNP. Second, cardiac performances influencing high-levels of BNP were determined.

**Conclusions:** Our study showed heart failure worsened the more in patients with BNP levels 100pg/ml over. This study also revealed that a variety of RV markers could use high-levels of BNP as the method of picking out the exhaustion for right ventricle and more severe heart failure in symptomatic infants with VSD.

### P1703
**Detection of elevated levels of autoantibodies to specific proteins of the nervous system in adult patients with congenital heart disease**

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The problem of cognitive and affective disorders is quite common in patients with congenital heart disease (CHD). The aim of the study was to search for pathological mechanisms of disorders of the central nervous system in adults with CHD. The object of the study was antibodies to the intermediate filaments of glial fibrillary acidic protein (GFAP) as a perspective marker of diseases of the central nervous system. The study involved 72 adults with CHD and 20 healthy controls with CHD. The object of the study was antibodies to the intermediate filaments of glial fibrillary acidic protein (GFAP) as a perspective marker of diseases of the central nervous system. The study involved 72 adults with CHD and 20 healthy controls with CHD.

**Results:** A total of 1185 patients from 16 articles were included. Patients with a classic Fontan had significantly higher BNP levels than patients after Fontan with a total cavopulmonary connection (TCPC). The plasma levels after TCPC were comparable to those of healthy controls. A strong correlation between BNP and severity of heart failure was observed in symptomatic patients. The ratio of pulmonal venous flow to systemic flow of patients with high levels of BNP was greater than those of patients with non-highly-elevated BNP. Second, cardiac performances influencing high-levels of BNP were determined.

**Conclusions:** The number of patients with high-levels of BNP was twenty-five. Birth weight (2.8kg vs 2.8kg), study age (3.7months vs 4.7months) and cardiopulmonary ratio (60% vs 59%) were not significantly different between two groups. But the level of BNP was related to the degree of RV dysfunction in patients with high levels of BNP as compared with patients with non-highly-elevated BNP. Therefore, high BNP levels are associated with RV dysfunction and can be useful for risk stratification and prediction of poor short-term outcomes. This study also revealed that a variety of RV markers could use high-levels of BNP as the method of picking out the exhaustion for right ventricle and more severe heart failure in symptomatic infants with VSD.

### P1705
**Pivotal role of the eNOS/caveolin system in the development of atherosclerosis**

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**Introduction:** Coronary restenosis is one of the major complications after coronary stent implantation. The main mechanism for developing restenosis after vascular injury is an ascending neointimal hyperplasia. Although the histological composition of the neointimal hyperplasia is well characterized, the molecular regulation remains poorly understood.

The eNOS/Caveolin interaction represents an important regulatory system for the integrity of the endothelial function and plays an essential role in initial stage of atherosclerotic plaque development. The relevance of Caveolin-1 in atherosclerosis is discussed conversely as confounding proatherogenic properties by regulation of pro-proliferative genes on one side and anti-atherogenic properties by regulation of protective lipoprotein metabolism on the other side.

Furthermore, there is strong evidence for negative regulatory influence of Caveolin-1 on endothelial nitric oxide synthase (eNOS), which plays an important role for physiological endothelial function.

All these studies focused selectively on Caveolin-1 and eNOS. Therefore we sought to investigate the interaction between Caveolin-1 and eNOS in the development of atherosclerosis using a vascular injury model in C57Bl/6 +/-, eNOS +/- and double Caveolin-1/eNOS +/- mice. Methods: In C57Bl/6 (WT), Caveolin-1 +/-, eNOS +/- and Caveolin-1/eNOS +/- mice a mechanical injury of the femoral artery was performed using a intraluminal wire. The development of the atherosclerotic lesions sections were examined with Elastica van Gieson staining and high digital microscopic images was taken to quantify the intima-media ratio and lumen-veinlel wall ratio. For differentiation of intra-neuronal cells GFAP-positive and GAP-45-positive muscle actin (SMA)-staining were used.
Results: After 42 days a significant reduction of the IMR in eNOS(-/-) mice compared to C57/B16 was observed, whereas Cav-1(-/-) mice showed significantly higher IMR. Double Cav-1/eNOS(-/-) mice lacked significant differences in IMR compared to WT. The contribution of SMA positive cells to significant higher in Cav-1(-/-) mice compared to WT. No significant differences in mononuclear cells were observed in the atherosclerotic lesions. 

Conclusion: The eNOS/Caveolin interaction plays a pivotal role in the development of atherosclerosis. The exclusive loss of Caveolin-1 leads to significant increase of atherosclerotic lesions, which may be reverted in the absence of eNOS. The downstream mechanisms triggered by Caveolin-1 and eNOS in the plaque development needs to be addressed in further studies.

Subclavian artery occlusive disease (SAS) is frequently an overt manifestation of atherosclerosis. The study aimed to assess the prevalence of concomitant to SAS significant stenoses in other major vascular locations, as well as possible associations between carotid-intima media thickness (CIMT) and internal carotid artery stenosis (ICAS) with cardiovascular (CV) risk. 

Monocyte and degree of ICAS were assessed in 218 patients (116M, aged 62±8.4 years with symptomatic SAS before PTA. Of those, CIMT measurement was repeated in 108 randomly chosen patients in the mean follow-up time of 36.5±26 months. The difference between follow-up CIMT and baseline CIMT (ΔCIMT) was assessed. Incidences of CV death, myocardial infarction and ischemic stroke (CVD/MIs) and lower extremities (PACO) were verified for the presence of atherosclerotic lumen reduction (≥50%) by means of ultrasoundography, CT or angiography.

Results: Normal baseline CIMT value (-1.1mm) was observed in 28 (12.8%), thickening (CIMT between 1.0-1.3mm) in 50 (22.9%), disseminated atherosclerotic plaques but ICAS <50% in 51 (23.4%), and ICAS ≥50% in 89 (40.8%) subjects with SAS. Isolated SAS was found in 46 (21%) subjects, while 1 concomitant arterial territory involvement was found in 83 (38.1, 2 in 55 (25.2%) and 3 or 4 other territorial involvements in 34 (15.6%) subjects. Baseline CIMT value and ICA atherosclerotic plaques were significantly related to the presence of CAD (p<0.01), PACO (p<0.003), ICAS (0.05), CAD severity (p<0.001) and the overall number of arterial territories with lumen reduction (p<0.001; p<0.001), CIMT value (RR=1.16, CI 1.05-1.28, p=0.005) and ICAS (RR=1.54, CI 1.39-1.7, p<0.001) occurred an independent marker of multi-territory arterial stenoses. During mean follow-up period of 56.6±36 months, CVD/MIs occurred in 27 (12.4%) subjects. In patients with CVD/MIs CIMT was observed, as compared to those with no CV event (ΔCIMT: +0.199±0.57 vs. +0.008±0.26mm, p=0.039). Also, CVD/MIs was more prevalent in patients with isolated SAS compared to concomitant arterial stenosis (45% vs 28%, p<0.001). When patients underwent afterwards (mean number of territories: 1.8±1.1 vs. 1.3±1.1, p<0.042). Multivariate regression analysis identified 2 independent risk factors for CVD/MIs: significant CAD (RR=1.32; CI 1.11-1.58, p<0.003) and CIMT progression (RR=2.12; CI 1.02-4.16, p=0.033).

Conclusions: CIMT and ICAS stenoses are independently associated with multi-territory arterial stenoses, while CIMT progression with risk of future CV events in patients with symptomatic SAS.

Carotid intima-media thickness as a predictor of multi-territory atherosclerotic occlusive disease in patients with symptomatic subclavian artery obstruction

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Subclavian artery occlusive disease (SAS) is frequently an overt manifestation of atherosclerosis. The study aimed to assess the prevalence of concomitant to SAS significant stenoses in other major vascular locations, as well as possible associations between carotid-intima media thickness (CIMT) and internal carotid artery stenosis (ICAS) with cardiovascular (CV) risk. 

Monocyte and degree of ICAS were assessed in 218 patients (116M, aged 62±8.4 years with symptomatic SAS before PTA. Of those, CIMT measurement was repeated in 108 randomly chosen patients in the mean follow-up time of 36.5±26 months. The difference between follow-up CIMT and baseline CIMT (ΔCIMT) was assessed. Incidences of CV death, myocardial infarction and ischemic stroke (CVD/MIs) and lower extremities (PACO) were verified for the presence of atherosclerotic lumen reduction (≥50%) by means of ultrasoundography, CT or angiography.

Results: Normal baseline CIMT value (-1.1mm) was observed in 28 (12.8%), thickening (CIMT between 1.0-1.3mm) in 50 (22.9%), disseminated atherosclerotic plaques but ICAS <50% in 51 (23.4%), and ICAS ≥50% in 89 (40.8%) subjects with SAS. Isolated SAS was found in 46 (21%) subjects, while 1 concomitant arterial territory involvement was found in 83 (38.1, 2 in 55 (25.2%) and 3 or 4 other territorial involvements in 34 (15.6%) subjects. Baseline CIMT value and ICA atherosclerotic plaques were significantly related to the presence of CAD (p<0.01), PACO (p<0.003), ICAS (0.05), CAD severity (p<0.001) and the overall number of arterial territories with lumen reduction (p<0.001; p<0.001), CIMT value (RR=1.16, CI 1.05-1.28, p=0.005) and ICAS (RR=1.54, CI 1.39-1.7, p<0.001) occurred an independent marker of multi-territory arterial stenoses. During mean follow-up period of 56.6±36 months, CVD/MIs occurred in 27 (12.4%) subjects. In patients with CVD/MIs CIMT was observed, as compared to those with no CV event (ΔCIMT: +0.199±0.57 vs. +0.008±0.26mm, p=0.039). Also, CVD/MIs was more prevalent in patients with isolated SAS compared to concomitant arterial stenosis (45% vs 28%, p<0.001). When patients underwent afterwards (mean number of territories: 1.8±1.1 vs. 1.3±1.1, p<0.042). Multivariate regression analysis identified 2 independent risk factors for CVD/MIs: significant CAD (RR=1.32; CI 1.11-1.58, p<0.003) and CIMT progression (RR=2.12; CI 1.02-4.16, p=0.033).

Conclusions: CIMT and ICAS stenoses are independently associated with multi-territory arterial stenoses, while CIMT progression with risk of future CV events in patients with symptomatic SAS.
Dendritic cells affect both inflammatory and immunosuppressive processes in human atherosclerotic plaques

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Introduction: Atherosclerosis is associated with a complex inflammatory process in the vessel wall, which can result in plaque instability. Dendritic cells (DC), which are characterized by their ability to induce a T-cell specific immune response, play a crucial role in plaque inflammation. Apart from that, DCs also have been shown to be involved in immunosuppressive processes, by interacting with regulatory T-cells, which in turn inhibit DC maturation as well as the proliferation of T-lymphocytes. The aim of our study was to investigate the existence of a possible correlation between the emergence of DCs and regulatory T-cells in atherosclerotic plaques.

Materials and methods: Cross-sections of 30 human carotid endarterectomy specimens were immunohistochemically analysed for the presence of activated DCs (Fascon), regulatory T cells (FoxP3+), T-lymphocytes (CD3) and COX-2 expressing cells, which are generally increased in the course of inflammation. Classification of atherosclerotic specimens into stable and vulnerable plaques was performed using Trichrome staining.

Results: Plaques were grouped into stable or vulnerable based on their morphological characteristics (lipid content, thickness of the fibrous cap). As compared with stable plaques, vulnerable lesions were characterized by increased levels of COX-2 positive cells, especially in the plaque shoulders and the fibrous intima, indicating an increased inflammatory process in those regions. In stable plaques, the numbers of activated DCs were significantly decreased in the plaque shoulders regions, which was associated with a reduction of recruited COX-2 positive T lymphocytes. On the contrary, the numbers of regulatory T-cells were increased in stable as compared to vulnerable plaques. Nearly all of the investigated plaques (stable and vulnerable plaques) showed a negative correlation between activated DCs and regulatory T-cells. Conclusion: Raised numbers of COX-2 positive cells indicate an increased inflammatory state in vulnerable as compared to stable plaques. The negative correlation between activated DCs and regulatory T-cells suggests an increased differentiation of native T lymphocytes into regulatory T-cells in the absence of mature DCs, which might contribute to an enhanced plaque stability.

P1712 Prognostic value of uric acid in patients with stemi undergoing primary angioplasty: two year follow-up

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Objective: Elevated uric acid levels have been associated with cardiovascular disease in epidemiological studies. The relationship between uric acid levels and long-term outcomes of STEMI patients undergoing primary percutaneous coronary intervention (PPCI) is not available.

Methods: Data from 2,249 consecutive patients with STEMI who underwent primary PPCI were evaluated. Patients were divided in two groups as either high or low uric acid using an upper limit of normal value of 6 mg/dl for female and 7 mg/dl for male in our central laboratory.

Results: There were 1,643 patients (mean age 55.9 ± 11.6 and 85% male) in the low uric acid group and 606 patients (mean age 60.5 ± 12.6 and 76% male) in the high uric acid group. Serum uric acid levels were 8.0 ± 1.5 in the high uric acid group and 5.2 ± 1.0 in the low uric acid group (p < 0.001). The in-hospital mortality rate was significantly higher in patients with high uric acid levels (9% vs. 2%, p < 0.001) as was the rate of adverse outcomes in patients with high uric acid. The mean follow-up time was 24.3 months. Cardiovascular mortality, re-infarction, target vessel revascularization, heart failure, and MACE were all significantly higher in high uric acid group (Figure). In a multivariate analyses, high plasma uric acid levels were an independent predictor of MACE during the in-hospital (odds ratio (OR) 2.03, < 0.05% confidence interval (CI) 1.25–3.75; p = 0.006) and long-term follow-up period (OR 1.64, < 0.95% CI 1.05–2.56; p = 0.03).

P1711 Incremental effect of hypercholesterolemia on coronary plaque progression and high-risk composition despite similarly low local endothelial shear stress (ESS)

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Purpose: The relative contribution of systemic risk factors and local low ESS to atherosclerosis is well documented, yet their interrelating effect in vivo is largely unknown. We investigated the combined impact of different levels of hypercholesterolemia and local ESS on subsequent plaque progression and histological composition.

Methods: Diabetic, hyperlipidemic pigs were grouped into a higher– total cholesterol (TC) (852 ± 32mg/dl, n = 4) and a lower-TC group (658 ± 34 mg/dl, n = 5), 3-veins coronary angiography and IVUS were performed in vivo at 3-5 time-points over 36 weeks. 3D-reconstructed arteries were divided into 3-mm segments. ESS was calculated using computational fluid dynamics. Segments were stratified according to systemic TC and local ESS. Change of plaque volume (APV) was measured between consecutive time-points. Arteries were harvested, and segments were analyzed using histopathology and RT-PCR. Gene expression of the LDL receptor (LDL-R), lectin-like oxidized LDL receptor-1 (LOX-1), and monocyte chemoattractant protein-1 (MCP-1) were assessed.

Results: APV over time was greater in low-ESS segments (< 1.2Pa) from higher-TC vs. lower-TC animals. At follow-up, low-ESS segments from higher-TC animals (n = 22; 19%) had the highest mRNA levels of LDL-R, LOX-1, and MCP-1, and the greatest lipid content and inflammation – greater even than segments from lower-TC animals with similarly low 1.2Pa). Figure 1: ESS, TC, and coronary plaque histology

Conclusion: The combination of higher TC and low local ESS leads to the most marked plaque progression and high-risk phenotype in the natural history of CAD. Local risk factors (low ESS) and systemic risk factors (hypercholesterolemia) synergistically exacerbate local plaque development and progression towards inflamed, high-risk lesions.
Decrease in regulatory T-cells and increase in pro-inflammatory cells in unstable compared to stable atherosclerotic lesions

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Background: Dendritic cells (DCs), T-cells, and macrophages are involved in the complex mechanisms of atherosclerosis. However, the role of regulatory T-cells (Tregs) in atherosclerosis is not completely understood. Therefore, we investigated in our present study the frequency of regulatory T-cells in unstable compared to stable carotid plaques and compared it to other inflammatory cells such as cytotoxic T-cells, THelper cells, as well as dendritic cells (DCs).

Methods: Advanced atherosclerotic lesions were obtained by thromboembolectomy (TEA), and they were classified as unstable (n=13) according to the size of their lipid core (<40%), their thickness of the fibrous cap (<100μm), or the presence of neovasculature, and they were compared with stable plaques (n=9) which did not fulfill the above criteria. The plaque specimens were immunostained using primary antibodies which are specific for T-cells (CD3), activated T-cells (CD25), cytotoxic T-cells (CD8), THelper cells (CD4), Tregs (FoxP3), DCs (CD123), and mature DCs (CD83). The results were compared for stable versus unstable plaques and their frequency was correlated with each other.

Results: Compared to stable plaques, we found in unstable plaques significantly higher levels of CD4+ T-cells (2.5-fold, p<0.001), CD8+ cytotoxic cells (2.9-fold, p<0.01), CD4+ T-helper cells (2.5-fold, p<0.02), CD4+ T-helper cells (4.1-fold, p=0.03), CD25+ activated T-cells (16.1-fold, p<0.001), CD209+ DCs (2.9-fold, p<0.01), and CD83+ DCs (5.0-fold, p<0.01), suggesting that the frequency of FoxP3+ Tregs in unstable plaques is higher than in stable plaques (3.0-fold, p<0.03).

Conclusions: We show a significant increase in inflammatory cells such as T-cells, cytotoxic T-cells, THelper cells, and dendritic cells in atherosclerotic plaques with unstable morphology. In contrast, the number of regulatory T-cells is significantly lower in unstable plaques. These results indicate that plaque destabilization is the result of an imbalance between pro-inflammatory and anti-inflammatory cells.

Hypoadiponectinemia is associated with severity of coronary atherosclerosis and poor long-term outcome in patients with angiographically documented coronary artery disease


Purpose: Adiponectin (APN) is an adipokine with cardioprotective effects. Patients with plasma APN levels <4.0μg/ml have a 2-fold increased prevalence of coronary artery disease (CAD), but the prognostic role of APN levels is unknown. We evaluated the relationship between APN levels, CAD severity and long-term prognosis.

Methods: Consecutive patients were enrolled from inpatients who underwent coronary angiography or percutaneous coronary intervention (PCI) for stable CAD or acute coronary syndrome (ACS) at our Institution. Venous blood was drawn after an overnight fast. APN levels were evaluated by an ELISA assay. In a subgroup of CAD or ACS patients, transmyocardial (Acorn/Coronary Sinus) APN levels were measured. Patients were divided into 2 groups according to the plasma APN levels below (low APN) or above (control group) the value of 4.0 μg/ml. Major adverse cardiovascular events (MACE) were considered death, acute myocardial infarction or acute coronary syndrome at our Institution. Venous blood was drawn after an overnight fast. APN levels were evaluated by an ELISA assay. In a subgroup of CAD or ACS patients, transmyocardial (Acorn/Coronary Sinus) APN levels were measured. Patients were divided into 2 groups according to the plasma APN levels below (low APN) or above (control group) the value of 4.0 μg/ml. Major adverse cardiovascular events (MACE) were considered death, acute myocardial infarction or acute coronary syndrome at our Institution.

Results: A total of 311 patients completed a follow-up of 18.4±5.6 months, with 252 patients in the low APN group (69% male, mean age 62±10.3) and 59 patients in the control group (78% male, mean age 64±8). No difference were observed between groups except for a higher rate of diabetes (29.4% vs 10.7%, p<0.001), hypertension (26.7% vs 9.5%, p<0.05), and dyslipidemia (27.1% vs 10.6%, p<0.001). Multivariable analysis revealed that low plasma APN was a significant predictor of cardiovascular mortality (HR 3.2, 95% CI 1.6-6.3, p=0.001) and all-cause mortality (HR 2.4, 95% CI 1.2-4.7, p=0.003). Additionally, low plasma APN was associated with a higher frequency of cardiovascular events (HR 2.4, 95% CI 1.2-4.7, p=0.003) and all-cause mortality (HR 3.2, 95% CI 1.6-6.3, p=0.001). Cox regression analysis identified low APN levels as an independent predictor of MACE after correction for other risk factors (HR 3.2, 95% CI 1.6-17.05, p=0.006).

Conclusions: Our results confirm that low APN levels are associated with severe CAD, and that ACS patients have lower APN values than stable CAD patients. Moreover we show a close relationship between low levels of peripheral and coronary APN suggesting a reduced cardioprotective action in the coronary circulation of these patients. At long-term follow-up, patients with lower APN levels have a higher incidence of AMI, rePCI and death with a 5-fold higher risk to develop MACE at long-term follow-up independently of other known risk factors.

Identification of carotid “vulnerable plaque” by microwave radiometry: correlation with ultrasound findings, plaque inflammation and angiogenesis

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Purpose: Carotid plaque inflammation and neangiogenesis, both play an important role in plaque progression. Microwave radiometry (MR) is a new non-invasive method that allows in vivo measuring of the internal temperature of tissues. The purpose of this study was to investigate in human carotid arteries whether thermal heterogeneity measured by MR is associated with ultrasound characteristics and immunohistochemical findings.

Methods: Patients scheduled for carotid endarterectomy underwent screening carotid ultrasound and MR. Carotid plaque inflammation by ultrasound and MR, and angiogenesis are present in instable plaques. Microwave radiometry (MR) is a new non-invasive method that allows in vivo measuring of the internal temperature of tissues. The purpose of this study was to investigate in human carotid arteries whether thermal heterogeneity measured by MR is associated with ultrasound characteristics and immunohistochemical findings. Patients scheduled for carotid endarterectomy underwent screening carotid ultrasound and MR. Carotid plaque inflammation by ultrasound and MR, and angiogenesis are present in instable plaques.

Results: Thirty-four consecutive patients with significant carotid artery stenosis and 15 healthy subjects as a control group were included. ΔT was higher in atherosclerotic carotid arteries (1.39±0.49 vs 0.23±0.01°C). Fatty plaques had higher ΔT compared to mixed and calcified (1.78±0.41 vs 1.38±0.30 vs 0.96±0.22°C, p<0.01). Plaques with ulcerated surface had higher ΔT compared to plaques with irregular and regular (2.08±0.14 vs 1.37±0.23°C vs 0.95±0.19°C, p<0.01). Heterogeneous plaques had higher ΔT compared to homogenous (1.78±0.41 vs 1.09±0.31°C, p<0.01). Specimens with thin fibrous cap had higher ΔT (1.69±0.42 vs 0.98±1.20°C, p<0.01). Specimens with intense expression of CD3 had higher ΔT compared to specimens with low (1.66±0.43 vs 0.98±0.21°C, p<0.01). Specimens with intense expression of VEGF had higher ΔT compared to specimens with low (1.70±0.46 vs 0.98±0.28°C, p<0.01).

Conclusions: Increased thermal heterogeneity detected in carotid arteries by microwave radiometry correlates with ultrasound and immunohistochemical findings. Further studies are needed to validate this method for the non-invasive assessment of carotid plaques.
Early inhibitory drug effect on the expression of pro-inflammatory and pro-oxidant genes in coronary regions of low endothelial shear stress: an in vivo study in diabetic hyperlipidemic juvenile swine

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Purpose: Low endothelial shear stress (ESS) activates pro-inflammatory pathways and critically determines the localization of atherosclerosis. Angiotensin receptor blockers and statins exhibit pleiotropic effects with anti-inflammatory actions in advanced plaques. However, the effect of drugs on the earliest pathobiologic manifestations of atherosclerosis is not well known. We tested the hypothesized hypothesis that valsartan (V) or V plus simvastatin (V/S) exerts an early vasculoprotective effect in coronary regions exposed to low ESS in a porcine model of human-like atherosclerosis.

Methods: Twelve diabetic-hyperlipidemic swine (age: 3 mo) were grouped into controls (n=4), and those treated with V (320 mg; n=4) or V/S (320 mg: n=4). 3D coronary artery reconstruction by angiography and intravascular ultrasound was performed in vivo at baseline and 8 (follow-up) weeks post-induction. Baseline local ESS was calculated by computational fluid dynamics and 3 mm segments with low (<1.2 Pa; n=60) or higher (>1.2 Pa; n=89) ESS were identified. Coronary arteries were harvested at follow-up. qRT-PCR was used for assessing the expression of pro-atherogenic, pro-inflammatory and pro-oxidant genes.

Results: The upregulation of sterol regulatory element-binding protein 1 (SREBP1), intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1) and lipopolysaccharide-associated phospholipase-A2 (LpPLA2) in low ESS segments was inhibited in the V and V/S groups compared to controls (Figure; *p<0.05). V/S also suppressed the upregulation of NADPH oxidase (gp91phox) expression.

Conclusions: V and V/S attenuate the pro-atherogenic effects of low ESS within only 8 weeks. These results suggest a drug-induced mechanism of regional atheroprotection early in the natural history of coronary artery disease.

Expansion of an unusual NK cell subset in intracoronary blood of patients with ST-Elevation Myocardial Infarction

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Background: Atherosclerosis is a chronic inflammatory disease of the arterial wall. While considerable evidence supports the involvement of different T lymphocyte subsets in atherogenesis and plaque instability, the role of NK and NKT cells in this pathology is still not completely understood. NK cells, with a functional profile that favors inflammation and atherosclerosis, have been found reduced in peripheral blood of patients with ST-segment elevation myocardial infarction (STEMI) compared with healthy controls, suggesting a probable recruitment of this cells in myocardial infarction. In the present study, we investigated the levels of NK and NKT cells within the culprit coronary artery in patients with STEMI treated with primary angioplasty.

Methods: 33 patients with STEMI (70% males, 62±10 years) within 24 hours of symptom onset were included. Blood samples were taken during the coro-
nary catheterization, from the arterial access and from the culprit coronary artery distal to the lesion using a monorail aspiration catheter. Peripheral and intra-coronary blood NK cell subsets were analyzed by 4-color flow cytometry, using anti-CD3, anti CD16, and anti-CD56 human monoclonal antibodies. To evaluate NK cell subset, we assessed the frequencies of CD3+CD56+CD16–, CD3–CD56+CD16–, CD3–CD56–CD16– cells and NKT cells (CD3+CD56+). Results: The percentage of CD3–CD56–CD16– NK cells was significantly higher in the intacrocoronary blood than in peripheral blood samples (median 4.05%, range 0.37% to 20.94% versus median 2.91%, range 0.25% to 21.9%, respectively. p=0.014). There were no significant differences in the levels of NK cells and CD3–CD56+CD16– cells between peripheral and intracoronary blood.

Conclusions: Overall our results show that pro-inflammatory CD3–CD56+CD16– NK cells are preferentially located at the occluded coronary artery of patients with STEMI. It has been suggested that this NK subset is functionally and phenotypically immature and likely being precursors of mature NK cells. Moreover, CD3–CD56+CD16– NK cells have higher proliferative capacity and produce more amount of IFN-γ than mature NK, suggesting a pathophysiological role of this population in coronary atherothrombosis.

P1721

Infusion of lin-/sca-1+ and endothelial progenitor cells improves proinflammatory and oxidative stress markers in atherosclerotic mouse

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Background: The impact of direct infusion or indirect mobilization of progenitor cells on atherosclerotic plaque development and progression is not clear. We sought to investigate the effects of lin-/sca+ cells (P), endothelial progenitor cells (E) and G-CSF (G) administration on the inflammatory and oxidative component of atherosclerosis.

Methods: Apolipoprotein-E deficient (apoE–/–) mice were splenectomized and treated with high-cholesterol diet for 6 weeks. Bone marrow derived lin-/sca-1+ cells were isolated and further cultured to early growth endothelial progenitor cells (EPCs). Mice were divided in four groups (n=10/group) and received two intravenous injections of 5x105 cells (lin-/sca+ or EPCs), or granulocyte colony-stimulating factor (G-CSF 100 mcg/kg/day) for 7 days or normal saline. sICAM-1, ICAM-1, sVCAM-1, IL-6, IL-8, ox-LDL, and lipid peroxidation (LPO) levels were evaluated at the day of the first infusion, 7 days later and 6 weeks post-treatment with enzyme-linked immunosorbent assay (ELISA).

Results: The administration of both G-CSF and progenitor cells significantly decreased the levels of sICAM-1 (G: p=0.014, P: p=0.007, E: p=0.003), sVCAM-1 (G: p=0.013, P: p=0.005, E: p=0.005), IL-6 (G: p=0.001, P: p=0.003, E: p=0.01), IL-8 (G: p=0.02, P: p=0.018, E: p=0.05) and lipid peroxide (G: p=0.006, P: p=0.002, E: p=0.005) 6 weeks after the initiation of treatment. No significant effects of lin-/sca+ cells, EPCs and G-CSF on PAI-1 and MMP-9 levels were observed. The effects of all treatments on the levels of pro-inflammatory molecules and oxidative stress parameters 7 days post-treatment were not significant. Interestingly, the levels of sICAM-1 and s-VCAM-1 were increased 7 days post-treatment. No significant difference between the G-CSF and progenitor cell groups was observed.

Conclusions: Direct infusion of progenitor cells and indirect mobilization of hematopoietic progenitor cells significantly decreased the levels of proinflammatory molecules and oxidative stress parameters in a murine model of atherosclerosis. Treatment with hematopoietic progenitors, EPCs or G-CSF may exert a beneficial effects on vascular inflammation and endothelial dysfunction.

VASCULAR INFLAMMATION AND SIGNALING

P1722

Invasive natural killer T cells are involved in the development of experimental abdominal aortic aneurysm formation in apoE deficient mice

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Purpose: The infiltration and activation of macrophage as well as lymphocyte within the aortic wall contributes to the pathogenesis of aortic aneurysm. We have demonstrated that invasive natural killer T (INKT) cells, a unique subset of T lymphocytes that recognize glycolipid antigens and secrete a large amount of TH1 and TH2 cytokines on activation, have a crucial role in the atherogenesis. However, it remains undetermined whether INKT cells are also involved in the development of aortic aneurysm. The role of Dll4 in the neointimal hyperplasia, however, remains unknown. This study tested the hypothesis that inhibition of Dll4 prevents lesion formation after vascular injury.

Methods and Results: Male apoE deficient mice were subcutaneously administered angiotensin II (AngII; 100 ng/kg/min) or phosphate-buffered saline (PBS) via osmotic minipumps after 8 weeks of age. The AngII-infused mice were divided into two groups according to intraperitoneal injection of OHC (0.1g/kg body weight, twice a week; AngII-OCH, n=10 and PBS-OCH, n=5), a specific activator of INKT cells, or PBS alone (AngII-PBS, n=15 and PBS-PBS, n=10) for 4 weeks. Flowcytometry analyses showed that

INKT cell infiltration into the aorta was comparable between PBS-PBS and AngII-PBS. OCH injection significantly enhanced the INKT cell infiltration in AngII-OCH compared to PBS-PBS by 20-folds (P<0.01). The maximal abdominal aortic diameter was significantly increased in AngII-OCH compared to PBS-PBS and the increase was significantly enhanced in AngII-OCH (1337±75 vs. 800±15 vs. 2042±327 μm, P=0.05). The incidence of aortic dissection did not change before or after OCH injection (in AngII-PBS, 8.2% vs. 5.4% vs. 8.7% vs. 5.7%, P<0.05). Real-time PCR showed that OCH increased the expression levels of MHC-class II, RANTES, and IFN-γ within the aorta in AngII-OCH compared to AngII-PBS by 1.5, 1.9, and 2.2-folds (P<0.05 for each), respectively. In situ zymography revealed that OCH increased MMP activity in media and adventitia of the aortic aneurysm in AngII-OCH compared to AngII-PBS.

Conclusions: INKT cells are involved in the development of experimental abdominal aortic aneurysm and dissection via activating macrophages and T lymphocytes and up-regulating MMP activity within the vascular tissue.

P1723

Paracrine effects of perivascular adipose tissue on neonotina formation after vascular injury: importance of leptin

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Clinical and experimental studies suggest that perivascular adipose tissue (PVAT) contributes to the accelerated atherosclerotic cardiovascular risk associated with advanced PVAT accumulation. The aim of this study was to determine the role of PVAT accumulation and local leptin overexpression on neonotina formation and to distinguish it from systemically high leptin levels in obesity. Wildtype mice (WT) fed high fat diet (HFD) increased body weight and serum leptin levels (P=0.001) compared to littersmates fed normal chow (NC). Moreover, a significant increase in neointimal area (P=0.01) and luminal stenosis (P=0.01) after vascular injury at the common carotid artery was observed, whereas these effects were absent in leptin-deficient ob/ob mice. HFD increased leptin mRNA and protein expression, both in visceral (VAT, 2- to 7-fold) and perivascular (3- to 16-fold) fat, and RT-PCR, cytokine and chemokine mRNA expression and MHC-class I, II, RANTES, and IFN-γ within the aorta in AngII-PBS by 1.5, 1.9, and 2.2-folds (P<0.05 for each), respectively. In situ zymography revealed that OCH increased MMP activity in media and adventitia of the aortic aneurysm in AngII-OCH compared to AngII-PBS.

Conclusions: INKT cells are involved in the development of experimental abdominal aortic aneurysm and dissection via activating macrophages and T lymphocytes and up-regulating MMP activity within the vascular tissue.

P1724

Notch ligand, delta-like-4, blockade inhibits lesion formation after vascular injury

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Purpose: Excessive neonotina hyperplasia after vascular injury contributes to restenosis, which remains as a major limitation of the coronary angioplasty. Monocytes/macrophages play causal roles in this disease process through the promotion of inflammation. The Notch pathway regulates embryonic development and contributes to physiological and pathological processes in adult tissues. We previously showed that Notch signaling triggered by delta-like-4 (Dl4), one of the Notch ligand, promotes inflammatory responses in human macrophages in vitro. In vivo studies showed that Dl4 was expressed in aortic lesion, but also conditioned medium from VAT of obese mice increased smooth muscle cell proliferation in a lesion (receptor)-dependent manner. Taken together, our findings reveal that leptin stimulates neointima formation in a paracrine manner, and thus that PVAT accumulation and locally elevated leptin levels may contribute to the increased cardiovascular risk in obesity.

Methods: We induced wire-mediated vascular injury to C57BL/6 mice. To block Notch-mediated Notch signaling in the mice according to the investigation, we administered well-characterized anti-Dl4 neutralizing antibody (Dl4-Ab) twice a week and harvested mice at one week or four week after surgery. To investigate potential roles of Dl4 in macrophage-dependent inflammation, we performed loss-of-function and gain-of-function ex...
A link between inflammation, extracellular matrix and coronary plaque rupture in ST-elevation myocardial infarction

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Atherosclerotic plaque rupture with subsequent mural thrombus formation is a cornerstone in event compromising epicardial flow in ST-Elevation myocardial infarction (STEMI). Although the crucial role of matrix metalloproteinases (MMPs) in coronary plaque rupture is well investigated, the trigger for enhanced MMP synthesis and activation has not been understood yet. The cell surface glycoprotein EMMPRIN (Epithelial Membrane Protein Inducible by TNF) may be the trigger for enhanced MMP synthesis and coronary plaque rupture in STEMI.

Proteomic shotgun analyses as well as western blots showed an accumulation of EMMPRIN in coronary thrombi. FACS analyses comparing EMMPRIN expression on mononuclear and polymorphonuclear cells revealed no differences between systemic blood and blood derived from the site of coronary plaque rupture in 40 patients with STEMI. However, soluble EMMPRIN, which is known to be generated by MMP mediated proteolytic shedding from the cell surface, has been found significant increase at the site of plaque rupture by ELISA analyses.

The enrichment of soluble EMMPRIN correlates with local MMP-9 activity. In vitro stimulation of PMNs, isolated from STEMI patients, with complement component C5a showed an upregulation of EMMPRIN by RT-PCR.

Our data suggest that EMMPRIN represents a crucial link between local inflammatory processes, enhanced MMP synthesis and coronary plaque rupture.

A link between inflammation, extracellular matrix and coronary plaque rupture in ST-elevation myocardial infarction

Vascular dysfunction and skin inflammation are mechanistically interconnected by IL17A and IL-6 signaling in a mouse model of psoriasis

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Introduction: Abnormal proliferation of inflammatory mediators, especially the IL-23/IL-17A axis, plays a decisive role in the pathogenesis of psoriasis and other autoimmune diseases. IL17 has as well been described to promote endothelial dysfunction and inflammation between vascular and immune system. Therefore, the roles of IL-17A and its ligand IL-17 receptor (IL-17R) in vascular dysfunction and oxidative stress as well as from chemically induced psoriasis was reported in several clinical studies assuming a correlation between upregulated cytokines as IL17A and cardiovascular disease. However, there has not yet been an experimental approach to address the correlation between IL-17A and endothelial dysfunction and psoriasis.

Methods and Results: Mice with a cre-inducibleoverexpression of IL17A in coro.

Platelet serotonin promotes the efficient recruitment of neutrophils to sites of acute inflammation

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Purpose: To study the role of serotonin in the recruitment of leukocytes and platelets to sites of inflammation.

Methods: Complete blood cell counts were determined in C57BL/6 (WT) mice and tryptophan hydroxylase (Tph) I-deficient mice, which do not produce non-neuronal serotonin. Platelet serotonin was depleted by long-term treatment with fluoxetine. Leukocyte-endothelial interactions were visualized by intravital microscopy in mesenteric venules. Platelet serotonin was induced by thrombin or collagen, and extravasated cells harvested. Aspecific wound were punched into dorsal skin and myeloperoxidase deposition was measured. Acute lung inflammation was induced by inhalation of lipopolysaccharide (LPS). Survival after intraperitoneal injection of 20mg/kg E. coli LPS was monitored.

Results: Absence of non-neuronal serotonin in Tph1-/- mice was associated with an increased leukocyte count as compared to WT (9.1±2 versus 6.1±1 x10⁶/l; p<0.001; n=18). Neutrophil surface expression of L-selectin was reduced in Tph1-/- mice and soluble L-selectin increased. Despite elevated leucocyte count, lower leucocytes rolled on unstimulated venous endothelium of Tph1-/- mice compared to WT (p<0.001; n=8-9). The velocity of rolling leukocytes was significantly higher in Tph1-/- mice than in WT mice (p<0.001). Leukocyte adhesion to LPS injection was significantly reduced in Tph1-/- as compared to WT (p<0.007, n=10). Blocking serotonin uptake into platelets by fluoxetine reduced serum serotonin in WT mice by >80%. Fluoxetine-treated mice also showed reduced leukocyte rolling and adhesion. Four hours after inflammatory stimulation, neutrophil extravasation into skin wounds, inflammation and peritonitis were significantly reduced in Tph1-/- mice as compared to WT mice (p<0.05, n=10). We identified that the serotonin receptor subtypes 5-HT1A and 5-HT1B are present on neutrophils but serotonin did not induce in vitro neutrophil chemotaxis. Sur-

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HMGB1 binds to activated platelets via platelet-expressed receptor for advanced glycation end products (RAGE) and is highly expressed in platelet rich coronary artery thrombi

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Background and Rationale: High-mobility group box 1 (HMGB1) facilitates gene transcription as an architectural nuclear protein but may also be secreted, thereby mediating inflammatory and immune responses. HMGB1 has recently been identified in human atherosclerotic lesions and induction of HMGB1 reduced atherosclerosis in ApoE−/− mice. Activated plateletsexpressed early stages of atherogenesis, therefore we hypothesized an interaction between HMGB1 and platelets.

Methods: Binding of recombinant HMGB1 to platelets was assayed in diluted human and mouse whole blood by flow cytometry. Expression of the HMGB1 receptor RAGE was discovered by RT-PCR with mRNA extracted from highly purified human and mouse whole blood by flow cytometry. Expression of the HMGB1 receptor RAGE on platelets was examined in diluted platelet-rich plasma (PRP) and isolated platelets, but did not have any effect on platelet adhesion.

Results: Recombinant HMGB1 (20 ng/ml) bound to thrombin-activated human platelets (mean fluorescence intensity MFI 2.49 vs 25.01, p<0.0079). RAGE is one of the known receptors for HMGB1. We identified RAGE in platelets by RT-PCR with mRNA extracted from highly purified platelets and confirmed expression of RAGE protein in platelets by Western blot. RAGE expression on platelets increased in response to cytokines (IL-1β, TNF-α, and INF-γ) in both resting and activated endothelial cells (HUVECs) and flow cytometry. HMGB1 expression in human coronary artery thrombi was studied by immunohistochemistry.

Conclusions: Platelets express and up-regulate upon activation mRNA and protein of RAGE. Activated platelets bind HMGB1 via RAGE and TLR-2. The high level of expression of HMGB1 in platelet-rich coronary artery thrombi points towards a central role of HMGB1 in atherothrombosis and warrants further exploration of the potentially HMGB1-mediated monocyte recruitment during atherosclerotic plaque development.

Interleukin-17 enhances PAR-1-mediated GPllb/IIa activation and platelet adhesion over endothelial cells in vitro

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Background: Interleukin 17 (IL-17) is a pro-inflammatory cytokine, which plays a vital role in inflammation. The aim of the present study was to evaluate the expression of IL-17 receptor A (IL-17RA) on platelets and its possible role in platelet aggregation, adhesion and aggregation in vitro.

Methods: Evaluation of the expression of IL-17RA on platelets was determined by flow cytometry and western blot analysis. The possible role of IL-17RA on platelets was evaluated in combination with other platelet agonists in platelet activation (glycoprotein GPllb/IIa activation and P-selectin expression) has been studied in platelet rich plasma (PRP) and isolated platelets with the help of flow cytometry. The possible role of IL-17 in platelet aggregation was studied with the help of light transmission aggregometry. The role of IL-17 in platelet adhesion over cultured resting and TNF-alpha/INF-gamma-activated endothelial cells (HUVECs) was investigated under high shear stress in vitro.

Results: IL-17RA is expressed on platelets, as shown by flow cytometry and western blot. Its expression is elevated upon TRAP-6-induced plateletactivation. IL-17 significantly enhanced the PAR-1-mediated GPllb/IIa activation studied in both PRP and isolated platelets, but did not have any effect on P-selectin expression. In order to evaluate the possible effect of IL-17 alone or in combination with ADP, TRAP or collagen on platelet aggregation, we performed a series of flow chamber experiments of washed platelets, pretreated with IL-17 or ADP or control vehicle, over resting and activated endothelial cells under high shear stress (2000 s^-1). Pretreatment of platelets with IL-17 significantly increased their adhesive properties over both resting and activated endothelial cells (P<0.05 for both). The initial step of platelet adhesion (rolling of platelets over HUVECs) was also significantly increased after pretreatment with IL-17.

Conclusion: Expression of IL-17RA on the surface of platelets may be involved in IL-17-induced vascular inflammation.

A2 adenosine receptors activation promotes angiogenesis through up-regulation of thrombospondin-1 production by macrophages

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Background: Formation of new capillaries is associated with postinfarct remodeling and has important implications for prognosis following myocardial infarction. Cardiac ischemic adenosine triggers the production of thrombospondin and the matricellular component thrombospondin-1 (TSP-1). Adenosine is thought to be involved in cardiac repair and is known to stimulate angiogenesis. The role of TSP-1 in angiogenesis is less clear, since both anti- and pro-angiogenic activities have been reported. We hypothesized that adenosine controls angiogenesis through modulation of TSP-1 production.

Methods: Primary human macrophages were obtained by differentiation of peripheral blood monocytes from healthy volunteers, and were treated with adenosine (0.1-50 μM) under ischemic conditions (hypoxia and starvation) or stimulation by cytokines (IL-1β and TNF-α). Angiogenesis was evaluated ex vivo using rat aortic ring explants and in vivo using matrigel plugs implanted in mice.

Results: Adenosine dose-dependently increased the production of TSP-1 by macrophages, reaching a 4-fold increase at 10 μM (n=11, P<0.001). A 13-fold induction of TSP-1 mRNA expression was measured. These effects were observed both under basal conditions, during ischemia, and after stimulation with cytokines. Use of antagonists and agonists of adenosine receptors, coupled to RNA interference experiments, involved the A2A and A2B receptors in the effect of adenosine on TSP-1. This effect was reproduced by cholera toxin (Gs protein activator) and forskolin (adenylate cyclase activator), and blocked by the PKA inhibitor H89. Conditioned medium from adenosine-treated macrophages enhanced microvessels outgrowth from aortic ring explants, and induced vessels formation in matrigel plugs. Addition of anti-TSP-1 antibodies to conditioned medium blocked angiogenesis in both models.

Conclusions: We show for the first time that adenosine up-regulates TSP-1 production by macrophages, resulting in a robust stimulation of angiogenesis. This effect involves the A2-type receptors and is mediated through the cAMP/PKA pathway. Therefore, we have identified a new mechanism by which adenosine improves angiogenesis. This mechanism is an important information for the design of adenosine-based therapies to limit left ventricular remodelling.
The addition of bevacizumab in the adjuvant chemotherapy of cancer patients increases the incidence of major cardiovascular events: a prospective study

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Purpose: The anti-angiogenic agent of bevacizumab is used widely in the treatment of various types of malignancies. A little number of retrospective trials has investigated the effect of bevacizumab on the cardiovascular system. We evaluated prospectively the incidence of major cardiovascular events and the predictors of adverse outcomes in patients treated with bevacizumab.

Methods: One hundred and forty seven cancer patients were divided into two groups, according the treatment selected by oncologists. Group 1 (76 patients) received conventional chemotherapeutic scheme with bevacizumab and group 2 (71 patients) similar chemotherapeutic schemes without bevacizumab. Baseline evaluation before the initiation of the therapy included recording of risk factors for coronary artery disease, previous medication and their electrocardiogram. All patients were prospectively followed up at 6 and 18 months and the incidence of the following adverse events were recorded: death, cardiac event, myocardial infarction and deep vein thrombosis.

Results: The two groups had similar baseline demographic characteristics. Total mortality had no difference between the two groups (28.94% versus 33.80%, p=0.52). On the contrary, cardiovascular events were significantly higher in the bevacizumab group compared to the control group (9.21% versus 1.40%, p=0.03). All cardiovascular events that were recorded in both groups and did not cause death. Moreover, patients treated with bevacizumab had higher incidence of deep vein thrombosis (5.26% versus 2.81%, p=0.45). Multivariate analysis using Cox proportional hazards with forward stepwise logistic regression analysis identified left bundle branch block on the baseline ECG, as well as the use of bevacizumab as the only independent predictors of cardiovascular events. (p<0.001 HR: 56.72, 95% CI: 7.38-436.10 for LBBB and p=0.03, HR: 13.18, 95% CI: 1.32-130.84 for bevacizumab).

Conclusions: The addition of bevacizumab in the conventional chemotherapeutic scheme for the treatment of metastatic breast or colorectal cancer, significantly increases the incidence of major cardiovascular events. Left bundle branch block on the baseline ECG is an independent predictor of myocardial infarction and cardiovascular death in such population.

Angiogenesis II promotes skeletal muscle angiogenesis induced by exercise training: role of microRNAs-27a and 27b

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Purpose: Exercise training (ET) promotes skeletal muscle angiogenesis related to high performance. MicroRNAs (miRNAs) are an emerging class of non-coding small RNAs that regulate gene expression posttranscriptionally by targeting mRNAs. miRNAs-27a and -27b target the angiotensin-enzyme converting (ACE). We investigated the effects of ET on soleus miRNAs-27a and 27b expression and whether they regulate the skeletal muscle renin angiotensin system (RAS) in ET-induced angiogenesis.

Methods: Wistar rats (n=30) were assigned to 3 groups: Sedentary (S), Trained 1 (T1) and Trained 2 (T2). T1: swimming training consisted of 60 min, 1/day/10 weeks, with 5% body weight workload. T2 the same as T1 until 8th week, in the 9th week they trained 2x/day and in the 10th week 3x/day. Blood pressure (BP) and heart rate (HR) were evaluated by direct measurement and angiogenesis by soleus capillarity-to-fiber ratio. Soleus miRNAs-27a and -27b were analyzed by RT-qPCR and ACE activity by fluorescence and western blotting, respectively. Soleus angiotensin II (ANG II) and VEGF concentration were evaluated by ELISA. Angiotensiogen (AGT) and ANG II type 1 receptor (AT1) mRNA expression were measured. RAS involvement in the skeletal muscle angiogenesis induced by ET was evaluated using AT1 receptor blockade (Losartan-20 mg/kg/day) during ET protocol.

Results: We found that by peak oxygen uptake and soleus citrate synthase activity in T1 and T2. BP was unchanged while resting HR decreased in all trained groups. Skeletal muscle angiogenesis obtained by T1 and T2 was 87% (p<0.01) and 137% (p<0.001), respectively. In contrast, Losartan prevented the increase in angiogenesis obtained by both trained groups. Soleus miRNA-27a levels decreased in both trained groups (23% in T1 and T2, p<0.05) compared with S group. Similarly, miRNA-27b reduced 23% in T1 (p<0.01) and 32% in T2 (p<0.001) paralleled with an increase in ACE protein levels (200% in T1 and 251% in T2, p<0.001). Soleus AGT levels (52% in T1 and 96% in T2, p<0.05), ANG II levels (26% in T1 and 46% in T2, p<0.05) and VEGF levels (30% in T1 and 60% in T2, p<0.05) also were higher in all trained groups. In addition, AT1 receptor protein levels increased after training (39% in T1 and 48% in T2, p<0.05).

Conclusions: Our data show that SRA participates ET-induced skeletal muscle angiogenesis, which could be associated with regulation of select miRNAs pro- viding a new target for modulating vascular formation and suggest that miRNA-27a and 27b can be potential therapeutic targets for pathological conditions involving capillary rarefaction.

Estrogen improves vascular function and morphology via peroxisome-proliferator-activated-receptor gamma

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Purpose: The exact mechanism of estrogen related atheroprotection is not fully understood. As estrogen receptors (ERs) the peroxisome-proliferator-activated-receptor γ (PPARγ) belongs to the family of ligand activated nuclear receptors regulating the transcription of atheroprotective genes. Aim of this project was to investigate whether atheroprotection of estrogen is mediated via PPARγ-regulation in the vascular compartment.

Methods and Results: We studied the effect of estrogen deficiency, endogenous and exogenous 17β-estradiol on vascular PPARγ-expression and function in female WT- and ApoE−/−mice. Estrogen deficient ovariec- tomized animals (OVX) displayed significant reduction of PPARγ-expression in aortic tissue compared to female mice with intact ovarian function (Sham). Hormone replacement with subcutaneous 17β-estradiol pellets significantly increased vascular PPARγ-expression in ovariec- tomized female mice (OVX/E2), ROS generation, endothelial dysfunction and atherogenesis were increased in estrogen-deficient OVX ApoE−/−mice with low vascular PPARγ-expression. Estrogen replacement (OVX/E2) rescued vascular PPARγ-expression, reduced ROS generation, monocyte recruitment, atherosclerotic lesion formation and improved endothelial function. Inhibition of PPARγ by GW9662, a specific PPARγ-antagonist reduced 17β-estradiol mediated vasuloprotection although estrogen replacement therapy was applied (OVX/E2+GW9662), provides the relevance of PPARγ in mediating 17β-estradiol vasculoprotection. Finally, treatment of OVX ApoE−/−mice with pioglitazone (OVX-pioglitazone), a selective PPARγ-agonist, compensates vascular dysfunction despite estrogen deficiency by rescuing PPARγ expression and providing subsequent anti-inflammatory and vasculoprotective effects.

Conclusions: In summary, 17β-estradiol regulates vascular PPARγ-expression in WT- and ApoE−/−mice. The presented data demonstrate the fundamental relevance of PPARγ as downstream target of 17β-estradiol-related anti-inflammatory and atheroprotective effects within the vascular wall independent of its cardiovascular risk factor modifications.

MMP-9 released angiogenesis inhibitors prevent adaptive capillary growth in hypertrophy and contribute to progression to heart failure

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Purpose: In left ventricular pressure-overload hypertrophy, lack of adaptive capillary growth contributes to progression to heart failure. Remodeling of the hypertrophied myocardium requires proteolysis of extracellular matrix (ECM) carried out by matrix metalloproteinases (MMPs). MMPs, specifically MMP-9, are known to contribute to progression to heart failure. Remodeling of the hypertrophied myocardium requires proteolysis of extracellular matrix (ECM) carried out by matrix metalloproteinases (MMPs). MMP-9, specifically MMP-9, is known to cleave ECM components which generate angiogenesis inhibitors (angiotensin, endostatin, tumstatin). We hypothesized that MMP-9 released anti-angiogenic factors during compensated hypertrophy, which resulted in lack of adaptive capillary growth and progression to heart failure.

Methods: Newborn rabbits underwent aortic banding. At compensated hypertrophy (4 weeks) and systolic heart failure (7 weeks) myocardial tissue from banded and sham-operated control animals was analyzed by immunoblotting for angiotensin, endostatin and tumstatin. MMP-9 activity was determined by zymography. A MMP-9 specific inhibitor (N-[1-(2-thienyl)-cyclohexyl]-2-sulfinylacetamide-1) was administrated orally (3 mg/kg/day, 4 times), and tissue was analyzed as stated above. Weekly echocardiography to determine mass/volume ratio and fractional shortening was performed.

Results: Results: MMP-9 was activated in hypertrophied myocardium versus controls (23±1 versus 17±1 p=0.04), which resulted in significantly increased levels of angiotensin (86±7 versus 115±10 p=0.003), endostatin (28±1 versus 33±1 p=0.02) and tumstatin (17±4 versus 35±6 p=0.003). Zymography confirmed inhibition of MMP-9 (hypertrophy: 17±1 versus hypertrophy+MMP-9 inhibitor: 4±0.6 p=0.01) and angiotensin, endostatin and tumstatin were down-regulated, accompanied by up-regulation of myocardial density (hypertrophy: 99±0.7 versus 95±0.7 p=0.05). Inhibition of MMP-9 prevented the dilation of the left ventricle and, as confirmed by echocardiographic measurements of fractional shortening, prevented systolic heart failure after 7 weeks.

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Identification of a novel soluble APOA-I truncated form increased in diabetic patients

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Apolipoprotein A-I (Apo-A-I) is the main protein of HDLs. In addition to its structural function, Apo-A-I has a functional role in reverse cholesterol transport by promoting the efflux of cholesterol from peripheral cells into HDL and activating lecithin-cholesterol acyltransferase. In fact, Apo-A-I modifications have an important impact on the cholesterol transport ability and in the regulation of the HDL particle size. By applying proteomic approaches we have investigated ApoA-I profile in serum and HDL samples and analyzed its changes in diabetic patients, that often have pro-atherothrombotic phenotype.

Methods: Characterization of serum and HDL ApoA-I was performed by 2D-electrophoresis (2DE) followed by mass-spectrometry (MALDI-TOF/TOF). Serum proteomic profile of diabetic patients was compared to non-diabetic individuals.

Results: ApoA-I characterization depicted a cluster of 5 spots (Mw: 28kDa; pl: 5.75). In addition, serum showed 1 spot of 26kDa and a pI of 5.75 that was not present in HDL MALDI-TOF/TOF analysis revealed that the 28kDa spot is a truncated form of Apo-A-I lacking a 1-38 (ApoA-I-Baciloma = aa 39-267). Diabetic patients showed decreased levels of total Apo A-I (p < 0.05) when compared to the non-diabetic group. A 2-fold increase intensity of the Apo-A-I-BCN form was detected (p < 0.05).

Conclusions: Our results demonstrate for the first time the presence of a soluble truncated Apo-A-I form (ApoA-I-BCN) that is not found in HDL particles. The increase of this truncated Apo-A-I form in the diabetic patients may contribute to their higher cardiovascular risk and may have effects in particle turnover.

Carbamylated low density lipoprotein (LDL) induces endothelial dysfunction by uncoupling of endothelial nitric oxide synthase (eNOS)

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Introduction: Cardiovascular events are the main cause of death in Western civilization. Lipoproteins play an important role in the regulation of vascular integrity. Recent evidence suggests that unaltered carboxylation of lysine residues may affect the functional properties of lipoproteins; however, its effect on endothelium-dependent relaxation is unknown. We therefore examined the effect of carboxylated low density lipoprotein (cLDL) on endothelial function.

Methods: LDL from healthy donors was isolated by sequential ultracentrifugation and carboxylated ex vivo using potassium cyanate. The degree of carboxylation and oxidation was assessed by HPLC/ESI-MS/MS and TBARS assay, respectively. Vascular reactivity after treatment with native (nLDL) or carboxylated (cLDL) LDL was examined in organ chamber experiments using aortic rings of wildtype or lectin-like oxidized LDL receptor-1 (LOX-1) transgenic mice. Superoxide and nitric oxide production in aortic rings and human aortic endothelial cells (HAEC) was determined using electron spin resonance (ESR) spectroscopy. Activation and uncoupling of endothelial NO synthase (eNOS) was assessed by Western blot techniques. In HAEC, silencing of LOX-1 was performed using LOX-1 specific siRNA.

Results: Carboxylation of LDL resulted in carboxyl-Lysine levels comparable to those in patients with chronic kidney disease; no oxidative changes were observed. In the cLDL impaired endothelium-dependent relaxation of aortic rings, whereas nLDL had no effect. Addition of superoxide dismutase/catalase restored vascular relaxation after cLDL treatment, indicating an important role of superoxide production in cLDL mediated endothelial dysfunction. cLDL directly induced superoxide production in aortic rings as well as in HAEC via eNOS uncoupling. cLDL induced endothelial dysfunction was enhanced in LOX-1 transgenic mice, revealing LOX-1 as the receptor mediating the actions of cLDL. Accordingly, knockdown of LOX-1 by siRNA improved NO production and attenuated superoxide release in HAEC.

Conclusions: These data newly demonstrate that cLDL induces endothelial dysfunction by causing eNOS uncoupling and increasing endothelial superoxide production via LOX-1. This indicates a new important mechanism in the pathogenesis of atherosclerotic diseases.

Effects of AMR101 on lipid and inflammatory parameters in patients with diabetes mellitus-2 and residual elevated triglycerides (200-500 mg/dL) on statin therapy at LDL-C goal: the ANCHOR study

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Purpose: To determine the effects of AMR101 (a novel omega-3 fatty acid agent containing ≥ 96% pure icosapentaenoic acid, the ethyl ester of eicosapentaenoic acid) on lipid and inflammatory parameters in patients with diabetes in the phase 3 12-week ANCHOR study (residual high fasting TG levels [200-500 mg/dL] despite optimized LDL-C [< 100 mg/dL]).

Methods: Intent-to-treat analysis of AMR101’s effects on median placebo-adjusted percent change from baseline in endpoint parameters was performed in 3 subgroups: total (all subjects with diabetes), well-controlled diabetes, and less-controlled diabetes (less than or greater than median baseline HbA1c).

Results: Of 702 patients randomized to AMR101 4 g/day, 2 g/day, or placebo, 514 (73%) had diabetes mellitus-2. Between the two dosage groups except for lower hsCRP in the well-controlled diabetes group. AMR101 significantly reduced TG, non-HDL-C, apo B, and RLP-C in all groups; LDL-C in the known group, and hsCRP in the total and less-controlled diabetes groups. Interestingly, decreases in hsCRP and apo B were far greater in patients with less-controlled diabetes. Importantly, Fbg, Hba1c, insulin, and HOMA-IR were not significantly changed in any group.

Effects of AMR101 4 g/day

Table: Change in lipids and hsCRP from baseline in the total diabetes group, with subgroup analysis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>AMR101 2 g/day</th>
<th>AMR101 4 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>-6.6, 0.063</td>
<td>-6.7, 0.1304</td>
<td>-6.3, 0.0277</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>-11.3, 0.0019</td>
<td>-18.0, -0.000</td>
<td>-14.4, -0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>-0.4, 0.0721</td>
<td>-3.6, 0.0002</td>
<td>-21.5, 0.0029</td>
</tr>
<tr>
<td>hsCRP (mg/dL)</td>
<td>22.6, 0.004</td>
<td>-21.3, 0.0034</td>
<td>-26.4, 0.0024</td>
</tr>
<tr>
<td>apo B (mg/dL)</td>
<td>-6.1, 0.0170</td>
<td>-12.8, -0.000</td>
<td>-9.5, -0.0001</td>
</tr>
</tbody>
</table>

P-values are from Wilcoxon rank-sum test. Abstract abbreviations: Apo B = apolipoprotein B; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; non-HDL-C = non-high-density lipoprotein cholesterol; HOMA-IR = homeostasis model index insulin resistance; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density (lipoprotein cholesterol); RLP-C = remnant-like particle cholesterol; TG = triglyceride.

Conclusions: In patients with diabetes and mixed dyslipidemia, AMR101 4 g/day significantly improved lipid and related parameters without worsening glycemic control, with possibly greater effects among those with less-controlled diabetes.

Palmioteine is increased in epididymal adipose tissue in heart failure and correlates with parameters of progressing failure


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Purpose: Epididymal adipose tissue (EAT) is a visceral fat depot which location and function are of growing scientific interest in regards to heart disease. The anatomical settings in the junctional area between EAT and the myocardium allows for widespread communication between the two tissues, as they exist and they share the same microcirculation. EAT has been shown to function as an endocrine organ by secreting a wide range of mediators, including factors known to be involved in development of cardiovascular disease in patients with coronary artery disease. However, little is known about a potential role of EAT in development of heart failure (HF). The aim of this study was to characterise EAT and SAT identified depot-specific transcription patterns, including groups of mediators involved in myocardial inflammation, hypertrophy and apoptosis. Further clustering analyses of EAT in HF and control patients also identified disease specific transcription patterns. Alterations in mRNA expression of genes involved in cardiac remodelling were observed using RT-PCR in both SAT and EAT and
in HF compared with control patients. Especially, significantly higher IL-6 mRNA levels were seen in the EAT of HF patients compared to SAT and controls. The FA analysis identified different profiles between EAT and SAT. In addition, several individual FA, like palmitoleate (POM) which is previously linked to cardiovascular disease and hypertrophy, were significantly increased in the EAT of HF patients compared to controls. POMG was also significantly correlated with increasing proBNP levels and left ventricular end-diastolic diameter.

Conclusion: Despite specific transcriptional and FA profiles were observed between EAT and SAT and between HF and control patients. The FA POMG was increased in the EAT of HF patients and correlated with parameters of progressing HF. Our findings suggest that adipose tissues are phenotypically different in regards to localization and that they may influence the progression of HF.

The effects of tocilizumab treatment on lipids and inflammatory/prothrombotic markers in patients (pts) with rheumatoid arthritis (RA): Data from the randomized, controlled, Measure study

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Purpose: Tocilizumab (TCZ), an anti-IL-6 receptor signaling inhibitor, has demonstrated efficacy in the treatment of RA. In MEASURE, a 2 part study, effects of TCZ on lipids and inflammatory/prothrombotic biomarkers in RA were investigated.

Methods: In the double-blind 24-wk phase, RA pts with inadequate response to methotrexate (MTX) were randomized to receive MTX qw + either TCZ 8 mg/kg IV or placebo (PBO) qw. Serum lipids were analyzed by NMR spectroscopy and biomarkers by ELISA. Data were analyzed using nonparametric analysis of variance, not corrected for multiplicity.

Results: Demographics were similar between groups. TCZ was superior to PBO in reducing RA disease activity, though 27 (42.9%) PBO pts and 12 (17.4%) TCZ pts entered open-label TCZ escape therapy at wk 12. The Table shows changes for TCZ vs PBO. Lipid changes occurred primarily in large VLDL/cholesterol and VLDL triglycerides. Though not significant (P > 0.1), LDL increases occurred primarily in small particles. TCZ induced an increase in paraoxonase and reductions in HDL-associated SAA and sPLA2-IIA, hs-CRP, and prothrombotic markers D-monomer, fibrinogen, and Lipa.

Conclusions: TCZ induces quantitative and qualitative changes in lipids, as well as suppressing inflammation and lowering thrombotic potential in RA patients. The net vascular effect requires further study.

Concentration-dependent biphasic effects of high density lipoprotein on endothelial progenitor cells in vitro and related vasculogenesis in vivo

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High-density lipoprotein (HDL) has the potential to prevent atherosclerosis. However, the mechanism by which native HDL may affect endothelial progenitor cells (EPCs), which are pivotal for the renewal of denuded or aging endothelium and neo-vasculogenesis, remains mostly unknown. Here, we studied the effects of native HDL (5-800 μg/mL) on late-outgrowth human EPCs.

Methods and Results: We explored that intracelular signaling, including the PI3K/Akt, NO, p38 MAPK, and JNK/SAPK-related pathways, are involving in the endogenous capability of EPC tube formation. HDL at low concentrations (5-50 μg/mL) reversed high HDL-induced EPC senescence and impairment of EPC tube formation both in vitro and in vivo.

Conclusions: We present the novel finding that HDL may have biphasic effects on EPC functions and related vasculogenesis; and our current results could possibly provide some preliminary explanations on the “paradoxical effects” of high HDL.

Effects of Pitavastatin on increasing of high-density lipoprotein cholesterol and regression of carotid artery plaque


Background and Objective: A low level of high-density lipoprotein cholesterol (HDL-C) and the increase of carotid intima-media thickness (IMT) are important risk factors for cardiovascular diseases. The aim of this study is to evaluate the efficacy of pitavastatin (NO, p38 MAPK, and JNK/SAPK-related pathways, are involving in the endogenous capability of EPC tube formation. HDL at low concentrations (5-50 μg/mL) further enhanced EPC tube formation via the PI3K/Akt/eNOS pathway. However, moderate to high concentrations of HDL (400-800 μg/mL) may enhance EPC senescence and impair EPC tube formation, which was found to be mediated by Rho-associated kinase (ROCK) activation, and promote the inhibition of PI3K/Akt phosphorylation as well as the inhibition of the p38 MAPK pathway. Treatment with ROCK inhibitors, either Y27632 or statins (atorvastatin and rosuvastatin), may reverse high HDL-induced EPC senescence and impairment of EPC tube formation both in vitro and in vivo.

Conclusions: We present the novel finding that HDL may have biphasic effects on EPC functions and related vasculogenesis; and our current results could possibly provide some preliminary explanations on the “paradoxical effects” of high HDL.

Effects of ezetimibe, simvastatin and ezetimibe/simvastatin on correlations between apolipoprotein B, LDL cholesterol and non-HDL cholesterol in patients with primary hypercholesterolemia

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Purpose: LDL-C is the primary target and non-HDL-C and apoB are secondary targets of therapy. Statin monotherapy lowers LDL-C and non-HDL-C more than apoB, thus statin-treated patients (pts) may be at increased coronary risk due to elevated levels of apoB-containing particles.

Abstract P1743 – Table 1

<table>
<thead>
<tr>
<th>N</th>
<th>apo B-LDL-C Pearson Correlation Coefficient (95% CI)</th>
<th>Predicted LDL-C (mg/dL) at apo B=0 mg/dL (95% CI)</th>
<th>apo B-non-LDL-C Pearson Correlation Coefficient (95% CI)</th>
<th>Predicted non-LDL-C (mg/dL) at apo B=0 mg/dL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>302</td>
<td>0.77 (0.72, 0.81) (0.60)</td>
<td>124.1 (94.8, 154.2)</td>
<td>0.88 (0.85, 0.91) (0.78)</td>
</tr>
<tr>
<td>EZE 10 mg</td>
<td>291</td>
<td>0.77 (0.72, 0.82) (0.60)</td>
<td>120.5 (91.5, 150.0)</td>
<td>0.86 (0.83, 0.89) (0.74)</td>
</tr>
<tr>
<td>Pooled SIMVA</td>
<td>1193</td>
<td>0.87 (0.85, 0.89) (0.75)</td>
<td>119.3 (98.8, 150.1)</td>
<td>0.87 (0.85, 0.89) (0.75)</td>
</tr>
<tr>
<td>Pooled EZE/SIMVA</td>
<td>1204</td>
<td>0.87 (0.85, 0.89) (0.75)</td>
<td>119.0 (97.4, 150.6)</td>
<td>0.87 (0.85, 0.89) (0.75)</td>
</tr>
<tr>
<td>Week 12 (following randomized treatment)</td>
<td>302</td>
<td>0.80 (0.76, 0.84) (0.64)</td>
<td>112.2 (76.8, 147.5)</td>
<td>0.90 (0.87, 0.92) (0.81)</td>
</tr>
<tr>
<td>EZE 10 mg</td>
<td>291</td>
<td>0.82 (0.78, 0.85) (0.67)</td>
<td>101.4 (73.9, 128.9)</td>
<td>0.91 (0.86, 0.95) (0.82)</td>
</tr>
<tr>
<td>Pooled SIMVA</td>
<td>1193</td>
<td>0.84 (0.81, 0.87) (0.70)</td>
<td>85.3 (72.8, 118.2)</td>
<td>0.94 (0.90, 0.98) (0.89)</td>
</tr>
<tr>
<td>Pooled EZE/SIMVA</td>
<td>1204</td>
<td>0.90 (0.86, 0.94) (0.82)</td>
<td>78.5 (51.8, 105.2)</td>
<td>0.95 (0.92, 0.96) (0.91)</td>
</tr>
</tbody>
</table>
Earlier senescent phenotype in Tangier disease skin fibroblasts

M. Puntoni, F. Bigazzi, A. Ragusa, S. Vacari, E. Grisanti, F. Strana, T. Sampietro, Gabriele Monasterio Foundation-CNR Region Toscana, Institute of Clinical Physiology, Pisa, Italy

Purpose: Tangier disease (TD) is characterized by virtual absence of high density lipoprotein (HDL) in plasma; TD patients are at increased risk for coronary artery disease (CAD). A relationship between cellular senescence and development of atherosclerotic CAD has been proposed and increased senescence in TD fibroblasts has been reported. We investigated replicative senescence of skin fibroblasts in vitro in an Italian homogeneous case of ABCA1 mutation (TDho) and his heterozygous father (TDhe).

Methods: Primary TDho and TDhe fibroblast cell lines, established from skin biopsies, were cultured according to the standard conditions. The cells were passaged by split to increase cumulative population doubling level. At the same passages of culture (early, intermediate and late) in TDho and TDhe fibroblasts, we analysed the expression of the particular isoform senescent-associated β-galactosidase (SA-β-gal). Furthermore, gene expression of ABCG1 and LDLr in involved in the cholesterol efflux and influx were analyzed at the same passages.

Results: TDho fibroblasts expressed the phenotype associated to senescence such as slow cell proliferation and increased staining for SA-β-gal compared to TDhe fibroblasts. TDho and TDhe cells were mildly stained with SA-β-gal at passage 8 (22.84% vs 20.35% respectively) and passage 17 (36% vs 29.62% respectively). The percentage of SA-β-gal positive cells was highly increased in TDhe at passage 22 compared to TDhe cells (66.15% vs 41.35% respectively). TDho fibroblasts expressed ABCG1 gene significantly more than TDhe cells, especially in first replication cycles (0.44 vs 0.14 arbitrary unit respectively) with a down-regulation at higher cycles (0.14 vs 0.08 arbitrary unit respectively). LDL expression showed small differences and an up-regulation in TDho and TDhe fibroblasts at higher replicative cycles (38.4 vs 34.3 arbitrary unit respectively) compared to replication cycles (15.4 vs 13.6 arbitrary unit respectively).

Conclusions: TDho fibroblasts showed accelerated senescence in vitro in a gene dosage way. These data highlight the need for further studies on the relationship between altered HDL metabolism, senescence and CAD in TD.

Heart rate reduction restores aortic compliance in apolipoprotein E deficient mice

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Background: Impaired vascular compliance is associated with cardiovascular risk and mortality. The effects of heart rate on vascular elastic properties are unclear. We characterized effects of heart rate reduction (HRR) by I(f) current inhibition on aortic compliance in apolipoprotein E deficient (Apoe-/-) mice.

Methods and Results: Male ApoE-/- mice fed a high-cholesterol diet were treated with ivabradine (IVA, 20 mg/kg/d) or vehicle for 6 weeks. IVA reduced heart rate (-48%) of the AT1 receptor and reduced Rac1 GTPase activity (-60%) by anti-inflammatory effects by reduction of aortic mRNA expressions of interleukin-6 (38% ±15%) and TNFα (p<0.05 for all comparisons).

Conclusions: Heart rate reduction induced by I(f) current inhibition restores aortic compliance in ApoE-/- mice. The underlying mechanisms include reduced AT1 receptor expression, vascular inflammation and Rac1 activity, reduced Rac1 activity and p47 phospho translocation. The results underline the importance of heart rate as a vascular risk factor.

Circling PCSK9 levels and additional LDL cholesterol-lowering after standard dose atorvastatin therapy: comparison with doubling dose and azetromine combination


Background: PCSK9 plays a pivotal role in LDL receptor mediated cholesterol metabolism. However, little is known about the clinical significance of its circulating levels during cholesterol-lowering therapy. To clarify this, relations between circulating PCSK9 levels and additional cholesterol-lowering after standard atorvastatin therapy was investigated in randomized comparative study by doubling its dose and ezetimibe combination.

Methods: Consecutive 27 patients (M:F=22:5) in whom JAS guideline target (LDL 100mg/dL & nonHDL 130mg/dL) was not achieved with atorvastatin 10mg were randomly assigned to doubling dose (DD) (n=14) or adding ezetimibe 10mg (EZ; n=13).

Results: After 6-months treatment, in DD group, TC changed from 189 (mean) to 173 (-9%) (p<0.05), LDL from 112 to 98 (-13%) (p<0.05), nonHDL from 144 to 127 (-12%) (p<0.01). In EZ group, TC changed from 192 to 154 (-25%) (p<0.01), LDL from 109 to 78 (-29%) (p<0.05), nonHDL from 143 to 109 (-23%) (p<0.01). Both absolute and % changes of LDL significantly differed (p=0.04) between 2 groups. Despite that PCSK9 heterodimer and free fragment in DD and EZ were both similar before randomization, levels of heterodimer, free fragment and total homodimer, showed significant and positive association with additional LDL reduction (r=0.576, p=0.039) in DD group, while these 2 forms did not show any association with LDL reduction in EZ group.

Conclusion: In patients receiving atorvastatin standard dose, PCSK9 heterodimer levels could predict additional LDL-lowering response to doubling dose.

Renal mass reduction decreases the synthesis and catabolic rates of cholesterol esters of high density lipoproteins (HDL) in vivo

J.E. Carreon-Torres, M. Luna-Luna, M. Franco, G. Vargas-Alarcon, O. Perez-Mendez. Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico

Purpose: To establish the kinetic basis of HDL-cholesterol esters enrichment previously demonstrated by our group in an animal model of functional renal mass reduction.

Methods: New Zealand rabbits were randomized into nephrectomized (Nx, n=6) and control groups (n=6). The animals assigned to Nx group were subjected to nephrectomy 75% by surgical resection and the control group was subjected to sham operation. Six weeks after nephrectomy, the CE kinetics studies were performed. Animals received HDL containing 1.0x10^5 cpm of [3H]-labelled CE by injection into the marginal ear vein. Blood samples were obtained at 5 min after injection and at different intervals up to 5 h. The radioactivity was measured in isolated fractions of VLDL/LDL and HDL that were separated by ultracentrifugation. Data were analyzed using multi-compartmental analysis and fitted to a 3-compartmental model: Fractional catabolic rates (FCR) were computed by fitting the percentages of initial radioactivity kinetics to a biexponential function (SAAM II software). 3H-CE-HDL production rates (PR) were determined using the formula [PR=FCR x plasma CE concentration(mg/L) x total plasma volume(L)/body weight (kg)].

Results: Our kinetic model considered that CE were removed from plasma via both, the HDL and LDL fractions and that CE were dynamically exchanged between such fractions. The fluxes between HDL and VLDL/LDL were same in both groups. However, the CE transfer from VLDL/LDL as HDL particles was significantly higher compared to control group [1.48±0.84 versus 4.21±1.56 mg/dL/min, respectively, p<0.05]. The flux of removal from CE via VLDL/LDL fractions was 0.13±0.10, and it was significantly different from untreated animals, (9.9±0.3 x 10^4/mg/dL/min, p<0.05). These results also showed that FCR of CE were significantly lower in nephrectomized rabbits, as compared with control group (0.16±0.05 versus 0.31±0.09 p<0.01, respectively, p<0.05). These changes were associated to a similar decrease in the PR (7.5±0.85 versus 2.22±0.89 mg/dL/min, p<0.05). The CE-FCR and PR associated with an increase in the cholesterol-HDL plasma concentration in the Nx group (30±2.25 mg/dL) as compared with control group (20.7±2.2 mg/dL, p<0.05).

Conclusions: The renal mass reduction results in important cholesterol esters

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accretion in the HDL particles. The kinetic basis of such accretion was an increased exchange of cholesterol esters from apoB-containing lipoproteins towards HDL. These results strongly suggests an important role of the kidneys to HDL-cholesterol metabolism.

**P1748**

The release of sphingosine-1-phosphate from human platelets during acute coronary syndrome is attenuated by aspirin

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**Purpose:** The sphingosine-derived lipid signaling molecule sphingosine-1-phosphate (S1P) is an important mediator of vascular homeostasis. It is stored in large quantities in platelets. Recently, we have shown that its release from platelets after activation of the protease-activated receptor-1 (PAR-1) by thrombin is dependent on thrombospondin (TX) formation. In the present study, we aimed to translate our in vitro-findings to a clinical setting and to determine if administration of the cyclooxygenase inhibitor aspirin (acetylsalicylic acid) affects the release of S1P in patients with an acute coronary syndrome (ACS). Second, by means of anti-thrombin-antithrombin (TAT)-complexes, we examined if an ACS leads to an enhanced intravascular thrombin formation. We hypothesized that administration of 500 mg aspirin during acute coronary syndrome inhibits the release of S1P from human platelets.

**Methods:** Blood samples were taken from patients with ACS before and after intravenous treatment with 500 mg aspirin. S1P was quantified in platelet-rich plasma (PRP), platelet-poor plasma (PPP) and washed platelets (WP) by mass spectrometry; TAT-complexes by ELISA. Patients characteristics were as follows (n=22), age 60±10 years, 60% male, 3±2 cardiac risk factors. 40% were on a 100 mg aspirin pretreatment, 9% on a dual antiplatelet therapy with 100 mg ASA and 75 mg clopidogrel and 61% were aspirin naive. Age matched patients (n=10) with stable coronary syndrome (all on aspirin) were used as control group.

**Results:** The concentration of S1P before and after acute aspirin treatment did not differ in PRP (866±70 pmol/mL vs 927±82 pmol/mL). However, aspirin treatment significantly decreased S1P levels in PPP (621±51 pmol/mL vs 548±46 pmol/mL) and increased WP (10±26 pmol/mL vs 362±45 pmol/mL). The levels of S1P in PRP, PPP and WP from ACS patients were significantly lower than in patients with a stable CAD (PRP: 866±70 pmol/mL vs 1768±47 pmol/mL, PPP: 621±51 pmol/mL vs 1265±34 pmol/mL, WP: 199±25 pmol/mL vs 634±39 pmol/mL). Enhanced formation of thrombin in patients with ACS was confirmed by detection of increased plasma TAT-complexes (11.6±4.9 μg/L) versus control patients (33±2 μg/L).

**Conclusions:** Acute coronary syndrome leads to S1P release from human platelets. This can be attenuated by intravenous treatment with 500 mg aspirin. The clinical implications require further clarification.

**P1750**

Protective effects and mechanisms of baicalein on lysophosphatidylcholine-induced injury in cardiomyocytes

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**Background:** Lysophosphatidylcholine (LysPC), a metabolite from membrane phospholipids, accumulates in the ischemic myocardium and plays important role in the development of myocardial dysfunction and ventricular arrhythmia. Baicalein is a flavonoid extracted from the root of Scutellaria baicalensis Georgi, a medicinal plant traditionally used in oriental medicine. The aim of this study was to determine the protective effects and mechanisms of baicalein on LysPC-induced cell death in H9c2 cardiomyocytes.

**Methods:** We first examined the cellular survival rate by MTT assay. The in vitro-finding of baicalein on LysPC-inducible production of reactive oxygen species (ROS) were then determined by flow cytometry using DCFH-DA as a fluorescent substrate. The level of intracellular Ca2+ concentration was measured by spectrophotomter. Finally, we examined the role of baicalein on LysPC-induced apoptosis of H9c2 cells by investigating caspase families. Bcl-2 and Bax protein activities with immunoblotting.

**Results:** Results of the MTT assay and morphological observation showed that LysPC reduces the viability of H9c2 cells, and these were attenuated by baikalein. Pretreatment with baikalein significantly inhibited LysPC-induced Ca2+ influx and phosphorylation of mitogen-activated protein kinase in H9c2 cells. Furthermore, incubation of H9c2 cells with baikalein significantly decreased the intracellular peroxide and Ca2+ concentration levels induced by LysPC. In addition, baikalein increased expression of anti-apoptotic Bcl-2 protein, inhibited expres- sion of pro-apoptotic Bax protein and attenuated expression of caspase3/9 induced by LysPC.

**Conclusion:** These results indicate that baikalein possesses abilities to suppress to LysPC-induced model of cardiomyocyte cell death through inhibition of Ca2+ influx and ROS generation and inactivation of the caspase/Bax/Bcl-2 pathway. These findings suggest that baikalein may be valuable in the prevention of lipid-induced cardiac damage.

**P1751**

Association of apolipoprotein A-I/IV A347T gene polymorphism and low density lipoprotein cholesterol among north Indians

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**Background:** In studies conducted among various ethnic populations, an inverse association between serum levels of high density lipoprotein cholesterol (HDL-c) and the risk for cardiovascular events including myocardial infarction, stroke and mortality. It is also noteworthy that lower levels of HDL-c are prevalent among Indians, who also demonstrate highest incidences of coro- nary artery disease(CAD) among various populations around the world. These lower levels of HDL-c among Indians may be attributed to several genetic polymorphisms especially those in the apolipoprotein(Apo) A-IVIIA1AN gene cluster. Some workers have demonstrated the association of Apo AIV A347T gene poly- morphism with low levels of high density lipoprotein cholesterol(HDL-c), however studies among subjects of Indian ethnicity are lacking.

**Objectives:** The aim is to find out whether the Apo AIV A347T gene polymorphism and the levels of HDL-c among healthy individuals of north Indian ethnicity.

**Methods:** We prospectively enrolled 200 healthy individuals of north Indian ethnic- ity consented and sampled them for serum lipids and subsequent genotyping. Genotyping technique used was standard polymerase chain reaction-restriction fragment length polymorphism (PCR/RFLP).

**Results:** A total of 163 (81.5%) of the subjects were males, mean age 44.5±33.38 years. Among CAD risk factors, a total of 44 (22%) were smok- ers, 83 (46.8%) hypertensives, 13 (6.5%) diabetics and 13 (6.5%) had family history of CAD. We found 19 (9.5%) homozygous mutant(TT), 75 (37.5%) het- erozygous(AG) and 106 (53%) of wild type(AA) genotypes in our sample. The results were found consistent with Hardy-Weinberg proportions. We found no significant difference in mean levels of total cholesterol(TC), low density lipoprotein cholesterol(LDL-c) and triglycerides(TG) among wild and mutant genotypes(p>0.05). Significant lower levels of serum HDL-c was seen among subjects carrying mutant genotypes(TT or AT) as opposed to wild type gene-
ApoB/apoA-I ratio and atherogenic index of plasma (AIP) in supposedly healthy individuals, students at a public university.

**Methods:** We included 110 students, with 44% male and 56% female, mean age of 20.9±1.7 years. Their blood pressure was measured in repose state. Anthropometric measurements such as height, weight, BMI, waist, and hip circumference were performed. Statistical analysis was performed by Student test after logarithmic transformation of data. The Pearson correlation test was used to verify the correlation between continuous variables.

**Results:** Cholesterol total, LDL and HDL were significantly higher in women than in men (p<0.001). No significant differences were observed between men and women for apoB/apoA-I ratio, LDL, triglyceride or apoB levels. The means obtained for apoB/apoA-I index and AIP were 0.62±0.35 and 0.09±0.09, respectively. AIP values were significantly lower (p=0.002) in females (0.033±0.009) when compared with men (0.038±0.010). Positive and significant correlations were observed between apoB/apoA-I ratio and BMI (r=0.25; p<0.04), abdominal circumference (r=-0.25; p=0.04) and LDL (r=-0.67; p<0.001). Both were also observed positive correlations between AIP and triglycerides (r=0.46; p<0.001) and between AIP and LDL (r=0.33; p<0.006). Negative and significant correlations were obtained between apoB/apoA-I ratio and HDL (r=-0.57; p<0.001), and between AIP and HDL (r=-0.86; p<0.001).

**Conclusions:** These findings indicate that apoB/apoA-I ratio showed a higher correlation with LDL than the AIP in studied subjects. Becomes necessary to consider that LDL, a parameter not used to calculate the lipid indices studied is widely used in clinical practice for cardiovascular risk assessment. Additional consideration that LDL, a parameter not used to calculate the lipid indices studied was also observed positive correlations between AIP and triglycerides (r=0.46; p<0.001) and between AIP and LDL (r=0.33; p<0.006). Negative and significant correlations were obtained between apoB/apoA-I ratio and HDL (r=-0.57; p<0.001), and between AIP and HDL (r=-0.86; p<0.001).

**Purpose:** Lipoprotein ratios can provide better information about metabolic and clinical interactions between lipid fractions than isolated LDL cholesterol levels. Apolipoprotein B (apoB)/apolipoprotein A-I (apo-A1) ratio and Atherogenic Index of Plasma (AIP) reflects the balance between atherogenic and protective particle. Additional consideration that LDL, a parameter not used to calculate the lipid indices studied was also observed positive correlations between AIP and triglycerides (r=0.46; p<0.001) and between AIP and LDL (r=0.33; p<0.006). Negative and significant correlations were obtained between apoB/apoA-I ratio and HDL (r=-0.57; p<0.001), and between AIP and HDL (r=-0.86; p<0.001).

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The "early repolarisation" phenomenon: association with other cardiovascular findings in middle-aged long distance runners

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Background: Although many echocardiographic studies are available about the adaptation of left ventricle to intensive training, right heart function has been poorly investigated in top level athletes and no data are available about the functional role of right atrium (RA). The aim of this study is to investigate RA function and dimension by standard echocardiography and by 2D speckle tracking echo-cardiography (STE).

Methods: From professional sports team 100 top-level athletes were recruited and compared with 78 controls. Athletes in an off-training period or during prolonged forced rest resulting from injuries were excluded from the study.

Results: Top-level athletes showed higher BSA as compared with controls and a lower resting heart rate (p ≤ 0.001). RA area and volume were significantly greater in athletes than in controls (p ≤ 0.001) and a significant difference was observed also when RA volume was indexed to BSA (20.96 ± 7.28 vs 19.89 ± 4.99, p < 0.001). Athletes exhibited greater right ventricular and inferior vena cava diameters (p < 0.001). A typical pattern of myocardial deformation dynamics was observed in athletes, with a lower peak atrial longitudinal strain (40.92 ± 8.86 vs 48.00 ± 12.68, p < 0.001) and a lower peak atrial contraction strain (13.05 ± 4.84 vs 15.99 ± 5.74, p < 0.001) in comparison with controls. Interestingly, while athletes presented a higher E/A ratio (p < 0.001), the E/e' ratio did not differ between the two groups.

Conclusions: Top-level athletes present a physiological remodeling of the RA associated with intensive training that encompasses not only a morphological but also a functional adaptation. We reported for the first time reference values of RA strain in athletes, demonstrating that 2D STE is a useful tool to investigate RA function in the athlete’s heart.

LAmax [mL/m2]:
- Athletes: 16.6 ± 5.4 mL/m²
- Controls: 14.2 ± 4.9 mL/m²

LAmin [%]:
- Athletes: 55.3 ± 3.1%
- Controls: 53.5 ± 3.6%

EF [%]:
- Athletes: 58.0 ± 3.9%
- Controls: 58.0 ± 3.9%

TVI [%] (m/s):
- Athletes: 6.7 ± 1.2 m/s
- Controls: 6.7 ± 1.2 m/s

FS [%]:
- Athletes: 27.7 ± 3.9%
- Controls: 27.7 ± 3.9%

GLS [%]:
- Athletes: 18.4 ± 1.7%
- Controls: 18.4 ± 1.7%

MIP [%]:
- Athletes: 0.36 ± 0.20%
- Controls: 0.40 ± 0.06%

HR (beats/min):
- Athletes: 70.7 ± 6.8
- Controls: 68.9 ± 6.8

*Significantly different from LAmin (p < 0.05).

Figure 1. Typical pattern of RA strain by 2D STE

Conclusions: The "early repolarisation" phenomenon: association with other cardiovascular findings in middle-aged long distance runners

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Characterization of right atrial function and dimension in top-level athletes: a speckle tracking study

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1University of Siena, Department of Cardiovascular Diseases, Siena, Italy; 2Santa Maria alle Scuole Polyclinic, Department of Cardiovascular and Thoracic Cardiology Division, Siena, Italy; 3Staff Siena Football Club, Siena, Italy

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Conclusions: The "early repolarisation" phenomenon: association with other cardiovascular findings in middle-aged long distance runners

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Different LV systolic function in Norwegian elite football players with large and small left atrial volumes

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Purpose: Previously we have shown that a threefold difference in LA volume did not affect LA global systolic function by 2D strain. Since this enlargement also leads to larger LV volume and thus total volume (LVTV on the left side, we wanted to explore any potential impact on LV systolic function.

Methods: From our database of 595 male Norwegian football players, the 30 football players with respectively the largest and smallest left atrial end systolic volumes (LAESV) were defined. LV end diastolic volume (LVEDV) was measured by 2D echo and LVTT was calculated as LAESV + LVEDV. The following measurements of LV systolic function were performed: Biplane LVEF by 2D, maximal atrial rate of septal and lateral mitral valves attachments by TVI, denotes TVVs, fractional shortening (FS) by M-mode, LV global longitudinal strain (GLS) by automated function imaging. LV myocardial performance index (MPI) was measured as a combined global parameter for LV systolic and diastatic function. All volumes were indexed by body surface area (BSA).

Results: All four echo indices for LV systolic and MPI were improved in athletes with large vs. small LAESV (Table). Moreover, EF, FS, TVI, GLS and MPI, correlated significantly to LTV with r values of 0.3, 0.5, 0.4, 0.3 and -0.3 (all p < 0.05), respectively. HR correlated only to FS, r = -0.3, and to MPI, r = 0.4 (both p < 0.05).

Table 1: Different LV systolic function in Norwegian elite football players with large and small left atrial volumes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Large LAESV</th>
<th>Small LAESV</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EDV/BSA (mL/m²)</td>
<td>85.3 ± 16.6</td>
<td>60.6 ± 7.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVTT/BSA (mL/m²)</td>
<td>145.1 ±16.4</td>
<td>80.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EF (%)</td>
<td>58.0 ± 3.9</td>
<td>55.3 ± 3.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TVVs (cm/s)</td>
<td>7.4 ± 1.2</td>
<td>6.7 ± 1.2</td>
<td>0.35</td>
</tr>
<tr>
<td>FS (%)</td>
<td>32.4 ± 2.6</td>
<td>27.7 ± 3.9</td>
<td>0.01</td>
</tr>
<tr>
<td>GLS (%)</td>
<td>19.5 ± 1.2</td>
<td>18.4 ± 1.7</td>
<td>0.11</td>
</tr>
<tr>
<td>MPI</td>
<td>0.36 ±0.20%</td>
<td>0.40 ±0.06%</td>
<td>0.01</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70.7 ± 6.8</td>
<td>68.8 ± 6.8</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Significantly different from LAmin (p < 0.05).
Electrocardiograms in young athletes, characteristics and prevalence of abnormalities

M. Di Valenzo1, P. Siragusa2, M. Maggi2, G.A. Romanò2, R. Pezzoli1, G. Moschovitis1, A. Galloni1, A. Menafoglio1,1 Hospital Garcia de Orta, Department of Cardiology, Almada, Portugal; 2Hospital Espírito Santo, Évora, Portugal; 3University of Siena, Department of Cardiovascular Diseases, Siena, Italy; 4Staff Siena Football Club, Siena, Italy; 5Santa Maria alle Scotte Policlinic, Department of Cardiovascular and Thoracic, Siena, Italy.

Purpose: Regular physical training is associated with structural and functional changes in the heart which are reflected on the 12-lead electrocardiogram (ECG). Such changes may simulate cardiac diseases rendering ECG interpretation of young athletes sometimes difficult. The aim of this study is to evaluate the ECG characteristics and the prevalence of ECG abnormalities in a cohort of young athletes.

Methods: ECG was analysed as part of an ongoing prospective study on the impact of cardiovascular screening with ECG in young (14-35 years) competitive athletes. ECG was interpreted according to the 2010 recommendations of the European Society of Cardiology (adapted) distinguishing common (physiologic) and uncommon (abnormal) changes.

Results: ECG of 920 athletes was analysed (75% males, age 19.6±6.5 years). The following common ECG changes were present: sinus bradycardia in 50 bpm in 10.2%, ectopic atrial rhythm in 4.2%, prolonged (> 200 msec) PR interval in 3.3%, incomplete right bundle branch block in 9.6%, voltage criteria (Sokolot-Lyon) for left ventricular hypertrophy in 16.7%, for right ventricular hypertrophy in 2.5%, a wave in inter-atrial leads in 34.6%. There were also 0.4% of Brugada type 1 (torso 3.8% and left 0.5%) and 0.2% of Brugada type 2 (torso 0.5% and left 0.5%). Atrial premature beats (< 1/ECG trace) in 0.5%, left axis deviation in 0.4%, Wolff-Parkinson-White pattern in 0.3%, prolonged QT interval (> 470 msec in men, > 480 msec in women) in 0.2%, abnormal Q-waves in 0.1%, right axis deviation in 0.1%, left atrial San Giovanni, Department of Cardiology, Bellinzona, Switzerland.

Conclusions: As has been reported, common ECG changes of young athletes are frequent. Following the European Society of Cardiology recommendations (adapted), the abnormal ECG are relatively rare rendering ECG a useful tool to the evaluation of young athletes.

P1761 Longitudinal variations of left ventricular mass and fat-free mass after intensive training in top-level athletes

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Background: Several echocardiographic studies have demonstrated that left ventricular mass (LVM) is increased in athletes. However, the difference in LVM between athletes and controls was due not only to training but also to body composition.

Methods: Twenty-three male top-level soccer players were recruited. LVM was assessed by echocardiography and body composition by DXA. Serial measurements were performed: at the beginning of the season, after 1, 4, and 8 months. Ten athletes a further evaluation was performed after 3 months of detraining.

Results: During the regular season, LVM significantly increased after 4 months and this variation remained significantly different between baseline and 8-month measurement (195.04±25.84 vs 213.51±22.86 g, p<0.05). The change in LVM was confirmed also when LVM was indexed to BSA or to FFM (p<0.05). While body surface area did not vary during the study period, FFM significantly increased during the study period with a significant difference between baseline and 8-month measurement (64.3±9.57 vs 66.27±9.46 g, p<0.05). Heart rate, stroke volume (SV) and left ventricular end-diastolic volume (LVEDV) increased during the season, reaching the highest values after 4 months. Interestingly, in the cohort of subjects not engaged in a regular training for 2 months after the end of the season, no significant differences were demonstrated between echocardiographic parameters collected at the beginning of the season and values obtained at the end of detraining. FFM and SV were independent predictors of LVM.

Conclusions: The present study reported for the first time the longitudinal variations of LVM and FFM in a selected cohort of top-level athletes engaged in an intensive training program, demonstrating that athletes exhibit a significant remodeling of the left ventricle and of the body mass during the entire regular season. Three months of detraining at the end of the season were able to determine a decrease of LV parameters to baseline values.

Screening of anomalous origin of the coronary artery in athletes: role of echocardiography and coronary computed tomography angiography

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Purpose: Evaluate the role and efficacy of Transthoracic echocardiography (TTE) and coronary computed tomography angiography (coronary CTA) in the screening of anomalous origin of the coronary artery (AOCA) in athletes. AOCA is a rare disease, but is the second leading cause of sudden death in athletes under 35 years old. These anomalies are rarely suspected or identified during life and are usually first recognized at autopsy, largely because there is insufficient clinical suspicion as well as the difficulties implicit in routine examination or clinical testing.

Methods: From 2002 to 2011, 11 years, 27,611 athletes underwent TTE. Twenty-three young athletes were referred for TTE because of chest pain, exertional dyspnea or syncope. Coronary CTA was performed in 13 of these athletes who confirmed the diagnosis or when TTE was inconclusive, especially if there was high clinical suspicion.

Conclusions: TTE is a noninvasive method effective in identifying coronary artery origin and initial course in most of the athletes. Coronary CTA can be used to confirm the diagnosis or when TTE is inconclusive, especially if there is high clinical suspicion.
ACUTE AND CHRONIC EFFECTS OF EXERCISE TRAINING

P1763 The interplay of exaggerated blood pressure response and delayed blood pressure recovery after graded exercise as predictor of incident arterial hypertension
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Purpose: Exaggerated blood pressure (BP) response to exercise and delayed BP decline at recovery after exercise have emerged as independent predictors of future arterial hypertension (AH). The aim of this study was to test the hypothesis that the combination of the 2 prognostic measures provides an additive predictive value for AH than its components.

Methods: A total of 374 normotensive individuals undergoing a diagnostic treadmill exercise testing were followed for new-onset AH during a 5-year period. A change in systolic BP from rest to peak exercise >65mmHg and a ratio of systolic BP at 30 min of recovery to peak exercise ≥0.90 (representing the 75th percentiles for the population) were considered as exaggerated BP response and delayed BP recovery, respectively. Cox regression analysis was applied to estimate the relative risk (RR) of AH and the 95% confidence intervals (CI) in patients positive for one or both exercise prognostic markers after adjusting for age, gender, family history, obesity, smoking and resting BP.

Results: New-onset AH was detected in 41 participants (11.0%). The 5-year incidence of AH was 3.6% for subjects with normal BP response and recovery (n=195), 16.7% for individuals with exaggerated BP response and normal BP recovery (n=84), 17.3% for those with normal BP response and delayed BP recovery (n=81) and 42.9% for participants with both abnormal BP response and recovery (n=14). The adjusted RR for AH in the last group was 2.48 (95%CI: 1.14-4.97; p=0.038) compared to individuals with exaggerated BP response and normal BP recovery and 2.18 (95%CI: 1.03-4.72; p=0.047) compared to subjects with normal BP response and delayed BP recovery.

Conclusions: The combination of abnormal BP response and BP recovery after graded exercise is stronger predictor of AH than its components.

Figure 1

P1765 Role of cardiopulmonary dysfunction and left atrial remodeling in development of acute decompensated heart failure in chronic heart failure with preserved left ventricular ejection fraction

Purpose: The presence of heart failure (HF) with preserived ejection fraction (HFPEF) is increasingly recognized. However, prognostic factors of HFPEF still remain unclear. In the present study, we aimed to clarify the predictive determinants of HFPEF focusing on cardiopulmonary function during exercise.

Methods: The data was derived from a single hospital-based cohort in the Shinken Database 2004-2010, a prospective cohort study comprising all the new patients who had visited our institute (n=15227). We defined HFPEF when a patient has symptomatic heart failure (New York Heart Association functional class II or greater) and preserved left ventricular (LV) ejection fraction (LVEF) (>55%). We examined 301 consecutive HFPEF patients and tracked them for average 3.5 years. Cardiopulmonary exercise testing (CPX), blood exams, and ultrasound cardogram (UCG) were performed at the first medical examination.

Results: Acute decompensated HF (ADHF) admission was observed in 19 patients (6.3%). There were no significant differences between the patients with ADHF and those without it in sex, body-mass index, serum hemoglobin level, prevalence of hypertension, dyslipidemia, diabetes mellitus and medications. Patients with ADHF admission tended to be older than those without (68.3±14.0 vs. 64.0±11.2years, p=0.113). Serum brain natriuretic peptide (BNP) level also tended to be higher in patients with ADHF admission than those without (329±254 vs. 208±314pg/mL, p=0.120). CPX showed that peak O2 uptake (VO2) tended to be lower in patients with ADHF admission than those without (13.2±4.3 vs. 15.2±4.9ml/min/kg, p=0.056). The anaerobic threshold (AT) was significantly lower (7.3±4.8 vs. 9.7±4.3ml/min/kg, p=0.02) and slope of the increase in ventilation to the increase in CO2 output (VE/VO2 slope) was significantly higher (40.6±5.8 vs. 34.6±7.9, p<0.01) in patients with ADHF admission than those without ADHF admission. UCG showed that left atrial (LA) dimension was significantly greater (47.0±15.8 vs. 41.0±9.9mm, p=0.01) in patients with ADHF admission than those without. Multivariate analysis showed that higher VE-VO2 slope and greater LA dimension were independent determinants of ADHF admission.

Conclusions: A higher VE-VO2 slope and greater LA dimension were associated with ADHF admission in patients with symptomatic HFPEF, suggesting the prognostic role of cardiopulmonary dysfunction during exercise as a remodelaring in the pathogenesis of decompensated HF development in HFPEF.

Figure 1

P1764 The interplay of delayed blood pressure and heart rate recovery after graded exercise as predictor of incident coronary artery disease
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Purpose: Delayed blood pressure (BP) and heart rate (HR) recovery after exercise have emerged as independent predictors of incident coronary artery disease (CAD). The aim of this study was to test the hypothesis that the combination of the 2 prognostic measures provides an additive predictive value for CAD than its components.

Methods: A total of 830 non-CAD patients (mean age 54 years, 66% males) were followed for new-onset CAD for 5 years after a diagnostic treadmill exercise testing (ET). A 30 min of recovery systolic BP to peak exercise ratio <0.90 (4th quartile) and a difference between peak HR and HR at the 1st min of recovery >32bpm (1st quartile) were considered as delayed BP and HR recovery, respectively. At the end of follow-up, patients without overt CAD underwent a 2nd diagnostic ET. Stress imaging modalities and coronary angiography, if necessary, were performed for ruling out CAD. Cox regression analysis was applied to estimate the relative risk (RR) of CAD and the 95% confidence intervals (CI) in patients positive for one or both exercise predictors.

Results: New-onset CAD was detected in 110 patients (13.3%). The 5-year incidence of CAD was 7.5% for subjects with normal BP and HR recovery (n=465), 16.0% for individuals with delayed BP and normal HR recovery (n=156), 18.2% for those with normal BP and delayed HR recovery (n=137) and 34.7% for participants with both abnormal BP and HR recovery (n=72). The adjusted (for potential covariates) RR for CAD in the last group was 1.95 (95%CI:1.28-2.98; p=0.011) compared to individuals with delayed BP and normal HR recovery and 1.71 (95%CI:1.08-2.75; p=0.014) compared to subjects with normal BP and delayed HR recovery.

Conclusions: The combination of abnormal BP and HR recovery after graded exercise is stronger predictor of CAD than its components.

Figure 1

P1766 The systolic blood pressure vs oxygen consumption slope at the cardiopulmonary exercise test predicts carotid atherosclerosis
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Purpose: Exercise-induced hypertension (EX-HTN), defined as a peak of systolic blood pressure (SBP) during exercise greater than 210 mmHg in men and 190 mmHg in women (Framingham criteria), is a marker of subclinical target organ damage in several studies. The slope of SBP increase related to oxygen consumption (ΔSBPΔVO2) is a new cardiopulmonary exercise test (CPET) parameter describing the BP level at any given metabolic rate. An abnormally steep
P1768 Change in mid-regional proadrenomedullin as a surrogate of change in peak oxygen uptake after training in patients with heart failure
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Purpose: Increased peak oxygen uptake (VO2) after exercise training in CHF patients is associated with an improvement in outcome. Among other effects, training improves arterial vasodilation and decreases inflammation.

Methods: We aimed at studying if the improvement in peak VO2 with training was associated with a parallel decrease in Mid-regional proAdrenomedullin (ProADM), a new plasma biomarker related with prognosis in heart failure.

Three groups of patients underwent a cardiac rehabilitation program. 23 CHF pts, LVEF < 40% (group 1); 34 patients with CAD and LVEF > 40% (group 2) and 10 patients after cardiac surgery with LVEF > 40% (group 3). Baseline values of proADM (pmol/L) were 0.85±0.31, 0.61±0.26 and 0.60±0.17 in groups 1, 2 and 3 respectively (p<0.01 by ANOVA). NT-proBNP (ng/L) values were 3445±4309, 930±1460 and 617±469 in groups 1, 2 and 3 respectively.

Results: NT-proBNP values decreased after training in all groups. ProADM decreased significantly after training only in group 1 (0.66±0.17, 0.57±0.12, 0.60±0.21 in groups 1, 2 and 3 respectively). Peak VO2 increased in all groups. Interestingly, figure, there was a close correlation between the changes in ProADM and in peak VO2 (r<0.00, p=0.045) and not significant in the others.

Conclusions: Physical training improved peak VO2 and biomarkers in CHF. The decrease in proADM seems to be specific to the CHF group. The tight correlation probably reflects the profound vasodilatory and anti-inflammatory effect of training in these patients. Moreover, changes in proADM may perhaps serve as surrogate for changes in peak VO2, a profound positive prognostic marker, in these patients.
Right ventricular systolic dysfunction is an independent predictor of reduced exercise capacity in patients after myocardial infarction
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Background: Right ventricular (RV) dysfunction reduces exercise capacity (EC) in patients with left ventricular (LV) dysfunction in chronic heart failure and causes poor prognosis. Data on the impact of RV dysfunction on EC in patients after inferior myocardial infarction (MI) with preserved LV function are scarce.

Aim: To assess influence of RV dysfunction on EC in patients with MI and preserved LV systolic function.

Methods: We prospectively enrolled 90 consecutive patients admitted to our department with the first ST-elevation inferior MI and preserved LV systolic function (EF > 45%). All included patients were treated by primary percutaneous coronary angioplasty. In a fixed pulse Doppler echocardiography systolic (Sm) and early diastolic (Em) myocardial velocities were assessed. RV systolic dysfunction was defined as RV Sm < 11.5 cm/s at the basal segment of RV free wall. Cardiopulmonary exercise test was done on day 14±10. We used a regression model to analyze the following variables for potential influences on EF: gender, age, body mass index, physical activity before MI, diabetes mellitus/impaired glucose tolerance, hypertension, smoking, LV ejection fraction, wall motion score index, maximal troponin concentration, RV Sm, RV Em, LV Sm and early transmitral inflow velocity to LV Em ratio. Parameters with no influence on EC were removed from the model (p > 0.1).

Results: According to the multivariate regression analysis independent factors that negatively influenced EC were: RV systolic dysfunction, female gender, age, lower body mass index, current smoking and maximal troponin I concentration (Table). Variables related to peak VO2 (L/min)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (β)</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right ventricular systolic dysfunction</td>
<td>-0.161 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-0.283 to 0.038</td>
<td>0.011 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Gender female vs male</td>
<td>-0.676 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-0.820 to -0.532</td>
<td>&lt;0.001 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Age (in decades)</td>
<td>-0.270 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-0.320 to -0.220</td>
<td>&lt;0.001 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.033 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.036 to 0.041</td>
<td>0.010 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Diabetes mellitus/impaired glucose tolerance</td>
<td>0.015 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.003 to 0.030</td>
<td>0.001 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Current smoker vs never/past smoker</td>
<td>-0.208 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-0.345 to -0.072</td>
<td>0.003 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Troponin I maximal concentration (at every 10 ng/ml)</td>
<td>-0.020 β&lt;sub&gt;1&lt;/sub&gt;</td>
<td>-0.054 to 0.002</td>
<td>0.055 β&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Conclusion: Presence of RV systolic dysfunction in acute MI independently decreases EC in patients without significant LV dysfunction.

Anti-inflammatory properties of HDL after short-term exercise training in patients with metabolic syndrome
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Background: Recent study showed that short-term exercise, associated with diet and weight loss, improves the anti-inflammatory properties of HDL in metabolic syndrome (MS). However, diet and weight loss, per se, can alter the functionality of HDL and, in real life, many patients do not follow the medical counseling of diet and exercise simultaneously.

We showed previously that the antioxidant characteristics and the capacity to accept lipids of HDL are early improved by short-term exercise training (Tr) with no diet associated.

We sought to verify whether the anti-inflammatory properties of HDL are affected by Tr, without any diet associated, in patients with MS.

Methods: Forty sedentary persons (30 with MetS,10 controls) were evaluated. Twenty of those with MS were subjected to a 3 times/week training load (45 min/day) for 3 months on a bicycle. Plasma high-sensitivity C-reactive protein (hs-CRP) was analyzed and HDL subfractions were obtained by plasma ultracentrifugation. Endothelial cells were cultured, stimulated with TNF-α and lipopolysaccharide, and coincubated with HDL subfractions obtained before and after Tr. Sequentially, the cultures of endothelial cells were coincubated with THP-1 cells labeled with a fluorescent marker. The labeled THP-1 cells that adhered on endothelial cells were counted under fluorescent microscope.

Results: Baseline plasma levels of HDL-C were lower in the MS group compared to controls and Tr did not change neither HDL-C nor weight in MS group. Hs-CRP plasma levels from patients with MetS were higher than controls (3.0±1.5 vs 1.5±1.5 mg/L respectively; p < 0.05) and did not change after Tr (3.0±1.5 vs 2.8±1.8 mg/L, before and after Tr respectively; p > 0.05). The number of adhered labeled THP-1 cells coincubated with endothelial cells did not change significantly when mixed with HDL2a or HDL3b from patients with MS after Tr, compared with HDL2a or HDL3b obtained before Tr.

Conclusion: Our results showed that Tr did not change an inflammatory serum marker (hs-CRP) and the adherence of THP-1 cells on endothelial cells, suggesting that the anti-inflammatory properties of HDL are not early improved by short-term exercise, when there is no diet associated.

Effects of aerobic exercise and resistance exercise training on oxidative stress in patients with lifestyle-related disease
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Purpose: Oxidative stress plays important roles in pathophysiology of lifestyle-related diseases (LDR). However, little is known about the effects of aerobic exercise and resistance exercise on the antioxidant defense systems in patients with LDR. The purpose of the present study was to examine the effects of aerobic exercise and resistance exercise training on oxidative stress in patients with LDR.

Methods: The study subjects were consisted of 31 sedentary patients with LRD (mean age, 50.1 years), and divided into three groups including aerobic exercise training (AT: n=18), aerobic exercise training and resistance training (ART: n=7), and non-training (NET: n=7) group. Patients underwent bicycle ergometer exercise test to measure the estimated maximum oxygen consumption (eVO2max). Aerobic training (50% eVO2max) consisted of 30-60 minutes of exercise, 3-5 days/week during 12-week training period. ART group underwent 3 resistance training (20-30% of 1-repetition maximum) per week before aerobic exercise sessions. Reactive oxygen metabolites (d-ROMs) and biological antioxidant potential (BAP) were measured using the FRAS4 (Diacon International, Italy). For evaluation of effects of exercise training, all measurements including d-ROMs, BAP, eVO2max were carried out before and after 12 weeks training.

Results: In the AT and ART group, eVO2max significantly increased after exercise training. In the AT group, although d-ROMs did not change, BAPs significantly increased after exercise training (1970±434 to 2301±288 μM/L, p < 0.05). As a result, BAP/d-ROMs ratio significantly increased (6.3±1.72 to 7.28±1.03, p < 0.05). In the ART group, d-ROMs decreased and BAP increased after exercise training. Consequently, BAP/d-ROMs ratio increased (7.9±0.9 to 9.38±1.62, p < 0.01) after training. In the NET group, no significant changes in eVO2max and oxidative stress parameters were observed after 12-week observation period. No significant differences in baseline values of d-ROMs were observed between AT and NET groups. However, after 12-week observation period, the mean value of d-ROMs in the NET group were significantly lower than those in the NET group (p < 0.05). A significant correlation was noted between BAP/d-ROMs ratio and eVO2max (r=0.45, p < 0.001).

Conclusions: These findings suggest that aerobic exercise and resistance exercise training may decrease oxidative stress by augmentation of the biological antioxidant potential in patients with LRD. Furthermore, the higher levels of exercise tolerance may be indicative of the higher levels of antioxidant defense against oxidative stress.
Methods: The study involved 317 patients after MI, in the sinus rhythm without AV blocks or branch blocks. Average age of patients was 57.2 years. Patients were randomly divided into the physical training group (TG: 275 patients) and non-training group (42 patients). Patients were of similar age, site of infarction and baseline stress test duration. In all subjects clinical examination, standard ECG and exercise test on treadmill according to Bruce protocol, were performed and after the TG patients were included in rehabilitation treatment for three weeks. TG of patients were instructed to follow a training program using the bicycle ergometer (10 min, 2 times a day). The patients continued to take the same medications in the same doses. From standard ECG corrected QT dispersion (QTd) was calculated.

Results: RI was present in 153 (55.6%) patients in the TG and in 24 (57.1%) patients in the control group. In the TG, before starting with the program of physical training, patients with RI had significantly higher values of QTd (83.6±29.6 vs 66.7±21.4 ms; p<0.001), while the values of DP did not significantly vary (12360.7±3120.8 vs 11942.5±1722.6 beat/min x mmHg; p-NS) in comparison to those without RI. After three weeks, in the TG, significant reduction of QTd was found (from 83.6±29.6 to 75.8±27.4 ms; p<0.02 in patients with RI and from 66.7±21.4 to 56.5±20.6 ms; p<0.01 in patients without RI). In the TG, significant reduction of DP was found (from 12360.7±3120.8 to 11763.8±1639.4 beat/min x mmHg; p<0.01 in patients with RI and from 11943.5±1722.6 to 10823.7±1424.8 beat/min x mmHg; p<0.001 in patients without RI). In contrast, the non-training group showed no significant changes.

Conclusions: The study showed that short-term exercise training has favourable effects on QT dispersion and double product in patients after MI. In patients without RI physical training had more favourable effects on the followed parameters. Physical training led to the significant decrease of myocardial oxygen uptake at rest and probably decreased the possibility of arrhythmia events, especially in patients without RI.

Impairment of heart rate recovery index in autosomal-dominant polycystic kidney disease patients without hypertension

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Background: We aimed to determine the status of the autonomic nervous system in patients with autosomal dominant polycystic kidney disease (ADPKD) who were normotensive and had normal renal function.

Methods: A total of 28 normotensive ADPKD patients with normal renal function and 30 healthy control subjects consented to participate in the study. Heart rate recovery (HRR) indices were defined as the reduction in heart rate from the rate at peak exercise to the rate at the 1st, 2nd, 3rd and 5th minutes after the cessation of the exercise stress test; these results were indicated HRR1, HRR2, HRR3 and HRR5 respectively.

Results: The 1st- and 2nd-minute HRR indices of patients with ADPKD were significantly lower than those of the healthy control group (27.1±7.9 vs 32.0±7.9; p = 0.023 and 46.9±11.5 vs 53.0±9.0; p = 0.025, respectively). Similarly, HRR indices after the 3rd, and 5th minutes of the recovery period were significantly lower in patients with ADPKD when compared with indices in the control group (56.7±12.0 vs 65.1±11.2; p = 0.008 and 62.5±13.8 vs 76.6±15.5; p = 0.001, respectively) (Figure).

Conclusion: Impaired heart rate recovery index is associated with normoten-tive early stage ADPKD patients. Increased renal ischemia and activation of the renin-angiotensin-aldosterone system (RAAS) may contribute to impairment in the autonomic nervous system in these patients before the development of hypertension. Even if ADPKD patients are normotensive, there appears to be an association with autonomic dysfunction and polycystic kidney disease.
Cardiopulmonary exercise test in patients with congestive heart failure and sleep disorder breathing

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Introduction: In patients with congestive heart failure (CHF) the presence of Obstructive Sleep Apnea Syndrome (OSAS) is very common, however few studies have investigated which is the relationship between the presence of OSAS and Cardiopulmonary performance, moreover even if it's well known that patients with CHF have higher probability to develop Central Sleep Apnea and Cheyne-Stokes Respiration (CSA-CSR) during the night, the mechanisms which link CSA and CHF are still unclear. The aim of this study was to improve the knowledge about the relationship between CHF and Sleep Disorder Breathing (SDB) and better understand the pathophysiology of CSA-CSR.

Methods: 35 patients with congestive heart failure underwent to cardiopulmonary test, transthoracic echocardiography, global spirometry, emogas-analysis (EGA) and full night polygraphy. The patients were divided in OSAS, CSA-CSR and noSDB according the result of nocturnal test. Statistical analysis was by ANOVA was applied to evaluate the differences among three groups. Spearman’s correlation test was used to analyze the correlation between each variables.

Results: 35 patients with congestive heart failure (FE% 36±11.4) were enrolled, 13 (37%) had OSAS, 15 (42%) had CSA-CSR while only 7 (20%) hadn’t any SDB. The patients were matched for BMI and FE% but not for age because the OSAS were older than others groups: 68±3,7 vs 56±7,1±14 (noSDB) and 60±2,5±14 (CSA-CSR). Any differences were found among the groups about PCT, echocardiographics, spirometry and EGA parameters. The percentage of CSR was correlated with VO2max (r=-0,42, p<0,05), AT (r=0,40, p=0,05) VE/VCO2 slope (r=-0,47, p<0,05), any other correlation was found between index of SDR like AH, ODI or TST90% and CTP performance. Conclusion: Our results confirm that in patients with CHF sleep disorder breathing are very common. The severity of heart failure evaluated by CPT is correlated with tendency of patient to develop CSR during sleep independently of the FE% or other echocardiographic parameters. On the contrary the presence of SDB hadn’t any influence on performance at CPT.

Myocardial perfusion defects detected by cardiopulmonary exercise testing: role of VE/VCO2 slope in patients with chest pain suggestive of coronary artery disease

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Purpose: Cardiopulmonary exercise testing (CPET) might aid in the diagnosis of coronary artery disease (CAD). The ventilatory response evaluation by the linear regression slope of the minute ventilation (VE) and the carbon dioxide production (VCO2) (VE/VCO2) during a CPET is of great interest in heart failure. In the present study we assessed the relationship among VE/VCO2 slope and the myocardial perfusion defects quantified by single photon emission computed tomographic myocardial perfusion study (MPS) in subjects with symptoms suggestive of CAD.

Methods: We prospectively enrolled 56 subjects (age 57±8 years, 30 men) with symptoms of chest pain suggestive of CAD. All subjects underwent at rest and a stress MPS, in conjunction with the standard exercise test with ventilatory expired gas analysis. Coronary angiography was performed by conventional technique in those subjects who showed perfusion abnormalities in MPS.

Results: Of the 56 subjects, 25 (45.4%) had positive MPS findings. Of these subjects with positive MPS findings, 1 vessel disease was present 12 subjects, 2 vessel disease in 9 and triple vessel disease in 4. There were differences in peak oxygen uptake (VO2) and VE/VCO2 slope, between patients with and without myocardial perfusion defects (Table). After adjusting by potential confounders, multiple regression analysis showed that VE/VCO2 slope was a significant predictor of myocardial perfusion defects (OR ranging from [1.840, CI 95% 1.335-2.537, p < 0.001] to [1.905, CI 95% 1.366-2.656, p < 0.001]). VE/VCO2 slope was a good predictor of CAD.
Exercise tolerance estimated from simple walk tests in patients with pulmonary arterial hypertension

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**Purpose:** The exercise tolerance (ET) in patients with pulmonary arterial hypertension (PAH) has been evaluated using 6-min walking test (6MWT), however the reliability of conventional 6MWT as a biomarker in clinical trials is still controversial especially the incremental shuttle walking test (SSWT) has been proposed as a more valid and reproducible alternative to 6MWT in the evaluation of ET in patients with chronic obstructive pulmonary disease or chronic heart failure. The purpose of our study is to assess the reliability of SSWT and 6MWT in PAH patients using the measurement of peak oxygen consumption (pVO2) and oxygen consumption at anaerobic threshold (AT) as the gold standard measurement of ET, and also to estimate ET from the walk distance in SSWT and 6MWT.

**Methods:** SSWT and incremental cycle ergometry test for measurement of pVO2 and AT were performed in 15 clinically stable PAH patients in WHO class II or III.

**Results:** There was a close correlation between walk-distance (WD) in SSWT (439±169 m) and pVO2 (15.1±3.3 ml/kg/min) (r = 0.862, P < 0.01) and AT (10.9±1.8 ml/kg/min) (r = 0.794, P < 0.01) and a moderate correlation between WD in 6MWT (427±165 m) and pVO2 (r = 0.763, P < 0.01). However, there was not a significant correlation between WD in 6MWT and AT. Under regression analysis, pVO2 could be estimated as: pVO2 = 0.027 x WD in 6MWT + 3.429 (p < 0.001, R² = 0.563); pVO2 = 0.016 x WD in SSWT + 9.930 (p < 0.001, R² = 0.744); AT could be estimated as: AT = 0.008 x WD in SSWT + 8.440 (p < 0.001, R² = 0.630).

**Conclusions:** This is the first study to demonstrate that VE/VCO2 slope could be valuable as a robust and independent predictor of myocardial perfusion defects. The original finding of our study is that VE/VCO2 slope measured from exercise using 

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The hemostatic response of hypertensive patients treated with blood flow restriction improves the peripheral blood circulation in the healthy elderly

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Recently, it was reported that the training with blood flow reduction (BFR) performed with compressing the stem of upper or lower extremities increased muscle strength of extremities even at shorter training period. Although the hypertonic stress is known to induce angiogenesis and increase blood flow in tissues, it is unclear whether or not the training with BFR improves the peripheral blood circulation.

**Purpose:** The purpose of the present study was to investigate whether the intervention of the training with BFR improves the peripheral blood circulation in the healthy elderly.

**Methods:** Twenty-four healthy old volunteers with a mean age of 72±3 years, 20 males and 4 females, were enrolled in the present study. They were divided into two training groups: 12 subjects performing the resistance training of the extremities with BFR by cuff compression in BFR group, and 12 doing without BFR in control group. Subjects performed 3 sets of the resistance training composed of 4 movements. Each movement was repeated 20 times by the 20% of 1 repetition maximum. All subjects performed a series of resistance training 3 times a week for 4 weeks. We measured blood lactate (Lac), serum growth hormone (GH) and plasma vascular endothelial growth factor (VEGF) before and after the initial resistance training. We also assessed the peripheral blood circulation and muscle strength before and after a 12-week intervention of the resistance training. Transcutaneous oxygen pressure (tcpO2) on the dorsum of the right foot was measured using transcutaneous O2/CO2 gas device as an index of the peripheral blood circulation. Subjects performed isokinetic leg extension with the maximal strength 3 times in each leg using isokinetic dynamometer as an index of muscle strength.

**Results:** The GH and VEGF increased significantly from 0.9±1.1ng/ml and 32.9±12.7ng/ml before the training to 3.0±1.5ng/ml and 49.0±13.3ng/ml after the training, respectively, in the BFR group (P<0.01 and P<0.05, respectively). The Lac in the BFR and control groups increased significantly significantly from 60.1±12.9mmol/L and 96.7±21.8mmol/L before the training to 43.6±19.1 mmol/L and 40.6±18.3mmg/L after the training, respectively (P<0.01 and P<0.01, respectively). The tcpO2 and muscle strength increased significantly from 60.1±12.9mmol/L and 96.7±21.8mmol/L before the 4-week training to 69.3±17.0mmol/L and 110.5±22.6mm/L after the 4-week training, respectively, in the BFR group (P<0.01 and P<0.01, respectively).

**Conclusions:** The resistance training with BFR improved the peripheral blood circulation in addition to the increase of muscle strength.

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The training with blood flow restriction improves the peripheral blood circulation in the elderly

Increased baseline but reduced endothelial progenitor cells after aerobic exercise in subjects at cardiometabolic risk

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**Purpose:** Cardiometabolic risk (CR) is associated with endothelial dysfunction. However, on the other hand the acute exercise is able to improve the function of circulating endothelial progenitor cells (EPC) contributing to endothelial repair in healthy subjects. However, it is unknown whether this mechanism is present in subjects at increased CR. Therefore, the aim of the study was to isolate and quantify circulating EPC after a single bout exercise in subjects at increased CR.

**Methods:** Five healthy subjects (CT group: 25±9 years, 2 men and 4 subjects at increased CR (CR group: 35±9 years, 4 men) were enrolled. The CR group presented none of the criteria for the diagnosis of metabolic syndrome, while the CR group presented none of the criteria for the diagnosis of metabolic syndrome.

**Results:** Compared to pre-exercise levels: a. PF 1+2 levels were found to be significantly decreased at post exercise (p < 0.05), b.PAP levels were significantly increased both at peak exercise (p<0.05) and post exercise (p<0.001) and d. sPsel was significantly increased at peak exercise (p<0.05).

**Conclusions:** An acute bout of submaximal exercise in hypertensive patients under ACE inhibitors led to a favorable impact on haemostatic activation. Particularly, the haemostatic system activation was attenuated while fibrinolytic activity along with endothelial activation were the dominant features of the haemostatic response but their clinical relevance and their association with specific antihypertensive treatment has not yet been clarified. In any case, the results underscore the favorable effect of exercise in hypertensive patients.
Acute coronary syndrome related to sport: profile and profile and
Regular supervised exercise training improves patient preferences for chronic treatment for stroke

Results: Twenty patients (80%) were doing a sport with high dynamic component; running (28%) and cycling (24%) were the most represented sports; 16 patients were regular exercisers (21%). In various groups were evaluated using multivariate logistic regression. Results: Age-adjusted prevalence (%) of risk factors in men/women was over- weight or obesity 41.1/45.2, obesity 8.3/15.8, high waist circumference 10.4/23.5, high waist-to-hip ratio 40.0/72.6, hypertension 32.5/30.4, hypercholesterolemia 24.8/25.3, low HDL cholesterol 34.1/53.0, high triglycerides 41.2/31.5, dia- betes 16.7/14.4 and metabolic syndrome in 7.2/2.7. Lifestyle factors were smoking 12.0/0.5, other tobacco use 12.7/6.3, high fat intake 51.2/48.2, low fruit and vegetable intake 60.2/64.6, and low physical activity 78.6/83.4. There was significant correlation of educational status with occupation class (men 0.35, women 0.31) and SES (men 0.15, women 0.15) (p<0.001). Prevalence of >3 risk factors was significantly greater in low (22.4%) vs. middle (17.8%) or high (15.7%) education. In low educational status there was greater prevalence of age- and sex-adjusted low HDL cholesterol (1.51, 1.27-1.80), total high/low HDL cholesterol ratio (1.18, 0.98-1.43), hyperglycemia (1.16, 0.97-1.37), hypertension 1.10, 0.91-1.33), smoking/tobacco use (OR 3.27, 2.66-4.01) and low physical activity (1.15, 0.97-1.37), and lower prevalence of alcohol abuse (0.51, 0.39-0.66), high fat diet (0.51, 0.38-0.63), high BMI (0.68, 0.56-0.82), high waist size (0.63, 0.51-0.77) and hypercholesterolemia (0.79, 0.66-0.94). In middle educational status there was greater prevalence of high triglycerides (1.10, 0.96-1.26), metabolic syndrome, smoking/tobacco use, low physical activity and clustering of >3 major risk factors.

Conclusions: Low educational status Asian Indian subjects have greater prevalence of low HDL cholesterol, high total cholesterol, hypertriglyceridemia, metabolic syndrome, smoking/tobacco use, low physical activity and clustering of >3 major risk factors.

Methods: The study was performed at eleven cities using cluster sampling. Subjects (n=4198, men 3426, women 2772) were evaluated for socioeconomic, demographic, biophysical and biochemical factors. They were classified into low, medium and high SES based on educational level (<10, 10-15 and >15 yr formal education), occupational class and socioeconomic scale. Differences in risks in various groups were evaluated using multivariate logistic regression.

Results: Age-adjusted prevalence (%) of risk factors in men/women was overweight or obesity 41.1/45.2, obesity 8.3/15.8, high waist circumference 10.4/23.5, high waist-to-hip ratio 40.0/72.6, hypertension 32.5/30.4, hypercholesterolemia 24.8/25.3, low HDL cholesterol 34.1/53.0, high triglycerides 41.2/31.5, diabetes 16.7/14.4 and metabolic syndrome in 7.2/2.7. Lifestyle factors were smoking 12.0/0.5, other tobacco use 12.7/6.3, high fat intake 51.2/48.2, low fruit and vegetable intake 60.2/64.6, and low physical activity 78.6/83.4. There was significant correlation of educational status with occupation class (men 0.35, women 0.31) and SES (men 0.15, women 0.15) (p<0.001). Prevalence of >3 risk factors was significantly greater in low (22.4%) vs. middle (17.8%) or high (15.7%) education. In low educational status there was greater prevalence of age- and sex-adjusted low HDL cholesterol (1.51, 1.27-1.80), total high/low HDL cholesterol ratio (1.18, 0.98-1.43), hyperglycemia (1.16, 0.97-1.37), hypertension 1.10, 0.91-1.33), smoking/tobacco use (OR 3.27, 2.66-4.01) and low physical activity (1.15, 0.97-1.37), and lower prevalence of alcohol abuse (0.51, 0.39-0.66), high fat diet (0.51, 0.38-0.63), high BMI (0.68, 0.56-0.82), high waist size (0.63, 0.51-0.77) and hypercholesterolemia (0.79, 0.66-0.94). In middle educational status there was greater prevalence of high triglycerides (1.10, 0.96-1.26), metabolic syndrome, smoking/tobacco use, low physical activity and clustering of >3 major risk factors.

Conclusions: Low educational status Asian Indian subjects have greater prevalence of low HDL cholesterol, high total cholesterol, hypertriglyceridemia, metabolic syndrome, smoking/tobacco use, low physical activity and clustering of >3 major risk factors.
ution in France, Germany, Italy, Spain and the UK for AF. Structured telephone interviews were then conducted between February and July 2011. Here, we describe patient treatment and preferences across the five EU countries surveyed.

Results: Interviews were conducted with 1507 patients (France, n=300; Germany, n=300; Italy, n=302; Spain, n=305; UK, n=300). Mean age was 70 years, with equal numbers of men and women. The survey revealed that many patients with AF were taking a vitamin K antagonist (VKA) for oral anticoagulation and therefore required routine anticoagulation monitoring and dose adjustment. VKA utilization varied widely between countries. In the UK, 49% of patients were pre-scribed generic warfarin, branded warfarin was prescribed to 36% of Italians, 47% of Germans received phenprocoumon, acenocoumarol was prescribed to 56% of Spanish patients and 26% of French patients had received fluindione. Overall, most patients (mean, 61%; range, 48–76%) were positive about the possibility of not needing regular anticoagulation monitoring, although fewer French and German respondents were positive about reduced monitoring (49% and 48%, respectively). Of patients expressing a preference for reduced monitoring, 28% (range, 20–32%) were in favour due to potential time savings, and 29% (26–35%) due to the reduced need to visit a monitoring centre. Moreover, the potential for no longer needing dose adjustment for anticoagulation was regarded as positive by patients (mean, 55%; range, 38–67%). Patients also expressed a preference for taking anticoagulation medicine once a day; responses ranged from 74% in favour in France, to 86% in the UK.

Conclusion: The EUPS-AF survey provides a patient-based perspective of healthcare provision in individuals with AF at risk of stroke. Although many patients currently receive oral VKA anticoagulation therapy, the high patient burden, including the need for regular monitoring and dose adjustment, associated with VKA therapy may result in decreased patient satisfaction. Most patients express a preference for once-daily medication.

Influence of socioeconomic status on Acute Myocardial Infarction (AMI) in China population: the Interheart China study

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Objectives: This study aimed to determine whether levels of education, family income and other socioeconomic status (SES) were associated with acute myocardial infarction (AMI) in a Chinese population. A secondary aim was to compare the difference of this association between northern and southern regions in China.

Methods: We conducted a case-control study. Cases were first AMI (n=2909). Controls (n=9847) were randomly selected and frequency matched to cases on age and sex. SES was measured using education, family income, possessions in the household and occupation.

Results: Low levels of education (8 years) were more common in cases compared to controls (53.4% and 44.1%, p=0.0001). After adjusted all risk factors, the levels of education was associated with AMI risk in Chinese population (Global P value, 0.0005). The odds ratio (OR) associated with education 6 years or less, compared with more than 12 years (trade school/college/university) was 3.39 (95% CI: 1.21-5.19), and for education 9-12 years 1.04 (95% CI: 0.88-1.13). The proportion of higher income population was in controls more than cases (39.4% and 27.9%, p=0.005). Number of possessions and non-professional occupation were only weakly or not at all independently related to AMI. The adjusted OR associated with the lower education was 2.38 (95% CI: 1.67-3.39) in women, and 1.18 (95% CI: 1.40) in men (p value for heterogeneity 0.0001). The interaction between levels of education and different regions was significant ( p value for interaction, 0.0026).

Conclusion: Several socioeconomic factors including levels of education, income were closely associated with increase of AMI risk in China, most markedly in northeast and southern area. The effect of education was stronger to AMI in the women than men.

Socioeconomic position and marital status as independent predictors for cardiovascular mortality in western Siberia, Russia: a prospective cohort study

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Background: Socioeconomic factors and marital status of individuals are associated with risk of cardiovascular mortality in developed societies but in our country this issue was not been studied sufficiently.

Purpose: To assess the relationship between socioeconomic factors, marital status and risk of cardiovascular mortality in working-age male population of Western Siberia.

Methods: A representative sample of 795 men aged 25-64 years living in Tyumen, Russia, was examined with standard epidemiological methods in 1996. Cardi ovascular death rate was studied during 12-year prospective follow-up (from 1996 till 2008). The relationship between cardiovascular mortality and education, occupation, and marital status was evaluated using Cox proportional hazards model. Hazard ratio (HR) was calculated after adjustment for the following confounders: age, systolic and diastolic blood pressure, body mass index, smoking status, level of education and manual occupation) and marital status (widowed, divorced or single) were significant predictors of cardiovascular mortality, independent of other traditional risk factors.

Results: Over 12 years of prospective study in the male cohort 85 deaths (10.6%) from cardiovascular disease were recorded. Compared to men with higher education, HR was higher for men with low education level - 1.92 (95% confidence interval (CI) 1.14-3.22). After adjusting for all mortality risk factors HR was significantly higher in manual workers - 2.72 (95% CI 1.42-5.33) compared to professionals. Compared to married men, HR was higher in single - 4.08 (95% CI 2.12-7.83), widowed - 3.19 (95% CI 1.22-8.34) and divorced men - 3.18 (95% CI 1.90-5.34).

Conclusion: Our results showed that socioeconomic position (low education level and manual occupation) and marital status (widowed, divorced or single) were significant predictors of cardiovascular mortality, independent of other traditional risk factors.

P1792 Does targeting cardiovascular screening programmes at deprived areas work equally well in ethnic minority groups? J. Baker, R. Mitchell, J. Pelli. University of Glasgow, Glasgow, United Kingdom

Purpose: Socioeconomic deprivation is an established risk factor for cardiovascular disease (CVD); targeting prevention programmes at deprived areas can identify a significant proportion of the White population with high cardiovascular risk. Some ethnic minority groups experience higher levels of socioeconomic deprivation and CVD than the White population. However, it is currently unknown whether targeting cardiovascular prevention programmes at deprived areas works equally well in different ethnic minority groups. The purpose of this study was to explore ethnic differences in how well area deprivation measures work as a tool for identifying individuals with important cardiovascular risk factors.

Methods: Cross-sectional analysis of the Health Survey for England 2003, 2004 and 2006. Adults aged 40-74 years from 8 ethnic groups (White, Black Caribbean, Black African, Indian, Pakistani, Bangladeshi, Chinese and Irish) were included. The area-based Index of Multiple Deprivation 2004 was used to divide participating areas into those living in the most deprived and less deprived areas. The prevalence of 5 cardiovascular risk factors (hypertension, smoking, body mass index (BMI), waist:hip ratio and total cholesterol:HDL ratio) was compared by deprivation category and ethnic group. The utility of area deprivation as a screening tool was investigated by calculating specificity, sensitivity, positive predictive value, and number needed to screen (NNS).

Results: Ethnic differences were found in the relationship between area deprivation and cardiovascular risk factors, and in the utility of area deprivation measures to screen for cardiovascular risk factors. Targeting CVD prevention programmes at areas of high socioeconomic deprivation may not be equally effective for all ethnic minority groups. Further research is continuing to model ethnic differences in the use of area deprivation measures to identify individuals with high cardiovascular risk scores.

Cost of venous thromboembolism in hospitalized medically ill patients

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Purpose: To examine the costs of venous thromboembolism in hospitalized medically ill patients including initial admission and subsequent to hospital discharge.

Methods: Using a database linking admission records from > 150 US hospitals to health insurance claims, we identified all persons, aged ≥40 years, who were hospitalized between 2003 and 2008. We excluded patients who: (1) underwent surgery; (2) were hospitalized in the prior 30 days; (3) were treated for VTE in the prior 30 days; (4) had hypercoagulability at admission; or (5) received low molecular weight heparin, unfractionated heparin, or fondaparinux at therapeutic dosages on hospital day 1 or 2. Occurrence of VTE between the first-noted hospitalization ("index" admission) and end of follow-up (180 days) was assessed based on a secondary diagnosis code for VTE (ICD9:415.1, ICD10: X11.9, 420.81, 451.81, 451.9X, 452.XX, 453.9X, 453.99, 497.7X, 999.2X) or PE (ICD10:J32.1) during the index admission, or a principal diagnosis code for VTE for a hospitalization occurring anytime between discharge from the index admission and day 180. Costs (inpatient, outpatient, retail pharmacy) were tallied from...
index admission to end of follow-up for patients with and without evidence of VTE. Ordinary least squares regression was used to estimate the relationship between total healthcare costs (log-transformed) and VTE, controlling for various patient characteristics.

**Results:** The study population consisted of 49,946 patients; mean (SD) age was 67 (13) years. A total of 559 study subjects (1.1%) had evidence of clinical VTE by day 180 – 242 (0.5%) during the index admission, and 317 (0.6%) following hospital discharge. Among patients who developed VTE during the index admission, adjusted mean total healthcare costs were $17,848 higher over 180 days ($74,146 vs $56,298 for those without VTE; p = 0.001). Among patients who developed VTE following hospital discharge, adjusted mean total healthcare costs were $51,863 higher over 180 days ($74,146 vs $22,273 for those without VTE; p < 0.001).

**Conclusion:** VTE is a costly complication in medically ill hospitalized patients, both in hospital as well as following discharge.

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**Increased anticoagulant effects of warfarin after a catastrophic earthquake in a stricken area**

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**Background:** On March 11, 2011, Northeast Japan was shaken by a magnitude 9.0 earthquake followed by a catastrophic tsunami, which damaged nearby nuclear power plants. This disaster displaced a large population and caused severe shortages of food, water, electricity, and fuel. Hypothesizing that the profound life changes caused by the earthquake, modified the diet in patients treated with warfarin K, we examined its effects on the international normalized ratio (INR) in victims treated with warfarin.

**Methods and Results:** We compared the INR measurements before and after the earthquake in two cohorts in different areas: 59 victims whose life was affected by the disaster and 155 controls whose life was not so affected. The dose of warfarin was adjusted according to the guidelines for pharmacotherapy of atrial fibrillation by Japanese Circulation Society (2.0-3.0 for ≥ 70 years, 1.6-2.6 for < 70 years). There was no significant difference among the three INR measured before the earthquake. In contrast, the INR measured after the earthquake (2.16±0.55) was significantly higher than the average of the three INR measured before the earthquake (1.96±0.31; p = 0.015) in victims. The INR was not changed before and after the earthquake in controls. Furthermore, among victims, the INR measured within the first 3 weeks after the earthquake was increased (2.29±0.62, n=35) compared with that before the earthquake (2.00±0.31; p = 0.018), although the INR measured 3 weeks after the earthquake were similar to that before the earthquake. The INR was above the upper limit of therapeutic range in 7 victims after the earthquake.

**Figure 1. INR before and after the earthquake.**

**Conclusions:** The anticoagulant effects of warfarin was increased after the disaster. The modified dietary intake may result in the increased anticoagulant effects of warfarin.

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**Ethnic differences in post-MI outcomes**

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Because of historical differences in the incidence of coronary heart disease (CHD) by area of immigration in Israel, we examined ethnic differences in post-myocardial infarction (MI) outcomes controlling for multidimensional measurement of socio-economic status (SES). Patients aged <65 years (n=1,040) belonging to Ashkenazi and other (predominantly Sephardic) ‘advantaged and disadvantaged’ ethnic groups discharged from 8 hospitals in central Israel after a first incident MI in 1992-1993, were followed up through 2005 for all-cause mortality, recurrent MI, heart failure, and ischemic stroke. Advantaged Ashkenazi had higher education, income, employment, and neighborhood SES compared with the other origin-advantage patient groups. Results showed gradual attenuation in the negative association between social advantage and all outcomes with increasing adjustment, when adjustment was made for demographics only, for demography and single SES measures, and for demography and multiple SES measures. For example, the hazard ratio for mortality in disadvantaged Sephardic compared with advantaged Ashkenazi was 1.87 (95% CI: 1.40, 2.48) in a model adjusting only for demography; 1.58 (95% CI: 1.18, 2.12) in a model adjusting also for income; and 1.03 (95% CI: 0.74, 2.04) in a model adjusting for multiple SES indicators. Further adjustment for clinical variables did not appreciably change the results. Findings highlight the importance of using multidimensional models of SES. Over-adjustment as a result of control of intermediate variables such as SES can result in underestimation of the role of ethnicity in health outcomes.

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**Age amplifies early to mid-term risks following acute coronary syndrome in elderly Asians with low high-density lipoprotein cholesterol**


**Background:** The relationship between high-density lipoprotein (HDL) cholesterol and acute coronary syndrome (ACS) among elderly Asian subpopulations has not been explored. The objective of this study was to assess magnitude of risk among elderly Asians with low HDL after ACS.

**Methods:** This was a prospective study of all patients with ACS defined as either unstable angina pectoris or non-ST elevation MI. Baseline characteristics of age, gender, diabetes mellitus, hypertension and TIMI score were analyzed and adjusted for outcomes. Lipid profiles were obtained after 12 hours overnight fasting from index hospital admission for ACS. Primary outcomes were major adverse cardiovascular events (MACE) of MI, target vessel revascularization (TVR) and death up to 12 months.

**Results:** We analyzed 585 patients with median follow-up of 9 months and median TIMI score of 4. 66% of the cohort had suboptimal HDL level < 1.0 mmol/L and 22% were aged 75 years or above. Patients with HDL < 1.0 mmol/L had more than 7-fold increased risk of MI at 6 months (OR 2.29 with 95% CI: 1.24-4.54, p = 0.003) and 12-months mortality (32% vs. 12%, OR 3.08 95%CI 1.56-6.42, p = 0.02). Compared to Chinese with HDL > 1.0, Indians were more likely to have 1-month TIMI score (3.6% vs. 0.3%, OR 8.43 95%CI 1.64-62.0, p=0.041) while the Malays were more likely to have 1-month nonfatal MI (6.5% vs. 1.2%, OR 6.06 95%CI 1.27-22.10, p=0.031). Indians aged > 75 years with HDL < 1.0 mmol/L were more likely to have early cardiac death at 1 month compared those aged > 75 years (14.3% vs. 1.0%, OR 16.3, 95%CI 1.70-157, p=0.039). Among the group with HDL > 1.0, 6-month nonfatal MI and 12-month MACE rates were significantly higher among the Malays and Indians who were aged > 75 compared to those aged > 75 years (33.3% vs. 25.9%, OR 1.95, 95%CI 2.67-94.7, p=0.016), (41% vs. 4.4%, OR 11.1, 95%CI 1.22-101.6), p=0.02).

**Conclusions:** Elderly Indians and Malays with low HDL have the highest risk of early and mid-term cardiac events. The excess burden of risk associated with age across ethnicity and in association with abnormal lipid profile is warrants further investigation.

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**PUBLIC HEALTH AND HEALTH POLICIES**

**Waist circumference combined with BMI; a better predictor of childhood obesity?**

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The World Health Organisation childhood growth surveillance system was established in 2008 to systematically measure childhood obesity in the European region. The present study provides an assessment of the prevalence of obesity from two sweeps of 6-9 year old Irish children measured in 2008 and 2010. The core objective was to measure weight, height and waist circumference and to examine prevalence of normal weight, overweight and obesity according to the WHO protocol. A nationally representative sample of schools was chosen. The overall relative weight in children was estimated to be 20, small schools having less than 20 pupils per class.

Body mass index (BMI) was standardised by age and sex and overweight and obesity were classified using the International Obesity Taskforce cut-off points. Statistical analysis was carried out using Pearson’s chi-squared test and logistic regression. BMI was the outcome variable and this was dichotomised to normal versus overweight and obese combined.

BMI measurements were recorded for 6609 children (3168 boys and 3441 girls, 48% and 52%, respectively) and 23% were classified as either overweight or obese. A significantly greater proportion of girls are overweight or obese compared with boys (25% compared with 20% y2 = 18.48, df = 1, P = 0.001). The proportion of normal versus overweight and obese children did not change between 2008 and 2010. Logistic regression demonstrated that overweight and obesity were more likely in females (OR 1.277, 95%CI 1.13-1.438), those who attended small schools (OR 1.203, 95%CI 1.063-1.360) and of borderline significance 8 years old (OR 1.262, 95%CI 1.026-1.551). The model was repeated including waist circumference in quadriles. Gender (Girls: OR 1.308, 95%CI 1.116-1.531) and school size (Smaller schools; OR 1.381 95% CI 1.17-1.631) remained significant predictors. However, the inclusion of waist circumference demonstrated a much stronger gradient across age groups (6 yr olds; OR 6.925 95% CI 5.12-
Statin prescription in Europe: the potential conflict between clinical guidelines and healthcare policies

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Purpose: Market data for statins in Europe highlight the potential for conflict between recommendations in clinical guidelines and healthcare policies designed to constrain costs. The potential impact is significant, particularly as statins vary considerably in terms of low-dose lipoprotein cholesterol (LDL-C) reducing potency.

Methods: The median doses of prescribed simvastatin, pravastatin and atorvastatin in 17 Western European countries (E17) were derived from IMS data for 2000-2010. Clinical guidelines for cardiovascular management in elderly patients (slightly more than 20% of total prescriptions) were sourced from the literature. Dose-specific, LDL-C modifying effects of the three statins were derived from published meta-analyses.

Results: In 2010, the median prescribed doses of pravastatin, simvastatin and atorvastatin were 40mg, 20mg and 20mg, respectively, for most of E17. However, in France, where clinical guidelines recommend less strict LDL-C targets, patients in both years were 20mg, 20mg and 10mg, respectively. In Sweden, where atorvastatin 10mg was removed from the reimbursement schedule in 2008, the atorvastatin median dose increased from 10mg in 2009 to 20mg in 2010. The opposite occurred in The Netherlands, where following the introduction of an authorisation form in January 2009, the atorvastatin median dose declined from 40mg in 2009 to 20mg in 2010. Concurrently, the simvastatin median dose from 20mg to 40mg. The simvastatin median dose in the UK is also 40mg, and comprises 69% of the market, reflecting NICE guidelines and Quality Outcomes Framework (QOF) policy.

Conclusions: The median statin doses in France, Sweden, the Netherlands and UK reflect the influence of national clinical guidelines and healthcare policies. Given the superior LDL-C reduction of atorvastatin compared to simvastatin and pravastatin, as well as the current “treatment gap” in many Western European countries, it will be interesting to observe whether the reduction in atorvastatin’s acquisition cost following loss of exclusivity in 2012 will lead to changes in guideline recommendations and national policies, and how quickly. The availability of generic atorvastatin has the potential to further improve cardiovascular outcomes, even without any change in current prescribing patterns.

Sexual Dysfunction in patients with chronic heart failure (CIBIS-ELD Study)

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Purpose: Sexual dysfunction is a common problem with increasing incidence in CHF. Due to under-reporting and under-recognition, data on presentation of sexual dysfunction in patients with chronic heart failure (CHF) is limited. We investigated the relationship between clinical signs and symptoms of heart failure and all-cause and CHF-relevant mortality.

Methods: Data from 780 CHF patients (75±5.5 years, 36.9% woman, NYHA II) of the CIBIS-ELD trial, a cross-sectional, observational, multi-centre trial in elderly CHF patients were analysed. Self-reported sexual function was assessed using data from question 10 of the MLWH questionnaire. Dyspepsia, peripheral edema, pulmonary rhonchi were assessed as signs and symptoms of CHF.

Results: 2388 patients filled in SF-36 and EQ-5D questionnaires. EQ-5D scores (measured to use SF-6D) Cr-square-test and Mann-Whitney-U Test were performed.

Results: A total of 271 patients (76±5.5 years, 45.8% women) provided sufficient data concerning sexual dysfunction. 33 patients (12.2%, 37% women) have reported changes in sex life due to heart failure. All patients were enrolled in the CIBIS-ELD trial and were invited to participate in an observational follow-up 1.6 to 5.5 years after the end of up-titration with beta-blockers. As the most frequent reasons for this change shortness the breath (20%), fatigue (13.3%) and medication (10%) have been stated. The presence of sexual dysfunction showed no significant correlation with signs and symptoms of heart failure. There are more changes in sexual function (P<0.001) in patients with symptoms of heart failure (P=0.023) reported by patients who consume (17.6%) alcohol then those who do not (8.6%). Patients with reported sexual dysfunction have significant lower scores in SF-36 questionnaires vitality (41.1 vs 50.7, P<0.025), psychosocial wellbeing (58.77 vs. 66.16, P<0.022) and psychosocial component (43.5 vs. 48.99, P<0.013), as well as a higher PHQ score (8.88 vs. 6.29, P<0.006).

Conclusion: Our data revealed no correlation of CHF symptoms with sexual dysfunction. However, psychological parameters, i.e. especially depression score, and alcohol consumption significantly contributed to sexual dysfunction. There is higher chance for lower scores of quality of life questionnaire and sexual dys-function occurrence.

Implantable cardioverter defibrillator (ICD) in Italy from 2000 to 2008: a population-based analysis using health administrative databases

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Purpose: We evaluated the trend in ICD therapy from 2000 to 2008 in Lombardy, an Italian region with universal healthcare coverage for more than 9 million people. Secondly we analyzed the consumption of healthcare services and the corresponding direct costs following a first implantation.

Methods: We extracted data from DENAME, a database that organizes healthcare administrative data concerning subjects covered by the Lombardy Health System (HS); demographic information, hospital discharges (HDs), drug prescriptions for outpatient claims. We identified HDs for ICD implantation (first or replacement) occurred between 2000 and 2008. We estimated the number of first implants (per million persons) in order to assess the trend time and compare it with European and American ones. We evaluated the substitution annual rate (per 100,000 inhabitants) estimating the total person-time at risk, as the time between the first implantation and its replacement cumulated over population members. In order to assess the economic burden of ICD, we selected subjects who underwent a first ICD implantation between 2005 and 2007 and we followed them from discharge to 31/12/2008. We calculated mean annual total cost per capita, and subdivided it into hospitalizations, drugs and outpatient expenditure.

Results: In Lombardy, the annual number of first ICD implants (per million persons) increased, from 55 in 2000 to 236 by 2008, with higher values in males and in subjects aged between 65 and 74 years. The use of ICD in Lombardy was approximately 2 times higher than in Europe and 3.4 times lower than in US. The replacement rate was around 9 (per hundred implant year) in almost all years with a peak in 2005 (15 per hundred implant year); subjects 75 years-old or older showed the highest replacement rate. 5.814 subjects underwent an hospitalization for first ICD implantation between 2005-2007 with a mean expenditure of €23,814 (confidence interval, CI95%: 23,676-23,960) per capita. During the follow-up the HS bore a mean annual cost of €4,354 (CI95%: 4,226-4,485) per capita: 17% due to drugs, 12% to outpatient visits and 71% to hospitalizations. Though mean total costs did not differ among age classes, younger patients reported lower costs in drug treatments and outpatient visits and a higher expenditure for hospitalizations.

Conclusions: ICD use is growing and it’s important to assess both the efficacy and the burden of this therapy, given the economic implications and differences in use among countries. Administrative databases are a useful tool, as they provide information about large unselected populations.

Influence of environmental parameters in the onset of myocardial infarction in Paris suburban area

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Background: Environmental parameters have been reported to be triggers of acute myocardial infarction (MI). However, the individual role of each parameter is unknown, probably due to low relative risks, a complex relationship between acute MI and air pollution, and difficulties in clearly determining the population exposure. We evaluated in a complex approach the role of pollutants, climate parameters and influenza epidemics in the onset of ST elevation MI (STEMI) in Paris and the surrounding small area.

Methods: Data from the CARDIO-ARSIF registry, a dedicated angiography and percutaneous coronary intervention base, were used between 2003 and 2008 in Paris and the small ring (6.5 million inhabitants). Pollution (CO, NO2, SO2, O3, Particulate Matter <2.5μm and <10μm) measured on background and on traffic stations, climate parameters (min and max temperature, temperature variation, humidity, atmospheric pressure, mean and max wind, radiation), and influenza epidemic data provided respectively from the certified AIR PARIF, Météo-France and GROG database. The relationship between parameters and STEMI occurrence is a time series modeling of daily STEMI count data, using Poisson regression with generalized additive model. We evaluated the relation between STEMI and pollution with a mean expenditure of €23,814 (confidence interval, CI95%: 23,676-23,960) per capita. During the follow-up the HS bore a mean annual cost of €4,354 (CI95%: 4,226-4,485) per capita: 17% due to drugs, 12% to outpatient visits and 71% to hospitalizations. Though mean total costs did not differ among age classes, younger patients reported lower costs in drug treatments and outpatient visits and a higher expenditure for hospitalizations.
Results: Out of 321 445 coronary angiography & PCI procedures in the ARISF Database between 2003 and 2008, 11 987 were performed in patients treated in Paris and the small ring in all the subjects. Differences between baseline and second measurements of COHb were described as ΔCOHb.

Results: Mean carboxyhemoglobin level was statistically higher at the end of exposure (when compared to baseline in all subjects (COHb % 0.5±0.1 vs. % 1.8±0.4; p<0.05). Heart rate and systolic blood pressure measurements were similar at 15th minute and 30th minute of exposure and significantly higher at baseline and 5th minute of exposure (68±3.2 beats/min and 90±3.7 beats/min vs. 76±3.9 beats/min and 78±4.5 beats/min; p<0.05, 135±1.1 mmHg and 147±4.0 mmHg vs. 115±3.7 mmHg, 119±5.0 mmHg; p<0.05). Diastolic blood pressure was significantly increased at 30th of exposure when compared to precedent measurements (90±1.1 mmHg vs. 74±2.2 mmHg, 71±1.4 mmHg; p<0.05). Heart rate and systolic blood pressure and diastolic blood pressure measurements were closely correlated with ΔCOHb values at the end of the exposure (r=0.76, p=0.001; r=0.81, p=0.001 and r=0.65, p=0.001, respectively).

Conclusion: Our result suggested that passive smoking has remarkable acute effects on heart rate and blood pressure that is closely correlated with COHb levels in healthy young females.

Results: The FEW-16 included assessment of data quality, scale assumptions, construct validity and reliability. Cronbach's α was 0.84 for resilience, 0.80 for ability to enjoy, 0.88 for vitality, 0.87 for inner peace and 0.95 for whole FEW-16 score. Pearson's Correlations of FEW-16 with SF-36 and PHQ-D are displayed in the Table 1. The Intraclass Correlation Coefficient is 0.87 (95% CI 0.84 – 0.89; F2,1). Table 1. Pearson’s ICC of FEW-16 with SF-36 and PHQ-D

| Resilience | Ability to enjoy | vitality | inner peace |
| SF-36 vitality | 0.679** | 0.669** | 0.714** | 0.664** | 0.763* |
| SF-36 psych. well-being | 0.579* | 0.631* | 0.602* | 0.779* | 0.745* |
| SF-36 social functioning | 0.568* | 0.569* | 0.588* | 0.677* | 0.680** |
| SF-36 physical functioning | 0.586** | 0.634** | 0.665** | 0.641** | 0.736** |

*Indicates significance of p<0.01 (both ways).

Conclusion: The FEW-16 shows good reliability, internal consistency and intra-class correlation and correlates well with SF-36. FEW-16 scores correlate more strongly with psychological well-being of SF-36 and PHQ-D than with clinical parameters of vitality such as 6MWT and LVEF. This may indicate that physical well-being is associated with mental factors rather than purely dependent on physical vitality. We suggest the FEW-16 Questionnaire is an adequate measure of well-being in patients with CHF.

Acute effects of passive smoking on blood pressure and heart rate in healthy females

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Common chronic cardiovascular disease that leads to heart attacks, strokes, chronic heart failure, and chronic renal failure. We aimed to investigate immediate acute effects of passive smoking on blood pressure and heart rate during and after exposure in healthy females. In addition, we tried to find out if carboxyhemoglobin (COHb) levels are correlated or not with heart rate and blood pressure measurements.

Method: 30 healthy nonsmoker female volunteers (mean age: 26±6.5 years) were prospectively enrolled to the study. Systolic and diastolic blood pressure and heart rate were obtained at baseline, 5th, 10th, 15th, 30th minutes of exposure and at 5th, 15th and 30th minutes after exposure. Blood samples for measuring carboxyhemoglobin (COHb) were taken at baseline and after spending 30 minutes in the smoking room in all the subjects. Differences between baseline and second measurements of COHb were described as ΔCOHb.

Results: Mean carboxyhemoglobin level was statistically higher at the end of exposure (when compared to baseline in all subjects (COHb % 0.5±0.1 vs. % 1.8±0.4; p<0.05). Heart rate and systolic blood pressure measurements were similar at 15th minute and 30th minute of exposure and significantly higher at baseline and 5th minute of exposure (68±3.2 beats/min and 90±3.7 beats/min vs. 76±3.9 beats/min and 78±4.5 beats/min; p<0.05, 135±1.1 mmHg and 147±4.0 mmHg vs. 115±3.7 mmHg, 119±5.0 mmHg; p<0.05). Diastolic blood pressure was significantly increased at 30th of exposure when compared to precedent measurements (90±1.1 mmHg vs. 74±2.2 mmHg, 71±1.4 mmHg; p<0.05). Heart rate, systolic blood pressure and diastolic blood pressure measurements were closely correlated with ΔCOHb values at the end of the exposure (r=0.76, p=0.001; r=0.81, p=0.001 and r=0.65, p=0.001, respectively).
Incidence and clinical significance of hypertension
Role of leptin on 24hr heart rate variability in overweight subjects with essential hypertension

Conclusion:

One hundred and eighty six patients (mean age 63.99 ± 12.34 years old) were included in the study. The study population consisted of 318 untreated essential hypertensives and a control group, consisted of 193 matched subjects. The gene mutation was determined using polymerase chain reaction (PCR) technique and appropriate restriction endonucleases. Plasma glucose, serum creatinine, uric acid and lipid levels were determined by routine methods. Serum Cystatin-C levels were measured by ELISA kit. We also assessed GFR by the Cockcroft-Gault formula and estimated Cystatin-C-dependent GFR (eGFR) using the following equation: eGFR = 127.7*(Cystatin C – 1.17)*(Age – 0.13)*(0.91 if female). Results:

Surprisingly, angiotensinogen 235TT genotype showed a trend towards a lower GFR compared with MM and MT genotype in hypertensive patients (104±31 vs 110±48, p=NS) and higher values of uric acid (5.3±1.8 vs 4.7±1.5 mg/dL, p=0.056) but neither genotype was associated with increased creatinine, cystatin-c nor eGFR (p=NS for all). With respect to Cystatin-C levels, TT homozygotes of G-344T polymorphism exhibited a trend for higher values compared to C-carriees (825.1±194.9 vs 799.9±204.6 ng/mL, p=0.6) and similarly eGFR did not differ across genotypes (CC: 74.9±23.4, CT: 71.9±15.1, TT: 72.1±17.8, p=NS). Combination of allelic variants of these candidate genes was not associated with worse renal estimates and different Cystatin-C levels (p=NS for all).

Conclusions: In the present study we have shown that variations in the angiotensinogen gene may affect uric acid levels, however according to our findings and those of others, the polymorphisms are not capable to affect further renal function in patients with essential hypertension.

ENDOTHELIAL DYSFUNCTION IN DIFFERENT HYPERTENSIVE POPULATIONS

Incidence and clinical significance of hypertension induced by anti-VEGF agents

Objective: Hypertension has been observed as an on target toxicity of anti-vascular endothelial growth factor therapy (VEGF), reflecting VEGF pathway inhibition. Bevacizumab is a monoclonal antibody approved as first-line treatment of colorectal cancer. We retrospectively analyzed the incidence of bevacizumab induced hypertension and its association with clinical outcomes.

Methods: We consecutively included 156 patients (median age 57 years) with colorectal cancer treated with bevacizumab (7.5 mg/kg every 2 weeks) at our Institute from 2006 to 2010. Office blood pressure monitoring (3 measurements at 3 separate visits) and home blood pressure monitoring (2 measurements morning and evening for 7 days) were performed. Blood pressure was graded according to the European Society of Hypertension criteria.

Results: 34 patients (22%) developed grade 3 hypertension, 27 patients (17%) developed grade 2 hypertension and 14 patients (9%) developed grade 1 hypertension. Home-based measurements detected more cases of hypertension than in-clinic measurements did (61.3% vs 29.4%; p<0.01). Patients with hypertension tended to have a better prognostic rate (82% achieved a complete or partial response as compared with 47.3% of patients who did not show this side effect).

Conclusions: Angiotensinogen 235TT genotype showed a trend towards a lower GFR compared with MM and MT genotype in hypertensive patients (104±31 vs 110±48, p=NS) and higher values of uric acid (5.3±1.8 vs 4.7±1.5 mg/dL, p=0.056) but neither genotype was associated with increased creatinine, cystatin-c nor eGFR (p=NS for all). With respect to Cystatin-C levels, TT homozygotes of G-344T polymorphism exhibited a trend for higher values compared to C-carriees (825.1±194.9 vs 799.9±204.6 ng/mL, p=0.6) and similarly eGFR did not differ across genotypes (CC: 74.9±23.4, CT: 71.9±15.1, TT: 72.1±17.8, p=NS). Combination of allelic variants of these candidate genes was not associated with worse renal estimates and different Cystatin-C levels (p=NS for all).

Conclusions: In the present study we have shown that variations in the angiotensinogen gene may affect uric acid levels, however according to our findings and those of others, the polymorphisms are not capable to affect further renal function in patients with essential hypertension.

The association of androgenic alopecia with target organ damage in newly diagnosed and never treated young male hypertensive subjects. A pilot study


Purpose: Several studies have demonstrated the presence of an association between androgenic alopecia (AGA) and cardiovascular disease. The aim of this study was to evaluate any target organ damage in newly diagnosed and never treated young male hypertensives with and without AGA by the incorporation of arterial stiffness (PWV, PP), left ventricular hypertrophy (LVH), microalbuminuria (MAU) and coronary flow reserve (CFR).

Methods: We performed a cross-sectional study in 21 newly diagnosed and untreated young male hypertensives with AGA (mean age 41.6±6 years) and 8 ones without AGA (mean age 40.1±12 years) who serum was used as controls. Carotid-femoral pulse wave velocity (PWV) and office pulse pressure (PP) were assessed as indices of arterial stiffness. Carotid ultrasonography was used to measure the IMT of the common carotid arteries. ECHO was performed in all subjects in order to estimate LVMI and CFR. 24hr urine collection was performed for MAU estimation. AGA was classified according to the Hamilton-Norwood scale, age of onset and duration while body height was estimated.

Results: No significant difference was found within groups regarding age, BMI, systolic and diastolic blood pressure, PP, PWV, IMT, LVMI, MAU and CFR. However, in AGA patients: a. Hamilton-Norwood scale was related with PP (r=0.64, p<0.01), b. age of onset of AGA was inversely related with PP (r= -0.48, p<0.05), c. duration of AGA was related with PP (r=0.61, p<0.01) and inversely with CFR (r=-0.55, p<0.05) and d. body hair growth was related with PWV (r=0.48, p<0.05).

Conclusions: Our results support the hypothesis that the severity, the early onset, the long standing of AGA as well as body hair growth are related with target organ damage in young untreated males with newly diagnosed essential hypertension. However, it is pending to be demonstrated with further studies if the release of substances from hair follicles or the over expression of androgen receptors or 5a-reductase in the kidney induce a hypertensive response.

Role of single-nucleotide polymorphisms in renal function of untreated hypertensives: impact on cystatin-C and classical estimates

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Purpose: Renin-angiotensin-aldosterone system (RAAS) participates in the development of renal impairment. Several genetic polymorphisms of its key components, such as M23ST and C-344T may be clinically relevant. We therefore aimed to investigate whether these polymorphisms have effects on quantitative measures of renal function in states of hypertension.

Methods: The study population consisted of 318 untreated essential hypertensives and a control group, consisted of 193 matched subjects. The gene mutation frequency was determined using polymerase chain reaction (PCR) technique and appropriate restriction endonucleases. Plasma glucose, serum creatinine, uric acid and lipid levels were determined by routine methods. Serum Cystatin-C levels were measured by ELISA kit. We also assessed GFR by the Cockcroft-Gault formula and estimated Cystatin-C-dependent GFR (eGFR) using the following equation: eGFR = 127.7*(Cystatin C – 1.17)*(Age – 0.13)*(0.9)^0.9. Results:

Interestingly, angiotensinogen 235TT genotype showed a trend towards a lower GFR compared with MM and MT genotype in hypertensive patients (104±31 vs 110±48, p=NS) and higher values of uric acid (5.3±1.8 vs 4.7±1.5 mg/dL, p=0.056) but neither genotype was associated with increased creatinine, cystatin-c nor eGFR (p=NS for all). With respect to Cystatin-C levels, TT homozygotes of G-344T polymorphism exhibited a trend for higher values compared to C-carriees (825.1±194.9 vs 799.9±204.6 ng/mL, p=0.6) and similarly eGFR did not differ across genotypes (CC: 74.9±23.4, CT: 71.9±15.1, TT: 72.1±17.8, p=NS). Combination of allelic variants of these candidate genes was not associated with worse renal estimates and different Cystatin-C levels (p=NS for all).

Conclusions: In the present study we have shown that variations in the angiotensinogen gene may affect uric acid levels, however according to our findings and those of others, the polymorphisms are not capable to affect further renal function in patients with essential hypertension.

The association of androgenic alopecia with target organ damage in newly diagnosed and never treated young male hypertensive subjects. A pilot study


Purpose: Several studies have demonstrated the presence of an association between androgenic alopecia (AGA) and cardiovascular disease. The aim of this study was to evaluate any target organ damage in newly diagnosed and never treated young male hypertensives with and without AGA by the incorporation of arterial stiffness (PWV, PP), carotid intima-media thickness (IMT), left ventricular hypertrophy (LVMI), microalbuminuria (MAU) and coronary flow reserve (CFR).

Methods: We performed a cross-sectional study in 21 newly diagnosed and untreated young male hypertensives with AGA (mean age 41.6±6 years) and 8 ones without AGA (mean age 40.1±12 years) who serum was used as controls. Carotid-femoral pulse wave velocity (PWV) and office pulse pressure (PP) were assessed as indices of arterial stiffness. Carotid ultrasonography was used to measure the IMT of the common carotid arteries. ECHO was performed in all subjects in order to
49.7 ± 1.9 vs. 53.3 ± 1.9, P = 0.047, 10.3 ± 3.9 vs. 8.2 ± 3.6, P = 0.036, 15.7 ± 6 vs. 11.6 ± 6, P = 0.007, respectively. Multiple regression revealed that leptin levels contributed to the variability of heart rate after adjustment for age, sex, fasting glucose, total cholesterol, and BMI (β = -0.24, P = 0.003).

Conclusions: Our data demonstrate that plasma leptin concentration is related to 24hr heart rate variability providing evidence that leptin may influence cardiovascular control in overweight hypertensive subjects. These findings may offer explanation for understanding the interactions between leptin and cardiovascular implications in overweight hypertensive subjects.

**P1813** Undiagnosed hypertension trumps trastuzumab as a risk factor for anxiety

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Introduction: A growing number of patients are at risk from chronic anticoagulant cardiotoxicity (CAC), a result of improving prognosis from cancer. This risk is even at adjunct doses of chemotherapy. Although the early risk of heart failure immediately treatment is low, the life-time risk of heart failure is significantly increased. The purpose of this study was to understand this problem remains poorly documented, especially in adults. Furthermore, while risk of AC is known to be highly idiosyncratic, effective tests to predict susceptibility are lacking. We undertook a study to look for genetic and non-genetic risk factors that predict CAC. Here we present data on the relationship baseline blood pressure, weight and percentage body fat (%BFat), and the cardiac response to anthracycline treatment

Methods: Patients receiving anthracycline-based chemotherapy for early breast cancer were recruited. Those with known cardiovascular disease or SBP >160/100 were excluded. LVEF was measured using cardiovascular magnetic resonance imaging (CMR) before chemotherapy. Follow-up was 1-year after the final dose of anthracycline, or 3-months after the end of Trastuzumab. Chronic AC was defined as a fall in absolute LVEF <5% (ΔLVEF <5%); Blood pressure, weight and %BFat were measured at baseline. Results: 164 subjects completed the study. The median dose of epirubicin was 400 mg/m². Thirty were treated with Trastuzumab. Thirty-four participants (20.7%) were estimated with polymerase chain reaction with use of primer pairs. The products of amplification were detected in 2% agaric gel using video documentation. C786C) was estimated in 98 hypertensive persons, age 45-62 years, Ukrainians of Bucovinian region. By addressing these report, the eventual hope is that we might design better therapeutic strategies to prevent endothelial dysfunction and atherosclerotic vascular disease.

Conclusions: Inclusion, relation between carriage of allele C of eNOS-3 gene and higher levels of cholesterol and low-density lipoproteines was found in Ukrainian population of Bucovinian region. By addressing these report, the eventual hope is that we might design better therapeutic strategies to prevent endothelial dysfunction and atherosclerotic vascular disease.

**P1815** Development of arterial hypertension in subjects with high normal blood pressure and antiendothelial cell antibodies level

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Purpose: Recent evidence demonstrate that elevated levels of circulating anti-cardiovascular neural control in overweight hypertensive subjects. These findings may offer explanation for understanding the interactions between leptin and cardiovascular implications in overweight hypertensive subjects.

**Table 1**

<table>
<thead>
<tr>
<th>Groupe A (n=36)</th>
<th>Groupe B (n=54)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG AEC</td>
<td>0.097±0.05</td>
<td>0.095±0.04</td>
</tr>
<tr>
<td>IgG AEC</td>
<td>0.105±0.07</td>
<td>0.093±0.08</td>
</tr>
</tbody>
</table>

Conclusions: Our results suggest that subjects with high normal blood pressure and high AEC levels are prone to future development of arterial hypertension. The possibility that high AEC levels may be a driving mechanism for the development of essential hypertension needs further investigation.

**RISK FACTORS FOR HYPERTENSION**

**P1814** The relationship of eNOS gene polymorphisms and cholesterol level at the patient with arterial hypertension in Ukrainian population

D. Shorkova, E. Shorkov. Bucovinan State Medical University, Chernivtsi, Ukraine

In our days the polymorphism of genes-candidates of cardiovascular diseases is actively studied as one of potential risk factors of the development of atherosclerotic process and alterations of endothelial nitric oxide synthase (eNOS) enzyme activity. Few studies have been assessed in this area with significant cardiovascular morbidity and mortality. The role of cholesterol and low density lipoproteines in these processes is reliable.

**Purpose**: In this study, we determined the prevalence and distribution of the above polymorphism and its relationship with the cholesterol level in the hypertensive patients, Ukrainians of Bucovinan region and significance of homoyzogotes and heterozygote mutations in this context.

**Methods**: The association of variants of eNOS-3 gene polymorphism (normal homoyzogotes – TT, heterozygotes – CT and homoyzogote mutations – C786T) was estimated in 98 hypertensive persons, age 45-62 years, Ukrainians of Bucovinan region. The types of endothelium NO-synthase gene polymorphism were estimated with polymerase chain reaction with use of primer pairs. The products of amplification were detected in 2% agaric gel using video documentation system.

**Results**: The prevalence of normal homoyzogotes with T-T among hypertensive patients was 9.2%, homoyzogotes with C-G mutation were 10.1%. The most part of the inspected patients were presented with polymorphism G-T – 80.7%. The level of general cholesterol at patients with T-T polymorphism was estimated as 7.01±1.10 mmol/l and 3.32±1.31 mmol/l was level of low-density lipoproteines. At the heterozygotes patients with polymorphism C-T the maintenance of general cholesterol arrived at 7.33±1.70 mmol/l and low-density lipoproteines - 3.85±1.16 mmol/l (p=0.05). In case of homoyzogote’s mutation and C-C polymorphism it was marked the considerably higher levels of both general cholesterol 8.07±1.87 (p=0.05) and lipoproteines of low-density 5.71±1.37 mmol/l (p=0.00).

Conclusions: In addition, relation between carriage of allele C of eNOS-3 gene and higher levels of cholesterol and low-density lipoproteines was found in Ukrainian population of Bucovinan region. By addressing these report, the eventual hope is that we might design better therapeutic strategies to prevent endothelial dysfunction and atherosclerotic vascular disease.

**P1816** The role of community-based lifestyle intervention on salt intake and blood pressure in Iran

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Background and aim: Data on the effect of lifestyle intervention programs on salt intake and blood pressure in developing countries are scarce. This study aimed to assess the impact of a healthy lifestyle community-based trial on salt intake and blood pressure among a representative sample of normotensive Iranian adults.

**Methods**: We compared the data for salt intake, urinary sodium levels and blood pressure from three cross-sectional surveys in time points of 1999, 2001-2002 (beginning of the community interventions), and 2007 (after the community trial) for normotensive adult population of Isfahan, Iran. Using multi-stage cluster sampling method, one of the family members at each household was randomly selected. Dietary salt intake was estimated based on urinary sodium levels. Systolic and diastolic blood pressures were measured according to standard methods.

**Results**: Dietary sodium intake and urinary sodium levels as well as systolic and diastolic blood pressure were significantly decreased during the 9-year study period. Unlike systolic and diastolic blood pressures that had a consistent decrease between 1999 and 2007, dietary sodium intake and urinary sodium levels were slightly raised from 1999 to 2000-2001 and then reduced between 2001-2 and 2007 evaluations. The same findings were reached when data were analyzed separately by gender or weight status.

**Conclusion**: A lifestyle community trial was effective in controlling the escalating
trend of blood pressure and salt intake in Iranian population. It can be adopted in other developing countries.

**P1817**

Assessment of dietary sodium intake among adults in Korean general population by 24 hour urine samples

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**Aims:** Korean Government has started sodium intake reduction policy since 2005. Accurate estimation of sodium intake by reproducible method and assessment of the effects of high sodium intake to cardiovascular health are crucial aspect in performing that policy. The present study was performed in 2011 to test the feasibility of 24 urine collection and to introduce it as a standard method of salt intake measurement in a nationwide survey (granted by Korea FDA, 11162KFDIA162, NCT01438619, NCT01323771).

**Methods and results:** Representative population (aged 20 between 65 years) was selected by List-assisted random-digit dialing method (LARD), from a city with one million population. Sodium and potassium intake (24HUNa, 24HUK, respectively) were measured with 24 hour urine collection. Out of 1623 telephone interviews, 496 adults (30.6%, age range 20 – 65 years) were recruited by LARD. Of those recruited, 368 subjects completed 24 hour urine sample collection. The estimated mean 24HUNa was 166.4 mmol/day, much lower than 208.2 mmol in 1988 (INTERSALT). 24HUNa was highest in population aged 30 to 49 years, with decrease in 24HUNa after 50 years. Men had higher 24HUNa than women (182.0 vs. 151.4 mmol/day). The estimated sodium intake is higher than that reported from UK and Scotland survey, and Finland, similar to that of Spain, and lower than that of Portugal and Slovenia. In contrast to 24HUNa, 24HUK was continuously increased as age increased. This trend is different from national health survey 2009, which showed low intake of potassium in population above 50 years. This difference indicates an increased concern about health, leading to ingestion of potassium rich food.

**Conclusion:** In the estimation of sodium intake, 24 hour urine collection method is feasible, and enables us to compare sodium intake to the result of other survey even in other countries. This method will be adopted in nationwide survey of Korea. Although high sodium intake is still a significant problem in population below 50 years, pattern of sodium intake seems to be changing due to high concerns on health.

**P1818**

The influence of high vs. low sodium intake on blood pressure and hemodynamics in patients with morbid obesity

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**Purpose:** Many patients with morbid obesity have hypertension. The complex pathophysiologic abnormalities linking hypertension to obesity have not been fully clarified, but abnormal sodium handling may be an essential mechanism. The purpose of the present study was to examine the hemodynamic responses to a short-term change in dietary sodium intake in patients with morbid obesity with and without hypertension.

**Methods:** Twelve hypertensive patients (5 male, 7 female) and twelve normotensive patients (5 male, 7 female) with severe obesity (BMI > 40 kg/m²) were examined after 5 days of a low-sodium diet (75 mmol/day) and 5 days of a high-sodium diet (250 mmol/day) in a randomized order. Plasma volume, glomerular filtration rate, body compartments, and hemodynamic examinations were performed on day 5 in each diet period. The hemodynamic examinations (non-invasive cardiac output measurements) were performed at rest and during bicycle exercise, whereas blood pressure was measured after 30 minutes of rest and as 24-hour blood pressure measurements.

**Results:** In hypertensive as well as in normotensive patients, high sodium intake as compared to low sodium intake was associated with an increase in plasma volume (5.1%, p<0.001), cardiac output (21.4%, p<0.001), and stroke volume (27.8% vs. 27.7%; p=0.84) similarly in both groups at rest, with no change in heart rate in either groups (6.3% vs. 4.3%; p=0.684). Twenty-four hour blood pressure measurements and resting blood pressure was unaltered in both groups, and therefore the total peripheral resistance decreased equally (11±3% vs. 10±3; p=0.848) during high sodium intake. Similar changes were observed during an incremental bicycle exercise test where cardiac output and stroke volume were higher while mean arterial blood pressure was unchanged at each exercise level during high sodium intake.

**Conclusion:** Neither hypertensive nor normotensive patients with morbid obesity seem to have a sodium sensitive blood pressure, despite a substantial increase in plasma volume, cardiac output and stroke volume during short term high sodium intake.

**P1819**

Association of different obesity indices with blood pressure in greek adolescents: the role of familial hypertension burden

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**Purpose:** To assess the associations between different obesity indices and blood pressure (BP) in Greek adolescent students, while the familial burden of hypertension was also been taken into consideration.

**Methods:** The study comprised of 496 students who were subjected to repeated BP measurements and anthropometric measurements (i.e. waist circumference, hip, waist-to-hip ratio, waist-to-height ratio, body mass index (BMI) and conicity index) were calculated. By means of a standard questionnaire, developed for the purposes of the study, we retrieved information about age, sex, number of siblings, several indicators of family’s socioeconomic status, smoking habits, time spent on sedentary activities, as well as information on family history of arterial hypertension (one, both or none of the parents) and hospitalizations of the children.

**Results:** Overall, the study population was divided in two groups according to the presence of morbid obesity (n=109) and the absence (n=887) of familial history of hypertension. Adolescents with family history of hypertension presented with significantly higher systolic BP (SBP) (p=0.003) and diastolic BP (DBP) (p=0.021) levels. Further, univariate analysis was conducted assessing correlations between obesity indices and blood pressure levels in the overall population. WHR was strongly associated with SBP and DBP [r=0.27, p=0.009] (r=0.13, p=0.09), while BMI was strongly correlated with SBP, DBP but not heart rate [r=0.47, p<0.001] [r=0.13, p=0.001; (P=NS), respectively]. Finally, CI was positively associated with SBP but not with DBP [r=0.185, p<0.0001 and (P=NS) respectively], while waist-to-height ratio was strongly correlated with SBP, DBP but not HR [r=0.32, p<0.0001, (r=0.24, p<0.0001), (P=NS), respectively].

**Conclusion:** Young adolescents with familial aggregation of hypertension have higher levels of both systolic and diastolic BP, independently of age, smoking and body weight, while obesity indices are strongly correlated with BP levels in these ages.

**P1820**

Role of aerobic capacity in inflammation state in diabetes with and without chronic kidney disease

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Our hypothesis is that in patients with both, better aerobic capacity (AC) is associated with less inflammatory state (IS) and arterial stiffness. The aim of this study was to determine if a better AC evaluated by VO2max is associated with attenuated chronic IS, arterial stiffness and carotid intima-media thickness (IMT) in CKD DM and non-DM. Thirty-nine CKD patients (17 in hemodialysis program), were clinically and laboratory evaluated. According to CKD etiology 2 groups were obtained: DM (GD) was formed by 11 and non-DM (GND) formed by 28. Central BP and arterial stiffness were evaluated by Sphygmocor. Average and max of left and right IMT by US were also performed. AC was measured by estimated VO2max according to treadmill test by Bruce protocol. The GD showed a higher frequency of CRP above our laboratory cut-off (p=0.044), higher frequency of male gender and a non-significant higher value of VO2max (p=0.099). The IMT was similar. Only better AC was associated with lower frequency of high CRP when adjusted to DM and gender in a logistic regression model. In conclusion, AC was associated with inflammatory state, in CKD patients, independently of DM presence.

### Table 1: Multiple linear regression: C-reactive protein

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>P</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.210</td>
<td>0.021</td>
<td>0.000 2.335</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.646</td>
<td>0.201</td>
<td>0.000 86.803</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO2max</td>
<td>0.024</td>
<td>0.070</td>
<td>0.000 0.976</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Effect of coffee consumption on blood pressure and exercise tolerance

B.M. Miolo¹, M.A. Moretti¹, D. Tarasoutchi¹, K.M. Dias¹, R.V. Amato¹, L. Massaroppe², C.B. Vianna², L.A. Machado Cesar³
¹Heart Institute, Univ. of Sao Paulo Medical School, Sao Paulo, Brazil; ²University of Sao Paulo (USP), Sao Paulo, Brazil

Purpose: Coffee is the most abundantly consumed stimulant worldwide. However, its cardiovascular safety remains controversial. Some studies suggest coffee consumption acutely can determine a slight blood pressure raise and improve exercise tolerance. AIM: We evaluated blood pressure and exercise tolerance before and after daily chronic coffee consumption in a group of healthy volunteers and in patients with coronary artery disease.

Methods: We did a prospective random cross-over trial to evaluate two different types of roasted coffee. All individuals were oriented by the same nutritionist and put on 3 weeks washout for cafferne beverages and foods. Then they were randomly assigned to start drinking filtered coffee first in one style-roasted coffee and then crossed-over to the other style. Ground coffee beans, provided for four weeks each, were medium-dark (MD) and dark (D) roasts. After 4 weeks they were cross-over with a total of 8 weeks of drinking coffee. All individuals were taught the amount of coffee to brew each time. They get instructions to drink 450 to 600ml every single day. In the baseline and after each period of drinking they were submitted to 9 min(t)est and ambulatory blood pressure monitoring (ABPM) for 4 weeks (24-h ABPM). We did analyze average systolic blood pressure (SBP) and diastolic blood pressure (DBP) from 24-h ABPM, total exercise time (J.T Exercise) and double product (DP) from treadmill test. Variables were evaluated by the analysis of variance for repeated measures.

Results: We evaluated 80 subjects (26 with coronary artery disease and 54 healthy volunteers) with 53.4±13.5 years old, 35 men and 45 women (see table).

<table>
<thead>
<tr>
<th>24-h ABPM and Treadmill Test</th>
<th>Baseline</th>
<th>D</th>
<th>MD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.T Exercise (s)</td>
<td>619.5±209.4</td>
<td>658.2±225.1</td>
<td>661.4±224.0</td>
<td>0.001</td>
</tr>
<tr>
<td>DP (SBP x HR)</td>
<td>23926.7±3819.7</td>
<td>23523.4±2412.3</td>
<td>23431.7±3928.8</td>
<td>0.272</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>109.5±10.3</td>
<td>107.9±15.4</td>
<td>112.6±11.7</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>66.8±7.8</td>
<td>66.4±8.4</td>
<td>68.7±8.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Measures expressed as average ± SD.

Conclusions: Both raised total exercise time capacity, without an increase in double product. Medium dark roasted coffee consumption, but not dark, promoted a slight blood pressure elevation. These findings suggest that there are substances other than caffeine that raises blood pressure and is degraded by roasting.

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Muscular endurance and maximal aerobic capacity as determinants of blood pressure in young men

Purpose: The relationship between blood pressure and physical work capacity as well as leisure time physical activity was studied in a group of young men.

Methods: The study participants were enrolled in 2008 during eight Finnish Defence Forces refresher courses for the army reserve and consisted of 846 young men (mean age 24.9±5.0 years). Body weight, height and waist circumference were measured. Muscular endurance was determined using a score based on the number of reps performed for the tests. Aerobic capacity was measured using a bicycle ergometer test. Blood pressure was measured. Muscular endurance, self-reported leisure time physical activity and alcohol consumption were not associated with blood pressure level. Thus, the present study suggests that even in young adults, measures that combat obesity and low fitness may prove effective in the prevention of hypertension.

<table>
<thead>
<tr>
<th>24-h ABPM and Treadmill Test</th>
<th>Baseline</th>
<th>D</th>
<th>MD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>85.5±7</td>
<td>86.7±7</td>
<td>115.9±6.7</td>
<td>96.1±11</td>
</tr>
<tr>
<td>R (mm Hg/ml·s)</td>
<td>0.92±0.23</td>
<td>1.01±0.29</td>
<td>1.13±0.23</td>
<td>1.13±0.27</td>
</tr>
<tr>
<td>Zr (10^4 mm Hg ml·s/m^3)</td>
<td>65.2±24</td>
<td>68.2±22</td>
<td>88.2±24</td>
<td>80.3±30</td>
</tr>
<tr>
<td>Zr LF (10^4 mm Hg ml·s/m^3)</td>
<td>45.8±23</td>
<td>55.2±21</td>
<td>66.3±34</td>
<td>58.2±27</td>
</tr>
<tr>
<td>C (ml ml−1·0.46)</td>
<td>1.55±0.40</td>
<td>1.40±0.45</td>
<td>1.34±0.43</td>
<td>1.40±0.48</td>
</tr>
<tr>
<td>Pes (mm Hg)</td>
<td>87.9±9</td>
<td>92.8±32</td>
<td>122.1±11</td>
<td>105.1±39</td>
</tr>
<tr>
<td>EAT (mm Hg/ml·kg·min/m^3)</td>
<td>3.62±1.76</td>
<td>5.40±1.68</td>
<td>7.13±2.52</td>
<td>6.19±1.90</td>
</tr>
<tr>
<td>EAT(E/I)</td>
<td>0.84±0.23</td>
<td>0.45±0.14</td>
<td>0.51±0.19</td>
<td>0.53±0.18</td>
</tr>
</tbody>
</table>

p<0.05 vs 6 months, *p<0.05 vs normal population

Conclusions: PE is characterized by increased proximal arterial stiffness and peripheral resistance following preeclampsia might contribute to the higher cardiovascular risk in future life.

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Preeclampsia (PE) is pregnancy induced hypertension and proteinuria, occurring after 20 weeks of gestation. We performed a study of arterial properties and ventricular-arterial coupling (VAC) at term and 6 months post-partum in women with PE and women with normal pregnancy (NP). Postpartum recordings were compared against non-pregnant values from women with previous preeclamptic pregnancy (PPEP).

Methods: 35 women (37±4 years) with PPEP (3.5±1.0 years), 40 (32±6 years) with PE and 65 (32±5 years) with NP. Aortic root flow and pressure obtained by Doopper transoderned (hodphats) and calibrated right subclavian artery pressure traces. Arterial compliance (C), characteristic impedance (Zo), and peripheral arterial resistance (R) were estimated by 3-element Windkessel model (WK) and Fourier analysis of pressure and flow. Arterial elastance, Ea, was calculated as end systolic pressure (Pse) over stroke volume (SV). Ventricular function was assessed by ELVI, which represents left ventricular systolic elastance (Pes/ESVI). The Ea/ELVI is an index of ventricular-arterial coupling.

Results: At term, Z0, Ea and R were higher and C was lower in PE pregnancy compared to NP, indicating a higher resistance in the artera tree. Z0, Ea and R remained elevated 6 months follow-up in PE and after 3 years in PPEP.

Conclusions: PE is characterized by increased proximal arterial stiffness and peripheral resistance at term, 6 months post partum, and at 3 years follow up. These results indicate that the cardiovascular changes of PE are not limited to the pregnancy period and might explain the higher risk of hypertension and cardiovascular disease in future life.

PREVALENCE OF HYPERTENSION IN DIFFERENT POPULATIONS

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¹Univ. Estadual Paulista (UNESP), Botucatu Medical School - Sao Paulo State University, Botucatu, Brazil; ²Faculdade Evadue Avaré, Avaré, Brazil

There are an inverse paradoxical relationship between diastolic blood pressure and mortality in hemodialysis patients. It means that the higher the diastolic blood pressure the lower the mortality rate. This has induced some authors to question the need for antihypertensive treatment in this subset of patients. But others confounding factors, besides hemodynamic load, could act to explain this relationship. So, the aim of this work is to verify the role of microinflammatory state in the excess of mortality of low diastolic blood pressure hemodialysis patients. We performed a longitudinal analysis of 113 hemodialysis patients of the Nephrology Clinic. A univariate Cox proportional hazard risk regression analysis identifies Non-diastolic blood pressure as a protective factor to mortality risk (HR): 0.954; 95% Confidence Interval (CI):0.912–0.999; p=0.044. But when adjusted to C-reactive protein (CRP) and left ventricular mass index (LVMI), only CRP (HR: 1.38; CI: 1.16–1.64; p<0.001) and LVMI (HR:1.02; CI: 1.01–1.03; p<0.00) were risk factors for hypertension / Prevalence of hypertension in different populations 301

Risk factors for hypertension / Prevalence of hypertension in different populations 301

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associated with mortality and no statistically significant association of low diastolic blood pressure with mortality was identified (HR: 0.96; CI: 0.90-1.02; p=0.231).

We concluded that biochemical and cardiac morphological changes could explain the excess of mortality in low diastolic blood pressure hemodialysis patients from our cohort.

**P1825 Increased prevalence of a hypertensive response to exercise in male patients with obstructive sleep apnea and essential hypertension**

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**Purpose:** Obstructive sleep apnea (OSA) is characterized by increased sympathetic activity that serves as a possible pathophysiologic mechanism for a hypertensive response to exercise (HRE). We sought to investigate the association of OSA with HRE in the setting of hypertension.

**Methods:** We studied 37 male patients with essential hypertension (age: 52±8 years, mean office BP: 141/93mmHg) and untreated OSA diagnosed with polysomnography (PSG) (apnea-hypopnea-index>5) and 39 hypertensive controls without OSA (negative PSG) matched for age and body mass index. All patients underwent office and ambulatory BP measurements, echocardiography, routine blood testing and exercise treadmill testing according to the Bruce protocol. A HRE was defined as peak systolic BP increase of 20mmHg or greater.

**Results:** The two groups did not differ significantly regarding office and ambulatory blood pressure, metabolic profile and left ventricular mass index. However peak systolic and diastolic BP were significantly higher in patients with OSA compared to controls (199±21 vs. 188±22mmHg, p=0.031 and 93±12 vs. 86±11mmHg, p=0.023 respectively). Furthermore, a HRE was significantly more prevalent in hypertensives with OSA compared to those without (46% vs. 20%, p=0.034). In a model of multiple logistic regression analysis, HRE was independently predicted by logA/G (OR=2.24, CI: 1.06-4.72).

**Conclusions:** HRE is more prevalent in hypertensive patients with OSA compared to their non-OSA counterparts. This finding may have important diagnostic and prognostic implications.

**P1828 The relationship between additional markers of cardiovascular risk and the complex metabolic and haemodynamic parameters in hypertensive patients with obesity**

O. Pionova. Kharkiv National Medical University, Kharkiv, Ukraine

**Objective:** The objective is to evaluate the relationship between indicators carbohydrate metabolism, serum apolipoprotein B (apo B) and apolipoprotein A1 (apo A1) levels and blood pressure in hypertensive patients with obesity.

**Materials and methods:** 105 patients on average age 54.9±9.94 with hypertension and obesity were examined. They were matched in age and sex. Control group consisted of 21 healthy men aged on average 53.40±11.60 years. All patients underwent clinical examination that included anthropometric examination, assessment of carbohydrate metabolism (fasting glucose, insulin, glycated hemoglobin (Hb A1c) levels) and determine the level of apolipoproteins (apo B and apo A1). We hypothesised that patients with OSA based on the criteria of the IDF, 2005 was diagnosed abdominal obesity and to define the glomerulometabolic profiles. Oral glucose tolerant test and glaciated hemoglobin was used to exclude patients with type 2 DM.

**Results:** In hypertensive patients with obesity revealed a positive significant association between rate of waist circumference and insulinaemia (R=0.24; p <0.01), apo B (R=0.21; p <0.02), and negative significant association with level apo A1 (R=0.29; p <0.002), For 57.84% of them identified insulin resistance (IR). In individuals with IR glycemia was associated with DBP (R=0.41; p <0.05), but not with SBP. In hypertensive patients without IR reliable relationship between metabolic and haemodynamic parameters haven’t been identified. In hypertensive patients with obesity and IR revealed an association between levels of apo B and total cholesterol (TC) (R=0.29; p <0.05), high density lipoproteins cholesterol (HDL-C) (R=0.28; p <0.05), low-density lipoprotein cholesterol (LDL-C) (R=0.32; p <0.05), triglycerides (R=0.46; p <0.05), but no relationship with levels of apo A1. On the other hand, hypertensive patients with obesity and without IR revealed the relationship between levels of apo B and TC (R=0.53; p <0.05), LDL-C (R=0.49; p <0.05). At the same time antihypertensive marker (apo A) is negative associated with TC (R=0.46; p <0.05), and LDL-C (R=0.48; p <0.05).

**Conclusion:** This study showed that in hypertensive patients with obesity the relationship between the levels of additional atherogenic markers in the presence of higher insulin resistance. Probably haemodynamic factors, together with insulin resistance contribute to the formation of atherogenic potential, especially if they have abdominal obesity.
Prevalence of cardiovascular risk factors in students

F. Aguirre on behalf of INPETU, Military Hospital, Guayaquil, Ecuador

Purpose: P.C.R.F. Study is a prospective, observational study designed to evaluate the prevalence of hypertension and the presence of cardiovascular risk factors in young people aged 11 to 13 years of age.

Methods: The study was conducted in two schools in Guayaquil chosen at random. Consent was obtained from school authorities and participating students, who were also informed of the reasons behind the study, in accordance with the Helsinki criteria. In total, 623 students were examined. This examination included collection of anthropometric data and measurement of blood pressure (BP) in the first phase of the study. In the second phase, students with elevated BP were re-examined and classified according to their BP response. They also underwent tests for microalbuminuria using turbidimetric methods. Central tendency (mean, median and mode) and dispersion values (standard deviation, standard error, 95% CI) were calculated for data analysis. Relative risk was also evaluated using Medcalc software. Body mass index (BMI) and BP was calculated in percentiles in order to define ranges in accordance with their weight, height and age.

Results: Of the sample population, 54.4% were men and 45.58% were women. The average BMI was 19.96 ± 0.175 kg. Underweight was found in 3.8% of the sample. The percentage of overweight in 63.7%, overweight in 17.6%, and obesity in 4.7%. Systolic SBP averaged 109±11mmhg, diastolic BP was 60±5mmhg, and mean arterial pressure (MAP) was 77.7mmhg. Participants were classified as BP of 121-129 and pre-HTA region 1 130-139 in the first measurement as white coat hypertension when there was subsequent normalization of the values in two subsequent measurements, and BP > 140 mmHg as hypertension (HTA).

Conclusions: Most young participants with elevated BP were classified as having pre-HTA, followed by white coat HTA and finally HTA. 9.3%, 3.2% and 0.80% respectively. The percentage was higher in men (54%) and overweight and obese youth. A correlation was not found between microalbuminuria values and BP. Of the 6.7% with microalbuminuria, 4.7% were obese as determined by BMI, 23.8% were overweight, and 28.5% had normal weight. This finding could serve as a practical tool to investigate metabolic disorders such as diabetes, obesity, or HTA. Finally, we found that there is a relationship between family cardiovascular history and the presence of HTA in youth, in contrast to the use of energy drinks, which showed no association.

Prevalence of hypertension in different populations / Controversial issues on thrombosis and antithrombotics treatment

Effect of rivaroxaban with or without acetylsalicylic acid on thrombus formation in an ex vivo perfusion chamber: an open-label, randomized study in healthy subjects

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Purpose: Although the pathogenesis differs between arterial and venous thrombosis, fibrin formation and platelet activation have important roles in thrombogenesis. This study investigated the effect of rivaroxaban, an oral, direct Factor Xa inhibitor, with or without acetylsalicylic acid (ASA), on thrombus formation in an ex vivo perfusion chamber at both low (as in the venous system) and high (as in stenosed arteries) shear rates.

Methods: Fifty-one healthy subjects were enrolled in this randomized, two-way crossover study involving rivaroxaban with and without ASA and parallel group study for comparison between the different dosing regimens of rivaroxaban and ASA plus clopidogrel. The treatment groups were: (A) rivaroxaban plus ASA (5 mg/day), and rivaroxaban 5.10 or 20 mg on day 0 and ASA once daily (od); (B) 4 consecutive days (from day –3 to day 0; ASA 300 mg loading dose followed by 100 mg); (B) rivaroxaban alone: single dose of rivaroxaban 5.10, or 20 mg on day 0; (C) clopidogrel plus ASA: (5 mg/day) and rivaroxaban 5.10 or 20 mg on days –3 to day 0; clopidogrel 300 mg loading dose followed by 75 mg) and ASA od on 4 consecutive days (as in group A). Thrombus formed in the perfusion chamber was measured with D-dimer levels (for fibrin deposition) and P-selectin content (for platelet deposition), which were performed at the time of Cmax of rivaroxaban and at the maximum effect of ASA or clopidogrel. Pharmacodynamic parameters measured from plasma included inhibition of Factor Xa activity, prothrombin time, activated partial thromboplastin time and endogenous thrombin potential.

Results: Rivaroxaban reduced fibrin deposition in the perfusion chamber thrombus as measured with D-dimer levels, which were decreased by 9%, 84% and 65% at low shear rate and 37%, 73% and 74% at high shear rate after rivaroxaban 5, 10 and 20 mg, respectively. Steady-state ASA with rivaroxaban 5 mg caused a greater reduction in D-dimer levels (63%) at low shear rate. Co-administration of ASA and clopidogrel was associated with a 30% decrease at low shear rate and a 14% decrease at high shear rate. No conclusive effect was observed for thrombus P-selectin content across the treatment groups. The effects of rivaroxaban on the pharmacodynamic parameters measured in plasma were similar to previous studies, and co-administration of ASA and rivaroxaban had no additional influence.

Conclusions: Rivaroxaban dose dependently inhibited ex vivo thrombus formation under low and high shear rates. Co-administration of ASA had a small additional effect on the antithrombotic action of low-dose rivaroxaban.
Use of proton pump inhibitors and the risk of coronary events in patients receiving low-dose acetylsalicylic acid in UK primary care

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Purpose: To estimate the risk of coronary events associated with proton pump inhibitor (PPI) use in patients taking low-dose acetylsalicylic acid (ASA).

Methods: Two patient cohorts were identified aged 50–84 years with a first prescription for low-dose ASA (75–300 mg/day) between 2000 and 2007. The first included patients in The Health Improvement Network (THIN) primary care database described ASA for secondary prevention of cardiovascular or cerebrovascular disease (CVD cohort; N = 39,513), and the second included patients in either THIN or the General Practice Research Database prescribed low-dose ASA after an acute coronary event or coronary artery revascularization (acute coronary syndrome [ACS] cohort; N = 42,542). New cases of non-fatal myocardial infarction (MI)/coronary heart disease (CHD) were identified after follow-up of 3.2 and 3.5 years, respectively. Controls (CVD cohort, n = 50,000; ACS cohort, n = 2,000) were frequency matched to cases by age, sex and calendar year.

Results: Compared with low-dose ASA use, there was a suggestion of a decreased risk of MI (ACS cohort: HR 0.81, 95% CI: 0.66–1.00) and CHD (CVD cohort: 0.85, 95% CI: 0.71–1.01) in patients on low-dose ASA. The HR for MI/CHD associated with current continuous use of both low-dose ASA and a PPI (CVD cohort; N = 50,000) was 0.78 (95% CI: 0.66–0.94).

Conclusions: The combination of rivaroxaban with single or dual antiplatelet drugs results in a synergistically enhanced antithrombotic potency.

Results of the EmbraceAC Trial: a comparison of warfarin to tecafrarin, a novel anticoagulant

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Purpose: Warfarin (W) remains an important drug for providing anticoagulant therapy (AC) for many patients (pts). It has a relatively narrow therapeutic window, however, owing to its cytochrome-based metabolism. Tecafrarin (T) is a novel vitamin K antagonist free of cytochrome-based metabolism. EmbraceAC was conducted to determine populations in which T is superior to W as measured by time in therapeutic range (TTR).

Methods: A total of 612 pts from 47 sites were followed for 6-9 months in a randomized, double-blind, study of W (305) vs T (307) using a dose control center (DCC). Prospective genotyping for VtamitK-K epoxide reductase subunit 1 (n=204) and glutathione S-transferase M1 (n=319) and W were performed in all patients. Data from weekly INR monitoring was analyzed on an ITT basis.

Results: Pts previously taking W accounted for 94.3% of the total. Indications for the use of W included 74.5% for AF, 15.7% for DVT/PE, 14.2% for cardiomyopathy, and 15.5% for mechanical heart valve. Treatment groups were similar with regard to VKORC1 and CYP2C9 genotype, and this information was used by the DCC in randomization. Heterozygosity for CYP2C9 was similar between W and T (49.9% and 33.1% vs T266, p = NS). Pts prescribed at least one medication known to inhibit CYP2C9 activity simultaneously during the study were 30% of the total (181/512). TTR for pts on W before study improved to 73.2% for W and 74.0% for T (p = 0.51).

The total number of dose adjustments was not significantly different between groups.

When INR values during an intercurrent medical event were excluded, the percent of TTR was significantly worse on W than on T (66.4% vs 70.7%, p = 0.0039).

Significant differences were seen using INR values with a lower percent of TTR on W vs T for both warfarin experienced switchers (64.2% vs 67.0%, p = 0.0022) and patients with the CYP2C9 wild type genotype (62.5% vs 66.1%, p = 0.016).

Conclusions: 1) The use of a DCC improves TTR for patients on W, and results in comparable TTR for T. 2) AC therapy patients require concomitant CYP2C9 inhibitors 30% of the time, and 3) for some subgroups, especially patients who are CYP2C9 heterozygotes on medications which inhibit the enzyme, improved TTR is seen in patients taking T compared to W.

Concomitant administration of antiplatelet agents enhances the antithrombotic effects of rivaroxaban in vitro and in vivo


Purpose: The antithrombotic efficacy of rivaroxaban – an oral, direct Factor Xa inhibitor – has been demonstrated in animal models of arterial and venous thrombosis. Rivaroxaban has shown potential in clinical studies for the secondary prevention of acute coronary syndrome in patients receiving antiplatelet therapies. We therefore investigated possible synergistic effects between rivaroxaban and P2Y12 receptor antagonists and acetylsalicylic acid (ASA) on thrombin generation (TG) and thrombin-induced platelet aggregation in human plasma, as well as on thrombus formation in an arterial thrombosis model in rats.

Methods: TG was measured with the Calibrated Automated Thrombogram method (0.5 pmol thrombin concentration (TF) using platelet-rich plasma spiked with rivaroxaban (15, 30, and 60 ng/ml), ticagrelor (0.1, 0.3, and 1 μg/ml) and ASA (100 μg/ml). TF-induced platelet aggregation was measured in platelet-rich plasma spiked with rivaroxaban (15 and 30 ng/ml), ticagrelor (1.0 and 3.0 μg/ml) and ASA (3 mg/ml) and their combinations.

Results: Rivaroxaban decreased TG in a concentration-dependent manner; ticagrelor only had an effect at 1.0 μg/ml and ASA had no influence. The effect of rivaroxaban on TG was enhanced with ticagrelor and tica- grelor plus ASA. Rivaroxaban and ticagrelor inhibited concentration-dependently TF-induced platelet aggregation; their combination increased the inhibition synergistically. In the rat arteriovenous shunt model, rivaroxaban dose-dependently reduced thrombus formation. The combination of low-dose rivaroxaban (0.01 or 0.03 mg/kg) with ASA or clopidogrel resulted in a further increase in the antithrombotic effect (ASA: 24% and 37% respectively; ASA plus clopidogrel: 43%). Co-administration of rivaroxaban 0.1 mg/kg with ASA, clopidogrel or their combination increased the antithrombotic effect to 39%, 52% and 51%, respectively (p<0.001 vs control). Clopidogrel caused a small, non-significant increase in bleeding time, which was slightly increased (non-significantly) with the combination of rivaroxaban, ASA and clopidogrel.

Conclusions: The combination of rivaroxaban with single or dual antiplatelet drugs results in a synergistically enhanced antithrombotic potency.

Multiple thrombogenic and atherogenic markers were involved in premature coronary artery disease

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Atherothrombotic factors are implicated in the pathogenesis of coronary artery disease (CAD). Polymorphisms in the lymphotixin-alpha (LTA) gene, a pro-inflammatory cytokine, have been also associated with susceptibility to myocardial infarction, but results in different studies are conflicting. We examined the association of atherothrombotic markers and the LTA promoter A252G polymorphism with risk of premature CAD.

Methods: A case-control study was conducted in 336 patients with documented premature CAD and 189 unrelated health controls both with less than 50 years old. Clinical characteristics and laboratory data which included thrombogenic factors (Ibiringen, protein C, protein S and antithrombin III); and atherothrombic factors (lipoprotein A, lipoprotein B and fraction A, apolipoproteins AI and B fractions) were evaluated. Genetic variability of LTA was determined by polymerase chain reaction.

Results: Male, history of premature CAD, smoking status, diabetes, hypertension and dyslipidemia were significantly more prevalent in the CAD group. Compared with controls, CAD cases had significantly lower mean concentrations of apolipoprotein A1 (1.34±0.21 vs 1.23±0.22 mg/dL, p<0.01), HDL-cholesterol (46.4±11.9 vs 41.1±11.3 mg/dL, p<0.01) and antithrombin III (100±12.7 vs 94.2±17.8%, p<0.02), and higher plasma concentration of fasting glucose (103.3±26.9 vs 112.2±45.3 mg/dL, p<0.01) and Lipoprotein (a) levels (38.2±32.6 vs 50.1±49.2 mg/dL, p<0.01). The LTA A252G polymorphism frequency for AA, AG and GG was respectively 55.0%, 37.6%, and 7.4% for control group and 42.7%, 46.0% and 11.3% for patients group (p=0.02). A multivariable logistic regression analysis showed that hyperglycemia (OR 2.29, 95% CI 1.29-3.716), smoker (OR 2.18, 95% CI 1.45-3.277), dyslipidemia (OR 1.94, 95% CI 1.33-2.337), family history (OR 7.13, 95% CI 4.383-11.606) and LTA polymorphism (OR 1.88, 95% CI 1.193-2.972) were independent risk factors for suscep-
tibility to CAD. LTA mutant was risk marker for CAD only in male without the tradi-

tional risk factors.

Conclusions: Worse traditional risk factors profile and atherothrombogenic markers were associated with susceptibility to premature CAD. LTA mutant al-

elic was independently associated with premature CAD in the absence of traditional risk factors. Premature CAD was associated with worse clinical and labo-

ratory multimarkers.

D-dimer, plasmin-antiplasmin complex and matrix
dimpolease 2 as markers of cardiovascular
events in patients with stable coronary disease

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Purpose: A series of biomarkers have been recently proposed as potential novel risk factors for the development of cardiovascular events (CVE). We examined markers of fibrinolytic function (D-dimer, plasminogen activator inhibitor (PAI)-1 activity), tissue plasminogen activator (tPA)/PAI-1 complex, plasmin-antiplasmin (PAP) complex) and circulating matrix metalloproteinases (total MMP-9 and free MMP-2). Aim of the study was to determine their predictive ability in pts with stab-

le coronary artery disease (CAD) after accounting for conventional risk factors.

Methods: 503 pts with stable CAD (male 77%, mean age 59 yrs) were included in this prospective observational study with a mean follow-up of 3.4 yrs. The primary outcome was the occurrence of major CVE: death, acute coronary syn-

drome (ACS) or stroke/transient ischemic attack.

Results: The frequency of major CVE was 21.1% (39/100 patient years). Strong interrelationships (p < 0.05) were noted for hemostatic variables that were closely biologically related, e.g., D-dimer and PAP complex (r=6,65), PAI-1 activity and IP-1 complex (r=0,48), D-dimer and IP-1 complex (r=0,29), MMP-2 and PAI-1 activity (r=0,34), MMP-2 and PAI-1 complex (r=0,38), MMP-2 and PAP complex (r=0,24). On univariable analysis (age- and sex-adjusted), only D-

dimer, PAP and MMP-2 were associated with risk of CVE. Their plasma levels were strongly associated with total load of conventional factors, which has prog-

nostic impact in our study, i.e. severity of angina, history of ACS, three vessel disease and other comorbidity (cerebrovascular or peripheral disease, obesity, chronic kidney disease): F value for D-dimer = 4.2 (p for trend = 0.01); F value for PAP = 7.4 (p for trend = 0.001); F value for MMP-2 = 7.0 (p for trend = 0.001). The multivariable relative risks (RR) for the four higher vs lowest quintile were 2.1 (1.1 - 4.1) for MMP-2, 1.8 (1.3 – 2.5) for PAP and 3.1 (1.1 - 8.7) for D-dimer. The age- and clinical-adjusted risk of CVE significantly increased with simultaneous elevations of both MMP-2 and PAP. RR = 3.6 (1.1-15.5).

Conclusion: D-dimer, PAP and MMP-2 were identified as independent predictors of major CVE in patients with stable CAD.

Correlation of platelet reactivity and C-reactive

protein levels to occurrence of peri-procedural myocardial infarction in patients undergoing

Percutaneous Coronary Intervention


Background: The incremental predictive value of high inflammatory status and high platelet reactivity (HPR) on the occurrence of peri-procedural myocardial infar-

ction (PMI) in the setting of percutaneous coronary intervention (PCI) has not been investigated. Aim was to evaluate the correlation of an elevated inflamma-

tory status and/or HPR with incidence of PMI in patients undergoing PCI.

Methods: Five-hundred consecutive patients treated with clopidogrel and under-

going PCI had pre-procedural measurement of C-reactive protein (CRP) levels and platelet reactivity by the point-of-care VerifyNow P2Y12 assay. Elevated inflamma-

tory status was defined as CRP > 3 mg/L. HPR was determined as residual platelet reactivity index (RIPA) > 240. Primary end-point was incidence of PMI according to the Euroscore pro-

tective coronary revascularization.

Results: Rates of PMI were increased in patients with CRP levels > 3 mg/L (10.9% vs 4.6% in those with normal inflammatory status; OR 2.4, 95% CI 1.2-4.5; P = 0.015) and in patients with HPR > 95% (11% vs 5.5% in those without HPR; OR 2.2, 95% CI 1.2-4.5; P=0.018). Occurrence of PMI was highest in the subgroup with both HPR and high inflammatory status (16.6% vs 3.6% in patients with CRP > 3 mg/L and RIPA > 240; OR 4,3, 1.5-12.6; P=0.003). Addition of HPR in association with elevated CRP levels resulted in a significant increase in the discriminatory

power of a model including clinical and procedural variables in predicting PMI (area under the curve 0.81; P=0.04).

Conclusions: In patients undergoing PCI, a baseline stratification according to both platelet reactivity and inflammatory status may identify those at higher risk for peri-procedural ischemic events.

Compared and independent impact of chronic kidney disease and elevated C-reactive protein on residual platelet reactivity

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Background: Chronic kidney disease (CKD) is characterized by a pro-

inflammatory phenotype. C-reactive protein (CRP), an inflammatory biomarker, augments cardiovascular risk in CKD. Whether or not this risk is due to changes in platelet reactivity in those with both CKD and elevated CRP is unknown.

Methods: We studied 401 clopidogrel-naive patients undergoing percutaneous coronary intervention (PCI) who underwent platelet function testing a minimum of 4 hours after a 600 mg clopidogrel load. High residual platelet reactivity (HRPR) was assessed using the VerifyNow P2Y12 Analyzer and defined as P2Y12 Re-

action Units (PRAU) values > 335. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 and elevated CRP was defined as CRP > 2 mg/dl. Patients were categorized by no CKD/no elevated CRP (n=142), ele-

vated CRP alone (n=144), CKD alone (n=51) and both CKD and elevated CRP (n=64).

Results: While mean age and proton-pump inhibitor use increased across groups there were no significant differences in time from clopidogrel load to platelet test-

ing. The frequency of HRPR increased across groups with the highest frequency among those with both CKD and elevated CRP (78%, Figure 1). The associa-

tion between both CKD and elevated CRP with HRPR remained significant after multivariable adjustment (OR 3.4 [95% CI]: 1.5 – 7.3; p=0.002).

Conclusions: CKD and elevated CRP exert a synergistic influence on platelet reactivity and may contribute to higher cardiac risk in patients with both abnor-

malities.

Magnetoliposomes for targeting activated platelets: development of a human compatible MRI contrast agent for detection of unstable atherosclerotic plaques

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Background: Unstable atherosclerotic plaques may easily rupture, which attracts platelets. This can finally result in a rapid occlusive thrombosis with myocardial infar-

ction or stroke. Early detection of unstable plaques by non-invasive techniques would therefore be helpful to identify patients at risk. We previously demonstrated that activated mouse platelets can be imaged by in vivo magnetic resonance imaging (MRI) using a platelet specific contrast agent. Those consisted of mi-

crostructures of iron oxide (MPIOs) bound to an antibody specifically targeting the activated GPIb/IIa receptor on platelets. Unfortunately, MPIOs are not suitable for human MRI applications, since they are potentially toxic. In order to develop a human compatible contrast agent, small superparamagnetic iron oxide particles (SPIOs) with a mean diameter of 10 nm were entrapped into liposomes (magne-

toliposomes).

Methods & Results: Magnetoliposomes were prepared by rehydration of lipid films with negatively charged SPIOs in a dual asymmetric centrifuge (DAC). Non-

liposomally associated SPIOs were removed by ion exchange chromatography (IEC). To calculate the liposomally associated iron, the iron and phosphatidyli-

cline amount was analysed before and after IEC. The quality of the magnetoli-
Hypertriglyceridemia - a predictor of platelet resistance to acetylsalicylic acid in patients with stable coronary artery disease

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Background and purpose: Acetylsalicylic acid (ASA) is commonly used in a stable coronary artery disease (CAD) patients for the prevention of cardiovascular events (CVE). However, resistance to ASA is observed to occur with a rate of 5-42%. We aimed to determine clinical and biochemical predictors of insufficient response in CAD patients undergoing elective coronary angiography.

Methods: 360 consecutive caucasian pts with stable coronary artery disease undergoing elective coronary angiography were included in the study (109 woman, 251 man, age 62±1.1±2 years, mean height 79.2±7.9cm, mean BMI 28.2±3.9 kg/m2). All patients have been receiving daily dose of 75 mg ASA for at least 7 days before admission. The study group was divided into two groups: I-resistant group (n=77), II-respondent group (n=289) to the treatment. Resistance to ASA was defined as ARU value ≥550 (aspirin reaction unit) obtained with point-of-care test Rapid Platelet-Function Assay (RPPA).

Results: In the population treated with a daily dose of 75 mg of ASA, 71 patients (19.7%) were resistant (mean age 59.4±9.8 years, ARU=612±34.4), and 289 patients (80.3%) were responsive (mean age 61.4±1.07 years, ARU=449±47). No significant differences were detected in the panel of clinical risk factors for CAD between resistant and responder groups including: diabetes (28.4% of responders vs. 29.7% of non-responders; p=0.55), hypertension (62% vs. 59.5%; p=0.88), and smoking (36% vs. 22.6%; p=0.74). In logistic regression analysis including laboratory tests, a statistically significant difference between both groups, was found regarding serum triglycerides concentration (TG): 165±54 (p<0.005), but the exact mechanism involved is insufficiently understood. In this report, we present preliminary data showing that patients undergoing treatment with high levels of Interleukin-17A and -F are expressed by platelets and that these molecules are associated with resistance to ASA.

Conclusions: AR subtype does exist in platelets and is an important regulator of aggregation. This novel finding requires validation in independent factor prognostic to ASA resistance in patients with stable coronary artery disease (CAD). However, resistance to ASA was defined as ARU value ≥550 (aspirin reaction unit) obtained with point-of-care test Rapid Platelet-Function Assay (RPPA).

P1844 High levels of Interleukin-17A and -F are expressed by neutrophils and neutrophil extracellular traps (NETs) fresh and lytic, but not organized intracoronary thrombus

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Background: Recent evidence has shown that neutrophils are important cellular sources of Interleukin 17A and -F. Moreover, upon activation neutrophils are able to secrete chromatin threads (containing DNA and histones) to form so called neutrophil extracellular trap (NETs). These NETs are embedded with components from the neutrophils cytoplasmic granules, e.g myeloperoxidase (MPO), and neutrophil elastase, and are able to capture and kill bacteria. Interestingly, recent experimental studies have shown that these NETs may also contribute to thrombosis by promoting fibrin deposition and platelet aggregation. IL-17A may also contribute to thrombosis by promoting platelet aggregation. At present nothing is known about the presence of NETs and IL-17 is human thrombus specimens.

Materials and Methods: In total 45 thrombectomy specimens of STEMI patients were investigated. To study the stage of thrombus evolution and propagation in which NETs and IL-17 can be operative, we selected from a large series of histopathologically pre-screened thrombectomies 15 fresh (early thrombus), 15 organized thrombi and 15 old (organized) thrombi. NETs were identified using histological (Feulgen reaction) and immuno histochemical staining (ant-Histone H1, myeloperoxidase, neutrophil elastase). Double staining and spectral image analysis was performed to study colocalization. In addition, the presence and distribution of IL-17A and F was further studied using immunohistochemistry, spectral analysis, nPCR and Western Blot.

Results: High numbers of neutrophils (up to 10-40% of the thrombus mass) were present in fresh (and lytic) but not in organized thrombus. NETs were frequently observed in fresh (4/15, 27%) and lytic (12/15, 80%), but not in organized thrombus (0/15) specimens. Immunohistochemical doublestaining with Feulgen reaction confirmed the co-expression of Histone H1, myeloperoxidase and neutrophil elastase with DNA. IL-17A was also abundantly present in fresh and lytic thrombus specimens, especially in neutrophils, but also in NETs, as confirmed by double staining. Western blotting confirmed the presence of IL-17A and IL-17F in human thrombus specimens.

Conclusion: NETs and IL-17 are prominent features of fresh and lytic, but not of old (organized) thrombus. These results show that by the formation of NETs and secretion of IL-17A and -F neutrophils may play a role during thrombus stabilization and organization.

P1845 Markers of endothelial and platelet activation are associated with high on-aspirin residual platelet reactivity

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Purpose: Despite COX-1 inhibition by aspirin, platelets in patients with coronary artery disease (CAD) can be activated through other mechanisms. Methods: 1001 stable CAD patients, all on single aspirin treatment, were classified by the PFA100 method as having high on-aspirin residual platelet reactivity (RPR) or not. Markers of hypercoagulability, endothelial and platelet activation as related to RPR, were evaluated to explore the potential mechanisms behind high on-aspirin RPR.

Results: 25.9% (n=259) of the patients had high on-aspirin RPR. S-thromboxane B2 levels were very low in both groups. Patients with high on-aspirin RPR had significantly higher levels of von Willebrand Factor (vWF) (p<0.001), platelet D-dimer (p<0.006), total tissue factor pathway inhibitor (TFPI) (p<0.005) and IL-1 receptor antagonist (IL-1Ra) (p=0.041) compared to patients with low on-aspirin RPR. No significant differences between the groups were observed in levels of endoge-
Paraoxonase-1 (PON1) activity is associated with clodipogrel response and intra-stent thrombus after drug-eluting stent implantation in the CYP2C19 loss-of-function polymorphism carriers

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Background: The impact of paraoxonase-1 (PON1) activity on the efficacy of clodipogrel has not been clarified. The aim of this study was to assess the association of PON1 activity and clodipogrel response in the CYP2C19 loss-of-function polymorphism carriers (LOF carriers) and non-carriers receiving drug-eluting stent (DES) implantation.

Method: This study included 112 Japanese patients receiving clopidogrel (75mg/day) and aspirin (100mg/day) who underwent optical coherence tomography (OCT) examination for the evaluation of intra-stent thrombus 9 months after DES implantation. The CYP2C19 genotype was analyzed and LOF carrier (*1/*2, *1/*3, *2/*2, *3/*3, *2/*3) was identified. Platelet reactivity was determined by measuring P2Y12 reactivity unit (PRU) with VerifyNow P2Y12 assay and the PON1 activity was evaluated by spectrophotometric assay.

Results: In 112 Japanese patients, 75 patients were LOF carriers (67.9%). The median PON1 activity was 245 U/L. In both LOF carriers and non-carriers, the patients were divided into High PON1 (PON1 activity was equal or above 245 U/L) and Low PON1 (below 245 U/L) groups. PRU was higher in LOF carriers than non-carriers (245.3±39.6 vs. 198.8±52.8; P<0.002) and intra-stent thrombus was observed more frequently in LOF carriers than non-carriers (37.3% vs. 16.2%; P<0.03). Among LOF carriers, PRU was higher in Low PON1 group than High PON1 group (275.8±36.2 vs. 227.0±29.3; P<0.001) and intra-stent thrombus was observed more frequently in Low PON1 group than High PON1 group (54.8% vs. 25.0%; P<0.01). Among non-carriers, PRU and incidence of intra-stent thrombus were not different between High and Low PON1 groups.

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Activation by ADP modulates miRNA expression profile in platelets, new insights into the pathophysiology of platelet activation

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Purpose: Acute thrombus formation on ruptured plaque is the main cause of acute coronary syndromes (ACS). Platelets play a key role in thrombus forma-

Method: To assess this hypothesis, a randomized, crossover study in 11 healthy male. Each subject was exposed to ambient and polluted air during 2 hours at rest and 1 hour of moderate exercise (4 different sessions). Blood samples were collected before and immediately after the exposures.

Conclusion: Elevated levels of platelet count, β-TG, TFPI and especially vWF might be explained by increased endothelial and platelet activation in these patients.

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Conclusion: The PON1 activity might ameliorate responsiveness to clopidogrel only in LOF carriers, but did not influence that in non-carriers.

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Purpose: Acute thrombus formation on ruptured plaque is the main cause of acute coronary syndromes (ACS). Platelets play a key role in thrombus forma-
Controversial issues on thrombotic and antithrombotics treatment

P1851 Collagen-induced platedlet aggregation is specifically suppressed, but coagulation and bleeding time are not altered up to 3 weeks after a single bolus of revacpet (dimeric GPVI-Fc; phase I trial)

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Purpose: The GS58 polymorphism on fibrinogen alpha (a) chain gene has been associated with increased fibrinogen levels in healthy individuals, but its effect on thrombosis in patients with coronary artery disease (CAD) remains unknown. In the present study we examined the impact of this polymorphism on fibrinogen and D-dimers levels as well as its interaction with established risk factors in the development of CAD.

Methods: The study population consisted of 339 patients with CAD and 260 healthy controls. The GS58 polymorphism was genotyped by PCR and restriction enzyme digestion. Fibrinogen levels and D-dimers were determined according to the biochemical measurements (routinely performed), clinical examination and medical history.

Results: In patients with CAD fibrinogen levels (mg/dl) were not significant higher for 58A homozygotes vs 58G allele carriers (p=NS). Similar difference occurred in controls (AA: 468.9±17.7 vs GG+GA: 445±5.107, p=NS). Importantly, there was a significant difference in D-dimers levels (μg/l) for 58G carriers vs 58A homozygotes for CAD patients (p=0.05), but not for controls (AA: 443.9±52.8 vs GG+GA: 345.9±34.2, p=NS). Although, 58A homozygotes developed CAD earlier (years) than 58G carriers, this difference was not significant (p=NS). In addition, between 58G carriers and 58A homozygotes developing CAD, there was no significant difference regarding to hypertension (p=NS), hypercholesterolemia (OR:1.16, 95%CI (0.497-2.709), p=NS) and DM2 (OR: 1.304, 95%CI (0.599-2.087), p=NS). Similarly, in CAD patients smoking as well as gender (p=NS) did not differ significantly.

Conclusion: We have shown that the GS58 polymorphism on fibrinogen a-chain gene affects D-dimers levels in patients with coronary artery disease. No significant relationship was found between this polymorphism and the risk for atherosclerosis. These findings provide a possible mechanism by which this polymorphism may affect thrombotic process/coagulation independently of risk factors for atherosclerosis.

P1852 Percutaneous coronary intervention causes increased platelet - derived microvesicle release

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Purpose: Microvesicles (MVs) are membrane-derived microparticles originating mostly from platelets (platelet-derived microvesicles, PMV). The role of MVs in cardiovascular disease (CVD) or the effect of percutaneous coronary intervention (PCI) on MV release was not elucidated. Accordingly, we aimed to determine the early and long-term MV and PMV release after PCI performed in stable angina (SA) and to assess the effect of combined antplatelet therapy (clopidogrel, aspirins) on MV and PMV absolute count.

Methods: We recruited 102 patients with SA undergoing elective coronary angiography. The direct and long-term effect of PCI was determined in 40-stable angina patients (PC, n=34) group. Individual was included with negative coronary angiography (NC, n=27) or those with positive coronary angiography, but without PCI (PC, n=34) served as controls. The total microvesicle count (MV), platelet derived (PMV) and P-selectin negative PMV (CD62P-CD41+ PMV) and P-selectin positive PMV (CD62P+CD41- PMV) absolute count was determined by flow-cytometry. Blood samples were taken on admission, 24 hours, and 1, 3, 6,12 months thereafter. In each time point, platelet aggregation was assessed by Born-aggregometry (in- ducers: 6 micromol ADP, 10 micromol ATP, 1 micromol/collagen, 2 microg/ml collagen, 0.5 microg/ml asarchidonic acid, and 10 microg/ml epiinephrine). As such, Results: No significant difference in baseline absolute count of MV, PMV, CD62P-CD41+ and CD62P+CD41- PMV was found between the study groups. 4 weeks after PCI the Mv (p<0.05), PMV (p<0.01) and P62+/41- PMV (p<0.05) absolute count showed significant increase compared to baseline levels. Diagnostic coronary angiography itself (PC, NC group) had no significant effect on the above parameters assessed at 24 hours. When analyzing patients according to the implanted stent type, the PMV (p<0.01), the P62+/41+ PMV (p<0.01) and the P62-/41+ PMV (p<0.05) absolute count was significantly higher in the drug eluting stent (DES) group compared to the bare metal stent (BMS) group. No significant correlation (Spearman correlation analysis) was found between the MV parameters, platelet aggregation values and the antplatelet therapy.

Conclusion: Percutaneous coronary intervention evokes total microvesicle absolute count and - predominantly - P-selectin negative PMV absolute count elevation. This early systemic and platelet response is independent from platelet aggregation and is not influenced by combined antplatelet therapy. At six months after PCI the PMV count was higher in case of DES implantation.

P1853 Serum- and glucocorticoid-inducible kinase 1 (SGK1) regulates platelet granule biogenesis and secretion

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Background: Platelet secretion is critical to the development of acute thrombotic occlusion. Platelet dense granules contain a variety of important hemostatically active substances. Nevertheless, the biogenesis of granules in the platelet pre- cursors, the megakaryocytes, is poorly understood. Platelet activation is regulated by phosphoinositol-3-kinase (PI3K) dependent signaling. PI3K-dependent AGC kinases include the serum- and glucocorticoid-inducible kinase 1 (SGK1). SGK1 has not been shown to be highly expressed in platelets and megakaryocytes, but its role in the regulation of platelet granule biogenesis and its impact on thrombosis has not been investigated so far.

Methods and Results: To study the functional role of SGK1, platelets were isolated from mice lacking SGK1 (sgk1−/−) and respective wildtype littermates (sgk1+/+). Electron microscopy analysis of platelet ultrastructure revealed a significant reduction in number and packing of dense granules in sgk1−/− platelets, coalesced membrane and lamellation. Dephosphorylated endogenous serotonin was found significantly reduced and activation-dependent secretion of ATP, serotonin and Lamp-3 (CD63) significantly impaired after stimulation with CRP or thrombin in platelets lacking SGK1. According to in vitro aggre-
High platelet reactivity by arachidonic acid and elevated c-reactive protein levels identify STEMI patients at risk of 5-year follow-up cardiac death

High platelet reactivity by arachidonic acid and elevated c-reactive protein levels identify STEMI patients at risk of 5-year follow-up cardiac death

Results: Patients with previous MI had 65% higher platelet aggregation levels compared with CAD patients without previous MI when evaluated by Multiplate/arachidonic acid (p<0.0001). In a multiple linear regression analysis, the importance of previous MI remained significant after adjustment for age, smoking, and diabetes (p<0.0001). Further, MI patients had increased serum thromboxane B2 levels compared with CAD patients (p<0.01). Multiplate/collagen platelet aggregation levels were 11% higher in MI patients than in CAD patients (unadjusted p<0.20, adjusted p=0.11). These findings were not in agreement with the VerifyNow test showing a 3% higher aggregation level in CAD patients compared with MI patients (adjusted p=0.002). Patients treated with aspirin prior to MI had significantly higher aggregation levels compared with non prior users when evaluated by Multiplate/collagen (p=0.02) and VerifyNow (p<0.0001).

Conclusion: Patients with previous MI had a reduced antiplatelet effect of aspirin shown by higher Multiplate aggregation levels and serum thromboxane B2 compared with CAD patients. Prior aspirin users had higher platelet aggregation levels compared with non prior users. Our findings suggest that patients with previous MI may have reduced cardiovascular protection from low-dose aspirin.

P1855 Increased platelet aggregation and serum thromboxane levels in aspirin-treated patients with previous myocardial infarction

Methods: We performed a study on 231 CAD patients, including 171 with previous MI. Among patients with only previous MI (116 patients) 59 patients were on aspirin treatment at the time of acute MI. All patients were treated with 75 mg non-enteric coated aspirin as single antiplatelet therapy. Platelet reactivity indices, P-selectin and CD40 ligand levels were measured using Multiplate/AA and VerifyNow.

Results: The intercorrelation between platelet reactivity index and serum thromboxane levels in patients with previous MI was low (rho 0.27, p<0.0001).

Conclusion: T2DM patients after NSTE-ACS had more thrombus, altered tensile strength, reduced thrombus retraction and loosely arranged but interlinked fibrin fibres despite optimal medical therapy. This may explain poor clinical outcomes in T2DM. Our data, using whole blood assays, provide a focus for further studies of antiplatelet agents in T2DM.
animals by bolus plus infusion administration of PRT prior to initiation of blood loss potentiated by enoxaparin (Enox), an indirect Xa inhibitor. To mimic clinically relevant bleeding due to anticoagulation, we tested the ability of PRT to mitigate blood loss in a tail-transaction model where a PRT bolus-only treatment was administered after injury. Anesthetized rats were intravenously (IV) administered either vehicle or Enox (4.5 mg/kg, IV bolus) followed by tail transaction 5 min later. A dose of PRT (0.1, 1, 2 or 4 mg) or vehicle was given at 15 min (10 min after tail injury) by IV bolus (n=7-10/group). Blood loss was measured for an additional 45 min following vehicle or PRT administration. Anticoagulation by the 5-fold supratherapeutic dose of Enox led to greatly increased bleeding loss (~11-fold) over vehicle-treated rats. Total blood loss in the Enox-treated group represented ~5% of the animal’s blood volume with ~26% of this loss occurring within the first 10 min prior to PRT treatment. Administration of PRT at 1, 2, or 4 mg produced a significant reduction in cumulative blood loss (60, 56 and 62%, respectively; Enox+PRT vs. Enox+vehicle: p < 0.02 for all 3 groups) with complete cessation of bleeding in 70-85% of the animals. The 0.5 mg dose of PRT had no effect on blood loss. In parallel, the anti-Xa activity was dose-dependently reduced by 13, 35, 52, 81% at 5 min following administration of PRT at 0.5, 1, 2 and 4 mg, corresponding to PRT peak plasma concentrations of 0.54, 1.1, 1.8 and 2.3 μM, respectively. Of note, the partial reversal of anti-Xa activity for a period as short as 15 min (in the case of the 1 mg dose group administered as a single IV bolus) was sufficient to reduce or completely halt bleeding. In conclusion, a partial and transient reversal of Enox-induced anticoagulation was sufficient to reduce blood loss in a clinically relevant model of hemostasis. These data suggest that a single bolus administration of PRT has the potential to rapidly reduce blood loss and reverse PD markers in patients anticoagulated with an indirect Xa inhibitor.

Conclusions: In vitro incubation with escalating concentrations of Enox achieves a dose-dependent reduction of platelet aggregation in healthy volunteers. Ongoing in vivo and in vitro studies will provide more insights on the pharmacodynamic effects and safety of Enox.

Unlike heparins newer oral anticoagulants do not interact with HIT antibodies and may be useful in the long term anticoagulant management of heparin compromised patients

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Introduction: Heparin and low molecular weight heparins are widely used in the management of thrombosis and cardiovascular disorders despite the possibility of inducing HIT antibodies. Oral anti-Xa agents [apixaban (Bristol-Myers Squibb), rivaroxaban (Bayer Healthcare)] and the anti-Xa agent, dabigatran (Boehringer Ingelheim) have recently been approved for use. The purpose of this study was to determine the effects of these newer anticoagulants on HIT antibody mediated platelet aggregation and other interactions with platelets.

Materials: Rivaroxaban was obtained in powdered form from Bayer Healthcare (Wuppertal, Germany) Apixaban and Dabigatran were synthesized. Enoxaparin was obtained from Sanofi-Aventis (Paris, France), All drugs were dissolved in buffered saline at a concentration of 100 μg/ml. Whole blood samples drawn from normal healthy volunteers were incubated with each of these agents at concentrations of 0-100 μg/ml for 60 minutes to determine the release of platelet factor 4 (PF4). To test the interaction of HIT antibody with each of these agents PRP was mixed with HIT positive sera collected from symptomatic HIT patients. Graded concentrations of EV-077 (vehicle, 10, 30, 100, and 300 nM). Citrated platelet-rich plasma (PRP) was incubated with vehicle or 100 μM of EV-077. Platelet aggregat-

Conclusions: In vitro incubation with escalating concentrations of Enox achieves a dose-dependent reduction of platelet aggregation in healthy volunteers. Ongoing in vivo and in vitro studies will provide more insights on the pharmacodynamic effects and safety of Enox.

P1850

In vitro pharmacodynamic effects of EV-077, a new inhibitor of isoprostane and prostanooid cellular activation

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Purpose: Low dose aspirin inhibits cyclooxygenase-1 and thus prostanooid production. However, some patients may have inadequate aspirin effects leading to persistent prostanooid and isoprostane production increasing atherothrombotic risk, vascular inflammation and oxidative stress. Thromboxane A2 (TxA2) synthase (TxA2S) and TxA2 receptor (TP receptor) antagonists have been developed as a potential treatment of these vascular conditions. The aim of the present study was to describe the in vitro pharmacodynamic effects of escalating concentrations of EV-077, a novel dual TxA2S/TP receptor inhibitor, on human blood.

Methods: Blood samples were collected from 10 healthy volunteers aged 35±3.6 years old. Whole-blood hirudin-tubes were incubated with escalating concentrations of EV-077 (vehicle, 10, 30, 100, and 300 nM). Citrated platelet-rich plasma (PRP) was incubated with vehicle or 100 μM of EV-077. Platelet aggregat-

P1860

Triple antithrombotic therapy is the independent predictor for the occurrence of major bleeding complications; results from the ICAS registry

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Purpose: An increasing number of patients requiring long-term oral anticoagulation with warfarin have undergone percutaneous coronary intervention (PCI) with drug-eluting stent implantation (DES). However, the benefits and risks of triple antithrombotic therapy (combination of aspirin, clopidogrel, and warfarin) are still unclear.

Methods: This study included 1626 patients (69±10 years; 1244 male; 382 female) who underwent PCI with DES in the Ibaraki Coronary Artery Disease Study (ICAS) registry and received dual antiplatelet therapy with or without warfarin. Clinical primary endpoints were defined as the occurrence of major bleeding complications and major adverse cardiovascular event (MACE) including cardiac death, myocardial infarction, and target vessel revascularization. The major bleeding complications were defined as a cerebral hemorrhage or a gastrointestinal bleeding.

Results: Among 1626 patients, 115 (7.1%) patients received warfarin. After a mean follow-up of 16.9±10.7 months, 24 (1.5%) and 232 (14.3%) patients had experienced the episode of major bleeding complications and MACE, respectively. There were no significant differences in age, gender, body mass index, a history of prior PCI, smoking, left ventricular ejection fraction between the patient with and without major bleeding complications. However, a prevalence of hyperlipidemia was lower (38% vs. 59%; p<0.05) and a prevalence of warfarin usage was greater (33% vs. 7%; p<0.001) in the patients with major bleeding complications than in those without. A multivariate Cox regression analysis revealed that triple antithrombotic therapy was the independent predictors for the occurrence of major bleeding complications (hazard ratio (HR) 7.25; 95% confidence interval (CI) 3.05–17.21; p<0.001). The patients with MAE had a greater prevalence of prior PCI (26% vs. 20%; p<0.05), cerebrovascular disease (14% vs. 8%; p<0.01), diabetes mellitus (52% vs. 43%; p<0.01) than those without. The prevalence of MACE was significantly lower in the patients received dual antiplatelet therapy with warfarin than in those without (8% vs. 15%; p<0.05), however, a multivariate cox regression analysis revealed that the prevalence of MACE did not differ between the patient received dual antiplatelet therapy with and without warfarin (HR 0.81; 95% CI 0.46–1.41; p=0.45).

Conclusions: Triple antithrombotic therapy predisposes patients to an increased risk of major bleeding complications. We should consider the optimal combination of anticoagulant and antiplatelet therapy to avoid the major bleeding complications following PCI with DES.
Controversial issues on thrombotic and antithrombotics treatment

P1861

Association of the cytochrome cytochrome 450 2c19 polymorphism monitoring on residual platelet activity after chronic clopidogrel medication by 3 different platelet function tests

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Background: Published data suggests that the presence of at least one CYP2C19*2 or 3 loss-of-function alleles results in increased residual platelet aggregation and are at a higher risk of adverse cardiovascular events despite clopidogrel administration. There is little evidence to show the correlations and agreements between LTA, MEA and VerifyNow data according to the consensus definitions of high residual platelet reactivity (HPR) to ADP. Objective: To assess the correlation and agreement in different devices for the prediction cut-off of for those carrying CYP2C19*2 or 3 loss of function allele carriers suggested by MEA, LTA and VerifyNow assays in Korean patients.

Methods: We enrolled 231 coronary stenting patients with chronic clopidogrel medication. Platelet inhibition was measured by LTA, MEA and VerifyNow assays and CYP2C19 genotypes were analyzed.

Results: Determination of cut-off levels for based on functional CYP2C19 gene carriers indicated LTA>48, MEA>33 and VerifyNow>245. The prevalence of HPR was 56.5% by MEA, 38.5% by LTA and 47.6% by VerifyNow. The MEA assay showed a significant correlation (r=0.54, p<0.001) with LTA and a moderate agreement (κ=0.4, p<0.001) with 68.8% of concordant values. A significant correlation was found between MEA and VerifyNow (κ=0.39, p<0.001) with mild agreement (κ=0.28, p<0.001) of 63.2% of concordant values. Significant correlation was also found between LTA and VerifyNow (κ=0.71, p<0.001) with good agreement (κ=0.51, p<0.001) and 75.3% concordant values (see figure).

Conclusions: Important regional differences in the use of AT for the management of ACS were observed, with EE and LA countries showing less aggressive patterns of AT than NE and SE countries.

Figure 1. Correlation between HPR cutoffs

Current regional differences in the use of antplatelet drugs for the treatment of acute coronary syndromes. Results from the EPICOR study


Background: In pts treated with aspirin (ASA) and clopidogrel(CL) following stenting, the needs for definition of high and low on-treatment platelet reactivity (HOTPR, LOTPR) remained unmet. Although multiple (MPL) is a novel assay, the long-term efficacy and safety issues of MPL-guided treatment need to be considered.

Methods: In this open, non-randomized and single-center prospective study (614 pts, 59±10.2 yrs), we aimed to investigate whether response (R) to ASA and CL on MPL relates to the events including definite stent thrombosis (dST), myocardial infarction (MI), target lesion revascularization (TLR), cardiovascular death (CVD) and stroke (S) as well as bleeding primary, urgent or elective bare-metal or drug-eluting stent (BMS, DES) placement.

Results: Mean FU period was 805±257 days, and visits were performed within first 7 and 30 days, 3, 6, 9, and 12 mo after PCI. Two and three-year MPL data were available in 98 and 65% of pts, respectively. Loading CL dose was 600 mg and daily dose was 150 mg, respectively. Dual HOTPR % was 7%, HOTPR for CL and ASA related to the composite of the five end-points were 0.9, 1.3, 2.6, 8.0, 7.0 and 6.6%, respectively. All dST episodes observed within the first 22 days of PCI. None experienced S. TIMI major and minor bleeding were noted in 2% and 3.6% of pts, respectively.

Conclusions: On-treatment platelet reactivity as assessed by multiple analyser in relation to early and long-term risks for ischemic and bleeding events following the stent placement


Purpose: To explore regional differences in the patterns of antplatelet therapy (AT) in patients hospitalized for acute coronary syndromes (ACS)

Methods: EPICOR is a prospective international observational study designed to describe the current use of antithrombotic therapies for the treatment of ACS. 10,568 patients hospitalized for ACS were enrolled from 555 hospitals in 20 countries between September 2010 and March 2011, prior to availability of ticagrelor. Patterns of pre- and in-hospital AT were described for 4 pre-specified regions: Northern Europe (NE; Belgium, Denmark, Finland, Germany, Luxembourg, Netherlands, Norway, UK; n=3762), Southern Europe (SE; France, Greece, Italy, Spain, n=2337), Eastern Europe (EE; Poland, Romania, Slovenia, Turkey, n=2380) and Latin America (LA; Argentina, Brazil, Mexico, Venezuela, n=2069).

Results: During the acute phase, the most frequent AT patterns were: aspirin (A) + clopidogrel (C), n=7369, 69.7%; triple AT (TAT) with A+C+GP IIb/IIIa inhibitors (GP) or A+prasugrel (P+GP), n=1706, 16.1%; P, 572, 5.4%; A alone, 559, 5.3%; C alone, 292, 2.8%.

AT use among STEMI patients was: 63.1% A+C, 24.7% TAT, 7.2% P, A; 2.9% A and 1.6% C alone, while the distribution for NSTE ACS patients was 75.5% A+C; 8.6% TAT, 3.8% P; A; 7.4% A alone ± GPI; and 3.8% C alone ± GP I (p<0.001 vs STEMI). There were marked regional differences in the use of AT. (Table), mostly related to a differential use of GPI and P.

Conclusions: Important regional differences in the use of AT for the management of ACS were observed, with differences showing less aggressive patterns of AT than NE and SE countries.

Table 1: Distribution of antithrombotic therapies among STEMI and NSTE ACS patients

<table>
<thead>
<tr>
<th>Region</th>
<th>STEMI (%)</th>
<th>NSTE ACS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>72.8%</td>
<td>77.5%</td>
</tr>
<tr>
<td>SE</td>
<td>69.7%</td>
<td>75.5%</td>
</tr>
<tr>
<td>EE</td>
<td>75.7%</td>
<td>83.1%</td>
</tr>
<tr>
<td>LA</td>
<td>79.8%</td>
<td>71.7%</td>
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</tbody>
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Evaluation of serum fibronectin degradation processes as an additional factor of acute coronary syndromes course defining and development of thrombotic and hemorrhagic complications

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Fibronectin (FN), the main matrix protein, which degradation causes the appearance of a great number of fragments (FFN) possessing new properties and having great impact upon thrombosis processes and inflammation during acute coronary syndromes (ACS), and hence complications development has not been studied enough yet.

The aim: To study FNF spectrum in patients with different ACS forms and to evaluate their association with thrombotic and hemorrhagic complications development.

Material and methods: 135 ACS patients (pts) who received standard medical treatment, amongst them 40 pts with ACS without ST elevation; 64 ACS pts with ST elevation early admitted (~6 hrs) and received thrombolysis, and 31 pts late admitted with acute QMI without repurification and 14 normal subjects matched for age and gender as a control group. FN fragmentation was detected by Western blot analysis, using rabbit antibodies to human blood plasma FN.

Results and discussion: Reliable activation of proteolytic processes has been observed in all pts comparing with the normal subjects irrespective of the pts’ gender (p < 0.05) and age (p < 0.05). Frequency of detection of some important FFN has reliably changed: FFN with molecular mass (MM) 20-38 kDa - binding fibrin and activating metalloproteinases genes (p < 0.0001); 100-110 kDa - inducing cardiomyocyte apoptosis and eliminating the excess of FN causing pathological fibrosis and remodeling (p = 0.006); 165-175 kDa, - defining the activity of anticoagulants interaction with cells (p < 0.041) was increased. Frequency of FFN with MM 60-72 kDa - locally actively binding collagen; FFN 75-80 kDa and 90-95 kDa with streptokinase activity (p < 0.05), simultaneously decreased.

Development of thrombotic ACS complications was associated (p < 0.05) with increase of FFN frequency with MM 60-72 kDa, 75-80 kDa, 90-95 kDa - reflecting pathological fibrosis and remodeling of new-formed atheroma. Use of anti-FFN monoclonal antibodies in ACS pts (p < 0.05) was positively increased in comparison with ACS course without complications (p < 0.05).

Conclusions: In all forms of ACS an activation of FN degradation processes take place, confirming their role of an important link connecting mechanisms of thrombosis and inflammation. The FFN spectrum reflects the individual prevalence of thrombotic or inflammatory mechanisms in the ACS pathogenesis; it is also associated with the development of thrombotic and hemorrhagic ACS complications and can be additionally used in early individual evaluation of their risk development.

Dual antiplatelet and oral anticoagulant treatment of patients discharged after PCI in acute myocardial infarction - current clinical practice and 12-month outcome - analysis from the PL-ACS Registry

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The aim of this analysis was to compare clinical presentation and 12-month outcomes of patients discharged after PCI for NSTEMI and STEMI on dual antiplatelet treatment with and without oral anticoagulant.

Methods: All with NSTEMI and STEMI (N=14403), discharged after PCI, registered in the prospective PL-ACS registry from 7.2007 to 11.2009 were included. Follow-up mortality was obtained from the government database.

Results (table): Patients with triple therapy comprised only 1.5% of the analyzed population. They were older and had significantly more comorbidities. More than one-third of them had atrial fibrillation and half of them had severe left ventricle dysfunction. We did not find significant difference in 12-month mortality between the groups. What more, after multivariate adjustment the hazard ratio for dual antiplatelet + oral anticoagulant was less than 1 (HR=0.87, 95%CI = 0.56-1.37, P=0.55).

Conclusion: Dual antiplatelet therapy together with oral anticoagulant treatment after PCI for myocardial infarction is rarely given, mostly in high risk patients with adequate comorbidities. Nevertheless, patients on dual antiplatelet together with oral anticoagulant have comparable 12-month mortality to patients on dual antiplatelet therapy.

Popurar Risk Score for individualized antiplatelet therapy following non-urgent PCI

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Background and relevance: Despite the use of dual antiplatelet therapy with aspirin and clopidogrel, approximately 10% of patients suffer from atherothrombotic events in the first year after PCI. Multiple risk factors, including high on-treatment platelet reactivity (HPR) and carriage of CYP2C19 gene polymorphisms, have been identified. Recently developed point-of-care tests allow rapid evaluation of platelet reactivity and CYP2C19 metabolizer status in routine clinical practice. Novel antiplatelet drugs – like prasugrel and ticagrelor – reduce atherothrombotic events in acute coronary syndrome (ACS) patients and are not influenced by CYP2C19 metabolizer status. However, the use of prasugrel or ticagrelor leads to a higher bleeding risk and more cost.
Objective: To develop a risk score for tailoring antiplatelet therapy for non-urgent PCI patients.

Methods: Based on recent literature and clinical relevance the following scoring system was developed: platelet function (2 points for HPR, measured by VerifyNow P2Y12), CYP2C19 gene polymorphisms (1 point for each ‘2’ or ‘3’ allele), clinical risk factors (DM, LVET <30%, connecting stent length >30mm; 0.5 point for diabetes; and ACS in the previous 14 days (1 point, platelet function not scored in these patients). Patients with a risk score ≥2 points received prasugrel or ticagrelor, otherwise clopidogrel was prescribed.

Results: We validated the risk score using the POPular study cohort, containing 1069 elective PCI patients (Breet et al. JAMA 2010). In a ROC curve analysis a cut off value of 2 points proved to be optimal. Patients with a risk score of ≤1.5 points had a 6.6% event rate for the combined endpoint of myocardial infarction, CVA, stent thrombosis and all-cause mortality in 1 year following PCI, compared to 12.0% for patients with ≥2 points (p<0.003).

Implementation into clinical practice: the POPular Risk Score was performed in >1000 consecutive non-urgent PCI patients. Tailoring antiplatelet drug advice based on the POPular risk score was achieved within 24 hours in 98% of patients. Clopidogrel was switched to prasugrel or ticagrelor in 31.3% of patients. Follow-up for atherothrombotic and bleeding events will be achieved by May 2012.

Conclusion: The POPular Risk Score can discriminate between patients with a high or low risk for atherothrombotic events in a large cohort of non-urgent PCI patients. Tailoring antiplatelet drugs based on platelet function results is feasible in daily clinical practice. Follow-up for atherothrombotic and bleeding events will be achieved by May 2012.

PI1868 Management of patients with acute coronary syndromes in the real world practice in Italy: an outcome research study focused on the use of anti-thrombotic agents. The MANTRA registry

G. Casella1, M.G. Pallaoti1, S. Zagroni1, L. Riva1, D. Lucchi2, P. Caldara1, L. Oltrona Visconti1, M. Scherillo1, A.P. Maggioni2, G. Di Pasquale3 on behalf of the MANTRA Study investigators.1Maggiore Hospital, Department of Cardiology, Bologna, Italy; 2Sarcone Hospital, Department of Cardiology, Terlizzi, Italy; 3Foundation IRCCS Policlinic San Matteo, Department of Cardiology - University of Pavia, Pavia, Italy; 4Tumminia Hospital, Department of Interventi Cardology, Benevento, Italy

Purpose: Treatment strategies for acute coronary syndrome (ACS) involve the use of aggressive anti-thrombotic therapies, early revascularization for no-ST-elevation ACS and reperfusion for ST-elevation ACS. While these combinations have led to a decline in adverse outcomes, bleeding complications remain an important risk mainly in the real world setting. Thus, this study aims to evaluate in-hospital management and outcomes of unrecognized patients (pts) with ACS focusing on anti-thrombotic therapies and bleedings.

Methods and Results: From April 24th, 2009 to December 29th, 2010, 6394 consecutive pts. admitted to 52 Italian Coronary Care Units were prospectively enrolled and followed for 6 months. Most of pts. had no-ST-elevation ACS (55.3%) and were mainly males. Among no-ST-elevation ACS pts., 78.9% received reperfusion (16.1% fibrinolysis and 63.7% primary percutaneous coronary intervention (PCI)). 78.3% of no-ST-elevation ACS pts. underwent coronary angiography and 54.6% PCI during hospitalization. Recommended treatments were consistent with current guidelines. In-hospital and 6-months crude total mortality rates were 4.2% and 7.8% for ST-elevation, 2.5% and 6.4% for no-ST-elevation ACS, respectively. TIMI major bleedings occurred in 75 (1.17%) pts. (1.3% ST-elevation and 1.1% no-ST-elevation ACS), respectively during hospitalization; while TIMI major bleedings occurred in 198 (3%). Pts. with major bleedings were older, more often females, and less likely treated with primary PCI or early PCI in no-ST-elevation ACS. In-hospital and 6-months crude total mortality rates were 3.1% and 6.7% for pts. without bleedings, 1.5% and 8.5% for pts. with minor bleedings and 18.6% and 25.3% for pts. with TIMI major bleedings, respectively (p<0.0001 for different groups). Multivariate predictors of in-hospital TIMI major bleedings were age (odds ratio (OR): 1.01, 95% confidence interval (CI): 1.01-1.02, male gender (OR: 2.17, (95% CI: 1.34-3.51)), peripheral vasculopathy (OR: 2.47, (95% CI: 1.49-4.06)), systolic blood pressure (continuous) (OR: 0.98, (95% CI: 0.97-0.99), 10 mmHg higher increased a 1% higher incidence of in-hospital intracranic balloon pump implantation (OR: 3.27, (95% CI: 1.47-7.90)), and creatinine ≥2 mg/dl (OR: 3.21, (95% CI: 1.59-6.47)).

Conclusions: The MANTRA registry demonstrated that despite aggressive therapies and interventions the rate of major and minor bleedings remains relatively low in an unselected population of ACS. However, known bleeding predictors are still valuable and physicians should consider them to selectively target anti-thrombotic treatment and interventions.

PI1869 Triple versus dual antiplatelet therapy in acute myocardial infarction in relation to renal function

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Background: Chronic kidney disease (CKD) is a strong risk factor for cardiovascular events, and there are consistence evidences about worse short- and long-term outcomes in CKD patients with acute myocardial infarction. The aim of this study was to evaluate the effects and safety of triple antiplatelet therapy (aspirin plus clopidogrel plus cilostazol) in CKD patients with ST-elevation myocardial infarction (STEMI) compared with dual antiplatelet therapy (aspirin plus clopidogrel).

Methods: Among over 21,000 patients in Korean Acute Myocardial Infarction Registry (AMIR) data. 5,138 STEMI patients who underwent successful primary PCI with drug-eluting stents were enrolled in this study. They were divided by estimated creatinine clearance (eCRI): ≥ 60 ml/min (n=3,445 dual = 2169, triple = 1276) and < 60 ml/min (n=1693 dual = 1120, triple = 573). Various major adverse cardiac events including major bleeding at 12 months were evaluated.

Results: The triple group had significantly lower incidences of total death, cardiac death, and total major adverse cardiac event than the dual group in both eCRI groups. In group with eCRI < 60 ml/min, triple therapy showed beneficial effect of 12-month total death in patients with older (>65) age, worse Killip class, and culprit lesion with left anterior descending artery. In group with eCRI ≥ 60 ml/min, triple therapy showed beneficial effect in patients with older (>65) age, and diabetes. But bleeding complications did not show significant difference between the 2 groups in both eCRI groups. Figure showed the cumulative incidences of all-cause mortality rates according to kidney function and antiplatelet strategies at 12 months.

Conclusion: Triple therapy is a safe and effective antiplatelet strategy in CKD patients with STEMI.
Contemporary pre-hospital management of ACS patients: results from the EPICOR study


Purpose: Little is known about current pre-hospital management in ACS patients from a global perspective. EPICOR is a multicentre, international study designed to describe the current use of antithrombotic therapies in a broad ACS popula-

Methods: EPICOR (NCT01714454) enrolled 10,568 patients with STEMI (47%) or NSTEMI (53%) in 555 centers in 20 countries across Europe and Latin America.

Results: Overall, 31% of patients (35% STEMI, 28% NSTEMI) received pre-hospital care. Drug treatment was started in 21% of patients before hospitalization (27% of STEMI and 15% of NSTEMI patients). Pre-hospital fibrinolysis was given in only 18% of STEMI patients (vs 10%; P<0.01). Pre-hospital aspirin was given in only ∼20% of patients, clopidogrel in fewer than 10%, and prasugrel very rarely. Pre-hospital antiplatelet therapy was more frequently initiated in STEMI patients: 72% for aspirin and 36% for clopidogrel among those receiving pre-hospital care. Among patients who had a pre-hospital ECG (36%), pre-hospital aspirin and clopidogrel were given to only 50% and 28% of STEMI patients, respectively, and to 31% and 9% of NSTEMI patients. In contrast, pre-hospital clopidogrel was only given to 2% of STEMI patients without a pre-hospital ECG. There were no differences in pre-hospital antithrombotic treatment between hospitals with or without on-site cath facilities.

Conclusion: Pre-hospital initiation of antiplatelet agents remains relatively infre-

P1872 Despite pharmacological equivalence, generic versions of enoxaparin may differ in their pharmacodynamic actions. Potential clinical implications

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Introduction: Most recently available generic enoxaparins are similar to Lovenox (Sanofi Aventis) in terms of potency and molecular profile. This study compared available generic enoxaparins with the branded version in various assays and investigated their pharmacokinetic/pharmacodynamic behavior in a primate model.

Methods: Cutenox, Lupenox, enoxaparin Sandoz and Lovenox were compared in terms of molecular weight profiling, NMR profile and in vitro anticoagulant activity. Groups of primates (n=8-10) were administered LMWH (1 mg/kg subcutaneously) in various assays – IPF and IPFH - have an independent prognostic value and maybe useful in improving risk stratification in ACS patients. Future prospective studies evaluating the role of RIP in determining cardiovascular eventss are needed.

P1874 In-hospital outcomes of patients treated with clopidogrel or prasugrel for acute myocardial infarction in the real world: Results from the FAST-MI 2010 registry

L. Belle1, F. Schiefe2, E. Puyimira3, G. Rouf4, G. Vanzetto5, R. Morice6, B. Ritz7, J. Ferretieres8, T. Simon9, N. Danchin10, 1Hospital, Annecy, France; 2University hospital, Besançon, France; 3University hospital, Paris, France; 4University hospital, Strasbourg, France; 5University hospital, Grenoble, France; 6Hospital, Aix-en-Provence, France; 7Hospital, Lyon, France; 8University hospital, Toulouse, France

Background: The TRITON trial showed that prasugrel was superior to clopido-

Methods: FAST-MI 2010 is a nationwide registry that included 4,169 patients with AMI in 213 centers representing 76% of French centres managing AMI patients at the end of 2010. Of those, 4,115 received thienopyridines: 2,866 clopidogrel only (C) (69%), and 1,259 received prasugrel (P) (31%) of whom 44% received the first dose prior to coronary angiography.

Results: Both groups differed markedly: age (69±14 vs 71±11, P<0.001), sex (% women: 33 vs 14%, P>0.001), GRACE score (147±37 vs 126±28, P<0.001), % STEMI (49% vs 74.5%, P<0.001) in the C and P groups respectively. CV risk factors, history of CAD, stroke, CKD or non-CV comorbidities were all more fre-

Conclusion: Although the generic enoxaparins are manufactured to be pharma-

P1873 Reticulated platelets predict the risk of cardiac death in acute coronary syndrome patients independently of mean platelet volume: data from AMI-Florence 2 study

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Introduction: Elevated mean platelet volume (MPV) has been associated with AMI and mortality/following myocardial infarction. Reticulated platelets (RP) are newly formed and larger in size platelets containing residual amount of RNA. Large platelets could be a reflection of the number of RP, although not all large platelets are young platelets. To date, there are no studies that investigated the possible association of RP in predicting the risk of cardiovascular death among acute coronary syndrome (ACS) patients.

Aim: To evaluate the impact of RP on the occurrence of cardiovascular death in ACS patients.

Methods: On the frame of the AMI-Florence 2 study, we investigated 229 ACS (154 M, 75 F) patients. RP were measured using the Sysmex XE-2100 haema-

Results: After one-year follow-up, 22 out of 229 patients (9.6%) died from cardio-

stroke 0.3% 0.3% 0.5% 3.32 (0.21-55.6)

death 3.6% 0.5% 0.4% 0.41 (0.05-3.30)

Any bleeding 1.2% 1.0% 1.4% 1.34 (0.36-4.97)

Major bleeding 1.2% 1.0% 0.4% 1.34 (0.36-4.97)

Conclusion: We have found, for the first time, that the immature plateletfrac-

P1871 Prehospital Rx (%) Total STEMI NSTE-ACS

Any medication 21 27 15

Aspirin 20 26 14

Clopidogrel 8 13 4

Anticoagulation (UFH or LMWH) 9 14 4

Overall, 31% of patients (35% STEMI, 28% NSTEMI) received pre-

Conclusion: Pre-hospital initiation of antiplatelet agents remains relatively infre-

P1874 In-hospital outcomes of patients treated with clopidogrel or prasugrel for acute myocardial infarction in the real world: Results from the FAST-MI 2010 registry

L. Belle1, F. Schiefe2, E. Puyimira3, G. Rouf4, G. Vanzetto5, R. Morice6, B. Ritz7, J. Ferretieres8, T. Simon9, N. Danchin10, 1Hospital, Annecy, France; 2University hospital, Besançon, France; 3University hospital, Paris, France; 4University hospital, Strasbourg, France; 5University hospital, Grenoble, France; 6Hospital, Aix-en-Provence, France; 7Hospital, Lyon, France; 8University hospital, Toulouse, France

Background: The TRITON trial showed that prasugrel was superior to clopido-

Methods: To assess the baseline characteristics and in-hospital outcomes of AMI patients treated with either clopidogrel or prasugrel in real world practice.

Methods: FAST-MI 2010 is a nationwide registry that included 4,169 patients with AMI in 213 centers representing 76% of French centres managing AMI patients at the end of 2010. Of those, 4,115 received thienopyridines: 2,866 clopidogrel only (C) (69%), and 1,259 received prasugrel (P) (31%) of whom 44% received the first dose prior to coronary angiography.

Results: Both groups differed markedly: age (69±14 vs 71±11, P<0.001), sex (% women: 33 vs 14%, P>0.001), GRACE score (147±37 vs 126±28, P<0.001), % STEMI (49% vs 74.5%, P<0.001) in the C and P groups respectively. CV risk factors, history of CAD, stroke, CKD or non-CV comorbidities were all more fre-

In-hospital outcomes

Clotopigrel (n=2866) Prasugrel only (n=391) Any Prasugrel (n=1259) Adjusted OR (P only vs C only)

death 3.6% 0.6% 0.4% 0.41 (0.05-3.30)

Any bleeding 8.6% 7.4% 6.4% 1.16 (0.73-1.87)

Major bleeding 1.2% 1.0% 1.4% 1.34 (0.36-4.97)

Stroke 0.3% 0.3% 0.5% 3.32 (0.21-55.6)
High frequency of CYP2C19*2 carriers in PCI-treated patients initially treated with clopidogrel and switched to prasugrel therapy based on a platelet function testing guided approach


Purpose: Among patients undergoing PCI, subjects with high on-clopidogrel treatment platelet reactivity (HCPR) exhibit a high risk for post-procedural thrombotic events. Both non-genetic and genetic variables impact on clopidogrel responsiveness. The impact of the common loss-of-function CYP2C19*2 variant on HCPR patients remains unknown. The aim of this study was to determine CYP2C19*2 allele carriage in PCI-treated patients initially treated with clopidogrel and switched to prasugrel therapy based on a platelet function testing guided approach.

Methods: Prevalence of the CYP2C19*2 allele was compared between two consecutively recruited cohorts. One cohort (n=1274) of patients with an adequate response to clopidogrel and without a switch of treatment stems from a trial including 1608 patients that we conducted between 2007-2008. A second cohort (n=124) was consecutively recruited between 2009-2011 and includes HCPR patients with a switch of treatment from clopidogrel to prasugrel in a setting of routine platelet function testing. Platelet aggregation (in AU x min) was tested on a Multiplate analyzer and repeated clopidogrel loading doses (LD) were given in the majority of patients (76/124) before switching over to prasugrel treatment. Geno-types were determined by a TaqMan assay.

Results: The rate of CYP2C19*2 allele carriers was significantly higher in HCPR patients switched to prasugrel as compared to patients showing an adequate response to clopidogrel (43.5% vs. 22.3%, respectively; P<0.0001). Following prasugrel LD administration, the ADP-induced platelet aggregation (median, interquartile range) was similar in 2 (n=54) vs. non 2 (n=70) allele carriers (148 [88-236] vs. 137 [88-236] AU x min, respectively; P=0.04).

Conclusions: The frequency of the CYP2C19*2 allele variant is very high in HCPR patients with a switch of treatment from clopidogrel to prasugrel in a setting of individualized and platelet function testing guided antiplatelet treatment. On-prasugrel treatment platelet reactivity is not influenced by this genetic variant. The clinical impact of these findings warrants further investigation.

Pharmacokinetics and pharmacodynamics of prasugrel 5 mg in low body weight patients and prasugrel 10 mg in higher body weight patients

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Purpose: The TRITON-TIMI 38 study showed that following PCI, low body weight (LBW) patients on 10mg prasugrel had an increased bleeding risk. Reducing the prasugrel dose to 5mg in patients ~60kg is recommended but not extensively investigated. The objective of this study was to investigate the impact of a reduced dose of prasugrel (5mg) on platelet function in LBW patients compared to HBW patients on 10mg and 5mg prasugrel.

Methods: In a 3 period (12 day each), randomized, crossover fashion, 34 LBW (54.6±3.7kg) and 38 HBW (84.7±14.9kg) patients received a daily dose of 5mg prasugrel, 10mg prasugrel, or 5mg clopidogrel on top of 75-100mg aspirin. We calculated the area under the plasma concentration-time curve (AUC0-last) of prasugrel active metabolite (AM) based on 5 measurements (0.5, 1, 2, 3, and 4 hours). For PD analysis, light transmission aggregometry (LTA), using 5 and 20μM ADP, VerifyNow P2Y12 (VN-PRI), and vasodilator-associated stimulated phosphoprotein (VASP-PRI) were performed.

Results: LBW patients on 5mg prasugrel had lower prasugrel AM concentrations than HBW patients on 10mg prasugrel (mean AUC0-tlast 29.0 vs. 46.7 ng*h/ml, LS mean 14.9% CI 0.5-24.7). Figure. There were no significant differences in platelet reactivity between LBW patients on 5mg prasugrel and HBW patients on 10mg prasugrel for either VN-PRI (Figure), VASP-PRI, or LTA (not shown).

Conclusions: While prasugrel AM concentrations in LBW aspirin-treated patients with stable CAD on 5mg prasugrel were lower compared to HBW patients on 10mg prasugrel, no significant differences were found in platelet reactivity measured by LTA, VN-PRI, or VASP-PRI. These data support the recommended dosing for 5mg in LBW patients.

Clopidegrel and prasugrel non-responder in the platelet function guided approach after cardiac arrest

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Summary: Background: In acute coronary syndromes the percutaneous coronary intervention with implantation of a coronary stent is the recommended treatment. Afterwards administration of AAS and a thienopyridine like clopidogrel or prasugrel is necessary to prevent thrombotic complications like stentthrombosis. High residual platelet reactivity after administration of platelet inhibitors is related to an increased risk of thrombotic complications. Objectives: To determine the effect of thienopyridines in patients in therapeutic hypothermia after cardiac arrest.

Patients/Methods: 83 patients with acute coronary syndromes were enrolled in a single center, prospective observational study (40 Patients in hypothermia, 43 in normothermia). All patients received a loading dose of 600 mg clopidogrel or 60 mg prasugrel and platelet reactivity Index (PRI-VASP) was measured 24 h after administration. A PRI-VASP above 50% was defined as high residual platelet reactivity. Major adverse cardiac events were recorded in the following.

Results: Mean values showed a significant higher PRI-VASP in the hypothermia group compared to the normothermia group, indicating a worse response to thienopyridine (61.1%±23.8 vs. 31.6%±22.2, p<0.01). The number of patients of thienopyridine non-responder in the hypothermia-group was higher compared to normothermia group (70.0% vs. 23.3%). Comparing prasugrel and clopidogrel in patients in hypothermia mean PRI-VASP was significantly lower in the prasugrel group (37.5%±28.3 vs. 68.9%±16.0, p<0.01). The non-responder rate in the prasugrel group was lower (30% vs. 83%).

Conclusions: High residual platelet reactivity is common in patients after cardiac arrest in therapeutic hypothermia. Non-responder rate is extremely high in these patients. Novel antiplatelet drugs like prasugrel can ameliorate platelet inhibition significantly. If better platelet inhibition leads to lower rates of thrombotic events has to be investigated in further studies.
patients, PCI was performed for acute coronary syndrome (65.4%). PR was significantly decreased after the 2nd LD (mean VASP after first LD = 66.8±1.0% vs 49.6±1.8% after second LD; p<0.0001). The second LD overcame HTPR in 47.7% of patients. The rate of in-hospital non-CABG bleeding was low with only one BARC 3 event.

Platelet reactivity after loading doses

<table>
<thead>
<tr>
<th>n=107</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Mean VASP after 1st LD</td>
<td>66.8±1.0%</td>
</tr>
<tr>
<td>Mean VASP after 2nd LD</td>
<td>49.6±1.8%</td>
</tr>
<tr>
<td>Patients with VASP &gt; 50% after 1st LD</td>
<td>71.2%</td>
</tr>
<tr>
<td>Patients with VASP &gt; 50% after 2nd LD</td>
<td>47.7%</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, p<0.0001 between mean VASP index after 1st LD and VASP index after 2nd LD. Loading dose.

Conclusion: HTPR can be overcome in a significant number of elderly patients treated with PCI thanks to a second 600mg loading dose of clopidogrel with a very low rate of bleeding events.

**P1879** Baseline or platelet reactivity on clopidogrel as predictor for clinical outcome

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Introduction: High on-treatment platelet reactivity is associated with worse clinical outcome in patients on clopidogrel. It is unknown whether baseline platelet reactivity before initiation of clopidogrel treatment or on-treatment platelet reactivity is the preferable long-term predictor of worse clinical outcome.

Methods: This study enrolled 765 consecutive patients undergoing elective coronary stent implantation. Baseline platelet reactivity was tested by light transmission aggregometry (LTA 100) before administration of clopidogrel 600mg. On-treatment platelet reactivity was determined on day 1 after coronary stenting and after intake of first maintenance dose of clopidogrel 75mg. Patients were followed up for 7 years. The combined primary endpoint was death of any cause or non-fatal myocardial infarction (MACE).

Results: The ROC derived optimal cut-off for MACE was 50% for baseline platelet reactivity and 14% for on-treatment platelet reactivity. Baseline platelet reactivity was neither predictive for MACE during the first year of follow-up (hazard ratio [HR] 1.82, 95% CI 0.81-4.06; log-rank P=0.14) nor during entire follow-up (HR 1.00, 95% CI 0.67-1.47; log-rank P=0.41). On-treatment platelet reactivity >14% was associated with a HR for MACE during the first year of 3.04 (95%CI 1.36-6.79; log-rank P=0.004) and during entire follow-up of 1.32, 95% CI 0.89-2.00; log-rank P=0.02. In multivariable cox regression analysis, high on-treatment platelet reactivity was an independent predictor for MACE within one year but not during entire follow-up.

**P1880** Switching patients with high-on-treatment platelet inhibition from prasugrel to clopidogrel after an acute coronary syndrome exposure to clopidogrel resistance

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Aim: Many physicians switch their patients from prasugrel to clopidogrel before the end of the suggested one-year treatment following PCI for ACS. The aim of this study was to assess platelet reactivity of these patients before and after the switch.

Methods: 294 ACS patients treated by a maintenance dose of prasugrel 10 mg after PCI were evaluated at 15 days by measuring the platelet reaction unit (PRU) using the VerifyNowTM P2Y12 platform. Patients at high risk of bleeding and/or high level of on-treatment inhibition were switched to clopidogrel 75 mg and were re-evaluated 15 days after. The rate of patients with high on-treatment platelet reactivity (HPR, PRU >208) and high on-treatment platelet inhibition (HPI, PRU>30) were evaluated before and after the switch.

Results: 68% of the patients had ST-segment elevation myocardial infarction, 27.5% were diabetics, 15.2% were more than 75 y/o and 12.2% had a body weight <60kg. In the overall population, the rate of patients on prasugrel with HPR was 4.4% (n=13) while 44.6% (n=131) had HPI. A group of 26 patients (9%) was switched to clopidogrel of whom 22 had HPI (84.6%). As expected, on-treatment PRU increased from 18±5 before to 169±18 after the switch (p<0.0001) and the rate of patients with HPI decreased from 84.6% to 3.9% before and after the switch respectively. No patient of this group displayed HPR on prasugrel while 38% (n=10) had HPR when switched to clopidogrel, reflecting resistance to clopidogrel (figure, black squares).
Profile and in-hospital outcomes of patients treated with a high (600 mg) clopidogrel loading dose versus prasugrel for acute myocardial infarction. The FAST-MI 2010 registry

E. Pyymyrä1, L. Bonello2, G. Ducrocq3, J. Boschat4, C. Robin5, C. Le Ray2, N. Delarche2, G. Mulak6, T. Simon7, N. Danchin8 on behalf of the FAST-MI 2010 investigators. 1AP-H, Hospital Georges Pompidou, Paris, France; 2AP-WM - Hospital Nord, Marseille, France; 3AP-HP - Hospital Bichat-Claude Bernard, Department of Cardiology, Paris, France; 4University Hospital of Brest, Department of Cardiology, Brest, France; 5Clinicove, Bourg en Bresse, France; 6Hospital of Vannes, Vannes, France; 7Hospital of Brest, Pau, France; 8French Society of Cardiology, Paris, France; 9AP-HP - Hospital Saint-Antoine, Faculty of Medicine Pierre & Marie Curie Paris 6, Paris, France

Background: In real-life, many AMI patients receive high doses of clopidogrel (≥600 mg loading dose) as an alternative to newer P2Y12 inhibitors.

Aim: To compare baseline profile and outcomes of patients receiving a high clopidogrel dose, vs those receiving prasugrel in AMI.

Methods: Nationwide French registry including 4169 AMI patients in 213 centres; 4115 with thienopyridine, 808 (High-C group: 20%) with ≥600 mg loading dose of clopidogrel (no later switch to prasugrel) and 391 (P group: 9.5%) with prasugrel only (no switch from clopidogrel). We compared baseline profile, bleeding and ischemic complications in High-C and P groups, and then used propensity-score matching to compare outcomes in 2 cohorts with similar baseline characteristics.

Results: High-C pts were older than P-group pts (65 vs 77 years; P<0.001), with a higher rate of hypertension (57 vs 27% in High-C group; P<0.001); more often presented with STEMI (77% vs 61%, P=0.001), and more often had PCI (93% vs 85%, P<0.001), but less often fibrinolysis (5% vs 10%). None of the complications differed significantly after multivariate adjustment (Table). The 2 propensity-score matched cohorts (335 patients each) had comparable baseline characteristics: none of the complications differed significantly (High-C vs P): any bleeding (8.1 vs 6.9%), major bleeding (0.3 vs 0.9%), stent thrombosis (0.1 vs 0.9%), stroke (0 vs 0.3%), reinfarction (0 vs 0.9%), inhospital death (0.9 vs 0.3%).

Conclusion: In this real-world registry, patients receiving high-dose clopidogrel had a more severe risk profile than those receiving prasugrel. In-hospital complications were uncommon and there was no significant difference between high-dose clopidogrel and prasugrel after adjustment for potential confounders.

Table 1

<table>
<thead>
<tr>
<th>Prasugrel only (n=391)</th>
<th>High-dose clopidogrel (n=808)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death</td>
<td>0.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Any bleeding</td>
<td>7.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Reocclusion M</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>0.8%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

In-hospital complications.

Conclusion: Among diabetic patients, prasugrel reduced ischemic events compared to clopidogrel without increasing the bleeding risk. Ticagrelor resulted in a non-significant reduction in ischemic events compared to clopidogrel, in the diabetic subgroup. We aimed to compare the antithrombotic effect of ticagrelor vs prasugrel in diabetic patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

Purpose: Among diabetic patients, prasugrel reduced ischemic events compared to clopidogrel without increasing the bleeding risk. Ticagrelor resulted in a non-significant reduction in ischemic events compared to clopidogrel, in the diabetic subgroup. We aimed to compare the antithrombotic effect of ticagrelor vs prasugrel in diabetic patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

Methods: This was a prospective, randomized, single-center, single blind, investigator-initiated, two-arm, crossover study. Patients aged ≥75 years with ≥60 kg on-treatment platelet reactivity (HTPR) post PCI. PR was assessed with the VerifyNow assay in platelet reactivity units-PRU with a value >230 indicating high on-treatment platelet reactivity (HTPR).

Results: There was no difference in patient’s demographic and clinical characteristics between ticagrelor (N=11) and prasugrel (N=11) group. Baseline PR did not differ significantly between groups (239.4 PRU vs 246.6 for ticagrelor vs 241.3±81.5 for prasugrel, p=0.9). The primary end point of PR assessed at the end of the two (precrossover and postcrossover) periods was lower for ticagrelor compared to prasugrel (48.9 PRU, 25.8±72.9 % inhibition vs 69.5 PRU, 95±69.5%, p<0.05 respectively). HTPR rate at baseline was 59% (13/22) and was eliminated both by ticagrelor and prasugrel. No deaths or strokes occurred in either treatment group.

Conclusions: In diabetic patients with ACS ticagrelor produced a significantly higher platelet inhibition compared to prasugrel. However, both agents effectively treated HTPR.

Low prasugrel vs high clopidogrel dose in patients aged greater than or equal to 75 years with ACS and high on clopidogrel platelet reactivity post PCI

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Purpose: In patients ≥75 years of age, if treatment with prasugrel is deemed necessary, a reduced maintenance dose (MD) of 5 mg is suggested, after a careful individual benefit/risk evaluation. We aimed to compare the antithrombotic action of prasugrel 5mg versus clopidogrel 150mg in patients ≥75 years of age with acute coronary syndrome (ACS) and high on-treatment platelet reactivity (HTPR) post percutaneous coronary intervention (PCI).

Methods: This was a prospective, randomized, single-center, single-blind, investigator-initiated, two-arm, crossover study. Patients aged ≥75 years with HTPR (>235 platelet reactive units-PRU by VerifyNow assay) 24 hours post PCI, were randomized in a 1:1 ratio to prasugrel 5mg or clopidogrel 150mg for 15 days, followed by crossover directly to the alternate therapy for an additional 15 days without an intervening washout period. Patients at increased risk of bleeding, with periprocedural complications, illibila inhibitor administration, on hemodialysis, prior stroke, age ≥75 years or <60 kg, at increased risk for bradycardic events, strong CYP2A inhibitors or inducers, severe uncontrolled obstructive pulmonary disease and severe hepatic impairment were excluded from the study. PR was assessed with the VerifyNow assay in platelet reactivity units-PRU with a value >230 indicating high on-treatment platelet reactivity (HTPR).

Results: There was no difference in patient’s demographic and clinical characteristics between ticagrelor (N=11) and prasugrel (N=11) group. Baseline PR did not differ significantly between groups (239.4 PRU vs 246.6 for ticagrelor vs 241.3±81.5 for prasugrel, p=0.9). The primary end point of PR assessed at the end of the two (precrossover and postcrossover) periods was lower for ticagrelor compared to prasugrel (48.9 PRU, 25.8±72.9 % inhibition vs 69.5 PRU, 95±69.5%, p<0.05 respectively). HTPR rate at baseline was 59% (13/22) and was eliminated both by ticagrelor and prasugrel. No deaths or strokes occurred in either treatment group.

Conclusions: In diabetic patients with ACS ticagrelor produced a significantly higher platelet inhibition compared to prasugrel. However, both agents effectively treated HTPR.
There was no difference in patient’s demographic and clinical characteristics between the 2 groups. The primary end point of platelet reactivity (PR) assessed at the end of the two (precrossover and postcrossover) periods, did not differ significantly between the 2 groups [382.2 PRU, 251.2–303.3 95% CIs for clopidogrel 150mg vs 245.4 PRU; 205.6–285.3 95% CIs for prasugrel 5mg, p=0.5]. HTPR rates remained high in both groups (76.9% for clopidogrel 150mg and 57.1% for prasugrel 5mg). No deaths or strokes occurred in either treatment group.

Conclusions: In patients ≤75 years old with ACS, exhibiting HTPR 24 hours post PCI, the antiplatelet effects of prasugrel 5 mg and clopidogrel 150 mg do not differ significantly. HTPR rates remained high in both agents, perhaps suggesting the need of using an alternative antiplatelet agent.

P1886 Clopidogrel is associated with weaker platelet inhibition, lower active metabolite concentration and more poor responders in higher body weight patients compared with lower body weight patients

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Purpose: Body weight is a predictor of clopidogrel response. However, no prospective studies have compared pharmacodynamic (PD) and pharmacokinetic (PK) data from higher vs. low weight patients. We compared the PD and PK effects of clopidogrel 75 mg in lower (LBW, ≤60 kg) and higher (HBW, >60 kg) body weight subjects with stable CAD.

Methods: LBW (n=34, 56.4±17 kg) and HBW subjects (n=38, 84.7±14.9 kg) on aspirin were given clopidogrel 75 mg for 12 days. The area under the plasma concentration-time curve from dosing through last measurable concentration (AUC0-tlast) of clopidogrel active metabolite (AM) was calculated by noncompartmental methods. For PD analysis, light transmission aggregometry (LTA, using 5 μM ADP), VerifyNow P2Y12 (VN-PRU), and vasodilator-stimulated phosphatase (VASP-PRI) were performed.

Results: Mean AUC0-tlast of clopidogrel AM was lower in HBW than in LBW subjects, 12.7 and 18.4 ng·hr/ml, respectively (Figure). In PD analysis with VN-P14, LBW subjects generated less clopidogrel AM and had higher PRI (not shown).

More subjects exhibited high on-treatment platelet reactivity (HPR) using consensus values of VN-P2Y12 PRU >225 or VASP-PRI >50% in the HBW group: PRU – 235.9 (4.3% vs. 35.3%, LBW vs. HBW, p=0.018) and PRI >50% (20.7% vs. 64.7%, LBW vs. HBW, p<0.003).

Weight correlated with VN and VASP responses (Pearson correlation coefficient 0.45, and 0.52, both p<0.001), and inversely with log transformed(AUC0-tlast) (-0.42, p<0.0005).

Conclusion: HBW subjects generated less clopidogrel AM and had higher platelet reactivity and higher rates of HPR than did LBW subjects, contributing to their sub-optimal response to clopidogrel.

P1887 Effects of ex vivo platelet transfusion on platelet aggregability in patients treated with clopidogrel or ticagrelor

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Purpose: Antiplatelet therapy reduces morbidity and mortality in patients with coronary disease but is also associated with an increased risk for bleeding. Platelet concentrate transfusion is often tried to restore platelet function when bleeding occurs but there is scarce knowledge about the efficacy. We assessed the effect of platelet transfusion on ADP- and acetylsalicylic acid (ASA)-dependent platelet aggregability in patients on different antiplatelet therapies.

Methods: Platelet aggregability was investigated ex vivo with multimethod impedance aggregometry with ADP and arachidonic acid as initiators in whole blood samples from healthy subjects without antiplatelet therapy (n=10), and in coronary artery disease patients treated with ASA (n=10), ASA+clopidogrel (n=10) or ASA+ticagrelor (n=8). Aggregability was measured before and after three doses of fresh platelet concentrate (+48,+96 and +144+108h). The aggregability (mean ±SEM) is reported in arbitrary aggregation units (AUmin).

Results: ADP-induced aggregability was significantly reduced in ASA+clopidogrel and ASA-ticagrelor at baseline compared to healthy subjects and ASA. Baseline arachidonic acid-induced aggregability was reduced in all three patients groups compared to healthy subjects. Addition of platelets had no effect on ADP-induced aggregability in healthy subjects and ASA-treated patients. In contrast, ADP-induced aggregability improved significantly in patients treated with ASA+clopidogrel and ASA-ticagrelor but the effect was limited, also with the highest dose of platelets (+48h+108h). Platelet transfusion restored completely ASA-dependent aggregability in all study groups.

Conclusions: Platelet transfusion has marginal effect on ADP-dependent platelet aggregability in patients on antiplatelet therapy with ASA, and clopidogrel or ticagrelor, while ASA-dependent aggregability is completely restored.

P1888 Which component of the composite endpoints in P2Y12 inhibitor trials drives the benefit: a meta-analysis of randomized controlled trials with 136,117 patients

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Purpose: Multiple randomized trials have shown that platelet P2Y12 receptor inhibitors significantly lower several cardiovascular endpoints in the setting of acute coronary syndromes (ACS). Traditionally, composite endpoints have been used to evaluate the safety and efficacy of these agents. Whether or not the beneficial composite effect of these agents is attributable to a benefit driven by one or multiple components of these endpoints has not been clarified.

Methods: We conducted a meta-analysis of all ACS randomized trials comparing a P2Y12 antagonist versus active control or placebo. We searched MEDLINE, EMBASE, Scopus, and Cochrane Controlled Trials Register (Central) databases from inception to December 2011 without language restriction. Data on the protocol-defined composite endpoints of major adverse cardiovascular events (MACE) were extracted, in addition to rates of death and myocardial infarction. Analyses were performed using an inverse variance weighted random-effects model.

Results: From a total of 2,347 articles, 179 underwent full-text review, and 13 met our inclusion criteria. Of these, 3 trials compared clopidogrel to placebo, 5 compared high dose vs. low dose clopidogrel, and 5 compared new vs. standard P2Y12 inhibitors. All patients received aspirin. The analysis included 136,117 patients, with an average age of 62.3 years and a mean follow-up of 114 days.

There was considerable heterogeneity among trial populations in terms of trial size, duration of follow-up, and endpoint definitions including MACE. Across all trials, P2Y12 antagonism was associated with a significant reduction in MACE (hazard ratio [HR] 0.87, 95% confidence interval [CI]: 0.82–0.93, p=0.004), myocardial infarction (HR 0.85, 95% CI: 0.78–0.92, p=0.01), and death (HR 0.91, 95% CI: 0.84–0.97, p=0.002). I-squared varied from 19 to 50% across endpoints.

Conclusions: From a total of 2,347 articles, 179 underwent full-text review, and 13 met our inclusion criteria. Of these, 3 trials compared clopidogrel to placebo, 5 compared high dose vs. low dose clopidogrel, and 5 compared new vs. standard P2Y12 inhibitors. All patients received aspirin. The analysis included 136,117 patients, with an average age of 62.3 years and a mean follow-up of 114 days.

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Safety and efficacy of adjuvant glycoprotein 2b/3a inhibitors during primary percutaneous coronary intervention (PCI) performed from the radial approach for ST elevation myocardial infarction (STEMI)

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Purpose: Use of glycoprotein 2b/3a inhibitors (GPI) in high risk acute coronary syndrome patients has demonstrated reduction in ischemic events with increase in bleeding complications. The role of GPI in patients who have PCI by transradial approach (TR) is not well studied. We conducted a post hoc analysis from the randomized prospective ATOLL trial (Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction) to assess the safety and efficacy of GPIs performed TR.

Methods: 910 patients were enrolled in ATOLL; 522 (67%) had PCI by TR. We conducted two comparative analyses: 1) Patients with TR, with GPI vs. NO GPI, 2) TR with GPI vs. Transfemoral (TF) with GPI. Composite endpoints of net clinical benefit, ischemic outcomes, and safety consisting of bleeding and translocation at one month are illustrated in Table 1. We constructed a propensity score and made weight adjustment for variables including but not exclusive to; age, weight, gender, renal function, concomitant use of other medications, Killip class, and past medical history, when analyzing the endpoints.

Results: There was no significant difference in net clinical benefit or ischemic outcomes between; 1) TR patients with vs. without GPI, NOR 2) TR with GPI vs. TF with GPI. However, TR with GPI had the fewest ischemic events. Additionally, there were significantly less major bleeds and blood transfusion in TR with GPI vs. TF with GPI.

Conclusion: Addition of GPI in the setting of primary PCI by transradial approach adds no liability. Use of GPI with transradial approach is safer than transfemoral. Our study is limited by being a non randomized retrospective analysis.

Abstract P1890

Regional trends in dual antiplatelet therapy non-adherence among patients undergoing percutaneous coronary intervention: insights from the paris registry

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Purpose: Dual antiplatelet therapy (DAPT) is the cornerstone of medical therapy in patients with coronary artery disease or after interventional procedures. Geographic patterns in the prevalence, modes and factors associated with non-adherence to DAPT in the US vs. Europe amongst patients undergoing percutaneous coronary intervention (PCI) with stent placement is not well characterized.

Methods: The PARIIS registry is an ongoing multicenter, multinational, observational study following 5,033 patients who underwent PCI with bare metal or drug eluting stents. Modes of non-adherence were defined as discontinuation (per recommendation of physician who felt that therapy is no longer needed), interruption (e.g. surgery; physician-guided; DAPT must be reinstated within 14 days) and discontinuation (due to bleeding). We compared differences in the prevalence, modes and factors of 6-month DAPT non-adherence among US and European participants.

Results: The overall non-adherence rate was 9.2% at 6 months. Non-adherence was significantly more common among US (n=3666) compared to European (n=1367) participants (10.09% vs. 6.73%, p=0.0001). Figure) Non-adherence mode also differed by region as discontinuation (5.6% vs. 1.5%, p=0.0001) and interruption (1.94% vs. 95%, p=0.0001) were more common in the US while patients in Europe showed a higher rate of DAPT disruption (4.24% vs. 2.59%, p=0.0001).

Abstract P1891

Gastrointestinal complications with clopidogrel: a nationwide population-based cohort study

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Background: Clopidogrel prevents cardiovascular events and remains the second most prescribed drug worldwide. The use of clopidogrel has been linked with gastrointestinal complications, particularly bleeding events. We aimed to investigate the risk of gastrointestinal ulcer or bleeding in patients treated with clopidogrel.

Methods: We conducted a nationwide population-based cohort study based on a nationwide population-based cohort study based on a nationwide population-based cohort study.
on linkage of three administrative registries in Denmark. All individuals who re-
determined at least one prescription of clopidogrel from 1996 to 2008 were included
as exposed subjects (n=77,503). For each exposed subject, three matched con-
trols were randomly selected from the background population (n=232,510).
The study population thus consisted of 310,013 subjects. Follow-up began on Jan-
uary 1, 1996, and was censored on December 31, 2007, or if patients emigrated
or died. The study endpoint was any event of gastritis, gastrointestinal ulcer or
bleeding. Analyses were adjusted for comorbidity and medication.
Results: Regardless of dose, adjusted odds ratios associating clopidogrel use with
the study endpoint were statistically significant and followed a dose-response
pattern. Accordingly, increasing doses of clopidogrel yielded increasing odds ra-
tios of suffering gastritis or gastrointestinal ulcer or bleeding (odds ratios 1.3-1.9,
p<0.01). Depending on the dose, numbers needed to harm ranged from 33 to 58
patients receiving 12 months of clopidogrel treatment.
Conclusions: Clopidogrel is associated with an increased dose-dependent risk
of gastritis, gastrointestinal ulcer or bleeding. The well-known cardioprotective ef-
cfect of clopidogrel must be carefully weighed against an increased risk of gas-
trointestinal complications.

Can platelet function test predict safety of prasugrel
after an ACS?
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Background: To evaluate platelet reactivity and 30-day bleeding events in patients
with ACS patients on maintenance dose of prasugrel 10mg after an acute coronary syndrome (ACS).
Methods: In two high volume centers, 443 ACS patients revascularized with PCI were treated with a maintenance dose of prasugrel 10mg/day. On-treatment platelet reactivity was measured 2 to 4 weeks after discharge by the Vasodilator-
stimulated phosphoprotein (VASP) index. Additional measures with the VerifyNow P2Y12 assay and Light Transmission Aggregometry were also performed. Bleed-
ings events (Bleeding Academic Research Consortium (BARC) definition) and is-
chemic events (death, myocardial infarction, and definite stent thrombosis) were
collected over 30 days of follow-up.
Results: Two thirds of the patients presented with an ST-segment elevation my-
ocardial infarction, 28.8% were diabetics and 12.4% were more than 75 y/o. PCI
was performed through a radial access in 96.4% of patients. High on-treatment
platelet reactivity (HPR) according to three prespecified definitions (VASP>50%,
P2Y12 reaction units (PRU) ≥ 235, residual platelet aggregation (RPA) ≥ 46.2%)
was found in 6.8%, 3.4% and 3.2% of patients, respectively.
Obesity (BMI>30 kg/m²) and multi-vessel disease were the only independent fac-
tors associated with HPR. At 30 days, there was no major bleeding complication
(BARC 3, 4 or 5) and 1.6% ischemic events.
The rate of nuisance bleeding (BARC 1) and minor bleeding (BARC 2) were
14.2% (n=63) and 2.5% (n=11), respectively. The AUC of the VASP as diagnostic
test to predict bleeding events was low: 0.57 CI (0.51-0.64, p=0.03). The cut off
value of VASP 15.05% offered a sensitivity of 35% with a specificity of 77% to be
showed HPR on prasugrel MD vs. LD (14.9% vs. 3%, P = 0.03). Prasugrel 5 mg
MD (n=12) resulted in significantly higher PA values as compared to 10 mg MD
(n=55) therapy (p=0.01, Fig 1C) with significantly higher HPR rates on 5 vs. 10
mg (41.7% vs. 9.1%, P=0.02);

Conclusion: In a high-risk cohort of PCI-treated patients showing HPR on clo-
pidogrel, the antiplatelet action of prasugrel was not uniform and showed a con-
siderable variability. Response variability was more pronounced on MD vs. LD
treatment. The clinical impact of these findings warrants further investigation.

Interaction between the effect of abciximab plus
unfractionated heparin vs bivalirudin in treatment of
myocardial injury among patients with non-ST-segment
elevation myocardial infarction
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Purpose: ISAR-REACT-4 showed the inability of abciximab plus unfractionated
heparin to improve outcomes of patients with non-ST-segment elevation myocar-
dial infarction (NSTEMI) undergoing percutaneous coronary intervention (PCI) as
compared to bivalirudin. However, the interaction of these antithrombotic drugs
with the severity of the heart attack was not fully elucidated.
Methods: In the patient cohort from ISAR-REACT-4, a double-blind randomized
trial comparing antithrombotic therapy with abciximab plus unfractionated heparin
to the therapy with bivalirudin, we divided the patients into quartile groups accord-
ing to the preprocedural Troponin-T level (Q1: 403 patients, Q2: 444 patients, Q3:
438 patients, Q4: 436 patients) and compared outcome. The primary endpoint
was a composite of death, large recurrent MI, urgent target-vessel revascular-
ization (TVR), or major bleeding within 30 days. Secondary endpoints included
the composite of death, any recurrent MI (efficacy endpoint) and major bleeding
(safety endpoint) within 30 days.

Results: Therewas no significant interaction regarding the primary endpoint be-
tween troponin level and antithrombotic therapy (Q1: 7.4% vs 6.1%, P=0.61, Q2:
9.1% vs 7.5%, P=0.55, Q3: 10.6% vs 14.0%, P=0.29, Q4: 16.1% vs 16.4%,
P=0.94, for patients treated with abciximab plus unfractionated heparin and the
patients treated with bivalirudin, respectively). The results regarding the sec-
dondary endpointsare shown in the figure.

Figure 1
Conclusions: In patients with NSTEMI undergoing PCI, the extent of preprocedural myocardial injury does not affect the relative merits of the abciximab plus unfractionated heparin versus bivalirudin observed in the overall cohort.

**P1896** Surgery after coronary stenting: the role of antiplatelet therapy on ischemic and hemorrhagic complications

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**Purpose:** Interruption or maintenance of oral antiplatelet therapy (OAT) during an invasive procedure may result in ischemic or hemorrhagic complications, respectively. Currently, there is limited guidance on management of OAT during surgical procedures. The aim of this study is to evaluate the rate of major adverse cardiac and cerebrovascular events (MACCE), as well as minor or blinding complications, and their associated independent correlates in coronary stented patients undergoing urgent or planned non-cardiac or cardiac surgery.

**Methods:** This study included 393 consecutive patients with coronary stents undergoing surgery from March 2003 to July 2011. The primary safety endpoint consisted of the incidence of in-hospital MACCE, defined as death, acute myocardial infarction, acute coronary syndrome (ACS) leading to hospitalization, stent thrombosis, acute heart failure, and stroke. Major bleeding was defined according to TIMI criteria.

**Results:** The rate of OAT use was 59%, with an average stent length of 22±21 mm (52% of PCI were performed during ACS), 37% of patients were on dual antiplatelet therapy at the time of surgery and time from PCI to surgery was 510±468 days. At the time of surgery, 57.7% of patients discontinued any antiplatelet therapy - 5 days (16.4% of patients discontinued both antiplatelet drugs; 7% discontinued only clopidogrel and 34.3% discontinued only aspirin). The mean time of washout was 5.2±2 days. At 30-day, the overall incidence of MACCE and TIMI major bleeding was 9.1% and 13%, respectively. The incidence of MACCE in patients who discontinued antiplatelet therapy >5 days was 12.1% versus 8.2% in patients who maintained the antiplatelet therapy (p=0.41). The incidence of TIMI major bleeding was 14.3% in patients who discontinued antiplatelet therapy >5 days versus 11.0% in those who maintained the antiplatelet therapy (p=0.47). Prior myocardial infarction was identified as an independent predictor of MACCE. There were no independent correlates of TIMI major bleeding.

**Conclusions:** Patients with coronary stents remain at high risk for surgery even if surgery is performed >1 year after PCI. The maintenance of the oral antiplatelet therapy might play a protective role, without increasing bleeding complications.

**P1899** Spaced administration of PA25450 and clopidogrel results in greater platelet inhibition than simultaneous administration of enterico-coated aspirin, enterico-coated omeprazole, and clopidogrel

**P1899** The efficacy of high dose clopidogrel for the patient with stable coronary artery disease in Japanese population: the primary result from the choice trial

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**Background:** PPI use and CYP2C19 LOF alleles are associated with reduced responsiveness to clopidogrel and increased cardiovascular events.

**Objectives:** To evaluate the interaction between PPI and PK and PD responses to clopidogrel loading doses (LDs) according to CYP2C19*2 allele.

**Methods:** Young post-MI patients heterozygous (*2/*2, n= 43) or homozygous (*2/*2, n=8) for the CYP2C19*2 LOF were matched with patients not carrying the variant (wt/wt, n=58). All patients were randomized to a 300- or 900-mg clopidogrel LD. 48 patients were receiving PPIs (26 on omeprazole (OPZ) or esomeprazole (EPZ), and 22 on pantoprazole (PTZ)). The relative reduction in residual platelet aggregation (RR-TPA, %) and the area under the plasma concentration-time curve of active metabolite from baseline to 6 h after loading (AUCO-6) were compared according to PPI use and CYP2C19*2 carriage.

Conclusions: Consistent with other randomized trials, high dose clopidogrel was effective in Japanese population, which have more activity-defective CYP2C19 polymorphisms than Western populations.
Results: After a 300mg clopidogrel LD, the maximal clopi-H4 concentrations and the AU0-6 were significantly lower in PPI users vs. non-users. This reduction was only observed in patients exposed to OPZ/EPZ (p<0.01 for both Camax and AU0-6 but not PTZ (p=0.26 and p=0.38 for Camax and AU0-6 respectively).

Similar trends were observed with the 900mg LD.

In multivariable linear regression, the use of OPZ/EPZ and CYP2C19*2 allele were significant predictors of clopi-H4 Camax and AU0-6 (AU0-6: p<0.005; AU0-6 900mg: p=0.01). A sigmoid function with a gamma exponent best described the relationship between IPA (%) and the Clopi-H4 AU (h/L).

There was no significant interaction between CYP2C19 and PPI status.

Conclusions: Both CYP2C19 and PPI status independently affects clopidogrel active metabolite generation and its antiplatelet effect which correlate as a sigmoid function with a cut-off value of 16 h/L.

P1900

Third generation P2Y12 antagonists inhibit platelet aggregation more effectively than clopidogrel in a real world myocardial infarction registry

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Introduction: The current standard of secondary prevention of atherosclerotic events includes acetylsalicylic acid (ASA) accompanied by the P2Y12 receptor antagonists with or without clopidogrel. In the real world myocardial infarction registry MITAP (registry for patients after Myocardial Infarction Treated with Antiplatelet agents - DRKS00003146) we analysed the antiplatelet effect of ticagrelor, prasugrel and clopidogrel in patients after myocardial infarction and coronary artery stenting.

Methods: Multiple electrode aggregometry was performed in whole blood of patients on day 3-5 after myocardial infarction. To specifically quantify the effect of P2Y12 antagonists, whole blood was stimulated with 6.4 μM ADP. To assess the overall capacity the platelet aggregation was quantified by stimulation with TRAP (final concentration 32 μM). Relative ADP induced aggregation (r-ADP-agg) was defined as the ADP/TRAP-ratio to reflect an individual degree of P2Y12 dependent platelet inhibition. Patients were grouped as follows: (1) 180 mg ticagrelor per day; (2) 10 mg prasugrel per day and (3) 75 mg clopidogrel per day.

Results: From July 2011 to February 2012 MITAP recruited 118 patients after myocardial infarction and percutaneous coronary intervention. Patients were grouped according to the antiplatelet medication: ticagrelor (n=49), prasugrel (n=23) and clopidogrel (n=36). The mean age was 67±13 years and 75% of the patients were male. The r-ADP-agg was significantly decreased in patients treated with ticagrelor or prasugrel compared with clopidogrel (ticagrelor 26±10%, prasugrel 28±8%, clopidogrel 36±14%; p=0.0002, 1-way ANOVA) while in STEMIs patients (n=64) prasugrel showed the lowest r-ADP-agg (ticagrelor (n=14) 31±12%, prasugrel (n=27) 27±8%, clopidogrel (n=23) 37±17% p=0.02, 1-way ANOVA).

Conclusion: We showed that the platelets of patients on day 3-5 after myocardial infarction treated with ticagrelor or prasugrel are inhibited more effectively compared with clopidogrel. This real world data supports the evidence from large clinical randomized controlled trials.
Prasugrel versus clopidogrel in daily clinical practice in patients undergoing primary PCI in the Austrian acute PCI registry

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Background: Prasugrel is recommended as first line drug for dual antiplatelet therapy after primary PCI (PPCI) in STEMI. There are few data on its use in daily practice of PPCI and clinical outcome in comparison with clopidogrel.

Methods: 2454 consecutive patients with STE-elevation myocardial infarction undergoing PCI between January 2010 and December 2011 and received either prasugrel or clopidogrel before arrival in the catheter laboratory were enrolled. Evaluation included baseline characteristics and in-hospital outcome. In addition, logistic regression analyses were performed to determine indicators for prasugrel treatment.

Results: 2017 (82.2%) patients received clopidogrel and 437 (17.8%) received prasugrel. Baseline and follow up data were available in 1985 (99.7%) patients. In subgroup with previous PCI were younger ages [53.0±7.4 yrs, p<0.01), more often male (71.1% vs 80.8%, p<0.01) and current smokers [58.4% vs 43.3%, p=0.01], but had less previous PCI (9.2% vs 12.5%, p=0.04). Left ventricular field transe was more common in the prasugrel group (73.7±6.3, p<0.01) and resulted in a shorter delay to PPCI (3.08h [1.93–5.71] vs 3.57h [2.23–6.6], p<0.01). In-hospital mortality was lower in the prasugrel group (1.8% vs. 4.7%, p<0.01) with no difference in TIMI major bleeding between prasugrel (0.2%), clopidogrel (0.9%, p=0.24). Multivariable logistic regression analyses revealed that age (HR 0.97 95% CI 0.96–0.98 p<0.01), male sex (HR 0.99 95% CI 0.95–1.04 p=0.02) and direct field transe (HR 1.59 95% CI 1.21–2.0; p<0.01) were independent predictors of prasugrel treatment.

Conclusion: In clinical practice prasugrel is predominantly used in younger male patients transferred directly from the field to PPCI. These factors may result in lower in-hospital mortality with similar TIMI major bleeding rates compared to clopidogrel.

Clopoidogel plus indobufen in patients with hypersensitivity to aspirin undergoing percutaneous coronary intervention

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Background: Aspirin (ASA) in combination with thienopyridine represents the standard treatment following revascularization by percutaneous coronary angioplasty (PCI) with the goal of reducing life-threatening stent thrombosis. However, the prescription of ASA could be harmful in a small, but significant number of patients known to be hypersensitive to ASA. Out of them, 30 male and 12 female patients (9.6%). The patients were randomly assigned to receive clopidogrel 75 mg daily, aspirin 100 mg twice a day (Group A), or clopidogel 75 mg daily, after 300 mg of loading dose (group B). Platelet activity and safety were monitored in both groups at 1, 3, 6, 12 and 18 months with laboratory and clinical evaluation. Platelet aggregation activity was tested by the Born’s method.

Methods: Between April 2005 and December 2008, among 1045 ACS patients treated with PCI and stent implantation, we identified 42 (4%) consecutive patients known to be hypersensitive to ASA. Out of them, 30 male and 12 female (mean age 61.6±10.9 years), 19 patients had a NSTEMI and 23 patients a STEMI. Definition of allergy to aspirin included: cutaneous sensitivity (urticaria in 25%, angioedema in 13%, rash in 25%), respiratory symptoms and/or rhinitis in 27.3%, anaphylactoid reaction in 5 patients (11.9%) and Quinke’s edema in 4 patients (9.6%). The patients were randomly assigned to receive clopidogrel 75 mg daily (loading dose 300 mg) and indobufen 100 mg twice a day (group A), or clopidogel 75 mg daily, after 300 mg of loading dose (group B). Platelet activity and safety were monitored in both groups at 1, 3, 6, 12 and 18 months with laboratory and clinical evaluation. Platelet aggregation activity was tested by the Born’s method.

Results: A lower value of Mean % platelet aggregation to arachidonic acid and collagen was found in group A compared to group B (19.5±10.9 vs 27.8±11.7, p<0.001) and 28.3±21.3 vs 37.6±17.71, p=0.001). There was no difference in Max % of platelet inhibition to ADP between the two groups (14.23±19.92 vs 10.31±18.97, p=0.23). Three patients (14.3%) in group B (2 with DES and 1 with a BMS) developed ACS within the first 6 months of follow-up. The coronary angiography documented a sub-occlusive stents thrombosis. No patient developed a cardiovascular event in group A. The combined treatment was well tolerated in group A patients.

Conclusion: This study suggests that the combined antiplatelet treatment with Clopidogel and indobufen could be an alternative medication in ACS patients with hypersensitivity to aspirin undergoing coronary stenting.

Fetal stem cells in combined treatment of chronic heart failure with left ventricular systolic dysfunction: results after 6 months

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Background: Chronic heart failure (CHF) is one of the topical health issues in all the developed countries calling for novel treatment methods. Conventional medication does not disregard cardiomyocyte reduction as one of CHF causes, and only transplantation of poorly differentiated cells with high proliferative and differentiation capacity can affect pathogenesis of this disease.

Goal of the study was study effect of fetal stem cell transplantation (FSCST) in CHF.

Materials and Methods: Study group included 7 patients (M-6, F-1, mean age 63±8.0, 2 with Class IV CHF caused by ischemic cardiomyopathy (72.7%), alcohol-induced cardiomyopathy (13.6%), diastolic cardiomyopathy (13.6%)). CHF was diagnosed on the basis of physical examination, laboratory (BNP) and instrumental findings (ECHO-G, EF, FDG). Mean N (%) of blasts, hCT, HTN, or diabetes. During the study, all the patients took diuretics, beta adrenergoblockers, ACE inhibitors and/or angiotensin II receptor blockers (ARB), cardiostimulants as well as other conventional medications.

All patients underwent transplantation of fetal hematopoietic mesenchymal and endothelial stem cells harvested from germ layers of internal organs of 5-6 weeks old cadaverous fetuses. 1, 3 and 6 months after the treatment, patients underwent physical examination, Echocardiogram and BNP test.

Results and Discussion: FSCST resulted in:

- NYHA Class downgrading
- Higher DASI score
- Improved tolerance (6-minute test)
- Reliable serum BNP reduction by 33.75% 1 month after FSCST, 57.17% after 3 months
- No reliable LVEF increase after 1 month, 10.5% increase after 3 months, 20.92% after 6 months
- Reliable LVED reduction 1 months after FSCST – 7.85%, 3 months – 11.49%, 6 months – 20.51%

Myocardium function restoration can be achieved through the increase of functional reserve of cardiomyocytes and, probably, their number increase through stimulation of hyperplasia, neoangiogenesis, and apoptosis inhibition.

Conclusions: FSC transplantation is safe and effective way of treatment that can be used as supportive treatment in patients waiting for heart transplantation, as preparation for reconstructive heart surgery and as substitution of post-infarction fibrous tissues with viable cardiomyocyte-like cells.

Left ventricular dysfunction is induced shortly after the deprivation of dietary choline in adult rats

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Purpose: Choline is an essential nutrient that is involved in a variety of vital biochemical functions. Choline deficiency seems to impair heart function and animals consuming inadequate amounts of choline develop significant cardiovascular morbidity. Taking into consideration that choline deficiency is frequently observed in the clinical setting such as in patients depending on parenteral nutrition and in patients with cirrhosis or renal failure, the investigation of its effect on heart mechanical properties would be of clinical importance. The present study evaluated the effects of choline deficiency on the functional parameters of the heart in adult rats.

Methods: Wistar Albino male rats, about 3 months old, were randomly separated into two groups: a) rats receiving standard laboratory diet (control-Ca) b) rats receiving choline deficient diet (control-Cb). Water and food were provided ad libitum and the duration of the dietary manipulation was four weeks. All animal procedures were carried out in accordance with the principles of the “Guide to the Care and Use of Experimental Animals”. After four weeks of treatment, cardiac function was assessed under isometric conditions in the Langendorff preparations. Left Ventricular Developed Pressure (LVPD), Positive and Negative first derivative of LVPD (dVdp/dt) and (dVdp/dt) were evaluated. Histopathological evaluation of the hearts specimens was performed using Eosin-Hematoxylin and Masson stains.

Results: Diastolic left ventricular function, assessed by (−)dVdp/dt, was significantly impaired in the CDD group compared to the control group (1911.42 (229.45) vs 2112.9 (268.58), p<0.002 vs CA). A trend towards compromised left ventricular function as assessed by LVPD (dVdp/dt) and (dVdp/dt)was evaluated. Histopathological evaluation of the hearts specimens was performed using Eosin-Hematoxylin and Masson stains.

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vealed a lymphocytic infiltration of the myocardium and cardiac valves along with interstitial oedema and fibrosis in the CDD group that were in accordance to the functional impairment.

Conclusion: Doxycycline-induced adult rats develop prominent early diastolic dysfunction probably caused by reduced compliance of the myocardium, along with left ventricular contractile dysfunction. These observations merit additional investigation to delineate the role of choline in the maintenance of the cardiovascular system in adulthood, since choline deficiency could be present in the daily clinical setting even when patients are considered initially free of heart problems.

Infarct size (IS) is a well-established determinant of adverse LV remodeling. Experimental evidence indicates that attenuation of LV remodeling is critically dependent on salvage of apoptosis-prone myocytes in the peri-infarct zone.

Objectives: To investigate relationships between myocardial uptake of transcoronary-delivered autologous bone marrow CD34+ cells in recent MI, IS and LVEF in the context of chronic LV remodeling.

Methods and Results: Thirty-one subjects (age 36-69 years) with pPCI-treated anterior STEMI, peak TRI 138 [58-356ng/dL] (median [range]) and sustained LVEF <45% were recruited. On day 10 (7-12), 4.3x10⁶ [0.7-9.9x10⁶] ⁹⁹mTc-exametazime-labeled CD34+ cells were administered transcoronary (LAD). Gadolinium late-enhanced total infarct mass (IS, cMRI) was 57 [11-112]g. One day after administration, 1.7-9.9% labeled cell activity localized in myocardium (whole-body γ-scan). Image fusion of labeled cells SPECT with LV perfusion SPECT or cMRI infarct images indicated peri-infarct zone cell uptake. Labeled cells early enrichment correlated with peak TRI (r=0.70, p<0.0001), Infarct Border Zone mass (IBZ, cMRI, r=0.82, p=0.0001), total IS (r=0.62, p=0.0006) and severely impaired perfusion segments number (SPECT, Q coefficient=0.83, p<0.01). IBZ mass correlated with ∆LVEF at 4years (r=-0.4, p=0.001). ∆LVEF was +3.48% (p=0.08 vs. baseline LVEF). With the peri-infarct zone cell uptake proportional to IS, IS was not a determinant of ∆LVEFV (p=0.41) or ∆LVEDV by cMRI (p=0.09) (Figure 1, "p=0.005)."

Conclusion: This largest human study with labeled CD34+ cell transplantation after recent STEMI suggests that the higher cell uptake in the peri-infarct zone in subjects with larger infarcts might be associated with inhibition of LV remodeling. Further strategies should focus on boosting this effect.

Infarct size-determined uptake of CD34+ cells in the peri-infarct zone and left ventricular remodeling: Insights from integration of labeled cells SPECT visualization with sequential cardiac MRI

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Proteolysis of calcineurin is prevented by conditional myocardial calpain-inhibition

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Objectives: To analyse the prognostic value of cytotoxic T-lymphocytes (CTLs: Perforin) in a large cohort of patients with inflammatory cardiomyopathy (CMI).

Method: Intramyocardial inflammation is known to have an adverse prognostic impact in CMI. However, the precise role of contributing pathogenic factors for prediction the long-term course remains elusive, yet.

Methods and Results: We studied n=495 consecutive patients with virus-negative CMI, undergoing endomyocardial biopsies (EMBs). We examined hemodynamic measurements after a mean follow-up period of 30±35 months. In EMBs myocardial inflammation was assessed by histology and immunohistology. At follow-up n=388 patients showed a stable normal or significant improvement of left ventricular ejection fraction (LVEF) from 46±14% to 58±12% (P<0.0001). No recovery of LVEF was observed in n=61 patients (development from 30.4±10.5% to 27.4±11.8%, and significant deterioration from mild to severe LV dysfunction was observed in n=46 patients (from 53.1±18.28% to 38.3±17.18%.
Targeted ablation of the plasma membrane calcium ATPase (PMCA) 1 indicates a critical role in heart failure

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Currently, up to 14 million people in Europe have heart failure (HF). Since the yearly incidence of heart failure in persons age >55 years is 15 per 1,000 of the population, it is important to provide new insights into disease development and progression. Recent several genome-wide association studies have identified single nucleotide polymorphisms (SNPs) in the PMCA1 gene as the single strongest association with blood pressure variance in humans. In spite of that, the role of PMCA1, a transmembrane calcium transporter known to eject calcium from the cells, in HF failure remains enigmatic.

Our recent experiments have shown that the protein expression of PMCA1 is significantly downregulated in human heart failure patients. Therefore, to further investigate the role of PMCA1 in cardiac disease we have generated mice carrying a cardiomyocyte-specific gene deletion of PMCA1 (PMCA1cko) using αMHC-Cre. PMCA1cko mice subjected to pressure overload induced by transverse aortic constriction (TAC) showed overt HF; TAC decreased fractional shortening (FS) in PMCA1cko in comparison to their age-matched controls (FS; PMCA1f/f/TAC: 21.6±3.1% vs. 26.6±3.2%, p<0.05, n=5). Cardiac relaxation was also impaired (Logistic tag: PMCA1f/f/TAC: 8.8±0.8; PMCA1f/f/TAC: 6.6±0.3; p<0.05, n=6). This was associated with severe lung congestion shown by elevated lung weight/body weight in PMCA1cko TAC (11.5±1 vs. 7.8±0.8 mg/gm in PMCA1f/f/TAC, p<0.05, n=6). Cardiomyocyte cross-sectional area and interstitial fibrosis were also increased in PMCA1cko. Our results show that PMCA1 has an additional role in maintaining cardiac rhythm. At 3 months of age PMCA1cko presented episodes of spontaneous ventricular tachycardia and exhibited downregulation of the expression of the voltage gated sodium channel Nav1.5. A significant reduction in the corresponding sodium current was also observed.

In conclusions, these observations point to an important role for PMCA1 in HF following an excessive work load and arrhythmia suggesting that PMCA1 might be a novel target of therapeutic potential in the treatment of heart failure.

Differential repolarization dynamics in transient apical and midventricular ballooning

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The aim of the present study was to assess potential differences in cardiac repolarization dynamics in patients with transient left ventricular apical ballooning syndrome (AB) and the midventricular variant (MB). Even though repolarization abnormalities and QT interval prolongation in the surface electrocardiogram (ECG) have been consistently reported, repolarization dynamics have not yet been investigated in the AB and MB variants. We hypothesized that differences in regional sympathetic denervation may induce differential effects on cardiac repolarization.

Methods: In a prospective single-center study, 49 consecutive patients with transient left ventricular dysfunction syndrome underwent 3-channel-Holter-ECG recording on the third day after admission. A total of 27 recordings of patients with AB and 10 recordings of patients with MB were valid for beat-to-beat-QT-interval analyses.

Results: There were no significant differences in baseline clinical characteristics between AB and MB patients. Patients with MB showed significantly lower values for mean RR interval (835±104 vs. 908±118 ms; P<0.05). Both, Bazett- and Fridericia-Adjusted QT-Intervals were significantly longer in MB patients (QTcB 441.9±38 vs. 483.4±40 ms; P<0.05; QTcF 435.0±36 vs. 469.4±36.5 ms; P<0.05). Parameters of QT-interval variability (GTSĐ) and QT-interval dynamicity (QT/RR-slope) also exhibited significant differences between groups (diagram).

The international takotsubo registry: a male gender effect

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TheBackground: Takotsubo cardiomyopathy (TTC) is often thought as a women disease, men can also be affected from this unique syndrome. A number ofstudies exist assessing the general clinical profile, however systematic data is lacking on gender specific clinical characteristics in male patients suffering from TTC. We have established an international multicenter registry with a large patient cohort to investigate this unique disease.

Objective: The aim of the present study was to investigate the clinical profile of male patients with TTC.

Methods: Between 2004–2010 out of 499 patients with TTC 58 (11.62%) male patients entered the TTC Registry. Diagnosed according to the Modified Diagnostic Criteria. The complete medical records were reviewed in detail and documented.

Results: The mean age of the study population was 61±15 years. A classical apical ballooning patternoccurred in 47 (81.0%) patients, a midventricular type was present in 5 (8.6%) and a basal type in 4 (6.9%) patients. A focal TTC type could be a novel target of therapeutic potential in the treatment of heart failure.
reduce the risk of sudden cardiac death (SCD). LVNC is associated with a wide spectrum of presentation and outcomes. The aim of the study is to describe the outcome of pts with LVNC.

**Method:** From November 1997 to November 2011, 91 pts with LVNC were recruited. 13 pts were excluded from the analysis because 6 pts underwent Status 1 heart transplant (HT), 1 pt died in Status 1 waiting list, 1 pt was lost to follow-up, and 5 pts caused the ICD and 1 pt had associated CAD. The selected criteria for ICD were Secondary Prevention (SP): SCD/VT or Primary Prevention (PP): LVEF ≤ 35% or ≥ 2 risk factors (family history of SCD [FH-SCD], syncope or NSVT).

**Results:** 78 pts with LVNC were analyzed: mean age 42±15 years (54 men), mean follow-up was 27±31 months. According to the selected risk-stratification criteria 40 pts (52%) received an ICD. ICD Group (40 pts): 70% men, 50% had NYHA class III-II, mean LVFVE was 32±12%. SP (5 pts): During the follow-up none of the pts died, 3 pts (60%) received appropriate shocks (AS) due to VT/VF (all of them with previous SCD) and 2 pts (40%) had inappropriate shocks (IS). PP (35 pts): 26% pts (74%) had LV EF ≤ 35% and 13 pts (37%); had ≥ 2 risk factor. During the follow-up none of the pts died, 1 pts underwent HT, 4 pts (11%) received appropriate AT/PS and 7 pts (20%) had IS. Non ICD group (37pts): Mean age was 41±16 years (36 men), 2% had NYHA class III-II, mean LVFVE was 48±17%. There were no deaths during the follow-up.

**Conclusion:** After an intermediate follow-up, prognosis of LVNC patients seems to be more favorable than previously reported. Patients with ICD for SP had no death but a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower. In the non-ICD group there was a high rate of AS; in PP the incidence was much lower.

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**At early phase of endotoxemic shock, cardiac dysfunction is independent of load conditions and the increased beta-adrenergic contractility is dependent of endothelium**

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**Purpose:** The cardiovascular alterations during the septic shock include an hypotension associated with a cardiomyopathy. The sympathetic regulation of the cardiovascular system is impaired during the shock and associated with an increase in circulating catecholamines. However, the altered load conditions lead to a difficult characterization of the cardiomyopathy and the cellular mechanisms involved in its pathogenesis. Thus, the aim of this project was to determine the cardiac dysfunction independently of load conditions as well as cardiac beta-adrenergic (β-AR) alterations in endotoxemic rats.

**Methods:** 12-week-old Sprague Dawley rats were killed. LPS was injected intravenously at a dose of 5 mg.kg-1. 3h later, cardiac parameters were evaluated in vivo by echocardiography, and ex vivo using isolated working heart perfused by the Papillary Muscle LPS rats were compared with LPS or saline treated rats.

**Results:** LPS rats presented altered systolic (shortening fraction -21±4% vs C -0.05) and diastolic (early diastolic peak flow velocity (E) -47±4% vs C -0.05) functions. At similar loads, LPS isolated hearts presented a huge decrease in diastolic filling period during the early phase of perfusion (∼74.8% vs C -p<0.05), and a decrease in developed pressure (∼26.4% vs C -p<0.05) associated with altered dP/dmax and dP/dtβ. These results are correlated with a decreased cardiac output (∼29.6% vs C -p<0.05). In papillary muscle, isoproterenol-induced contractility was increased in LPS (∼105% vs C -p<0.05). Conversely, β1-AR expression was decreased (∼66.5% vs C -p<0.05), β1-AR-induced contractility was increased by 94±16% (∼0.05 vs C). This increase was abolished when endothelium was disrupted.

**Conclusions:** Our study demonstrates that systolic and diastolic alterations are independent of load conditions at early phase of shock. We also demonstrate, for the first time, an increased β1-AR response, which is dependent of the functional endothelium suggesting that this increase could be involved in the persistent tachycardia observed in septic shock even after resuscitation. This data indicates that selective β1-AR blockers should be used in this disease.

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**Low incidence and mortality of peripartum cardiomyopathy in a European country: a study of the whole population of Scotland**

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**Purpose:** Prior studies of the incidence of peripartum cardiomyopathy (PPCM) report rates of 1 in 8661 live births in the USA to between 1 in 1000 to 1 in 100 live births in Africa. There are no published data from Europe. We describe the incidence and short term mortality of PPCM in a whole European country.

**Methods:** The whole Scottish population (5.2 million) receives free care from the National Health Service (NHS) and each person has a unique NHS electronic record. We screened all hospitalizations for a diagnosis of PPCM or any other form of heart failure (HF) and linked these to birth/maternity records and death registrations over the same period. An incident hospitalization for PPCM was defined by the ICD10 code 090.3 in a primary or secondary position between the year 2000 and 2009 (with no prior discharge with a diagnosis of PPCM or HF in the prior 5 years). Further potential PPCM cases were defined by a diagnosis of HF found in the 1 month prior to birth and up to 5 months after. An expanded definition was also explored, looking for diagnoses of heart failure from 3 months prior to birth and up to 12 months after. The number of live births over this period was obtained from the General Registrar Office of Scotland.

**Results:** During the study period there were 550,206 live births. There were 50 diagnoses of PPCM, a rate of 1 per 11004 live births. The median age at discharge was 34.9 years (interquartile range [IQR] 29-39). There were further 30 cases of HF within 1 month prior to and up to 5 months after birth (i.e. a total of 80 potential PPCM cases and a rate of 1 in 6687 live births) suggesting a number of potential cases are not labelled as having PPCM. Median age at discharge was 32(IQR 29-37) for both extended definitions. The proportion of those with a definite diagnosis of PPCM dead at 30 days was 2.5%, there were no further deaths by 6 months and 1 year. When the additional cases of HF in the period before and after birth (using both definitions) were included, the proportion dead at 30 days was 1.3% with no further deaths by 6 months and 1 year.

**Conclusions:** The incidence mortality of PPCM in a predominantly white European population is low. The rate is in keeping with studies of the white population in the USA. Mortality is similarly low and in keeping with prior studies from the USA. There is potential under diagnosis of the condition. Further collaborative efforts are needed to understand the epidemiology of this rare disease.
Diagnosis of cardiac AL amyloidosis: the grey area of wall thickness


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Background: The amyloidoses constitute a large group of diseases in which aggregates of insoluble toxic protein are deposited in forms of fibrils in several tissues. AL amyloidosis, in which fibrils are composed mainly by the N-terminus of a monoclonal immunoglobulin light chain, has an incidence of approximately 1 case per 100,000 person-years in western countries. Cardiac involvement is not only frequent, but it is also the most common cause of death. The diagnosis of cardiac amyloidosis is relatively simple in AL patients with increased wall thickness (WT) and normal NT-proBNP levels, but it is much more challenging in patients with normal wall thickness and raised NT-proBNP. Objective: To evaluate cardiac function in patients with normal WT and increased NT-proBNP.

Methods: We enrolled 292 consecutive never-treated subjects, in whom a first diagnosis of primary cardiac heart failure leading to heart transplantation or cardiac echo color-Doppler data were evaluated at diagnosis. According to cardiac WT and NT-proBNP values, the cohort was divided into three groups: Group 0: WT <12 mm and NT-proBNP <332 pg/ml; Group 1: WT =12 mm, NT-proBNP >332 pg/ml and normal renal function; Group 2: WT >12 mm and NT-proBNP >332 pg/ml. Results: When compared with Group 0, despite comparable WT, chamber volumes and global function, Group 1 patients showed higher prevalence of regional systolic dysfunction and altered diastolic parameters, with lower mitral annulus longitudinal excursion (lateral: 13.4±4.0 vs 15.18±2.67 mm; septal: 10.80±3.08 vs 13.21±2.52 mm), and higher E/E’ ratio (6.81±4.29 vs 6.04±2.83) [p<0.05 for all]. Intermediate values of endocardial shortening fraction, transmural E/A, and pulmonary vein S/D ratios were observed in Group 1, which did not differ from the other Groups, although these trends fell short of statistical significance. Notably, 1-year survival was 94% in Group 0, 78% in Group 1, and 60% in Group 2 patients (p<0.0009).

Conclusions: Beyond confirming NT-proBNP diagnostic value, this study underscores the limitations of the currently used echocardiographic diagnostic criteria (i.e. wall thickness >12 mm). Systolic diastolic dysfunction is already evident in the “grey” area of patients with amyloidosis and subclinical cardiac involvement.

Impact of dendritic cell-derived interleukin-10 in the post-infarction infarct remodeling and left ventricular remodeling

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Purpose: Inflammation and immune responses play a crucial role in infarct healing and request left ventricular (LV) remodeling. Recently, we have shown that the immunoprotective role of bone marrow (BM)-derived dendritic cell (DC) after myocardial infarction (MI) via controlling monocyte/macrophage homeostasis. The goal of this study was to clarify the inhibitory molecule derived from DCs in tissue repair and LV remodeling after MI.

Methods and Results: BM chimeric mice were introduced by reconstitution of BM cells from C571c-diphtheria toxin receptor/GFP transgenic donor mice into lethally irradiated wild-type (WT) recipient mice. CD11c+ GFP+ DCs were enriched into the heart, peaking on day 7 after MI. Selective DC depletion was induced by diphtheria toxin administration in these mice, and ablation of DCs resulted in attenuated inflammatory response and LV function after left coronary ligation mainly through enhanced inflammatory monocyte/macrophage infiltration and sustained matrix metalloproteinase (MMP)-9 activation. Seven days after MI, BM-derived DCs (BMDCs), BM cells from WT and IL-10 knockout (KO) mice were cultured with recombinant mouse granulocyte-macrophage colony-stimulating factor for 6 days and CD11c+ BMDCs were then positively collected by magnetic sorting. We confirmed that intravenously injected CFSE-labeled BMDCs reached infarcted zone based on an immunofluorescent staining. Adoptive transfer of BMDCs from WT mice into DCM-depleted LV function and negated the increases of inflammatory Ly6Chigh monocytes and myocardial MMP-9 activity following MI, interestingly, five were nonsense-type mutations. There were twenty-four carriers altogether, who were mostly characterized by DCM and heart failure with conduction system disease and/or ventricular arrhythmia necessitating ICD implantation and heart transplantation, although four were asymptomatic. In three families subclinical HCM was identified, and in four LMNA mutation carriers. Among the LMNA mutation carriers, six received HTx, fourteen ICD and five were treated with pacemaker. In addition, we present the results of a prospective study on TM510TyrfsX42 mutation, as well two expression studies (Sen431Stop and Tyr481Stop) by transient cell transfections. Conclusions: In the two referral centre populations, the screening revealed five (7.6%) mutations among 68 patients HTx recipients or patients referred for HTx and four (9.1%) mutations within 44 consecutive DCM patients referred for familial evaluation. DCM patients with LMNA mutations have poor prognosis, however clearly clinical variability is present among family members.

Fulminant myocarditis associated with Influenza A H1N1 pdm2009 in Japan

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Background: An influenza pandemic occurred in 2009. We performed a national survey of H1N1 pdm2009 myocarditis patients in the 2009/2010 season in Japan, and reported the clinical feature of 15 H1N1 pdm2009 myocarditis patients. Methods: We performed a retrospective national questionnaire survey about H1N1 pdm2009 myocarditis patients in the 2009/2010 and 2010/2011 seasons in Japan and collected data from 360 hospitals. The diagnosis of myocarditis was performed using the guidelines for Diagnosis and Treatment of Myocarditis (JCS2009). Results: Twenty-nine patients with influenza A H1N1 pdm2009 myocarditis were reported, with 25 from the 2009/2010 season, and only 4 patients from the 2010/2011 season. Seventeen patients (12 men, 5 women mean age, 34±20 years) were diagnosed with fulminant H1N1 pdm2009 myocarditis with fatal arrhythmias, and/or varying degrees of cardiogenic shock. Fifteen fulminant myocarditis patients were seen in the 2009/2010 season, and only two in the 2010/2011 season. Myocarditis was proven by endomyocardial biopsy and or autopsy in 9 patients. On the other hand, adoptive transfer of BMDCs from IL-10 KO mice did not improve LV function after MI. Furthermore, inflammatory Ly6Chigh monocyte infiltration and myocardial MMP-9 activity post-MI were comparable between DC-depleted mice with and without IL-10 KO BMDCs transfer.

Conclusions: DC suppresses inflammatory Ly6Chigh monocyte-mediated inflammation and subsequent extracellular matrix degradation in the healing process following MI, at least in part, through IL-10 secretion. DC-derived IL-10 plays an important role in the post-infarction healing process, and this could be a novel therapeutic target in heart failure after MI.
nant myocarditis patients treated without IABP/PCPS died. Sixteen (96%) fulmi-
nant myocarditis patients were treated with anti-neuromuscular inhibitors.

Discussion: H1N1pdm2009 fulminant myocarditis seemed to be more com-
mon in the 2009/2010 season, compared with seasonal influenza seasons. Ap-
propriate treatment with neuromuscular inhibitors and mechanical circulatory support (IABP and/or PCPS) was required to rescue patients with fulminant H1N1pdm2009 myocarditis.


P1923 Cardioprotective effects of seapolynol (polyphenol purified from Ecklonia cava) against adriamycin-induced cardiomyopathy in an animal rat model

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Background: The purpose of this study was to elucidate the cardioprotective ef-
fects of seapolynol (polyphenol purified from Ecklonia cava) against adriamycin-
induced cardiomyopathy in an animal rat model. Seapolynol, as approved as a new di-
aphy (NDI) from US Food and Drug Administration (FDA) in 2008 (FDA-1995 - S-0039-0176), is known to protect cells by its potent and wide spec-
trum of antioxidant functions.

Methods: Of total forty-two rats, we divided 21 rats into Group 1 (low-dose seapolynol plus adriamycin, n=7), Group 2 (high-dose seapolynol plus adri-
mycin, n=7), and Group 3 (single adriamycin, no seapolynol, n=7) for efficacy of seapolynol. We administrated seapolynol (326 mg/kg, daily, oral) one week before adriamycin (2.5mg/kg, weekly, intraperitoneal) was injected for 6 weeks. For safety of seapolynol, the other 21 rats were divided into Group 4 (low-dose seapolynol only, n=7), Group 5 (high-dose seapolynol only, n=7), and Group 6 (neither seapolynol nor adriamycin, n=7). We performed transhochastic echocar-
diography (15MHz linear array,GE VIVID 7) before (baseline) and after (4-
week) injection of adriamycin and analyzed cardiac function.

Results: Adriamycin-induced cardiomyopathy was identified by Group 3 and 
there was no adverse interaction in Group 4, 5 and 6. In Group 1, relative wall
thickness (RWT: 0.6±0.0mm baseline vs. 0.4±0.1mm 6-week, p<0.001), frac-
tional shortening (FS: 63.6±3.1% baseline vs. 59.2±6.5% 6-week, p<0.007), and 
left ventricular ejection fraction (LVEF: 88.7±1.8% baseline vs. 76.8±5.8% 6-
week, p=0.005) significantly decreased and the left ventricular end diast-
olic/systolic dimension(LVEDD: 5.8±0.2mm baseline vs. 7.1±0.7mm 6-week, p=0.002/ LVEDV: 2.1±0.2mm baseline vs. 3.4±0.6mm 6-week, p=0.003, respec-
tively) significantly increased. However, there were no interval changes in Group 2, LVEDV and the change of LVEF(Δ) upon 6-week adriamycin injection were significantly higher in Group 1 compared with Group 2 (LVEDV: 7.7±1.0mm vs. 6.3±0.4mm, p=0.016, ΔLVEF: -11.1±6.9% vs. -2.0±8.5%, p=0.048, respec-
tively). 

Conclusion: Our rat-model study results showed that Seapolynol was safe and 
cardioprotective against adriamycin-induced cardiomyopathy in a dose-
dependent manner.

P1924 The role of cardiac biomarkers, conventional echocardiography and tissue Doppler imaging in early detection of future doxorubicin-induced cardiotoxicity

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Doxorubicin is an effective drug widely used in cancer treatment, but its appli-
cation is limited by the cumulative dose-dependent cardiotoxicity. Assessment of left ventricular ejection fraction (LVEF) and fractional shortening (FS) are recom-
manded to diagnose cardiac dysfunction; however, their normal values can mask subclinical LV impairment. We assessed whether early conventional echocar-
diography imaging and cardiac biomarkers determined before therapy help to 
predict later doxorubicin-induced cardiotoxicity. Cardiotoxicity was defined as a reduction of the LVEF of <5% to ±55% with symptoms of heart failure or an 
asymptomatic reduction of the LVEF of >10% to ±55%.

Methods: We analysed 70 consecutive patients (53±12 years) in sinus rhythm, 
without known cardiac disease and LVEF>50%, referred for echocardiography be-
fore therapy with doxorubicin. Echocardiographic parameters (LVEF and 
NT-proBNP) were obtained before and after 6 and 36 weeks after start of chemotherapy. Peak systo-
tic (S), peak early (E) and peak late (A) diastolic velocities were obtained at the 
mitral annulus and lateral segment of the mitral annulus and the average of the values was 
used. The E/E' ratio was obtained (E = early transmural flow velocity). The differ-
ence between the baseline value of analysed variables and the value determined 
after 6 weeks of chemotherapy was calculated (Δ).

Results: Nine patients (12.8%) met the criteria for cardiotoxicity. Averaged cumu-
lative doxorubicin dose was 177±59 mg/m². Univariate logistic regression identi-
fied ΔLVEF, ΔFS, Δ isoosclasmatic relaxation time, ΔS', ΔE', ΔD/A, ΔTNT as pre-
dictors of patients who developed cardiotoxicity (all p < 0.05). Age, sex, cardiac risk 
 factors, Δ blood pressure, Δ heart rate, ΔLV end-diastolic volume, ΔLV end-
 systolic volume, Δ left atrial volume, Δ pulmonary artery systolic pressure, Δ 
myocardial performance index, ΔE/A (late trasmitral flow velocities), ΔE/E' and ΔNTproBNP were not associated with future cardiotoxicity. On multiple 
logistic regression analysis, including all the univariate predictors, ΔTNT emerged as 
the only independent predictor of later cardiotoxicity (Odds ratio = 1.22, p = 
0.009).

Conclusion: The change of TnT level after 6 weeks of treatment with doxorubi-
acin was able to predict future doxorubicin-induced cardiotoxicity, unlike Tissue 
Doppler imaging and conventional echocardiographic parameters.

P1925 Primary AL-amyloidosis in the structure of a cohort of patients with chronic heart failure of the Russian population

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Purpose: To establish the share of AL-amyloidosis in the structure of chronic heart failure and to examine clinical features with systemic AL-amyloidosis, mainly 
affecting the heart.

Material and methods: The study included 182 patients with severe congestive 
heart failure with preserved ejection fraction association developed of hyper-
trrophic, restrictive or dilated phenotype. The patients’ ages ranged from 37 to 84 
years. Instrumental study of cardiovascular system included echocardiography 
(M-modal, two-dimensional and Doppler modes). Assessment of diastolic func-
tion during echocardiography was performed with a pulsed (PW) and tissue (TDI) 
Doppler. The diagnosis of AL-amyloidosis was suspected clinically and confirmed 
by immunomorphological examination of biopsy specimens, bone marrow 
and buccal mucosa (using histological stains hematoxylin and eosin, Congo red, 
Van Gieson by pikrofuksinom and polarizing microscopy - immunohistochemical reac-
tion with A. Amyloid cathodic monoclonal antibodies and A. Amyloid cardiol-
himoclonal antibodies. 

Results: Systemic AL-amyloidosis, mainly affecting the cardiovascular system 
was diagnosed in 20 patients (11%). Plasma cell dyscrasia was proved by in-
balance κ and λ (1:7). The most severe course was found in 5 patients aged 
37 and 40 years. Life expectancy after the onset of symptoms to death was 5.5 and 
8 months respectively. The relatively benign course was observed in 2 patients 
aged 70 to 84 years. Life expectancy after the onset of symptoms to death was 
36 months or more. In cases sAL-amyloidosis with predominant renal survival was 
56 months or more. Remodeling of the heart consistent with RCM, HCM and 
DCM (3, 3 and 3, respectively). Overdiagnosis of coronary heart disease and hy-
pertension was found in 11 patients (%). In 16 cases, leading to the clinic was 
progressive congestive right ventricular heart failure with preserved ejection frac-\tion. Recurrent venous and arterial thrombosis were the leading symptom in one 
patient. We were leading in three patients with weight loss, intoxication, fever. 
4 within years of follow - death was diagnosed in 17 patients (6 cases there was a sudden 
death (35%) and 11 patients (65%) of death from cardiac causes. 

Conclusion: AL-amyloidosis with lesions of the cardiovascular system is about 
11% of the cohort of patients with CHF of Russian population. Cardiac involve-
ment in AL amyloidosis can occur under the guise of various cardiovascular 
lesions: restrictive, dilated, hypertrophic cardiomyopathy, and ischemic heart 
disease. A high incidence of sudden death in patients with AL-amyloidosis
Serum levels of placental growth factor is associated with biventricular dysfunction following administration of anthracycline-based chemotherapy in breast cancer: a prospective multicenter study using advanced cardiac imaging and biochemical markers

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Background: Previous studies have shown that subtle left ventricular [LV] dysfunction can be detected early following anthracycline chemotherapy but none have prospectively correlated this with myocardial oedema or necrosis. Furthermore, although right ventricle [RV] systolic dysfunction is an adverse prognostic marker in cardiomyopathy states, the RV effects of chemotherapy are not well defined.

Methods: 36 breast cancer patients [pts] undergoing anthracycline-based therapy underwent serial CMR imaging (for LV/RV volumes, myocardial oedema and necrosis), advanced echocardiography (for LV global longitudinal strain [GLS], diastolic function and tricuspid annular plane systolic excursion [TAPSE]), pro brain natriuretic peptide [pro-BNP], high-sensitivity [hs] troponin T [hs-TnT] and hs creatinine measurements. Tests were conducted at baseline, 1 month [mth], and 3 mths.

Results: In the study pts, significant changes in CMR volumes and systolic function were observed in both the ventricles (see table). 23% of pts had reduction of CMR RV EF below the lower limit of normal range at 3 mths. GLS and TAPSE decreased from -21.2±3% at baseline to -19.0±2%; p<0.001 and 23.5±3.5 to 21.1±3.7; p<0.001 at 3 mths respectively. Diastolic function did not change with time. No variation was observed in pro-BNP, however hs-TnT and hs-CRP increased from 3.8±1.7 to 9.7±9.8; p<0.001 and 2.8±3.1 to 6.7±5.9; p<0.001 at 3 mths respectively. 52% of pts had an abnormal T2 signal (SI increase to >5%), although no correlation was observed. One patient developed new sub-epicardial interstitial hyperechogenicity at 3 mths.

Conclusions: Both CMR and advanced echo techniques detect RV and LV functional changes within 3 mths of anthracycline chemotherapy. These changes are likely mediated by myocardial inflammation. These findings may be a basis for development of early predictors of cardiac damage facilitating earlier intervention/preventive strategies.

Novel data on cardiomyopathies 329

Gender-related prognosis of syncope associated with underlying heart disease


Purpose of study: To evaluate the influence of gender on the results of electro-physiological study (EPS) performed for syncope associated with heart diseases and its impact on prognosis. The management and the prognosis of some HD’s may depend on the gender of the patient. EPS is recommended in patients with syncope, HD, left ventricular ejection fraction (LVEF) >30% whilst the implantation of a defibrillator (ICD) is recommended when LVEF is <30% without evaluation of the cause of syncope.

Methods: 523 patients, 89 women, 434 men were admitted for syncope. They had an HD, either ischemic HD (n=400) or a left ventricular impairment of other origin (n=123). Echocardiography, Holter monitoring and head-up tilt test were systematic. EPS was complete including the evaluation of AV conduction and sino-atrial conduction, programmed atrial and ventricular stimulation (PVS). Patients were followed from 1 to 10 years.

Results: Women had the same age (67±14.5 years) and the same LVEF (41±15%) as the men (64.5±11 years, 40±13.5%). Ischemic HD was less frequent in women (68.5%) than in men (78%) p<0.001. Moromorphic sustained ventricular tachycardia (VT) >270 bpm was induced less frequently in women than in men (10 vs 25.5%) (p<0.001). The frequency of non specific VT (ventricular flutter or fibrillation) was similar in women and men (16 vs 18%). The frequency...
of negative programmed ventricular stimulation was higher in women than in men (72 vs 56%) (p=0.005). Syncope was related to hyperventilation more frequently in women than in men (15 vs 7%) (p=0.01). Other causes of syncope were similar in men and women as supraventricular tachycardia (13 vs 14.5%) (NS), AV conduction disturbances (9 vs 8%) (NS), coronary ischaemia (9 vs 8%) (NS). Noninvasive and invasive studies remained more frequently negative in women (31%) than in men (17%) (p=0.007). Implantable defibrillator (ICD) was implanted less frequently in women than in men (7 vs 15%) (p=0.03). After a mean follow-up of 5.4 years, the frequency of sudden death (7 vs 57%) heart failure-related death (15 vs 13%), atrial fibrillation or atrial flutter (2 vs 3%) or death due to cardiac disease (11 vs 6%) was similar in women and men.

Conclusion: Women with heart disease and syncope had less inducible monomorophic VT than men, had more hyperventilation and unexplained syncope than men. However, despite a similar LVEF and rarer inducible life-threatening arrhythmias, their prognosis was similar probably due to a lower frequency of ICD implantation.

P1931

Non invasive evaluation of left ventricular filling pressure in patients with advanced heart failure using ASEE/AEE recommendations

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Purpose: Despite recent ASE/AEE recommendations, there is still debate on the role of the mitral E/e ratio to evaluate the level of left ventricular filling pressures (LVFP) and to adapt therapy in patients with low cardiac output and diluted cardiomyopathy. The objective of this study is to assess the reliability of the parameters recently recommended by the ASE/AEE guidelines to evaluate the level of pulmonary capillary wedge pressure (PCWP) in patients hospitalized in intensive care unit for severe decompensation of advanced chronic systolic heart failure.

Methods: 27 consecutive patients (6±11 years old) with advanced decompenated heart failure were prospectively enrolled after admission in intensive care unit and followed during 48 hours. They underwent both haemodynamic evaluation by Swan Ganz catheter and echocardiographic for simultaneous measurement of LVFP assessed by pulmonary capillary wedge pressure (PCWP).

Results: Analysis of echocardiographic, the following parameters were analyzed: mitral E/e ratio (E: annulus mitral velocity was the average of the lateral and septal values); reverse annulus mitral velocity was the average of the lateral and septal values); reverse annulus mitral velocity was the average of the lateral and septal values). A mitral A wave (A) during the difference for the mitral a (Am) and Ap duration (ms).

Results: At admission, mean LV ejection fraction was 32±7% and PCWP was 19.6±6 mmHg. Mitral E/e ratio was 14.5±7 and was not significantly correlated with PCWP (r=0.30; p=NS). Using ROC curve analysis, E/e ratio poorly predicted increased PCWP>18 mmHg (AUC: 0.48). In addition, changes in PCWP values under therapy were not correlated with E/e changes.

Conclusion: In patients with advanced and decompensated systolic heart failure, E/e ratio is not reliable for both the initial evaluation of PCWP and evaluation under therapy. In contrast, pulmonary venous flow parameters provide a better assessment of PCWP in this high risk population.

P1932

Differences between males and females in intrinsic myocardial properties of the left ventricle established by “automated function imaging”

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Purpose: Ischemic heart disease is mostly a male problem. Genetic, hormonal and environmental factors are undoubtly decisive but intrinsic myocardial qualities could also be important. Strain measurement give a correct idea about the contractile reserve of the myocardium. Automated function imaging(AFI) is a novel algorithm based on speckle-tracking imaging that can be used for assessment of segmental and global longitudinal strain of the left ventricle(GLPSsawg).

Methods: The study population consisted of 1040 subjects, equally divided in 26 groups of 40 patients. 480 females(I) divided in 8 age groups healthy subjects (H) and in 4 age groups coronary patients(C); 560 males(II) divided in 8 age groups healthy subjects(II) and in 6 age groups coronary patients(II); for age: 20-29 years; 30-39 years; 40-49 years; 50-59 years; 60-69 years; 70-79 years; 80-89 years. All subjects underwent AFI for determination of GLPSsawg and for assessment of average strain of the 5 myocardial segments with the lowest strain(LVSS). Statistical analysis was performed by Anova, Levene’s test and t-test for equality of means.

Results: The GLPSsawg in healthy females is in all age groups higher than in healthy males. In all age groups the GLPSsawg is significantly(p=0.001) lower in coronary patients. Some findings significantly(p=0.001) different between males and females for AvgLVSS. In all age groups left atrium and left ventricle diameters are smaller in females and are increased in coronary patients. GLPSsawg (H:I): 20:24; 45:42; 20:23; 9:23; 9:49; 15:99; H:11-17.87; H:11-17.65; H:11-17.87; H:11-17.65; H:11-17.87; H:11-17.87. LVES volume(rs)= - 0.878 ± 22 patients developed new tricuspid regurgitation by 3rd year. Trans-tricuspid pressure gradient increased from 28.65 mmHg at baseline to 56.60 mmHg at 5 years (p=0.01).

LVEF declined from 63.60% at baseline to 52.09% at 5 years (p=0.02). 46 patients developed new atrial fibrillation at 3rd year and had persistent atrial arrhythmias thereafter. E/A ratio reversal occurred after a mean of 2.5 years. E/A ratio and deceleration time at baseline and at 5 years were 0.96 and 1.58 (p=0.392), and 251 and 199 ms (p=0.092) respectively.

RA function showed an inverse relationship to new onset atrial fibrillation during the follow up. A significant difference was found in the inverse relationship to LV dimensions for both LVED volume(rs)= - 0.954 and LVES volume(rs)= - 0.878.

Conclusion: Single chamber pacing at the RV apex led to significant RA dilatation and dysfunction which may explain the worsening TR, new onset atrial arrhythmias and deterioration of LV function.

P1933

Effects of long term right ventricular apical pacing on the right atrium

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Purpose: To investigate anatomical and functional changes in the right atrium and its relationship if any to left ventricular function.

Method: 96 patients with VVI pacemakers implanted between 2002 and 2004 were included. Pacing was at the RV apex in all cases. Transsthoracic echocardiographic measurements were obtained at baseline and annually.


Mean and standard deviations were analysed using independent T tests.

Relationships between RA function and new onset TR as well as changes in LV parameters were investigated using Pearson’s and Spearman’s correlations.

Results: 86 patients were enrolled. Only 75 patients were follow up for a mean of 5.5 years. 25 patients' data were available for analysis till 7 years. Mean age was 68.7±12.17 years old. 67.89% had complete heart block, 15.78% had sick sinus syndrome and 7.98% had AV nodal disease.

Mean RA area, RA end-diastolic volume and RA end-systolic volume increased from 18.79 to 20.58 cm³ (p=0.047), 50.78 to 69.30 ml (p=0.043) and 31.28 to 50.20 ml (p=0.036) respectively at baseline and 5 years.

22 patients developed new tricuspid regurgitation by 3rd year. Trans-tricuspid pressure gradient increased from 28.65 mmHg at baseline to 56.60 mmHg at 5 years (p=0.01).

LVEF declined from 63.60% at baseline to 52.09% at 5 years (p=0.02). 46 patients developed new atrial fibrillation at 3rd year and had persistent atrial arrhythmias thereafter. E/A ratio reversal occurred after a mean of 2.5 years. E/A ratio and deceleration time at baseline and at 5 years were 0.96 and 1.58 (p=0.392), and 251 and 199 ms (p=0.092) respectively.

RA function showed an inverse relationship to new onset tricuspid regurgitation and trans-tricuspid pressure gradient with Spearman’s correlation(rS= - 0.954, a linear relationship to declining LVEF with Pearson’s correlation(r= - 0.958 and an inverse relationship to LV dimensions for both LVED volume(rs)= - 0.955 and LVES volume(rs)= - 0.878.

Conclusion: Differences between years of right atrial pacing and untreated patients (CHF and SDB).

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Introduction: The high incidence of sleep disordered breathing (SDB) in patients with congestive heart failure (CHF) is well known. We compared adaptive pressure support servo-ventilation therapy (ASV) with nocturnal oxygen therapy (N-HOT) therapy in patients with CHF and SDB.

Methods: Thirty four patients (26 men; 68.5±11.3 years old; mean left ventricular ejection fraction(LVEF): 31.5±9.5%) with sleep disordered breathing(SDB): apnea-hypopnea index (AHI): <15) with impaired cardiac function (LVEF <50%) who were admitted due to congestive heart failure were analyzed retrospectively. All patients received polysomnographic evaluations during steady state of heart failure. Patients who received ASV or N-HOT therapy (non-randomized). Cardiac events (cardiac death, and hospitalization due to congestive heart failure) were analyzed.

Results: Mean follow up period was 69±61 day. Mean AHI of all patients was 11±4.6. Kaplan-Meier survival analysis showed that there was a significant difference between ASV and N-HOT in heart death and hospitalization due to congestive heart failure event (P=0.004). There were no significant differences between ASV and N-HOT in patients’ baseline characteristics.
Significance of periodic leg movements during sleep in patients with chronic heart failure and sleep-disordered breathing


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Background: Periodic leg movements during sleep (PLMs) are a disorder characterized by regularly recurring movements of the legs during sleep. Recent reports demonstrated that PLMs was highly prevalent and independently associated with increased mortality in chronic heart failure (CHF) patients. The purpose of this study is to investigate the prevalence and significance of PLMs in Japanese CHF patients with sleep-disordered breathing (SDB).

Methods: We enrolled 60 consecutive CHF patients with SDB (apnea-hypopnea index [AHI] ≥ 15/h) who diagnosed by attended polysomnography (PSG). After a few days, all patients received positive airway pressure (PAP) titration during PSG for treatment of SDB. The PLMs index (PLMI) was quantified as the frequency of PLMs per hour of sleep.

Results: PLMI was negatively correlated with AHI (r = -0.27, p = 0.035). Seventeen patients (28%) had PLMI ≥ 5. They were similar in age, gender, body mass index, Epworth Sleepiness Score, creatinine, left ventricular ejection fraction, B-type natriuretic peptide and AHI compared to those of the patients without PLMs (PLMI < 5). During PAP titration, PLMI significantly increased in patients without PLMs (from 0.9±2.6 to 6.5±1.4/h, p = 0.016), whereas PLMI in patients with PLMI ≥ 5 maintained at high level (from 48.4±69.1 to 36.8±43.0/h, p = ns). Some patients with severe SDB have an increase in severity of PLMs after PAP therapy.

Conclusions: These results show that the prevalence of PLMs is high in CHF patients with moderate to severe SDB. PSG should be recommended to CHF patients to evaluate not only SDB but also PLMs.

Which subtypes of cardiorenal syndrome is associated with worse clinical outcomes?

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Background: The cardiorenal syndrome (CRS) is characterized by an intimate interplay between dysfunctional heart and kidney, among which primary disorder of one organ often results in secondary damage to the other. Although there have been classifications of five, proposed to discriminate the complexity of this cluster of conditions, whether their clinical impacts on cardiovascular morbidity and mortality are different or not remain to be elucidated.

Methods: A nationwide population-based study using the Taiwan National Health Insurance database was conducted from 2001 to 2010. A total of 2838 patients who presented with both heart failure (HF) and chronic kidney disease (CKD) during 1997 to 2009 were identified. The control group consisted of 28380 subjects by matching age and sex.

Results: Among 2838 subjects with CRS, 1203 patients presented with HF ahead of CKD (group 1), 1839 presented with initial CKD (group 2), and 284 subjects had concurrent HF and CKD within 1 month (group 3). The group 3 was younger, more likely to be women, and had less diabetes. During a median follow-up duration of 2.84 years, patients with CRS had higher adverse events for coronary heart disease (CHD) (79.7 vs. 8.5/1000 person-year), stroke (45.8 vs. 18.3), and death (55.1 vs. 9.1) comparing to the control group. Among 2838 subjects with CRS, group 3 had the lowest event rate for stroke, CHD, and death comparing to the other groups (Table 1). Such the survival advantage remained true in multivariate analyses when age and comorbidities were accounted for.

Conclusions: The CRS indeed carried high risks for cardiovascular morbidity and mortality. However, a leading chronicity of HF or CKD rather than an acute insult to both organs is associated with worsened clinical outcomes.

Adaptive-servo ventilation may be a new additional therapy to improve symptoms and cardiac function for patients with chronic heart failure regardless of accompanying sleep disordered breathing

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Introduction: Adaptive servo ventilator (ASV) was developed as a device to abolish sleep disordered breathing (SDB) in heart failure patients. Recently, ASV is getting widely used for heart failure patients not only with SDB but also without SDB in Japan, because it may improve hemodynamics through its favorable effect on preload and afterload. However, there have been very few evidences on ASV therapy for heart failure patients without SDB. This study “SAVIOR-R” was carried out to establish real-world evidences on this therapy.

Methods: We performed a retrospective cohort study of 115 chronic heart failure patients who were firstly treated with ASV in 16 institutes from January to December 2009. Data on symptoms, echocardiography, chest X-ray, plasma BNP and sleep study were obtained from medical records for baseline and on ASV for one year.

Results: After ASV therapy, the ratio of NYHA class III patients decreased significantly from 43.2 to 23.5% (p = 0.0002), LVEF increased significantly from 34.9±16.0 to 39.8±16.6% (Mean ± SD, P = 0.0092). The improvement in LVEF was more remarkable in the low LVEF group as compared with the preserved-LVEF group. BNP and CTR were also improved, although these changes did not reach statistical significance. These effects of ASV were consistent irrespective of the degree of SDB.

Conclusion: ASV therapy would improve symptoms and cardiac function in chronic heart failure patients regardless of accompanying SDB. A randomized controlled trial to confirm the effects of ASV not through the attenuation of SDB is needed.

A single night use of adaptive servo ventilation improves renal function in heart failure patients with sleep disorders breathing

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Background: Sleep-disordered breathing (SDB) deteriorates the prognosis of patients with chronic heart failure (CHF). Adaptive servo ventilation (ASV) is a new therapeutic modality to treat SDB including Cheyne-Stokes respiration associated with central sleep apnea (CSR-CSA). SDB is thought to cause renal dysfunction because of intermittent hypoxia and sympathetic nervous activation. Renal function plays a critical role in the progression of CHF and is a strong predictor of clinical outcomes. Cystatin C is a more sensitive biomarker of renal function than creatinine. The purpose of present study was to examine whether ASV is effective for cardiac overload and renal dysfunction in CHF with SDB.

Methods and Results: Fifty patients with CHF and SDB (mean age 59.9±9.9, male 45, mean left ventricular ejection fraction 34.0±12.4%) were examined. We performed polysomnography for two consecutive days (baseline and on ASV), and measured levels of serum N terminal pro B-type natriuretic peptide (NT-pro BNP), cystatin C, creatinine, and estimated glomerular filtration rate by the MDRD formula (eGFR). ASV significantly improved apnea hypoapnea index (12±18.2 to 9.1±13.3, p = 0.01), central apnea index (16.4±13.7 to 11.8±1.5, p = 0.01), obstructive apnea index (3.2±5.9 to 1.2±2.0, p = 0.05), arousal index (25.8±10.6 to 15.7±7.4, p = 0.01), mean SPO2 (94.5±5.6 to 96.5±1.6, p = 0.01), and lowest SPO2 (79.2±9.7 to 88.9±5.6, p = 0.01) compared to
baseline. ASV reduced mean heart rate (71.9 ± 10.5 to 67.5 ± 9.6 bpm, P < 0.01), ASV decreased serum levels of NT-pro BNP (1109.0 (3173.2) to 912.8 (2576.7) pg/ml, P = 0.05) and cystatin C (1.391 ± 0.550 to 1.348 ± 0.469 mg/l, P = 0.05), but not creatinine (1.236 ± 0.07 to 1.25 ± 0.02 mg/l, P = 0.30) and eGFR (92.2 ± 8.3 to 64.9 ± 3.5 ml/min/1.73 m², P = 0.18).

Conclusions: ASV improved SDB, reduced cardiac overload, and protected renal function in CHF patients with SDB. ASV has short-term (a single night) beneficial effects on not only SDB but also cardio-renal function. ASV might be a promising tool for chronic heart failure as an important non-pharmacotherapy with cardio-renal protection.

Adaptive servo ventilation improves cardiac function and reduces re-hospitalization in chronic heart failure patients with Cheyne-Stokes respiration after cardiac resynchronization therapy

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Backgrounds: Cardiac resynchronization therapy (CRT) has been accepted as a useful therapeutic modality for heart failure (HF). Sleep disordered breathing (SDB), especially Cheyne-Stokes respiration (CSR), is often observed in HF patients and is associated with poor prognosis. CRT is thought to improve CSR. Although adaptive servo ventilation (ASV) is effective for CSR, it is unclear whether ASV improves cardiac function and prognosis of HF with CSR after CRT.

Methods and Results: In this study, 51 HF patients with moderate to severe SDB who were scheduled to implant CRT were enrolled. Although, mean apnea hypopnea index (AHI) decreased 6 month after CRT (31.1 ± 19.5 to 29.3 ± 17.1/hr), all 51 patients still had moderate severe SDB (AHI > 15/hr). CSR dominant, n=24; obstructive apnea dominant, n=27). The present study examined 24 HF patients with persistent CSR 6 month after CRT. Twenty four patients were randomly divided into 2 groups: 12 patients treated with ASV (ASV group) and 12 patients without ASV (Non-ASV group). LVEF, eGFR and echocardiographic parameters were measured before and 6 months after ASV. Patients were followed up to register cardiac events (average follow up period 656 days).

ASV improved SDB, reduced cardiac overload, and protected renal function in CHF patients with SDB. ASV might be a promising tool for chronic heart failure as an important non-pharmacotherapy with cardio-renal protection.

Conclusions: ASV improved cardio-renal function and long-term prognosis in HF patients with CKD and SDB.
Diagnosis of hypothyroidism is associated to an increased risk of acute decompensated heart failure occurrence, but not of mortality among heart failure outpatients

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It has been demonstrated that a hypothyroid status could affect the prognosis of patients with cardiovascular disease. The aim of this study was to better clarify the prognostic role of hypothyroidism in patients with chronic heart failure (CHF).

We enrolled 384 consecutive outpatients (65±13 years, 296 male, NYHA 2±0.6, left ventricular ejection fraction, LVEF, 32±9% with CHF (ESC criteria), in stable clinical conditions (at least 30 days) and in conventional therapy (at least 6 months) (91% ACE-inhibitors and/or AT1R antagonists, 89% betablockers, 87% diuretics, 54% aldosterone antagonists). The presence of hypothyroidism was defined according to the history of hypothyroidism and to its diagnosis at the enrollment or during follow-up. Patients with diagnosis of hypothyroidism were excluded.

In 91 (24%) patients of study population hypothyroidism was detected. During follow-up (31±10 months), 96 patients were hospitalized for acute decompen-sated heart failure (ADHF) and 58 died. Hypothyroidism was significantly assosiated to ADHF occurrence at univariate (HR: 2.17; Cl: 1.44-3.27; p<0.001) as well as at multivariate Cox regression analysis (HR: 1.58; Cl:1.02-2.45) after correcting for the time-up grade of ischemic cardiomyopathy, arterial systolic pressure, NYHA class, LVEF and levels of creatinine. Sodium and NT-proBNP. No association was found between hypothyroidism and mortality (HR: 1.15; Cl: 0.639-2.07; p<NS). Figure shows Kaplan Meier curves for events in patients with and without hypothyroidism.

Conclusions: Both baseline LVEF values and RDW changes have a prognostic significance among patients with chronic heart failure, as already demonstrated. RDW baseline values are related with other clinical characteristics, while RDW changes are possibly related with change in clinical conditions and hence prognosis, independent from other clinical variables.

High incidence of transitory arterial hypotension in patients with chronic heart failure

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Purpose: The aim of this study was to determine the incidence of arterial hypotension in patients with chronic heart failure (CHF) according to the results of Ambulatory Blood Pressure Monitoring (ABPM).

Methods: 152 patients with CHF (90 males and 62 females, mean age was 57.2±11.2 years) were studied. 19 patients had functional class I of CHF, 72 - Class II, 60 - Class III, 1 patient - Class IV according to NYHA classification. Causes of CHF were: arterial hypertension in 24 patients, coronary artery disease (CAD) - 5 patients, CAD and arterial hypertension - 120, other diseases of cardiovascular system - in 3 patients. Patients were treated according to Russian National Guidelines for Diagnosis and Management of Chronic Heart Failure, 2008. The ABPM was performed according to criteria P.E. Owens and E.T.O'Brien (1996). The time index of hypotension, also was taken into account.

Results: Among our database of outpatients with chronic HF, arterial hypotension were observed in 149.8±3.04 mmHg, diastolic blood pressure (DBP) - 91.0±15.9 mmHg. Office systolic arterial hypotension was diagnosed in 4 (2.6%), diastolic arterial hypotension in 3 (2.0%), systolic-diastolic hypotension in 5 (3.3%) patients. So, systolic and/or diastolic hypotension was identified in 12 (7.9%) patients. During ABPM average systolic blood pressure was 133.4±18.9 mmHg, average DBP - 78.4±12.2 mmHg. Episodes of systolic arterial hypotension during the 24-hour were revealed in 4 (2.6%), of diastolic arterial hypotension - in 47 (30.9%), systolic-diastolic hypotension - in 64 (42.1%) patients. Systolic and/or diastolic arterial hypotension was revealed in 115 (75.7%) patients more often in the daytime: 63 (41.4%) patients in daytime versus 3 (2.0%) in nighttime (χ²=69.67, p<0.001). Also 49 patients had arterial hypotension both in daytime and nighttime.

Conclusions: Using ABPM improve the diagnosis of arterial hypotension in patients with chronic heart failure. Episodic arterial hypotension are diagnosed in 75% of patients with CHF more often in the daytime. Further researches are necessary to define the connection between arterial hypotension and increased mortality in patients with CHF.

Effects of nocturnal oxygen therapy on cardiac arrhythmias in patients with chronic heart failure and central sleep apnea

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Purpose: Central sleep apnea (CSA) is a modifiable prognostic factor in patients with chronic heart failure (CHF), and oxygen supplementation has been shown to improve sleep-disordered breathing (SDB). We assessed the effects of 12-week nocturnal home oxygen therapy (HOT) on cardiac arrhythmias in patients with CHF and CSA.

Methods: We analyzed anti-arrhythmicogenic effects of nocturnal HOT for the first 12 weeks in combined patients enrolled in the previous two randomized, open-label, multi-center clinical trials, which confirmed the usefulness of nocturnal HOT for improvements in SOB and symptom of heart failure based on New York Heart Association (NYHA) functional class and Specific Activity Scale scores in patients with CHF and CSA. A total of 97 patients with CHF (NYHA class II - III, left ventricular ejection fraction [LVEF] ≤45%) and CSA with Cheyne-Stokes respiration were assigned to receive either nocturnal HOT (45 patients) or not (52 patients).

Results: The nocturnal HOT was associated with greater improvements in ap-no呼吸指数 (11.1±11.0 vs. -0.4±7.5/hr, p<0.01), in the Specific Activity Scale (0.7±1.2 vs. 0.0±0.6, p<0.01), and in NYHA functional class (p<0.01). Overall improvements of the number of premature ventricular complexes after 12 weeks were not different between the HOT and the control groups (18.4 vs. 17.0%, p=0.30). However, in 12 patients with NYHA functional class > III and apnea hypopnea index >20 events/hr, the number of episodes of ventricular ar-rhythmias was significantly reduced by HOT from 38 to 9/hr (p=0.02) together with a marked improvement in apnea hypopnea index (21.1±4.7 vs. 13.5±7.3/hr, p<0.01) and LVEF (10.1±7.8 vs. 2.0±7.5%, p=0.02).

Conclusions: The nocturnal HOT appears to be effective in reducing ventricular arrhythmias in patients with severe CHF and severe SDB.
Impact of positive airway pressure therapy for cardiovascular outcomes in heart failure patients with sleep-disordered breathing

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Background: The aim of this observational study is to determine whether positive airway pressure (PAP) therapy affects the long term outcomes of patients with heart failure (HF) and sleep-disordered breathing (SDB).

Methods: We studied 1,693 consecutive patients who underwent polysomnography from November 2004 to July 2011, and enrolled 121 patients with SDB (apnea-hypopnea index (AHI) ≥15), who had been admitted to hospital because of HF before polysomnography. They were divided into two groups: a PAP-treated group (AHI ≤15/hour and treated with continuous positive airway pressure or adaptive servo ventilation) and an untreated SDB group (AHI >15/hour and untreated with PAP devices). The frequency of death and hospitalization due to cardiovascular events (heart failure, acute coronary syndrome, stroke, and fatal arrhythmia) between the groups was analyzed using multivariate analysis.

Results: The mean follow-up period was 27.8±22.6 months and 35 patients (29%) died or were re-admitted to hospital due to CVD. Kaplan-Meier survival curve indicated that event-free survival was significantly higher in the PAP-treated group than in the untreated SDB group (Figure). Multivariate analysis showed that the risk for CVD was significantly higher in the untreated SDB group (hazard ratio [HR], 3.49; 95% confidence interval [CI], 1.13 to 12.3; p = 0.03) than the PAP-treated group.

Conclusion: In HF patients with SDB, PAP therapy improves long-term cardiovascular outcomes.

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Stroke volume response to adaptive-servo ventilation (ASV) in chronic heart failure

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Purpose: The aim of this study was to evaluate the acute effects of ASV to stroke volume in chronic heart failure.

Methods: Consecutive 32 patients with chronic heart failure (average EF=44%), New York Heart Association class III/IV were performed in the cardiac catheterization laboratory in the supine position. Right heart catheterization was performed with thermodilution catheter and aortic pressure was measured via artery. Hemodynamic measurements were made in patients with CHF at baseline and then repeated when the patients had been on ASV for a period of 10 minutes.

Results: Before the initiation of ASV therapy, the average hemodynamic parameters showed heart rate (HR) (67.7±11.3), cardiac output (CO) (3.74±0.88 l/min), cardiac index (CI) (2.35±0.48 l/min/m²), stroke volume (SV) (56.6±14.3 ml), pulmonary capillary wedge pressure (PCWP) (14.3±7.1 mmHg), pulmonary artery pressure (PAP) (33.9±13.3 mmHg), right atrial pressure (RAP) (4.4±3.2 mmHg), systolic aortic blood pressure (SBP) (142±83.5 mmHg), diastolic aortic blood pressure (DBP) (68.8±14.8 mmHg), systemic vascular resistance (SVR) (1972±531 dyne sec cm⁻²), and pulmonary vascular resistance (PVR) (212±161 dyne sec cm⁻²). After the initiation of ASV therapy, the average hemodynamic parameters showed HR (64.9±12.0), CO (3.43±0.77 l/min), CI (2.15±0.42 l/min/m²), SV (54.3±3.4 ml), PCWP (13.5±5.5 mmHg), PAP (31.5±10.9 mmHg), RAP (6.1±2.4 mmHg), SBP (141±34.6 mmHg), DBP (69.1±15.3 mmHg), SVR (2191±149 dyne sec cm⁻²) and PVR (219±149 dyne sec cm⁻²). HR, CO and CI were significantly decreased and other parameters have no significantly change after the 10 minutes initiation of ASV therapy. Otherwise, acute change in stroke volume was a significant positive correlation with acute change in HR (r=0.77, p=0.001), CI (r=0.66, p=0.001), and SVR (r=-0.56, p=0.001). Acute change in stroke volume was a significant negative correlation with acute change SVR (r=-0.622, p=0.001), RAP (r=0.474, p=0.006) and PCWP (r=0.358, p=0.044). Acute change in stroke volume was a significant positive correlation with acute change SVR (r=0.622, p=0.001) and HR (r=0.467, p=0.007). There was no significant correlation with acute change in SVR and HR.

Conclusion: In the higher PCWP/PAP and PAP the so-called congestive state, ASV has a tendency to increase SV due to the reduction of afterload and decrease of HR.
Left atrial enlargement in sickle cell disease patients: remodelling associated with haematological parameters or index of left ventricular filling pressures

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Purpose

Diastolic left ventricular (LV) dysfunction is a common finding in sickle cell disease. Furthermore, left atrial (LA) size usually reflects left ventricular filling pressures. The aim of our study was to determine if LA size is an expression of left ventricular filling pressures or reflects remodelling associated with anemia and/or haemolyticis in sickle cell disease.

Methods: We evaluated 127 patients with sickle cell disease in stable condition (mean age 28.6±8.5 years, 63 women) and 38 age and sex-matched healthy controls. LA size was measured with Simpson’s method in apical 4-chamber view. LV filling pressures were assessed using ratio between pulsed Doppler peak E velocity and peak Ea velocity obtained with tissue Doppler imaging of the lateral annulus (E/Ea ratio). Clinical and biologic data were collected from clinical records.

Results: Compared with the normal group, patients with sickle cell disease had a LA volume and E/Ea ratio significantly increased (48.4±11.2 mL/m² and 5.9±1.7, 30.5±7.6 mL/m² and 4.5±1, respectively, p<0.0001).

In multivariate analysis, LA enlargement in patients is only influenced by age and haematological parameters (haemoglobin and reticulocyte levels).

No correlation was found between LA volume and E/Ea ratio (figure).

Conclusion: Subjects with sickle cell disease have LA enlargement. However, in this population, LA dilatation is not an index of left ventricular filling pressures.

Plasma NGAL predicts mortality but not post discharge worsening renal function in patients with chronic heart failure

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Background: In patients with heart failure (HF), urinary Neutrophil Gelatinase Associated Lipocalin (NGAL), a marker of renal tubular damage, is elevated and associated with worse outcome, independent of glomerular filtration rate (GFR), whereas the prognostic value of plasma NGAL in HF is not well established.

Methods: In the COACH study, discharging alive from hospital after recovery from acute HF, we assessed the association between plasma NGAL and estimated GFR, worsening renal function (WRF; > 0.3 mg/dL and > 25% increase in creatinine) and HF hospitalization or all-cause mortality at 18 months, and all-cause mortality at 3 years.

Results: Mean age was 71±11, 62% were men and 96% were in New York Heart Association functional class II or III at discharge. Mean baseline eGFR was 54±20 mL/min/1.73m² and median plasma NGAL was 85 (60-123) ng/mL. WRF occurred in 17%, but plasma NGAL did not predict WRF (Odds ratio 1.29 per doubling NGAL, confidence interval (CI): 0.88 - 1.89, P = 0.194). Plasma NGAL levels were univariately associated with the incidence of the combined endpoint of HF hospitalization or all-cause mortality (P < 0.001), but not in multivariate analysis (Hazard ratio (HR) 1.22 per doubling NGAL, 95% CI 0.98 - 1.52, P = 0.071). Higher plasma NGAL levels were independently associated with 3 year mortality rates (HR: 1.98, 95% CI 1.44 - 2.73, P < 0.001), even in patients without chronic kidney disease (CKD: eGFR < 60 mL/min/1.73 m²; HR: 1.80, 95% CI 1.07 - 3.02, P = 0.027).

Conclusions: Plasma NGAL predicts mortality in patients with heart failure, independent of eGFR and even in patients without chronic kidney disease. However, plasma NGAL does not predict worsening renal function post discharge.

Interaction of heart failure and obstructive sleep apnoea: cycle length of obstructive sleep apnoea are dependent on left ventricular filling pressures

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Purpose: Obstructive sleep apnoea (OSA) may lead to or worsen heart failure (HF), however it is controversial if HF itself may influence OSA per se. Previous studies documented increased cycle lengths (CL) ventilation delays (VL), and circulatory delays (CD) of OSA in HF patients. Aim of the present study was to verify these results in a cohort of well-defined HF patients and to investigate possible correlations with parameters of HF severity.

Methods: A total of 39 patients with established OSA (apnoea-hypopnoea index, AH1 > 10 h) with (NYHA class ≥ II, LV-EF ≤ 40%, n=26, 18 male, 67.2±9.4 years) and without (EF ≥ 50%, NFproBNP < 400; n=13, 6 male, 72.7±6.8 years) HF underwent simultaneous right- and left-heart catheterization at 12h of cardiorespiratory polygraphy recording.

Results: AH1 as well as obstructive apnoeae-index (oAHI) were comparable in both groups (AH1= 34.3±26.5 h vs. 32.3±18.0, p=n.s.; oAHI=8.5±7.8 h vs. 10.0±10.8, p=n.s.). We were able to verify increased CL, VL, time to peak ventilation (TTPV) and circulatory delay (CD) in patients with HF (CL: 37.8±10.6 s vs. 46.0±10.0 s, p=0.004; VL: 21.3±7.1 s vs. 25.4±6.3 s, p=0.044; TTPV: 8.3±2.5 s vs. 10.6±3.0 s, p=0.021; CD: 22.6±3.7 s vs. 28.5±7.5 s, p=0.005). Apnoea length (AL) was higher in HF patients (10.5±3.9 s vs. 20.5±4.9 s, p=0.013). Positive and robust correlations between parameters of OSA and degree of congestion were found in OSA patients with HF exclusively: CL, VL, and TTPV increased with elevation of PCWP (CL: r=0.53; p=0.006; VL: r=0.55; p=0.004; TTPV: r=0.47; p=0.015).

Conclusions: Plasma NGAL predicts mortality in patients with heart failure, independent of eGFR and even in patients without chronic kidney disease. However, plasma NGAL does not predict worsening renal function post discharge.

Apixaban after acute coronary syndrome in patients with heart failure: insights from the APPRAISE-2 trial

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Background: In APPRAISE-2, participants in the APPRAISE-2 study were randomized to apixaban or placebo. In high-risk post-ACS patients it did not lead to a meaningful reduction in ischemic events.

Methods: We assessed the association between history of HF or acute HF and outcomes as well as the efficacy and safety of apixaban vs placebo.
Results: HF was present in 2995 (41%) patients. Compared with no HF, patients with only history of HF only had a higher overall baseline risk profile, presented more often with NSTEMI and were more often medically managed. Patients with only acute HF only had less frequent prior MI or PCI and presented more often with STEMI than patients with no HF. History of HF only was associated with a 2-fold increase of primary endpoint (PE), CV death or MI, while acute HF only was associated with a higher risk of CV death and TMI major bleeding. There was no significant interaction between HF status at any time and effect of apixaban (P = 0.193 for HF).

Conclusions: In high-risk ACS, both history of HF or acute HF are associated with worse ischemic and bleeding outcomes than patients without any HF.

Methods and Results: In 45 patients with NYHA ≥ II, elevated NT-proBNP levels and echocardiographic and/or cardiopulmonary exercise testing signs of HF, moderate to severe SDB (apnoea-hypopnoea-index, AHI ≥ 15/h with central and mixed apnoeic events was diagnosed by polysomnography (PSG). All PSG results were explained individually and ASV treatment (Somnoven CR™, Weimann) was offered to every patient. In 23 patients, efficacy of ASV treatment and HF status was evaluated after 3.6±1.2 months. Respiratory events were suppressed effectively (AHI baseline 24.8±17.5/h vs. 12.9±11.8/h during initial therapy initiation vs. 8.9±5.8/h at follow-up, p < 0.05 for each comparison). Central apnoea-index (cal) decreased from 10.4±12.0/h at baseline to 1.3±3.0/h at ASV initiation vs. 0.3±0.6/h at follow-up; p < 0.05 for each comparison) (figure) while overall satisfaction improved significantly while p<0.02 was reached from 36.4±3.1 to 37.9±3.8 mmHg (p<0.05), indicating a possible positive effect on respiratory control stability.

Conclusions: In selected HF patients, tri-Level ASV treatment using the Somnoven CR™ device is able to sustained decrease central and mixed sleep apnoea, may improve HF symptoms and increase cardiopulmonary exercise capacity.

Purpose: Chronic heart failure (CHF) is a multisystem disorder in which intestinal blood flow, morphology, permeability and absorption are modified. An increased number of bacteria within the mucosal biofilm of the sigmoid colon have been reported in patients with CHF. Composition of stool bacteria and gastrointestinal symptoms in patients with heart failure and have not been investigated yet.

Methods: We investigated 63 patients with CHF (LVEF 36.9±1.5%, peak VO2 27.3±1.4 mL/kg/min). Gastrointestinal symptoms were evaluated by Gastrointestinal Symptom Rating Scale (GSRS). Total bacterial and bacterial groups in fixed blinded faecal samples were studied by Fluorescence in situ hybridization (FISH) and epifluorescence microscopy in a subgroup of 21 patients and 17 controls. Mucosal bacterial biofilm was assessed by FISH in biopsies taken during sigmoidoscopy.

Results: CHF patients compared to controls stated more often feelings of repletion, burping, flatulence and murmurs from the intestine (34/58 vs. 4/18, 15/59 vs. 0/18, 43/59 vs. 8/18 and 34/59 vs. 5/18, all p<0.04). However, pain in the upper abdomen, abdominal discomfort in general, defecation frequency and nausea/vomiting were similarly reported in CHF patients vs. controls (all p>0.3).

The higher total concentration of mostly anaerobic bacteria in the mucosal biofilm of the sigmoid in patients did not correlate with the concentration of anaerobes or the ratio of anaerobes to aerobes in stool (all p>0.39). However, the higher occurrence rate of the strictly anaerobic Escherichia recta group in intestinal

Abstract P1953 - Table 1

<table>
<thead>
<tr>
<th>Event</th>
<th>No Prior HF + No HF at Index</th>
<th>No Prior HF + HF at Index</th>
<th>No Prior HF + No HF at Index</th>
<th>P Value</th>
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<tr>
<td>CV death, MI or ischemic stroke</td>
<td>Events per 100 yr</td>
<td>10.75</td>
<td>12.77</td>
<td>18.19</td>
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<tr>
<td>CV death</td>
<td>Events per 100 yr</td>
<td>HRR (95% CI)</td>
<td>1.19 (0.90, 1.57)</td>
<td>1.83 (1.45, 2.29)</td>
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<tr>
<td>MI</td>
<td>Events per 100 yr</td>
<td>HRR (95% CI)</td>
<td>2.8</td>
<td>7.17</td>
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<tr>
<td>Safety: Bleeding</td>
<td>Events per 100 yr</td>
<td>HRR (95% CI)</td>
<td>2.8 (1.51, 3.45)</td>
<td>2.61 (1.78, 3.81)</td>
</tr>
<tr>
<td>TMI major bleeding</td>
<td>Events per 100 yr</td>
<td>HRR (95% CI)</td>
<td>6.5</td>
<td>12.57</td>
</tr>
<tr>
<td>p</td>
<td>0.5 to 1.9</td>
<td>0.4 to 0.5</td>
<td>0.0001</td>
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</tr>
</tbody>
</table>

*HRR compares the hazard of HF groups.

P1954 Evaluation of psychological pain, a measure of suicidal tendencies among heart failure patients at an academic hospital in west Africa

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Purpose: Psychological pain (Psychache) defined as lasting, unsustainable and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self is a measure of suicidal tendencies amongst patients with psychiatric disorders. It has been studied in some medical conditions but not in chronic heart failure (HF) patients with various limitations and loss of function. We decided to evaluate the degree of psychological pain among chronic HF patients attending our cardiology clinic.

Method: Adult stable chronic HF patients were recruited into the study. Patients’ demographic and clinical data were obtained and echocardiographic data were retrieved from these clinical notes. The thirteen item psychache questionnaire by R.R Holden and K Mehta was then administered to the patients. A group norm score of ≥ 30.66 and gender norm scores of ≥ 33.26 for males and 28.04 for females were used for further analyses based on the validated scores for my country. The score was then correlated with socio-demographic variables, disease state and quality of life (QoL) scores of the patients.

Result: Data set for 180 HF patients, 91 males and 99 females was analysed. The mean age of the subjects was 51.90 ± 13.21yrs, duration of illness 35.82 ± 13.03yrs. Most were married, 81.6% and Christians, 80.5%.

Long-term effects of tri-level adaptive servosventilation (ASV) therapy for central and mixed sleep apnoea in heart failure patients

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Purpose: Sleep disorders breathing (SDB) is of major prognostic impact in heart failure (HF). Combined central and mixed apnoeic events are challenging to treat. Aim of the present study was to investigate long-term effects of a new tri-level adaptive servosventilation (ASV) therapy on respiratory and cardiac parameters in HF patients.

The mean psychache score was 24.28 ± 13.21yrs, duration of illness 35.82 ± 13.03yrs. Most were married, 81.6% and Christians, 80.5%.
biotin in patients (18/20 vs. 15/22) was associated with a higher concentration of anaerobes, aerobes and total bacteria in stool (6.4±0.3 vs. 4.6±0.2, p<0.015; 8.3±0.2 vs. 6.5±0.7, p<0.02 and 8.3±0.2 vs. 6.5±0.7, p<0.02 respectively). The same applied to the increased occurrence rate of strictly anaerobic Fusobacterium prausnitzii in patients’ biotins (18/20 vs. 12/22) which was reflected by more anaerobes, aerobes and total bacteria in stool of these patients (8.3±0.2 vs. 6.4±0.7, p<0.015; 8.3±0.2 vs. 6.5±0.7, p<0.015; 8.3±0.2 vs. 6.5±0.7, p<0.02, respectively).

**Conclusion:** Concentration of stool bacteria reflects the increased occurrence rate of strictly anaerobic bacteria within the mucosal biofilm of the sigmoid indicating better conditions for these specific anaerobes directly at the surface of the mucus membrane in CHF. This may contribute to gastrointestinal symptoms in patients with CHF.

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**P1957**

Brain natriuretic peptide (BNP): A general mortality predictor in HIV-infected patients? - Results from the 5-year follow-up of the HIV-HEART trial

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**Background:** HIV-infected patients exhibit an increased rate of cardiac diseases, due to an elevated rate of cardiac risk factors and side effects of antiretroviral therapy. The present study was to analyze the impact of B-type natriuretic peptide (BNP) as a prognostic parameter for death in HIV-infected individuals.

**Methods:** This prospective multi-center observational cohort study elucidates cardiovascular disease prevalence by standardized non-invasive cardiovascular screening program and laboratory tests including BNP in 790 HIV-infected patients from four specialised outpatient clinics in Germany between 2004 and 2011. Within the 5-year follow up period 50 (6.3%) of the individuals died. Characteristics of survivors and deceased patients were compared and evaluated for their predictive value.

**Results:** At baseline, 83.3% of the 790 patients were male, 88.5% Caucasians, 83.3% HIV-infected individuals, 51.7% were CDC-categorised C and 48% immunological stage 3. The mean age was 44.3 years and the mean measured CD4 cell counts were 507 cells/μl. 687 (87.0%) patients underwent antiretroviral treatment, of whom 77.0% had an HIV-RNA <50 copies/ml. 30 of 790 patients (3.8%) had BNP values >100 ng/L. 13 of these patients (43.3%) died, compared to 37 deaths (4.9%) in subjects with normal BNP level (P<0.001). In multivariate Cox regression analysis, the following parameters were independent mortality predictors: advanced HIV infection (Odds ratio=11.46; p<0.001), creatinine clearance (p<0.001), presence of pretibial edema (p<0.001), HF related rehospitalization (p<0.001), and C-reactive protein levels (p<0.002). Parathyroid hormone, LVEF, NYHA functional class, C-reactive protein, pretibial edema, HF related rehospitalization, TAPSE, BNP Disease duration, Sodium, Left atrium size, creatinine clearance, left ventricle systolic diameter, and female gender were associated with worse BOS in univariable analysis. In multivariable logistic regression model, PTH level (Odds ratio=1.035, p=0.003), LVEF (Odds ratio=0.854, p<0.004), NYHA Functional Class III/IV (Odds ratio=28.022, p=0.005), C-reactive protein (Odds ratio=1.088, p=0.020), and presence of pretibial edema (Odds ratio=12.341, p<0.000) were found to be independent predictors of worse BOS after adjustment of potential confounders.

**Conclusion:** Patients with moderate to severe depression had higher serum levels of PTH and CRR, poor functional status and lower left ventricle EF, all of which are predictors of advanced HF. The association of depression with predictors of advanced HF may explain the contribution of depression to hospitalization and mortality in HF.

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**P1959**

The hidden truth: stage B heart failure among diabetics and the obese

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**Purpose:** Diabetes mellitus (DM) is an independent predictor of heart failure (HF). The optimal approach to this problem involves identifying patients at risk early in the course of the condition. Previous studies have shown a high prevalence of diastolic dysfunction in diabetic subjects. We set out to study the wider burden of structural and functional problems that could lead to heart failure.

**Methods and Results:** The STOP-HF cohort consists of subjects over 40 with at least one cardiovascular risk factor. Each had a Brain Natriuretic Peptide level and Doppler-Echocardiography performed. Stage B heart failure was defined as structural heart disease (consisting of ejection fraction <50%, left atrial volume index<34 ml/m² and/or left ventricular mass index>149g/m² [M], >122g/m² [F]) in the absence of symptoms of heart failure. Of 1025 total patients, 234 (22.8%) were documented as having DM. Prevalence of stage B HF was 19.8% in the total population, 23.5% in those with DM and 18.8% in those without (p<0.01).

Age distribution was similar across the two groups. Considering only those patients with BMI>30 kg/m², 82 (57%) of the total of 303 had DM: 32% of these had stage B HF. Prevalence of stage B was 44% in those with DM and BMI>30 kg/m² compared to 28% in non-diabetics (p=0.013).

**Conclusions:** Though asymptomatic, a significant proportion of the diabetic population had stage B HF, particularly those with BMI>30 kg/m². At a time of limited resources, this identifies a cohort of patients requiring more intensive risk factor control to prevent progression to symptomatic heart failure.

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**P1960**

Differences in general health status and functional capacity in patient with chronic heart failure and chronic obstructive pulmonary disease after one-year of hospital discharge

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**Background:** The aim of this prospective observation study was to assess self reported health status and functional capacity in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) one-year after hospitalisation for acute dyspnea.

**Methods:** 684 consecutive patients presenting to the emergency department with acute dyspnea were included in the study. The final diagnosis was adjudicated by two independent cardiologists. General health status and functional capacity was determined at presentation and one-year after hospital discharge, by EuroQol-5

Figure 1. EQ-5D dimensions at one-year follow-up.
dimensions (EQ-5D), VAS (0 = worst and 100 = best possible health) and 12-item Duke Activity Status Index (DASI) questionnaire.

Results: A total of 184 patients (27%) died within 360 days. At one-year follow-up out of the 500 patients alive, the questionnaires were completed and returned by 179. Within these, 94 patients with CHF and 39 with COPD were included in the analyses. No statistically significant difference was found in neither of the two disease groups regarding EQ-5D dimensions. Additionally Figure 1 shows the sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions. The median (interquartile range) of EQ- VAS score was 60 (50–76) for patients with CHF and 60 (39–70) for COPD (p=0.1). Average DASI-estimated functional capacity was 8.3 (7.6–9.2) metabolic equivalents (METs) in CHF and 8.9 (7.35–9.4) METs in COPD patients, without significant difference (p=0.07).

Conclusions: Our analysis demonstrates high prevalence of poor general health status and functional capacity in patient with CHF and COPD even after One-year hospital discharge. Therefore future research is needed in outpatient management and advanced care planning is justified.