A blood pressure genetic risk score predicts incident cardiovascular events in 36,950 Finnish individuals

Background and purpose: Recent genome-wide association studies (GWAS) have identified several genetic variants associated with blood pressure (BP). We investigated whether genetic risk scores (GRS) constructed of these variants would be significant predictors for incident cardiovascular (CVD) events in the prospective, population-based setting.

Methods: We genotyped 33 genome-wide significant variants in several Finnish cohorts (FINRISK 1992, 1997, 2002, 2007, Health 2000 and the Helsinki Birth Cohort), altogether in 36,950 individuals. Persons with prevalent CVD at baseline were excluded and the cohorts were followed for events through December 31, 2009. GRS were constructed for each individual by summing BP elevating alleles weighted by the beta coefficients from the earlier GWAS, separately for systolic and diastolic BP. We used Cox proportional hazards regression, adjusting for relevant covariates, for analyzing various complications of high BP, including incident CVD events. Characterization of confounding, coronary death and revascularization, (incident stroke, and their combination (incident CVD). The results were summarized with inverse variance weighted meta-analysis.

Results: Cross-sectional analysis of baseline data confirmed associations of most GWAS hits for systolic and diastolic BP. GRS were strong predictors for systolic and diastolic BP hypertension (all p < 0.57). Altogether, 2,111 incident CVD events occurred during the follow-up. GRS showed significant, independent and roughly linear associations with the CVD risk. The highest quintile of systolic BP GRS had the hazard ratio of 1.28 (95% confidence interval 1.1 – 1.5, p = 0.0005) and the highest quintile of diastolic BP GRS 1.31 (95% CI 1.12 – 1.54, p = 0.0005) compared with the respective lowest quintiles when adjusted for standard Framingham risk factors, excluding BP. After further adjustment for systolic BP measured at baseline, the hazard ratios were reduced only slightly (to 1.22 and 1.26, respectively) and remained significant.

Conclusions: Our study provides an independent confirmation for most GWAS hits for association with systolic and diastolic BP. An aggregate GRS, constructed of these variants, was a strong predictor of systolic and diastolic BP and hypertension. Most importantly, BP GRS was a significant predictor of future CVD events, independently of standard CVD risk factors including BP measurement at a single point in time, suggesting that GRS captures lifelong exposure to elevated BP.

A variant in the ABO gene explains the variation in soluble E-selectin levels - results from dense-genotyping in two independent populations

Background: Adult vascular disease is caused by multiple risk factors. Recent genetic variants in the ABO blood group have been related to sE-selectin levels in a small cohort of patients with type 1 diabetes. We evaluated whether this association is reproducible in large samples of Caucasians.

Methods: We genotyped 33 genome-wide significant variants in several Finnish cohorts (FINRISK 1992, 1997, 2002, 2007, Health 2000 and the Helsinki Birth Cohort), altogether in 36,950 individuals. Persons with prevalent CVD at baseline were excluded and the cohorts were followed for events through December 31, 2009. GRS were constructed for each individual by summing BP elevating alleles weighted by the beta coefficients from the earlier GWAS, separately for systolic and diastolic BP. We used Cox proportional hazards regression, adjusting for relevant covariates, for analyzing various complications of high BP, including incident CVD events. Characterization of confounding, coronary death and revascularization, (incident stroke, and their combination (incident CVD). The results were summarized with inverse variance weighted meta-analysis.

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Gene-gene interactions in coronary artery disease

Background: Only a small fraction of the heritability of coronary artery disease (CAD) has been explained by common variants identified by genome-wide association studies. Gene-gene interactions could explain some of the missing heritability. Using a custom-built array, we investigated whether interactions between common alleles in genes and pathways of known importance to cardiovascular regulation contributes to the heritability of CAD.

Methods: The study population consists of 2101 CAD cases recruited into the ICA/KORA Augsburg study (n = 1,482) and the case-control based LURIC study (n = 629). We genotyped 33 genome-wide significant variants in several Finnish cohorts (FINRISK 1992, 1997, 2002, 2007, Health 2000 and the Helsinki Birth Cohort), altogether in 36,950 individuals. Persons with prevalent CVD at baseline were excluded and the cohorts were followed for events through December 31, 2009. GRS were constructed for each individual by summing BP elevating alleles weighted by the beta coefficients from the earlier GWAS, separately for systolic and diastolic BP. We used Cox proportional hazards regression, adjusting for relevant covariates, for analyzing various complications of high BP, including incident CVD events. Characterization of confounding, coronary death and revascularization, (incident stroke, and their combination (incident CVD). The results were summarized with inverse variance weighted meta-analysis.

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Purpose: In the present study we identified two compound heterozygous mutations (p.D1690N and p.G1748D) in the gene (SCN5A) encoding the alpha subunit of the cardiac Na+ channels (Nav1.5) in a proband diagnosed of type 1 Brugada Syndrome. Furthermore, in the allele encoding p.D1690N mutation, the p.H558R polymorphism was also detected. Therefore, we analyzed the functional properties of the mutated channels as well as the putative modulator effects produced by the presence of the polymorphism.

Methods: Native (WT) and mutated human Nav1.5 channels were expressed in Chinese hamster ovary cells (CHO) and studied using the whole-cell patch-clamp.

Results: Separately, both p.D1690N and p.G1748D mutations produced a marked reduction in peak Na+ current density (by 80% and 90% compared to WT, respectively), which was mainly attributed to their limited trafficking into the membrane. Furthermore, p.G1748D mutation shifted 14 mV rightward both activation and inactivation curves. p.G1748D also accelerated the time-course of recovery from fast inactivation thus, p.G1748D profoundly affected the channel's gating. Both p.D1690N and p.G1748D produced a marked dominant negative effect on the WT channel, i.e., p.D1690N channel with WT or p.H558R channels. Indeed, p.D1690N+WT and p.G1748D+WT reduced peak Na+ current density by 68% and 85%, respectively. Conversely, p.H558R was able to rescue defective trafficking of p.D1690N channels into the membrane when both, polymorphism and mutation, were in the same construct as demonstrated by using confocal microscopy of CHO cells transfected with GFP-tagged Nav1.5 channels, generating currents that were indistinguishable from those generated by WT. Surprisingly, cotransfection with p.D1690N, either alone or together with the polymorphism (p.H558R:p.D1690N) completely restored the profound gating defects exhibited by p.G1748D channels while only slightly rescued their trafficking.

Conclusion: Our results add further support to the hypothesis that Nav1.5 subunits interact among them before trafficking into the membrane and shows that a missense mutation can ‘rescue’ the defective gating produced by another missense mutation when present in different alleles.

NOVEL MECHANISMS AND IMAGING TOOLS INATHEROSCLEROSIS

Impaired neoformation in mice lacking the coronary artery disease risk gene ADAMTS-7 after cessation of blood flow

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Purpose: ADAMTS-7 has been identified as a coronary artery disease (CAD) risk gene in gene-wide association studies (GWAS). Interestingly, ADAMTS-7 plays rather a role in plaque formation than rupture, as hypothesized by a GWAS subgroup analysis. ADAMTS-7 is involved in rheumatoid arthritis pathogenesis, where it has been shown to degrade cartilage oligomeric matrix protein (COMP). Therefore, in this study, we investigated ADAMTS-7 in a murine knockout (KO) model regarding remodeling of injured arteries and metabolic parameters.

Methods: Adamts-7-KO mice were generated by interrupting the Adamts-7 gene with an internal ribosome entry site followed by the beta-gal sequence and a neomycin cassette. The transgene was confirmed using PCR, RT-PCR and LacZ-staining of various tissues. Phenotyping was carried out on young common carotid artery ligation (CCAL). Ten days after ligation occluded and sham-treated vessels were harvested and morphometrically analyzed. COMP was detected by immunofluorescence in injured and sham-treated arteries. To investigate metabolic effects, KO- and WT-mice were fed a Western diet for 15 weeks. Weight was assessed weekly, and blood lipid levels before and after the diet. Atherosclerotic lesions at the sinus aortae were quantified after Oil-Red-O-staining.

Results: Our data add further support to the hypothesis that Adamts-7 knockout mice have reduced atherosclerosis. Further, COMP is highly enriched in CCAL vessels. Furthermore, the atherosclerotic lesion area in the aortic sinus is significantly lower in KO-mice. In addition, the atherosclerotic lesions of the aortic sinus were smaller in KO-mice. In contrast, weight gain, blood lipid levels or lipid deposition measured as lesion area were not observed between WT- and KO-mice.

Conclusion: We conclude that ADAMTS-7 plays an important role in the pathophysiology of CAD as it seems to be pivotal for the remodeling of arteries following vascular injury. The degradation of COMP may be part of the downstream signaling pathway. Since lack of ADAMTS-7 did not alter metabolic parameters or lipid metabolism, we suggest that the association of ADAMTS-7 and CAD involves a remodelling mechanism in the vessel wall itself.
In vivo detection of activated platelets allows characterizing rupture of atherosclerotic plaques with molecular magnetic resonance imaging in mice

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Introduction: Platelets are found on the surface of ruptured plaques, and their early and noninvasive detection is of clinical interest for the timely evaluation of stroke or myocardial infarction. Molecular magnetic resonance imaging (mMRI) of platelets using targeted contrast agents is a promising imaging strategy. In this study, we performed mMRI of activated platelets in an animal model of plaque rupture in Apoe-/- mice.

Methods and Results: We constructed a contrast agent using an antibody targeting ligand-induced binding sites (LIBS) on the glycoprotein IIb/IIIa receptor of activated platelets. This antibody was conjugated to microparticles of iron oxide (MPIO), causing a signal-extinction in T2*-weighted MRI, which resulted in the LIBS-MPIO contrast agent. Apoe-/- mice at the age of 60 weeks were fed with a western-type high fat diet for 5 weeks. Thereafter, plaque rupture in the carotid artery was mechanically induced, using a small needle introduced through a side branch of the external carotid artery for scenting the plaque surface. In vivo and in vitro Tesla MRI was performed before and repetitively after intravenous injection of either LIBS-MPIO or a control contrast agent (control-MPIO). Plaque-rupture was induced experimentally in Apoe-/- mice, and LIBS-MPIO injected animals showed a significant signal extinction (p<0.05) in MRI, corresponding to the site of plaque rupture in histology. History further confirmed significant binding of LIBS-MPIO to the thrombus developing on the surface of ruptured plaques (p<0.01).

Conclusion: We established in vivo molecular MRI of activated platelets on the surface of ruptured atherosclerotic plaques in Apoe-/- mice. This is a unique opportunity for the noninvasive detection of this pathology, which has a profound clinical impact, and could also allow for further noninvasive characterization of plaque rupture on a molecular level.

M1 and M2 macrophages expression profiles in human atherosclerosis and modulation by major cardiovascular risk factors

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Purpose: Atherosclerosis is characterized by chronic inflammation of arterial intima associated with macrophage infiltration. Recent studies have shown that 2 macrophage subpopulations, M1 and M2, coexist in human atherosclerotic plaques. Macrophages have the capacity to express many mediators such as pro/anti-inflammatory cytokines, Tissue Factor (TF), the primary initiator of coagulation cascade and its major physiological inhibitors, the Tissue Factor Pathway Inhibitors (TFPI and TFPII-2), pro-angiogenic factors (VEGF, Vascular Endothelium Growth Factor) and matrix metalloproteinases (MMP) involved in plaque vulnerability. We aimed at comparing the expression levels of these mediators in M1 and M2 circulating monocytes derived macrophages (MDM) from atherosclerotic patients and then, evaluating the impact of major cardiovascular risk factors on these expression profiles.

Methods: MDM obtained from 35 atherosclerotic patients were cultured with IL-1β (10 ng/ml) and IL-4 (10 ng/ml) to induce M1 and M2 phenotype, respectively. The atherosclerotic mediators expression profiles were evaluated by quantitative RT-PCR.

Results: In the present study, we confirmed the pro-inflammatory properties of M1 vs. M2 (increased expression of TNFα and IL-1β, p<0.001 for both) and anti-inflammatory properties of M2 vs. M1 (increased expression of IL-10, p<0.0001). We observed that M1 were antiphlogistic (significantly increased expression of pro/anti-inflammatory cytokines, Tissue Factor (TF), the primary initiator of coagulation cascade and its major physiological inhibitors, the Tissue Factor Pathway Inhibitors (TFPI and TFPII-2), pro-angiogenic factors (VEGF, Vascular Endothelium Growth Factor) and matrix metalloproteinases (MMP) involved in plaque vulnerability. We aimed at comparing the expression levels of these mediators in M1 and M2 circulating monocytes derived macrophages (MDM) from atherosclerotic patients and then, evaluating the impact of major cardiovascular risk factors on these expression profiles.

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Galectin-3 binding protein/90K induces expression and shedding of the hemoglobin-haptoglobin scavenger receptor CD163 in human atherosclerotic plaque macrophages

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Objective: Macrophages are important during atherogenesis. Galectin-3 binding protein (90K) is a secreted immunomodulatory protein. We have previously shown that 90K inhibits foam cell formation through downregulation of CD36 and scavenger receptor-A and that high 90K plasma levels in coronary artery disease patients are associated with protection from adverse cardiovascular events. We therefore hypothesized that 90K may have atheroprotective effects on macrophages with relevance to human atherosclerosis.

Methods and Results: Human primary macrophages were treated with recombinant 90K or control for 48 hours and mRNA was measured using gene arrays. The local pooled error test revealed upregulation of 125 and downregulation of 92 genes, which could be attributed to immune response, chemotaxis, and the inflammatory response as identified by gene ontologies. 90K significantly increased CD163 gene expression coding for the hemoglobin scavenger receptor and induced dose- and time-dependent upregulation and shedding of CD163 protein. Macrophages pre-treated with 90K responded to stimulation with hemoglobin-haptoglobin and hemoglobin-Hb-Hp complexes with increased upregulation of 3.5% HO-1 message and heme oxygenase-1 (HO-1) protein expression as compared to control cells, in which Hb-Hp-induced IL-10 and HO-1 upregulation was significantly lower. Immunohistochemical analysis showed an enhanced upregulation of atheroprotective HO-1 in response to intra-plaque hemorrhage may represent an important mechanism by which 90K exerts atheroprotective action.

Conclusions: 90K may represent a relevant modulator of human atherosclerotic plaque macrophages. 90K-dependent induction of CD163 in combination with enhanced upregulation of atheroprotective HO-1 in response to intra-plaque hemorrhage may represent an important mechanism by which 90K exerts atheroprotective action.

Novel Cardiovascular Risk Factors

The paradox of elevated adiponectin; reduced cardiovascular risk factors, but increased all-cause mortality and MACE

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Background: Adiponectin exerts anti-inflammatory and anti-atherogenic effects and appears to protect against arteriosclerosis. Accordingly an association between low concentrations of plasma adiponectin and cardiovascular disease (CVD) has been demonstrated in several studies. Conversely elevated plasma adiponectin has been associated with increased mortality and increasing number of traditional CVD events. Due to these conflicting results the true role of adiponectin remains to be elucidated.

Methods: In the Copenhagen City Heart Study we prospectively followed 5,901 randomly selected men and women from the community. Plasma adiponectin was measured at the beginning of the study. Median follow-up time was 7.8 years (IQR: 7.3-8.6years). Endpoints were all-cause mortality (n=895) and the combined endpoint MACE, consisting of CV mortality or a nonfatal myocardial infarction or ischemic stroke (n=576).

Results: High adiponectin was inversely associated to increasing number of traditional CV risk factors (p=0.0001), geometric mean adiponectin concentrations were 10.4mg/L (95% CI: 10.2-10.7mg/L) for persons with no CV risk factors present versus 6.0 (95% CI: 4.8-7.4mg/L) for persons with four CV risk factors. In increasing adiponectin concentration was linearly associated with increased risk of CV mortality and MACE. Additionally adjusted for conventional risk factors including age, sex, diabetes, smoking, hypertension and 7 novel biomarkers (BNP, sTfN, Lp(a), PL-PLA2, hsCRP, MR-proANP and P1M amyloid C) adiponectin remained an independent predictor of death and MACE.

Conclusion: Adiponectin exerts anti-inflammatory and anti-atherogenic effects and appears to protect against arteriosclerosis. Accordingly an association between low concentrations of plasma adiponectin and cardiovascular disease (CVD) has been demonstrated in several studies. Conversely elevated plasma adiponectin has been associated with increased mortality and increasing number of traditional CVD events. Due to these conflicting results the true role of adiponectin remains to be elucidated.

Elevated D-dimer levels predict long-term thromboembolic and cardiovascular events in patients with prior myocardial infarction or unstable angina: results from the Lipid trial

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Background: The role of D-dimer in predicting long-term vascular events in patients with prior CHD is not clearly defined. We assessed the independent value of D-dimer levels in predicting venous thromboembolic (VTE) and cardiovascular (CVD) events during 6 years median follow-up.

Methods: 9014 patients with cholesterol 4.0-7.0mmol/L were randomized to placebo or pravastatin after MI or unstable angina 3-36 months previously. D-dimer levels (Abbott Quantia) were measured at randomization and at 1 year. Proportional hazards models were fitted for vascular events by baseline quartiles of D-dimer. Results: 1112, 1112-173, 173-273, >273nm/L and adjusted for treatment. The 23 conventional risk factors including age, sex, lipids, diabetes, smoking, hypertension and 7 novel biomarkers (BNP, sTfN, Lp(a), PL-PLA2, hsCRP, MR-proANP and P1M amyloid C) adiponectin remained independently associated with CHD events only (P=0.03) and by 15.4% for VTE (P<0.007). Increases in D-dimer at 1 year independently predicted risk of total mortality. Pravastatin reduced CVD events for each outcome except VTE.

Elevated D-dimer levels predict long-term thromboembolic and cardiovascular events in patients with prior myocardial infarction or unstable angina: results from the Lipid trial

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Levels of GDF-15 increase over time in an elderly population and are a strong predictor of all-cause mortality

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Purpose: Growth-differentiation factor-15 (GDF-15) is induced in cardiomyocytes and vascular cells during inflammation and tissue injury. Circulating levels of GDF-15 have emerged as a powerful risk indicator in the general population and across a wide spectrum of cardiovascular diseases. In this first longitudinal study on GDF-15 in the general population, we determined if GDF-15 levels may change over time, and if changes in GDF-15 are related to prognosis.

Methods: GDF-15 was analyzed using a sandwich immunoassay in a sample of elderly community-dwellers who were participating in the PIYUS-study. Measurements were performed both at the age of 70 (n=1004) and 75 years (n=813). Total follow-up was 8.0 years.

Results: The median GDF-15 level at 70 years was 1135 ng/L (25th, 75th percentiles 948-1390 ng/L). GDF-15 levels independently predicted all-cause mortality (adjusted HR for 1-SD increase in GDF-15; 4.0 (95% CI 2.2-7.3); p<0.001) with a stronger association to outcome as compared to NT-proBNP or CRP. GDF-15 improved also prognostic discrimination and reclassification beyond established cardiovascular risk indicators (IIDI=0.030 [p=0.04]; NRI=1.141 [p=0.001]). GDF-15 levels increased by 11.9% from 70 to 75 years of age (p<0.001). The change of GDF-15 levels was related to male sex (p=0.02), and baseline information on hypertension (p=0.002), diabetes (p<0.001), self-reported heart failure (p=0.02), the estimated glomerular filtration rate (p=0.07) and NT-proBNP levels (p<0.001), but not to levels of CRP or echocardiographic estimates of left-ventricular abnormalities at baseline. In an extended model considering also biomarker results obtained at 75 years of age (n=802), additional significant relationships emerged between the change of GDF-15 and changes of levels of NT-proBNP (p<0.001), CRP (p<0.001) and of the estimated glomerular filtration rate (p<0.001). The R2-value of this model was 0.20.

Conclusion: GDF-15 is a powerful predictor of mortality in an elderly population from the community. GDF-15 levels increase with aging, and these changes are explained only partially by cardiovascular risk factors, renal function and NT-proBNP. These data indicate that GDF-15 reflects an independent pathological process that is closely related to prognosis.

Insomnia is associated with an increased risk of developing and/or dying from cardiovascular disease.

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Objective: Increasing evidence suggests an association between insomnia and cardiovascular disease. We performed a systematic review with meta-analysis of all available prospective studies that investigated the association between insomnia and risk of developing and/or dying from cardiovascular disease.

Design: Systematic review and meta-analysis of prospective cohort studies.

Methods: We conducted an electronic literature search through MedLine, Embase, GoogleScholar, Web of Science, The Cochrane Library, and bibliographies of retrieved articles up to December 2011. Studies were included if they were prospective, had assessment of insomnia or sleep complaints at baseline, evaluated subjects free of cardiovascular disease at baseline and measured the association between insomnia and risk of developing and/or dying from cardiovascular disease.

Results: After the review process 16 prospective studies (13 cohort of patients) were included in the final analysis. These studies included 122,501 subjects followed for a time ranging from 3 to 20 years. A total of 6,332 cardiovascular events occurred during the follow-up. Insomnia was assessed through questionnaire and defined as either difficulty of initiating or maintaining sleep or presence of restless, disturbed nights. The cumulative analysis for the studies under a random-effects model showed that insomnia determined an increased risk (44%) of developing or dying from cardiovascular disease during follow-up (RR 1.45, 95% CI 1.29-1.62; p<0.001), with no evidence of heterogeneity across the studies (I2: 19%; p=0.14).

Conclusion: Insomnia is associated with an increased risk of developing and/or dying from cardiovascular disease.

EPIDEMIOLOGY OF HYPERTENSION AND RISK FACTORS

Body mass index and the risk of developing hypertension in healthy young- and middle-aged Japanese males: 10-year follow-up study

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Objective: Asians likely develop hypertension and hypertension-related stroke in a moderate body mass index (BMI) which is considered under obese in Caucasian. However, few prospective studies have evaluated BMI across the range of normal weight and overweight as a risk factor for hypertension in large Asian populations. We conducted a prospective cohort study to examine the relationship of BMI to the onset of hypertension in healthy Japanese males.

Method: Apparently healthy Japanese males aged 18-50 (n = 25,764) without prevalent hypertension at baseline were enrolled in 2000. All subjects took an annual medical checkup including blood pressure measurement and medical interview until 2010. The participants were categorized into 4 groups according to the quartiles of BMI (1st, 2nd, 3rd, and 4th). Incident hypertension was defined as newly detected blood pressure ≥140/90 mmHg and/or initiation of antihyper-
Use of angiotensin receptor blockers and risk of Alzheimer’s disease in hypertension population: a nationwide cohort study

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Purpose: Although emerging evidence showed angiotensin II receptor blockers (ARBs) may have a protective effect against Alzheimer’s disease (AD), but the strength of the evidence is still questionable. Besides, the association between ARBs and the incidence of AD in patients with hypertension has not been investigated in Asians. We aimed to investigate this association.

Methods: A nationwide population-based study was conducted to investigate the possible influence of ARBs on the occurrence of new AD in patients with systemic hypertension by using the Taiwan National Health Insurance database. A total of 87,424 patients with newly diagnosed hypertension were identified from a cohort database of 1 million individuals from January 1, 2000, to December 31, 2006. Among them, 16,426 patients matched the enrollment criteria had received ARBs for at least one year. The association between ARBs and the incidence of AD in patients with hypertension was studied. Serum glucose, cholesterol (total, HDL), triglycerides, apolipoprotein A1 and B were measured, left ventricular mass index (LVMi), estimated glomerular filtration rate (eGFR), 10-year CV risk according to Framingham Risk Score (FRS) and HeartScore (HS) were calculated.

Results: Only 10% of patients had no concomitant RFs. 53% had one (49% dyslipidemia, 3% smoking, 1% diabetes), 33% had two (26% dyslipidemia and smoking, 7% dyslipidemia and diabetes, 0.3% smoking and diabetes) and 4% had all four traditional RFs. Obesity was present in 30%, metabolic syndrome in 38%, low eGFR in 24% and LV hypertrophy in 49%. Mean FRS risk was 8% for males and 6% for females while in high risk (≥ 20%) were 69% and 51% respectively (p = 0.0001). Mean HS risk was 8% for males and 6% for females while in high risk (≥ 5%) were 4% and 36% respectively (p < 0.0001). Age was correlated to pulse pressure, eGFR, LVMi and CV risk in both genders (p < 0.0001). Age increased the risk difference between genders (Figure) for total (p < 0.001) but not for fatal events (pNS). In the age spectrum 45-54 years, postmenopausal
women (n=1271) had an elevated mean CV risk compared to premenopausal females (n=1076) even after adjustment for age (16.9 vs 13.8% according to FRS and 1.1 vs 0.7% according to HRS, p<0.001 for both). Gender and age distribution of arterial stiffness in the general population: results from the Copenhagen City Heart Study. 1Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands; 2Rigshospitalet - Copenhagen University Hospital, Heart Centre, Department of Cardiology, Copenhagen, Denmark; 3Bispebjerg Hospital of the Copenhagen University Hospital, Department of Cardiology, Copenhagen, Denmark; 4University Medical Center Mainz, Center for Thrombosis and Hemostasis, Mainz, Germany

Purpose: Arterial stiffness (AS) determined by digital volume pulse analysis using stiffness index (SI) might represent a low-cost and easily performable method for cardiovascular (CV) risk assessment. Our aim was to determine gender- and age-specific reference limits for SI and to examine its associations with CV risk factors and scores for CV risk assessment in the general population.

Methods: Data from 10,000 participants of the population-based Gutenberg Health Study, stratified for age, gender and residence were used. All data were collected according to standard operating procedures with detailed quality control using computer-assisted personal interview data, laboratory measurements and clinical ORS data. AS was assessed by a PulseTrace 2000 device (Cardinal Health) and SI was calculated.

Results: Arterial stiffness was available in 8,060 subjects (4,226men (M)/3,834 women (W); age range 35-74 yrs) due to technical and logistic constraints. We calculated age- and gender-specific reference values and cut-off values for categories indicating the grade of deviation from the reference. The gender-specific SI (m/s) in reference, intermediate, mild, moderate, severe categories were <13.7; 13.7-14.9; 14.9-16; 16-17; >17 in men and <11.1; 11.1-12.1; 12.1-13.5; 13.5-14.2; >14.2 in women. As expected, SI was significantly higher at older age. Moreover, women demonstrated a markedly lower SI compared to men (7.56 vs 9.85 m/s; p<0.0001). Age-adjusted linear regression analysis modeling for AS revealed smoking as the strongest associated factor in men and women (β (M)=0.930.43; both p<0.0001), followed by hypertension (β (M)=0.740.40; both p<0.0001). Additional correlates included dyslipidemia and smoking history in both genders (β (M)=0.270.31; p=0.047 for M and p=0.006 for W) and obesity in men only (β=0.36; p=0.004). After additional adjustment for CV risk factors, smoking and hypertension remained positively and independently associated with SI in both genders (β (M)=0.990.44 and 0.800.35; both p<0.0001). Furthermore, a strong correlation of SI with the German EURO-Score (M=0.400.38) and with the Framingham general CVD risk score (M=0.400.39) was found. Finally, a significant increase in SI was observed throughout the groups with increasing risk for each score and with the highest values revealed in the high risk group.

Conclusion: Our data show a strong association of SI with determinants of global CV risk and underline its clinical significance in CV risk stratification. This is the first study to report gender- and age-specific reference values for SI in the population.

RBBB, Prevalence, risk factors and outcome in the general population: results from the Copenhagen City Heart Study

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Purpose: To determine the prevalence, predictors of newly acquired and prog- ression of right bundle branch block (RBBB) and incomplete right bundle branch block (IRBBB) on a resting 12-lead ECG in men and women from the general population.

Methods and results: We followed 18,441 participants included in the Copenhagen City Heart Study.
The importance of global economic level on AMI outcomes. Data from the Euro Heart Survey 2009 AMI snapshot.


Methods: The EHS ACS 2009 snapshot surveyed consecutive data on 4314 patients admitted for AMI (STEMI or NSTEMI) <48 hours from symptom onset as a very brief period of time (one week, 7-13 December 2009); 47 member countries participated, with 465 active centres + all centres participating in the MINAP and Swedish registries. GDP and national health expenditures were used to determine a global economic indicator (gross domestic product, GDP) on in-hospital mortality and major complications in the Euro Heart Survey 2009 AMI snapshot.

Results: No significant difference in mortality was observed with increasing GDP: adjusted OR (95% CI) vs 1st quartile of GDP: 2nd quartile: 0.68 (0.50-0.93), 3rd quartile: 0.60 (0.43-0.85) p for interaction with gender 0.01. Presence of IRBBB was not associated with adverse outcome.

Gender-pooled hazard ratios

<table>
<thead>
<tr>
<th>Total number of cases</th>
<th>Age-adjusted hazard ratios (95%CI)</th>
<th>Multiple-adjusted hazard ratios (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no RBBB</td>
<td>9874</td>
<td>reference</td>
</tr>
<tr>
<td>IRBBB</td>
<td>327</td>
<td>1.02 (0.91-1.14)</td>
</tr>
<tr>
<td>RBBB</td>
<td>145</td>
<td>1.31 (1.11-1.54)</td>
</tr>
<tr>
<td>Coronary mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no RBBB</td>
<td>3248</td>
<td>reference</td>
</tr>
<tr>
<td>IRBBB</td>
<td>105</td>
<td>0.98 (0.81-1.19)</td>
</tr>
<tr>
<td>RBBB</td>
<td>73</td>
<td>1.87 (1.46-2.36)</td>
</tr>
</tbody>
</table>

*Adjustment for age, Body Mass Index and systolic blood pressure.

Conclusion: In this cohort study, RBBB and IRBBB were two to three times more common among men than women. RBBB was associated with cardiovascular risk and all-cause mortality whereas IRBBB was not. Contrary to common perception, RBBB in asymptomatic individuals should alert clinicians to cardiovascular risk.

Effects of atorvastatin and rosuvastatin on renal function in patients at high cardiovascular risk: a meta-analysis of 21 randomized trials

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Purpose: Atorvastatin (A) and rosuvastatin (R) are highly effective and widely used statins. Yet, conflicting results have been reported regarding renal effects. Purpose of the study was to evaluate the effects of A and R on glomerular filtration rate (GFR) and new proteinuria onset in patients at high cardiovascular risk.

Methods: MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for studies reporting A or R treatment until February 2012. Study inclusion criteria were: report of GFR at baseline and at end of follow up or report of change of GFR from baseline to end of follow up; report of new proteinuria onset; randomized protocol design. Meta-analysis was performed to assess the influence of treatments on GFR and new proteinuria onset.

Results: 21 trials enrolling 26,577 participants followed up for a mean of 55.37±63.03 weeks were included. A significant reduction in GFR was detected in placebo-treated compared to statin-treated patients (standard mean difference [SMD]: 0.05, 95% confidence interval [CI]: 0.02 to 0.08, p=0.001, heterogeneity=0.036). A significant reduction in GFR was detected in placebo vs treated-R patients (SMD: 0.05, CI: 0.02 to 0.08, p=0.001, heterogeneity=0.095). No significant difference in GFR was detected in 3 head-to-head studies (4414 patients) comparing A to R (SMD: 0.03, CI: 0.071 to 0.137, comparison p=0.533, heterogeneity=0.728). In 9 studies comparing A to R, treatment significantly increased the risk of new proteinuria onset when compared to A (odds ratio [OR]: 0.63, CI: 0.44 to 0.97, comparison p=0.038, heterogeneity p=0.026), but this effect was no longer significant when studies using higher therapeutic doses of R (40 mg/daily) were excluded from analysis, abolishing significant heterogeneity (OR: 1.50, CI: 0.827 to 2.739, comparison p=0.181, heterogeneity p=0.473).

Conclusions: A and R show similar nephroprotective effects in patients at high risk, with comparable effects on new proteinuria onset when commonly used doses are considered.

Long-term prognostic value of N-Terminal Pro-Brainnatriuretic Peptide (NT-proBNP) changes within one year in patients with coronary heart disease

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Purpose: There is limited information about the prognostic value of longitudinal measurements of NT-proBNP over longer periods of time. We evaluated the prognostic value of a 12-month longitudinal change in NT-proBNP on subsequent cardiovascular disease (CVD) events in patients with stable coronary heart disease.

Methods: NT-proBNP serum concentrations were measured at baseline and one year follow-up in a cohort of patients aged 30-70 years participating in an in-patient cardiac rehabilitation program (mean follow-up 8.4 years). Cox-proportional hazard models were used to determine the prognostic value of changes of NT-proBNP after additional adjustment for the baseline values of NT-proBNP, age, gender, left ventricular function, and history of diabetes, in relation to subsequent secondary CVD events (myocardial infarction, stroke, and cardiovascular death). We examined relative changes using a cutoff of ±30% from baseline level, considered clinically relevant, and by quartiles. We evaluated absolute changes by building categories (low-low, low-high, high-low, high-high) across a set of threshold values from 100 to 1000 pg/mL.

Results: Among 5215 patients (mean age 59 years) there were 121 CVD events. Women showed higher median values of NT-proBNP at baseline (677.1 versus 536.3 pg/mL) and at one year follow-up (266.0 versus 177.0 pg/mL). The median relative change between 30- and 360-day baseline value. The analysis of relative change by quartiles showed a steady decrease in the hazard when comparing 3rd, 2nd, and bottom quartile to the top one with the lowest reduction (0.60 [95% CI: 0.37; 0.92]) for a secondary CVD event compared to an ARI event. In particular, an absolute reduction of 30% and 300% on the baseline value. The analysis of relative change by quartiles showed a steady decrease in the hazard when comparing 3rd, 2nd, and bottom quartile to the top one with the lowest relative change between 30- and 360-day baseline value. The analysis of relative change by quartiles showed a steady decrease in the hazard when comparing 3rd, 2nd, and bottom quartile to the top one with the lowest reduction (0.60 [95% CI: 0.37; 0.92]) for a secondary CVD event compared to an ARI event. In particular, an absolute reduction of 30% and 300% on the baseline value.
absolute changes in stable cardiac patients, clinicians may consider lower threshold levels of NT-proBNP in contrast to the suggested levels for patients with heart failure.

**5217 Educational status and cardiovascular risk factor profile of coronary patients in Europe: results of EUROASPIRE III survey**

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**Purpose:** To determine the association between educational level and the control of lifestyle and medical risk factors in patients with coronary heart disease who participated in the EUROASPIRE III survey.

**Methods:** EUROASPIRE III was a cross-sectional survey, performed in 2006-2007 in 22 European countries, investigating implementation of clinical recommendations in everyday clinical practice. Patients, who underwent elective or emergency revascularisation procedures, such as coronary artery bypass grafting or percutaneous coronary artery angioplasty, or were diagnosed with acute myocardial infarction or acute ischaemia, were identified retrospectively and interview 6 months after the event. Educational level was categorised into primary, secondary, and higher education. The study aimed to determine the association of educational attainment with prevalence and control of cardiovascular risk factors.

**Results:** A total of 8966 patients were interviewed. The proportion of patients with primary, secondary, and higher educational level was 25.1%, 56.3% and 18.6%, respectively. Obesity, hypertension, diabetes, persistent smoking, low HDL cholesterol, and obesity, but not hypercholesterolaemia, were significantly more prevalent in patients with primary education (table 1). The risk (OR, 95% CI) of obesity, persistent smoking and hypertension was significantly lower in the higher educational level group compared to patients with only primary education, by 48% (1.48; 1.29-1.7), 47% (1.47; 1.22-1.77) and 39% (1.39; 1.22-1.58), respectively.

**Table 1**

<table>
<thead>
<tr>
<th>Education Level</th>
<th>Primary</th>
<th>Secondary</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructed (%)</td>
<td>40.0</td>
<td>35.1</td>
<td>30.3</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>16.1</td>
<td>18.4</td>
<td>15.0</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>40.6</td>
<td>32.9</td>
<td>31.6</td>
</tr>
<tr>
<td>BP ≥ 140/90 mmHg or ≥ 130/80 in diabetes (%)</td>
<td>60.6</td>
<td>56.4</td>
<td>50.0</td>
</tr>
<tr>
<td>Total cholesterol ≥ 4.5 mmol/l (%)</td>
<td>48.7</td>
<td>52.9</td>
<td>51.9</td>
</tr>
<tr>
<td>Low HDL cholesterol (%)</td>
<td>39.8</td>
<td>36.2</td>
<td>34.2</td>
</tr>
</tbody>
</table>

**Conclusions:** A clear inverse association of educational level and cardiovascular risk factors was demonstrated. Involvement of a multidisciplinary team in the management of all coronary patients is crucial. A particular support has to be provided to patients who attained only primary education.

**SECONDARY PREVENTION: STILL IMPROVING AFTER ALL THESE YEARS**

**5218 Effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) on cardiovascular mortality in hypertension: a meta-analysis of randomized controlled trials**

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**Reduction in cardiovascular (CV) and all-cause (AC) mortality is the ultimate goal of HT (HT) treatment. Our previous meta-analysis of HT trials reported significant further reduction in AC mortality with ACE inhibitors (ACEIs) vs control. The effect of ARBs was neutral. We decided to study the impact of ACEIs and ARBs on CV mortality in hypertension.**

**Methods:** Pooled analysis of 16 randomized ACEI or ARB trials since January 2000 reporting CV mortality. In each trial, at least two-thirds of patients had hypertension. Trials in HF, ACS, acute stroke, postcardiac surgery, AF, dialysis, or with ACEI or ARBs in both arms were excluded. In 149,713 patients (92% hypertensive; 295,619 patient-years of follow-up). In patients randomized to ACEIs (n=76,615), there were 9.1 CV deaths per 1,000 patient-years, vs 11.2 CV deaths per 1,000 patient-years in controls. ACE inhibitors were associated with a 12% reduction in CV death (HR 0.88; 95% CI, 0.77-1.00, P<0.051). No significant reduction in CV mortality (HR 0.96; 95% CI, 0.96-1.01; P=0.128) could be demonstrated with ARBs (n=73,098). We found evidence of heterogeneity with respect to CV mortality reduction with different ACEIs (P for heterogeneity 0.031, F 57%). Periodorp-based regimens were associated with a significant 22% reduction in CV mortality (HR<0.78; 95% CI, 0.70-0.87, P<0.001), whereas the remaining ACEIs were not (Figure). No heterogeneity was observed for the effects of the different ARBs.

**Conclusions:** ACE inhibition is associated with a further reduction of 12% in CV mortality in hypertensive patients versus control. Because of the high prevalence of hypertension, preferential use of treatment with proven efficacy on mortality reduction may lead to a considerable number of lives saved.

**5219 A phase 3 study of the microsomal triglyceride transfer protein (MTP) inhibitor lomitapide in patients with homozygous familial hypercholesterolemia**

M. Cuchel on behalf of The Phase 3 HoFH Lomitapide Study Investigators, University of Pennsylvania School of Medicine, Institute for Translational Medicine and Therapeutics, Philadelphia, United States of America

**Purpose:** Patients with homozygous familial hypercholesterolemia (HoFH) are at very high risk for premature cardiovascular disease and are refractory to existing lipid-lowering drug therapy. We conducted a phase 3 study to assess the efficacy and safety of the MTP inhibitor lomitapide in adults with HoFH when added to concomitant lipid lowering therapies, including apolipoprotein.

**Methods:** HoFH patients enrolled into the single arm, open label study were instructed to maintain current lipid lowering therapy unchanged from six weeks prior to baseline through week 26. Lomitapide was initiated at 5 mg and escalated individually to the maximum tolerated dose up to 60 mg/day. The primary endpoint was mean percent change in LDL-cholesterol (–C) from baseline at week 26 (intent to treat analysis), after which patients remained on lomitapide for assessment of safety and long-term effects and were permitted to modify concomitant lipid lowering therapy.

**Results:** Of the 29 HoFH subjects enrolled, 23 completed weeks 26, 56 and 78 (end of study) evaluations. Median dose was 40 mg/day. As compared with baseline, LDL-C levels were reduced by 40% at week 26 (336±114 mg/dl vs 190±104 mg/dl; P<0.001). In the subjects that completed week 26, mean change was 50% and was maintained through weeks 56 and 78 (-44% and -38% respectively, P<0.001 for all). Similar % reductions were observed for apolipoprotein B. Eight subjects had LDL-C levels <100 mg/dl at weeks 26. Four of them either discontinued LDL apheresis or increased the time interval between apheresis treatments and were able to maintain decreased LDL-C levels until the end of the study. Lomitapide was generally well tolerated. Gastrointestinal symptoms were the most common adverse events observed. Four patients had confirmed elevations in alanine transaminases between 5 and 11×ULN. All 4 were able to continue in the study with temporary dose reduction or temporary suspension of study medication. There were no concomitant changes in bilirubin or alkaline phosphatase. No patients discontinued treatment due to liver function abnormalities. Liver fat content assessed by NMRS was 0.91±0.01% at baseline, 0.9±0.7% at week 26 and remained stable at weeks 56 and 78 evaluations (7.3% and 8.2%, respectively).

**Conclusions:** These data demonstrate robust and durable efficacy with an acceptable safety profile in this high risk patient population. Lomitapide is a promising agent as therapy for patients with HoFH.

**5220 Addition of cilostazol to conventional dual antiplatelet therapy reducing the risk of cardiac events and restenosis after drug-eluting stent implantation: a meta-analysis**

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**Backgrounds:** Relative efficacy and safety of triple antiplatelet therapy (TAT, addition of cilostazol to aspirin and clopidogrel) compared with conventional dual antiplatelet therapy (DAT, aspirin and clopidogrel) remained controversial.

**Objective:** This meta-analysis was performed to compare the risk of cardiac events and restenosis of TAT versus DAT in drug-eluting stents (DES) implantation patients.

**Methods:** We performed PUBMED, MEDLINE, EMBASE and Cochrane CENTRAL searches for randomized clinical trials of TAT versus DAT in patients after DES implantation. Five clinical trials (5,526 patients) were involved in the meta-analysis. Period of clinical follow-up ranged from 9 to 12 months.
Results: TAT was associated with a 36% reduction in major adverse cardiac events (MACE) (odds ratio=0.64; 95% CI=0.51-0.81; P<0.01), a 40% reduction in target lesion revascularization (TLR) (OR=0.60; 95% CI=0.44-0.80; P<0.01), and a 44% reduction in in-segment/in-stent restenosis (P<0.01) and lower in-segment/in-stent late loss (P<0.01). As regards to the safety assessment, there was no significant difference about the risk of stent thrombosis (OR=1.0, P=1.0) and bleeding (OR=1.18, P=0.49) between TAT and DAT group, while the risk of gastrointestinal trouble was significantly higher in TAT group (OR=2.46, 95% CI=1.25-4.86; P<0.01).

Conclusions: Addition of clostozol to conventional DAT reduced the incidence of MACE, TLR and TLR in patients after DES implantation. TAT also reduced the risk of angiographic restenosis and late loss in patients after DES implantation.

Impact of physical exercise and inflammatory state on endothelial progenitor cells in acute coronary syndrome patients attending a cardiac rehabilitation program

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Purpose: Among the benefits of a cardiac rehabilitation (CR) program for patients after an acute coronary syndrome (ACS) there is the mobilization of endothelial progenitor cells (EPCs). However not all patients respond to CR with an increase of EPCs. We performed this study to identify the characteristics of patients who will not benefit from the increase of EPCs at the end of the CR program.

Methods: 112 ACS patients were admitted to a four-weeks CR program. EPCs, high sensitivity C-reactive protein (hsCRP) and NT-proBNP levels were determined at the beginning (T1) and at the end (T2) of the CR program. All patients performed a cardiopulmonary exercise test at T1 and at T2. EPCs were defined as CD34+KDR+, CD133+KDR+ and CD34+CD133+KDR+. hsCRP and NT-proBNP were measured by nephelometric and immunoassay method, respectively.

Results: At T2, we observed a significant increase of EPCs (p<0.001), VO2 peak, Watt max HDL-cholesterol (p<0.0001) and a significant decrease (p<0.001) of hsCRP and NT-ProBNP, triglycerides, Hba1c, systolic blood pressure and waist circumference. Moreover, variations of VO2 peak were significantly correlated with the variations of EPCs. Patients with increased EPCs showed significantly (p<0.01) lower baseline levels of CRP and higher basal Watt max (p<0.04). In a multivariate logistic regression analysis, the lowest tertile of baseline hsCRP significantly affected the likelihood of having an increase of EPCs at the end of the CR program.

Conclusions: A CR program determines an increase of EPCs with a decrease of CRP and NT-ProBNP. A different trend for EPCs can be detected among patients correlated to CRP levels and exercise tolerance.

Predictive value of CHADS2 score for death, stroke, and myocardial infarction both in patients with and without atrial fibrillation

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Background: CHADS2 is a widely used for risk stratification for stroke in patients with atrial fibrillation (AF). We investigated the predictive value of the CHADS2 for death, stroke and myocardial infarction (MI) in patients with or without AF using the database of the prospective nation-wide Japanese cohort, the J-TRACE.

Methods and Results: J-TRACE recruited 8,087 stable out-patients with a history of MI, stroke and/or atrial fibrillation. One-year follow-up data were available for 7,513 patients, 2,056 of them were AF while 5,457 were not. The primary end-point (death/MI/stroke) was reported in 3.53 events per 100 person-years within a year, and the event rate rises as the CHADS2 score increases in AF patients group as well as in all patients group (Figure 1).
Healthy lifestyle: still the cornerstone of primary prevention

Lifestyle modification and risk factor management for healthy lifestyle traits compared with those having none. Keeping normal weight have a remarkable effect on the development of hypertension, at least moderate physical activity, daily consumption of vegetables and adjustment of baseline systolic blood pressure and the exclusion of those subjects (HOMA-index -0.81 [p=0.002] in men and -1.67 [p=0.001] in women) was lowered in FITback by 26.6% in men and 25.1% in women (p=0.001). Blood pressure (BP) in hypertensive patients was 160 mmHg systolic or 95 diastolic did not appreciably change the results.

Conclusions: Four modifiable lifestyle traits: no or moderate alcohol consumption, at least moderate physical activity, daily consumption of vegetables and keeping normal weight have a remarkable effect on the development of hypertension. The risk of hypertension was only one third among people having all four healthy lifestyle traits compared with those having none.

Lifestyle modification and risk factor management for cardiovascula prevention in a workplace setting - the fit in life - fit on the job study

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We assessed the effectiveness of the workplace based primary prevention program “FIT IN LIFE – FIT ON THE JOB” in modifying CVD risk factors and promoting lifestyle changes.

The participation rate was exceptionally high reaching >90% of all entitled employees at an age of 40+ years in the first round (“FIT1/2”). We report the results of 312 men and 223 women, who completed the second round (“FITBack”) after a mean follow-up of 3.4 years: Smoking cessation rates were 31.9% (p=0.006) in men and 17.5% in women (p=0.035). Blood pressure (BP) in hypertensive patients was lowered in FITBack by 14.1 mmHg in men (p=0.001) and 16.6 mmHg in women (p=0.001). BP control rates in known hypertensives rose from 26.6% to 42.8% in men and from 38.2% to 54.2% in women. In insulin resistant subjects (HOMA-index >2.6) insulin sensitivity was significantly improved (HOMA-index -0.01 [p=0.002] in men and -1.67 [p=0.001] in women). The median 10-year-risk for CVD in high risk patients (upper tertile of the risk distribution) was lowered in FITBack by 26.6% in men and 25.1% in women (p=0.001).

CVD Risk Reduction (RR) in the second round (FIT recall) for men and women, who were in the upper tertile of 10-year-CVD risk (Reynolds Risk Formula) in the first round (FIT 1).

<table>
<thead>
<tr>
<th>Trait</th>
<th>RR recall</th>
<th>Abs RR</th>
<th>Rel RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man</td>
<td>7.73%</td>
<td>6.15%</td>
<td>2.05%</td>
<td>0.001</td>
</tr>
<tr>
<td>Women</td>
<td>22.23%</td>
<td>1.85%</td>
<td>0.58%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: A comprehensive, workplace based primary prevention program can have a substantial impact on lowering CVD risk.

Association of thoracic aortic calcium with incident myocardial infarction and mortality in the general population: the Heinz Nixdorf Recall Study

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Background: Thoracic aortic calcium (TAC) is associated with cardiovascular risk factors and prevalent coronary artery disease. We aimed to investigate, whether TAC burden is associated with incident myocardial infarction and all-cause mortality in a general population cohort without known coronary artery disease.

Methods: Participants from the community based Heinz Nixdorf Recall Study were included for this analysis. TAC and coronary artery calcium (CAC) scores were quantified from non-contrast enhanced electron beam computed tomography. Cox regression analysis was used to determine the association of TAC with incident myocardial infarction or all-cause fatal events during follow-up. Adjustment was performed for cardiovascular risk factors and ancillary for CAC-score. A potential predictive value of TAC was assessed using Harrell's C index.

Results: Overall, 4040 participants without known coronary artery disease (59.4 years, 47% male) were included in this analysis. Median(Q1; Q3) TAC-score was 17.5 (0; 124.7). With increasing TAC-scores traditional risk factors such as blood pressure, use of antihypertensive medication, diabetes, lipid lowering medication and smoking increased or had higher prevalence. During a mean follow-up period of 7.2±1.5 years, 121 subjects developed myocardial infarction and 245 subjects suffered a fatal event. Both coronary event rates and all-cause mortality rate increased significantly (p<0.001) with increasing TAC scores. Logarithmic increase of TAC (Log(TAC)+1) was associated with 1.04-fold increase hazard ratio (HR) of coronary events and a 1.11-fold risk for fatal events when adjusting for cardiovascular risk factors (HR (95%CI): 1.04 (0.97; 1.13) vs. 1.11 (1.05; 1.17). For all-cause mortality associations remained significant after further adjustment for CAC-Score (HR (95%CI): 1.07 (1.01; 1.15) but not for coronary events (0.773 to 0.772, p=0.66).

Conclusion: TAC is associated with incident myocardial infarction and all-cause fatal events independent of traditional cardiovascular risk factors and CAC-score in the general population. Further investigation might find even more predictive value over CAC events in coronary events. However, the predictive value of TAC complements prognostic information above CAC-score and cardiovascular risk factors regarding all-cause mortality.

Predictors of low physical activity in patients with stable coronary heart disease in the global STABILITY study

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Purpose: Many individuals with coronary heart disease (CHD) do not take regular physical exercise as recommended in international guidelines. A better understanding of reasons why CHD patients remain sedentary is needed to guide more effective interventions. The aim of this analysis was to identify clinical and demographic factors associated with low physical activity (PA) in high risk patients with CHD participating in the ongoing STABILITY study, a global clinical outcomes trial which is evaluating the lipoprotein phospholipase A2 inhibitor darapladib.

Methods: Before randomisation 15,486 (97.8%) STABILITY study participants from 38 countries completed a lifestyle questionnaire including information on PA. Each subject estimated the number of hours taking mild, moderate and vigorous (2, 4 and 8METs, respectively) PA during a typical week. Participants were classed as sedentary if reported PA was in the lowest and active if in the highest third of the study population. A cross sectional analysis identified clinical and demographic variables more prevalent in sedentary subjects.

Results: 5280 (34%) subjects were sedentary (≤4MET-hours/week). Compared to active subjects (≥58 MET-hours/week), sedentary subjects were more likely to be limited (a lot) by tiredness or fatigue (12.6% vs 8.5%), dyspnea (11.9% vs 7.4%), muscle weakness (10.2% vs 5.8%), chest tightness/discomfort (7.4% vs 5.4%) or arthritis (10.8% vs 8.9%). However most sedentary subjects were either not or only a little limited walking 100m (83.2%) and walking 1km or ≥ mile (68.2%). Subjects with ≥3 co-morbidities, (41.2% vs 26.8%), fair or poor rated health (39.2% vs 29.2%) and >70 years old (35.6% vs 30.0%) were more likely to be sedentary than active, but women were not more sedentary (31.9% vs 33.8%). Compared to whites (31.0% vs 36.5%) other race/ethnic groups (4.5% vs 21.7%) were more likely to be sedentary than active as were subjects living in Latin America (55.0% vs 17.5%) and Asia (49.4% vs 21.2%), and those with <8 years of education (41.6% vs 26.8%).

Conclusion: Exertional symptoms do not limit most sedentary patients with CHD. Socio-economic, geographic and cultural factors are likely to be important determinants of PA.

Fatter - but fitter? Leisure time physical activity and estimated peak oxygen uptake in a Norwegian population 1964-2008. The Nord-Trondelag Health study (HUNT 1-3)

T. Moholdt, B. Nes, U. Wilsolf. Norwegian University of Science and Technology, Trondheim, Norway

Purpose: As all western countries experience an increase in the prevalence of overweight and obesity, one could expect a decrease in leisure-time physical activity (LTPA) level. The aim of this study was to describe changes in LTPA in a general Norwegian population from 1984-86 to 2007-08, and to analyze these changes in relation to changes in body mass index (BMI), resting heart rate, blood pressure and estimated peak oxygen uptake (VO2peak) in the same time period.
We hypothesized that the population had become fatter, but to exercise more, and hence become fitter during this time period.

Methods: We used data from the Nord-Trondelag health study (HUNT, part 1-3), with data on self-reported LTPA amount and intensity from 61 547 subjects in HUNT1 (1984-1986) and from 42 753 subjects in HUNT3 (2007-2008). We compared LTPA in subgroups of participants, according to gender, age, and BMI, and considered LTPA-data in light of population changes in BMI, blood pressure and resting heart rate. VO2peak was estimated based on direct measurement in 4631 subjects in HUNT3, using gender, age, resting heart rate, BMI and physical activity as predictors.

Results: The main changes in physical activity from 1984-1986 to 2006-2008 include a decline in the proportion of the population reporting < once weekly LTPA (from 41.0% in HUNT1 to 21.8% in HUNT3), and an increase in the proportion reporting ≥ twice weekly LTPA (from 35.0% in HUNT1 to 56.7% in HUNT3). In this time period, BMI (in kg/m²) increased from 25.2 (SD 3.9) to 27.1 (SD 4.4). Resting heart rate (in beats/min) decreased from 74.7 (SD 12.5) to 70.4 (SD 11.7), and systolic and diastolic blood pressure (in mmHg) decreased from 136.5 (SD 23.5) to 130.8 (SD 18.5) and from 84.6 (SD 11.6) to 73.5 (SD 11.2), respectively. We saw similar increases in frequency, duration and intensity of LTPA across genders, age groups and BMI subgroups from HUNT1 to HUNT3. Estimated VO2peak (in mL/min/kg) decreased significantly from 43.4 (SD 7.8) to 40.9 (SD 6.5) for men and from 34.0 (SD 5.6) to 32.6 (SD 7.4) in women.

Conclusion: Although self-reported LTPA increased in a Norwegian population from 1984-1986 to 2006-2008, BMI increased, and fitness decreased in the same time period. We think these changes are due to increased sedentary time.

InVESTIGATIONS FOR BETTER HEALTH CARE

Short TErn Psychotherapy IN Acute Myocardial Infarction (STEP IN AMI) Trial. Final results from a randomized trial

A. Roncella1, C. Pristipino1, C. Ciarroccca1, V. Pasceri1, D. Inni1, S. Scorza1, A. Varven1, J. Denollet2, S.S. Pedersen3, G. Speciale1.

Background: Psychosocial factors play an important role in the pathophysiology of acute myocardial infarction (AMI) however, it is not known if a psychotherapy after medical and interventional treatment of myocardial infarction may be beneficial on cardiovascular prognosis.

Aim: To assess the effects of a short-term psychotherapy (STP) on the clinical outcomes of patients (pts) who underwent an angiography angioplasty for AMI.

Methods: One week after an emergency angioplasty performed for their first AMI, 101 consecutive pts were randomised to medical therapy (MT group: 47 pts) or to MT+STP (STP group: 54 pts). STP consisted of individual and group meetings over a 6 months interval after AMI onset. The clinical follow-up visits were scheduled at 6 months and 1 year while psychometric tests (for evaluation of stress level, vital exhaustion, depression, social support, quality of life, main life events before AMI, Type D personality) were scheduled after 1 year. The main changes in physical activity from 1984-1986 to 2006-2008 include a decline in the proportion of the population reporting < once weekly LTPA (from 41.0% in HUNT1 to 21.8% in HUNT3), and an increase in the proportion reporting ≥ twice weekly LTPA (from 35.0% in HUNT1 to 56.7% in HUNT3). In this time period, BMI (in kg/m²) increased from 25.2 (SD 3.9) to 27.1 (SD 4.4). Resting heart rate (in beats/min) decreased from 74.7 (SD 12.5) to 70.4 (SD 11.7), and systolic and diastolic blood pressure (in mmHg) decreased from 136.5 (SD 23.5) to 130.8 (SD 18.5) and from 84.6 (SD 11.6) to 73.5 (SD 11.2), respectively. We saw similar increases in frequency, duration and intensity of LTPA across genders, age groups and BMI subgroups from HUNT1 to HUNT3. Estimated VO2peak (in mL/min/kg) decreased significantly from 43.4 (SD 7.8) to 40.9 (SD 6.5) for men and from 34.0 (SD 5.6) to 32.6 (SD 7.4) in women.

Conclusion: Although self-reported LTPA increased in a Norwegian population from 1984-1986 to 2006-2008, BMI increased, and fitness decreased in the same time period. We think these changes are due to increased sedentary time.

High-intensity interval training activates telomerase and reduces p33 expression

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Background: The cellular effects of physical activity may involve a beneficial influence on the aging process by telomeres and senescence factors. Aging on the cellular level depends on the activity of telomerase, which counteracts telomere erosion. We tested the hypothesis that a controlled, high-intensity interval running exercise may activate cellular anti-senescent pathways in untrained healthy subjects.

Methods and results: N=10 subjects without regular physical exercise and with normal exercise capacity (age 44 years, BMI 24 kg/m²) were subjected to a supervised high-intensity interval running exercise for 3 months. Before the first training, systolic and diastolic blood pressure (in mmHg) decreased from 138.5 (SD 23.5) to 134.6 (SD 18.5) and p33 expression was increased from 10.6 ± 1.5km/h pre-training to 11.8 ± 2.2km/h post-training (p<0.03) and PWCV150 (physical working capacity at 150 beats/min) increased from 6.6 ± 1.4km/h to 7.4 ± 1.6km/h (p<0.02).

Conclusion: The data of this pilot study suggest that a controlled high-intensity interval training for three months leads to an increase in telomerase activity and a reduction in the expression of senescence markers in circulating blood cells in healthy subjects without relevant training experience. In concert with previous studies, these findings set the stage to address the question which training modality, intensity and duration are optimal to exert vascular “anti-aging effects” and whether monocyte senescence proteins are useful markers of the preventive modality, intensity and duration are optimal to exert vascular “anti-aging effects” in healthy subjects without relevant training experience. In concert with previous studies, these findings set the stage to address the question which training modality, intensity and duration are optimal to exert vascular “anti-aging effects” and whether monocyte senescence proteins are useful markers of the preventive...
there were no differences in the level of perceived control. Patients and partners self-assessed knowledge on HF, the medications and prevention of deterioration was significantly higher in the intervention group (p < 0.001).

Conclusions: We have conducted the first major randomised controlled study to examine the long term effects of education and support in dyads. The intervention group scored higher level of physical health than the control group and had better knowledge. Further the effects of the intervention over the 24 months follow up period were minor for the dyads. Additional interventions seem to be necessary to have a higher impact on dyad outcomes.

Results: We detected a large variation in the absolute numbers of PPCI per million population between the different countries with highest use in Germany (Figure 1). The implementation increased with 0.84 to 1.4 per year. Number of physicians per 100,000 population (adjusted β 5.11-11.98) and of acute care beds per 100,000 population (adjusted β 4.29-8.29) were both positively correlated with the use of PPCI.

Conclusions: We found large variation in the use of PPCI between the different countries. The yearly increases in implementation were similar between countries. The random coefficient model revealed a positive correlation between number of physicians and acute care beds with use of PPCI.

Variation in treatment access to primary angioplasty in selected european countries

K. Laut1, T.L. Lash1, S.O. Kristensen1, 1Aarhus University Hospital, Skejby, Department of Cardiology, Aarhus, Denmark; 2Aarhus University Hospital, Skejby, Department of Clinical Epidemiology, Aarhus, Denmark

Purpose: Inequality in access to treatment is a topical issue. Primary Percutaneous Coronary Intervention (PCI) is the recommended treatment for patients with acute ST-segment elevation myocardial infarction (STEMI). However, it is estimated that only 40% to 60% of European STEMI-patients are presently treated with PCI. We studied: 1) the temporal implementation of PCI and variation in access to PCI, and 2) whether characteristics of the country and the healthcare system explains differences in the use of PCI in 12 selected European countries.

Methods: An ecological study based on aggregated data from collected national and international registries in Austria, Belgium, England, Germany, Italy, Portugal, Scotland, Sweden, Northern Ireland and Wales. Main outcome was number of PPCl per 1 million population, collected for the years 2003-2008. The individual country’s yearly increase in implementation of PCI was investigated by use of linear regression. We applied random-effects models to study the relation between usage of PCI and a set of health care-associated and economic county-level parameters.

Comparison of study cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAFETY</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.0±11.0</td>
<td>71.4±8.6</td>
<td>73.0 (65-78)</td>
<td>70 (63-78)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>53.0</td>
<td>64.3</td>
<td>60.3</td>
<td>64.5</td>
</tr>
<tr>
<td>Paroxysmal AF (%)</td>
<td>3.9</td>
<td>32.1</td>
<td>18.9</td>
<td>15.1</td>
</tr>
<tr>
<td>Persistent AF (%)</td>
<td>87.1</td>
<td>32.4</td>
<td>81.1</td>
<td>84.9</td>
</tr>
<tr>
<td>Permanent AF (%)</td>
<td>9.0</td>
<td>35.4</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Mean CHADS2 score</td>
<td>1.9±1.3</td>
<td>2.1±1.1</td>
<td>3.4±0.94</td>
<td>2.1±1.1</td>
</tr>
<tr>
<td>Prior Stroke/TIA (%)</td>
<td>13.1</td>
<td>19.9</td>
<td>54.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Prior AMI (%)</td>
<td>24.6</td>
<td>16.8</td>
<td>16.6</td>
<td>14.5</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>31.8</td>
<td>23.4</td>
<td>40.4</td>
<td>25.0</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>72.5</td>
<td>78.8</td>
<td>90.3</td>
<td>87.3</td>
</tr>
<tr>
<td>Cognitive impairment (%)</td>
<td>70.0</td>
<td>--</td>
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</tr>
</tbody>
</table>

Conclusions: Data from the SAFETY cohort highlight potentially important demographic and clinical differences that may impact on benefit to risk ratios when applying newly approved anti-thrombotic therapies in ‘real world’ patients with chronic AF.

Do clinical trial cohorts reflect the complexities of real-world patients with chronic atrial fibrillation?

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Purpose: Recent regulatory approval of novel anti-thrombotic agents used to treat patients with Atrial Fibrillation (AF) offer significantly improved options for the prevention of thrombo-embolic events. However, the conundrum of maximising benefit and minimising risk are potentially different when considering the complexity of ‘real world’ high risk, hospitalised patients with AF.

Methods: We undertook a like-for-like comparison of the patient cohorts of 3 seminal clinical trials (RE-LY, ROCKET-AF and ARISTOTLE) which tested the most recently introduced novel anti-thrombotic agents (Dabigatran, Rivaroxaban, Apixaban) with the patient cohort of the Standard versus Atrial Fibrillation specific management (SAFETY) study. SAFETY is a multicentre, randomised controlled trial of AF-specific, nurse-led intervention versus usual post-discharge care for the optimal management of patients with AF.

Results: We summarised the key baseline characteristics of each clinical trial and compared these with the SAFETY cohort. Although similar in many respects there were potentially important differences (e.g. more women with AF in SAFETY). None of the clinical trials reported on cognitive function: in SAFETY 70% were found to have some form of cognitive impairment.

Conclusions: The nationwide French campaigns to assess quality of discharge prescription reveal a temporal trend towards an increase in quality between 2008 and 2010, identify factors of variation, and permit public reporting of centre benchmarking.

Hospital ranking based on discharge prescriptions after acute myocardial infarction. A national assessment over 3 consecutive years

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Background: Assessment of quality of care and hospital benchmarking are of paramount importance. We report results of 3 consecutive campaigns implemented by the French National Authority for Health to measure Quality Indicators (QIs) for management of Acute Myocardial Infarction (AMI).

Methods: Specific QIs were defined to evaluate discharge prescriptions. Appropriate prescription (AP) was defined as prescription in the absence of documented contra-indication, or non prescription in case of contra-indication. AP was recorded for aspirin, clopidogrel, beta-blocker, ACEI (in patients with left ventricular ejection fraction <0.40) and statins. In all French centres, up to 100 randomly selected files were examined. A composite indicator (“all-or-none” method) was used to rank centres into above average, average and below average categories.

Results: In total, 39777 records were examined from 291 centres in 2008 (n=14644), 2009 (n= 11638) and 2010 (n= 13495). Average AP rates were 97.9% for aspirin, 94.2% for clopidogrel, 89.3% for beta-blockers, 89.4 for ACEI, 93.3% for statins and 72.9% for the composite, with a significant increase from 2008 to 2010. Volume of activity and centre type were related to quality of discharge prescription. Benchmarking using the composite was possible for centres with >30 cases per year (35711 records). Compared to the national mean, the proportion of centres in the top category was 33.3% to 41%, and in the bottom category from 17.9% to 23.4%. The composite indicator and category were used for public reporting.
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Eliminating creatinine kinase-mb (CKMB) in ruling out acute myocardial infarction (MI) when troponin (Tn) is available can lead to saving hundreds of millions of healthcare dollars.

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**Background:** According to the Joint ESC/ACC/AHA/WHF Task Force, Tn is the preferred marker for the diagnosis of acute MI. However, it is still common practice to order both serial CKMB and Tn to rule out acute MI. Our hypothesis is that most clinicians only use Tn and not CKMB in further management decisions when both test results are available.

**Methods:** At our large regional academic medical center 65,950 patients who presented to the Emergency Department (ED) during a 5 year period (01/01/05 to 12/31/10) were included. A total of 20 sets of Tn and CKMB were obtained and the analysis of the results was performed. To determine cell death, cardiomyocytes were co-loaded with propidium iodide and Annexin V. Heart rate, systolic blood pressure, creatinine, troponin, CKMB, and lactate dehydrogenase (LDH) were also measured.

**Results:** Our results show that there was no statistically significant difference between the two groups in further testing and disposition pathways based on CKMB results (See Table 1).

**Conclusions:** Of 9,605 patients admitted to our Clinical Decision Unit, with the express purpose of ruling out acute MI. These patients were then divided into Group 1 (9204 patients - normal serial Tn and CKMB): mean age 57.33 years, males 45.22%, Caucasian 72.11%, African-American 22.36% and Group 2 (401 patients - normal serial Tn and elevated CKMB): mean age 58.33 years, males 72.62%, Caucasian 67.58%, African-American 27.37%. Results from the two groups indicate that no statistically significant difference between the two groups in further testing and disposition pathways based on CKMB results (See Table 1).

**UPDATE ON CARDIOPROTECTION IN EXPERIMENTAL STUDIES**

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Intramycocardial lipids affect the cardiac TGFβ1/Smad signaling pathway regulating cardiac healing post-myocardial infarction

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**Purpose:** Autopsy and non-invasive imaging-studies in humans have shown lipid accumulation in the scar tissue of patients with a history of myocardial infarction. Its origin and clinical significance remains unknown. As such, whether intramyocardial lipid deposition affects the fibrotic remodeling process and cardiac performance post-myocardial infarction (MI) has yet to be addressed. We hypothesize that intramyocardial lipids attenuate the signaling pathways involved in the fibrotic response post-MI impairing cardiac healing and performance.

**Methods and Results:** Pigs (n=24) were fed 10-days a high-cholesterol diet (HC) or regular chow (NC) before balloon-induced MI and, upon revascularization (HC/R-). At sacrifice, tissue from scar, ischemic, and non-ischemic myocardium was obtained for molecular/cellular/histopathological analysis. Infarct size and cardiac function (echocardiography assessment) were evaluated. At the time of infarction HC animals showed impaired coronary vasodilation assessed by coronary-flow Doppler. A higher incidence of ventricular dysrhythmia (P<0.05 vs NC). Intramyocardial lipids were absent in HC/R-. In HC/R+ higher lipid content was found in the jeopardized myocardium (intracellularly and the interstitial space: p<0.05) than in NC/R+ animals. Intramyocardial lipid deposits were ApoB-, cholesterylester-, and triglyceride-rich (P<0.005). HC/R+ animals also showed a 3-fold downregulation of TGFβ1/Smad2/3 signaling (Fig. 1). Series 1 (young): Control (Con) was untreated. Different doses of PKA activator forskolin (For, 10, 30, 100 and 300 μg/kg). Series 2 (young): Con and different doses of mBKCa activator NS1619 (NS; 0.3, 1, 3, 10 and 30 μg/kg/min). Series 3 (aged): Con, For30; For300, NS10, NS30. Infarct sizes were measured by TTC staining. In addition, CAMP levels (ELISA) and phospholamban phosphorylation (pPLB, western blot) as marker of PKA activity were analyzed 5min after For30 or vehicle. Statistic: ANOVA followed by Tukey's post hoc test: p<0.05.

**Conclusions:** In young animals, both forskolin and NS1619 reduced infarct size (Fig. 1A+). In aged animals, forskolin did not reduce infarct size while NS1619 initiated cardiac protection (Fig. 1C). For30 increased CAMP both in young (5.3±0.6 vs. 4.3±0.4 pmol/mg protein) and aged (5.1±1.2 vs. 3.4±0.5 pmol/mg); pPLB was increased For30 both in young (2.4±0.7 vs. 1.1±0.4) and aged (2.4±1.3 vs. 0.9±0.5).

**Figure 1. Infarct size**

**PKA activation initiates cardioprotection in young but not in aged animals. This difference is not caused by age-dependent alterations in PKA regulation. Activation of mBKCa might be a therapeutic strategy to protect the aged heart.**

**5237**

Protecting the aged heart by activation of mBKCa channels

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**Protection by preconditioning is lost with increasing age, but opening of mitochondrial Ca2+-sensitive K+ channels (mBKCa) might restore protection. An upstream activator of mBKCa is protein kinase A (PKA). We investigated whether 1) the protective effects of PKA- and mBKCa-activation are age-dependent and 2) PKA regulation is altered in the aged heart.**

Experiments were performed according to the “Principles of laboratory animal care” (NIH Publication no. 85-23 revised 1985) and to the national law in young (2-4 months) and aged (20-24 months) Wistar rats. Animals underwent 25min myocardectomy model of hypoxia-reperfusion, and were randomized to 16 groups. Series 1 (young): Control (Con) was untreated. Different doses of PKA activator forskolin (For, 10, 30, 100 and 300 μg/kg). Series 2 (young): Con and different doses of mBKCa activator NS1619 (NS; 0.3, 1, 3, 10 and 30 μg/kg/min). Series 3 (aged): Con, For30; For300, NS10, NS30. Infarct sizes were measured by TTC staining. In addition, CAMP levels (ELISA) and phospholamban phosphorylation (pPLB, western blot) as marker of PKA activity were analyzed 5min after For30 or vehicle. Statistic: ANOVA followed by Tukey’s post hoc test: p<0.05.

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before reoxygenation and was maintained during the first 10 min of reoxygenation. 

**Results:** In control cells, H/R induced mPTP opening at reoxygenation as measured by the drop in calcein fluorescence occurring with a mean time value (TmPTP) of 25±2.3min. Two profiles of fluorescent signal decrease were observed: a rapid (65.8±6.3% of total cells) or a gradual drop (34.2±6.3% of total cells) in calcein fluorescence corresponding probably to either long-lasting (irreversible) opening of mPTP, respectively. H/R-induced mPTP opening preceded cell death as it was followed by plasma membrane permeabilization, as attested by the increase in nuclear staining with propidium iodide. MI strongly and improved cell survival by reducing the number of cells showing long-lasting mPTP opening (-44.5%) with a parallel increase in cells showing transient mPTP opening (+86%) compared to control cells (p<0.05). This shift in the profile of mPTP opening was also observed with TRO40033 which reduced the number of cells (-43%) with a long-lasting profile of mPTP opening with a parallel increase in cells showing transient mPTP opening (+83%).

**Conclusion:** These data suggest that moderate hypothermia and TRO40033 have a similar effect both on the delay of the mPTP opening and the reduction of long-lasting and irreversible mPTP opening during H/R. The shift from long-lasting to transient opening of mPTP appears as a common protective mechanism that could result in the preservation of mitochondrial function and subsequent inhibition of cell death.

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**Genetic deletion of p66Shc adaptor protein leads to increased myocardial infarction size**

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**Background:** Formation of reactive oxygen species (ROS) contributes to many pathological processes. Although ROS production is also involved in some physiological processes, the imbalance between their generation and removal, i.e. oxidative stress, plays a major role in particular in myocardial injury caused by ischemia-reperfusion (I/R). The mammalian Shc locus encodes three Shc isoforms: p46Shc, p52Shc and p66Shc. The p66Shc is not involved in mitogenic signals as p46Shc/p52Shc, but it functions as a critical mediator of intracellular oxidative stress response. Various studies relate p66Shc to cardiovascular disease; however, few data are available on the role of p66Shc in myocardial I/R.

**Methods and Results:** 8-12-week-old male p66Shc deficient (p66Shc-/-) mice on C57Bl/6 wild-type (WT) control mice were subjected in vivo to different durations of ischemia (up to 60 min) followed by 24h of reperfusion. Infarct size was assessed morphologically and by MRI. After 30 min of ischemia, p66Shc-/- mice on C57Bl/6 wild-type background together with corresponding C57Bl/6 mice showed markedly larger infarcts as compared to WT (infarct size [I]/area at risk [AAR]: 20.46±5.02% vs. 7.72±1.31%, n=12-14, p<0.05). This effect was confirmed by measurement of serum cardiac troponin I (cTnI). P66Shc-/- mice showed elevated serum levels of cTnI as compared to WT controls at 24 h of reperfusion (27.2±3.51 ng/ml vs. 10.05±1.3 ng/ml, n=13, p<0.05). However, by increasing ischemia duration to either 45 or 60 min ischemic size did not longer differ between p66Shc-/- and WT mice. Moreover, differently from WT, infarct size in p66Shc-/- was not significantly larger with increasing duration of ischemia (from 30 to 60 min).

**Conclusions:** Our data suggest that genetic deletion of p66Shc leads to an increased sensitivity to myocardial infarction with larger infarcts with shorter, but not prolonged ischemia. Therefore, activation of p66Shc may provide resistance to ischemia and represent a novel therapeutic target in the early phase of myocardial infarction.

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**Ghrelin protects the heart against ischemia-induced arrhythmias by modulating autonomic nerve activity**

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**Background:** Vagal neural stimulation has been postulated to confer an anti-arrhythmic effect. Recently, we demonstrated that ghrelin modulates cardiac autonomic activity and attenuates early left ventricular remodeling in rats after myocardial infarction. In this study, we hypothesized that ghrelin administration would exert an antiarrhythmic effect via modulation of autonomic neural activity in rats after acute myocardial infarction (MI). Second, we evaluated the effect of ghrelin on autonomic neural activity in human subjects.

**Methods and Results:** Male Sprague-Dawley rats were exposed to a 30 minutes of ischemia following ligation of the left coronary artery. Animals were then randomized to receive either ghrelin (n=26) or saline (n=26) during the period of coronary ligation. Power spectral analysis of heart rate variability revealed that the administration of ghrelin increased the high-frequency (HF) power and decreased the low-frequency (LF)/HF ratio of heart rate variability. Ventricular tachyarrhythmias were less frequent in rats after MI who received ghrelin in comparison to rats who received saline. Immunoblotting revealed that rats given saline alone during MI exhibited a marked reduction in phosphorylated connexin43 (Cx43) within the left ventricle, whereas those that received ghrelin displayed only minor reductions in comparison to rats subjected to sham operation. Immunohistochemistry confirmed that the MI-induced loss of Cx43 was abrogated by ghrelin administration. This effect of ghrelin was diminished by the co-administration of atropine. Blockade of vagal afferents also abolished the antiarrhythmic effect of ghrelin. In 10 human subjects, an intravenous bolus of human synthetic ghrelin (10μg/kg) was administered. Ghrelin significantly decreased the LF/HF ratio of heart rate variability and increased the standard deviation of normal RR intervals (SDNN) and HF. Ghrelin also elicited a marked increase in circulating GH, but not insulin-like growth factor-1.

**Conclusions:** Ghrelin administration reduced ventricular arrhythmias concomitant with prevention of the loss of Cx43 during acute MI. The beneficial effect of ghrelin might be mediated by modulation of cardiac autonomic nerve activity. These data suggest the potential usefulness of ghrelin as an antiarrhythmic agent.

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**Novel synthesized radical-containing nanoparticles augment cardioprotection after ischemia-reperfusion injury via nitric oxide in canine hearts**

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**Purpose:** Although antioxidant nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) have been demonstrated to scavenge free radicals, their short half-life and side effects such as hypotension and bradycardia of TEMPO have limited their clinical application. A radical-containing nanoparticle (RNP) can deliver nitroxyl radicals with prolonged half-life and PH-sensitivity, suggesting that RNP is more effective in ischemic myocardium. We investigated whether RNP reduces infarct size without significant side effects in dogs and whether nitric oxide (NO) is attributable to the cardioprotection of RNP.

**Methods:** After the randomization to either RNP (n=6) or control group (n=8), the left anterior descending coronary artery of the dog was occluded for 90 minutes followed by reperfusion for 6 hours. Either RNP (3mg/kg) or saline was infused into a systemic vein for 5 min before reperfusion respectively. We evaluated the spectra of RNP using the electron paramagnetic resonance assay. The levels of NO of coronary venous and arterial blood were assessed. Risk area and infarct size were assessed after reperfusion.

**Results:** Hemodynamic parameters did not differ between the two groups. Nevertheless, RNP reduced infarct size normalized by risk area (21.0±4.09% vs. 40.1±8.18%, p<0.05). The differences in NO levels between coronary venous and arterial blood increased in RNP group (7.56±3.35 μM vs. -3.82±1.05 μM, p<0.05). There were no differences in either risk area or collateral flow between the two.
MEDICAL THERAPY FOR CORONARY ARTERY DISEASE: DEFINING OUR TREATMENT OPTIONS

5242 Betablocker use in patients with chronic pulmonary disease during acute phase of myocardial infarction. Insights from Euro Heart Survey Acute Coronary Syndromes III

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Background: Chronic Pulmonary Disease (CPD) is commonly considered as a contra indication for betablocker treatment (BB), even though the risk of ischemic complications and heart failure is greater than the risk of asthmatic complications. Using data from EHS-ASC III, we determined the impact of betablocker use in patients with a history of CPD.

Methods: EHS-ASC III included patients with ACS between 2006 and 2008 from 138 centres in 36 countries. Recorded variables corresponded to the CARDS dataset, including history of CPD. Baseline characteristics, management and in hospital death were compared between groups according to CPD status. Multivariate regression was used to determine the impact on in-hospital death of betablocker use in patients with vs without CPD, adjusted for baseline characteristics and treatments.

Results: Among 16,269 patients, 1279 had a history of CPD and a final diagnosis of acute MI. Patients with CPD were on average 5 years older, had more diabetes, hypertension, previous MI, stroke, heart and renal failure and had a higher GRACE risk score. They less often received aspirin, clopidogrel and BB. In-hospital death was almost twice as high in CPD patients (10.2% vs 5.7%, p<0.0001). Among patients with CPD, 54% received BB, and use of BB was associated with lower mortality (figure). Multivariate analyses showed a 60% higher mortality in CPD patients without BB. The benefit of BB in CPD patients was more associated with lower mortality (figure). Multivariate analyses showed a 60% higher mortality in CPD patients without BB. The benefit of BB in CPD patients was more associated with lower mortality (figure).

Conclusions: Patients with a history of CPD and acute MI have higher in-hospital mortality. Even though betablockers are less used in this group, they are associated with lower mortality. However, further research is needed to confirm these findings.

5244 Addition of proton pump inhibitors to clopidogrel may effectively reduce upper gastrointestinal bleeding without increases in adverse events: a meta-analysis of randomised controlled trials

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Background: To date, although several meta-analyses have been conducted regarding the effects of proton pump inhibitors (PPI) on clinical outcomes in patients receiving clopidogrel, the findings have been inconclusive between randomised controlled trials (RCT) and observational studies. One possible reason includes the presence of few RCT comparing patients directly randomised to either PPI or control group.

Methods: To investigate the clinical effects of PPI added to clopidogrel, a meta-analysis was performed on RCT comparing patients with coronary artery disease or stroke randomised to clopidogrel with or without PPI administration. Databases searched for RCT included PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, escardio.org, poronline.com, the U.S. National Institute of Health, and TCTMD.com.

Results: A total of 5 RCT were included in this meta-analysis, involving 5076 patients (2542 patients were randomised to PPI and 2534 patients were control). Up to 6 months, PPI administration showed a similar incidence of all-cause death (odds ratio (OR): 1.00, 95% confidence interval (CI): 0.90-1.10, p=0.91), myocardial infarction (OR: 1.10, 95% CI: 0.50-2.09, p=0.77), or stroke (OR: 0.97, 95% CI: 0.31-2.99, p=0.94) compared with control. On the other hand, the incidence of upper gastrointestinal bleeding was significantly reduced in the PPI group compared with the control group (figure). Heterogeneity across an individual RCT was not observed by the Cochran’s Q test (p=0.10 for each outcome).

Conclusions: In this meta-analysis, PPI added to clopidogrel was associated with a significant reduction in upper gastrointestinal bleeding without any increase in all-cause death, myocardial infarction, or stroke in patients with atherothrombosis.
Predictors of non-adherence to dual antiplatelet therapy after percutaneous coronary intervention in a large multinational registry

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**Purpose:** Multiple clinical and sociodemographic factors are associated with non-adherence to dual antiplatelet therapy after percutaneous coronary intervention (PCI). We investigated the major correlates of non-adherence in a large contemporary multinational study.

**Methods:** This analysis was derived from the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Regimens in Steentjes Patients) registry, a multicenter prospective registry of PCI patients. Our primary outcome was the self-reported incidence of non-adherence to either aspirin or thienopyridine at 6 months. Independent variables included baseline demographics, co-morbidities, and clinical presentation. Selection of candidate variables as predictors of non-adherence was performed using backward stepwise selection on a multivariable logistic regression model. The significance levels for removal and addition of covariates were 0.1 and 0.2, respectively. We restricted this analysis to those patients who had received a drug eluting stent (DES).

**Results:** Among 5033 patients, the average age was 64 years, 74.5% were male, and 40.9% presented with ACS. At 6 months, the overall incidence of non-adherence in 4216 DES patients was 6.4%. Univariate analysis revealed that female gender, dyslipidemia, higher education, and prior coronary artery bypass graft (CABG) were associated with better adherence. Increasing age was associated with non-adherence. The results of the multivariable model are tabulated.

**Conclusions:** Routinely collected biomarkers in the electronic health record can reliably be used to assess long-term risk in stable CAD patients to monitor treatment benefit and target patients for more invasive prognostic tests.

Table 1. Multivariable analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.01-1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.74 (0.59-0.93)</td>
<td>0.011</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>0.69 (0.46-1.03)</td>
<td>0.067</td>
</tr>
<tr>
<td>Secondary Education Level</td>
<td>0.75 (0.58-0.96)</td>
<td>0.024</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.37 (0.18-0.79)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Development of clinical risk score for predicting cardiac events in patients with vasospastic angina - a report from the multicenter registry study by the Japanese coronary spasm association

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**Purpose:** Previous studies demonstrated various predictive factors of cardiac events (e.g., smoking and organic stenosis) in patients with vasospastic angina (IVA). In this report, we aimed to develop a new clinical risk prediction score in patients with IVA that takes into account the various factors associated with the development of cardiac events and their accumulation in individual patients.

**Methods:** The VISA database of the multicenter registry study by the Japanese Coronary Spasm Association (n=1429; median 6 years; median follow-up of 32 months) was utilized for score derivation. Multivariable Cox proportional hazard model was used to select the correlated factors of major adverse cardiac events (MACE). They were subsequently weighted according to the adjusted hazard ratio (HR) and integrated into the scoring system.

**Results:** Six variables selected from Cox model were weighted: smoking (2 points), angina at rest (2 points), life-threatening arrhythmia during angina (2 points), multivessel spasm (2 points), organic stenosis (2 points) and ST elevation during angina (1 point). According to the total score, 3 risk strata were defined: low (score 0-3, n=715), intermediate (score 4-6, n=496) and high (score 7-9, n=50). The incidence of MACE in the low-, intermediate- and high-risk patients were 2.8%, 8.3% and 20.0%, respectively (P<0.001). Kaplan-Meier curve for MACE showed prognostic utility of the scoring system throughout the follow-up period.
Impact of interventional versus conservative approach on 5-year mortality of patients with stable angina and documented coronary artery disease in clinical practice: results of the Star-Registry

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Background: Approximately 1.6-3.2 Mio patients in Germany suffer from stable angina (AP). Little is known about the impact of interventional versus conservative treatment on long-term outcome of patients with coronary artery disease (CAD) and stable angina in clinical practice.

Methods: Between Sept 2001 and March 2003, a total of 2,002 consecutive patients with AP and first angiographic diagnosis of CAD were enrolled in the STAR-Registry. We examined the impact of an initial interventional (INTERV) versus conservative (CONSERV) treatment approach on 5-year-mortality of stable CAD in clinical practice in Germany.

Results: At the time of first angiographic diagnosis of CAD in patients with stable AP, 926 patients (46.3%) were initially treated with PCI (INTERV). These patients were younger, less often had prior MI, diabetes and multi-vessel disease and impaired LV-function as compared to CONSERV treated patients. INTERV patients were more likely to undergo repeated subsequent PCI during the 5-year follow-up (50.4% vs 18.2%), and less likely to refer to CABG (11.2% vs 53.9%). INTERV patients had a lower 5-year-mortality (17.0% vs 20.6%, univariate analysis). After correction for differences in baseline characteristics and treatment over time using propensity score analysis, no difference was found in 5-year-mortality between INTERV and CONSERV (OR 1.0, 0.77-1.31).

Conclusion: About half of the patients with stable AP and first angiographic diagnosis of CAD in Germany were treated interventional. After 5-year follow-up no differences could be observed between patients with initial interventional versus conservative treatment in clinical practice.

Coronary microvascular dysfunction after elective percutaneous coronary intervention: correlation with exercise stress test results

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Purpose: Previous studies showed that exercise stress test (EST) is poorly reliable in predicting restenosis after percutaneous coronary interventions (PCIs); some studies also showed that coronary microvascular dysfunction (CMVD) is present in the territory of the treated vessel. We assessed whether EST results are related to the presence of CMVD in patients undergoing elective PCIs.

Methods: We studied 29 patients (age 64±6 years, 23 M) with stable coronary artery disease and isolated stenosis (>75%) of the left anterior descending (LAD) coronary artery, undergoing successful PCI with stent implantation. EST and assessment of coronary microvascular function were performed 24 hours, 3 months and 6 months after PCI. Coronary blood flow response (CBFR) to adenosine and to cold-pressor test (CPT) was assessed in the LAD coronary artery by transonic Doppler echocardiography.

Results: CBFR to adenosine is shown in the figure. Early after PCI, patients with EST-induced ST-segment depression (EST) had a lower CBFR to adenosine compared to those without ST (1.65±0.4 vs. 2.11±0.4, respectively, p=0.003). At 3-month and 6-month follow-up EST-induced ST occurred in 12 (41%) and 13 (44%) patients, respectively. Patients with positive EST had lower CBFR to adenosine compared to those with negative EST (3 months: 1.69±0.3 vs. 2.20±0.3; 6 months: 1.66±0.2 vs. 2.32±0.3; p<0.001 for both). CBFR to CPT did not significantly differ at 24 hours and 3 months after PCI, but was lower in patients with positive compared to those with negative EST at 6 months (1.42±0.2 vs. 1.86±0.4; respectively, p=0.001).

Conclusion: Positive EST after elective successful PCI consistently reflects impairment of hyperemic CBF due to CMVD, which persists over a follow-up period of 6 months.

Invasive findings in patients with angina equivalent symptoms but no coronary artery disease; results from the Heart Quest cohort study

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Background: The cause of angina in patients presenting at coronary angiography without significant coronary artery disease (CAD) has not been systematically assessed in a large prospective cohort. This study aimed to identify the cause of angina in these patients.

Methods: This prospective cohort comprised 718 consecutive patients with angina equivalent symptoms and no CAD (defined as no coronary stenosis ≥50%) between January 1st 1997 and July 31st 2008. All patients underwent additional invasive testing (intracoronary acetylcystein administration, fast atrial pacing). Small vessel and vasospastic disease were diagnosed according to symptoms and vessel reaction during testing.

Results: Mean age was 56.3±11.0 years (range 15 to 81 years). A majority of 431 patients (60.0%) had small vessel and/or vasospastic disease (233 patients had small vessel disease, 145 vasospastic disease and 53 a combination of both). Additional 87 patients (12.1%) had another cardiac disease. Only in a minority of 200 study participants (27.9%) the symptoms were attributed to an extracardiac problem. Patients with small vessel disease were more likely to be female, to have hypertension, to have a family history of CAD and to have effort-related symptoms. Patients with vasospastic disease were more likely to be current smokers, to have angina at rest or to present as myocardial infarction, and to have coronary sclerosis and/or endothelial dysfunction.

Conclusion: In a majority of patients with angina but no significant CAD, a cardiac cause of their symptoms can be found. Systematical invasive testing may help optimizing the medical management of these patients. Study registered at ClinicalTrials.gov (NCT01318629)

Do United Kingdom guidelines for the assessment of suspected angina underestimate the likelihood of coronary artery disease and major adverse cardiac events?

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Purpose: In March 2010, the National Institute for Health and Clinical Excellence (NICE) released guidelines for the investigation of chest pain of recent onset.
These guidelines recommend clinical assessment and risk stratification within a diagnostic algorithm. Patients with pain considered ‘non-anginal’, and those with atypical/typical anginal pain but a likelihood of coronary artery disease (CAD) < 15% are not routinely recommended for cardiac investigation. This study sought to assess whether clinical outcomes support these patients being considered at low risk of CAD.

Methods: 557 consecutive patients (50.4% male; median age 55yrs) attending rapid access chest pain clinics (RACPC) at two hospitals were risk stratified using NICE criteria. Frequency of admission with suspected angina, diagnosis of CAD and incidence of major adverse cardiac events (MACE: myocardial infarction (MI), cerebrovascular accident (CVA), emergency recatharrization or cardiac-related death) were compared for all risk categories at six months.

Results: Of 360/557 patients with ‘non-anginal’ pain, 14 (3.9%) were subsequently admitted with angina, 34 (9.4%) were diagnosed with CAD, 3 (0.8%) with MI and 2 (0.6%) with CVA. This group accounted for 36.9% of all patients diagnosed with CAD and 38.5% of all patients with MACE. Of 10/557 patients with atypical/typical anginal pain and a likelihood of CAD <10%, 1 (10%) was diagnosed with CAD. None were admitted with angina or diagnosed with MACE. This group accounted for 1.1% of all patients diagnosed with CAD.

Conclusions: This study suggests one in ten patients routinely excluded from cardiac investigation by the NICE algorithm have CAD and just over one in a hundred meet the criteria for a MACE episode. Although these patients are considered low risk, they account for one third of adverse cardiac events in patients attending RACPC.

**UNDERSTANDING AND IMPROVING CARDIAC PERFORMANCE**

**5254 Therapeutic hypothermia exerts beneficial effects on cardiac performance in patients after out of hospital cardiac arrest**

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Accumulating evidence indicates that mild therapeutic hypothermia is beneficial in patients resuscitated successfully after cardiac arrest since it appears to improve neurological outcome. Based on these results, the International Liaison Committee on Resuscitation recommends moderate hypothermia in these individuals. However, the optimal cooling method (surface vs. intravascular) is not specified in current guidelines. Since most of these patients suffer from a substantial heart disease the hemodynamic effects of cooling may be of importance in the short term. In this trial, we analyzed the hemodynamic response to moderate hypothermia in patients treated with different cooling methods (surface vs. intravascular).

All study subjects (n=63) received standard care at the discretion of the treating physician and where randomly assigned to either intravascular (n=40) versus surface cooling (n=23). The patients were monitored by virtue of an arterial line and a pulmonary artery catheter which provided continuous cardiac output as well as mixed venous oxygen saturation measurements. In patients with intravascular cooling target temperature of 33 °C was reached after 100 minutes as compared to a reached minimal temperature of 32.5 °C established after 436 minutes in patient with surface cooling. The hemodynamic parameters at this time were recorded in both groups. Invasive cooling resulted in a higher systemic vascular resistance index (733.6 vs. 505.1 dyn/cm²·m², p<0.001). Moreover, a marked reduction of the heart rate (67.7 vs. 98.2 bpm, p<0.001), a higher mixed venous oxygen saturation (78.4 vs. 69.9%, p<0.001), a significant higher stroke volume index (43.0 vs. 30.0 ml/m², p<0.008) was evident. Notably, intravascular cooling dynamic effects pulmonary vascular resistance index was not altered (72.4 vs. 115.0 dyn/cm²·m², p=0.02) as compared to external cooling. Despite these positive hemodynamic effects pulmonary vascular resistance index was not altered (72.4 vs. 72.4 dyn/cm²·m², p=ns). Importantly, in both groups vasoactive drugs were applied in almost identical doses.

These data suggest that mild hypothermia achieved by intravascular cooling as compared to surface cooling results in a more rapid induction of target core temperature and should therefore be preferred. Furthermore, mild hypothermia exerts beneficial hemodynamic effects and might be viewed as an adjunctiropathic therapy avoiding the undesired side effects of vasoactive substances.

**5255 Non-invasive regional work reflects myocardial metabolic demand in patients with left bundle branch block**


Background: Left bundle branch block (LBBB) causes heterogeneous left ventricular (LV) work distribution. The aim of cardiac resynchronization therapy (CRT) is to synchronize LV contraction to improved pump function and reverse remodeling. Therefore, assessing regional work is of great interest in this patient group. In the present study we calculate regional work by a previously validated noninvasive method using strain by speckle tracking echocardiography (STE) and non-invasively estimated LV pressure (LVP) and assess its ability to reflect regional metabolism by FDG-PET.

Methods and Results: Six patients with LBBB (QRS 165±16 ms, mean±SD) and no coronary disease were studied. Segmental strain was measured by STE, and estimated LV pressure curve was calculated using a standard waveform fitted to the relevant cardiac cycle using valvular timing by ultrasound. Brachial cuff pressure was used to scale systolic pressure. Work was calculated as area of the pressure-strain loops. PET acquisition was started 60-80 min after intravenous administration of FDG, with 8 gates per RR interval. The correlation between segmental values of the loop area and FDG uptake for all patients was r=0.81 with an individual range of 0.70-0.87. The figure shows bull’s eye plots for regional glucose uptake (A) and non-invasive pressure-strain loops (B) and the respective correlation (C) in one of the patients.

Conclusions: This study suggests that non-invasively estimated LV pressure-strain loops reflect regional metabolism in patients with LBBB.
Left ventricular dyssynchrony induced by chronic right ventricular pacing is associated with long-term poor outcome

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Background: Right ventricular apical (RVA) pacing may induce left ventricular (LV) dyssynchrony. The long-term impact of LV dyssynchrony induction was further evaluated in cohort of patients who underwent RVA pacing.

Methods: A total of 169 patients (mean age 62±13 years, 69% male) were included. Echocardiographic evaluation of LV volumes, ejection fraction and dyssynchrony were performed before and after device implantation. LV dyssynchrony was assessed by 2-dimensional radial strain speckle tracking echocardiography. Patients were followed-up for all-cause mortality, heart failure hospitalization (HFH) and a combined outcome of death or HFH for a median duration of 70 months (interquartile range 42-96 months).

Results: Baseline mean LV ejection fraction was 51±11%. Median LV dyssynchrony value was 40 ms (12-85 ms) before RVA pacing and increased to 91 ms (81-138 ms) after median of 13 months (3-26 months) after RVA pacing. Patients with induced LV dyssynchrony (LV dyssynchrony value >91 ms) showed worse long-term survival (log-rank P<0.001), HFH rates (log-rank P<0.001) and the composite end point of HFH and death (log-rank P<0.001) than patients without induction of LV dyssynchrony (LV dyssynchrony <91 ms) after RVA pacing (see figure). Induction of LV dyssynchrony was an independent predictor of combined event of death or HFH (HR [95% CI]: 3.369 [1.73-6.55], P<0.001).

Conclusion: The LV dyssynchrony induction by RVA pacing is associated with increased all-cause mortality and HFH rates.

Long-term therapy with a partial adenosine A1-receptor agonist improves left ventricular ejection fraction and prevents progressive ventricular dilatation in dogs with chronic heart failure

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Background: Adenosine (AD) elicits cardioprotection through A1-receptor (A1R) activation. Therapy with AD A1R agonists, however, is limited by undesirable actions of full agonism such as bradycardia. We examined the effects of capadenoson (CAP), a partial AD A1R agonist, on left ventricular (LV) systolic function and chamber dilation in dogs with heart failure (HF) (LV ejection fraction, EF <30%).

Methods: 12 HF dogs were randomized to 3 months of oral therapy with CAP (7.5 mg Bid, n=6) or to no therapy (Control, n=6). LV end-diastolic (EDV), and end-systolic (ESV) volumes, EF, heart rate (HR) and arterial pressure (Ap) were measured before (PRE) and 3 months after (POST) therapy. LV tissue obtained after POST was used for histomorphometry to assess volume fraction of interstitial fibrosis (VFF), capillary density (CD), myocyte cross-sectional area (MCSA), and oxygen diffusion distance (ODD). LV tissue from 6 normal (NL) dogs was used for comparison.

Results: In Controls, EDV and ESV increased and EF decreased significantly while HR and Ap did not change. In CAP-treated dogs, EDV, HR and Ap were unchanged, while ESV decreased and EF increased significantly. Compared to NL dogs, HF controls showed increased VFF, ODD and MCSA and decreased EF.

Conclusion: HFH significantly increase a patient’s mortality risk. Haemodynamic management using implantable systems may reduce this risk by reducing HFH in patients while improving their quality of life.

Device Options for Advanced Heart Failure

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Introduction and Objectives: The use of short term ventricular assist devices (VAD) in patients waiting for high urgency (HU) heart transplantation (HTx) in Spain has steadily increased due to longer waiting times and new heart allocation system. It is unknown whether the use of short term VAD support in patients with cardiogenic shock affects the outcome of HTx. We aimed to investigate long-term
outcomes of HU transplanted patients with VAD compared to HU transplanted patients without device support. Methods: We retrospectively evaluated a prospective database of patients who had HU-HTx between 1999 and 2011 in our institution. Actuarial survival rates of HU-HTx patients with and without VAD were studied. Results: From a total of 237 transplanted patients, 55 (23%) were HU-HTx, 19 were listed on VAD support and 39 without VAD. Mean time in the HU waiting list was 6.5±6 days and mean VAD support was 8.4±8 days (1-31 days), 3 VAD patients died before HTx (16%), VAD used were Levitronix Centrimag (6), Abdomen (9) and ECMO (1). After a mean follow-up of 4.6±4.1 years (0-13 yr), 22 patients died (5 in VAD-group and 17 in the non-VAD group). The post-HTx 12-month survival rate was 63% and 69% respectively (p=ns). Kaplan-Meier and Cox regression analysis did not show survival differences, HR 1.11 (95% CI 0.41 to 3.02), p=0.84.

Figure 1

Conclusions: In our experience, long term outcome of patients receiving a high urgency heart transplant under short-term VAD support is comparable to that of patients undergoing HU-HTx without VAD support.

Device options for advanced heart failure

The improvement of cardiac status should be the focus rather than the prevention of worsening renal function in patients admitted for acute decompensated heart failure


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Purpose: The balance between the contribution of the improvement in cardiac status and of the deterioration in renal function to the outcome of patients admitted for acute decompensated heart failure (HF) is unclear. The aim of our study was to investigate to which extent parameters of renal function in combination with NT-proBNP predict outcome.

Methods: Our study population was assembled from six prospective cohorts with in total 1232 patients admitted for acute decompensated HF. The endpoints studied were all-cause mortality and the composite of all-cause mortality and/or readmission for cardiovascular reason within 180 days after discharge. Results: The cumulative mortality was 15% and the composite event rate was 44%. Our bi-variable analysis of renal parameters showed that the absolute eGFR level (<30 mL/min/1.73m2) determines prognosis (all-cause mortality: HR 1.97, 95%CI 1.42-2.75; composite endpoint: HR 1.7, 95% CI 1.39-2.13). A significant reduction in NT-proBNP during hospitalization was not associated with worsening renal function. Moreover, a combined analysis of renal parameters and NT-proBNP shows that an unfavorable NT-proBNP (reduction of ≥30%) during hospitalization may improve the prognosis. Conclusion: The prognostic value of renal function is best represented by the absolute value of eGFR (<30 mL/min/1.73 m2). NT-proBNP is the leading prognostic indicator of adverse events and supersede renal function. Hence, the improvement of cardiac status should be the focus rather than the prevention of renal dysfunction.

Short term effect of adaptive servo-ventilation compared with continuous positive airway pressure on sympathetic nerve activity in patients with heart failure

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Background: Sleep disordered breathing and sympathetic overactivation are common in patients with heart failure (HF). Recently, we have shown that application of adaptive servo-ventilation (ASV) reduced muscle sympathetic nerve activity in patients with an acute decompensated HF.

Methods: Forty-eight patients with HF (ejection fraction <0.45, obstructive apnea index <5.0 h), NYHA II, III and IV were assigned to either ASV (n=32) or CPAP (n=16). MSNA, heart rate, blood pressure and respiration (using electrical bioimpedance) and oxygen saturation level were monitored continuously before and during application of the devices (30 min). Severity of respiratory instability was determined by coefficient of variation of tidal volume (CV-TV).

Results: Although heart rate remained unchanged, the oxygen saturation level was increased during application of ASV and CPAP. CV-TV was improved by ASV (24±14 to 17±8%, p<0.001), but not by CPAP (31±18 to 32±18%, ns). MSNA was decreased in ASV group (64±23 to 59±23 bursts/100 beats, p<0.001), but unchanged in CPAP group (62±22 versus 60±21 bursts/100 beats, ns).

Conclusion: Short term ASV adjusts respiratory instability and reduces MSNA in patients with HF; however, short term CPAP does not. These differential responses might influence the difference in clinical effectiveness between ASV and CPAP.

Implantable cardioverter-defibrillators in ventricular assist device-supported heart failure patients


Purpose: Implantable cardioverter-defibrillators (ICDs) reduce mortality in heart failure (HF). In patients requiring a ventricular assist device (VAD), the benefit from ICD therapy is not well established. The aim of this study was to define the impact of ICD on outcomes in VAD-supported patients.

Methods: We reviewed data for consecutive adult HF patients receiving VAD as a bridge to transplantation from 2003 to 2010. The primary outcome was survival to transplantation.

Results: A total of 82 VADs were implanted (33 left ventricular (LVAD), 49 biventricular (BiVAD), mean age 40±12 years, 80% male, left ventricular ejection fraction 18±9%, 74% dilated cardiomyopathy). Mean length of support was 400 days (range 30–770); 55 patients survived to transplantation. Sixty-five patients had an ICD (25 LVAD, 40 BiVAD). More LVAD patients had an appropriate ICD shock before implantation than after (16 vs 7; P=0.02). There was a trend toward higher shock frequency before LVAD implant than after (3.3±5.2 vs 1.1±3.8 shocks/p). Mean time to first shock after VAD implant was 129±199 days. LVAD-supported patients with an ICD were significantly more likely to survive to transplantation (1-y actuarial survival to transplantation: LVAD: 91% with ICD vs 57% without ICD; BiVAD: 54% vs 47% ICD vs non-ICD on VAD support when appropriate and frequent predicted adverse outcomes and hospitalizations such as aortic regurgitation or right heart failure when on LVAD support.

Conclusions: Shock frequency decreases after VAD implantation, likely owing to ventricular unloading, but appropriate ICD shocks still occur in VAD patients. An ICD is associated with improved survival in LVAD-supported HF patients.

Intermittent versus continuous thoracic spinal cord stimulation for treatment of ischemic heart failure

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Background: Prior experimental studies showed that spinal cord stimulation (SCS) improved left ventricular (LV) function in animal model of ischemic heart failure (HF). Nevertheless, the optimal approach and duration of thoracic SCS is unknown.

Methods: We performed chronic thoracic SCS at T1-T2 level (50 Hz frequency, pulse width 0.2ms) in 30 adult pigs with ischemic HF induced by myocardial infarction (MI) via coronary embolizations of left circumflex artery followed by rapid ventricular pacing for 4 weeks (MI+HF). All animals were treated with daily oral metoprolol (20 mg) plus ramipril (2.5 mg), and randomized into control group (n=10), intermittent SCS (6 hrs x3, n=10) or continuous SCS (24hrs, n=10) for 10 weeks.
Do patients awaiting cardiac transplantation benefit from ICD implantation, propensity matched analysis?

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The limited availability of heart donors together with increase in potential heart recipients numbers result in long waiting time on heart transplantation (OHT) list. Approximately 20% of patients per year die while awaiting for OHT. The aim of our study was to find out if implantable cardioverter defibrillators (ICD) modify the survival in patients qualified for OHT.

Material and Methods: The study group was composed of 658 patients (POLKARD-HF Registry) with severe heart failure (HF), qualified for OHT. The average observation time was 601 days (min. 1 – max. 1462 days). The composite end point consisted of either death or (E-OHT) emergency heart transplantation (UNOS status 1). The comparative analysis was carried out using the propensity matched analysis within 2 subgroups of patients with (ICD+, n=49) and without ICD (ICD-, n=48).

Results: Both subgroups ICD- vs ICD+ did not differ significantly with respect to the etiology (Dilated/Ischemic/Other - 58/31/11% vs Dilated/ischemic/Other – 52/35/14%), age (49±11 vs 48±13 years, respectively); BMI (26±4 vs 25±4 kg/m²); LV EF (21±6 vs 20±6%), LVEDD (75±10 vs 70±17 mm), LVESD (62±15 vs 60±16), HR (77±13 vs 78±16/min), sBP (102±14 vs 101±14 mmHg), dBP (66±11 vs 66±10 mmHg). CI (1.8±0.5 vs 2.0±0.5 l/min), hsCRP (20±68 vs 16±28 mg/l, p<0.005), Na (135±5 vs 134±5 mEq/l), except for NTproBNP level (3489±2872 pg/ml vs 927±1±1105 pg/ml, p=0.04, respectively). Among all parameters in unvariable Cox regression analysis, adjusted to NTproBNP level, the significant association between hsCRP level and survival time (p=0.0081) was found. Based on Kaplan-Meier with the log-rank test we did not find significant difference in the end point free survival time between both subgroups (ICD+ vs ICD-: number of endpoints 10 vs 8 respectively). However in the subgroup with ICD+ (>50% of patients were treated with appropriate ICD interventions).

Conclusions: 1. In end-stage HF patients on OHT list the presence/absence of ICD didn't modify the crude survival rate. However in ICD+ population 50% of patients were treated in appropriate way by ICD intervention. 2. The additional biochemical evaluation - NTproBNP, hsCRP, can help define the high risk group, independently of the presence/absence of ICD.
Relationship between site enrollment and outcomes in acute heart failure: insights from EVEREST trial

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Purpose: To assess if enrollment/site in an acute heart failure (AHF) trial is related to events (cardiovascular mortality or HF hospitalization).

Methods: EVEREST trial data on 4,133 patients enrolled among 395 sites was assessed. Patients were grouped based on enrollment into ≤10, 11-30, and >30 patients/site. Results: Enrollment ranged from 0 to 75/site. Several clinical and regional differences in enrollment (North America 75%, 23%; 2nd: South America 56%, 240%; 20%; Western Europe 78%, 21%, 1%; and Eastern Europe 23%, 50%, 27% for ≤10, 11-30, and >30 patients/site). Baseline characteristics were comparable across regions (P=0.43). After adjustment, enrollments ≤10, 11-30, and >30 patients/site were associated with better survival (HR 1.12; CI 1.03, 1.40 compared to 11-30/site enrollment). This was comparable across regions (P=0.43). After adjustment, enrollments ≤10, 11-30, and >30 patients/site were associated with better survival (HR 1.12; CI 1.03, 1.40 compared to >30 patients/site).

Conclusions: The characteristics and outcomes of patients vary with enrollment. These findings generate the hypothesis that number of patients/site may determine the response to a study drug and should be taken into account.

Self-rated general health is an independent predictor of long term mortality in heart failure

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Purpose: Heart failure (HF) has a large impact on the length and quality of life of patients. Poor quality of life has proven to affect patient outcome in terms of mortality and hospital readmissions. However, little is known about the impact of quality of life on mortality in patients with HF when adjusted for an independent and reliable marker for disease severity. This study examined whether self-rated general health is an independent predictor of long-term mortality and renal dysfunction of B-type Natriuretic Peptide-cutoffs.

Methods: Data were collected as part of the COACH study (Coordinating study of Co-Ace). Patients were enrolled over 2 years at the time of hospital admission for AHF and followed-up for 1 year. At univariate analysis, after computation of both logistic regression analysis testing linearity of predictors and ROC curves, two cut-off values were identified: eGFR < 50 ml/min/1.73m² and BUN ≥ 30 mg/dl. Population was then split into 3 groups according to the selected cut-offs: G1: eGFR yes/BUN yes (n=370), G2: eGFR no/BUN no (n=700), G3: eGFR yes/BUN no (n=114). Patients with BUN ≥ 37 mg/dl (G1 and G4) and a reduced systolic blood pressure at entry and were treated with higher dose of diuretic as compared to G2 and G3. Distribution of events were as follow: In-Hospital death: G1 15.9% vs G2 2.3%, G3 8.1%, G4 6.1%, p<0.001; 1 yr all cause death: see KM curves in the figure.

Conclusion: In AHF association of elevated BUN and reduced eGFR at entry allows to identify a group at higher risk of in-hospital and 1 year mortality, thus confirming that BUN should be considered carefully in AHF management. High dosage of intravenous diuretic and reduced renal efferent pressure may be a sustained stimulus to BUN increase.

Copeptin in heart failure: associations with clinical characteristics and prognosis

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Background: Vasopressin (AVP) is central in the regulation of sodium, water homeostasis and renal function. Whereas measurement of AVP is not feasible in clinical routine, its C-terminal precursor peptide (copeptin) is stable and has
recently been shown to improve diagnosis in the setting of myocardial infarction. Further, elevated copeptin levels correlated with worse outcome in patients with heart failure (HF). We investigated associations of copeptin with clinical characteristics, laboratory parameters, comorbidities and outcome in patients with HF.

**Methods:** 926 patients of the Interdisciplinary Network Heart Failure Study were included (left ventricular ejection fraction (LVEF) ≤ 40%, enrolled prior to discharge after hospitalisation for cardiac decompensation). Besides comprehensive clinical assessment an extensive blood profile was obtained including markers of inflammation, NT-proBNP, and copeptin. Patients underwent serial follow-up after six months intervals.

**Results:** Mean age was 68.±8 years, 71% were male, 44% were in NYHA class III or IV, and mean LVEF was 38.±6%. The median copeptin level was 20.4 (quartiles 12.6 to 56.1) pmol/L. 30% of patients remained in the normal range (< 10 pmol/L). Higher copeptin levels were associated with increased morbidity and mortality (table). Patients in the highest copeptin quartile had a doubled all-cause mortality risk (HR 2.2; 95%CI 1.3-3.8; adjusted for age, sex, NYHA class, renal function).

**Conclusion:** Elevation of copeptin is frequent in HF patients and associated with factors and comorbidities known to adversely affect prognosis. Higher levels of copeptin are independent predictors of increased mortality risk.

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**INTERVENTIONS FOR STRUCTURAL HEART DISEASES, AN UPDATE**

5280

**Efficacy of transcatheter closure of patent foramen ovale assessed by transesophageal echocardiography, impact of device type**

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**Background:** Transcatheter echocardiography (TEE) with bubble testing during Valsalva manoeuvre is a sensitive method to determine closure rates after percutaneous transcatheter device implantation for closure of patent foramen ovale (PFO).

**Methods:** In a prospective observational study 353 patients were selected for 3 and 12 months TEE after device implantation in 10%

**Results:** The prevalence of ASA was significantly different between the devices with 20% for Amplatzer, 16% for BioSTAR, 44% for Cardia and 30% for Premere (p=0.01).

**Conclusion:** Transcatheter left atrial appendage occlusion in atrial fibrillation: a 100 cases single center experience

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**Objectives:** In patients with atrial fibrillation (AF), 90% of embolic strokes originate from the left atrial appendage (LAA). Transcatheter occlusion of the LAA has been proven as an alternative to oral anticoagulation (OAC) in patients with CHADS2 Score ≥ 2.

**Methods:** The Amplatzer Cardiac Plug (ACP) is a modification of Amplatzer shunt occluders. It consists of a lobe with tiny hooks for anchorage in the LAA, a thin waist, and in comparison to other devices, of a disc for sealing the orifice (the LAA, the ACP (singles principle). We report on 100 consecutive ACP patients (age 72.±10 years) with non-valvular AF (mean CHADS2 Score 2.6±1.3, CHADS2-VASc Score 3.7±1.5). The LAA was entered via femoral vein treated, and transseptal access under fluoroscopic control. Diameter of the LAA orifice were determined angiographically and the ACP was deployed via dedicated 9-13F sheaths under fluoroscopy only, i.e. without transesophageal echocardiography (TEE) assistance. The procedure was often combined with other cardiac interventions.

After ACP Implantation, OAC was stopped. Acetylsalicylic acid 100mg/d and clopidogrel 75mg/d were prescribed for ≥3 and 1 months respectively. Follow-up with TEE and neurological evaluation were performed after 3 months.

**Results:** Device sizes ranged from 16 to 30mm (mean 22.8±3.9mm). The LAA was successfully occluded in 98%. Procedural complications occurred as follows: Two cardiac tamponades, one with need for pericardiocentesis (1%) and one with conservative management (1%), device embolization (2%, one needing semi-elective surgery), one air embolization with transient symptoms (1%), one stroke (1%). The procedure was combined with coronary angiography in 65%, coronary stenting in 25%, closure of atrial shunts in 34% and transcatheter aortic valve implantation in 10%.

**Conclusion:** Transcatheter occlusion of the LAA with the Amplatzer Cardiac Plug can be performed as an alternative to OAC with high procedural success rates, acceptable rates of complications, and good results during early follow-up.

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**Clinical and echocardiographic follow-up 2 years after MitraClip therapy for significant mitral regurgitation in high-surgical-risk patients**

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**Background and Objective:** MitraClip implantation is an evolving therapeutic alternative to surgery for patients with significant mitral regurgitation (MR). Several studies to date have demonstrated the safety and mid-term efficacy of this approach, yet long-term data are lacking. In patients deemed not amenable to surgery, we assessed changes from baseline in left ventricular (LV) volumes, ejection fraction, and forward stroke volume (FSV) as well as in NYHA functional class, 6-minute walk distance and patient-assessed quality of life at 2 years after MitraClip therapy.

**Methods and Results:** Of 270 consecutive patients with significant MR (≥3+) who had undergone MitraClip therapy at our center by 31 December 2011, 61 patients had died within 2 years of the intervention and 43 of 187 successfully treated, surviving patients (MR at discharge ≤ 2+; 74% ± 9 years, 29 men) were followed for 23.8±2.9 months. NYHA functional class at baseline was III and IV in 26 (61%) and 17 patients, respectively. At follow-up, NYHA class had improved in 22 patients (74%), with 25 patients (58%) in NYHA class I or II. No change vs. baseline was seen in 9 patients and 2 patients had clinically worsened. Six-minute walk distance assessed in 32 matched patients had improved from a median of 330 m to a median of 330 m (P = 0.0003) and quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire in 33 patients had improved from a median score of 38 to a median score of 26 (P = 0.0067).

**Conclusion:** Transcatheter echocardiographic variables were obtained from all 43 patients. With baseline MR severity 3+ and 4+ in 21 and 22 patients, respectively. MR grade

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**Abstract 5271 – Table 1**

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<td>139 (137; 142)</td>
<td>140 (136; 142)</td>
<td>8.06</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1401 (465; 3222)</td>
<td>2166 (986; 4724)</td>
<td>4187 (1748; 8006)</td>
<td>7864 (2841; 16243)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>7.2 (2.3; 5)</td>
<td>7.8 (2.0; 9.8)</td>
<td>10.2 (3.4; 27.1)</td>
<td>15.8 (5.3; 42.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>31 (27.38)</td>
<td>33 (26.37)</td>
<td>30 (23.35)</td>
<td>30 (25.35)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mortality after 3 yrs</td>
<td>10</td>
<td>12</td>
<td>19</td>
<td>39</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are median (quartiles) or percent.
Interventions for structural heart diseases, an update / New horizons of antithrombotic therapy in atrial fibrillation

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at 2 years was 1+ and 2+ in 8 and 31 patients, respectively, corresponding to improvements over baseline by at least 1 MR grade in 40 and no change in only 3 patients. Statistically significant reductions vs. baseline were observed for LV end-diastolic volume (median 188 ml vs. 212 ml [median relative decrease by 8.4%]; P = 0.015) and LV ejection fraction (median 39% vs. 47% [median relative decrease by 9.4%]; P = 0.0007), but not for LV end-systolic volume (median 117 ml vs. 116 ml; P = 0.422). PSV had increased significantly by 15.6% from a median of 48 ml to a median of 56 ml (P = 0.0035).

Conclusions: MitraClip therapy appears to entail marked clinical improvement in the majority of successfully treated high-risk patients surviving out to 2 years. Reduced MR severity is sustained, LV end-diastolic volume decreases and forward stroke volume increases. More data are needed to support these findings.

Transcatheter Aortic Valve Implantation (TAVI): a 5-year single-center experience

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Background: TAVI has rapidly evolved to the standard-of-care for inoperable patients with severe, symptomatic aortic valve stenosis and to an accepted treatment option for high-risk, but operable patients. We report our 5-year single-center experience using transfemoral (TF) and transapical (TA) access and both the balloon-expandable Edwards Sapien (XT) (ES) and the self-expandable Medtronic-CoreValve (MCV) bioprosthesis.

Methods: From 2006 to 2011, 375 high-risk patients underwent TAVI (TF: n=262 [ES n=163; MCV n=99]; TA: n=113). We analysed procedural data and outcome of this cohort.

Results: Patients undergoing TA-TAVI were significantly sicker than TF-TAVI patients (EuroScore 30±15% vs. 20±12%; P<0.001). We found a non-significant trend towards a higher 30-day mortality (11% vs. 8%, P=0.415) in the sicker TA-TAVI group. The cumulative survival over 5 years showed a worse survival of the TA-TAVI group at one year, but at the period of three years the both survival curves equalized (Figure 1). Interestingly, in both groups there was an apparent learning curve which was reflected in a significantly better survival. The more recent experience depicted TF group had better survival rates explained by a significant reduction of vascular complications (31% vs. 8%; P<0.001) and procedural improvement. After treating excessive riskpatient at the beginning of the study period the majority of successfully treated high-risk patients surviving out to 2 years. Reduced MR severity is sustained, LV end-diastolic volume decreases and forward stroke volume increases. More data are needed to support these findings.

Figure 1

Conclusion: TAVI can be performed with high procedural success rates. There is an institutional learning curve. There are no differences between TF and TA in longer-term outcome except valve specific complications. Longer-term data show stable hemodynamics without structural valve deterioration.

Endothelialisation of cardiovascular implants in vivo: histology and immunohistochemistry

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Objective: Neoendothelialisation of cardiovascular devices after interventional or surgical application is of major clinical relevance. Thrombus formation can cause malfunction of the implant or may be a source for embolism and subsequent organ damage. Data on optimal duration of anticoagulation or anti-thrombotic therapy following implantation are scarce. For this purpose, we evaluated endothelialisation in 71 human explanted cardiovascular devices.

Methods: and materials Three aortic and/or mitral valve explant devices (Amplatzer or Cardiosave/Starflex; implantation time 5 days to 8 years); 24 right ventricular outflow tract (RVOT)-conduits (Homograft n = 10; Contegra n = 3; Hancock n = 11; implantation time 6 months to 19 years), and 24 ductus arteriosus stents (implantation time 5 days to 13 months) were processed using a uniform protocol. After explantation, the devices were fixed in formalin and embedded in methylmethacrylate. We employed standard histology and immunohistochemistry for evaluation of endothelialisation.

Results: Principal finding in devices with implantation times of less than 4 weeks was superficial fibrin coverage with spreading of single endothelial cells. Complete endothelialisation could be demonstrated as soon as 31 days after implantation of a ductus stent. In both the cludker group and the RVOT-conduit group, complete endothelialisation was demonstrated in all specimen with implantation times of more than 6 months. Presence of endothelial cells was confirmed by immunohistochemical staining with antibodies against von Willebrand factor and CD-31.

Conclusion: Our results indicate that anticoagulant or antiplatelet therapy for 6 months following implantation of cardiovascular devices may be sufficient to bridge the time interval until complete neoendothelialisation has been achieved.

Prognostic value of cerebral injury following transfemoral aortic valve implantation

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Objectives: To evaluate the predictive factors and the prognostic value of serological, imaging and clinical measures of cerebral injury after transcatheter aortic valve implantation (TAVI).

Background: Silent and apparent peri-interventional brain injury is frequently observed after TAVI. However, its impact on patient self-sufficiency and survival has not been elucidated.

Methods: Before and three days after TAVI, subclinical and clinical measures of cerebral injury were assessed, comprising neuro-specific enolase (NSE), new embolic events in cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) and neurological performance utilizing National Institutes of Health Stroke Scale (NIHSS). Besides established clinical endpoints, autarky was determined with established score systems (instrumental activities of daily living score, Barthel-Index). Parameters of cerebral injury were tested for their impact on self-sufficiency and all-cause mortality after 30 days and one year.

Results: Sixty-one patients were enrolled (mean logistic Euroscore: 26.4±18.1, mean StS-Stroke: 7.9±5.7). The incidences of NSE-increase, new embolic events in DW-MRI, neurological deficit early after TAVI were 52.4%, 71.8% and 6.6%, respectively. The degree of concomitant co-morbidities, reflected by established risk scores, but not TAVI-related cerebral injury had significant impact on outcome. Plasma levels of NSE and signs of emboli in DW-MRI were neither related to mid-term self-sufficiency nor to outcome. However, severe clinical impairment in neurological performance that was assessed by the NIHSS was predictive for both, sustained dependent lifestyle and non-survival up to one year after TAVI.

Conclusion: Clinically apparent, but not silent cerebral injury is predictive for adverse outcome after TAVI.

Impact of renal function on use of antithrombotic therapy in atrial fibrillation: real-world perspective from the global anticoagulant registry in the FIELD registry

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Background: Renal dysfunction may be associated with an increased bleeding risk with the use of anticoagulants, depending on the agent used and the severity of kidney disease. We sought to assess the impact of kidney dysfunction on current use of stroke thromboprophylaxis in patients with atrial fibrillation (AF) from the 1st cohort of the GARFIELD registry.

Methods: GARFIELD is a worldwide registry that will enroll 55,000 patients as 5 sequential prospective cohorts (including a retrospective validation group in cohort 1) at ~1000 sites in up to 50 countries. Eligible patients are ≥18 years old, diagnosed with non-valvular AF, with ≥1 additional investigator-determined stroke risk factor. We analysed use of antithrombotic agents in each stage of AF, using the NKF KDOQI guideline classification according to the NKF KDOQI guideline.

Results: Of the 10,427 patients recruited in the 1st cohort of the GARFIELD registry, data on glomerular filtration rate were available in 7536 (73%) subjects. Most (n=5074; 67%) were in stage I (Table). Approximately half of the subjects were treated with anticoagulants; use of anticoagulant monotherapy decreased with increasing severity of renal dysfunction, whereas combination treatment with anticoagulants and antiplatelets increased.

Conclusion: In the current era of vitamin K antagonists as the standard of care,
Inadequate anticoagulant therapy during end of study transition to open-label vitamin K antagonist therapy: experience in ROCKET AF

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Background: In ROCKET AF, excess thromboembolic events (rivaroxaban 22 vs warfarin 6) occurred during 30 days at the end of the study (EOS) when subjects transitioned from blinded therapy to open-label VKA anticoagulation.

Methods: The protocol recommended stopping study drug at EOS, starting open-label VKA, measuring INR 3 days later to preserve blinding, and recording all INR values. We analyzed INR assessment and time to therapeutic INR (2.0–3.0).

Results: Among 14,264 enrolled patients (mean CHADS2 score=3.5), 55% had prior thromboembolism, and 62.5% had heart failure. Among the 14,264 randomized patients, the median age was 73; mean CHADS2 score was 3.5, 55% had prior thromboembolism, and 62.5% had heart failure. The primary efficacy endpoint (stroke or non-CNS embolism) was examined by quartiles of cTTR.

Conclusions: Among patients transitioned to open-label VKA at EOS, those in the warfarin group reached therapeutic INR faster than those completing rivaroxaban. If transition from rivaroxaban to VKA is needed, timely monitoring and careful dosing should be used to assure consistent and adequate anticoagulation.
Cost-effectiveness of apixaban versus current standard of care (SoC) for stroke prevention in atrial fibrillation patients

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Purpose: Warfarin, a vitamin K antagonist (VKA) has been the standard of care (SoC) for stroke prevention in patients with atrial fibrillation (AF). Aspirin (ASA) is recommended for low risk patients and those unsuitable for warfarin. Apixaban is an oral anticoagulant that has better efficacy and safety against warfarin as well as ASA in the ARISTOTLE and AVERROES studies. We evaluated the potential cost-effectiveness impact of apixaban compared to warfarin and ASA from the perspective of the UK National Health Services (NHS).

Methods: A lifetime Markov model was developed to evaluate the clinical and economic impact of apixaban compared to warfarin and ASA in VKA-suitable and VKA-unsuitable patients, respectively. From a third party payer’s perspective. Clinical events captured include ischemic stroke and hemorrhagic stroke (further categorized as mild, moderate or severe), intracranial hemorrhage, other major bleeds, clinically relevant non-majour bleed, myocardial infarction, cardiovascular hospitalization and treatment discontinuations. Outcomes were assessed as life years gained (LYs) and quality adjusted life years gained (QALYs). Key input data sources were: clinical data derived from ARISTOTLE and AVERROES studies; UK life tables; UK NHS Healthcare Resource Group (HRG) tables; published literature for resource use and QOL decrements with stroke and bleeding. 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 increase life expectancy versus warfarin as well as ASA which was also associated with corresponding increase in quality-adjusted life years (QALYs). These gains were achieved at nominal cost increase over life-time, primarily due to higher drug acquisition costs versus generic comparators. One-way and probabilistic sensitivity analyses indicated that results were robust to a wide range of inputs.

Cost-effectiveness of apixaban versus standard of care at lifetime horizon

Population Comparator %Cost QALY ICER
Warfarin Warfarin 3.14 0.21 0.01 £16,151/QALY
Aspirin £2,622 0.21 0.22 £12,136/QALY
Warfarin unsuitable Warfarin £3,148 1.05 0.01 £10,151/QALY
Aspirin £2,622 0.21 0.22 £12,136/QALY

Conclusions: Based on the results of CE model, apixaban is a cost-effective alternative to warfarin as well as aspirin, in VKA-suitable and VKA-unsuitable patients with AF, respectively.

Atrial Fibrillation: The Scope of the Problem

Female gender and risk of stroke in atrial fibrillation: a nationwide cohort study

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Purpose: Female gender has been suggested as a risk factor for stroke/ thromboembolic events in patients with non-valvular atrial fibrillation (AF) and therefore been included in the CHA2DS2-VASc score. The purpose of this study was to investigate if the risk of stroke associated with female gender was homogeneous or concentrated to specific age-segments.

Methods: Using the national Danish registers we identified non-anticoagulated patients discharged with non-valvular AF (1997-2008). We calculated stroke rates according to gender, and assessed the stroke risk associated with female gender using Cox regression analysis.

Results: We included 87,202 AF patients, and 42,458 (51.3%) were female. We subdivided the population into three age intervals: <65, 65-74, and ≥75 years. For females aged <65 and 65-74, the stroke rate was not increased compared to males. For patients aged ≥75 years, the stroke rate was 12.08 (95% CI 11.64-12.53) in women and 9.78 (9.30-10.30) in men, at 1-year follow up (see figure). At both 1- and 12-years follow-up, female gender did not increase the risk of stroke for patients aged <75 years. The hazard ratio (95% CI) associated with female gender was 0.86 (0.76-0.98) and 0.98 (0.90-1.07) for patients aged <65 years and 65-74 years, respectively, at 12-years follow-up. Females ≥75 years had an increased risk of stroke; at 1-years follow-up the risk associated with female gender was 1.10 (1.05-1.15).

Conclusion: Our study shows that female gender is only a significant risk factor for stroke among patients aged ≥75 years. Further research may be needed into the contribution of female gender to stroke risk on subjects under 75 years of age.

Increased levels of D-dimer in atrial fibrillation identify patients with higher risk of thromboembolic events and death

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Purpose: D-dimer is known to be associated with thromboembolic outcomes in patients with atrial fibrillation. Our purpose was to evaluate D-dimer as an independent risk marker for death and stroke/systemic embolism (SEE) in patients with atrial fibrillation and the effect of apixaban or warfarin across quartiles of D-dimer:

Methods: In the ARISTOTLE trial 18201 patients with atrial fibrillation were randomized to apixaban 5 mg twice daily or warfarin. D-dimer was analyzed in 14878 (82%) patients at randomization before starting study treatment. The association between D-dimer levels in quartiles on cardiovascular death and the composite of stroke/SEE were evaluated by Cox proportional hazard models, after adjusting for CHADS2 score and randomized treatment.

Results: There was a strong and positive association between D-dimer level and death (p<0.0001) and stroke/SEE (p<0.0017) across all CHADS2-categories and among patients whether warfarin naive or not at baseline.

Obesity is a powerful predictor of atrial fibrillation in fertile women

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Purpose: Obesity is a risk factor for atrial fibrillation (AF) in subjects with advanced age, but this risk has never been investigated among young individuals,
Atrial fibrillation on initial EKG is associated with major adverse cardiovascular events in patients admitted for heart failure: analysis from the EVEREST trial

Atrial fibrillation on initial EKG is associated with major adverse cardiovascular events in patients admitted for heart failure: analysis from the EVEREST trial

P. Pang, M. Vaduganathan, M. Gheorghiade, R. J. Mentz, M. A. Konstam, M. Kwesigama, A. Fought, F. Zannad, K. Swedberg, A. Maggioni on behalf of EVEREST trial investigators. Northwestern University, Feinberg School of Medicine, Department of Emergency Medicine, Chicago, University of Pennsylvania, A-1 Northwestern Univ., Feinberg School of Medicine, Dpt of Medicine/Cardiology & Cardiovascular Surgery, Chicago, United States of America; Duke University Medical Center, Department of Medicine, Division of Cardiology, Durham, United States of America; Tufts Medical Center, Boston, United States of America; CIC INSERM-CHU Pierre Drouin, Institute for Heart and Vessels Louis Mathieu, Vandoeuvre les Nancy, France; University of Gothenburg, Gothenburg, Sweden; AMICO Research Center, Florence, Italy

Purpose: Heart failure (HF) complicated by atrial fibrillation (AF) is associated with worse outcomes in stable outpatients. However, the clinical profiles and outcomes of patients hospitalized for HF with AF has not been well studied. Methods: Post-hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan or Placebo. After excluding paced rhythms and other baseline arrhythmias, patients were divided into two groups: AF/Atrial Fibrillation (n=1195) and sinus rhythm (SR, n=2071). The primary endpoints of all-cause mortality (ACM) and composite cardiovascular mortality and HF hospitalization (CVHF-MF) were analyzed by log-rank tests and multivariable Cox regression models. Results: Compared to patients in SR, AF patients were older, had more prior HF hospitalizations and higher natriuretic peptide levels but less diabetes and higher EFs. At median follow-up of 9.9 months, AF patients experienced higher rates of ACM (26.9% vs. 21.3%) and CVHF-MF (40.4% vs. 35.3%) compared to patients in SR (p=0.001 for both). After adjustment for baseline covariates, AF remained a significant predictor of ACM (aHR=1.24 (1.04-1.46)) and CVHF-MF (aHR=1.25 (1.09-1.43)). Conclusions: AF independently predicts major adverse CV events in patients admitted for HF with reduced EF.

3300 Epidemiology and management of atrial fibrillation in the community in Italy: the Italian Survey of Atrial Fibrillation Management

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Purpose: Atrial fibrillation (AF) is an important public health problem and an important cause of healthcare expenditures. AF prevalence is changing over time. Therefore it is crucial to know its real impact on the healthcare systems to allocate resources. Aim of the study was to ascertain the current frequency distribution of AF, the clinical characteristics of AF patients (Pts) and the heart rhythm treatment strategy pursued in the community in Italy.

Method: ISAF is an observational study; 233 General Practitioners (GPs) homogeneously distributed across Italy were asked to screen their Pts (aged≥15 years) and to segregate those with AF. Each GP had to fill out an electronic questionnaire to provide information on the clinical profile and treatments pursued for the management of AF Pts.

Results: Among the 259906 screened Pts: 6036 (2.04%) had AF. The frequency distribution of AF for age and sex is shown in the Table. Of the 6036 AF Pts: 2% had paroxysmal, 24.4% persistent AF. The prevalence of AF lasted 1-5 years (yrs) in 39%, 6-10 yrs in 30% and >10 yrs in 18% of pts; AF was asymptomatic in 25.4% of pts and associated with palpitation in 41%, asthenia in 24.4% and dyspnea in 23.7%. Hypertension + LV hypertrophy was present in 33.3%, coronary artery disease in 19%, valvular disease in 12.2%, diastolic CMP in 5.9%; 24.3% of pts had heart failure, 25% renal failure, 18.0% COPD, 18% stroke/TIA, and 15% dementia. “Rhythm control” treatment strategy was pursued in 44% of pts. “Rate control” treatment strategy was in 55%.

Conclusion: Our results show that in a representative large sample of Italian people: 1) AF prevalence is greater than that usually reported, 2) AF prevalence increases with ageing, more frequently affects males, 3) pts with AF are burdened by a high prevalence of multiple comorbidities, in particular dementia, and 4) “Rate control” is the most pursued treatment strategy.
Clinical features in 215 carriers of a cardiac ryanodine receptor mutation RyR2 (G357S)


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Background: Ryanodine receptor (RyR) is a huge protein encoded by RyR2 gene. This protein releases calcium from endoplasmatic reticulum lumen to cytoplasm, and mutations in RyR2 have been linked to catecholaminergic polymorphic ventricular tachycardia (CPVT). The p.G357S mutation was described in 2009 as linked to CPVT, but no genotype-phenotype correlation data has been published about the mutation to date.

Objective: To describe the clinical features of 215 carriers of (p.G357S) RyR2 gene mutation.

Methods: Relatives of individuals presenting with sudden cardiac death (SCD) suggestive of CPVT underwent genetic in a few families apparently non-related, after discover a common ancestor in a genealogic investigation. A mutation in RyR2 (p.G357S) was identified and a clinical protocol (clinical evaluation based in consecutive exercise tests (ET) and holters (H)); treatment and follow-up protocol was offered to all family members. Control population included family members non-carriers of the mutation.

Results: Two hundred and fifteen carriers of (p.G357S) RyR2 mutation (G) were identified; 179 C alive, 6 C deceased by SCD and 30 individuals deceased by SCD with no genetics available. Seventy-seven patients (40%) presented symptoms before genetic diagnosis (40% SCD at a mean age of 18±9, 67% of them during stress, none of them under betablockers (BB), 80% presented previous syncope). During a mean follow-up of 52.2±1 months (range 1-125), 68 of 147 C (47%) presented ventricular arrhythmias (VA) in basal ET, without pharmacological treatment (significantly higher than the control population: 12.9%, p<0.001). If we consider VA in consecutive ET during follow-up, this proportion grows to 76% (ET 1 - 5), and 91% (ET 1 - 10).

Implantable cardioverter-defibrillator was implanted in 40 C (22%); 20 due to syncope (16 due to documented complex ventricular arrhythmia and 4 due to presyncope despite BB treatment). During follow-up there were 3 ICD discharges: 2 due to polymorphic VT and 1 to VF (FG 303±21 bpm). A non sustained VT (287 bpm) was also detected.

Conclusions: Our clinical data strongly suggest that p.G357S mutation in RyR2 gene may be responsible for CPVT. This is the largest series of CPVT published in literature, with the peculiarity that all carriers have the same mutation. Genetic and familial study is fundamental in early detection of CPVT. The genetic screening of a predisposing mutation in a large population sets a new perspective to clinical approach of inherited diseases.

KATP channels and Early Repolarization Syndrome

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Purpose: Previous studies showed an association between early repolarization pattern and idiopathic ventricular fibrillation. Heritability of early repolarization has been shown in a recent population-based study. Our team first describe a variant in KCNJ8 (c.1265C>T, p.S422L) in a 14-year-old female with a clinical history of ventricular fibrillation and early repolarization in intero-lateral leads. Thereafter, functional analysis showed that p.S422L mutation lead to a gain-of-function of KATP channel current by reducing sensitivity to intra-cellular ATP. This mutation was identified twice in two others patients with early repolarization pattern. These studies support the hypothesis that KATP channel are associated with ER Syndrome and point to KCNJ8-S422L as a possible hotspot mutation. A recent candidate-gene approach, were performed and led to the identification of ion channel genes (CACNA1C, CACNB2B, CACNA2D1 and SCNSA).

Methods: These results on ATP-sensitive potassium channels led us to hypothesis the implication of other cardiac KATP channel subunits. We screened by direct DNA sequencing KCNJ11 and ABCC9 in 96 patients with early repolarization syndrome.

Results: We identified 5 rare variants in ABCC9 in 5 probands: 4 missense variants and one nucleotide substitution in a splice-site. Three missense variants were not found in exome variant server database and dbSNP (p.L3F, p.A665T and p.V139H). One missense variant (p.A535S; rs14555570) was found in only 1/10755 European and African American alleles controls. All these patients presented ventricular fibrillation (VF) associated with early repolarization pattern. VF occurs in average at 30 years old (17-47y). Family’s studies and functional analysis are in progress for these 5 rare variants in order to evaluate the familial segregation and to understand implication of these variants in ventricular action potential.

Conclusions: ER could involve a transmural repolarization gradient across the ventricular wall, caused by an anomaly of epicardial action potential. This anomaly can be due to an increase of current IKATP. The identification of 5 patients among 96 (5.2%) with a variant in SUR2 KATP channel subunits reinforces the implication of ATP-sensitive potassium channels in early repolarization syndrome.

Novel CACNA1C mutations identified in Japanese patients caused both Brugada syndrome and idiopathic Ventricular Fibrillation without QT shortening

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Background: Mutations in the cardiac L-type calcium channel (LTCC) have been reported to be associated with Brugada syndrome (BrS) and idiopathic ventricular fibrillation (IVF). The frequency of mutation carriers in Asian populations, however, remains unknown. This study aimed to elucidate the disease-causing LTCC mutations in Japanese patients that were diagnosed as BrS or IVF and to compare the phenotype differences between patients with SCN5A mutations.
Arrhythmogenic cardiomyopathy: phenotypic differences of desmosomal versus phospholamban mutation carriers

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Purpose: Arrhythmogenic cardiomyopathy (AC) is frequently related to pathogenic desmosomal mutations. However, in The Netherlands a substantial part of AC patients carry the non-desmosomal phospholamban (PLN) founder mutation c.40_42delAGA. We assessed specific phenotypical differences in AC patients with a desmosomal versus the PLN mutation.

Methods: From our cohort of 171 proven AC index patients, 62 patients (44 men, age 49±13 years) with both 1) AC diagnosis according to the Task Force Criteria and 2) screening of all desmosomal genes (PKP2, DSP, DSC2, DSG2, JUP) and PLN, those with either a desmosomal or PLN mutation underwent meticulous phenotypical evaluation.

Results: In 50/62 (81%) a pathogenic desmosomal mutation and in 12/62 (19%) the PLN mutation was found. There were no significant age (48±13 vs. 55±11 years) or sex differences (74% vs. 58%, men) between groups. Differences in biventricular structural and functional involvement, no SCD has been reported in this group. Two SCD (16 and 31 years) occurred to all genetic carriers. After 4 years of applying the above mentioned protocol the p.G357S mutation. A clinical protocol (follow-up and treatment) was offered to all genetic carriers (26% vs. 75%, p-value 0.003).

Conclusions: AC patients carrying the non-desmosomal PLN mutation display a distinct AC phenotype characterized by inversion of T in left precordial leads V4-6 (4% vs. 58%, p-value <0.001), LV wall motion abnormities (WMA: 6% vs.33%, p-value 0.023), and low voltage ECG (voltages ≤5.5mV; 16% vs. 67%, p-value 0.001) were more frequent. RV involvement (inverted T in V1-3, RV WMA, RV delayed enhancement (DE), or RV ejection fraction (EF) ≤45%) was identified in both groups (96% vs. 92%, p-value 0.482). In contrast, LV involvement (inverted T in V4-6, LV WMA, LV DE, or LVEF ≤50%) occurred more frequently in PLN mutation carriers (26% vs. 75%, p-value 0.003).

Usefulness of familial study in a genetically-determined arrhythmogenic cardiomyopathy disease

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Introduction: The catecholaminergic polymorphic ventricular tachycardia (CPVT) is an arrhythmogenic familial disease characterized by high incidence of sudden cardiac death (SCD) in young people with normal basal ECGs and structurally normal heart. Thus, a high degree of suspicion is required to diagnose the disease. Up to 60% of CPVT patients have mutations in the cardiac ryanodine receptor, encoded by RyR2 gene.

Background: Between 1994 and 2007, four apparently non-related families from the South of Gran Canaria Island (Spain) have been investigated due to 11 reported events of SCD in young individuals (15-37y; range 9-37) with structurally normal heart. CPVT was suspected to be the cause of the events, the given characteristics of the affected individuals. Biological samples of death members and survivors of SCD identified a mutation in RyR2 (p.G357S), transmitted in an autosomal dominant way of inheritance, as the possible cause of the events in the population object of study.

Objective: To demonstrate the usefulness of cascade screening, combining family and/or genetic analysis, to identify a large group of CPVT patients.

Methods: Genealogical research was planned and carried out by a centralized, multidisciplinary team. We constructed an extensive family tree, starting with the deceased individuals, exhaustively reviewing written (municipal registries, church registers, old newspapers) and oral sources (testimony of old people). All individuals related to those affected by CPVT and carriers of RyR2 mutation were included and underwent genetic analysis.

Results: As a result of this search, all the families studied were related to a common ancestor that was born in a village of this region in 1749. Our family included more than 2000 individuals, candidates to be carriers of the causative RyR2 mutation, and underwent genetic analysis. Of them, 215 were positive for the p.G357S mutation. A clinical protocol (follow-up and treatment) was offered to all genetic carriers. After 4 years of applying the above mentioned protocol no SCD has been reported in this group. Two SCDs (16 and 31 years) occurred in 2 family members that refused to undergo clinical and genetic evaluation and treatment.

Conclusions: Early genetic detection of CPVT is mandatory to primary prevention arrhythmic events. An exhaustive familial study should be a part of the study protocol of CPVT, increasing the number of potentially affected individuals. We think that this type of diseases benefit of being managed by Inherited Cardiopathies Units.

Finding cardiac abnormalities in family members of cardiac arrest or sudden death victims through comprehensive clinical and genetic screening: results from the CASPER registry

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Introduction: Unexplained cardiac arrest (CA) or sudden unexpected death (SUD) with normal LV function and the absence of coronary artery disease may be due to an inherited cardiac abnormality. Family members (FM) of such individuals thus potentially at risk. CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry) prospectively evaluated first-degree FM of SUD victims (SUD) or unexplained CA survivors (CA) to determine the ability of cardiac and genetic testing to detect potentially lethal cardiac abnormalities.

Methods: Complete results are available on 183 first-degree FM (101 females; 82 males) who underwent comprehensive clinical evaluation (history, physical, ECG, signal averaging, exercise testing, Holter monitoring, echocardiography) to detect subclinical electrical or structural cardiac disease. Genetic testing was performed when a mutation had been identified in the proband. They ranged in age from 10 to 76 years (mean ± 38±16).

Conclusions: Definite or possible cardiac abnormalities were detected in 47/183 (25.8%) FM by clinical testing (41 ± 82%) or genetic testing (6 ± 12.8%). Abnormalities included LQTS (25), CPVT (12), ARVC (5), Brugada Syndrome (3), Short-QT (3) and familial cardiac sarcoidosis (1). Overall detection yield was similar between FM of SUD and CA probands (22% ± 27% p=NS) but LQTS was more common in the FM of the SUD group (p=0.06 Table).

Abnormalities detected

<table>
<thead>
<tr>
<th>Group (diagnoses/total)</th>
<th>LQTS</th>
<th>CPVT</th>
<th>ARVC</th>
<th>Brugada</th>
<th>SUDTS</th>
<th>Sarcode</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (34/125)</td>
<td>10 (76.9%)</td>
<td>2 (15.4%)</td>
<td>1 (7.6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SUD (13/58)</td>
<td>5 (38.5%)</td>
<td>5 (38.5%)</td>
<td>2 (15.4%)</td>
<td>1 (7.6%)</td>
<td>3</td>
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</tbody>
</table>

Mitrval valve disease: from balloon to clip

The impact of the presence and extent of valve calcification on long-term results of percutaneous mitral commissurotomay


Purpose: The indication of percutaneous mitral commissurotomy (PMC) is debated in patients (pts) with calcified mitral stenosis. We report outcome up to 20 years according to the presence and the extent of valve calcification.

Methods: PMC was performed in 1004 consecutive pts between 1986 and 1995: 710 pts had non-calcified valves (NCAL group) and 314 had valve calcification (CAL group).
Immediate and 20 years follow-up results of percutaneous balloon mitral valvotomy for severe mitral stenosis

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Background: Percutaneous balloon mitral valvotomy (PMV) is safe and effective in selected patients (PTS) for the treatment of symptomatic mitral stenosis with immediate and long-term results comparable to those of surgical intervention.

Objective: To report long-term follow-up results of the first 200 PMV performed in our institution and to identify predictive factors of restenosis.

Methods: From 1967 to 1991, two hundred patients underwent PMV in our hospital. Clinical evaluation and echo-Doppler studies were performed 48 hours after PMV and annually in the follow-up. Evaluation included NYHA class, Wilkins scoring, mitral area (MVA) calculation (pressure half-time method), mean transmitial gradient, mitral regurgitation (MR) estimation (by color-Doppler semi-quantitative method) and left atrial diameter. Good immediate results were defined as MVA ≥1.5cm² without mitral regurgitation ≥2/4. Restenosis was defined as loss of ≥50% of initial gain and MVA <1.5cm². Survival curves (Kaplan-Meier) were used to estimate the rates of restenosis-free PTS. Stepwise Cox regression analysis was used for determining the predictors of restenosis. A value of p<0.05 was used as the minimum value for statistical significance.

Results: Mean age was 32±11 years; 27 were men. 27 PTS (14%) had mild MR pre PMV. 39 PTS (19%) were in NYHA class II and 161 (81%) in NYHA class III or IV. 8 PTS (4%) were in atrial fibrillation, and 5 PTS (2.5%) had prior commissurotomy. Echocardiography showed a Wilkins score of 7.6±1.2, only 32 PTS (16%) had ≤8. Immediate surgical intervention was needed in 7 PTS (3.5%) secondary to severe MR, and 18 PTS (9%) related to technical problems associated to the learning curve. 175 PTS (88%) had good immediate results. Of those, 129 PTS (74%) completed an average follow up of 140±79 months and 46 (26%) were lost to follow up. During the follow up 60 PTS (46%) developed restenosis, 25 (19%) required a second PMV and 4 PTS (3%) a third one. The probability of being restenosis-free was approximately 85% at 5 years, 60% at 10 years and 36% at 20 years. Predictors of restenosis were: left atrial diameter ≥3cm (p=0.034), preoperative and postoperative mean transmitial gradient (p=0.013 and p=0.038 respectively). MVA pre and post intervention and Wilkins score were not statistically significant as predictors of restenosis.

Conclusion: After 20 years, 36% of patients were free of restenosis. The identification of predictive factors of restenosis provides useful information for patient selection and good outcomes.

What are long-term results of percutaneous mitral commissurotomy in patients with few or no symptoms?


Purpose: Percutaneous mitral commissurotomy (PMC) has enabled patients (pts) to be treated at an earlier stage of their disease than by surgery. However, very long-term results have not been specifically studied in this context.

Methods: From 1986 to 1995, 237 patients in NYHA class I or II underwent PMC in our center. Mean age was 46±12 years (74% pts) had atrial fibrillation and 22 (9%) had a history of commissurotomy. Most patients were in NYHA class II (232 patients, 98%). As assessed by echocardiography, mean valve area was 1.1±0.2 cm² (≤1.5 cm² in all cases), 40 patients (17%) had pliable valves and mild subvalvular disease, 145 (61%) had pliable valves and severe subvalvular disease, and 52 (22%) had calcified valves. PMC used a single-balloon in 5 patients, a double-balloon in 93 and the Inoue balloon in 139.

Results: After PMV, valve area increased to 1.9±0.3cm² as assessed by 2D echo. Severe mitral regurgitation (grade ≥3/4) occurred in 4 patients (1.7%). There were no other severe immediate complications. Good immediate results (valve area ≥1.5 cm² without mitral regurgitation ≥2/4) were obtained in 223 patients (94%). The 20-year actuarial rate of survival without surgery or repeat PMC and in NYHA class I or II was 41±4% in the whole population.

After good immediate results, the 20-year rate of good functional results was 42±3%. A Cox multivariate model identified 2 predictors of good late functional results after good immediate results: young age (p=0.05) and a large valve area after PMC (p=0.002). In the 142 patients aged ≤50 years, the 20-rate of good functional results was 50±6%.

Conclusion: In patients with severe mitral stenosis and few or no symptoms, PMC: 1) Can be safely performed; 2) Provides good immediate and long-term results in a large variety of patients. 3) Should be considered in particular in patients aged ≤50 years, in whom it prevents functional deterioration in half of the cases 20 years after PMC.

Prognostic importance of exercise brain natriuretic peptide in asymptomatic degenerative mitral regurgitation

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Background: Exercise stress echocardiographic (ESE) can be of interest in the management of asymptomatic patients with primary MR. The incremental prognostic value of BNP response during exercise is unknown. We aimed to identify the determinants of exercise brain natriuretic peptide (BNP) level and to evaluate its prognostic value in asymptomatic patients with primary mitral regurgitation (MR).

Methods: Comprehensive resting and ESE was performed in 113 consecutive asymptomatic patients with moderate to severe degenerative MR and preserved LV function. Blood samples were collected both at rest and exercise.

Results: The BNP level significantly increased from rest to exercise (p<0.0001). The independent determinants of exercise BNP were resting E/Ea ratio (p=0.043), indexed left atrial volume (p=0.022) and exercise LV global longitudinal strain (p=0.001). There was a significant graded relationship between increasing BNP level at exercise (according to tertiles) and increased incidence of cardiac events (1-year: 11.5±14.6 vs. 43.5±9.3%; 2-year: 21.7±15.8 vs. 40.8±7.7%; in tertiles 1, 2 and 3, respectively, Fig, panel A). On multivariable analysis (fig, panel B), after adjustment for demographic and echocardiographic data and for resting BNP level, exercise BNP remained significantly associated with increased risk of cardiac events during the follow-up (hazard ratio= 2.8 and 3.4, p=0.041 and 0.023, for tertiles 2 and 3, as compared to tertile 1).

Impact of the etiology of mitral regurgitation on long-term survival after MitraClip therapy

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Background and Objective: Mitral regurgitation (MR) of functional as opposed to degenerative origin are different morphological entities that have mostly been grouped together and analysis of studies published to date on MR therapy using the MitraClip. We sought to assess the impact of MR etiology on 2-year survival after MitraClip implantation.

Methods and Results: By November 2011, 256 consecutive patients (74±9 years, 162 men) with significant MR not amenable to surgery underwent MitraClip therapy at our center. Functional MR (FMR) and degenerative/mixed MR (DMM) were present in 156 (61%) and 99 patients, respectively. Endpoints assessed by Kaplan-Meier (K-M) analysis were overall survival, rehospitalization for car-
dian reasons, mitral valve surgery post MitraClip, and the EVEREST-II composite efficacy endpoint of death, mitral valve surgery and MR > grade 2+. Overall sur-
vival was not different between FMR and DMR patients, with K-M estimates of 2-year survival at 85.8±6.6% and 64.3±8.4% respectively (P = 0.054). Although K-M curves for freedom from rehospitalization diverged after 6 months in favor of DMR patients, the difference did not reach statistical significance (P = 0.217; 2-
year estimate for DMR 51.6±7.2%, for FMR 29.8±7.0%). There was, however, a statistically significant difference (P = 0.0065) in freedom from mitral valve surgery post MitraClip, which was 96.9±1.5% at 3 months and 94.6±2.8% at 2 years in FMR patients and 86.8±3.9% at 3 months and 80.3±4.2% at 2 years in DMR pa-
tients. Freedom from the EVEREST-II endpoint was not different between groups (P = 0.111), with 1- and 2-year estimates of 73.1±6.3% and 53.9±8.8% in FMR patients and 87.5±3.4% and 63.3±6.2% in FMR patients.

Conclusions: FMR and DMR patients fared similarly over 2 years with respect to overall survival, freedom from rehospitalization, and freedom from the EVEREST-II efficacy endpoints. However, DMR patients had to undergo mitral valve surgery within 3 months of MitraClip therapy significantly more often than FMR patients.

Determ inants for survival and hospitalisation because of congestive heart failure after percutaneous mitral valve repair

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Aims: We sought to identify predictors for outcome after percutaneous mitral valve repair with MitraClip.

Methods: In a single-centre cohort of 127 consecutive surgical high-risk patients treated with MitraClip for severe mitral valve regurgitation (MR) since April 2009 (Age 74±2 years, left ventricular ejection fraction (LV EF) 38.3±3.0, log. EuroScore 28.3±3.1, baseline demographics and procedural characteristics were screened for their eligibility to predict survival and hospitalisation because of congestive heart failure by using Kaplan-Meier analyses. The 6-month mortality in the total cohort was 15.4%. Statistically significant predictors for mortality were failure of acute procedural success defined as MR grade 3 or 4 at discharge (6 month mortality 38.5 vs. 9.6%, hazard ratio 14.8 [95% confidence interval: 4.6–47.5], P [log rank] < 0.0001), clinically overt right heart failure at baseline (25 vs. 7.8%, HR 3.7 [1.3–9.3]; P = 0.01), chronic obstructive pulmonary disease (30.8 vs. 11.3%; HR 3.6 [1.4–9.7]; P = 0.01) and a logistic EuroScore I ≥ 30% (21.0 vs. 12.2%; HR 2.4 [1.1–5.3]; P = 0.04). Hospitalisation because of heart failure was 26.6% at 6 months in the total cohort. Heart failure symptoms stage IV according to NYHA (53.6 vs. 20.7%; HR 4.4 [1.7–11.6]; P = 0.003) and a LVEF ≥ 30% before clip (38.6 vs. 20.5%; HR 2.1 [1.0–4.4]; P = 0.05) predicted an increased risk for hospitalisation because of congestive heart failure.

Conclusions: The present data demonstrate the necessity for thorough patient selection for MitraClip therapy in order to ensure procedural success. Moreover, due care has to be exercised in the post-procedural management of patients with end-stage heart failure. Dedicated heart teams are mandatory for best results.

Coronary artery disease unveiled by multidetector computed tomography in populations at risk

High prevalence of coronary artery disease detected by Cardiac Computed Tomography in asymptomatic patients with Heterozygous Familial Hypercholesterolemia and negative LDL receptor mutations

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Purpose: Heterozygous Familial Hypercholesterolemia (HeFH) associates with early coronary artery disease (CAD) in otherwise asymptomatic patients. Objectives of the present study were to assess the prevalence and magnitude of subclinical CAD in HeFH patients by means of coronary computed tomography angiography (CCTA) and to determine the clinical and genetic profile of HeFH patients at the highest risk of CAD.

Methods: CCTA findings from a study group of 50 consecutive patients (50% male, mean age 48.4±4 years) with HeFH diagnosed by MedPed Criteria were compared with those from a control group of 70 healthy subjects matched for age, gender and clinical risk factors other than dyslipidemia, who were referred for CCTA as a part of a preventive medical examination. In 82% (41/50) of HeFH patients genetic DNA was screened for LDL receptor (LDL-r) gene defects by using a microarray (Lipochip®; Progenika Biopharma, Denis, Spain).

Results: Computed tomography showed a significantly higher Agatston calcium score in the study group in comparison with controls (260.18±150 vs 45±4; p <0.002). Prevalence of CAD in HeFH patients was 48%, with significant ob-
struction in 26%, involving mainly the proximal segments of coronary arteries. In

the control group, prevalence of CAD was 33% with significant obstruction in 5% (p = 0.05 for both prevalence and severity of CAD compared with HeFH patients). In HeFH patients, increased age, receptor negative mutations and low HDL blood levels at diagnosis associated statistically significantly with CAD (p < 0.05). Analytical follow-up after 12 months under optimal lipid-lowering therapy showed no differences in the lipid profile between HeFH patients with or without subclinical CAD.

Conclusions: HeFH patients present with higher prevalence, extension and severity of subclinical CAD than the general population mainly involving the prox-
imal coronary segments from multiple vessels, with a high degree of calcification.

Evidence of subclinical coronary artery disease and abnormal myocardial perfusion reserve in newly diagnosed obstructive sleep apnoea patients without clinical cardiovascular disease

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Purpose: The multiple disease mechanisms activated by obstructive sleep apnoea (OSA) and the severe hypoxemia may cause myocardial ischaemia. There is however, limited data on subclinical cardiovascular events (CVE) in OSA patients with OSA compared with patients without OSA.

Methods: Consecutive patients without evidence of CVE (n=135, 14 females undergoing polysomnography were recruited. The patients received a 2-D Doppler and Dipyridamol-stress myocardial contrast echocardiography (MCE using Sonovue echocontrast; Philips, IE 33), non contrast (Agatston score) and con-
tраст enhanced cardiac CT-scan (13 coronary segments assessed for degree of stenosis; 64-slice GE). Cardiot artery intima media thickness (IMT) measurement and Brachial artery vascular reactivity assessment by flow mediated dilation (FMD).

Results: Patients with an apnoe-hypopnoea index (AHI) of > 15 (gr 1, n=117; age 50±10 years; AHI 53±3.15, 64-slice GE), Carotid artery intima media thickness (IMT) measurement and Brachial artery vascular reactivity assessment by flow mediated dilation (FMD).

Conclusions: The present results provide direct evidence of endothelial dysfunc-
tion and the presence of subclinical CAD with associated reduction in myocardial blood flow reserve in OSA patients without clinical evidence of CAD. The OSA and FMD were best predictors of coronary plaque.

Can cardiac MDCT predict cardiovascular events in asymptomatic diabetic subjects? Results of a five-year follow-up


Purpose: Diabetes has been considered as an equivalent of coronary artery dis-
ease, however it is doubtful whether all asymptomatic diabetics (AD) share the same cardiovascular risk (CVR). This study aims to evaluate the usefulness of MDCT to predict fatal and non-fatal cardiovascular events (CVE) in AD.

Methods: Case-control study of 85 consecutive AD (without dyspnea or chest pain) who underwent cardiac MDCT (Philips Brilliance): 49.4% men, 60±10 years, 50.6% under insulin treatment, with a mean diabetes duration of 13±9 years and a mean hemoglobin A1c of 8.2±6.1 years; AHI 53±3.15, 64-slice GE), Carotid artery intima media thickness (IMT) measurement and Brachial artery vascular reactivity assessment by flow mediated dilation (FMD).

Conclusions: The present data provide direct evidence of endothelial dysfunc-
tion and the presence of subclinical CAD with associated reduction in myocardial blood flow reserve in OSA patients without clinical evidence of CAD. The OSA and FMD were best predictors of coronary plaque.

Conclusions: The present data provide direct evidence of endothelial dysfunc-
tion and the presence of subclinical CAD with associated reduction in myocardial blood flow reserve in OSA patients without clinical evidence of CAD. The OSA and FMD were best predictors of coronary plaque.
The presence of CAP and CCS ≥ 0.5 identified the AD at higher risk of CVE, while the CCS = 0 was associated with a better risk profile. According to these data, the MDCT may be useful in AD stratification, emphasized given to CCS as a simple, easy and fast method associated with low-dose radiation.

**Impact of body mass index and the metabolic syndrome on the characteristics of coronary plaques using computed tomography angiography**

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**Background:** The purpose of this study was to investigate association between combinations of body mass index (BMI) categories and metabolic syndrome (MetS) and the characteristics of coronary plaques using computed tomography angiography (CTA).

**Methods:** Four hundred seventy-one patients with suspected coronary artery disease underwent 64-slice CTA to assess the plaque morphology. Vulnerable plaques were defined as positive remodeling (RI > 1.10) and low-attenuation plaques < 50 HU. According to BMI-MetS status, they were categorized into 6 groups according to BMI categories (normal—< 25, overweight 25-30, obese—≥ 30 kg/m²) and presence or absence of MetS (by Japanese criteria).

**Results:** The number of vulnerable plaques per patient was significantly higher in patients with MetS and obese patients without MetS than in normal weight patients without MetS (Figure). In multivariable logistic analysis that adjusted for age, smoking and low-density lipoprotein cholesterol, the association of vulnerable plaques was observed in normal-weight patients with MetS (OR 0.53, 95% CI 0.29 to 0.89 for BMI < 30 and MetS), overweight patients with MetS (OR 6.31, 95% CI 3.34 to 12.2), obese patients without MetS (OR 3.43, 95% CI 1.16 to 9.72), and obese patients with MetS (OR 6.66, 95% CI 2.75 to 17.0), but not observed in overweight patients without MetS (OR 1.84, 95% CI 0.86 to 3.79), compared with normal-weight patients without MetS.

**Conclusion:** Metabolic syndrome and obese patients without MetS are associated with coronary vulnerable plaques, whereas overweight patients without MetS had no significant increasing risk of plaque vulnerability.

**Prevalence of coronary atherosclerosis in patients with pre-diabetes: insights from coronary CT angiography**

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**Aim:** The aim of this analysis is to determine the prevalence and plaque characteristics of coronary atherosclerosis and stenosis on coronary CT angiography in symptomatic patients with pre-diabetes.

**Methods:** We enrolled 498 consecutive symptomatic patients without known coronary artery disease (CAD) who underwent coronary CT angiography for the evaluation of coronary anatomy. Patients were divided into three groups: Patients with diabetes mellitus (DM, n=183), glycated Hemoglobin (HbA1C) > 7 mg/dl), pre-diabetes (PreDM, n=101), HbA1C between 6.9 and 6.1 mg/dl) and normoglycemic patients (Ni, n=214, HbA1C < 6.1 mg/dl). All CCTA scan were interpreted by two investigators based on the 15 segment model of coronary arteries for plaque presence and characteristics.

**Results:** The baseline characteristics of the study cohort are shown in the table below. In univariate analysis, there was no difference in the prevalence of obstructive CAD among patients with PreDM compared to Ni patients, but lower than DM patients. (Table) Coronary atherosclerosis was more prevalent in PreDM group (table). After adjusting for age, hypertension, gender and dyslipidemia, there were no differences in the number of diseased coronary segments nor the plaque composition among patients with PreDM compared to non-diabetic patients.

<table>
<thead>
<tr>
<th>Diabetes status</th>
<th>N=183</th>
<th>N=101</th>
<th>N=214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68±11</td>
<td>68±11</td>
<td>68±11</td>
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<tr>
<td>Male</td>
<td>48±2%</td>
<td>48±2%</td>
<td>48±2%</td>
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<tr>
<td>Hypertension</td>
<td>87±8%</td>
<td>86±8%</td>
<td>86±8%</td>
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<td>Dyslipidemia</td>
<td>84±9%</td>
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<tr>
<td>Prevalence of obstructive CAD (≥ 70%)</td>
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</tr>
<tr>
<td>Mean number of segments with plaques</td>
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<td>Mean number of segments with mixed plaques</td>
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</tr>
<tr>
<td>Mean number of segments with non-calcified plaques</td>
<td>1±1±1</td>
<td>1±1±1</td>
<td>1±1±1</td>
</tr>
<tr>
<td>Mean number of segments with plaques per patient</td>
<td>1±1±1</td>
<td>1±1±1</td>
<td>1±1±1</td>
</tr>
</tbody>
</table>

**Conclusion:** Our analysis suggests that pre-diabetes state is not associated with increased coronary atherosclerosis or stenosis compared to non-diabetic patients.

**Impact of epicardial adipose tissue on atherosclerosis**

M. Piikla1, M. Kruk2, R. Praccon2, M. Opolski3, C. Kepka1, 1Military Medical Institute, Department of Interventional Cardiology. Warsaw, Poland; 2Institute of Cardiology. Department of Coronary and Structural Heart Diseases, Warsaw, Poland

**Purpose:** Epicardial adipose tissue (EAT) may be regarded as a physiological extension of obesity into pericardial compartment. The aim of our study was to investigate whether EAT volume as assessed on non-contrast scans is associated with coronary atherosclerosis and what is its relation to obesity.

**Methods:** The study included 235 consecutive patients (126 females, mean age 59.5±10.57 years) undergoing MSCT angiography on a 64-slice scanner for suspected coronary artery disease (CAD). EAT was defined as the adipose tissue located within the pericardial sac and its volume was obtained based on non-contrast scans (calcium score scans) using Volume/Syngo (Siemens). Atherosclerosis was defined as coronary artery calcification (CAG) determined by Agatston score or the presence of at least one ≥ 50% coronary stenosis (CAD). Obesity was defined as either BMI> 25 kg/m² or waist circumference (WC)> 102/88 cm (men/women).

**Results:** CAD was diagnosed in 53 (22.6%) and CAC above zero was calculated in 119 (56.6%) patients. Obese patients, according to BMI and WC measurements, comprised 157 (66.8%) and 145 (61.7%), respectively. Obese subjects had higher EAT volume than non-obese (respectively, 162.2±59.4 vs 112.7±41.3, p<0.001 according to BMI; and 158.3±61.4 vs 125.6±48.2, p=0.001 according to WC). EAT volume was an independent predictor (according to multivariable regression analysis) of atherosclerosis in non-obese as opposed to obese (p=0.19 vs p=0.8; p=0.005 vs p=0.85 according to WC, p=0.029 vs p=0.89; p=0.03 vs p=0.45 according to BMI, respectively CAD; CAG). The interaction term between EAT volume and obesity with respect to the presence of atherosclerosis was significant (p=0.016 according to BMI; p=0.036 according to WC; p=0.012 according to BMI, p=0.003 according to WC, respectively CAD; CAG).

**Conclusions:** The relationship between EAT volume (measured by MSCT without the use of contrast agents) and coronary atherosclerosis differs with respect of the obesity status, pointing at the EAT in non-obese subjects as being significant in the prediction of coronary atherosclerosis.
MULTIMODALITY IMAGING INFORMS PROGNOSIS IN CORONARY ARTERY DISEASE

Dual imaging stress echocardiography versus computed tomography coronary angiography for risk stratification of patients with chest pain of unknown origin

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Background: Dual imaging stress echo, combining the evaluation of wall motion and coronary flow reserve (CFR) on the left anterior descending artery (LAD), and computed tomography coronary angiography (CTCA) are established modalities to assess prognosis in chest pain patients. In this study we compared the prognostic value of the two techniques in a cohort of patients with chest pain having suspected coronary artery disease (CAD).

Methods: 131 patients (76 men; age 68±9 years) with chest pain of unknown origin underwent dipyridamole (up to 0.84 mg/kg over 6') stress echo with CFR assessment of LAD by Doppler and CTCA. A CFR < 1.9 was considered abnormal, while > 50% lumen diameter reduction was the criterion for significant CAD at CTCA.

Results: Of 131 patients, 34 (26%) had ischemia at stress echo by wall motion criteria, and 56 (43%) had impaired CFR. Significant CAD at CTCA was found in 58 (44%) subjects. Forty-four (79%) patients with abnormal CFR on LAD had significant CAD at CTCA (p = 0.001). In addition, calcium score was higher in patients with reduced CFR than in those with normal CFR (265±404 vs 131±336, p = 0.04). During a median follow-up of 9 months, 18 events (4 deaths, 14 myocardial infarctions) occurred. The event-free survival was markedly better for patients with preserved CFR and no stress-induced ischemia than in patients with abnormal CFR and/or stress-induced ischemia (Log Rank: 6.82, p = 0.04). During a median follow-up of 9 months, 18 events (4 deaths, 14 myocardial infarctions) occurred. The event-free survival was markedly better for patients with preserved CFR and no stress-induced ischemia than in patients with abnormal CFR and/or stress-induced ischemia (Log Rank: 6.82, p = 0.04). However, the event-free survival showed no significant difference in patients with and without significant CAD at CTCA (Log Rank: 1.43, p = 0.23, Figure).

Conclusions: Dual imaging stress echocardiography provides superior prognostic capability as compared to CTCA in patients with chest pain and suspected CAD.

Tissue heterogeneity in patients with impaired left ventricular function after acute ST-segment elevation myocardial infarction predicts all-cause mortality

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Purpose: Following an acute ST-segment elevation myocardial infarction (STEMI), infarct-related tissue heterogeneity of the left ventricle (LV), assessed with magnetic resonance imaging, is present and predictive of worse outcome. Recently, in patients with ischemic cardiomyopathy, tissue heterogeneity was assessed using two-dimensional (2D) speckle tracking echocardiography. However, the use of this technique for the risk stratification of STEMI patients with reduced LV ejection fraction (LVEF) is not clear. This study aimed to correlate all-cause mortality and tissue heterogeneity, assessed by 2D speckle tracking echocardiography, in STEMI patients with LVEF ≤40% at 3 months follow-up.

Methods: In total, 195 patients with first STEMI treated with primary percutaneous coronary intervention and LVEF ≤40% at 3 months follow-up were evaluated. Longitudinal strain speckle tracking data were used to assess the function of the core infarct, border zone and remote area (tissue heterogeneity). Data on all-cause mortality were collected during long-term follow-up.

Results: During long-term follow-up (median 47 months), 18 patients (9%) died. At baseline, no significant differences were found in longitudinal strain values of infarct, border or remote zones between survivors and non-survivors. However, at 3 months follow-up, all 3 zones were significantly more impaired in patients who died (P < 0.005). ROC curve analysis showed that 3-month longitudinal strain at the border zone was most accurate to identify all-cause mortality (Figure 1) with a sensitivity of 78% and specificity of 65% for a 9.5% cut-off value.

Conclusions: CTA provides incremental prognostic value to MPI. Combined functional and anatomical assessment may allow improved risk stratification in patients with previous CABG.

Prognostic value of computed tomography angiography and gated single-photon emission computed tomography in patients with previous coronary artery graft surgery

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Purpose: To determine whether coronary computed tomography angiography (CTA) has an incremental prognostic value over single-photon emission computed tomography myocardial perfusion imaging (MPI) in patients with previous coronary-artery-bypass grafting (CABG).

Methods: We studied 184 patients (83% male, mean age 69±7.2) undergoing CTA and MPI for cardiac evaluation. CTA defined the number of unprotected coronary territories (UCTs) (0, 1, 2, or 3) by evaluating bypass grafts, distal runoffs vessels, and nongrafted vessels. The following events were recorded: cardiac death, non-fatal myocardial infarction (MI), and unstable angina requiring revascularization.

Results: Fifteen patients (8.9%) had events for a mean follow-up of 30.6±17.1 months. In univariate analysis, dyslipidemia (p = 0.034), time since CABG (p = 0.016), using ITA (p = 0.027), summed stress score [SSS] by MPI (p = 0.0042), and UCT (p = 0.001) were predictors of events. After correction for baseline characteristics in a multivariate model, UCT was an independent predictor (hazard ratio: 2.20; 95% confidence interval: 1.07 to 4.52; p = 0.031) though SSS was not (1.05; 0.99-1.11; p = 0.096). In comparison with SSS, UCT was associated with an 18.7% net reclassification index (NRI).

Conclusions: The longitudinal strain value of the border zone 3 months after STEMI predicts all-cause mortality and may be useful for risk stratifying patients following STEMI.
Stress contrast enhanced CT for diagnosing myocardial ischemia comparison with stress myocardial perfusion MRI and fractional flow reserve

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Purpose: Contrast enhanced CT with vasodilator stress may provide comprehensive assessment of coronary arterial stenosis and myocardial ischemia. The purpose of this study was to assess the accuracy of 320-slice contrast enhanced CT with adenosine stress for the detection of myocardial ischemia by using stress perfusion MRI and fractional flow reserve (FFR) as reference methods.

Methods: Seventy-two vessel territories in 24 patients (12 men, age 67.1±9.4 years) with known or suspected coronary artery disease (CAD) underwent stress-contrast enhanced CT as well as stress-rest perfusion MRI followed by late gadolinium enhancement (LGE) MRI. FFR was determined in 13 coronary vessels and FFR<0.80 was considered hemodynamically significant. CT and MRI images were visually analyzed by two blinded observers.

Results: The sensitivity and specificity of stress contrast enhanced CT for predicting myocardial ischemia on stress perfusion MRI was 80% (20/26) and 45% (40/47), respectively. In 3 of 7 false positive territories, myocardial infarction was observed on LGE MRI. When compared with FFR, stress contrast enhanced CT elucidated 78% (7/9) of flow limiting CAD and correctly identified 75% (3/4) of the vessels without significant CAD.

Conclusion: The results in the current study demonstrated that stress contrast enhanced CT can accurately identify myocardial ischemia caused by flow limiting CAD.

Differential properties of arteries in Erdheim Chester disease / Special populations: special challenges

S. Nakamoto1, T. Tanigawa2, K. Onishi1, K. Kitagawa2, H. Nakajima1, T. Sawat1, J. Masuda1, M. Nakamura1, H. Sakakura2, M. Ito1, 1Me University Graduate School of Medicine, Department of Cardiology, Tsu, Japan; 2Mie University Graduate School of Medicine, Department of Radiology, Tsu, Japan; 3Mie University Graduate School of Medicine, Department of Clinical Cardiovascular Research, Tsu, Japan

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Effect of intensive statin treatment on coronary hyperintense plaque detected by non-contrast T1-weighted magnetic resonance imaging: the AQUAMARINE pilot survey

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Background: We previously showed that coronary hyperintense plaques (HIP) visualized by non-contrast T1-weighted imaging (T1WI) on cardiac magnetic resonance imaging (CMR) are associated with positive remodeling, ultrasound attenuation, and lower Hounsfield units. It remains unclear, however, whether the volume of HIP is reduced by statins, which slow the progression of coronary atherosclerosis in proportion to their ability to reduce low-density lipoprotein cholesterol (LDL-C).

Method: We performed serial CMR and computed tomographic angiography (CTA) in 40 consecutive patients with coronary artery disease at baseline and after 1 year of treatment with pitavastatin (2 to 4mg daily). HIP was defined as presence of the signal intensity on plaque to myocardium ratio (PMR) was <1.0. A representative case of HIP (arrow) is shown in the Figure. Patients with HIP positive (61 lesions, n=35) were analyzed in terms of the effects of intensive lipid-lowering treatment on the following parameters: changes in PMR, plaque area, remodeling index, percent volume of low-attenuation plaque (<50 Hounsfield units) based on CTA, and high-sensitivity C-reactive protein (hs-CRP) as an inflammatory marker.

Results: The mean (SD) baseline LDL-C level of 125 (29) mg/dL declined to 68 (16) mg/dL, a reduction of 11.9% (P<0.001). The mean change in hs-CRP level was -61.3% (P<0.001 vs. baseline). There were no significant changes in plaque area or remodeling index, whereas the percent volume of low-attenuation plaque showed a 20.3% median reduction (P<0.001 vs. baseline). Change in PMR showed in 15.8% median reduction (P<0.001 vs. baseline).

Conclusions: A significant reduction in PMR was observed during plaque-stabilizing therapy with statin. Non-contrast T1WI may provide important information regarding plaque vulnerability.

Distal protection device aggravated microvascular obstruction evaluated by cardiac MR after primary percutaneous intervention for ST-elevation myocardial infarction

C.H. Yoon1, W.Y. Chung2, J.W. Suh1, Y.S. Cho1, T.J. Yoon1, E.J. Chun1, S.I. Choi1, I.H. Chae1, D.J. Cho1, 1Seoul National University Bundang Hospital, Division of Cardiology, Seongnam, Korea, Republic of; 2Seoul National University Boramae Hospital, Seoul, Korea

Background: Protection of distal embolization by balloon occlusion and thrombus aspiration has not improved microvascular circulation nor decreased myocardial injury during primary percutaneous intervention (PCI) for ST-elevation myocardial infarction (STEMI) in randomized trials. In a prospective randomized trial, we investigated the mechanism of the poor effect of distal protection and thrombus aspiration (DP-PA) in 126 patients with STEMI.

Methods: Patients with first-diagnosed STEMI were randomly assigned to DP-PA pretreatment or conventional PCI (c-PCI). Primary endpoint was reduced left ventricular end-diastolic volume (LVEDV) measured by MRI at post-PCI and 6 months after PCI. Secondary endpoints were infarct ratio (infarct size to entire LV size) by delayed enhancement (DE) area at risk (AAR) ratio (AAR to entire LV size) by DE high signal, microvascular occlusion index (MVO) ratio (MVO to entire LV size) by DE, and myocardial salvage index (MSI: AAR-infarct size)/100AAR used for quantification of microvascular reperfusion (MVR) at 3 days after PCI.

Results: Baseline characteristics of the patients including cardiovascular risk factors and lesion characteristics were similar between the two groups. DP-PA failed to improve LV remodeling at 6 months (LVEDV 140±29 vs 133±37 in c-PCI group, p=0.418). Infarct ratio, AAR ratio and MSI were not statistically different between DP-PA group and c-PCI group. However, MVO ratio were significantly larger in DP-PA group than c-PCI group (2.4±2.7 vs 1.1±1.9, p<0.045).

Conclusions: DP-PA was potentially hazardous in primary PCI for STEMI by increasing MVO. DP-PA should not be used in STEMI.

Differential properties of arteries in Erdheim chester disease, a model of non langerhans histiocytosis

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Objectives: To study structural and functional alterations of arteries in patients with Erdheim-Chester disease, a rare acquired idiopathic histiocytosis characterized by a circumarferential fibrosis of the aorta and its main branches.

Methods: For ten patients underwent peripheral arteries assessment with measurement of intima media thickness (IMT), carotid femoral pulse wave velocity (PWV), radial and carotid augmentation index (AI), and ankle brachial index (ABI) by SCVLD. Blood pressure was assessed by 24h measurement. Aortic lesions were assessed by 16FDG PETscan coupled with computed tomography.

Results: Our population consisted in 72.7% of men from 30 to 76 years old. There was 45% of treated hypertensive (all controlled), 30% of dyslipidemic patients, 15% of diabetics and 57% of current or former smokers. One third was under interferon, 30% under corticosteroids and the rest were untreated. Mean disease duration was 10.2 years. An typical periarterial carotid fibrosis was noted in 21%. A coated aorta was found in 57% but only 24% of the patients had a active aortitis on PETscan. An augmentation of the global aortic stiffness (PWV) was present in 85% of the patients with 52% above the expected 95th percentile. There was a significant increase of all aortic stiffness parameters (pulse pressure, central pressure, amplification pressure) in patients with carotid or aortic inflarative lesions compared to those with no periarterial fibrosis. All ABIs were normal. Radial distensibility was not altered.

Conclusions: This non langerhans histiocytosis is characterized by a carotid periarterial fibrosis in 21% of the patients. An aortic infiltration was more frequent (57%) but active aortitis was found in only half the coated aortas. Aortic stiffness was increased in 85% of the patients in association with infiltrative inflammatory
lesions presence. This study highlights the link between anatomy and function in this new type of inflamed arteries

Utility of 320 slice mapping CT for adrenal vein sampling in subject suspected having primary aldosteronism compared with digital subtraction angiography and selective retrograde CT adrenal venography

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Background: Right-sided adrenal vein (AV) sampling (AVS) in subjects suspected to have primary aldosteronism (PA) is especially difficult because right AV is small and difficult to distinguish from other vessels. To evaluate the utility of preliminary 320 slice mapping CT for AVS in subjects suspected to have PA, we compared 320 slice mapping CT with digital subtraction angiography (DSA) and selective retrograde CT adrenal venography (SRCT AV) in successful AVS cases.

Materials and Methods: 64 subjects (28 male, mean age 55.2±11.1 years) who were suspected of having PA and who underwent preliminary 320 slice mapping CT (Aquilion one, Toshiba Medical). DSA, and SRCT AV with success of AVS re

Results: In all 64 subjects, successful AVS was confirmed. As the AVS gold standard, left- and right AV could be observed in 100% and 88% subjects in mapping CT, 100% and 78% subjects in DSA, and 100% and 100% subjects in SRCT AV, respectively, and detection of right AV was lower in mapping CT and DSA than in SRCT AV (both p<0.01). The right AV could not be visualized in DSA in 14 subjects because of vessel spasm, or joined to the right accessory vein. The right AV could not be visualized in mapping CT in 8 subjects because it was narrow or joined to the accessory hepatic vein or due to inappropriate acquisition time.

Conclusions: Preliminary 320 slice mapping CT could detect the AV, especially the right AV as accurately as DSA and SRCT AV. To improve visualization of the right AV, improvement of acquisition methods of CT may be needed.

Prognostic role of resistant hypertension for cardiovascular outcome: a prospective study in 2345 Greek hypertensives

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Purpose: To investigate the prevalence and the predictive value of resistant hypertension (RH) for the incidence of cardiovascular disease in essential hypertensives.

Methods: We prospectively followed up for a median period of 3.5 years (IQ 2.7-5.3 years) a non-selected uncomorbid hypertensives aged 56±11 years. All subjects were referred or self-referred in the hypertension unit of our institution and had at least one visit annually. RH at baseline was defined as office systolic BP >140 mmHg despite the concurrent use of 3 antihypertensive agents one of them being a diuretic. End-points of interest were the incidence of coronary artery disease (CAD), stroke, atrial fibrillation (AF) and their composite.

Results: A total of 7419 patients (2251 women, 4568 men) were included in the final analyses. A total of 944 sudden death, 534 cardiac death and 777 heart failure hospitalization occurred within an average of around 4.5 years follow-up.

Conclusion: The results have demonstrated that small to moderate dosages of anti-anxiety medications are associated with decreased risk of cardiac mortality and heart failure hospitalization in patients after new MI independent of traditional risk factors. Further work is needed to clarify the putative causal relationship.

Improved survival and nephroprotection in hypertensive rats by BAY 94-8862, a novel non-steroidal mineralocorticoid receptor antagonist

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Purpose: Blockade of the mineralocorticoid receptor (MR) can reduce morbidity and mortality in patients with heart failure. However, the use of currently available MR antagonists is limited by the occurrence of hyperkalemia, particularly in patients with co-existing renal insufficiency. In this study, we investigated our novel non-steroidal MR antagonist BAY 94-8862 vs. available steroidal MR antagonists in a preclinical model of cardio-renal hypertensive damage.

Methods: Male spontaneously hypertensive, stroke prone rats (SHRSP, age 10 weeks) were placed on a high salt diet for 7 weeks and randomized to receive orally either BAY 94-8862 (10 mg/kg/d), eplerenone (30 mg/kg/d), spironolactone (30 mg/kg/d), or vehicle (n=12 per group). We monitored survival and determined the total protein, creatinine and the inflammatory marker osteopontin (OPN) and performed histopathology (semiquantitative scoring) of kidney damage in surviving animals.

Results: There was a significant protection (p<0.05) from mortality after a treatment period of 7 weeks in the BAY 94-8862 group versus placebo while no mortality benefit was observed from eplerenone or spironolactone treatment. We could observe a significant reduction of the urinary protein/creatinine ratio in the BAY 94-8862 group (0.4±0.09) compared to vehicle control (1.9±0.40) and significant reductions of urinary OPN protein and OPN mRNA in kidneys from BAY 94-8862 treated animals. The steroidal MR antagonists spironolactone and eplerenone did not reduce OPN concentrations at the applied dosages of 30 mg/kg in this study. Histopathological analysis of the kidneys revealed substantial reduction of vascular, glomerular and tubulo-interstitial damage in the BAY 94-8862 group (mean grade 3.3), compared to placebo (mean grade 3.0), whereas eplerenone (mean grade 2.58) and spironolactone (mean grade 3.7) were not effective.

Conclusion: The novel, non-steroidal mineralocorticoid antagonist BAY 94-8862...
protector from both, cardiac and renal end-organ damage and improves survival in severe arterial hypertension. The norepinephrinergic effect of BAV 94-8682 offers a potential benefit over the use of traditional, steroidal MR antagonists. The compound is currently being tested in a clinical Phase II trial.

Sympathetically-mediated cardiovascular responses to acute hypoxia exposure are attenuated by acetazolamide

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Acute Mountains Sickness (AMS) is characterized by hypoxia-induced sympathetic overactivation. Acetazolamide (ACZ), established therapy for AMS, has been suggested to be beneficial for its respiratory stimulant properties in conditions characterized by chronic hypoxia exposure: heart failure, pulmonary diseases, sleep apnea syndromes. However, ACZ mechanism of action is still not completely understood. We aimed to explore the effects of ACZ on full cardiopulmonary responses to selective stimulation of peripheral chemoreceptors (PC) and of central chemoreceptors (CC). Meth: 43 healthy volunteers, double-blindly randomized to ACZ 250 mg BID or placebo (PL) underwent 6-min stimulation of PC (isocapnic hypoxia: 10% O2) and CC (hypoxic hypercapnia: 95% O2, 7% CO2) at sea level. VE, O2 saturation (satO2), end-tidal CO2 (ETCO2), heart rate (HR), systolic blood pressure (SBP) were continuously recorded.

Results (table 1): Isocapnic hypoxia. ACZ did not affect VE increase and satO2 decrease during hypoxia (p > 0.05). If decreased baseline SBP, and attenuated SBP and HR increase compared to PL (p < 0.01, p < 0.05). Hypoxic hypercapnia. VE increase was greater with ACZ (p < 0.001) compared to PL (p < 0.05). ACZ did not affect the increase (p > 0.05) in SBP and HR compared to PL.

Table 1

<table>
<thead>
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<th>SBP (mmHg)</th>
<th>HR (beats/min)</th>
<th>VE (L/min)</th>
<th>satO2 (%)</th>
<th>ETCO2 (mmHg)</th>
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<td>114±9</td>
<td>81±11</td>
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<td>PL 6-min hypoxia</td>
<td>120±11</td>
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<td>PL 6-min hypercapnia</td>
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<td>72±12</td>
<td>12.4±5.9</td>
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<td>ACZ baseline</td>
<td>106±13</td>
<td>65±10</td>
<td>3.3±0.9</td>
<td>98±1</td>
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<tr>
<td>ACZ 6-min hypoxia</td>
<td>105±13</td>
<td>70±10</td>
<td>5.2±1.6</td>
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<td>ACZ 6-min hypercapnia</td>
<td>126±19</td>
<td>76±13</td>
<td>15.3±7.4†</td>
<td>98±4</td>
</tr>
</tbody>
</table>

p < 0.001 vs baseline, p < 0.05 vs PL; *p < 0.05 time effect.

Conclusions: Our data confirm that ACZ potentiates the ventilatory response to CC stimulation. While ACZ does not affect the ventilatory response to acute hypoxia, it does attenuate the sympathetically mediated increase in HR and SBP observed with PC stimulation. Besides AMS, this newly described cardiovascular effects of ACZ may favorably come into play in the treatment of pathological cardiopulmonary conditions characterized by hypoxia exposure.

Sympathetically-mediated cardiovascular responses to acute hypoxia exposure are attenuated by acetazolamide

STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension

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Purpose: The STARTS-2 trial is assessing long-term sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension (PAH) patients. The aim of this study was to examine the function of BRAP2 in the heart. Meth: Upon load induced cardiac hypertrophy in a proteomic study. Accordingly, the aim was to identify proteins differentially regulated in hearts of heterozygous mice compared to wild-type controls. Heterozygous mice were born and survived without any phenotypic abnormalities.

STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension

The effect of continuous positive airway pressure on hypertension management beyond optimal antihypertensive treatment: a 3-year follow-up study


Purpose: We investigated the long-term efficiency of Continuous Positive Airway Pressure (CPAP) on blood pressure (BP) management of hypertensive patients with Obstructive Sleep Apnea (OSA) on top of optimal antihypertensive medical treatment. Meth: We prospectively studied 91 non-sleepy patients (aged 54±9 years, 69 males) with essential hypertension and moderate-to-severe OSA, newly diagnosed with polysomnography (apnea hypopnea index-AHI<15) for a mean period of 3.1 years. Subjects initially underwent office evaluation, and were switched to carefully designed antihypertensive treatment targeting office BP <140/90 mmHg (<130/80 mmHg in diabetics). Subsequently, participants underwent regular visits to optimize hypertension management and control. In a subgroup of patients (N=34), ambulatory BP monitoring was performed at baseline and at the follow-up visit. Depending on the acceptance and persistence of CPAP application, two groups were defined those that adhered to CPAP treatment during the whole follow-up period (N=41) while those that did not follow CPAP therapy served as controls (N=50).

Results: At baseline, on-CPAP subjects compared to controls did not differ regarding systolic and diastolic BP levels, ambulatory BP levels and number of antihypertensive drugs prescribed but exhibited more severe OSA (66% vs. 38%, p < 0.015). By the end of the follow-up period, in the entire population, office systolic and diastolic BP were significantly lower compared to baseline (133±12 vs. 146±15 and 85±9 vs. 96±10 respectively, p < 0.001) while number of antihypertensive drugs applied was higher (2.44±1.21 vs. 2.37±1.1, p < 0.001). On-CPAP subjects and controls exhibited similar office BP levels (133±12 vs. 133±13 mmHg, 84±9 vs. 85±9 mmHg, respectively; p=NS), ambulatory BP levels (125/76 vs. 107/67 mmHg, p=NS), number of patients with controlled hypertension (71% vs. 70%, p=NS), and number of antihypertensive drugs to achieve BP control (2.2±1.09 vs. 2.1±0.72, p=NS). In multiple linear regression models, CPAP application was not associated with changes in BP levels or a need for less antihypertensive drugs for better BP control. Carefully designed drug treatment should be regarded as the mainstay of therapy in these patients.
until more than 12 months of age. Brap2flox/flox mice, but not Brap2flox/flox MHC-Cre/+, developed severe heart failure and died shortly after birth (P5–6). Echocardiographic examination revealed ventricular dilatation and strong functional impairment at day 4 after birth. Real-time RT PCR revealed a decrease in MHCα/MHCβ ratio, consistent with the phenotype of heart failure (Brap2flox/flox MHC-Cre/+; 17.3±4.6%; n=6; Brap2flox/flox MHC-Cre/−; 4.0±0.1%; n=6; p<0.005). While analysis of histological sections by tunel staining displayed no signs of increased apoptosis, immunohistological staining of the cell cycle regulator Cyclin D1 and proliferation marker PCNA suggests a marked attenuation in cardiomyocyte cell cycle progression (PCNA positive cells: Brap2flox/flox MHC-Cre/−: 94.2±10.4%; n=6; Brap2flox/flox MHC-Cre/+; 46.7±10.4%; n=4; p<0.0005). Moreover, BrdU assay showed a diminished rate of DNA synthesis in the BRAP2 deficient myocardium.

**Conclusion:** In the present study we demonstrate that BRAP2 is essential for cardiac development and deletion of BRAP2 results in early heart failure and attenuated cardiomyocyte proliferation.

**Endothelial microparticles (EMP) derived from Glucose treated endothelial cells differ in function and miR-expression from EMP derived from untreated cells**

**Methods and results:** EMP were generated after 24 hours starvation from human coronary artery endothelial cells (HCAEC). In addition, HCAEC were treated for 72h with 30mM Glucose (hyperglycaemic condition) and EMP were generated after 24h starvation. We defined them as modified EMP as ‘‘injured’’ EMP (EMP). Imaging of the releasing process and the uptake of EMP by HCAEC was performed with confocal and fluorescence microscopy. EMP significantly reduced TNF-alpha induced adhesion protein expression (ICAM-1, VCAM-1) in HCAEC compared to control and EMP treatment. Additionally, EMP, but not iEMP protected HCAEC from apoptosis (pos. control: 100%; EMP: 70%; p<0.05) and improved migration of HCAEC (EMP 60% vs. iEMP 43%; p<0.05). In vivo, reendothelialization was improved in EMP treated mice compared to control and iEMP (29.8% vs. 42.8% vs. 58% remained denuded area; p<0.05). To evaluate if the described effects are mediated through miRNAS, Tagman miRNA-array of 384 different miRNAS was performed in EMP and iEMP. In EMP, 9 miRNAS were upregulated and 21 were downregulated compared to iEMP.

**Conclusion:** We present first evidence that EMP derived under pathological conditions (high Glucose exposure) lose their protective effects on target cells compared to EMP from untreated cells. Differences in miRNA expression in EMP and iEMP might be a possible explanation.

**Development of autologous tissue small caliber vascular grafts (BIOTUBES)**

**Objectives:** There are actually no small-caliber synthetic vascular grafts (<6 mm) with acceptable patency rate for the use of coronary bypass or peripheral vascular repair below the knee in case the autologous vessels are not available. We have reported that small diameter autologous tubular tissues without synthetic support materials ‘‘BIOTUBES’’ could easily be constructed by simple and safe in vivo tissue engineering. They were useful as small-caliber vascular grafts in the rabbit model for the short experimental periods, exhibiting rapid regeneration of hierarchical vascular wall structure within 12 weeks. In this study, we summarize the development of BIOTUBES.

**Method:** Silicone rod molds (diameter: 1.5–5.5 mm, length: 20–50 mm) were placed into subcutaneous pouches of Wistar rats, Japan white rabbits or Beagle dogs. After 1 month, BIOTUBES formed around the molds were autoplanted to the aorta (1.5 mm; rats) or the carotid arteries (2 mm; rabbits and 5 mm; dogs) of their respective animals. They were evaluated after determined period of implantation.

**Results:** Irrespective of species, BIOTUBES had thin wall (ca. 0.1 mm) and mainly composed of homogeneous and mainly elastic collagen fibers.

**Rats:** After 12-week implantation, other than the oriented endothelial layer and smooth muscle layer, multilayered elastin fiber formation was observed in the grafts.

**Rabbits:** Little thrombus was formed on the luminal surfaces completely covered with endothelial cells within 2 weeks. During 2 year-implantation, neither formation of aneurysm nor rupturing was observed in BIOTUBES.

**Conclusions:** By rapid arterization, completely autologous BIOTUBES with no synthetic support materials withstand systemic blood pressure and exhibited-
Percutaneous intramyocardial delivery of secretome of apoptotic white blood cells (APOSEC) improves myocardial viability and left ventricular function in experimental ischemic cardiomyopathy

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Purpose: Despite promising preclinical and clinical results of the cell-based therapy in chronic ischemic heart failure, the achievable benefit still remains suboptimal. We have previously shown the regenerative capacity of the secretome of the apoptotic white blood cells (APOSEC) in acute myocardial infarction (AMI). In the present experiment we have investigated the effect of Aposec on the ventricular function and ischemia in experimental ischemic cardiomyopathy.

Methods: Closed chest reperfused Aml was induced by 90-min occlusion of the mid left anterior descending coronary artery in 14 domestic pigs, followed by baseline echocardiographic measurements. Aml was complicated with AMI. Three months later (day 90), pigs were randomly divided and received echocardiography (FD, DE, parameters) or M-mode echocardiography at baseline and at 1, 3, 6, and 9 months post-Aml. Myocardial infarction was identified by the presence of an ischemic area (10-13 treatments locations). After 1 month follow up (FUP) (day 60), control cardiac MRI with late enhancement and measurements of myocardial viability via diastolic electroanatomical mapping were performed. Gene expression of an infarcted area and the non-infarcted areas were evaluated. For the in vivo study, tamoxifen was injected via tail vein injection the day prior to the MRI scan.

Results: APOSEC treatment was associated with a significant improvement of left ventricular function in terms of ejection fraction (EF) and end-diastolic function (LVEF), as compared with the Medium group. APOSEC treatment was associated with a significant improvement of left ventricular function in terms of ejection fraction (EF) and end-diastolic function (LVEF), as compared with the Medium group. Conclusion: The APOSEC treatment was associated with a significant improvement of left ventricular function in terms of ejection fraction (EF) and end-diastolic function (LVEF), as compared with the Medium group.

Angiogenesis effect improvement of anti-ICAM-1 targeted microbubbles for mediation of transfected hAng-1 gene in ischemic myocardium

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Objective: This study aimed to verify the feasibility and effectiveness of using targeted anti-ICAM-1 microbubble as a gene carrier, which was capable to specifically transport therapeutic gene to the myocardial infarction area in vivo, and enhance the angiogenesis effects, as compared with the gene delivery system of non-targeted microbubbles.

Methods: For gene therapy mediated by microbubbles and ultrasound irradiation, AMI rabbits were divided into four groups: control group, non-targeted microbubbles delivery group (non-TMB), ICAM-1 targeted microbubble delivery group (ICAM-TMB), and direct myocardial injection group (MI). The hAng-1 genes via venous and direct injection into rabbit ischemic myocardium were transferred under ultrasound irradiation. Two weeks after gene transfection, myocardium contrast echocardiography (MCE) was applied for regional myocardial perfusion analysis. One week later, the rabbits were sacrificed, and the myocardium from the infarct area was collected for histological examination and Western blot analysis. The expression of anti-ICAM-1 targeted microbubbles was identified by the most efficient method of myocardial injection. The ICAM-1 microbubbles would be regarded as a new targeted gene carrier which was capable to induce therapeutic angiogenesis after myocardial infarction, and may provide new strategy for future clinical gene therapy.

CONCLUSIONS: The ICAM-1 targeted microbubbles were capable to transfect the hAng-1 gene to the ischemic myocardium directly and efficiently and the transfection efficiency of the ICAM-1 targeted microbubbles was identified by the most efficient method of myocardial injection. The ICAM-1 microbubbles would be regarded as a new targeted gene carrier which was capable to induce therapeutic angiogenesis after myocardial infarction, and may provide new strategy for future clinical gene therapy.
Emergency catheter ablation for sustained ventricular tachyarrhythmias in patients with acute heart failure decomposition

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Purpose: Ventricular tachycardia (VT) and ventricular fibrillation (VF) are uncommon in patients hospitalized with acute heart failure (AHF). While pharmacological treatment is the first-line approach, radiofrequency catheter ablation (RFCA) could be another therapeutic option for recurrent VT/VF under pharmacological therapy. We sought to elucidate the efficacy of emergency RFCA for sustained VT/VF in AHF patients.

Methods: We reviewed the medical records over the 10 most recent years. Patients eligible for the present analysis were those who underwent an emergency RFCA for drug-refractory sustained VT/VF during AHF decompensation. The anatomic substrates were found in the electrophysiological studies (EPS) in 20 patients. Radiofrequency catheter ablation (RFCA) was performed in all patients. Success was defined as an area with biphocal amplitude of the session was achieved in 15 patients (88%). Successful site electrograms showed discrete Purkinje potentials in all patients with premature contractions triggering VF (100%) and three of the thirteen patients with monomorphic VTs (23%). Although five patients (29%) underwent the second session 10±4 days after the first. Ablation sites were located 25±22 months, five patients died without any sudden cardiac death. Emergence of sustained VTs seen in six patients was not associated with patient death (p<0.05).

Conclusions: Emergency RFCA for sustained ventricular tachyarrhythmias during AHF decompensation is an effective and promising therapeutic option, which might improve the prognosis of patients with advanced heart failure. Purkinje fiber can be an ablation target not only in those with premature contractions triggering VF, but also in about 20% of those with monomorphic VTs.

Long term follow-up after ablation of intra-atrial reentrant tachycardia in repaired congenital heart disease: mechanisms, ablation success and maintenance of sinus rhythm


Intra-atrial reentrant tachycardia (IART) is a common complication during the follow-up of surgically repaired congenital heart disease (CHD) patients, not only involving a circuit around scar tissue but also typical atrial flutter. Ablation of these circuits can be a challenging procedure, but potential benefit is especially high in this group of patients. We describe IART type, ablation success and follow-up.

Methods: A total of 54 CHD patients (31 male, mean age of patients who remain in sinus rhythm after long follow-up. The tachyarrhythmias associated with T AVNs were unique in these groups. AT or PVC/VT occurred long term after operation. The access to the atrium or ventricle is restricted after Fontan operation, therefore arrhythmogenicity should be evaluated before Fontan operation.
**P5365 Evaluation of gold and platinum electrode multipolar phased RF ablation in a swine model in vivo: microembolus production and energy delivery performance**

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Production of microemboli has been implicated in the occurrence of cerebral lesions seen on diffusion-weighted MRI scans. We hypothesized that ablation with multidetector (9 or 10), duty cycled, phased RF catheters (PVC, Medtronic) with gold (Au) electrodes, compared to platinum (Pt), would have improved passive convective cooling and more uniform temperature distribution resulting in higher power delivery without an increase in microbubble (MB) formation.

**Methods:** In 20 swine, right and left anterior venous (PV) ablations were performed with Pt and Au PVC catheters. An endocarpial loop from femoral artery to vein was created with cannulae and tubing. A Pall filter (73 um) and 2 microbubble (MB) detectors (GAMPT) were placed in series to detect MBs and particulate debris during ablations. Ablations were performed in 4:1 or 2:1 (bipolar, unipolar) modes with temperature feedback power control at 60°C and a max of 8 or 9 watts respectively.

**Results:** Intracardiac ablations performed without altering distal and proximal Pt electrodes to come in close proximity resulted in similar microbubble volumes, see graph. Compared to Pt, Au electrodes had a higher rate of being power limited (43% vs 32%, p<0.001), and for temperatures ≥41 and 2:1 modes were 0.5W (p=0.03) and 0.7W (p=0.0005) higher power respectively. All lesions were free of endocardial disruption and adherent thrombus.

**Conclusions:** Au catheters produced more consistent power delivery than Pt without an increase in MB production. This may be due to better passive convective cooling of the electrodes.

**Figure 1. Microbubbles during ablations**

**P5366 Catheter ablation of Ventricular Arrhythmias in patients with ischemic cardiomyopathy utilizing the magnetic robotic system: results from a prospective multicenter registry**

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**Introduction:** Remote magnetic navigation (RMN) and ablation has been reported as a feasible and safe technique for the treatment of ventricular arrhythmias (VA). The introduction of the magnetic irrigated tip catheter has improved the success rate of the VAs ablation. We report data from a prospective registry on consecutive cases of VAs ablation with the RMN in pts with ischemic cardiomyopathy (IC).

**Methods:** Consecutive pts with IC undergoing VAs ablation with the RMN and the magnetic irrigated catheter at different Institutions were enrolled in this prospective registry. Conventional mapping techniques including pace mapping, activation mapping and entrainment mapping as well as substrate mapping techniques were utilized to define the mechanism of the arrhythmias and to identify potential site for ablation. Procedural endpoints included substrate modification by endocardial scar border ablation and elimination of late potentials. Post-ablation pacing maneuvers and isoproterenol were used to verify the inducibility of the VAs.

**Results:** A total of 104 consecutive pts (86% male, 67±10 years, LVEF 31±15) with IC were included in this study. Ninety-eight (94%) patients had LVD; implanted. The population had high prevalence of hypertension (92%), diabetes (35%), and hyperlipidaemia (66%). Endocardial mapping was performed in all patients, while both endo-epi mapping in 21 (20%) patients. VT was inducible in 81 (78%) patients with a cycle length of 360±107. An average of 416±62 endocardial and 384±58 epicardial mapping points were obtained for the reconstruction of the chamber of interest. VA were successfully ablated with RMN in 87 (94%) patients; 17 (16%) patients required cross over to manual ablation. Acute ablation success was achieved in all patients. The mean procedural duration was 2.9±1.6 hours. The total duration of radio frequency and fluoroscopy time were 68±18, and 26±14 minutes respectively. In 4 (4%) patients, VT rapidly deteriorated to VF during RF application. 3 (3%) pts had hemodynamic instability requiring CPR. At 14±6 moth follow-up 75 (72%) patients were VA-free. No acute complications were reported.

**Conclusion:** This prospective registry shows that VAs ablation using RMN is feasible and effective in pts with IC.

**P5367 Innovative twelve-hole open irrigation gold electrode allows for reduced irrigation flow rate without compromising ablation safety and effectiveness**

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**Introduction:** Novel electrode materials and configurations of irrigation holes are applied for more efficient cooling of RF ablation electrodes, aiming at safe creation of large lesions at low irrigation flow rate. We tested the hypothesis that a novel gold RF ablation electrode with innovative configuration of 12 irrigation holes allows for safe and effective lesion creation a reduced irrigation flow rate without compromising safety and effectiveness of ablation.

**Methods:** In 5 dogs, the skin over the thigh muscle was incised and skin edges raised to a cradle which was flushed with blood (37 °C, 250 ml/min). Settings: electrode orientation: parallel and perpendicular to the muscle surface; irrigation flow rate (F): 8 and 15 ml/min; contact force: 10 g; RF power: 30 W, applied for 60 s. Electrode temperatures (Te), coagulum formation and steam pops were recorded and lesion volumes (V) determined by microscopy. A novel gold electrode design (12H Au; AlCaFlux Extra Gold, 12 holes) was compared to a standard platinum-iridium electrode (6H Pt; AlCaFlux Circle, 6 holes) (both 7F, 3.5 mm, Biotronik, Berlin, Germany).

**Results:** Coagulum was not observed on muscle surface and on electrode. Steam pop occurrence was not significantly influenced by irrigation flow rate. At reduced flow rate 12H Au resulted in larger or similar lesions compared to 6H at normal flow rate.

**Table 1.**

<table>
<thead>
<tr>
<th>F [ml/min]</th>
<th>12H Au Parallel</th>
<th>12H Au Perpendicular</th>
<th>6H Pt Parallel</th>
<th>6H Pt Perpendicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>14</td>
<td>12</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>14</td>
<td>12</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>V [mm³]</td>
<td>861±864</td>
<td>908±949</td>
<td>104±769</td>
<td>629±805</td>
</tr>
<tr>
<td>Te (°C)</td>
<td>39.4±37.3</td>
<td>42.1±36.7</td>
<td>53.8±50.2</td>
<td>46.7±41.0</td>
</tr>
</tbody>
</table>

*p<0.05 (8 ml/min vs 15 ml/min).

**Conclusions:** The 12H Au electrode allows for reduction of irrigation flow rate without compromising safety and effectiveness of ablation. This feature is particularly important with respect to ablation in heart failure patients.

**P5368 Forces on cardiac implantable electronic devices during remote magnetic navigation**

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**Purpose:** Remote magnetic navigation systems are used for catheter navigation in cardiac electrophysiological ablation procedures. In this setting, ferromagnetic particles will be moved by changes of the magnetic field. It is unknown to what extent cardiac implantable electronic devices (CIED) are affected by the magnetic field when using magnetic navigation and whether these forces may exceed the limit of 5 N that is demanded in the DIN VE norm as maximal force that could be applied to the connected leads.

**Methods:** A total of 119 rhythm devices were examined in a magnetic field of 0.1 Tesla using the NIobe® Magnetic Navigation System (Stereotaxis, St. Louis, USA). Forces acting on the devices were measured with the force measurement tool Futuk LRF 400 (Futuk Advanced Sensor Technology Inc., Irvine, California, USA). A standardized protocol of different movements of the magnetic field including all three dimensions was performed and maximal forces on the CIED were assessed.

**Results:** Out of 119 devices, 77 pacemakers (58 different model families from 11 manufacturers) and 42 cardioverter-defibrillators (28 different model families from 6 manufacturers) were examined. The mean force that could be observed was 0.33±0.13 N for pacemakers (range 0.16 – 1.12 N) and 1.05±0.11 N for cardioverter-defibrillators (range 0.88 – 1.38 N) when exposed to the magnetic field.

**Conclusions:** Exposure of pacemakers or implantable cardioverter defibrillators to a magnetic field of 0.1 Tesla does not result in a tension force exceeding the regulatory demanded 5 N that could damage the connected leads.
Dabigatran in patients post atrial fibrillation ablation

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Background: Patients undergoing catheter ablation for atrial fibrillation (AF) are at increased thromboembolic risk and require oral anticoagulation for at least 3 months. Dabigatran, an oral direct thrombin inhibitor, has recently been approved for stroke risk reduction in patients with non-valvular AF. Experiences with this drug after AF catheter ablation are limited to two studies with a short follow-up and controversial results. Thus, we aimed to assess the longer-term safety and efficacy of an anticoagulation approach with dabigatran in patients undergoing AF catheter ablation.

Methods: From July 2010 until September 2011 patients with AF undergoing catheter ablation were prospectively included. Anticoagulation with dabigatran was started the same evening depending on the status of femoral puncture sites. Clinical follow-up was performed at 3, 6, and 12 months post ablation with continuation of anticoagulation for at least 3 to 6 months depending on results of semi-7 day Holter ECGs and on patient's CHA2DS2-VASc Score. Clinical outcome (stroke, thromboembolic events, major bleeding), adverse effects and anticoagulation status were assessed at discharge and follow-up.

Results: 89 patients with symptomatic AF (63 ± 8 years, 78% male, 57% paroxysmal AF, left atrial diameter (PLAX) 42 ± 6 mm, LVEF 60 ± 9%) were included. All patients were treated with dabigatran twice daily for at least 3 months. 78% of patients received dabigatran at a dose of 110 mg twice daily and 22% at 150 mg twice daily. Thromboembolic risk [CHA2DS2-VASc-Score 2 (CHA2DS2-VASc Score 1 (CHA2DS2-VASc Score 0)] was intermediate and bleeding risk (HASBLED Score 1 (CHA2DS2-VASc Score 0) low. During follow-up electrocardioscans for arrhythmia recurrence was performed in 9 patients. Only 1 patient underwent additional transesophageal echo as he had discontinued dabigatran. During follow-up (274 [59, 497] days) no stroke, systemic embolism, no minor or major hemorrhage could be observed. Acceptance and compliance was high with no relevant adverse effects leading to cessation of dabigatran.

Conclusion: Anticoagulation approach with dabigatran proved safe and effective in preventing thromboembolic events at mid-term follow-up and was associated with high patient acceptance. Due to its predictable dose-response relationship without the need of "bridging" and laboratory monitoring this anticoagulation approach represents an attractive alternative to the conventional approach with warfarin.

Evaluation of gold and platinum electrode multipolar phased radiofrequency ablation in a swine model: characteristics of energy delivery performance in a swine thigh muscle preparation

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Effective cooling of tissue during RF ablation is needed to effectively ablate tissue. We hypothesized that ablation with multielectrode, duty cycled, phased RF catheters (Medtronic) with gold (Au) electrodes, compared to platinum (Pt), would have more effective passive convective cooling resulting in higher power delivery and deeper lesion formation based on the thermal properties of Au.

Methods: In 4 swine, 8 thigh muscles were ablated using Au and Pt multipolar test catheters under high and low blood flow conditions. Test catheter electrodes included a thermocouple (TC) on both the tissue and blood facing (opposite) sides of electrodes. Duty cycled RF power modulation targeted the tissue interface temperature at 60°C in phased 2.1 (9 W max) and 4.1 (8 W max) bipolar/unipolar ratios.

Results: Lesions with Au were deeper than Pt in low flow with both 4.1 (p = 0.004) and 2.1 (p = 0.014) while not different in high flow. Powers were also higher in low flow conditions with Au (p = 0.0001). For all electrodes, powers were lower and temparatures were higher in low vs high flow (p = 0.0002; and p = 0.0001). The delta between the tissue and blood contact thermocouple was much lower with Au (p = 0.0001) demonstrating better thermal conduction in the Au electrodes.

Safety of adjunctive antiplatelet therapy in patients undergoing radiofrequency ablation in left atrial procedures A Retrospective Registry

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Background: Periprocedural anticoagulation strategy during left atrial ablation procedures (LAAPs) is still a matter of debate. Increasing number of patients at high risk of systemic emboli who are on adjunctive antiplatelet therapy (aspirin and/or thienopyridine) after percutaneous coronary intervention are referred for left atrial ablation procedures. Safety and periprocedural potential complications of a concomitant antiplatelet therapy are still unknown. Objective: Evaluate the safety and management of adjunctive antiplatelet therapy during LAAPs.

Methods: Between March 2011 and January 2012 LAAPs were performed in 619 consecutive patients. 583 patients of the pre-defined groups W (only warfarin), WA (warfarin and aspirin) or WAT (warfarin and antiplatelet therapy) were evaluated concerning the periprocedural anticoagulation therapy. All ablation procedures were performed under continuous warfarinization.

Results: In the W and WAT groups the preprocedural mean INR were respectively (2.1 ± 0.44 vs 2.1 ± 0.35; p = 0.75). Baseline and maximum ACT were collected (see Table). Periprocedural pericardial tamponade occurred in 8 patients (4 on W and 4 on WAT). No other major bleeding complications were recognized. Significant periprocedural pericardial tamponade were detected in patients on WAT (0.81% vs 4.54%; p < 0.0021). Stroke occurred in only one patients on WAT.

Conclusions: Major bleeding complications

Ablation of supraventricular tachycardias. A randomized trial on catheter ablation: simplified technique versus conventional technique

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Purpose: To compare the use of a minimal (SIN) with a conventional (CON) catheter approach for the mapping and ablation of regular supraventricular tachycardias (SVT) in the setting of a randomized-controlled trial.

Methods and results: Two hundred sixty six patients (age 48 ± 11.2 years, 137 male) were randomized to a SIN or CON group. The SIN approach involved using a maximum of two catheters for SVT (ablation catheter included), whereas the CON approach involved more than two catheters, respectively. Acute procedural success was similar between the two groups. There was significant difference in overall procedure times (63 ± 11 vs 85 ± 5 min) (P < 0.01) and fluoroscopy times (20 ± 8 vs 35 ± 15 min) (P < 0.01). Catheter costs were significantly lower in SIN compared with CON, (P < 0.001). At 12 month follow-up, seven patients in MIN (5.5%) and eight patients in CON (5.4%) had documented recurrence of the index arrhythmia. There were no major complications in both groups.

Conclusions: The use of a SIN approach in the treatment of SVT is as effective and safe as using a CON approach. The SIN approach is faster and more cost-effective.

Idiopathic right ventricular tachycardia and premature ventricular contractions: ablation strategy and further look into pace map guided by non-contact mapping

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Background: The spatial resolution between activation and pace mapping was still controversial. In this study, we would compare the spatial resolution between them associated with non-contact mapping.

Methods: The non-contact mapping was used to identify the earliest activation (EA) and the breakout (BO) site. Patients were divided into the distance between the EA and the BO site < 6 mm group (group A) and ≥ 6 mm group (group B). Activation was randomized either at the BO site or the EA site. The non-contact mapping combination with activation mapping or pace mapping was used to calculate
the area of myocardium activated (EAA) and the area of myocardium captured (ECA).

**Results:** There were 90 women and 36 men. The mean age was 45.76 ± 10.13 years old. The acute success rate was 96.83% (152/156). Ablation was successful at the BO site in 40 patients, and succeeded at the EA site in 91 patients (P < 0.01). Pace score is similar between the EA and the BO site and between the group A and the group B (P > 0.05, respectively). The ECA within the first 1 ms, 7 ms, and 10 ms was bigger than the corresponding EAA at the EA site (P < 0.01, respectively). Similarly, the ECA within the first 1 ms, and 5 ms was bigger than the corresponding EAA at the BO site (P < 0.05, respectively). However, no significant difference between the ECA within the first 7 ms, and 10ms and the corresponding EAA at the BO site (P > 0.05, respectively).

**Conclusion:** Activation mapping provide better spatial resolution than pace mapping for identifying the origin of ROVIT/PV by the non-contact mapping. Clinical Trial Registration: ChiCTR-TRC-11001584.  

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**P5376**  
**Operator chosen procedural variables determine the effectiveness of cavotricuspid isthmus ablation: a post-hoc analysis of the aurum study**  
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**Background:** Radiofrequency catheter ablation of typical atrial flutter (AFL) can vary largely in duration from patient to patient. The objective of this post-hoc analysis was to identify independent predictors of the acute ablation success rate versus cumulative ablation time.

**Methods:** 448 patients undergoing AFL ablation with non-irrigated 8-mm catheters at 19 clinical centers were included in this retrospective multivariate analysis. Twelve patient and 8 procedural variables (including catheter-tip material (gold vs. platinum-iridium) and the ablation technique (maximum voltage-guided vs. conventional anatomical approach)) were used as covariates in Cox constant proportional hazards model.

**Results:** Among easily controllable procedural variables, independent predictors of better success rate were: higher presets of maximum temperature [hazard ratio (HR): 1.06 per 1°C; empirically determined optimal value: 70°C], higher presets of maximum power [HR: 1.02 per 1 W; optimal: 70 W], gold-tip catheter [HR: 1.276], and maximum voltage-guided ablation technique [HR: 1.79]. The combination of optimal settings for these variables reduced the median cumulative ablation time (compared with the entire study cohort) from 8.3 to 4.3 min, median procedure duration from 76 to 55 min, and median fluoroscopy time from 14 to 7 min. Additional independent predictors were peak temperature and mean temperature (partly controllably by the operator), and hypertension and left heart hypertrophy (non-controllable). Among non-indicative variables were: history of persistent AFL, history of atrial fibrillation, AFL at the start of ablation, coronary artery disease, age, body surface, and ejection fraction.

**Conclusion:** The maximum voltage-guided gold-tip ablation at 70°C and 70 W was associated with maximal effectiveness for non-irrigated AFL of.
Incidence and mechanisms of cardiac perforation during radiofrequency ablation in medium size centers.


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Introduction: Radiofrequency catheter ablation of atrial fibrillation (CAAF) is being increasingly performed in medium size centers. In a recent meta-analysis it was shown that Cardiac perforation (CP) occurs in 1.3% of patients (pts) undergoing CAAF in many high volume centers. In moderate volume centers little is known about the rate and mechanism of CP.

Methods: A 14 item questionnaire was sent to 8 medium-size EP centers (30 to 150 CAAF's per year) in European countries. The per-procedural (1-24 h) incidence rate and the mechanisms of CP were analyzed.

Results: Between 1998 and 2011, 3027 CAAF were performed and 42 pts (31 male; mean age 60.5 ±10.2 y) presented CP (incidence rate of 1.4%). In the past year, the CAAF median range performed per center was 78 (42 to 110). CAAF was done under general anesthesia for 349 pts (11.7%). Indications of CAAF were paroxysmal atrial fibrillation (AF) in 28 pts (65.1%), persistent AF in 12 pts (27.9%) and atrial tachycardia post AF in 3 pts (6.9%). Mean left atrial size was 35.3 ±10.9 mm. A transesophageal echocardiography was used to guide transseptal puncture in 6 pts (13.9%). The occurrence of CP in 16 pts (37.2%) was related to transseptal puncture, in 9 pts (20.9%) it was due to steam popping during radiofrequency delivery, and in 6 pts (13.9%) it was attributed to high pressure catheter manipulation. In the remaining 12 pts CP mechanism was unknown. One pt had CP during a magnetic navigation procedure (the likely mechanism being steam popping). Invasive blood pressure monitoring was not performed in any of the CP cases. The management of CP was conservative in 18 pts (41.8%). Puncture and high pressure during catheter manipulation. In the remaining 12 pts CP mechanism was unknown. One pt had CP during a magnetic navigation procedure (the likely mechanism being steam popping). Invasive blood pressure monitoring was not performed in any of the CP cases. The management of CP was conservative in 18 pts (41.8%). Puncture and high pressure during catheter manipulation.

Conclusion: The incidence of CP in medium-size centers appears to be similar to the results of previous studies in high volume centers. The three main CP mechanisms identified are steam popping during radiofrequency delivery, transseptal puncture and high pressure during catheter manipulation.

Irrigated gold-tip catheter ablation of persistent atrial fibrillation: safety, feasibility and outcome of a magnetically guided technique

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Purpose: Magnetically guided irrigated ablation has been introduced for atrial fibrillation (AF) ablation. However, data on ablation of persistent AF is scarce and first generation platinum-iridium catheters were burdened by char formation at the catheter tip. Furthermore, electromagnetic transmission of these catheters may be suboptimal. Irrigated gold-tip catheters have been introduced to overcome these issues.

Results: Antral pulmonary vein (PV) isolation (PVAI) was performed using a 5-mm irrigated gold-tip magnetic catheter. Power setting: 48°C maximum, 50 W, 15 s lesion duration, flow-rate: 30 ml/min. The catheter tip was guided by a uni- directional magnetic field and a motor driven steerable catheter. Left atrial maps were created using an impedance-based left atrial reconstruction and fused with a preprocedural CT or an intraprocedural rotational angiography based scan. Follow-up performed 3, 6, 12, 18 and 24 months after ablation included a clinical visit, a 12 lead ECG and an intraprocedural rotational angiography based scan. Follow-up performed 3, 6, 12, 18 and 24 months after ablation included a clinical visit, a 12 lead ECG and an intraprocedural rotational angiography based scan.

Conclusions: Remote magnetic navigation for PVAI in persistent AF provides high procedural success rates and seems to be safe and feasible using an irrigated gold-tip catheter. Effectiveness of this novel technique can be confirmed by mid-term follow-up.

Characterization of radiofrequency redo procedures for recurrence of atrial fibrillation following cryoballon pulmonary vein isolation

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Cryoballon (PB) pulmonary veins isolation (PVI) is recognized as an alternative to radiofrequency (RF) in atrial fibrillation (AF) ablation. However, as with RF energy, AF recurrences may occur after CB PVI. We sought to characterize redo procedures following CB PVI in terms of procedure duration and location of PV conduction recovery.

Twenty-eight (28) pts (with recurrent AF after CB PVI) underwent a second procedure, using irrigated RF catheter. Circumference of each vein was divided in 4 segments (supero-medial, supero-lateral, infero-medial, infero-lateral) in order to locate sites of PV conduction recovery.

Mean procedure time (including TEE and 30 minutes of waiting period) was 116 ±29 min, and mean fluoroscopy time was 16.5 ±9.3 min. A 3-D mapping system was used in only 7 pts (25%). PV re-conduction was observed in 27 pts, with a mean of 2.7 ±1.2 veins reconnected per patient. Both inferior PV were reconnected in 23 pts (82%), right superior PV was reconnected in 16 pts (57%) and left superior PV in 13 pts (46%). Conduction gaps were focal at left and right superior PV (1.0 ±0.2 and 0.9 ±0.2 segments, respectively), whereas they were broader at left and right inferior PV (1.6 ±1.0 and 2.0 ±1.4 segments, respectively), as seen in figure 1.

PV conduction gaps after CB PVI preferentially occurred at inferior parts of inferior PV and at the ridge between left PV and left atrial appendage. These gaps were easily ablated with focal RF delivery, which explained the lack of need of 3-D mapping system and short duration of the procedures.
value for clinical recurrence after RFCA on PeAF and SND might be closely related to the remodeling process of PeAF.

**P5382** Getting more bang for your buck in persistent atrial fibrillation ablation: re-do procedures should not be discouraged as there is a sequential improvement in success rates

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**Introduction:** Catheter ablation (CA) for Persistent AF (PeAF) is facing a funding threat, partly due to a perception that success rates are modest.

**Methods:** We analysed the acute and follow up results of consecutive patients undergoing CA for PeAF at a single centre between 2008 and 2010. All patient records were analysed independently by 2 physicians who were not involved in the initial CA procedures. Both arrhythmia recurrence and clinical symptom relief was assessed. Referencing hospitals and GPs were contacted to collect missing follow up data.

**Results:** 188 consecutive patients with PeAF (157 male, mean age 57.3±9.7 years, 18% with long standing PeAF) underwent 296 CA procedures (mean 1.5±0.7 range 1-4) by 5 physicians using 3 different ablation techniques (Carto, NavX and fluoroscopy). Mean follow up was 18.5±9.9 months and follow up data was obtained for 99% of patients. 7 (2.3%) procedures were associated with major complications, including 4 tamponades requiring surgical or percutaneous drainage. No patient suffered procedure related death or stroke. Freedom from any atrial arrhythmia, post blanking period, was lowest after the first procedure (30%, 57/188). Of 85 patients who had a second procedure, 48% (42/85) subjected to AF elimination after their last ablation. 73% of patients derived marked symptomatic improvement. 14% of patients felt slightly improvement and completely free of arrhythmias after their last ablation. 73% of patients derived a catheter ablation (CA) result predictors

<table>
<thead>
<tr>
<th>CA result predictors</th>
<th>Successful CA</th>
<th>Unsuccessful CA</th>
<th>p-value</th>
<th>AUC</th>
<th>Best cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>wNMSE_1 [%]</td>
<td>65.68±19.27</td>
<td>37.59±21.88</td>
<td>0.008</td>
<td>0.84</td>
<td>45.57</td>
</tr>
<tr>
<td>NMSE_V1,%</td>
<td>59.00±25.49</td>
<td>60.40±22.88</td>
<td>0.056</td>
<td>0.71</td>
<td>76.34</td>
</tr>
<tr>
<td>D(V1) [mV]</td>
<td>0.08±0.03</td>
<td>0.06±0.01</td>
<td>0.030</td>
<td>0.80</td>
<td>0.65</td>
</tr>
</tbody>
</table>

**Conclusion:** Across a range of operators and techniques, a catheter ablation strategy has a high chance of making patients with PeAF experience marked improvement over follow up, even if this is not always accompanied by arrhythmia eradication. The likelihood of arrhythmia eradication increases dramatically with recurrent procedures and the threshold for performing these procedures should be lower than for initial procedures.

**P5383** A new anatomical index using 3-D CT image predicts the suitable patients for catheter ablation of atrial fibrillation

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**Subjectives:** We had previously reported that the shorter mitral isthmus and the larger cross-sectional area of RSPV were associated with AF elimination after catheter ablation (CA). In this study, using a new index, which is combined with those parameters, we sought to predict the suitable patients for CA.

**Methods:** Eighty-three consecutive patients with AF (mean LA size 41±15 mm, paroxysmal 67% underwent CA and were followed for 9±3.3 months. The distance of mitral isthmus (dMI) (mm) and the cross-sectional area of RSPV (cRSPV) (cm²) were measured on 3-D CT image using the special software EnSite NavX Versimo (St. Jude Medical, Inc., St. Paul, Minnesota). The new index was defined as the ratio of cRSPV to dMI.

**Results:** 62 patients (73%) were free from AF after a single procedure. Receiver-operator characteristic curve analysis yielded an optimal cutoff value for the new index of 0.062 (AUC 0.819, 95% confidence interval: 0.71 to 0.92, p<0.001) (Figure 1). Sensitivity, specificity, positive and negative predictive values for this cut-off value were 92%, 82%, 93% and 76%, respectively.

**Conclusion:** The new anatomical index, combined assessment of cRSPV and dMI using 3-D CT imaging can be useful to select the suitable patients for CA of atrial fibrillation.

**P5384** Mathematical analysis of atrial spatiotemporal complexity on standard ECG for catheter ablation outcome prediction in persistent atrial fibrillation

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**Introduction:** Patient selection is a critical issue for improving results of radiofrequency catheter ablation (CA) of persistent atrial fibrillation (AF). Classical standard lead ECG activity (AA) parameters such as mean amplitude and cycle length were studied in a single lead, thus neglecting AA spatial variability and temporal evolution. We aimed to investigate the potential role of AA spatiotemporal variability in CA outcome prediction.

One-minute lead ECGs were acquired at the start of CA. Unlike single lead methods, we combined short-time state (ST) and anti-arrhythmic drugs for at least successive AA segments in the 8 independent leads of the standard ECG to quantify AA spatiotemporal diversity. Principal component analysis (PCA) estimates their rank-1 approximations and extracts the most descriptive AA components common to the leads retained. Mean NMSE values/lead are then weighted by their inverse variance into a pondered sum wNMSE_1, so emphasizing leads with more confounding factors. CA success is defined from ECG/Holter documented AF recurrence (≤30 s) during follow-up. We enrolled 20 patients (pts): 19 males, 60±11 y with a median AF episode duration of 4.5 months (m; 2-84). After 1.15 procedures/pt and a median follow-up of 9.5 (4-19), CA was effective in 13 pts (65%). Higher wNMSE_1 values suggest more organized and repetitive AA patterns and are significantly correlated with CA success, Table I. Prediction power is assessed by the area under the ROC curve (AUC) index. Our method is compared with results in V1 for AA amplitude (D(V1)) and mean NMSE (NMSE_V1).1

**CA result predictors**

Successful CA | Unsuccessful CA | p-value | AUC | Best cutoff
--- | --- | --- | --- | ---
wNMSE_1 [%] | 65.68±19.27 | 37.59±21.88 | 0.008 | 0.84 | 45.57
NMSE_V1,% | 59.00±25.49 | 60.40±22.88 | 0.056 | 0.71 | 76.34
D(V1) [mV] | 0.08±0.03 | 0.06±0.01 | 0.030 | 0.80 | 0.65

**Our multilead parameter predicts more accurately CA outcome than standard single lead approaches.**

**P5385** Drug-refractory atrial fibrillation associated with hyperthyroidism: its prevalence and long-term outcome after catheter ablation

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**Introduction:** Hyperthyroidism is usually regarded as a reversible cause of atrial fibrillation (AF); however, one-third of patients remain in AF despite euthyroid restoration. Catheter ablation of AF (AF ablation) has now been established as a curative therapy for drug-refractory AF. We hypothesized that a significant number of patients with drug-refractory AF related to hyperthyroidism (Hyperthyroid-AF) as well as normal thyroid cohort (Nonthyroid-AF) would benefit from AF ablation. Therefore, this study aimed to clarify the prevalence of hyperthyroidism in candidates for AF ablation and to compare the long-term outcome of AF ablation between the Hyperthyroid-AF and Nonthyroid-AF groups.

**Methods:** This study consisted of 336 consecutive patients (61±9 years old, 65 females) with drug-refractory AF (193 with paroxysmal AF and 143 with persistent AF) who were referred for their first AF ablation. Hyperthyroidism had been restored to euthyroid state by treatment with anti-thyroid agents for at least 3 months before participation. Exclusion criteria were failure of euthyroid restoration, left atrial thrombi, and structural heart disease. All anti-arrhythmic drugs were discontinued for 5 half-lives before admission, except for amiodarone which was for at least 6 weeks.

**Results:** AF ablation was performed in 15 patients (4.5%) with Hyperthyroid-AF and 321 (95.5%) with Nonthyroid-AF. Females were more frequent in the Hyperthyroid-AF group (n=6, 40%) than Nonthyroid-AF group (n=59, 18%, p=0.049). Except for the gender, the patient characteristics were comparable between the two groups. During a mean follow-up period of 4±1 years, AF recurred in 7 patients (47%) with Hyperthyroid-AF and 139 patients (43%) with Nonthyroid-AF (p=0.993 by the log-rank test). In the univariate Cox regression models, the independent risk factors of AF recurrence were a larger left atrial diameter (hazard ratio, 1.413; 95% confidence interval, 1.119 to 1.784; p=0.004) and persistent AF (hazard ratio, 1.492; 95% confidence interval, 1.054 to 2.111; p=0.024); the presence of hyperthyroidism was not associated with a higher risk of AF recurrence (hazard ratio, 0.925; 95% confidence interval, 0.429 to 1.998; p=0.843).
Conclusions: Hyperthyroidism after euthyroid restoration was neither rare nor relevant to a higher risk of AF recurrence in the AF ablation candidates without structural heart disease. AF ablation provided the possibility to cure drug-refractory AF in a significant number of patients with hyperthyroidism as well as normal thyroid cohort.

**P5386** Results of pulmonary veins epicardial ablation with high-intensity focused ultrasounds in atrial fibrillation

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**Purpose:** To evaluate the results of epicardial ablation of the pulmonary veins using high-intensity focused ultrasounds (HiFU).

**Methods:** From March 2006 to August 2011, 67 patients in our Division have received some type of atrial fibrillation (AF) ablation. Of these, 58 have been treated exclusively with epicardial ablation of pulmonary veins with HiFU. In 19 (33%) AF was paroxysmal, in 5 (9%) persistent and in 34 (58%) permanent. They were 68% male, mean age 65±11 years (33-79). Mean time of AF was 7±10 years (1 month-46 years). The average size of the left atrium was 50±7 mm (35-77).

**Results:** Overall, 54% of patients are in sinus rhythm at one month, 63% at 6 months and 1 year, 69% at 2 years and 74% at 3 years. In paroxysmal AF, sinus rhythm rate is 82% at one month, 79% at 6 months, 90% at one year and 100% at 2 and 3 years. For persistent and permanent AF, sinus rhythm rate is 42% at one month, 56% at 6 months, 54% at one year, 62% at 2 years and 69% the third year.

**Whole group follow-up**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Sinus</th>
<th>AF</th>
<th>Flutter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>29 (54%)</td>
<td>19 (37%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>6 months</td>
<td>25 (53%)</td>
<td>15 (30%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>1 year</td>
<td>22 (50%)</td>
<td>13 (27%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>2 years</td>
<td>25 (57%)</td>
<td>20 (43%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>3 years</td>
<td>14 (33%)</td>
<td>14 (29%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

**Persistent/Permanent AF**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Sinus</th>
<th>AF</th>
<th>Flutter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>13 (26%)</td>
<td>10 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>6 months</td>
<td>9 (18%)</td>
<td>9 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1 year</td>
<td>9 (18%)</td>
<td>9 (18%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>2 years</td>
<td>10 (20%)</td>
<td>10 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>3 years</td>
<td>7 (15%)</td>
<td>7 (15%)</td>
<td>0 (0%)</td>
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</table>

**Conclusions:** The epicardial ablation of the pulmonary veins using HiFU can achieve sinus rhythm in 74% of patients at three years. The benefit is significantly higher in patients with paroxysmal AF but up to 69% of patients with persistent/permanent AF maintain sinus rhythm at 3 years.

**P5387** Use of 3D-echo for atrial fibrillation ablation

M. Acena, F. Regoli, F. Faletra, A. Auricchio, T. Moccetti on behalf of Fondazione Cardiocentro Ticino, Foundation ‘Cardiocentro Ticino’, Department of Cardiology, Lugano, Switzerland

**Introduction:** Percutaneous ablation is a validated therapy for AF. However, it is an expensive procedure and still requires long X-ray exposure times. New methods must be developed to solve these disadvantages.

**Objective:** To assess the feasibility of 3D-transeosophageal echocardiography (3D-TEE) to visualize the ostia of the pulmonary veins (PV). In a latter study we will compare the 3D electroanatomical mapping-fluoroscopy versus 3D-TEE for AF ablation.

**Methods:** We included 30 patients referred for AF ablation in May 2010-December 2011. For each patient we performed a preprocedural echo-TEE for the exclusion of atrial tachycardia. We used the 3D-echochardiography to check the visualization of the PV ostia.

**Results:** We classified the visualization of the veins into: a) optimal, which allows circumferential vision of the whole PV ostium; b) partial: part of the ostial circumference is missing and c) absence of visualization of the PV ostium. The results are showed in the table.

<table>
<thead>
<tr>
<th>Visualization for each pulmonary vein</th>
<th>LSPV (%)</th>
<th>LIPV (%)</th>
<th>RSPV (%)</th>
<th>RIPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>90</td>
<td>50</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Partial</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td>20</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

**Conclusion:** Visualization of the upper veins and LIPV was possible in the majority of cases, which makes the echo-guided AF ablation feasible for these veins. RIPV presented the worst visualization because of its proximity to the esophagus and the small size of its ostium.

**P5388** Prognostic value of heart rate at the next day of catheter ablation for atrial fibrillation


**Purpose:** To evaluate the effects of radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) is partly conveyed by vaso-dilatation. Little is known about the association of HR at the next day of RFCA and post-ablation arrhythmia recurrence.

**Methods:** One hundred forty consecutive patients undergoing RFCA for AF were investigated between October 2009 and May 2011. Serial Holter monitoring and 12-lead ECGs were performed at 1 day, 1, 3, 6 and 12 months after RFCA. Thirty-six patients with implantable pacemaker (n=12) or atrial tachyarrhythmias (ATs, >30 seconds) at post-RF day 1 (n=24) were excluded. Primary outcome was defined as ATs that lasted at least 30 seconds after 3 months (blanking period).

**Results:** We enrolled 104 patients (24 women, mean age 56±9.3 years). The median follow-up duration was 13.2 months (interquartile, 7.0 to 18.5 months). Mean HR was 76.7±11.6 bpm at post-RF day 1. On 12 month follow-up examination, 18 patients (17.3%) had recurrent ATs. The recurrence of ATs was associated with a lower mean HR at post-RF day 1 (77.9±11.3 bpm vs. 71.0±11.6 bpm, p<0.02) and persistent AF (10.5% vs. 33.3%, p<0.02). In the multivariable analysis, lower mean HR at post-RF day 1 (Hazard ratio: 1.53 for each decrease per 10 bpm, 95% confidence interval: 1.01 to 2.32, p=0.04) was independent risk factors for the recurrence of ATs. On receiver operating characteristic curve analysis, we found that mean HR at post-RHF days 1 >65 bpm predicted AFs-free survival. ATs-free survival rate was 87% in patients with a mean HR >65 bpm, while it was 59% in patients with a HR below 65 bpm (p=0.002) (Figure 1).

**Conclusion:** Lower (<65bpm) mean HR at post-RF day 1 is significantly associated with a recurrence of ATs after RFCA of AF.

**P5389** Incidence and predictors for development of atrial fibrillation in patients with hypertrophic cardiomyopathy


**Purpose:** Hypertrophic cardiomyopathy (HCM) can be accompanied by atrial fibrillation (AF), which associates with higher morbidity and mortality. Patients with apical HCM are distributed abundantly in Japan and the clinical characteristics remain to be elucidated. In this study, we analyzed the development of AF in patients with apical HCM compared with other types of HCM, and clinical factors that can predict AF incidence.

**Methods:** We recruited 333 patients with HCM diagnosed by echocardiography in our hospital from 1991 to 2010 and analyzed retrospectively 279 patients (65±14 years, 197 males) who had no history of AF at the initial visit from the medical records. Subtypes of HCM consisted of 172 apical HCM, 11 hypertrophic obstructive CM, 7 dilated HCM and 89 HCM. Incidence of AF occurrence was analyzed.
comparing apical HCM with other HCM and clinical predictive factors were also assessed.

**Results:** AF occurred in 67 patients (37 in apical HCM, 30 in other HCM) during a follow-up period of 7.5±0.6 years, and the cumulative survival from AF occurrence was 85±2% at 5 years (apical HCM vs. other HCM: 86.5% vs. 82.4%, p=NS) and 75±3% (77.4% vs. 68.6%, p=NS) at 10 years of follow-up. Comparing patients with AF vs. without AF, the values at the initial visit of BNP (369±38 vs. 177±245 pg/ml, p=0.001) and left atrial diameter (LAD (4.0±0.7 cm. 3.7±0.5 cm, p=0.001) were larger and eGFR (62.16 vs. 66.22, p=0.029) was less in patients with AF than in controls. According to the multivariante analysis, BNP > 200 pg/ml (odds ratio (OR) 3.1, p=0.01), LAD > 4.0 cm (OR, 2.6, p=0.008) and age > 65 years (OR 2.2, p=0.024) were predictors for development of AF.

**Conclusions:** Annual incidence of AF is approximately 3% in HCM patients, which was not significantly different between apical HCM and other HCM. BNP, LAD and age can be predictors for development of AF in HCM patients.

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**Predictors and prognosis of de novo atrial fibrillation during acute coronary syndromes**

C. Galvao Braga, V. Ramos, C. Vieira, J. Martins, S. Ribeiro, 95% confidence interval 0.99-1.12, P=0.15. Whereas self-rated mental health did not differ between groups (P=0.20), physical health was impaired in individuals with AF (P<0.0001).

Physical activity was lower in AF individuals (physical activity score (SQUASH-questionnaire) 5400 (2837-5682) in AF versus 7058 (4839/9276) in participants without AF). Results were similar in subgroups of individuals with heart failure, living in partnership and elevated inflammatory activity measured by C-reactive protein.

**Conclusions:** In ambulatory AF patients in the general population we did not observe a higher burden of depressive symptoms despite lower physical activity and impaired physical health. Our findings need to be confirmed in the future and suggest a different impact of AF on physical health compared to physical activity and inflammation in the clinical setting and need further evaluation to identify the reasons for the observed discrepancy.

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**Post-operative atrial fibrillation prophylaxis in clinical practice: results from the CAPS-Care STS registry**

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**Purpose:** Risk of post-operative atrial fibrillation (AF) following CABG is high, yet effectiveness of guideline-recommended pre-operative prophylaxis remains uncertain. We compared rates of postoperative AF in patients with and without use of prophylaxis in a large at-risk patient population.

**Methods:** Using the Society for Thoracic Surgery multicenter CAPS-Care registry, we determined the utilization and variation of pre-operative AF prophylaxis and assessed the comparative efficacy across drugs between 1/2004 and 1/2005 at 50 registry sites.

**Results:** Among 2390 patients who underwent CABG surgery, the mean age was 61±6 years; 66% were male; 27% had chronic lung disease; 22% had cerebrovascular disease; and the mean CHADS2 score was 2.4±1.2. A history of AF was present in 13% (n=313). Overall use of AF prophylaxis was 83% and varied across sites. Following surgery, 28% of the overall cohort developed post-operative AF at a median of 2 (25th, 75th: 1.3) days after surgery. Among those without AF before surgery, increasing age, height, white race, BMI >35, NYHA Class IV heart failure, preoperative dialysis, concomitant aortic valve replacement, and pulmonary valve replacement were associated with greater odds of post-operative AF. The rate of post-operative AF was 27% in those who received no pre-operative prophylaxis. Post-operative AF was less frequent in those treated with amiodarone and other antiarrhythmics (Table). After adjustment with the full non-parsimonious model, the odds of post-operative AF were not statistically different across the different agents.

**Pre-operative Prophylaxis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall Use (%)</th>
<th>Post-op AF (%)</th>
<th>Risk Adjusted Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>12</td>
<td>25</td>
<td>0.75</td>
</tr>
<tr>
<td>AAdrine</td>
<td>12</td>
<td>25</td>
<td>0.75</td>
</tr>
<tr>
<td>Sotalol</td>
<td>1</td>
<td>30</td>
<td>1.54</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>24</td>
<td>0.87</td>
</tr>
<tr>
<td>Beta-block</td>
<td>7</td>
<td>19</td>
<td>1.91</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>18</td>
<td>30</td>
<td>0.86</td>
</tr>
</tbody>
</table>

**Table. Rate of post-operative AF relative to pre-operative prophylaxis.**

**Conclusions:** Post-operative AF remains a frequent complication of CABG. There is significant variation in the drugs used for preoperative prophylaxis. In routine clinical practice, outside of controlled clinical trials, these medications are not associated with significant reduction of AF following surgery.
lower a' velocities, in subjects later developing AF (Table 1). Among various clinical parameters, use of statin related to longer cycle length in patients with new-onset atrial fibrillation. Possible anti-remodeling effect of statin (P5396)

Healthcare policy and patient satisfaction with chronic treatment for stroke prevention: results from the European Patient Survey in Atrial Fibrillation (EUPS-AF)

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Purpose: To assess how healthcare systems in different European countries impact on patients with atrial fibrillation (AF) receiving long-term anticoagulant treatment for the prevention of stroke.

Methods: The 2008 Commonwealth Fund International Health Policy Survey of Chronically Ill Adults was adapted for patients with AF. Computer-assisted digital telephone dialing was used to screen a random sample from the entire adult population of France, Germany, Italy, Spain and the UK for AF. Structured telephone interviews were then conducted between February and July 2011. Here, we describe results relating to patient and provider satisfaction with healthcare, focusing on ease of access and experience of care in hospital.

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 percentage of patients able to get an appointment with a doctor on the same day varied from 21% (Italy) to 55% (UK); overall, 17% of patients had to wait at least 1 week before seeing a doctor. Use of helplines to obtain medical information was highest in France (27% had called a helpline within the past 2 years) and lowest in Germany (4%). Experience of hospital treatment also varied between countries. Of patients hospitalized during the past 2 years, 51% were given a new prescription on leaving hospital; 65% of patients in Spain and 49% in Italy discussed the implications of the new prescription medicine with their physician. Between 44% (Germany) and 78% (UK) of patients had follow-up visits arranged with a doctor on leaving hospital.

Conclusions: The EUPS-AF survey provides a patient-based perspective of healthcare provision in individuals with AF at risk of stroke. It indicates that the level of patient satisfaction could be increased particularly by improving access to physicians and ensuring clear communication with patients. The EUPS-AF also highlights variations between different countries in the levels of patient satisfaction. These may reflect national difference in the organization of healthcare systems and the prioritization of chronic care. For example, in the UK, there has been a recent focus on the care of chronically ill patients, which may reflect the relatively high level of patient satisfaction. Levels of satisfaction with healthcare may also be related to age and the high prevalence of co-morbidities. This survey highlights the need to adopt best practice in the treatment of patients with AF throughout Europe.

Rhythm monitoring after therapies for atrial fibrillation: in search of a new gold standard? Insights from a large population of continuously monitored patients


Background: Intermittent heart rhythm monitoring (IRM), despite of its inherent limitations, is considered the gold standard for the evaluation of the success of therapeutic interventions and the management of patients with AF. Using data from a large population of continuously monitored patients combined with a novel methodology, we aimed to identify the sensitivity of IRM strategies of various frequencies and durations on the detection of AF recurrence and discuss the implications on patient management and evaluation of therapeutic interventions.

Methods: 147 patients (age 68±12.2y, male AF: 60%, mean AF burden: 0.12±0.22, 687 patient-years) monitored with implantable continuous monitoring devices (RevealTM/TS9529 or AT506 pacemaker; Medtronic Inc., MN, USA) were interrogated and the complete rhythm history of every patients was reconstructed. With the rhythm history of every patients reconstructed, computationally intensive simulation was employed to perform virtual IRMs of various frequencies and durations in order to evaluate the sensitivities of IRMs of various frequencies and durations in identifying AF recurrence in every patients. Sensitivity was defined as the proportion of patients the IRM identified as having AF recurrence to the number of patients withproven AF recurrence identified by with the continuous monitor.

Results: The sensitivity of prolonged IRM duration was significantly superior to short duration IRM (p<0.0001), however even with aggressive IRM strategies AF recurrence was not detected in up to 50% of patients. The most often used monitoring strategy, four 24h HM strategy per year, would fail to detect AF recurrence in almost 50% of patients with proven AF recurrence. Although prolonged IRM achieves a higher sensitivity, the effectiveness of prolonged monitoring measured as sensitivity per monitored day, is significantly lower (p<0.0001) in with prolonged IRM than with shorter IRM.

Conclusion: All evaluated IRM strategies were significantly inferior to continuous monitoring for AF recurrence detection and IRM strategies will not identify AF recurrence in agreement proportion of patients at risk. Although prolonged IRM can achieve higher sensitivities, this required a disproportionally higher monitored time than short IRM, which will affect patient compliance. For the scientific, evidence based evaluation of AF treatments and for confident patient management, continuous monitoring should be strongly recommended.

P5397 Atrial fibrillation post myocardial infarction without long term outcome

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Introduction: Atrial fibrillation (AF) confers poor outcomes in patients with acute myocardial infarction (AMI) and is associated with increased risk of death. Our aim was to investigate the interaction between AF occurring after AMI and VF. We also aim to determine the mechanism by which AF increase mortality post MI.

Method: In prospectively collected cohort of 2460 MI patients, 96 MI patients with...
new onset AF were matched with 288 MI pts with no AF (1:3) by ejection fraction (EF). The incidence of VF during hospital admission and long-term mortality over 5.5±2.3 years was assessed. All data was collected on formulated database registry in which a wide range of variables were recorded including past medical history, co-morbidities, electrolyte disturbances, and drugs therapies.

**Results:** Baseline characteristic for AF group vs. control were as follows: age (75.2 vs. 65.1±14, P=0.001), male (65% vs. 69%, P=0.02) and EF (52.12±12 vs. 48.1±13, P=0.4). There was no difference between the groups in other cardiovascular risk factors or drug therapy. Incidence of in hospital VF in the AF group was higher than the control group (12.5% vs. 2%, P=0.03). On univariate analysis AF (OR 5.45, 95%CI: 1.16-18; P=0.008) and ST segment elevation MI (P=0.03) were predictors of in-hospital VF but not age, sex. On multivariate analysis, AF remained an independently significant predictor of VF (OR 2.6, 95% CI: 1.33-5; P=0.005). In addition, ST segment elevation was also predictor of VF (P<0.05).

Although there was no difference in-hospital mortality between the groups (7% vs. 4%, P=0.08), long-term mortality was significantly higher in the AF group compared to no AF group (29% vs. 11.8%, P=0.005).

**Conclusion:** New onset AF post AMI is associated with increased risk of in-hospital VF and long-term mortality independent of LVEF.

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**P5398**

**Electrical versus pharmacological cardioversion in patients admitted to hospital for new onset atrial fibrillation: results of the German rhythm-AF study**

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**Background:** Atrial Fibrillation (AFib) is the most common arrhythmia in clinical practice, accounting for approximately one third of hospitalizations for cardiac rhythm disturbances. Little is known about the use of cardioversion (CV) and its success in clinical practice.

**Methods:** As part of the international RHYTHM-AF Registry consecutive patients with documented AFib who were considered being candidates for CV were prospectively enrolled in 23 university and non-university hospitals in Germany to document patient characteristics as well as CV strategies and success in clinical practice. CV was considered successful if sinus rhythm or atrial rhythm was obtained within 1 day after start of pharmacological treatment and if sinus rhythm was achieved and maintained for at least 10 min after electrical CV.

**Results:** Out of 645 consecutive patients with AFib considered for CV, 29.3% finally did not undergo CV mainly due to spontaneous CV before the planned procedure or due to documented left atrial thrombi or echo contrast; 63% did undergo electrical and 6.8% pharmacological CV. Compared to pharmacological CV, patients undergoing electrical CV were more likely to be men, more often present with persistent AFib, and more often evaluated by transesophageal echocardiography. Main amiodarone and flecainide were used for pharmacological CV (45.2%, 29.5%). Electrical CV had a higher rate of success after the 1st attempt of CV than pharmacological CV, reflected also by the higher rate of sinus rhythm at hospital discharge.

**Conclusion:** In Germany, only a minority of patients with AFib considered for CV underwent pharmacological CV. The success rate of electrical CV was significantly higher compared to pharmacological CV, and more patients were discharged with sinus rhythm. Observations seen here highlight a need for more effective cardioversion treatment therapies as an alternative to electrical cardioversion.

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**P5400**

**Remote monitoring system: clinical relevance in monitoring implanted devices: consultation, workload and analysis**

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**Purpose:** New advances in the technology associated with defibrillators and pacemakers have developed systems for remote monitoring of these devices, which could reduce the witnessing activities number, increasing levels of security and confidence of patients. The objectives are:

1. To assess the impact of relevant clinical alarms.
2. To value the burden of time involved in implementing the follow-up visits of this remote monitoring system.

**Methods:** The sample was of 109 patients. All received training interview for remote monitoring of their device, using home monitoring system. Bimonthly periods were reviewed automatically to wireless devices, and by calendar were delivered to the patient, in the case of non-wireless. To assess the importance of transfers, we defined as relevant clinical events as those forced to take a clinical performance from the device or the patient, regarding of number of diagnostic tests, given that could reduce the witnessing activities number, increasing levels of security and confidence of patients. The objectives are:

1. To assess the impact of relevant clinical alarms.
2. To value the burden of time involved in implementing the follow-up visits of this remote monitoring system.

**Results:** For the 17 months, with a median follow up of 10.1 months. We calculate the average time spent on each training (12'), average time for each telephone call to patient (6'), average time for review of a transmission without events (2') and events (6'). The average time a device-face consultations resynchronized is 20' and a conventional 10'. We received a total of 702 transfers, 387 free and 315 events with events. There were 150 transmission losses that forced

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**P5399**

**Implantable cardioverter defibrillator recipients: who are the ones with highest interest in remote monitoring?**

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**Purpose:** Remote monitoring (RM) of implantable cardioverter defibrillators (ICD) is a feasible and safe new development in ICD therapy. Advantages of RM in comparison to traditional follow-up (FU) in the outpatient clinic include daily monitoring of data concerning system safety and integrity, daily transmission of stored electrograms/ICD diagnostics, and early interventions in case of abnormal findings. Disadvantages of RM include false positive alarms and an unfamiliar way of FU (may degrade the trusting doctor-patient relationship). The aim of SAN REMO 1 (Treatment Satisfaction with Remote Monitoring in Implantable Cardioverter Defibrillator Recipients) study was to investigate factors associated with patients' willingness to accept a FU by RM.

**Methods:** SAN REMO 1 was a single centre, non-randomised, cross-sectional anonymous survey among 450 consecutive patients (292 responded; response rate 65%). A self-administered questionnaire was sent out, examining baseline sociodemographic data and other factors associated with the patients interest in RM recorded using a visual analogue scale under the premise that this would completely replace all routine FUs. Main endpoint of the study was correlation of patients' interest in receiving RM FU according to the visual analogue scale with baseline characteristics.

**Results:** Patients were grouped according to their level of interest (none/partial/significant) in using RM as a surrogate for regular face to face FU. Significant differences were found for whether patients were treated only in our center or not (more patients who were treated in our center were interested in RM, 45.2% vs. 29.3%, p=0.046), interest for RM was more frequently present in those who had an earlier ICD admission (25.6% vs. 28.9%, p=0.025); and in relation to patient exercise tolerance - those with strong limitations were more frequently interested in RM (37.0% vs. 25.3%, p=0.019). No significant differences were found in relation to education level, distance from our center, gender, living situation, working status, physical activity, the time from the initial implant of the device, having been resuscitated, having had myocardial infarction, shock or device complication.

**Conclusions:** There is a group of patients quite interested in replacing standard face to face FU for a RM. Main qualities of this group include treatment only in our center, having had an emergency admission because of the device and having strong limitations in exercise; other factors such as distance to our centre do not seem to play an important role.
Mild to moderate renal insufficiency predicts all-cause mortality but not shocks in patients with implantable cardioverter defibrillators

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**Introduction:** Severe renal dysfunction is a risk factor for sudden cardiac death. The aim of this retrospective registry study was to investigate mild to moderate renal dysfunction as a predictor of mortality and implantable cardioverter defibrillator (ICD) shock in a large single-center population.

**Methods:** At our institution, 1,272 pts underwent ICD or CRT-D implantation between 1998 and 2010. Age, gender, ischemic or non-ischemic heart disease, primary or secondary prophylactic indication, heart rate, NYHA class, LVEF, diabetes, hypertension, and others, as well as serum creatinine were retrieved for primary or secondary prophylactic indication, heart rate, NYHA class, LVEF, diabetes, hypertension, and others, as well as serum creatinine were retrieved for the implant date. Estimated glomerular filtration rate (eGFR) was calculated as published and pts grouped to eGFR < 60 (N=195), 60-90 (N=576), 90-130 (N=438), and < 30 ml/min/1.73 m^2 (N=63). No pts were on dialysis. Kaplan-Meier estimates for mortality (N=353) and first appropriate ICD shock (N=274) as separate end-points were assessed from follow-up over 53±32 months.

**Results:** Mean age was 67±13 yrs, LVEF 30±11%, 244 pts were female. Pts with an eGFR < 60 (N=438), or < 30 ml/min/1.73 m^2 (N=63), respectively, showed significantly higher all-cause mortality (P<.0001, see figure). There were no differences in appropriate ICD shocks between the groups (P=0.229). Upon Cox regression analysis, eGFR was a strong independent predictor of mortality (P<.0001), in addition to age (P<.0001), chronic obstructive pulmonary disease (P=0.004), and primary prophylactic indication (P=0.012).

**Conclusions:** A decreased eGFR indicating mild to moderate renal dysfunction is a strong independent predictor for all-cause mortality in ICD and CRT-D patients. Appropriate shocks are not predicted.

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What is the value of in-person evaluations prompted by alert notifications during ICD remote monitoring? The Trust trial

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Continuous remote monitoring promises improved patient care by problem discovery via alert notifications (ANs), but demands discrimination of out-of-bounds parameters with reliable transmission. These abilities are unknown but critical to use of continuous surveillance instead of conventional evaluation at set time points (in-person or remote). The TRUST trial tested this.

**Methods:** 1,339 ICD patients were randomized 2:1 to Home Monitoring (HM, Biotronik) or to conventional (C) groups and followed for 15 months. Follow-up occurred every 3 months in both groups, in person office visits (OV) in C, and remotely at 6, 9, and 12 months in HM. Unscheduled visits were tracked. In HM, continuous monitoring was activated and technology self-tested daily and triggered ANs.

**Actionability** (ie change(s) in programming/antiarrhythmic drugs/system components) was compared between scheduled evaluations (C and HM), unscheduled OVs (C and HM, patient and physician driven), and OVs prompted by ANs in HM. **Results:** HM and C patients were similar: age 63±13 vs 64±12 yrs, 72 vs 73% male, NYHA II class 56 vs 60%, LVEF 29±11 vs 26±10%, CAD 65 vs 72%, primary prevention 72 vs 74%, DDD implants 57.8 vs 56.6%. In total, 4,328 ANs were received during a possible 363,450 transmission days. Daily transmission success was 87% ± 11%. 32 months. 2,386 ANs resulted in an OV, of which 54% were actionable, compared to ~30% of unscheduled OVs. Systems of scheduled follow up, in person or remote, had 81% and 78% lower actionability respectively (figure).

**Conclusion:** Alert notifications are reliably transmitted during continuous remote monitoring and convey higher clinical value than a follow up system of periodic checks.

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Long-term follow-up after implantable cardioverter defibrillator in patients with Brugada syndrome: a multicenter French experience

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**Background and Objective:** Implantation of a cardioverter defibrillator (ICD) is a frequently recommended treatment for symptomatic Brugada syndrome (BrS). However, complications related to the device have been reported.

**Methods and Results:** We assessed the benefit/morbidity ratio of this mode of therapy in a cohort of 34 patients implanted in 3 French experienced centers between January 1, 2002 and November 30, 2010. The mean age at the time of implantation was 48±14 years, 4 (12%) female. Twenty nine (85%) patients had spontaneous typical coved Type I ECG pattern, 15 (44%) had family history of sudden cardiac death (SCD) and 24 (70%) had positive EP study. ICD implantation was based on aborted sudden cardiac arrest (SCA) in 3 (9%), syncope in 19 (56%) or high risk status (spontaneous type I ECG in conjunction with a family history of SCD and/or a positive EP study) in 12 (35%). The median follow-up period was 74±56 (9-127) months. One patient with prior cardiac arrest died of a non-cardiac cause, 5 (15%) patients had appropriate device therapy; all with spontaneous type I ECG and previous syncope but none with prior cardiac arrest. Overall complication rate was 26%, Six (27%) symptomatic and 3 (25%) asymptomatic patients experienced complications. Five (14%) patients (4 with previous syncope and 1 asymptomatic) experienced inappropriate shocks and 4 (12%) had other complications: 2 patients had lead rupture, 1 lead displacement, and 1 pneumothorax during device replacement. These complications occurred in 2 asymptomatic and 2 symptomatic (1 syncope and 1 prior aborted SCA) patients. No case of SCD was observed in ICD carriers.

**Conclusion:** Appropriate device therapy after a median follow-up period of 6 years was observed in patients with prior syncope and none in asymptomatic patients. Complication rate was leading not to recommend ICD implantation in
asymptomatic Brugada patients and to carefully evaluate the risk/morbidity ratio in subject with non spontaneous coved type ECG pattern.

P5404 Correlation of intracardiac electrogram (IEGM) with surface ECG in Brugada syndrome patients

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Introduction: Electrocardiogram (ECG) is the cornerstone for Brugada syndrome diagnosis, however, the type 1 form often occurs intermittently and may be difficult to detect. Continuous monitoring for the occurrence of this morphology could play an important role in identifying patients (pts) at risk and providing necessary therapeutic intervention. The objective of this study was to investigate whether, in type 1 Brugada syndrome pts, the intracardiac electrogram (IEGM) from an ICD correlates with surface ECG during Ajmaline challenge.

Methods: 16 pts with type 1 Brugada syndrome and implanted with St Jude Medical Angest™ ICDs were enrolled and received Ajmaline challenge according to a standard protocol. IEGMs and 12 lead ECG signals were collected continuously over the duration of the study and analyzed off-line.

Results: Two pts were excluded from the analysis due to signal noise issues in the surface ECG. Of the remaining 14 pts, 12 and 2 pts were adjudicated to have positive (A+) and negative (A-) Ajmaline challenges, respectively, based on standard ECG criteria. In the A+ pts, the IEGM T wave amplitude changes were more prominent than those of the ST segment (383±463 vs. 307±178 μV, p<0.05). Furthermore, all of these A+ pts exhibited changes in the IEGM T wave amplitude in the negative polarity, whereas the polarity change of the ST segment was mixed. In the A- pts, the changes in the IEGM T wave amplitude and ST segment were much smaller than those of the A+ pts (21±158 [p<0.05] and 101±54 [p=0.05] μV, respectively). Linear correlation indicated that the ECG ST change correlated better with the IEGM T wave change (R = 0.74) than the IEGM ST change (R = 0.66). Applying an IEGM T wave amplitude change cut-off of 400 μV for determining the outcome of the Ajmaline challenge yielded 92% sensitivity (11/12) and 100% specificity (2/2).

Conclusions: In this study IEGM T wave amplitude changes were greater in magnitude than those observed on surface ECG. IEGM T wave changes correlated well with surface ST changes during Ajmaline challenge in Brugada syndrome pts. Additional investigation is warranted to better understand the potential of IEGM monitoring in detecting type I Brugada syndrome.

P5405 Calcium handling proteins gene variants and the risk of ventricular arrhythmias in ICD recipients with heart failure: focus on extremely opposing phenotypes

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Introduction: Genetic predisposition to ventricular arrhythmias in heart failure (HF) has been suggested. Ca2+ plays a crucial role in cardiac electrical stability. We investigated whether variants of the genes encoding Ca2+ handling proteins are associated with ventricular tachycardia (VT) or ventricular fibrillation (VF) in HF patients with a primary prevention ICD.

Methods: 107 patients with severe HF of ischemic and non-ischemic origin were followed from ICD implantation to the time of first ICD-treated or recorded sustained VT/VF, death, or last follow-up visit. Patients were then divided into a high-risk group (VT/VF occurring within 6 months after ICD implantation) and a low-risk group (no VT/VF after at least 4 years from ICD implantation). Subjects were genotyped with respect to the following SNPs: SERCA2 rs1860561 and rs56243033; RYR2 rs4142933; Calsequestrin 2 rs4074536; Na(+)-Ca(2+) exchanger (NCX1) rs12198461; and voltage-gated Ca(2+) channel β1 subunit rs7568163. The primary endpoint was the time to the occurrence of the first VT/VF. Hazard ratios were derived from Cox proportional-hazards regression analysis.

Results: After a mean follow-up of 724 days (IQ range, 195-1099), 38 patients (36%) had at least one sustained VT/VF. History of ICD-recorded non-sustained VT (NSVT) (HR: 3.6; 95% CI: 1.4-9.1; p = 0.01) and coronary artery disease (CAD) (HR: 2.1; 95% CI: 1.0-4.4; p = 0.04) predicted VT/VF occurrence. Prevalence of the SERCA2 variant rs1860561 was 17% in patients without VT/VF and 71% in subjects with sustained ventricular arrhythmias (p = 0.04). After stratification for NSVT and CAD, the rs1860561 gene variant remained independently associated with lower incidence of VT/VF (HR: 0.4; 95% CI: 0.1-0.9; p = 0.04). We identified 17 patients with VT/VF occurring ≥ 6 months after ICD implantation (high risk group; mean time-to-event: 2.3±1.9 months) and 14 patients without VT/VF after at least 4 years from ICD implantation (low-risk group; mean follow-up without events: 63±12 months). Prevalence of the SERCA2 rs1860561 variant was 6% in the high-risk group and 25% in the low-risk group (p = 0.03).

Conclusions: The SERCA2 rs1860561 variant is associated with lower incidence of life-threatening arrhythmias in HF and may help to identify patients who will benefit most from ICD therapy. Comparison of allelic/genotypic distributions between extremely opposing phenotypes provided reliable information on genetic contributors to arrhythmia occurrence in a complex disease.

P5406 RFID gates at ski resorts - Is there a risk for patients with ICDs?

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Background: Recently published in vitro tests with radiofrequency identification readers (RFID) revealed clinically significant electromagnetic interference with implantable pacemakers and implantable cardioverter-defibrillators (ICDs). Incidents in patients with pacemakers and ICD’s have not been reported yet. The aim of this clinical study was to evaluate the risk of electromagnetic interference (EMI) during use of RFID-based access control systems used in ski resorts in patients with ICDs and cardiac resynchronization therapy-defibrillators (CRT-Ds).

Methods: 34 patients implanted with an ICD or CRT-D were included in the study. Tests were performed using two commercially available RFID access control systems (gates) used at ski resorts operating on different frequencies of 125 kHz and 13 MHz. After initial device interrogation, patients were standing upright within each gate for a minimum of 30 seconds both at a random position as well as with the ICD positioned at the closest possible distance from the RFID source, simulating a worst case scenario. Electrocardiographic and telemetric real-time monitoring of devices and patients’ heart rhythm was performed throughout the study.

Results: ECG monitoring by body surface ECG demonstrated RF artefacts in all patients. However, real-time telemetry of intracardiac electrograms did not show artefacts or evidence of EMI causing inappropriate pacing, changes in pacing rate, or delivery of antitachycardia pacing. Interruption of devices after the test revealed no inappropriate tachycardia detection, programming changes, oversensing or ICD malfunction during all tests in all patients.

Conclusions: Although in vitro test demonstrated the ability of RFID systems to interfere with the function of ICDs, this clinical study showed no evidence of EMI during use of RFID-based access control systems used in ski resorts simulating a real-world setting. Therefore, the use of these access-control systems seems to be safe for patients implanted with an ICD or CRT-D. However, patients should be advised to avoid prolonged standing in close proximity to RFID antennas.

P5407 Is it useful to program antitachycardia pacing for ICD recipients that have neither dilated nor ischemic cardiomyopathy? Experience of one center

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Antitachycardia pacing (ATP) is an effective treatment for monomorphic ventricular tachycardia (VT) in dilated or ischemic cardiomyopathy. It is debatable its use in purely electric diseases or hypertrophic cardiomyopathy (HCM) where polymorphic VT (PVT) is expected. Our aim was to analyze PVT incidence and ATP efficacy in ICD patients (pts) with neither dilated nor ischemic cardiac disease (NDNCD).

Methods: Out of 935 ICD recipients followed at our center, 110 had NDNCD (56 pts with HCM; 26 Brugada syndrome, 13 idiopathic ventricular fibrillation (VF), 4 idiopathic VT, 7 long QT 4, with Steinert myopathy). All had VT zone programmed with 2 burst at 88% of cycle length (CL) and 2 ramps at 91% CL followed by shock. We analyzed all ICD registered episodes. PVT was defined as any VT episode with more than 10% variations of amplitude and/or CL.

Results: Mean age 55.08±15.62, 31 female (28.18%), 40 pts in secondary prevention (36.26%), mean left ventricle ejection fraction 62±10.6%. Duration of ICD 7.8±5.1 years.

Figure 1. Results

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of follow-up was 5.26±4.15 years, during which 19 pts (17.27%) suffered 225 episodes (11 HCM pts, 4 idiopathic FV, 2 Brugada, 1 long QT and 1 Steinert). 48/255 were identified as PV (21.61%), 33/255 episodes (14.66%) were treated directly by cardioversion (FY zone) and 152 (63%) with ATP. The efficacy of ATP was 86.97% (VT stopped in 167/192). Shock was delivered in 15 occasions when ATP was ineffective (<7.6%) and in 4 occasions ATP induced VT acceleration (2.08%). In efficacy in PV was 70.33% (19 effective ATP of 27 administered). Efficacy adjusted to the number of episodes/patient was 72.46%.

Conclusions: ATP seems effective in cardiac conditions that are thought to produce non-monomorphic VT. Programming ATP in these cases appears safe and could reduce the shock burden and thus improve quality of life.

Purpose: Since primary prevention implantable cardioverter defibrillator (ICD) therapy in reducing mortality was proven in several studies, ICDs are indicated in patients with ischaemic (CMF) and non-ischaemic dilated cardiomyopathy (dCMP) and left ventricular ejection fraction (LVEF) ≤50%. Current guidelines do not recommend device therapy in patients with life expectancy less than 1 year since benefit in these patients is low. However, at present, clinical risk models for predicting 1-year mortality are available. In this study we evaluated the predictive ability of these algorithms and predictors of early mortality (<1 year after implantation) in a primary prevention population.

Methods and results: We evaluated 861 consecutive patients with an iCMPor dICMP (mean age 62.7±10.2 years, 79% male) who received a prophylactic ICD between September 2002 and December 2008 in the Academic Medical Center (Amsterdam) or Medisch Spectrum Twente (Enschede). All patients were followed for one year. The primary endpoint was all cause mortality. First year after implantation, a total of 41 deaths (4.8%) occur. Only 4 of these patients received an appropriate shock, with no life gain in 2 of them (shock at day of death), and a life gain of 57 and 116 days in the other 2 patients. Univariate predictors of early mortality included age ≥75 years (odds ratio 4.09; 95% confidence interval 1.90-8.76). After multivariate analysis, age ≥75 years (p=0.01, HR 3.93, CI95% 1.95-7.89), LVEF ≤50% (p=0.04, HR 2.00, CI95% 1.04-3.83), a history of atrial fibrillation (p=0.02, HR 2.16, CI95% 1.10-4.29) and eGFR ≤30ml/min (p=0.06, HR 3.14, CI95%. 0.96-10.31) proved to be independent predictors of early mortality. Using this predictors a low (<1 risk factor), intermediate (2 risk factors) and high (≥3 risk factors) risk group can be identified with 1-year mortality of respectively 3.4%, 10.9% and 38.8%.

Conclusion: In patients with CMF or dCMF and prophylactic ICD implantation, early mortality occurs in 4.8% of the ICD recipients. Age ≥75 years, LVEF ≤50%, history of atrial fibrillation and eGFR ≤30% are significant predictors of early mortality. Using these predictors a low, intermediate and high risk group can be identified.

Purpose: Chronic heart failure (CHF) is a common condition in elderly individuals. Despite great improvements in medical therapy, mortality is persistently high in patients suffering from the most severe forms of disease. Implantable cardioverter defibrillator (ICD) proved to significantly lengthen survival of very diseased CHF subjects. Epidemiological data show that sudden cardiac death has great relevance in aged patients, too. Aim of this study was to compare the age-related effects of ICD on mortality in a real world Italian population.

Methods: According to the end-point of the study, all consecutive patients who underwent an ICD implantation in the 30 Italian centres participating to the “Clinical Service Project” were divided into three age-groups (<65, 65-74 and ≥75 years). Clinical and instrumental variables were collected at baseline and during the follow-up.

Results: Between March 2004 and May 2011, 6276 patients were enrolled in the project (LVEF: 29±9%). Subjects aged <75 years represented the 23.9% of the whole series (<65: N=2455, age: 55±10, 65-74: N=2318, age: 70±3; ≥75: N=1503, age: 78±3). The proportion of men was >80% in all groups. The prevalence of all main comorbidity conditions increased with age. CHF was most frequently due to coronary artery disease in elderly individuals, who also showed the worst NYHA class. The use of beta-blockers was inversely correlated with age (<65: 87.8%; 65-74: 79.8%; ≥75: 74.0%, p<0.001). At the end of the follow-up (median length: 31 months), all-cause mortality increased with age (<65: 7.0%; 65-74: 12.1%; ≥75: 15.2%; univariate Cox model - HR=1.65, p<0.001). At multivariate analysis, age-group, NYHA Class, LVEF, chronic renal failure and p values <0.001 and COPD (p=0.004) were significant predictors of prognosis. After adjustment, the age-group HR for mortality decreased to 1.57, a 16% reduction for the oldest patients explained by disease-related causes.

Conclusions: The analysis of the “Clinical Service Project” database shows that ICD use is also useful in elderly individuals with severely depressed systolic function. Overall mortality is associated not only with age, but with CHF severity and comorbidities, also. Pharmacological under-treatment still constitutes a relevant problem.

Purpose: Remote monitoring in heart failure patients with implantable defibrillator: reduces healthcare utilization and improves quality of care

Methods: The EVOLVO trial involved 200 patients followed until 16 months visit. This multicenter, randomized trial compared remote monitoring with standard patient management, consisting of scheduled visits and patient response to audible device alerts.
Results: The rate of cardiac or device related unplanned emergency department or in-hospital visits (primary endpoint) was reduced by 36% in remote arm (75 versus 117, Incidence density: 0.59 versus 0.93 events/year; p<0.001). There was a 23% reduction in the rates of all hospital admissions (planned and unplanned) for cardiac or device-related events (4.40 versus 5.74 events/year; p<0.001). The time from an ICD alert condition to the data review was 1.4 days in the remote arm and 24.8 days in the standard arm (p<0.001). The patient’s clinical status, measured by the Clinical Composite Score, was similar in the two groups, while a more favorable change in quality of life (Minnesota Living with Heart Failure Questionnaire) was observed from the baseline to the 16-month in the remote arm (p=0.026).

Conclusions: As compared to standard follow-up with in-office visits and audible ICD alerts, remote monitoring resulted in increased efficiency for healthcare providers and improved quality of care for the patients. In addition remote monitoring reduced unplanned hospital admissions and in general total healthcare utilization in patients with ICD.

P5412 CRT-Implantation in patients with moderate heart failure: How important is the QRS width to predict the outcome?

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Introduction: The cardiac resynchronization therapy (CRT) is a well-established therapy for patients with severe systolic heart failure. According to the results of MADIT-CRT, RAFT and REVERSE the indication for CRT was expanded to patients with moderate heart disease. Subgroup analyses suggest that the benefit is significant only in patients with broader QRS-complexes (at least 140 ms).

Methods: In a prospective, multi-center registry (Institut fuer Herzinfarkt- forschung, Ludwigshafen) 186 consecutive patients with NYHA classes I and II undergoing CRT-implantation were included. 92/186 (49.5%) had a QRS width >150ms (group A), 94/186 (50.5%) had a QRS width between 120 and 150ms (group B).

Results: Group A and B did not differ with respect to age (65 years vs. 67 years, p=0.07), sex (79% vs. 80% male, p=0.94), ejection fraction 28% vs. 30%, p=0.17, atrial fibrillation (6.5% vs. 11.7% p=0.22) and left bundle branch block (80.4% vs. 73.1% p=0.14). There was also no difference concerning clinical symptoms of heart failure. In group A 8.7% of the patients were in NYHA class I and 91.3% in NYHA class II, in group B 8.5% in NYHA class I and 91.5% in NYHA class II (p=0.96).

The mean QRS duration in group A was 178ms and 140ms in group B (p=0.0001).

Follow up: 137 patients (67 in group A and 70 in group B) who were included in the registry at least one year ago could be followed. The mortality in both groups was low and not different (Group A: 4.4%, Group B: 3.2%, p=0.68). Regarding symptoms of heart failure a significant difference between both groups were obvious: The percentage of patients being in NYHA-class I one year after CRT-implantation was significantly higher in group A (57.4%) than in group B (35.9%) (p=0.02). The percentage of patients with missing heart failure to NYHA class III and IV had only 7.0% in group A vs. 12.5% in group B (p=0.22).

Conclusion: CRT is an effective therapeutic approach forpatients with moderate heart failure. Although patients with QRS complexes >150ms benefit most, cardiac resynchronization therapy is also effective in less broad QRS-complexes. Thus, CRT-Implantation is recommended even for patients with moderate heart failure and less pronounced QRS-width.

P5413 Effect of programmed heart rate on cardiac function in patients with a cardiac resynchronization device

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Background: Whether it is better to reprogram cardiac resynchronization therapy (CRT) devices to permit or prevent bradycardia in patients with heart failure is uncertain.

Methods: We investigated the effects of programming heart rate of CRT devices either to prevent heart rate dropping below 70 beats per minute (bpm) or below 45 bpm in a double-blind cross-over study with 3 month treatment periods.

Results: Of 63 patients enrolled, the mean age was 64 years and 52 were men (83%). Baseline NYHA class I-II was present, nearly half of patients (n = 31) were in NYHA FC II heart failure (HF), one third (n = 20) were in class III HF and 12 patients (19%) were in class I. Fifty seven patients (91%) completed the ≤45 bpm arm, and 54 patients (89%) completed the >75 bpm arm. X Patients dropped out before cross-over and 5x patients completed both arms (83%). The mean heart rate was 66 bpm at baseline, 66 bpm and 77 bpm in the low and high rate groups respectively. Symptoms were unchanged during follow-up. The average 6 minute distance walked at the start of the study was 236±100.6 meters which increased slightly and similarly to 248±101 meters in the low and high rate groups respectively. Baseline LVEF was 33.4±9% and increased slightly and similarly to 34.4±9.5% and 34.9±8.8% respectively.

Conclusions: This study suggests that substantial differences in programmed heart rate do not have a profound overall effect on symptoms, functional capacity or ventricular function in this population. Subtle differences may have been missed due to the modest size of the study and duration of intervention.

P5414 Systematic review of genuine symptomatic response to cardiac resynchronization therapy: acknowledging the contribution of spontaneous improvement

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Background: Symptomatic response rates cited for biventricular pacing (cardiac resynchronization therapy, CRT) are variable and have never been systematically evaluated. Whether reports rarely subtract spontaneous improvement rate in the control arm, to establish symptomatic response rate genuinely attributable to CRT. Method and Results: First, we identified 150 CRT papers through Pubmed to assess perceptions of the symptoms of benefit of CRT. Of these 29 described the concept of “response” and “non-response” to CRT. The response rates to CRT quoted ranged from 50% - 72%. Second, we examined symptomatic response rates in the randomised CRT trials CARE-HF, COMPANION, CONTAK-CD, MIRACLE, MIRACLE-ICD, MIRACLE-ICD II, MUSTIC, and REVERSE, totalling 3904 patients. For NYHA class, improvement was seen in 51% for those randomised to CRT versus 35% with no CRT. Using the clinical composite score the values were 54% and 40% respectively. For NYHA Class, improvement rates were significantly greater in open than blinded studies (20% versus 13%, p<0.001).

Amongst other markers of response, those most susceptible to psychological effects (6-minute walk and Minnesota Living with Heart Failure Score, MLWHFS) showed relatively good response with placebo (blinded implantation of device not delivering CRT) versus relatively poor response to no device (unblinded studies in which no device was implanted). With MLWHFS, 56% of the improvement with CRT was seen in controls for the blinded studies, versus 23% in the open studies. Conclusions: Quoting CRT responder rates in isolation, without recognising “spontaneous responders”, is common but invalid. Response rate with CRT, at 51%, is over triple the response rate incrementally attributable to CRT, which is only 16%. Two thirds of those who “responded” with CRT would have done so even without CRT. This value, derived from large trials, is much lower than the range of response rates quoted in the literature. CRT definitely prevents death and reduces symptoms, but symptomatic impact should not be exaggerated.

P5415 Association of pre-operative complement C3a concentrations with the clinical outcome following cardiac resynchronization therapy

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3 Biventricular pacing by cardiac resynchronization therapy (CRT) therapy improves the clinical state of the majority of severe heart failure patients with intraventricular conduction delay. As some patients do not benefit from the therapy, the need for pre-operative identification of non-responders is emerging. Previously we have described, that the complement system might play an important role in the pathogenesis of heart failure and complement anaphylatoxin C3a is independently associated with disease severity. Our aim was to determine the predictive value of complement components and inflammatory markers on the clinical outcome following CRT.

One-hundred forty-seven patients on optimal medical therapy with wide QRS (>120 ms), NYHA II-IV class severe heart failure and decreased LVEF (<35%) were included in this prospective study. Primary endpoint was cardiovascular mortality or heart transplantation; secondary endpoint was device failure. Statistical analysis was done by 6 months following CRT implantation (at least one class improvement on the NYHA state or at least 10% improvement on the 6 minutes walking distance). Complement components (C3, C3a, kC5b-9) inflammatory proteins (C-reactive protein

Figure 1. Secondary outcomes across study phases

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Is delayed enhancement the only parameter to predict response to resynchronization therapy?

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Background: The detection of myocardial fibrosis within left ventricular walls at cardiac magnetic resonance (CMR) has been shown to be a good marker of non-response to cardiac resynchronization therapy (CRT). However, CMR also provides information on left ventricular (LV) and right ventricular (RV) volumes, mass and function with a greater spatial resolution and a greater accuracy than any other imaging technique. It is still unknown whether such data can be useful to identify responders to CRT.

Methods: 34 heart failure (HF) patients underwent echocardiography and CMR the day before CRT implantation; echocardiography was repeated after 6 months. Using cine steady-state free precession sequences we measured LV and RV volumes and ejection fraction (EF), the ratio of LV mass to LVEF (as an indicator of negative LV remodelling) and we measured scar burden with segmented inversion recovery pulse sequences. Response to CRT was defined as a reduction >15% in LVEF at 6 months.

Results: At 6 months after CRT 18/34 pts (53%) turned out to be responders. Responders to CRT had smaller LVEDVi (160±53 ml vs 196±44 ml, p=0.01), smaller LVEF (41±8 vs 44±2 ml, p<0.05), greater LVEF (25±5 vs 24±6%, p<0.003) and higher mass/LVEDVi ratio (0.53±0.14 vs 0.42±0.11, p=0.008); the presence of delayed enhancement (DE) was similar in responder and in non responder patients (73% vs 87%, respectively, p=0.4); nonetheless responders showed a greater amount of delayed enhancement (6.3±7 ml vs 16±1.4 ml, p=0.004) that is consistent with smaller myocardial scar burden. Finally responders had smaller RVEDi (56±16 ml vs 74±21 ml, p=0.03), smaller RVEF (22±11 ml vs 41±33 ml, p=0.04), greater RVEF (63±9% vs 40±7%, p=0.003). At statistical analysis LV mass/LVEF ratio was a good predictor of response to CRT (AUC ROC curve 0.74 for cut off 0.45, SE 77%, SP 69%). The amount of delayed enhancement within LV walls predicted response with better sensitivity but lower specificity (AUC ROC curve 0.69 for cut off 11%, SE 88%, SP 54%). All other parameters describing LV or RV structure and function showed worse accuracy.

Conclusion: In heart failure patients eligible for CRT, an extensive negative remodeling of the left ventricle, identified by a low ratio of LV mass to LVEDVi, should be considered another useful parameter obtainable at CMR, in addition to the measurement of scar burden, to predict the response to CRT.

Distribution of the device based intrinsic atrio-ventricular conduction delay in a broad pacemaker population with sinus node dysfunction or atrio-ventricular block


Purpose: The detection of myocardial fibrosis within left ventricular walls at cardiac magnetic resonance CMR has been shown to be a good marker of non-response to cardiac resynchronization therapy (CRT). However, CMR also provides information on left ventricular (LV) and right ventricular (RV) volumes, mass and function with a greater spatial resolution and a greater accuracy than any other imaging technique. It is still unknown whether such data can be useful to identify responders to CRT.

Methods: 268/872 (30%) patients were assigned to group A, 308/872 (36%) in group B. There was no difference in primary and secondary endpoint (mortality or heart transplantation or non-responder clinical state: 228/872 (18.6-32.4%) vs 191/9 (14.7-203.9%) mg/dl; p=0.01). We found no association between TNF-α, sC5b-9 or total C levels and the clinical outcome. According to our results, complement activation is strongly linked to unfavorable outcomes in heart failure. CMR may be a promising marker in the prediction of clinical response following CRT. Anaphylatoxin C3a might have a direct causative role in the progression of heart failure by edema formation due to increased fluid extravasation. Determining C3a concentrations preoperatively might improve the efficacy of appropriate patient selection. Grants: T ÁMOP-4.2.2.08/1/KMR-2008-0004.

Differences in the benefit of Cardiac Resynchronization Therapy (CRT) according to the QRS duration of patients with advanced heart failure


Purpose: Spontaneous AV conduction Delay (AVD) determines the amount of intraventricular conduction delay in a broad pacemaker population with sinus node dysfunction (SND) or atrio-ventricular block (AVB).

Methods: 642 patients (pts) were implanted with a dual chamber PM (74±11 years, 55.2% males, 50% Sinus Node Dysfunction (SND), 50% AV Block (ABV)). After 1-month, pts were randomized to either SafeR(R) or DDDR(R) for a 3-years (Y) period. Intrinsic AVD following atrial sensing (PR) or pacing (AR) were retrieved from PM memories of pts randomized to SafeR at 1Y. Data from 175 pts were considered in this analysis.

Results: Mean AR & PR values differed by 89±42 ms (AR: 209±64 ms, PR: 291±70 ms, p<0.001) (Figure 1). AVB pts had significantly longer AR & PR than SND pts (AVB: AR 233±75 ms, PR 235±70 ms, p<0.020; SND: AR 204±62 ms, PR 203±52 ms, p<0.002). The atrial paced-sensed (AR - PR) difference did not differ in AVB vs SND pts (86±31 ms vs 91±50 ms, p<0.05). AR & PR beyond nominal (0.80, 0.70) were considered in this analysis.

Conclusion: The SafeR mode allows an in-depth analysis of the intrinsic AV conduction in implanted pts. DDDR(R) pacing with standard AV settings is likely to produce a high proportion of unneeded VP. Although avoiding very low PR, the SafeR mode does not primarily depend on PR duration and enables intensified VP prevention. The analysis of the primary clinical endpoint of ANSWER will allow appraising the clinical usefulness of VP prevention.
The influence of right ventricle pacing site on the occurrence of permanent atrial fibrillation

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Introduction: Permanent pacing of the right ventricle apex (RVA) may lead to systolic heart failure. It is due to non-physiological depolarization and contraction pattern, which turn may cause ventricular remodeling. PACING OF THE SAME PART OF RIGHT VENTRICLE OUTFLOW TRACT (s-RVOT) IS OFTEN USED IN CLINICAL PRACTICE AS AN ALTERNATIVE TO RVA PACING. HOWEVER, DATA ON s-RVOT PACING ADVANTAGES ARE AMBIGUOUS. THERE ARE NO DATA CONCERNING VENTRICULAR PACING SITE INFLUENCE ON AF INCIDENCE.

Purpose: The aim of the study was to assess the influence of right ventricular pacing site (s-RVOT vs RVA) on the incidence of permanent AF.

Material and methods: The study group consisted of 239 patients (82 female, 158 male), aged 23-91 years with dual chamber (DDD) pacemaker implanted for atrio-ventricular block who were followed-up for at least 12 months after implantation. The exclusion criteria were the following: impairment of left ventricular systolic function before the implantation (left ventricle ejection fraction [LVEF] <50%), heart failure, use of antiarrhythmic medications (with the exception of beta-blockers), thyroid pathologies, and coexisting sick sinus syndrome. In 150 pts ventricular lead was placed in s-RVOT whereas in 89 pts in RVA. The lead position in s-RVOT was confirmed using ECG (negative polarity of paced QRS in leads I and aVF, and X-ray (45° LAG projection). Permanent AF was diagnosed using surface ECG and data obtained from pacemaker memory (histograms, stored electrocardiograms) during a routine follow-up at 12 months after implantation. Results: AF in RVA groups did not differ significantly in respect to age and gender. There were no significant differences in incidence of paroxysmal AF prior to implantation, diabetes or arterial hypertension. Medications used in both groups (beta-blockers, antiplatelet agents, statins) were also similar. Permanent AF was diagnosed in 7 pts (2,9%) - 1 pt in RVOT group and 6 pts in RVA group. Multivariate statistical analysis showed that the pacing site was the only significant factor influencing the development of permanent AF (p<0,03).

Conclusion: PACING OF s-RVOT IS ASSOCIATED WITH DECREASED RISK OF PERMANENT AF INCIDENCE AS COMPARED TO RVA PACING.

The effect of changes in the expression of genes related to contractile function and hypertrophy of the left ventricle in chronically paced patients from the right ventricular apex (preliminary results)

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Background: Long term asynchronous ventricular activation from right ventricular apex stimulation results in increased wall stress and hypertrophy of the left ventricle, neurohumoral activation, molecular changes and ventricular remodeling leading to reduced systolic and diastolic function. The purpose of this study is to assess in the peripheral blood, in the expression of genes regulating left ventricular sarcoplasmic reticulum calcium ATPase (SERCA), and 2) β-myosin heavy chain (β-MHC). Related to contractile function and hypertrophy. These findings are traceable, while at the same time left ventricular function has not been deteriorated.

Methods: In this study, we enrolled patients who underwent pacemaker implantation because of bradycardic indications. These patients were divided into two categories, based on the cumulative percentage of ventricular pacing post implant. Group A consisted of individuals who were paced due to atrioventricular conduction disturbances and ventricular pacing exceeded 90%, while group B who served as controls, suffered sinus node dysfunction and had preserved intrinsically atrioventricular conduction. At the time of implantation and 3 months later, we evaluated in the peripheral blood, in the expression of genes regulating left ventricular end-diastolic diameter, left ventricular end-systolic diameter and left ventricular ejection fraction.

Results: Up to now, we have collected data for 30 patients during a period of 3 months follow up. Group A consists of 14 patients with QRS duration 142±12ms and the remaining 16 patients, group B, have a mean QRS duration 120±9ms.

In group A at 3-months follow-up, mRNA levels of SERCA were decreased (9.3±1.49 vs 4.03±1.13 p=0.021) and β-MHC mRNA levels were increased though not significantly (62.12±46.97 vs 424±245 p=0.127). Left ventricular end-diastolic diameter, left ventricular end-systolic diameter and left ventricular ejection fraction remained unaltered (46.5±2.2 vs 47.85±2.18 p=0.7, 27.8±2.2 vs 32.4±2.2, p=0.4 and 61±2.8 vs 59±2.1, p=0.7 respectively). In controls all measured parameters showed no significant changes.

Conclusions: Permanent right ventricular apical pacing is associated with alterations in the peripheral blood, in the expression of genes regulating left ventricular contractile function and hypertrophy. These findings are traceable, while at the same time left ventricular function has not been deteriorated.
Biodegradation of the outer silicone insulation of the endocardial lead

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Purpose: To determine the role of macrophages (M) and Staphylococcus (S.) aureus strains in the outer silicone lead insulation degradation.

Methods: A new silicone insulated lead was cut into fragments. The outer insulation was untouched or scraped by syringe needle. The fragments were placed in a 24-well Multitwell Plate and cultured with a RAW 264.7 macrophage cell line at 37°C, 5% CO2 for 9 weeks. Additional lead fragments were placed with S. aureus strains ATCC 25923, ATCC 29213, and K93284. All strains were cultured for nine weeks. Lead fragments previously cultured with 3 different strains for 6 weeks were then placed into RAW M cultures with medium and incubated for additional 3 weeks. The condition of outer insulation was analyzed with optical microscopy and scanning electron microscope (SEM).

Results: Lead fragments with untouched or scraped by syringe needle outer insulation were covered by macrophages, with large clusters of M present in the regions prior damaged with syringe needle. In SEM analysis diminution in silicone was observed. All S. aureus strains provoked insulation damage after 9 weeks. The lowest level of degradation of outer insulation concerned ATCC 25923. Silicone lead fragments cultured with S. aureus strains and M presented a further gone level of silicone biodegradation (Figure A normal silicone insulation, B and C silicone biodegradation).

Conclusion: S. aureus, macrophages separately, and S. aureus and macrophages co-cultures initiate the biodegradation of outer silicone insulation. A difference in the level of biodegradation between strains of S.aureus was observed, with the most aggressive reaction towards silicone visible in the co-cultures.

Geometrically-correct 3D OCT: proof of concept, methodology and First-in-Man validation study

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Purpose: The geometrically correct three-dimensional (3D) reconstruction of human coronary arteries by integrating optical coherence tomography (OCT) and biplane coronary angiography has not yet developed and validated. The purpose of this study was to describe the methodology for 3D OCT and validate it in vivo.

Methods: We studied 9 coronary arteries (mean length, 40.1±5.1 mm) from 9 patients with OCT and biplane angiography. From each angiographic plane a single end-diastolic image was selected for the reconstruction of the OCT catheter pullback in 3D space. In each OCT frame we outlined the lumen-wall contour and placed the contours along the reconstructed OCT catheter trajectory. The OCT contours were oriented appropriately and interpolated creating a geometrically correct 3D reconstructed lumen (Figure A). The reconstructed lumen was back-projected onto the corresponding angiographic planes and the agreement between the back-projected lumen and the actual angiographic lumen in each plane was assessed with Bland-Altman analysis.

Results: The length of the 3D reconstructed arteries showed significantly high association (r=0.99, p<0.0001) and agreement with the OCT pullback-derived length. Bland-Altman plots of differences between the back-projected and actual lumen against their means showed that 3D OCT was in good agreement with the reference angiograms (mean difference: ±0.04 mm; limits of agreement: ±1.4 to 1.3 mm) (Figure B).

Conclusions: Geometrically correct 3D OCT is a novel imaging method with considerably high in-vivo feasibility and accuracy. This methodology is anticipated to facilitate precise shear stress, plaque morphometry and vascular remodeling analyses.

Detection of plaque neovascularization by optical coherence tomography: ex vivo feasibility study and in vivo observation in patients with angina pectoris


Background: Plaque neovascularization is related to plaque vulnerability. The feasibility of OCT for detecting the neovascularization characterized as microchannel (MC) in OCT image was investigated ex vivo, and serial OCT examination was conducted to assess impact of MC on coronary plaque progression in patients with angina pectoris.

Methods: In the ex vivo study, 78 coronary plaques from 36 human cadavers were examined by OCT. Plaque neovascularization was defined as a presence of MC by OCT. In the in vivo study, consecutive patients in whom IVUS and OCT were performed immediately after stent implantation and at follow-up were in-
Relationship between tissue protrusion within stented segment on optical coherence tomography and coronary flow during percutaneous coronary intervention

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Purpose: Tissue protrusion after stent implantation is sometimes detected on optical coherence tomography (OCT) after percutaneous coronary intervention (PCI) in patients with coronary artery disease. However, the relationship between the existence of tissue protrusion on OCT and outcomes after PCI has not been fully investigated. We sought to investigate the association between tissue protrusion, plaque morphologies and coronary flow during PCI.

Methods: We investigated 109 lesions that underwent PCI with pre- and post-intervention OCT. We measured quantitatively the whole volume of tissue protrusion (tissue protruding within the stent struts) throughout the stented segments after PCI. According to the volume of protrusion, all lesions were divided into the three groups: group L (protrusion < 1.53 mm^3; n = 36), group M (0.55 mm^3 < protrusion < 6.26 mm^3; n = 37) and group S (protrusion ≥ 6.26 mm^3; n = 36). In the three groups, we evaluated the differences of plaque morphologies such as lipid-rich plaque (lipid arc > 180 degrees), thin-cap fibroatheroma (TCFA) (lipid arc > 180 degrees and fibrous cap thickness < 70 μm) and plaque rupture, and coronary flow during PCI.

Results: Of 109 lesions, TCFA and plaque rupture was detected in 39 lesions (35.8%) and 18 lesions (16.5%), respectively and slow-flow phenomenon during PCI in 14 lesions (12.8%). Vascular healing process was assessed as percentage of uncovered struts, neointimal thickness, neointimal area and stent/stent area obstruction.

Conclusion: The results of this study provide important knowledge for identifying high-risk patients with PCI.
Synergistic Effect of combination therapy with Cilostazol and probaUcol on plaque stabilization and lesion regression (SECURE) trial

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Background: The study purpose was to investigate effects of cilostazol and proaUcol combination therapy on coronary plaque volume and composition us- ing VH-IVUS in comparison with cilostazol monotherapy.

Methods: The SECURE study was designed as a double-blind, randomized, con- trolled trial. A total of 119 patients undergoing coronary PCI were randomized either in the combination therapy group (n = 59) or in the cilosta- zol monotherapy group (n = 60). The primary end point was the change in the per- cent atheroma volume (PAV) of index intermediate lesions between baseline and 9-month follow-up.

Results: Baseline characteristics were similar between the two groups. Clinical outcomes regarding death, MI, and TVR did not differ between the two groups at 9 months. The plaque volume decreased significantly in both groups. However, the change in PAV at the index intermediate lesion did not differ be- tween the combination therapy and the cilostazol monotherapy (-3.32 ± 8.23%, p = 0.589). Change in plaque composition of the intermedi- ate lesion by Virtual Histology did not differ between the two groups either. The change in LDL cholesterol was similar between the two groups (-36.0 ± 8.23 mg/dL, p = 0.008). Decrease in HDL cholesterol level was observed in the combination group (-10.0 ± 8.70 mg/dL, p < 0.001). The percent neointimal obstruction in the index PCI target lesions treated with zotarolimus-eluting stents did not differ between the two patient groups (0.70 ± 0.54% vs. 0.72 ± 0.39%, p = 0.788).

Conclusions: There was significant decrease in plaque volume in both groups. However, the 43% change did not significantly differ between the proaUcol and cilostazol combination therapy and cilostazol monotherapy possibly due to rela- tively short follow-up period and limited study population volume.

Reproducibility of intracoronary Fourier-domain optical coherence tomography analysis

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Background: Frequency-domain optical coherence tomography (FD-OCT) is a novel technology which provides high-resolution cross-sectional images of coronary arteries. Despite the need for reproducibility data to design longitudinal stud- ies, such information remains unexplored. The aim of the present study was to evaluate in vivo reproducibility of quantitative FD-OCT measurements of coronary artery plaques.

Methods: We examined 20 stent-treated coronary lesions by using FD-OCT (C7, LightLab Imaging, Inc., Westford, Massachusetts, USA). Following FD-OCT im- aging, the guidewires were removed and the angiographic guiding catheter, an additional acquisition was performed using a new FD-OCT catheter. The acquisition of FD-OCT images was performed using the automatic pull-back at a speed of 20 mm/s during manual injection of contrast (Ultravist-300, Bayer Schering Pharma) at a rate of 4 mL/s. Lumen area was measured at every 1 mm cross-section. Volumetric FD-OCT analysis was performed using Simpson’s rule. Results: There was excellent correlation for minimum lumen area (n = 98, r = 0.98, p < 0.001), lesion length (n = 98, p < 0.001) and lumen volume (n = 98, p < 0.001) between 1st pullback and 2nd pullback. The Bland-Altman test also demonstrated good agreement for the geometric OCT measurements between 1st pullback and 2nd pullback; the absolute difference for minimum lumen area, lesion length and lumen volume was 0.22 ± 0.16 mm², 0.17 ± 0.10 mm, and 5.1 ± 3.9 mm³, respecti- vely; and the lower and upper limit of agreement for minimum lumen area, lesion length and lumen volume was 0.58 ± 0.48, 0.36 ± 0.42, and 13.4 ± 12.1, respectively.

Conclusions: The quantitative FD-OCT measurements from repeated pullbacks showed excellent reproducibilities. Our result emphasizes the value of FD-OCT as a tool for the clinical long-term assessment of coronary lesions.

Fractional flow reserve and intravascular ultrasound relationship study: the FIRST study

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Background: Assessment of intermediate coronary lesions is still challenging. Fractional flow reserve (FFR) measurements of 0.75-0.8 or lower are considered as a tool for the clinical long-term assessment of coronary lesions. Overall the patient population was 61.5±9.9 years old and 30.3% diabetic. Of the 320 lesions 28.7% had and FFR < 0.8 while 37.8% underwent PCI. The FIRST Study demonstrates modest correlation of IVUS anatomical to FFR physiological measurements in intermediate lesions with the new IVUS cutoff for FFR of 0.80 is 2.99 mm². Lesions without CaTCFA or TCFA had better correlation to FFR when compared to lesions with CaTCFA or TCFA. FFR was correlated with plaque burden but was not correlated with plaque morphology.

Conclusions: These data suggest that the new cutoff that best correlates to FFR for IVUS is an MLA of 3.0 mm². The utility of IVUS as a tool to determine whether to intervene on borderline lesions should be studied in a prospective study.

Multicentre national survey of patient exposure to X-rays during coronary angiography and percutaneous transluminal coronary intervention. The RAY ACT study

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Background: Patient exposure to radiation from invasive cardiac procedures is high and may be deleterious. Few multicentre data from large populations exist concerning radiation doses to patients during interventional coronary procedures (ICP).

The purpose of this nationwide, multicentre, French survey was to evaluate cur- rent practices for patient radiation protection (RP) in French non-university public hospitals, which represent >30% of the national activity for ICP and 60% of the emergency cases.

Methods: RP parameters from 35,257 coronary angiographies (CAs) and 28,604 percutaneous transluminal coronary interventions (PTCAs) were routinely collected in professional software were extracted and retrospec- tively analysed. Extreme values were validated and/or corrected by centres. Dose-area product (DAP, Gy.cm²), fluoroscopy time (FT, min), number of acquired frames (NF) and runs (NR), and estimated total air kerma dose (TAD, mGy) were analysed separately for CAs and PCTAs (elective and ad hoc potted).

Results: DAP was routinely registered in 94% of the centres, and in 88% of proce- dures for CA (median, interquartile range [IQR]: 27.2 [15.5-45.2] Gy.cm²) and in 89% of procedures for PCI (median [IQR] : 58.6 [32.9-84.6] Gy.cm²). FT was rou- tinely registered in 98% of the centres and in 81% of procedures (median [IQR] : 3.7 [2.3-6.3] min for CA, 10.3 [6.7-16.2] min for PCI). NF, NR, and TAD were routinely registered in only 20%, 28%, and 48% of the centres, and in 17%, 16%, and 31% of the procedures, respectively.

Conclusions: This survey showed a very high rate of compliance with dose regis- tration during the routine practice of ICP in French non-university hospitals. These data allow the definition of new reference levels (75th centile) for DAP, FT, NF and TAD for CA and PCI.
Effect of pitavastatin on tissue characteristics of atherosclerotic plaque in watanabe heritable hyperlipidemic rabbit: serial observation with IVUS and iMapTM

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Background and Purpose: It has been reported that administration of statin can reduce atherosclerotic plaque volume. However, its exact mechanism in histology is still unclear. This study was to investigate the change in tissue components within atherosclerotic plaque in Watanabe Heritable Hyperlipidemic rabbit (WHHL-MI) by pitavastatin with use of serial observation of IVUS and iMapTM.

Methods: Eight WHHL-MI rabbits at the age of 12 months were divided into two groups: Pitavastatin group (group P, n=4, 0.5mg/kg/day for 16 weeks) and controls (group C, n=4). A total of 34 atherosclerotic plaque cross-sections (in brachiocephalic artery were imaged twice by IVUS at the baseline and 16 weeks later. Then, Masson’s trichrome stain and RAM-11 stain were performed for the same sections after the IVUS imaging at the follow-up period.

Results: The level of LDL-Cholesterol at the follow-up was significantly reduced compared to the baseline in group P (-22.5%), but not significantly changed in group C. Total plaque area was significantly increased in group C (n=17) (baseline vs. follow-up, 7.03±2.16mm² vs. 7.82±6.22mm², p=0.021), while it tended to increase in group P (n=17) (7.06±1.81mm² vs. 6.60±1.31mm², p=0.055). During the follow-up, iMapTM revealed that %fibrotic and %necrotic area were significantly increased in group C, whereas %fibrotic and %lipidic area were significantly reduced in group P. However, when limited to the surface half of plaque, nominal change of %fibrotic area was plus in group P, while it was minus in group C (2.1±1.19% vs. -7.8±19.4%, p=0.047).

Postmortem histology at the follow-up showed that in group P %fibrous area was larger (49.0±12.2% vs. 38.3±13.4%, p=0.001), and %lipidic area was smaller (20.0±21.1% vs. 44.6±15.5%, p=0.001) than those in group C. The stain with RAM-11 indicated that macrophages were less accumulated in plaque surface of group P than in group C.

Conclusions: It was suggested that pitavastatin reduced plaque volume, and that it stabilized plaque with decrease in lipidic area and macrophage accumulation, and with increase of surface fibrotic area. These findings might give an insight into mechanism of reduction of plaque by statins.

Therapeutic impact of the stent visualization enhancement technique (stentboots) in percutaneous coronary intervention

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Background: Underdeployment and malaposition of stents during percutaneous coronary interventions (PCI) may lead to in-stent thrombosis and restenosis. Coronary angiography is limited for the analysis of the stent geometry and structure after deployment. Intravascular ultrasound remains the gold standard but its routine use is costly and time-consuming. StentBoost® (SB) is a new software developed by Philips Medical System®, which enhances stent visualization from a short digital cine run (30 frames/sec) acquired with a deflected balloon in place. SB allows a simple, real-time assessment of stent deployment.

Aims: Assessment of the results of SB in a large series of unselected routine PCI, to compare them to results of PCI by conventional angiography, and to evaluate the additional value of SB for the assessment of stent deployment and procedure optimization.

Methods: We retrospectively analyzed 260 coronary lesions treated by stent implantation, during 168 consecutive PCI procedures performed between November 2010 and March 2011.

Results: A total of 275 stents were implanted, 45% of them were drug eluting stents (DES). Direct stenting was performed in 78%. Results of SB and angiography were concordant for 209 lesions: 196 stents correctly deployed (75%) and 14 underdeployed (5%), detected by both techniques. In 47 patients (18%), SB detected an underdeployment of the stent whereas angiographic result was good. A post-dilatation was performed, on the basis of SB only, in 89% of these cases (vs 6% and 72% respectively for angiography and IVUS). The adverse event rate was lower for left main lesions and for DES, and was not affected by coronary calcifications.

Conclusion: This study confirmed the usefulness in current PCI practice of the stent visualization enhancement technique StentBoost®. SB revealed about 20% underdeployed stents not detected by conventional angiography, and allowed to optimize the procedure by ad hoc effective postdilatation.

Prognostic information of the SYNTAX- and Gensini-score on long-term outcome in Coronary Artery Disease - results of the AtheroxGene study

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Aim: Severity of coronary artery disease (CAD) is related to cardiovascular outcome. However, little is known on the complexity of CAD measured by the SYNTAX and Gensini Score in relation to cardiovascular event rate in a general CAD cohort.

Methods: We determined complexity and extent of CAD by the SYNTAX and the Gensini Score in the AtheroxGene cohort, a sample of consecutive cath lab patients (N=1997; 24.9% women). The cohort was stratified according to the SYNTAX Score applying the commonly used distribution: low (<22, N=1407), medium (23-32, N=315), and high score (>32, N=257) as well as according to the Gensini Score by usage of tertiles as for the SYNTAX Score. The adjudicated endpoint was the first event from baseline follow-up to cardiovascular infection and cardiovascular death (N=291 cases) over a median follow-up of 5.4 years.

Results: Stratified according to the SYNTAX- and Gensini-Score, Kaplan-Meier survival curves showed increased cardiovascular event rates across tertiles (both p<0.001). Patients within the highest SYNTAX tertile had a higher event rate (56 cases, 22.4% of patients in this category) compared to the lowest tertile (179 cases, 12.8%) and to patients in the middle tertile (60 events, 18.2%). Cox regression analysis revealed a hazard ratio of 1.57 (95% confidence interval 1.41-1.77, p<0.001) for the SYNTAX Score and of 1.43 (95% confidence interval 1.41-1.77, p<0.001) for the Gensini Score. The association remained statistically significant after additional adjustment for N-terminal pro B-type natriuretic peptide with hazard ratio of 1.54 (95% confidence interval 1.18-1.86, p<0.001) for the SYNTAX and of 1.43 (95% confidence interval 1.41-1.77, p<0.001) for the Gensini score.

Conclusion: The complexity of CAD quantified by the SYNTAX- or the Gensini Score was strongly and independently related to cardiovascular long-term prognosis in an everyday cohort of CAD patients.

Therapeutic and prognostic value of SYNTAX score for evaluation of coronary artery disease

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Background: Coronary segments distal to coronary total occlusions (CTO) have shown negative remodelling with respect to non-diseased coronary segments. Lumen and plaque changes after successful re-canalization of CTO at follow-up remain unknown.

Methods: A total of 92 CTO in 86 patients successfully treated with drug-eluting stents (DES) underwent angiographic follow-up at 15 months; 27 CTO in 27 patients of these series were imaged with intravascular ultrasound (IVUS) at least 20 mm distal to the stent edge at baseline and follow-up. Coronary angiograms and IVUS recordings were acquired after ≥ 0.2 mg of intracoronary nitro-glycerine. Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) changes were analyzed in minimal lumen diameter (MinLD), mean lumen diameter (MeanLD) and maximal lumen diameter (MaxLD) from the stent edge to at least 35 mm distally to the stent edge between matched segments at baseline and follow-up. Volume-metric analysis of lumen, vessel and plaque volume were assessed for matched segments using clear landmarks between baseline and follow-up. Both QCA and IVUS analysis were performed by our institutional core-laboratory.

Results: Angiographic MinLD increased 20.2% from baseline to follow-up (1.46±0.59 to 1.93±0.62 mm; p<0.001); MeanLD increased 18.6% from baseline to follow-up (1.75±0.62 to 2.15±0.62 mm; p<0.001); MaxLD increased 15.2% from baseline to follow-up (2.06±0.68 to 2.34±0.65 mm; p<0.001). A post-dilatation was performed, on the basis of SB only, in 89% of these cases (vs 6% and 72% respectively for angiography and IVUS). The adverse event rate was higher for left main lesions and for DES, and was not affected by coronary calcifications.

Conclusion: This study confirmed the usefulness in current PCI practice of the stent visualization enhancement technique StentBoost®. SB revealed about 20% underdeployed stents not detected by conventional angiography, and allowed to optimize the procedure by ad hoc effective postdilatation.
Characterization of non-calcified culprit plaque with napkin-ring sign in patients with stable angina pectoris by integrated backscatter intravascular ultrasound

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Background: Recent studies have demonstrated that atherosclerotic plaque with napkin-ring sign on coronary multidetector computed tomodraphy (MDCT) may be vulnerable plaque. However, little is known about tissue characteristics of coronary plaque with napkin-ring sign (NRS).

Objectives: The aim of this study was to assess the characteristics of atherosclerotic plaque with NRS on MDCT using integrated backscatter intravascular ultrasound (IB-IVUS) in patients with stable angina pectoris (SAP).

Methods: Of 213 consecutive SAP patients who underwent pre-intervention MDCT and percutaneous coronary intervention (PCI), 32 patients having 36 non-calcified plaques at the culprit lesion were studied. Patients were divided into two groups according to the presence of NRS on MDCT (NRS group: n=16, non-NRS group: n=19). Culprit plaques were evaluated by IB-IVUS before PCI and the findings were compared between two groups.

Results: HS-CRP level was significantly higher in the NRS group than in the non-NRS group. The plaque burden, remodeling index, and the incidence of ultrasricular attenuation by gray-scale IVUS were significantly higher in the NRS group than those in the non-NRS group. IB-IVUS demonstrated that culprit plaques at minimal lumen area site in the NRS had higher %lipid area (56±11% vs. 41±16%, p<0.01) and lower %fibrous area (35±8% vs. 48±14%, p<0.01) than those in the non-NRS group. In volumetric analysis, culprit plaques with NRS showed higher lipid component compared with those without NRS (67±27 mm³ vs. 39±33 mm³, p<0.01).

Conclusion: Atherosclerotic culprit plaque with NRS in patients with SAP had a lipid-rich characteristics, suggesting high risk plaque.

Relationship between regression of plaque and adverse cardiovascular events: a meta-regression of randomized clinical trials


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Atherosclerotic plaque represents the main substrate for coronary artery disease (CAD), and its regression, investigated with coronary artery intravascular ultrasound (IVUS), has been used as a surrogate endpoint in various studies. No conclusive data are however present showing a relationship between adverse clinical events and regression of plaque evaluated through IVUS.

Methods: PubMed, Cochrane and Biomed Central were searched for randomized clinical trials investigating variations of plaque with IVUS and clinical events. Selected end points were an adverse cardiovascular event, defined as death, myocardial infarction or repeated revascularization. Meta-regression analysis were performed to test the relationship between plaque variations and clinical events.

Results: 11 studies with 7864 patients were included, 2 studies including patients with acute coronary syndromes (ACS) and 9 including patients with stable angina. After a median follow up of 18 months (13-24), regression of plaque volume evaluated as percent atheroma volume (PAV) was 0.50 (0.25 to 1.1), with 15.02% (9.62-22.54) of adverse events and 14.12% (10.15-19.50) of myocardial infarction and need for revascularization. Variations in plaque volume did not significantly correlate with adverse cardiovascular events, either at 6 months (Beta=0.134; p=0.657) or at long-term follow up (18; 13-24 months) (Beta=0.321; p=0.208) (Figures 2 and 3). Modification of plaque volume was however significantly related to the incidence of myocardial infarction and repeat revascularization at long-term follow up (Beta=0.30; p=0.042) but not at 6 months (Beta=0.012; p=0.147).

Conclusions: Regression of coronary plaque measured at IVUS directly relates to reduction of combined clinical end point long-term follow up.

Detection of coronary artery disease in postmenopausal women: the significance of integrated stress imaging tests


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Background: In women, especially postmenopausal, non-invasive tests for detecting coronary artery disease (CAD) are less accurate than in men, leading to a high proportion of unnecessary coronary angiographies (CAs). Therefore, the present prospective study investigated whether an integrated approach consisting of two different stress imaging modalities may improve the diagnostic accuracy and prognostic impact of non-invasive CAD tests.

Methods: We prospectively enrolled 522 consecutive postmenopausal women (mean Framingham Risk Score 14.6% with symptoms suggestive of CAD. Each patient underwent CA, cardiovascular magnetic resonance (CMR), dobutamine stress echocardiography (DSE), and single-photon emission computed tomography (SPECT) within 7±3 days. 424 women (mean 61±7 years) completed the invasive and non-invasive test protocols and were followed up for 4±1 years.
**INVASIVE CORONARY IMAGING II**

**P5443**

**Difference between tissue characteristics in late in-stent restenosis lesions and those in early in-stent restenosis lesions assessing with optical coherence tomography**


**Purpose:** The morphological assessment of neointimal tissue is highly significant to clarify the pathophysiology of in-stent restenosis (ISR) after drug-eluting stent (DES) implantation. Recently, the differences of morphological characteristics according to the period from stent implantation to occurrence of ISR were reported. In this study, we clarify the difference between tissue characteristics in late ISR lesions and those in early ISR lesions.

**Methods:** Between May 2008 and February 2012, we assessed the morphology of neointimal tissue at the minimum lumen area site by OCT, including restenotic tissue structure (homogeneous, heterogeneous, and layered type), restenotic tissue backscatter, visible microvessels, lumen shape, and the presence of intraluminal material in 281 ISR lesions after DES implantation in 245 lesions and bare-metal stent implantation in 36 lesions. We divided them into two groups (Group A = 127 late ISR lesions; lesions more than one year after stent implantation, Group B = 154 early ISR lesions; lesions less than one year after stent implantation).

**Results:** The patients were 230 men and 51 women, and the mean age was 68.9±9.8 years. There was a significant difference between the distributions of restenotic tissue structure type in two groups as shown in figure 1 (p<0.01). Lumen border irregular was more frequently observed in Group B than Group A (44.9% vs. 29.1%, p=0.01). Intraluminal material tended to be frequently observed in Group B than in Group A (28.6% vs. 19.7%, p=0.096). There were no other differences in other parameters including restenotic tissue backscatter and visible microvessels.

**Conclusions:** The pathophysiology of in-stent restenosis might be different according to the period from stent implantation to occurrence of ISR.

**P5444**

**Assessment of neointimal hyperplasia at overlapping stent region of multiple everolimus-eluting stent in patients with diabetes mellitus using optical coherence tomography (from XILLION registry)**


**Background and Purpose:** Diabetes mellitus and diffuse long coronary artery lesion is the major predictor for target lesion revascularization even in the drug eluting stent era. The purpose of this study was to evaluate the different vascular response of overlapping stent strut region compared to single stent strut region in diabetic patients with multiple everolimus eluting stents (EES) implantation for the diffuse long coronary artery lesion using optical coherent tomography (OCT).

**Methods:** We enrolled 34 patients (including 17 diabetic patients) from the prospective, multi-center study of XILLION registry to assess the efficacy of multiple EES for 450 long coronary diseases. They were imaged with motorized OCT pull back system (1mm/s) analyzed at 0.3 mm interval and follow up OCT images were obtained at 9 months. Percent neointimal hyperplasia area (%NIH area) was calculated as (stenot area - lumen area)/ stent area in cross sectional area.

**Results:** At single stent strut region, average neointimal thickness (NIT) in diabetic patients was significantly higher and lumen area was smaller than that in non diabetic patients. However, average NIH and lumen area at overlapping stent strut region in diabetic patients was not significantly different compared to that in non diabetic patients (see Table).

**Conclusions:** Overlapping multiple EES is effective and safety treatment method even in the patients with diabetes mellitus and long coronary artery disease.
Conclusions: For the first time, RenalGuard, CVVH and hydration with sodium bicarbonate and N-acetylcysteine were compared in a real-world population: RG demonstrated to be safe and to significantly reduce risk of In-Hospital, 1 month and 6 month MACES, compared to continuous veno-venous Hemofiltration and Hydration.

Lipid core coronary plaques detection by serial intracoronary imaging with a NIRS catheter in atheregenic, diabetic swine.


During atherosclerosis progression, lipid-rich coronary plaques (LCPs) develop and it has been shown that such plaques underlie most acute coronary syndromes. Recently, a new near-infrared spectroscopy intravascular system (NIRS) for LCP detection was developed. Since the natural history of atherosclerosis progression and coronary LCP formation is difficult to assess in humans, studies in large animal models of atherosclerosis are essential. We investigated coronary atherosclerosis development in a diseased porcine model by intracoronary imaging with the NIRS. 15 male swine were fed an atherogenic diet for 15 months (M). Part of the animals were rendered diabetic by infusion of streptozotocin. Serial NIRS intracoronary imaging was performed at 9, 12 and 15M follow-up (FU); the vascular segments were matched at the three FU times using side-branches as landmarks (LM Fig.). Since no differences were observed between the diabetic and non-diabetic animals, data were pooled. Data show that the lipid core burden index (LCBI) increases from 9±3%A.U. at 9M to 20±10 respectively 45±28 at 12 and 15M FU (Fig, yellow shows detected lipid in the vessel wall). The maximal LCBI indicating the most important LCP also increased from 61±19 at 9M to 114±50 resp. 160±72 at 12 and 15M. Furthermore, the distribution of LCP probability along the vascular segment increased from distal to proximal in all three coronaries.

Conclusions: We demonstrate that MMP levels are associated with vulnerable plaque.

The feasibility and diagnostic yield of optical coherence tomography guided thrombus aspiration in patients with non-S-thrombolysis myocardial infarction undergoing initial conservative therapy.

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Purpose: Impaired myocardial perfusion due to embolisation of atherothrombotic material is a common phenomenon in percutaneous coronary intervention (PCI) for acute coronary syndromes. Thrombus Aspiration (TA) is shown to be feasible and useful in retrieval of thrombotic material, resulting in improvement of flow in the culprit coronary artery. However, the role of thrombotic material in initially conservatively managed patients with non-S-thrombolysis myocardial infarction (NSTEMI) is less well established.

Optical coherence tomography (OCT) enables the detection of intracoronary thrombus during PCI. The aim of the study was to investigate the feasibility and diagnostic yield of OCT guided manual TA in initially conservatively treated patients with NSTEMI.

Methods: OCT of the culprit vessel was performed before TA, immediately after TA, and after stent implantation in 30 patients with NSTEMI after initial conservative therapy (PCI three or more days after clinical symptoms). The OCT images were analyzed with dedicated software. An identical region of interest (ROI) was defined (including the culprit lesion) in all three pullbacks. The presence of thrombus was visually assessed. Coronary artery lumen volumes of ROI were calculated in all three pullbacks. To compensate for the difference between the pullback lengths between the patients, a normalized ROI was calculated for each ROI (normalized ROI = [ROI volume/number of slices in pullback] x median number of slices in study population). Effectiveness of thrombus aspiration was assessed with OCT by computing the difference of ROI volumes before and after TA.

Results: TA was successfully performed in all 30 patients. Thrombus was visually observed on OCT ROI’s in 17 (57%) patients before TA, 19 (63%) patients after TA, with minimal amounts of thrombus detectable post stent implantation in 19 (63%) patients. There were no significant differences between ROI volumes before and after TA (141.2±80.8 vs. 138.2±78.5; p=NS). Likewise, there were no significant differences between normalized ROI volumes before and after TA (133.2±55.2 vs. 131.6±57.3; p=NS). ROI volumes and normalized ROI volumes were significantly larger after stent implantation (191.6±104 and 185.7±61.1; p<0.001 for comparisons with both before and after TA).

Conclusions: Small amounts of thrombus can be observed on OCT images in 57% of patients with NSTEMI after initial conservative therapy. Moreover, small amounts of thrombus may be induced by PCI procedure itself in case thrombus is initially absent. In this patient group TA is not effective in reducing thrombus load as assessed with OCT.

Comparison of neointimal coverage of biolimus-eluting stent and everolimus-eluting stent at 1, 2 and 3-month follow-up: evaluation by optical coherence tomography.

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Background: Second-generation drug-eluting stents (DESs) have been used to optimize the results of percutaneous coronary intervention in terms of efficacy and safety now. Everolimus-eluting stent (EES) is a flexible cobalt chromium alloy with 81μm strut thickness, and coated with a durable polymer. On the other hand, Biolimus-eluting stent (BES) is a flexible stainless steel alloy with thick struts (137μm), and coated with a biodegradable polymer which is applied solely to the abluminal surface. Confirming complete neointimal coverage after DES implantation is clinically important, because incomplete stent coverage is responsible for stent thrombosis. However, the short-term analyses of neointimal coverage in patients with EES and BES have not been reported. The aim of this study was to

Figure 1

In conclusion, serial NIRS imaging was able to detect changes in LCP during disease progression in coronary arteries of atherosclerotic swine. The LCPs were detected at regions prone to LCP development as acknowledged in humans.

Serum levels of matrix metalloproteinases and cystatin-c are associated with coronary plaque features assessed by optical coherence tomography.


Background: Matrix metalloproteinases (MMP) are involved in coronary plaque vulnerability, while cystatin-c (Cys-C) has a stabilizing effect. Evidence for in vivo disease progression in coronary arteries of atherosclerotic swine. The LCPs were demonstrated to be safe and to significantly reduce risk of In-Hospital, 1 month and 6 month MACES, compared to continuous veno-venous Hemofiltration and Hydration.

Methods: We enrolled 30 consecutive patients undergoing coronary angiography. We evaluated plaque characteristics at the culprit lesion by OCT. Patients were classified according to plaque morphology in fibrous, fibrolipidic or fibrocalcific plaque. We assessed cap thickness and thin-cap fibroatheroma (TCFA) presence. MMP-2 (ng/L), MMP-9 (ng/L), and of Cys-C (mg/L) serum levels were measured. Biomarker level comparisons were performed according to plaque morphology and cap thickness was correlated to biomarker levels.

Results: Fibrolipidic composition was detected at the culprit lesion in 51 (80%) patients, fibrous plaque in 11 (17%), and fibrocalcific plaque in 2 (3%). In the whole study population, MMP-9 was significantly higher in patients with fibrolipidic plaque compared to fibrous and fibrocalcific plaque [14.1 (0.07-57) vs 5.69 (0.04-13.2) vs 7.15 (0.1-14.4); p=0.001]. No difference was found for MMP-2 (p=NS). MMP-9 and MMP-2 levels were higher in patients with TCFA compared to no-TCFA [17.6 (0.9-57) vs 11.4 (0.04-44); p=0.02, and 28 (6.9-51.2) vs 19.9 (7.6-51.9); p=0.025]. MMP-9 and of MMP-2 levels had an inverse correlation with cap thickness (p=0.015 and p=0.02). Cys-C levels were higher in patients with fibrous plaque as compared to fibrolipidic and fibrocalcific plaque [0.94 (0.02-2.1) vs 0.49 (0.02-0.95) vs 0.38 (0.32-0.45); p=0.005], and lower in patients with TCFA compared to no-TCFA [0.23 (0.02-0.94) vs 0.57 (0.03-2.1); p=0.031]. A positive correlation was found between Cys-C and cap thickness (p=0.002).

Conclusions: We demonstrate that MMP levels are associated with vulnerable plaque and can be used to identify high risk patients.
Intra stent neo-atheroma rupture as a potential impact of Cytochrome P450 2C19 loss-of-function (death+reinfarction+urgent PCI+stroke) was observed during the first 30 days PCI in n=5 patients (DES in 80% of the cases). No adverse cardiovascular event including initial manual thrombectomy that was completed by subsequent redo intra-stenting stent (DES) was involved in 50% of the cases. 66% of the patients were under these results suggest that the relatively rapid neo-atheroma coverage might be related to a biodegradable polymer in abluminal coating of DES.

Methods: A total of 48 stents (28 BES and 20 EES) in 29 patients with de novo coronary native lesions were enrolled in this study. OCT examination was performed at 1.2 and 3-month follow-up. The strut apposition to the vessel wall and neointimal coverage on struts were evaluated by OCT.

Conclusions: BES struts rapidly covered at 1-month. It could be speculated that either the biodegradable polymer coating only on the outer surface of the stent or better drug release kinetics could have contributed to this finding. These data suggest that the presence of characteristic neointimal tissues in stent restenosis. We investigated the presence of intra-stent neo-atheroma lesions in patients with VLST using optical coherence tomography (OCT) imaging techniques.

Methods: Patients with VLST from two middle volume catheterization facilities were included in this multicenter registry. All patients who presented an acute coronary syndrome related to VLST underwent a standard coronary angiography and intra coronary OCT imaging. Two operators reviewed OCT images. Neointima was defined as reported as the combination of neointimal diffuse proliferation + lipid-laden intima with plaque organization and fibrous cap.

Results: A total of 1389 patients were admitted for acute coronary syndromes in both centers between October 2010 and January 2012. Eight subjects (n=8) presented very late stent thrombosis (50% of ST elevation myocardial infarction). Among this group, we identified n=7 subjects with evidences of neo-atheroma, including fibrous cap rupture and thrombus. No evidence of stent under-expansion, neo-intimal hyperplasia or incomplete endothelialization was reported by OCT analysis.

Among this group, we identified n=6 subjects with evidences of neo-atheroma, including fibrous cap rupture and thrombus. No evidence of stent under-expansion, neo-intimal hyperplasia or incomplete endothelialization was reported by OCT analysis. The lesions with hetero-ISR on OCT had more frequent findings as assessed by angioscopy and OCT. The lesions with hetero-ISR on OCT had more frequent findings as assessed by angioscopy and OCT. The lesions with hetero-ISR on OCT had more frequent findings as assessed by angioscopy and OCT. The lesions with hetero-ISR on OCT had more frequent findings as assessed by angioscopy and OCT. The lesions with hetero-ISR on OCT had more frequent findings as assessed by angioscopy and OCT.
Conclusion: The heterogeneous neointimal tissues on OCT in stent restenosis may suggest the presence of atheromatous-like tissues with great amount of thrombi, which might lead to the occurrence of stent thrombosis.

P5453
Increased circumferential vessel wall calcification predisposes to stent strut malapposition as assessed by optical coherence tomography
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Purpose: The purpose of this study was to use optical coherence tomography (OCT) to investigate the relationship between the extent of arterial wall calcification and stent strut malapposition following percutaneous coronary intervention (PCI).
Methods: 23 consecutive patients underwent OCT both before and after PCI. Image analysis was performed by a blinded experienced observer (M.P.) using proprietary software (LightLab Imaging, St JudeMedical). The length of the lesion, minimal luminal area (MLA), minimal lumen diameter (MLD) and length of stent used were noted, and in addition the degree of circumferential vessel wall calcification was quantified by measuring the angle subtended by an arc drawn from the edge of the calcified area towards the centre of the lumen (see figure). Strut malapposition was assessed using a novel software package (Ovidia v2.2, Catholic University Leuven, Belgium).
Results: The mean lesion length was 25.2±10.8 (mm ± SD), with a mean minimal lumen area of 2.2±1.2 (mm²) and a mean minimal lumen diameter of 1.6±0.5 (mm). Calcium was present in 96% of lesions, with a mean circumferential arc angle of 186.8°. A total number of 632 post PCI frames were analyzed, including 5710 struts. The number of well-apposed struts was 5246 (91.9%). By univariate analysis, the circumferential extent of calcium was correlated with the percentage of malapposed struts (p=0.048).

Figure 1. Malapposed stent struts

Conclusions: As measured by OCT, the circumferential extent of plaque calcification was found to correlate with stent strut malapposition following PCI.

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Choosing the distal cell for bifurcational stenting: OCT guidance significantly reduces stent malapposition
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Purpose: PCI on bifurcated lesions are complex and lead to an increase rate of malapposed struts with a potential increase in stent thrombosis. The position where the wire recrosses is equally important for 1 or 2 stents techniques. Primary aim of this study is the assessment of the ability of the use to OCT to guiderecrosing and reduce strut malapposition after kissing balloon dilatation.
Methods: 18 patients with bifurcated coronary lesions were included in the analysis. OCT catheters were inserted and pull-back at 20 mm/sec was performed. In the group of blind recrossing (n=9), OCT assessed sizing of the balloons and stents. In the group of OCT guiding a distal recrossing (n=9), OCT was performed after side branch wire crossing and repeated. A new pullback was performed after kissing and proximal optimisation in both groups.
Results: Both groups were comparable in demographics (age,cardiovascular risk factors, CCS class, vessel size, lesion location, sizes of balloons and stents and number of OCT runs). There was a significant decrease in the rate of malapposed struts in the bifurcation segment when OCT was used to verify a distal recrossing of the guidewire into the SB (12.7±1±5.84 vs 34.21±18.8, p= 0.005).

P5455
Correlation between intravascular ultrasound parameters and fractional flow reserve assessed by intracoronary pressure wire in very long coronary lesions. A 3D intravascular ultrasound study
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Purpose: Demonstration of physiologic significance of coronary artery lesions is a challenging issue to decide coronary revascularization in clinical practice. Minimal lumen area (MLA) assessed with intravascular ultrasound (IVUS) is the parameter that better correlates functional repercussion of coronary artery lesions. Though, this measure does not take into account the length of the lesion and it has not been well validated in long coronary artery lesions.
Methods: 61 consecutive moderate (40-70% visual angiographic stenosis) and long (length of ≥20 mm stenting in case of treatment) coronary artery lesions were studied. An intracoronary pressure wire study and an IVUS study (0.5 mm per second automatic pullback) were performed in all lesions. An off-line 3D IVUS analysis of the lesions was made, blinded to the result of fractional flow reserve value (FFR) obtained with an intracoronary pressure wire. Different 2D and 3D parameters obtained with IVUS were correlated to FFR. Intracoronary adenosine bolus (≥300 μg) were used to obtain maximal hyperaemia.
Results: 12% of the lesions were found in right coronary artery, 57% in left anterior descending artery, and 31% in circumflex artery. The mean angiographic measurements of studied lesions were: proximal reference luminal area: 10.5±5.7mm²; distal reference luminal area: 6.3±2.7mm²; MLA 2.7±1.1mm²; plaque volume 236.6±137.4mm³. The median FFR value observed was: 0.79±0.01. A poor linear correlation (R) was obtained between IVUS parameters that didn’t take into account lesion's length and FFR: FFR-MLA (R=0.4; p=0.003) FFR%stenosis area (R=0.42; R=0.003). A good correlation was found when length was taken into account: FFR-plaque volume(R=−0.65; p<0.0005) FFR-MLA/length (R=−0.73; p<0.0005). The best correlation was obtained with the product: mean stenosis/lesion length (R=-0.80; p<0.005).
Conclusions: Minimal lumen area assessed by IVUS has not a good correlation with functional significance of long coronary artery lesions. In this setting, if a FFR study is not performed, the length of the lesion should also be taken into account to decide coronary revascularization.

P5456
Impact of microvascular dysfunction on reduced coronary vasodilator function in remote normal myocardium after primary coronary intervention for acute myocardial infarction
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Purpose: It has been reported the vasodilator function might be impaired in
the myocardium perfused by normal coronary vessels after acute myocardial infarction (AMI). Recent studies have shown that severe microvascular dysfunction can be evaluated from coronary flow velocity (CFV) pattern by using a Doppler guidewire in patients with AMI. However, the relationship between microvascular dysfunction and vasodilator abnormality in the remote myocardium has not been evaluated. The aim of this prospective study was to examine whether the microvascular dysfunction may influence the vasodilator abnormality in the infarcted and remote myocardium.

Methods: The study population consisted of 55 consecutive patients with a first anterior AMI successfully treated with primary coronary intervention (PCI). We examined the CFV pattern immediately after PCI using a Doppler guidewire. According to our previous reports, we defined severe microvascular dysfunction as a diastolic deceleration time <600 ms and the presence of systolic flow reversal. Patients were divided into two groups: those without severe microvascular dysfunction (n=31; group 1) and those with severe microvascular dysfunction (n=24; group 2). Using a Doppler guidewire, we measured coronary flow reserve (CFR) in the infarcted-related and normal arteries 1 month after infarction. We evaluated the association between the severe microvascular dysfunction and CFR 1 month after the onset.

Results: The CFR was 2.58±0.78 in the infarct-related coronary artery and 3.11±0.67 in the normal coronary artery (P=0.001) in patients with group 1. In patients with group 2, the CFR was 1.96±0.58 in the infarct-related coronary artery, which is lower than group 1 (P=0.0046) and 2.64±0.66 in the normal coronary artery (P=0.001 for the comparison with the infarct-related artery in group 2; p=0.0225 for the comparison with the normal coronary artery in group 1).

Conclusion: There are vasodilator abnormalities involving not only resistance vessels in the infarcted myocardium, but also those in the remote myocardium perfused by normal coronary vessels especially in patients with severe microvascular dysfunction after AMI.

Angiographic and clinical outcomes following hybrid stenting with drug-eluting stents in chronic total occlusion intervention

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Background: The implantation of multiple overlapping stenting in patients (pts) with a diffuse long coronary lesion is relatively safe and effective in drug eluting stents (DES) era. However, the safety and efficacy of overlapping stenting with a different type of DES in chronic total occlusion (CTO) intervention remain unknown.

Methods: A total 267 consecutive pts who underwent percutaneous coronary intervention (PCI) with DESs for CTO lesions were enrolled for this study. We compared the angiographic and clinical outcomes of Same DES strategy (n=228) vs. Different DES strategy (n=39) to hybrid DES strategy (n=28) to hybrid DES strategy (n=28) to hybrid DES strategy (n=28) to hybrid DES strategy (n=28).

Results: Baseline clinical characteristics were similar between the two groups. At index procedure, angiographic and procedural parameters were also similar except for CTO length which was longer in hybrid stenting group (45.47±27.02 vs. 38.87±25.57, p=0.035). At six months angiographic follow up, late loss was higher in the hybrid stenting group. The incidence of target vessel revascularization (TVR), TVR-major adverse cardiac event (MACE) and all MACE were higher in the hybrid stenting group at 12 months (Table).

Conclusions: In the current study, hybrid DES stenting for long CTO lesion showed higher late loss at 6 months and subsequent increased repeat PCI and MACE at 12 months. However, this need further randomized study with larger study population to get final conclusion.

Operator vs. independent adjudication of angiographic reperfusion markers in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction

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Background: There is very little data on the reliability of operator (Op) estimation of Thrombolysis in Myocardial Infarction (TIMI) flow and TIMI Microvascular Perfusion Blush Grade (TMPGMBG) when compared with an Angiography Core Laboratory (ACL).

Objective: To determine the agreement level between Op and ACL for TIMI flow and TMPGMBG, before and after PCI, in the HORIZONS AMI trial and to evaluate the prognostic impact of Op TMPGMBG on 3-year death.

Methods: Op and ACL estimation of TIMI flow and TMPGMBG were compared using the Cohen’s Kappa coefficient. A multivariable model for long-term survival derived from HORIZONS AMI was used to assess the independent value of Op TMPGMBG and MBG.

Results: There were 3,345 subjects eligible for this study. x was highest for pre-PCI TIMI flow (0.52±0.62) and lowest for post-PCI TMPGMBG (0.11±0.22). Critical discordance between Op and ACL reading for final TIMI flow (0.2±0.3) occurred in 12.9% of patients and for final TMPGMBG (01-0-1 vs. 2-3) in 22.4%. Of the 798 patients with final TMPGMBG 0 or 1 by ACL, 563 (79.7%) were classified as TMPGMBG 2 or 3 by Op. In “discordant” patients, mortality was low and tracked more closely patients with concordant optimal reperfusion. When discordant grading of TIMI flow occurred, ACL TIMI flow was a better predictor of mortality than Op TIMI flow.

Conclusion: Op assessment of angiographic markers of reperfusion in STEMI demonstrates only modest agreement with ACL findings and there is directionality in these disagreements with overestimation of unfavorable results. Further education of operators may improve quality of PCI in STEMI and reliability of site reported findings in clinical investigation.

Gender differences in the composition of coronary atherosclerotic plaque

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Background: Gender differences should be considered in the management of coronary atherosclerosis and risk factors. However, it has not known enough about gender differences of coronary atherosclerotic plaque.

Methods and Results: 121 lesions of 109 patients were investigated by integrated backscatter intravascular ultrasound (IB-IVUS) before coronary stent implantation for left anterior descending artery (LAD). The total vessel and plaque volumes were calculated from the cross section measurement per 1mm through the whole target lesion. Moreover the plaque composition of the target lesion was investigated by the color code analysis of IB-IVUS. The vessel volume of target lesion per 1mm lesion length was significantly larger in men than in women (15.1±9.2 vs. 12.0±3.1mm3, p=0.044). The plaque volume of target lesion per 1mm lesion length tended to be larger in men (9.9±6.9 vs. 7.8±2.6 mm3, p=0.074). The ratio of lipid component in the target plaque was significantly higher in men than in women (57.3±14.9 vs. 50.9±15.2%, p=0.029). Multivariate regression analysis revealed that gender, as well as diabetes mellitus, was an independent predictor for the ratio of lipid component in the coronary plaque (p=0.046).

Conclusion: Gender differences of coronary atherosclerotic plaque exist not only vessel size and plaque volume but also plaque component.
**Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography**

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**Purpose:** Characterizing the vascular response to acute incomplete stent apposition (ISA) and looking for predictors of incomplete healing.

**Methods:** A total of 36 lesions were included (SES n=17, EES n=19). Mean follow-up periods were similar (SES 10.6±4.6 month vs 5.9±4.7 month, p=0.326). A total of 728 cross sections and 6884 struts were analyzed. There were no difference in strut area, lumen area and neointimal area (SA: 5.6±1.5mm² vs 5.9±1.2mm², p=0.599, LA: 5.0±1.3mm² vs 5.2±1.1mm², p=0.691, NIA: 0.64±0.48mm² vs 0.72±0.37mm², p=0.613). NIT of SES and EES were 110±46mm² and 95±45mm², respectively (p=0.339). Conversely, area, angle and depth of ESL in SES group were significantly greater than those in EES group (0.14±0.18 mm vs 0.03±0.03 mm², p=0.011, 54±55° vs 31±48°, p<0.001, 0.20±0.27mm vs 0.04±0.06mm, p<0.001).

**Conclusions:** OCT study showed that the efficacy of suppression of neointimal growth is similar between SES and EES whereas the adverse vascular response after EES implantation is less than that after SES implantation.

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**Confidence estimation with random walks of IVUS based radio-frequency plaque characterization**

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**Background:** Shadowing in intravascular ultrasound (IVUS) is due to strong reflection of signals from dense/calcified tissue. The resulting loss of ultrasound energy, textural and spectral features raise uncertainty on the accuracy of radio-frequency (RF) derived plaque characterization algorithms in these regions.

**Methods:** We computed confidence (Conf) maps based on a novel formulation of the random walk framework integrating beam-width, depth dependent attenuation and ultrasound transmission physics. RF data were acquired in vitro using 40 MHz IVUS pullback in dissected pressure-fixed coronary arteries of autopsied hearts. Conf was computed on raw digitized RF signal @200 Mhz and characterized using non-linearly co-registered histology images and IVUS B mode (see figure).

**Results:** As demonstrated on the figure, lower Conf were found in guide-wire artefact (w), at media-adventitia border, in large necrotic core and behind highly reflective echoes from calcium (Ca) with shadowing. A total of 16 arteries from 10 cadavers were imaged. At the selected ROI demonstrating Ca by histology and shadowing on IVUS (mean area of 59±36), plaque burden was 57±13%. Conf in lumen (saline filled) was 93±8% and in the plaque 57±13% on average. However, Conf was statistically lower in the shadowing regions (16±6%) and behind wire (51±20%) than in well insonnified selected plaque regions (76±14%).

**Conclusion:**: IVUS shadow regions demonstrate very low confidence values where there is too few information for reliable plaque characterization. Further evaluation of tissue-types quantification integrating the proposed weighting Confidence Map, which is catheter independent and can be computed for recording from 20 to 45 MHz, is warranted e.g. to decrease “noise” in IVUS plaque progression/regression studies.
Adiponectin produced in perivascular adipose tissue as a defence mechanism against vascular oxidative stress in human vein grafts

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Purpose: The adipokine adiponectin (AdN) exhibits anti-inflammatory properties in experimental models. In clinical studies however, the biological role of AdN is controversial. We hypothesized that AdN produced in adipose tissue surrounding human saphenous vein (SV) grafts may constitute a defence mechanism against oxidative stress.

Methods: Study 1 consisted of 293 patients with normal left ventricular systolic function, undergoing CABG. Vasorelaxations of SV grafts in response to acetylcholine were examined ex vivo, and superoxide (O2-·) generation (+/−NO synthase inhibitor (eNOS), LNAME), by lucigenin-enhanced chemiluminescence. AdN gene expression was quantified in per-SV adipose tissue in 60 of those patients. In Study 2, SVs from 9 patients were exposed to AdN (10 µg/ml) ex vivo for 6 hours and its effect on vascular redox state was examined.

Results: O2-· generation was associated with better NO bioavailability (A), lower vascular O2-· (B) and better eNOS coupling (C) in SV grafts. However, high vascular O2-· (D) and uncoupled eNOS-derived O2-· (E) were associated with higher local AdN expression in peri-SV adipose tissue. In study 2, AdN directly reduced O2-· (F) and improved eNOS coupling (G) in these SV grafts.

Conclusions: Circulating AdN is associated with better endothelial function and improved redox state of SV grafts. However, increased O2-· in SV grafts leads to an up-regulation of AdN gene in peri-SV adipose tissue. Therefore, AdN produced in peri-SV adipose tissue may be a paracrine defence mechanism of SV grafts against vascular oxidative stress, by improving eNOS coupling. These novel findings introduce the concept that maintenance of perivascular adipose tissue during graft preparation in CABG, may have a protective effect against oxidative stress in these grafts.

Nicorandil prevents microvascular dysfunction and myocardial damage resulting from percutaneous coronary intervention


Background: Studies suggest that the status of the coronary microvasculature in patients with stable angina pectoris is important in determining long-term outcome. Nicorandil, an ATP sensitive potassium-channel opener, may reduce the incidence of microvascular dysfunction after percutaneous coronary intervention (PCI) by dilating the coronary resistance vessels. We examined a novel coronary pressure wire-derived Index of Microcirculatory Resistance (IMR) for evaluating the microvasculature in patients with stable angina pectoris undergoing PCI.

Methods: Intravascular ultrasound (IVUS), fractional flow reserve (FFR), index of microcirculatory resistance (IMR) and blood examination (CK, CK-MB, cardiac troponin (cTn) immediately post PCI and 24 hours later) were performed in 62 consecutive patients with stable angina pectoris undergoing PCI. Patients were randomized to control (n=29) or nicorandil groups (n=33). In the nicorandil group, nicorandil was intravenously administered as a 6 mg bolus injection just before PCI and as a constant infusion at 6 mg/hour for 24 hours thereafter.

Results: All volumetric IVUS parameters and FFR were similar between the 2 groups both pre and post PCI. However, IMR immediately post PCI and cTn 24-hours post PCI were significantly higher in the control group compared to the nicorandil group (IMR: 34.9±12.1 vs 25.8±9.1 units, and cTn: 0.21±0.13 vs 0.12±0.08 ng/mL, for control vs. Nicorandil, p<0.05 for both). The incidence for cTn elevation more than 5-fold of normal range (>0.20 ng/mL) was significantly larger in control group than nicorandil group (41% vs. 12%, p<0.001).

Conclusions: Administration of nicorandil during PCI of patients with stable angina pectoris reduces microvascular dysfunction and myocardial damage.

Effects of coronary sinus occlusion on myocardial ischemia

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Background: Coronary sinus occlusion (CSO) is thought to salvage ischemic myocardium. In animal models, efficacy of CSO to reduce infarct size has been rarely documented. We tested the hypotheses that CSO reduces myocardial ischemia and that the amount of ischemia reduction is related to coronary collateral function.

Methods: Seventeen patients with chronic stable coronary artery disease (CAD) underwent CFI and coronary collateral assessment. Collateral flow index (CFI) was calculated at 2 minutes of coronary occlusion: CFI = (Pcacci-CVP)/(Pcacci+CVP) [mmHg/ml/ml].

An intracoronary EGG obtained from the guidewire distal to the balloon occlusion was registered during coronary occlusion with CSO and without CSO. The ST segment shift from the intracoronary ECG was measured at 2 minutes of coronary occlusion.

Results: Seventeen patients were randomly assigned to the protocol “CSO first” or “CSO second”. Absolute intracoronary ECG ST segment shift was significantly lower at the end of the procedure with vs without CSO: 1.46±1.24 mV vs 1.83±1.13 mV, p=0.0148. The amount of ST segment shift reduction during CSO was related to collateral function best fitting a Gaussian distribution. Ischemia reduction with CSO was greatest with moderate collateral function, in the low and high range of CFI the effect of CSO was absent.

Conclusions: The amount of ischemia reduction of CSO depends on coronary collateral function. A minimal degree of collateral function appears necessary to render CSO effective. Obviously, CSO cannot manifest an effect when collateral function prevents ischemia in the first place.
Role of neuronal versus endothelial nitric oxide synthase in the coronary blood flow response to pacing

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Purpose: Endothelial nitric oxide synthase (eNOS) has been assumed to be the major source of nitric oxide (NO) regulating human coronary blood flow (CBF). In recent first-in-human studies with a neuronal NO synthase (nNOS)-selective inhibitor, we reported that nNOS-derived NO tonically regulates basal CBF whereas eNOS mediates increases in flow in response to the endothelial agonist, substance P. This study investigated the effects of nNOS versus eNOS inhibition on the CBF response to increased heart rate.

Methods: We studied the effects of the nNOS-selective inhibitor, S-methyl-L-thiocitrulline (SMTC), and the non-selective NOS inhibitor, NG-monomethyl-L-arginine (L-NMMA) at doses previously shown to inhibit nNOS or both nNOS and eNOS, respectively. 20 patients undergoing elective cardiac catheterisation for clinical reasons and found to have normal coronary arteries were included. An intracoronary doppler flow wire was positioned in the coronary artery for measurement of blood flow velocity whereas coronary artery diameter was measured by quantitative angiography. An incremental pacing protocol that raised heart rate to a maximum of 150 bpm was undertaken in all patients via a temporary right atrial pacing wire. Pacing was performed in the presence of saline vehicle and then either L-NMMA or SMTC (one inhibitor per patient; n=10 each group).

Results: SMTC (0.625 μmol/min) and L-NMMA (25 μmol/min) both reduced basal CBF to a similar extent (±19.2±3.25% vs. -25.0±2.67%; P=0.10; NS). During saline infusion, CBF increased with atrial pacing from 56.7±9.27 to 83.5±14.2 ml/min (n=10, P<0.01). During L-NMMA, the maximum CBF elicited by atrial pacing was significantly blunted (61.6±9.49 vs. 83.5±14.2 ml/min during saline; n=10, P=0.01 by 2-way ANOVA; ΔCBF 16.1±3.91 ml/min vs 26.7±5.73 ml/min during saline). In patients receiving SMTC, however, the maximum CBF with pacing was unchanged (102.1±16.0 vs. 98.5±12.9 ml/min during saline; n=10, P=NS). SMTC and L-NMMA both reduced basal coronary artery diameter to a similar extent (P=NS). L-NMMA blunted the pacing-induced increase in coronary artery diameter (P<0.001 vs. saline vehicle) whereas SMTC had no effect (P=NS).

Conclusions: These results suggest that increases in CBF in response to increased heart rate in humans are mediated by nNOS-derived NO rather than nNOS-derived NO.
Anatomical variants of circumflex coronary artery and coronary sinus inter-relationships

Methods: In 320 (126W, age 59 ± 11) patients, a 64-slice CT (Aquilion 64) was performed due to coronary artery disease suspicion. A scan with ECG-gating was performed using a slice thickness of 0.5 mm during a breath-hold. Helical pitch was 12.8. Rotation time: 0.4 s, average tube voltage: 135 kV at 380 mA, 100 ml of non-ionic contrast agent at an average rate of 4.5 m/s was given in three phases. In each case, 10 (3D) volume rendering and 2D MP reconstructions of the vessels were created (Vitea 2).

Results: CS was visualized in all cases and LCx in 315 (98.4%). In 302 cases (94.4%) the CS was a dominating vessel, in 10 (3.1%) both vessels were equal and Cx was dominating only in 3 cases (0.9%). 52 anatomical variants were identified, 3 of them are the most common (in 167/320 cases; 52.2%). The CS usually lies above AV sulcus (239 – 74.7%) and the Cx within the AV sulcus (173 – 54.1%). In 235 cases (73.4%) the Cx was closer (then CS) to the MV (fig. A - 3D VR). In these cases there was a need to re-analyze all phases of cardiac cycle. Accordingly, in 78 cases (24.4%) the Cx entered beneath the CS in selected phases (risk of Cx occlusion by PMA device). The Cx run closer to the mitral valve, considered as a safe feature for PMA, was observed in only 75 (23.4%) cases (fig. B). The most dangerous pattern was found in 19 (5.9%) cases - 2 or 3 CS/Cx crosses (fig. C).

Conclusions: Huge anatomical variability of anatomy CS/LCx strengthens the role of MSCT before PMA implantation.

Stenosis significance by angiography: small versus large vessels

Methods: Between 2001 and 2012, 6281 coronary artery stenoses were assessed by QCA and FFR measurement: reference lumen diameter (RLD) and QCA-derived DS were calculated and FFR was measured in every case.

Results: Stenoses were grouped according to the size of the artery into small vessels (RLD smaller than 2.5 mm), intermediate vessels (RLD between 2.5 and 3.5 mm) and large vessels (RLD bigger than 3.5 mm). Diagnostic value of QCA-derived DS in identifying functionally significant lesions (FFR<0.80) was
assessed by calculating the ROC curves for each group (Figure). By comparing the areas under the curves (AUC), the diagnostic accuracy of QCA was found significantly lower in small vessels (AUC=0.70; SE=0.01) than in the large vessels (AUC=0.81; SE=0.01; p < 0.0001).

Especially, in angiographically intermediate stenoses (DS between 30-60%), i.e. the clinically relevant range, the discordance between DS and FFR occurs significantly more often in small vessels than in large vessels (42.07% vs 34.68%, respectively; p < 0.05).

**Conclusion:** The accuracy of angiographically derived DS in identifying the functional significance of coronary stenosis. [clinicaltrials.gov NCT01400230]

**P5477**

**Use of simultaneous intra-coronary pressure-flow measurements to investigate epicardial-microvascular interactions and changes induced by coronary angioplasty**

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**Purpose:** To investigate physiological characteristics of epicardial stenoses and of distal microvascular compartment and variations induced by coronary angioplasty, by performing simultaneous intra-coronary pressure-flow measurements.

**Methods:** Baseline and hyperemic pressures of pressure and flow velocity were determined, using a dual sensor (pressure-flow) equipped wire. In 105 coronary lesions of 50 patients undergoing coronary angiography. Indexes of functional stenosis severity based on isolated pressure (FFR) or flow (CFVR) values, as well as stenosis (HSP) and microvascular (HMR) hyperemic resistance indexes were derived. Pressure-flow measurements were measured, in the basal and hyperemic state, after PCI and stenting of 40 functionally significant (FFR < 0.75) stenoses.

**Results:** Concordant outcomes between pressure-based (FFR) and flow velocity-based (CFVR) indexes, in identifying flow-limiting stenoses at the actually revascularized site. Concordant outcomes between HSR and FFR values (r = 0.80) were observed in 73 (95.9%) stenoses and discordant outcomes in 32 (30.5%) stenoses. Within the "discordant group", mean HMR values were higher in the subgroup of stenoses characterized by FFR < 0.75 and CFVR < 2.0, compared with the subgroup of "compliant" stenoses characterized by FFR<0.75 and CFVR>2.0 (2.6±1.47 versus 1.50±0.49 mmHg/cm/s respectively; p < 0.05). There was a closer relationship between HSR and FFR values (r=0.83; p < 0.0001). PCI was associated with a marked reduction in total coronary resistance due primarily to reduction in epicardial hyperemic resistance (65%), but reduction in microvascular resistance (35%) contributed substantially to the total increase in system conductance. Low CFVR with normal FFR values persisted in 47,5% of treated vessels, exclusively due to low CFVR and high HMR values, indicating persistent post-PCI microvascular dysfunction.

**Conclusion:** Use of isolated pressure- or flow-derived parameters, to identify ischemia generating stenoses, yields discordant results in a substantial proportion of vessels (30.5%), leading to potentially different treatment strategies. Hyperemic microvascular resistance is a fundamental variable in the relationship between the two indexes and shows a wide variability between different perfusion territories; moreover reductions in HMR values contribute substantially to the increase in conductance associated with PCI. Simultaneous measurements of pressure and flow values may offer a better characterization of the interplay between epicardial and microvascular compartments, particularly in case of discordant FFR and CFVR values.
Comparison of clinical outcome after revascularization versus conservative treatment in patients with borderline fractional flow reserve measurements

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Purpose: Measurement of fractional flow reserve (FFR) is useful tool for assessing the functional severity of coronary artery stenosis and for clinical decision of treatment strategy. Many studies have shown that FFR measurement <0.75 is specific for ischemia, but there is a controversy about whether we need to intervene the lesion with FFR measurement 0.75-0.80 or not. The objective of this study is to compare the clinical outcomes of revascularization versus conservative treatment in the borderline FFR measurement lesions.

Methods: We used the FFR-Registry database out of 4 centers in Korea. In 277 patients (mean age 63±10 years, mean 69%), 301 lesions (LAD, 221; LCX, 54; RCA, 26) with FFR measurement between 0.75 and 0.80 (mean 0.77±0.017) were included in this study. The rate of major adverse cardiac events (MACE; cardiac death, myocardial infarction, target lesion revascularization) and lesion-related outcomes (17 target lesion revascularization, 0 lesion-related myocardial infarction) were evaluated at follow-up. 193 patients underwent PCI (PCI-group) and 84 patients underwent medical treatment. (Conservative-group)

Results: Ninety-four lesions were deferred from revascularization (Conservative-group) and 203 lesions were treated with PCI (PCI-group). Twelve cases of MACE (1 cardiac death, 1 myocardial infarction, 10 target lesion revascularization) occurred at 1 year follow-up. During 50 months of median follow-up, 17 lesion-related outcomes (17 target lesion revascularization, 0 lesion-related myocardial infarction) occurred until final follow-up. By using Cox proportional hazard model, there was no difference in lesion-related outcomes between Conservative-group and PCI-group (hazard ratio 2.283, 95% CI 0.607-8.581, P = 0.222).

Conclusions: HMR is significantly increased in a porcine chronic myocardial infarction model. This can be explained by loss of function and vasculature loss of matrix consistency. HMR may serve as a sophisticated parameter, and novel therapies for ischemic heart disease should aim to restore it towards the reference value.

P5480
Comparison of vardenafil and adenosine for vasoreactivity testing in patients with pulmonary hypertension

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Purpose: The present study investigated the acute hemodynamic responses to vardenafil compared to adenosine in patients with PH.

Methods: This was an open-label, cross-over study including 20 patients with PH who underwent acute vasoreactivity testing using intravenous adenosine (n=18) and oral vardenafil (n=20) during right heart catheterisation. Acute hemodynamic responses were detected according to consensus guidelines criteria and related to long-term follow-up data.

Results: Both vardenafil and adenosine significantly decreased PAOP and PVR and significantly increased CO and CI. Vardenafil also induced significant reductions of PVR/SVR ratio, while adenosine significantly increased pulmonary and systemic oxygen saturation. Three out of 16 patients (17%) showed a positive response to adenosine while five out of 20 patients (25%) responded to vardenafil. During a follow-up time of up to three years responders to oral vasodilators exhibited improved WHO functional class, exercise test (6MWD) and reduced NT-proBNP.

Conclusions: Vardenafil may be superior to adenosine in acute vasoreactivity testing for detecting PH patients who might benefit from vasodilator treatment.

Abstract P5480 – Table 1. Hemodynamic measurement

<table>
<thead>
<tr>
<th>Adenosine (n=18)</th>
<th>Vardenafil (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Maximal dose</strong></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 (56, 94)</td>
</tr>
<tr>
<td>MaxAorta pressure (mmHg)</td>
<td>93 (79, 139)</td>
</tr>
<tr>
<td>mRAP (mmHg)</td>
<td>42.5 (26, 65)</td>
</tr>
<tr>
<td>PVR (dynes cm⁻¹)</td>
<td>625 (208, 144)</td>
</tr>
<tr>
<td>SVR (dynes cm⁻¹)</td>
<td>1690 (660, 2968)</td>
</tr>
<tr>
<td>PVR/SVR</td>
<td>0.39 (0.1, 0.6)</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>4.1 (2.1, 10)</td>
</tr>
<tr>
<td>PVR (mmHg)</td>
<td>2.5 (1.4, 5)</td>
</tr>
<tr>
<td>PA sat (%)</td>
<td>63.8 (45.9, 78)</td>
</tr>
<tr>
<td>Artery sat (%)</td>
<td>91.2 (85, 93.5)</td>
</tr>
</tbody>
</table>

Data are presented as median (min, max). PAP = pulmonary arterial pressure, PVR = pulmonary vascular resistance, SVR = systemic vascular resistance, CO = cardiac output, CI = cardiac index, PA = pulmonary artery, sat = saturation. P-value from Wilcoxon signed-rank test.
also significant correlates of IMR post PCI. ADMA was not correlated with pre or post PCI IMR. Multivariate linear regression demonstrated that IMR measured pre PCI (Beta 0.31; p<0.014) and the baseline transit time (Beta 0.38; p<0.003) were independent predictors of post PCI IMR.

**Conclusion:** Baseline microvascular function and resting coronary blood flow are independently predictive of post PCI microvascular dysfunction. Diabetes appears to amplify microcirculatory dysfunction following PCI.

**P5482** Effective ionizing radiation dose exposure during coronary computed tomography and conventional angiography combined with coronary physiology measurements

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**Background:** Multislice coronary computed tomography scan (CCTA) visualizes non-invasively the coronary anatomy with a small but not negligible ERD exposure. Conversely, coronary angiogram (CA) combined with FFR provide accurate anatomic and functional information on the coronary artery stenoses severity, although currently with an unknown ERD “price.”

**Objectives:** To investigate the effective radiation dose (ERD) during cardiac computed tomography angiography (CCTA) and fractional flow reserve (FFR) measurements in contemporary clinical practice.

**Methods:** From January 2009 till February 2011 consecutive patients (n=649) submitted to: a) CCTA (n=426) and b) CA and FFR measurements (n=223) were prospectively enrolled. A conventional dual source CCTA scanner (C-CCTA) was used in 66% of the patients and a low ERD flash scanner in the rest (L-CCTA). Conventional biplane X-ray systems (C-FFR) were implemented in 89% of the FFR measurements and a low ERD system (L-FFR) in the rest. ERD was carefully recorded in all the groups.

**Results:** ERD was lower in the L-CCTA as compared to C-CCTA group (6±0.5 vs 19±0.2 mSv, p<0.001). Similarly, ERD decreased significantly in the L-FFR group (11.1±18.0±0.5 mSv in the C-FFR group, p<0.002). When only ERD during CA was taken into account, there was no significant difference between L-FFR and C-FFR groups (6±0.6 vs 6±0.5, p=0.9). ERD during FFR did not change significantly in the L-FFR group (5±0.8 vs 5±0.3 in the C-FFR, p<0.9).

**Conclusions:** ERD has been significantly reduced during CCTA and CA. Important prognostic information about the functional severity of the coronary artery stenoses assessed by FFR, can be obtained with a very low additional ERD exposure.

**P5483** Quantitative assessment of the peripheral artery collateral circulation in patients with coronary artery disease

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**Purpose:** Numerous studies pursued the strategy of improving collateral function in peripheral artery disease (PAD). However, there is currently no method available to quantify collateral function of the lower limb.

**Methods:** Pressure-derived collateral flow index (CFIp) of the left superficial femoral artery (SFA) was obtained in patients with stable coronary artery disease (n=26). 81% men) undergoing elective angiography using a pressure sensor-tipped guidewire [CFIp = (Poccl-CVP)/(Pao-CVP)]. Distal occlusive pressure (Poccl) and toe oxygen saturation (Sao2) were measured for 5 minutes (min) under resting conditions, followed by repetitive plantar-flexion movements (n=24) for another 5 min or until pain occurred.

**Results:** In all patients, balloon occlusion of the SFA over 5 min was painless under resting conditions; while CFIp increased during the first 3 min to 53% of normal antegrade flow (0.53±0.165, see figure), Sao2 decreased to 91±8%. With exercise, CFIp dropped within 1 min (P<0.0001) and reached its minimum after 2 min of exercise (0.351±0.189) while Sao2 decreased to 85±6%. Of all patients, 3 (13%) remained symptom-free for an occlusion time of 10 min. Fifteen patients (65%) experienced pain after 478±74 seconds (sec) and 9 (38%) suffered from cramps or tired muscles after 502±66 sec. Mean total occlusion time was 528±104 sec. CFIp values positively correlated with the time patients remained pain free (r=0.717, P=0.003) and with Sao2 (r=0.460, P=0.041).

**Conclusions:** CFIp at rest determined in the SFA amounts to more than half the normal antegrade flow and is sufficient to prevent ischemic symptoms during a total occlusion of 5 minutes. To a lesser extent, CFIp is sufficient also with exercise, although its strong decline indicates a steal phenomenon.

**P5484** Influence of the amount of myocardium subtended by a stenosis on fractional flow reserve: clinical implications

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**Purpose:** Aim of our study was to evaluate the influence of the amount of myocardium subtended to an intermediate stenosis on Fractional Flow Reserve (FFR), especially in relation to lesion-specific characteristics assessed by Quantitative Coronary Angiography (QCA). FFR is able to specifically relate severity of a stenosis to the mass of tissue to be perfused. Accordingly the larger is the territory to be perfused, the greater is the flow and the pressure gradient induced by maximal hyperemia. Although this notion may be considered intuitive its unequivocal demonstration is still lacking.

**Methods:** The severity of each lesion was assessed by FFRl and two-dimensional QCA. The amount of jeopardized myocardium subtended by an intermediate stenosis was assessed using three well validated scores specifically adapted to this aim: the Duke Jeopardy score (DJS), the Myocardial Jeopardy Index (MJl) and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPRACh) lesion Score (ALS). We also tested the impact of proximal LAD and of a comitant collateralized chronic total occlusion (CTO) on FFR.

**Results:** 213 intermediate coronary stenoses in 184 patients (age 65±10; male 78%) were enrolled. FFR values were correlated to minimal lumen diameter (MLD, r=-0.34, p<0.0001) and diameter stenosis (DS; r=-0.28, p<0.0001). FFR was inversely correlated with DJS, MJl and ALS (r=-0.28, p<0.0001; r= -0.40, p<0.0001; r=-0.34, p<0.0001). At multivariate analysis only MJI, MLD, presence of a collateralized CTO and current smoking habit were confirmed as significant predictors of FFR (MJl beta=-0.38, p<0.0001; MLD beta=0.32, p<0.0001; CTO: beta=0.14, p=0.02) and current smoking (beta=0.12, p=0.04).

**Conclusions:** Our study demonstrates that the amount of myocardium subtended by an intermediate coronary stenosis represents a major determinant of its functional significance. This evidence, in light of the well-known prognostic relevance of the amount of jeopardized myocardium, helps to understand why FFR is not only a precise diagnostic but also a potent prognostic tool.

**P5485** Use of sedation-analgesia for the prevention of radial spasm. A randomized prospective study of two treatment strategies


**Introduction:** Different pathophysiological mechanisms are involved in the pathogenesis of radial spasm (RS). One of the most important ones involves the theory of: Pain-Anxiety-Spasm. Objective: To evaluate the effect of sedation-analgesia use in terms of RS rate reduction.
Methods: This is a prospective and randomized study to receive sedation-analgesia or not in all procedures performed by radial access. 109 consecutive p were included (54 p received sedation-analgesia and 55 p did not). All p received conventional spasmolytic cocktail with 3000 IU of NFH + Verapamil 2.5 mg. Ad- ministered sedation-analgesia consisted of a dilution of Midazolam 2 mg + 1 amp of Fentanyl (0.05 mg/ml), dissolved in 10 ml of saline. RS was defined according to the following criteria: the delivery of the procedure or of the catheter at the end of the procedure; MINOR CRITERIA: persistent pain during the procedure, pain with catheter manipulation, direct injection of contrast, pain during withdrawal or introduction of the introducer. RS was considered if there was: one major criteria or two minor criteria.

Results: In the table we can observe the patients’ basal characteristics. The rate of RS in the group that received sedation-analgesia was 3.7% vs. 14.5% in the group that did not receive it (p=0.043). In the multivariate analysis use of sedation-analgesia behaved as a protecting factor of RS: OR 0.067 (0.04-1.08), p=0.029.

Conclusions: Use of sedation-analgesia in our study has been related with a significant reduction in the rate of RS, behaving in the multivariate analysis as a protecting factor.

P5487 Variability of index of microcirculatory resistance and its determinants in patients with intermediate coronary lesions
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Background: The index of microcirculatory resistance (IMR) (which is calculated by distal coronary pressure and thermodilution-derived mean transit time) may represent microvascular dysfunction. It has been reported to be independent of epicardial stenosis and correlates well with microvascular resistance. However, the distribution of IMR values in patients with intermediate coronary lesions and its determinants have not been elucidated.

Objectives: Using IMR as a specific marker for coronary microvascular resis- tance, we sought to assess the association of cardiovascular risk factors and mi- crovascular function and to determine the range of distribution and determinants for IMR.

Methods: Fractional flow reserve (FFR) and IMR measurements were performed in 70 coronary arteries of 56 patients with intermediate coronary lesions. The re- lationship between IMR corrected for coronary wedge pressure and clinical vari- ables, clinically based risk scores, including Framingham risk score and SCORE (Systematic Coronary Risk Score), anatomy-based risk scores such as ACC/AHA lesion classification and SYNTAX score, were assessed.

Results: FFR=0.8 was observed in 22 vessels and FFR=0.8 was detected in 48 vessels (Range 0.31-0.96). Mean IMR was 20.9 and IMR values distributed in the wide range (3.1 to 103.4). There was no significant relationship between FFR and IMR. There was no significant relationship between IMR and any of the clinical/biochemical variables or any risk scores. LV mass index calculated from LV summary was higher in patients with IMR≥30.

Conclusion: IMR in patients with intermediate coronary lesions distributed in the wide range. In the present study, no historical cardiovascular risk factors without LV mass index showed a significant association with IMR. The absence of cor- relation between FFR and IMR values suggests that epicardial coronary artery stenosis is not necessarily associated with abnormal microvascular resistance.

P5488 Usefulness of fractional flow reserve in angiographically severe lesions
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Background and Objectives: The usefulness of fractional flow reserve (FFR) has been demonstrated in angiographically moderate lesions. The aim of this study was to assess its usefulness in angiographically severe lesions. We anal- ized outcomes in patients with lesions that were classified as severe on coronary angiography and which were not revascularized because of the FFR value ob- tained by intracoronary pressure wire.

Methods: A retrospective study of a cohort of patients where the fractional flow reserve was used to decide whether to revascularize angiographically severe le- sions that because of their anatomical characteristics (circumscript or excen- tric lesions, ectatic vessels) or low correlation with the patient’s clinical symptoms were assessed with pressure wire. The use of the pressure wire was at the discre- tion of the interventional cardiologist. All procedures used intracoronary adeno- sine bolus up to maximum dose. We analyzed the follow-up of these patients by evaluating major cardiovascular events: death, nonfatal myocardial infarctions, revascularization of the target lesion and remission for cardiac causes.

Results: The study included 133 patients with 154 lesions over 70 between January 2006 and December 2010. Patients characteristics: mean age 66.5±10 years, male 77%, multivessel disease 39.3%, FEVI 63.9±13.8%, mean angiographic stenosis 75.6±5.6%, mean fractional flow reserve (FFR) 0.83±0.01. Based on the fractional flow reserve results, 117 lesions (75.9%) were not revascularized- ized because of FFR was >0.75. There were no major complications attributable to the use of the pressure wire. The mean follow-up was 20.7±12 months. The events observed in the follow up were: 1 death (0.7%) because of acute coronary syndrome with occlusion of a vessel different to the one measured with the pressure wire, 0 non-fatal acute myocardial infarction, 1 (0.7%) target lesion revascu- larization and 13 (9.7%) readmissions for cardiac causes. The rest of the patients remained asymptomatic.

Conclusions: Fractional flow reserve assessed by intracoronary pressure wire can be useful in a subset of angiographically severe lesions and may prevent unnecessary revascularizations.

P5489 Incremental diagnostic value of cardiac magnetic resonance with adenosine stress perfusion for coronary heart disease detection
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Purpose: A multiple-test strategy in often needed in the evaluation of patients (pts) with suspected coronary heart disease (CHD). Cardiac magnetic resonance (CMR) has potential advantages in this context allowing simultaneous evaluation of ventricular function, myocardial perfusion and coronary anatomy without radi- ation and high spatial resolution. We aimed to assess the diagnostic accuracy of CMR with adenosine stress perfusion (CMR-P) for the detection of CHD using invasive coronary angiography (CA) as the reference standard and comparing it with exercise stress test (EST).

Methods: Prospective single-center study with enrollment of pts with interme- diate/high probability of CHD referred to a cardiologist. All pts underwent a se- quential protocol including: treadmill EST, CMR-P and CA. The EST was dichto- mously classified and deemed positive if reproduction of clinical symptoms during effort or additional ST-segment depression ≥1 mm. CMR-P exams were eval- uated by 2 independent cardiologists, blinded to the results of the EST. Significant CHD was defined as ≥70% stenosis of first order coronary artery at CA, or left main stem stenosis >50%. Multiples protocols integrating EST and CMR-P were tested using ROC curves.

Results: 80 pts were recruited (mean age, 61 ± 8 years), 68% male, with at least 1 cardiovascular risk factor (diabetes 75%, hypertension in 71% and diabetes mellitus in 43% of cases). All pts were symptomatic: typical angina (25%), dyspnea 4% or dyspnea and chest pain (4%), CHD was detected in 33 pts (41%). CMR-P and EST correctly identi- fied 21 pts (77 vs 77%, equal sensitivity and specificity). PPV=71 vs 55% (p=0.001). In the integrated protocol with better per- formance (AUC = 0.63), pts with both CHD and EST were identified to direct CA: the remaining pts with negative, doubtful (only clinically or electrically positive) or inconclusive (submaximal) EST were enrolled to CMR-P. The other tested protocols with referral to CMR-P only the pts with double or inconclusive EST or only the pts with negative or inconclusive EST had worst performances (AUC=0.81 and 0.70, respectively, p<0.001).

Conclusions: CMR-P has high sensitivity and specificity for detection of obstruc- tive CHD. In our pts with high probability of CHD, the indication of CMR-P in an integrated protocol for the detection of CHD improved the overall diagnostic ac- curacy, particularly in pts with negative, doubtful or inconclusive EST.
Methods: Fifty-three patients referred for angiography underwent rest and adenosine stress 3D myocardial perfusion CMR at 3 Tesla. For conventional coverage analysis three equally distributed slices, representing apical, mid-myocardial and basal sections, intended to simulate conventional 2D myocardial perfusion CMR methods were reviewed in aseparate analysis session and the resulting diagnostic values calculated on aper patient and vessel basis.

Results: Sensitivity, specificity and diagnostic accuracy of whole heart CMR analysis per patient was 90%, 91% and 91%. Using conventional three-slice analysis, the sensitivity, specificity and diagnostic accuracy were 85%, 84% and 85% on a patient basis. These values were not significantly different to the whole-heart analysis.

Conclusion: Although there was improved detection, whole heart analysis did not statistically outperform the analysis of only three equally distributed slices (Figure 1). However 3D perfusion may have added advantages including estimation of ischaemic burden.

Gaeclent-3: relation to infarction scar and myocardial function after STEMI
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Aims: Fibrosis after acute myocardial infarction (AMI) is the leading cause of heart failure and results in late enhancement of scar by cardiac magnetic resonance imaging (CMR). Gaeclent-3 is suggested to be involved in the development of heart failure appearing to directly mediate proinflammatory pathways. The relationship between gaeclent-3 and the extent of myocardial infarction scar is unknown.

Methods: 29 AMI patients (n=29, mean age: 58.1±10.1 yrs, 3 females) successfully reperfused by primary angioplasty underwent a 4-month (4-mo) follow-up CMR at a median of 125 days (range: 92-200 days) after the index event. Blood samples were routinely drawn at baseline and follow-up. Gaeclent-3 was determined from serum samples drawn at the follow-up.

Results: 4-mo gaeclent-3 values (mean 12.29±5.6 ng/ml) correlated significantly with 4-mo infarct size (r=0.496, p=0.016), with 4-mo NT-proBNP concentrations (r=0.420, p=0.023) as well as with 4-mo creatinin levels (r=0.486, p=0.016). Patients with 4-mo gaeclent-3 concentrations above the median level of 10.66 ng/ml presented significant impaired 4-mo lower ejection fraction (75.9±8.2% vs. 65.1±5.8%, p=0.011), larger mid-term infarct sizes (15.6±7.8% vs. 8.3±6.1%, p=0.022) as well as higher 4-mo NT-proBNP concentrations (642.6±666.0 ng/ml vs. 261.4±183.1 ng/ml, p=0.047) than patients with gaeclent-3 concentrations below 10.86 ng/ml.

Conclusion: Elevated gaeclent-3 levels 4 months after AMI are associated with larger infarct sizes, lower global myocardial function as well as with higher concentrations of NT-proBNP, highlighting the potential of gaeclent-3 as a biomarker of adverse remodeling after AMI.

Early and 6 months cardiovascular magnetic resonance characteristics of patients with anterior myocardial infarction and moderate to severe pericardial effusion

Background: Moderate-severe pericardial effusion (>10 mm) (PE) in ST elevation myocardial infarction (STEMI) is associated with increased hospital mortality. Cardiac magnetic resonance (CMR) data on the STEMI characteristics and its possible relationship with subacute cardiac rupture and follow up left ventricular remodelling is lacking.

Objectives: To evaluate CMR parameters of anterior STEMI associated with PE in the early course and at 6 months follow-up.

Methods: CMR studies were performed in 184 consecutive patients with a first anterior STEMI within the first month and repeated in 120 at 6 months. Cine and late gadolinium enhancement sequences were used to assess left ventricular (LV) volumes, infarct size and segmental analysis of the myocardium. Segmental necrosis was evaluated as the percentage of myocardial wall affected, being considered as transmural when the percentage was >50%. Adverse LV remodelling was defined as >20% increase in LV end-diastolic volume at follow-up.

Results: Patients with PE (n=30) were older (67±11 vs 69±13 years, p=0.001) and presented a similar rate of Killip Class I-II (83% vs 90%, p=0.233) and a similar number of segments with >75% necrosis (4.3±2.3 vs 2.6±2.4, p=0.001) than those without (n=154). Moreover, they also showed larger LV end-diastolic volume (p=0.028), LV end-systolic volume (p=0.001), infarct size (p<0.001) and lower ejection fraction (p=0.018).

Conclusions: In patients with anterior STEMI the consistent association of PE with extensive myocardial and transmural PE supports ventricular link with a self-limited cardiac rupture and frequent left ventricular remodelling.
Circulating microRNA-133a as predictor of myocardial infarction

**Purpose:** Circulating microRNA-133a as predictor of myocardial infarction is the key predictor of poor right ventricular function.

**Methods:** We analyzed clinical, cardiac magnetic resonance and angiographic data of prospectively collected 114 patients (males 79, females 35, mean age 60 ± 10 years) with an acute inferior myocardial infarction treated with primary percutaneous coronary intervention on the right ventricular (RV) contractility in patients with right ventricular infarction (RVI) with ST-segment elevation.

**Results:** Based on late gadolinium enhancement CMR detected RVI in 48 of 114 (42%) patients with acute inferior MI. Stented vessel was RCA. Angiographically successful result in the main vessel was achieved in all except one case. The incidence of side branch occlusion in patients with and without RVI was 28 (58%) and 0 (0%) (p < 0.001), respectively. Multivariable model was constructed to identify predictors of RVF < 10. TIMI in main RCA vessel before and after procedure, site of RCA occlusion, Rentrop Score, antecedent angina, Gensini Score, side branch loss of right ventricular branch, distal embolization of posterior interventricular artery were analysed. In a multivariable logistic regression analysis right ventricular side branch compromise was the only and independent predictor of RVF < 40% (odds ratio = 4.1, 95% confidence interval: 1.7 to 8.9, p = 0.0004).

**Conclusion:** Right ventricular side branch compromise after primary PCI of RCA in inferior myocardial infarction with ST-segment elevation is an independent angiographic predictor of right ventricular systolic dysfunction.

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**P5495 Rapid binding of electrostatically stabilized iron oxide nanoparticles to THP-1 monocytic cells via interaction with glycosaminoglycans**

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**Purpose:** Magnet resonance imaging (MRI) with iron oxide nanoparticles is a promising technology for visualisation of atherosclerotic plaques. Citrate-coated very small superparamagnetic iron oxide particles (VSOP) can be detected very rapidly with MRI in atherosclerotic plaques of Watanabe heritable hyperlipidemic rabbits. In vivo data suggest that VSOP colloclize with cell-bound glycosaminoglycans (GAG) and components of the extracellular matrix. The aim of this study was to evaluate the usefulness of cellular and extracellular binding of VSOP.

**Methods and Results:** Binding and uptake of VSOP compared to codeixtrentin-coated Resovist was estimated in THP-1 monocytic cells (THP-Mo), THP-derived macrophages (THP-M6), and THP-derived apoptotic membrane vesicles by colorimetric measurement of cell associated iron. Uptake of VSOP in both THP-Mo and THP-M6 was more efficient compared to Resovist without inducing cytotoxicity or modifying normal cellular functions (no changes in ROS levels, caspase-3 activity, proliferation, cytokine production). Importantly, light and confocal microscopy revealed that VSOPs are not only incorporated intracellularly in THP-1 monocyes and THP-1 derived macrophages but also bind to extracellular structures and to apoptotic membrane vesicles. Inhibition of GAG interaction with glycosaminoglycans (GAGs) was associated with a significant reduction in VSOP binding, whereas Resovist uptake was unchanged.

**Conclusions:** VSOP are rapidly taken up by monocytes and macrophages. VSOP interact with high affinity with the cellular surface of these cells as well as with apoptotic membrane vesicles via binding to negatively charged GAGs. We thus established a new marker-target combination for characterization of atherosclerotic plaques using electrostatically stabilized VSOP. This unique property of VSOP makes them a promising candidate for further clinical development.
Flow Quantification (MBF, ml/g/min), Endothelium-dependent Vasodilatation Index (ENDEVI, CPT MBF/rest MBF, normal >1.5), %MBF (normal =50%) and Coronary Flow Reserve (CFR, stress MBF/rest MBF, normal =2.5) were calculated as Endothelial function parameters. Total CCS was calculated using a dedicated software.

**Results:** Mean age was 36.2±9.5 for the SLE/PAPS group and 34.7±9 years for the control group. Compared to the control group, the SLE/PAPS group had a significantly lower ENDEVI (1.18±0.55 vs 1.55±0.37, p = 0.015), %MBF (18.5±43 vs 55±37, p = 0.015) and a non-significant lower CFR (2.58±0.81 vs 3.27±0.72, p = 0.26). All of the SLE/PAPS patients, as well as the healthy volunteers had a Total CCS of zero.

**Conclusion:** In this study we have shown that patients with SLE or PAPS have Endothelial Dysfunction in spite of the absence of coronary calcifications. We can conclude that Endothelial dysfunction precedes the development of overt coronary atherosclerotic disease.

**P5499**

**Carotid artery intima media thickness, but not coronary artery calcification, predicts coronary vascular resistance in patients evaluated for coronary artery disease**


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**Purpose:** There is growing evidence that coronary artery disease (CAD) affects not only the conduit epicardial coronary arteries but also the microvascular coronary bed. Moreover, coronary microvascular dysfunction (CMDV) often precedes the stage of clinically overt epicardial CAD. Coronary artery calcification (CAC) and carotid intima media thickness (C-IMT) measured with computed tomography (CT) and ultrasound, respectively, are among the available techniques to non-invasively assess atherosclerotic burden. An increased CAC score and C-IMT have also been associated with CMDV. It is therefore of interest to explore and compare the potential of CAC against C-IMT to predict minimal coronary vascular resistance (CVR).

**Methods:** We evaluated 120 patients (mean age 56±9 years, 58 men) without a documented history of CAD in whom obstructive CAD was excluded. All patients underwent C-IMT measurements, CAC scoring, and vasodilator stress 150-water PET/CT, during which the coronary flow reserve (CFR) and minimal CVR were analyzed.

**Results:** Minimal CVR increased significantly with increasing tertiles of C-IMT ($p<0.05$), but not CAC, independently predicts minimal CVR in patients with multiple cardiovascular risk factors and suspected of CAD.

**Conclusion:** In this study we evaluated the accuracy of quantitative H215O PET/CT imaging compared to stand alone imaging in a clinical cohort of patients suspected of CAD who underwent both cardiac hybrid H215O PET/CT imaging and invasive coronary angiography (ICA).

**Methods:** A total of 120 patients (mean age 61.1±10 years, 77 men) with a predominantly intermediate pre-test likelihood (55%±30) for CAD underwent both hybrid quantitative H215O PET/CT imaging and ICA. The results were compared with the gold standard ICA where a stenosis ≥50% was considered significant.

**Results:** Obstructive CAD was diagnosed in 49 out of 120 patients (41%), On a per patient basis, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and diagnostic accuracy of CTCA were 100, 34, 100, 51, and 61, respectively, as compared to 76, 83, 76, and 80%, respectively, for H215O PET with an optimal cut-off value of 1.86 MBq/mg/min. Quantitative hybrid H215O PET/CT reduced the number of false positive CTCA studies from 47 to 6, although 12 out of 49 true positive CTCA were incorrectly reclassified as false negative hybrid scans based on (presumably) sufficient MBF. Total diagnostic accuracy for the hybrid approach was significantly improved (85%) compared with CTCA (61%) or H215O PET (80%) alone (both $p<0.05$). Sensitivity, specificity, NPV, and PPV were 76, 92, 84, and 86, respectively, for the hybrid approach.

**Conclusion:** Diagnostic accuracy of quantitative hybrid H215O PET/CT is superior to either H215O PET or CTCA alone for detection of clinical significant CAD.

**P5501**

**MIP with 13N-ammonia and PET: added diagnostic value of CFR**


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**Objective:** Quantitative measurement of flow and coronary flow reserve (CFR) has been perceived as an important advantage of PET over SPECT MPI. We analyzed the added diagnostic value of CFR over PET MPI alone as assessed with 13N-ammonia and PET/CT to predict angiographic coronary artery disease (CAD).

**Methods:** Seventy-three patients underwent one-day adenosine-stress/rest 13N-ammonia PET/CT MPI and global CFR was calculated. The added value of CFR as an adjunct to MPI for predicting CAD (luminal narrowing ≥50%) was evaluated using in vivo coronary angiography as a standard of reference.

**Results:** Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of MPI for detecting significant CAD was 79%, 80%, 91%, 59%, and 79%, respectively. Adding the cut-off for global CFR>2.0 to MPI findings significantly improved the above values to 96%, 80%, 93%, 89%, and 92%, respectively ($p<0.005$).

**Conclusion:** The quantification of the global CFR in 13N-ammonia PET/CT MPI provides a substantial added value in diagnosing CAD. Particularly in patients with normal MPI it helps to unmask clinically significant CAD.

**P5502**

**Correlation between calcium score on attenuation correction CT and gated non-contrast computed tomography**


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**Objective:** We sought to determine the correlation between coronary artery calcium score (CCS) using low dose radiation non ECG gated Computed Tomography (CT) and coronary artery calcium score (CAC) obtained using noninvasive coronary angiography (CTCA). The results were compared with the gold standard ICA where a stenosis ≥50% was considered significant.

**Results:** Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CTCA for detecting significant CAD was 79%, 80%, 91%, 59%, and 79%, respectively. Adding the cut-off for global CFR>2.0 to MPI findings significantly improved the above values to 96%, 80%, 93%, 89%, and 92%, respectively ($p<0.005$).

**Conclusion:** The quantification of the global CFR in 13N-ammonia PET/CT MPI provides a substantial added value in diagnosing CAD. Particularly in patients with normal MPI it helps to unmask clinically significant CAD.
Diagnostic accuracy of quantitative H215O PET measurements of hyperemic myocardial blood flow versus coronary flow reserve for the detection of obstructive coronary artery disease

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Background: Cardiac PET has the unique ability to allow noninvasive, and accurate quantification of myocardial blood flow (MBF), mI/mIg. PET parameters such as hyperemic MBF and coronary flow reserve (CFR) ratio of hyperemic to resting perfusion have been extensively studied for their relationship with stenosis severity. However, data are scarce on the diagnostic accuracy of hyperemic MBF and CFR for the detection of obstructive CAD.

Methods: A total of 120 patients (mean age 61±10 years, 77 men) with a predominantly intermediate pre-test likelihood (55±30) for CAD underwent quantitative H215O PET imaging (during rest with and without untargeted LVEF depression) and invasive angiography. Significant CAD was defined by the presence of a stenosis >50% at the coronary angiogram.

Results: Out of 120 patients (41%) displayed a significant stenosis at the angiogram. On a per vessel analysis, the area under the ROC curve (AUC) analysis of hyperemic MBF (AUC = 0.86, 95% CI 0.81-0.90) was greater compared to that of CFR (AUC = 0.81, 95% CI 0.75-0.86) for the detection of obstructive CAD (p = 0.02). Optimal cut-off values were 1.86 mI/mIg and 2.30 for hyperemic MBF and CFR, respectively. On a per patient basis, sensitivity (76 vs 70%, p = 0.01) was comparable for hyperemic MBF and CFR, whereas specificity (83 vs 62%, p = 0.01) was higher for hyperemic MBF. Consequently, total diagnostic accuracy was superior for hyperemic MBF compared to CFR (80 vs 68%, p = 0.02).

Conclusion: Hyperemic MBF, as determined by quantitative cardiac H215O PET, is more accurate than CFR for diagnosing obstructive CAD. These data suggest that a single measurement of hyperemic MBF could suffice in diagnostic imaging protocols, obviating the need for rest imaging to calculate CFR.

Ischemia is the only predictor of post-stress LVEF decrease detected by gated SPECT after myocardial infarction

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Background: Gated SPECT (gSPECT) is able to detect restenosis or progression of coronary artery disease in the early systematic follow-up of myocardial infarction (MI). Although post-stress left ventricular ejection fraction (LVEF) decrease is often associated with ischemia, its predictive factors after MI remains unclear.

Aim: To identify the clinical and gSPECT characteristics associated with a 5% or more post-stress LVEF decrease in patients with early MI.

Methods: Two-hundred and thirty six consecutive patients admitted in intensive care unit for acute MI were prospectively included. 6 months after discharge, a gSPECT was performed following an injection of 99mTc-sestamibi after an exercise-induced stress and at rest. LVEF was automatically calculated (QGS® software). Post-stress LVEF drop was considered significant if ≤5% when compared with LVEF at rest. Summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) were visually evaluated using a 17 segments model.

Results: Post-stress LVEF drop was observed in 56 (24%) patients (group A). Demographic, infarct and stress test characteristics were similar when compared with patients with unaltered LVEF (group B). Patients with LVEF drop had significantly more peak MBF (p = 0.02), the presence of a high SDS (p < 0.001), and smaller summed difference score (p = 0.03). In group A, a higher SDS (p = 0.001) and a lower MIAD (p = 0.02) were observed. Multivariate analysis identified SDS (HR: 1.89, 95% CI: 1.06-3.39) and nMAD (HR: 1.50, 95% CI: 1.01-2.19) as independent predictors of LVEF drop.

Conclusion: In patients with previous myocardial infarction, a post stress LVEF decrease ≥5% is associated with higher incidence of reversible perfusion defect. These data thus validate the model of myocardial stunning and excluded the potential influence of an extended myocardial necrosis or left ventricular remodeling on post stress LVEF fall.

Ischemia response to exercise testing in the recovery phase: real ischemia? Correlation with gated-SPECT data


Purpose: The diagnostic and prognostic value of ST-segment depression (ST) occurring during the recovery period is less well defined as compared with that appearing during exercise testing (ET). Only few studies have investigated the clinical significance of this finding.

Objective: The aim of this study was to compare ST in recovery with the gated-SPECT imaging incidence of myocardial ischemia.

Methods: Seventy patients (pts) with ST only during recovery, who underwent gated-SPECT associated with ET Los Angeles, David Geffen School of Medicine, Los Angeles, United States of America; 2. Wake Forest University School of Medicine, Winston-Salem, United States of America; 3. Columbia University Medical Center, New York, United States of America; 4. Northwestern University, Feinberg School of Medicine, Chicago, United States of America; 5. National Institutes of Health, Bethesda, United States of America

Background: Global strain predicts events, but measurement is presently not available for MRI. Measurements of the Mital annulus displacement (MAD) can be adjusted to correct for individual differences in end diastolic LV length to obtain normalized MAD (nMAD), which represents an easily available analog to long axis fractional shortening or global longitudinal strain. We propose that nMAD is a sensitive and powerful predictor of cardiovascular events and heart failure.

Method: 168 participants (53% men, 65±10 years) from the Multiethnic Study of Atherosclerosis (MESA) were included. Average LV length was measured at end diastole (EDL) and end systole (ESL) from the epicardial apex to the mitral valve insertion by 2- and 4 chamber cine cardiac MRI, and nMAD was calculated as 100*(EDL-ESL)/EDL. Participants were followed for 6.8±1.8 years for a first composite end-point (heart failure, myocardial infarction, stroke or cardiovascular death). The ability to predict the composite end-point was assessed for nMAD, LVEF, and LV mass indexed to BSA (LVMi) using Cox regression unadjusted and adjusted for ethnicity, traditional risk factors (Heart rate, blood pressure, smoking, age, gender, diabetes, hypertension, hypercholesterolemia), and blood pro-BNP, CRP and eGFR.

Results: Events were observed in 116 participants. Mean nMAD was lower at baseline compared to those who developed events compared to participants who did not (10.0±2.7% vs. 11.7±2.5%, p<0.01). Only LVMi and nMAD remained significant in the multivariable regression (Table). Hazard ratios (HR) for development of heart failure or hard carovascular events according to indices of LV function

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Can 123I-mIBG imaging identify implantable defibrillator candidates for primary prevention?

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Purpose: The AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRe-HF), was a prospective, multicenter study evaluating the prognostic usefulness of 123I-mIBG scintigraphy for identifying patients (pts) with NYHA functional class III/IV with left ventricular ejection fraction (LVEF) < 35% who will experience a major adverse cardiac event. Although 123I-mIBG was able to risk stratify and add incremental value, identification of patients with improved outcomes with cardiac defibrillator (ICD) implantation for primary prevention was not examined.

Methods: We identified 961 patients enrolled in ADMIRe-HF followed up for 2 years. We excluded patients with an ICD at the time of study enrollment and censored pts receiving ICD for secondary prevention at the time of the procedure, leaving a total of 676 patients. 123I-mIBG results were dichotomized using heart/mediastinal ratio (HM) of 1.6. A propensity score was developed to adjust for nonrandomized referral to ICD after enrollment. To avoid overfitting, a clinical risk score based on all pre-imaging data was developed. All cause death (ACD) was the primary endpoint. The association between 123I-mIBG results and other clinical and laboratory information and ACD was assessed using Cox Proportional Hazards analysis (CPH). The primary analysis focused on testing for an interaction between HM and ICD.

Results: Over a mean follow-up of 612±242 days, 66 ACD occurred (9.8%) and 196 pts (29%) were censored for ICD. CPH analysis revealed that after adjusting for BNP levels, LVEF, fixed defects on SPECT, and baseline clinical risk, 123I-mIBG results (HM) were predictive of ACD (model c-index 0.77, p = 0.001). The presence of a normal HM was associated with a 78% reduction in risk (hazard ratio 0.22 (95%CI 0.07, 0.69)). However, no significant interaction between ICD placement and HM was present. No such interaction was present with any other covariate.

Conclusion: Inpts without prior ICD, 123I-mIBG is strongly predictive of ACD and adds incremental value, but cannot identify which pts may benefit from ICD placement for primary prevention.

Cardiac I-123 Metaiodobenzylguanidine imaging predicts the risk of cardiac death in patients with chronic heart failure, irrespective of the metabolic syndrome: a long term follow up study


Background: Cardiac I-123 Metaiodobenzylguanidine (MIBG) imaging, which reflects cardiac sympathetic activity, provides prognostic information in patients with chronic heart failure (CHF). On the other hand, metabolic syndrome (MetS) characterized by a marked sympathetic overactivity was also reported to be associated with poor outcome in CHF patients. Thus, we tried to prospectively investigate whether MetS would influence the prognostic value of cardiac imaging MIBG in CHF patients.

Method: In 109 consecutive CHF outpatients with radionuclide LVEF <40% (55% of the MIBG washout rate (WR) was calculated from the chest anterior view images obtained at 200 and 200 min after isotope injection. Abnormal WR was defined as WR >27%. MetS was defined according to National Cholesterol Education Program expert panel criteria.

Results: Twenty-seven of 109 patients had MetS. During a mean follow up period of 6.6±0.3 years, cardiac death was observed in 33 of 109 patients. At multivariate Cox analysis, WR was a significant predictor of cardiac death in patients both with (p=0.049) and without (p=0.0009) MetS. Kaplan-Meier analysis revealed that patients with abnormal WR had a significantly higher risk of cardiac death than those with normal WR, in patients both with (60% vs 9%, p=0.02; HR: 8.0, 95% CI 1.0 to 63.5) and without MetS (43% vs 14%, p=0.0099; HR: 5.4, 95% CI 2.0 to 14.7).

Conclusion: Cardiac MIBG imaging would be useful to predict the risk of cardiac death in CHF patients, irrespective of the presence or absence of metabolic syndrome.

Ischemia change in heart failure patients with stable coronary artery disease is an independent predictor of death and myocardial infarction


Aims: Recent randomized trial data in heart failure (HF) patients with stable coronary artery disease (CAD) have suggested that revascularization does not improve outcomes compared to optimal medical therapy (MT). In contrast, a nuclear study in the general CAD population (i.e. non-HF) found that revascularization led to greater ischemia reduction and improved unadjusted outcomes. The effects of MT vs revascularization on ischemia change in HF patients and its independent prognostic significance requires further investigation.

Methods and Results: From Duke Cardiovascular Disease and Nuclear Cardiology Databanks, we identified 278 consecutive patients with angiographically documented CAD and ejection fraction (EF) >40%, who underwent two serial Myocardial Perfusion Scans (MPS) between 9/1993 and 6/2009. Ischemia change was calculated for patients undergoing MT alone, or revascularization. Patients were followed for a median of 3.9 years (1.6-6.3) after the second MPS scan. The magnitude of ischemia reduction was greater with revascularization than with MT alone (0% with IQR of -5.4% to 2% for MT vs. -5.9% with IQR of -11.8% to 6% for revascularization, P<0.01). After multivariable risk adjustment, >5% ischemia worsening remained a significant independent predictor of death or MI (HR = 0.57 (0.35, 0.94), P=0.03) however in the opposite direction. Findings likely reflect better outcomes in patients with low EF and ischemic viable myocardium rather than “scar” tissue.

Conclusion: Ischemia change on nuclear imaging is an independent predictor of death or MI in patients with HF and stable CAD independent of treatment allocation.

Assessment of left ventricular mechanical dyssynchrony in patients with chronic kidney disease

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Background: The presence of left ventricular mechanical dyssynchrony (LVMD) in patients with end stage renal disease (ESRD) has been reported. However, the severity and extent of LVMD in patients with chronic kidney disease (CKD) have not been fully clarified. Abnormal loading has capability to enhance LVMD in CKD patients.

Objectives: The aim of this study was to assess the severity of LVMD and its relation to systolic function in CKD patients.

Methods: A total of 219 patients (age 69±10, 156 men with CKD underwent stress/rest gated myocardial perfusion SPECT (MIPS). For the evaluation of LV function and LVMD, measurements of LVEF and image bandwidth (HBW)
were determined by GMPS using phase analysis. All subjects consisted of 106 patients (age 70±10, 68 men) without ischemia (summed stress score (SSS) <4), and were classified into three groups according to estimated GFR (42 patients with CKD stage 1-2, 54 patients with CKD stage 3-4, and 10 patients with CKD stage 5). Results: HBW was significant correlated negatively with LVEF in all 106 patients (r=-0.65, p<0.0001). HBW in CKD stage 5 were significantly greater than those of CKD stage 1-2, and stage 3-4 (p<0.01, ANOVA).

Conclusions: LVMD was demonstrated to be enhancement in end-stage renal disease.

NOVEL IMAGING TECHNIQUES

P5512 Mapping of normal values of left ventricular T2 relaxation times at 3.0 T
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Purpose: T2-mapping using cardiovascular magnetic resonance imaging (CMR) promises quantitative myocardial tissue characterization, specifically to detect myocardial edema. We evaluated T2-mapping at 3 Tesla and provide normal values.

Methods: 52 healthy volunteers (26 males, age 45±16 years) underwent CMR at 3T. ECG-gated, breath-hold, single-shot steady-state free precession (SSFP) acquisitions (vmax=1.9x1.9x6mm3) with different T2-prep-times (0ms, 25ms, 55ms) were obtained in end-diastole in three short axes. T2-times were quantified for each slice and for each myocardial segment. In a sub-group (n=25), T2-prepared SSFP was compared to T2-prepared fast low-angle shot (FLASH) imaging. As proof-of-principle, T2-mapping was acquired in 3 patients with acute myocardial infarction.

Results: Image acquisition was feasible in all subjects. Due to banding artefacts, 4 of the 312 basal, 6 of the 312 midventricular and 6 of the 208 apical segments were excluded. Global T2-times were 44.9±4.2ms (basal), 45.9±2.4ms (midventricular) and 47.4±2.2ms (apical), ranging from 40.5 to 50.2ms, 40.4 to 54.5ms and 41.0 to 54.1ms, respectively. The figure show segmental T2-values. T2-times increased significantly from base to apex (p<0.001). Higher heart rate (>70/min; p<0.005) and female sex (p=0.004) were associated with higher T2-values. In vivo FLASH-based T2-times did not differ (p=0.888). In patients, mean T2-time of infarcted myocardium was 62.4±6.9ms compared to 44.1±1.1ms of remote.

Conclusions: Myocardial T2-mapping at 3T is feasible with low incidence of high-field-related artefacts. When interpreting absolute T2-times, the wide range in normals must be considered as well as the basal-to-apical increase and the heart rate dependency, which are potentially attributable to partial volume effects.
In Vivo assessment of myocardial inflammation
A new method to detect myocardial ischemia using Changes in global and regional left ventricular wall

estimated T1 with a bias (SD) of -19.3 (10.6) ms, while centric-paired MOLLI underestimated T1 with a bias (SD) of -39.0 (170.5) ms.

Conclusions: Centric-paired MOLLI performed well in vitro, but showed increased artefact and noise in vivo as compared to conventional MOLLI; perhaps due to signal oscillations during the approach to steady state. However, 3-3 MOLLI offers a robust and reproducible T1 quantitative measurement in only 9 RR intervals, which will benefit patients who are intolerant of long breath holds.

P5515 In vivo assessment of myocardial inflammation following myocardial infarction and cardiac surgery

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Purpose: Inflammation has detrimental effects on myocardial repolarisation, remodelling and function. Here we assessed myocardial cellular inflammation using magnetic resonance imaging (MRI) of ultrasound superparamagnetic particles of iron oxide (USPIO).

Methods: Ten patients post ST-segment elevation myocardial infarction (STEMI) and 10 patients following coronary artery bypass graft (CABG) surgery underwent cardiac-MRI (3 Tesla) at baseline, and 24 hours following USPIO infusion (4 mg/kg; Ferumoxytol, AMAG). Six control post-STEMI patients underwent the same scanning protocol without infusion of USPIO. Data was analysed by one-way ANOVA (Kruskal-Wallis, Dunn’s post-test). T2*-weighted sequences were acquired and R2* maps (1/T2*) generated to assess USPIO accumulation. Baseline scans were registered to 24-hour scans, and infarct zones defined by Gadolinium-enhancement. Defined corresponding regions of interest (ROI) were used to calculate R2* values.

Results: In the STEMI control group, the R2* value in the infarct zone remained constant. In the infarct zone of the USPIO group, the R2* value increased from 0.041±0.012 (baseline) to 0.155±0.045 s−1 (p < 0.001) at 24 hours. In CABG patients, the myocardial R2* signal increased: 0.046±0.0082 (baseline) to 0.12±0.016 s−1 (p < 0.05) at 24-hours.

Conclusion: USPIO are taken up into the inflamed myocardium following acute myocardial infarction and CABG surgery. This represents an important novel method of assessing myocardial inflammation.

P5517 A new method to detect myocardial ischemia using color encoded perfusion maps at 3 tesla

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Purpose: The aim of our study was to compare new automated, motion-corrected automated navigator gated high temporal resolution tissue phase mapping

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Objective: The purpose of this study was to evaluate age-related changes in left ventricular (LV) wall motion, as detected by navigator gated tissue phase mapping.

Methods: Myocardial velocities as well as LV torsion and longitudinal strain rates were assessed in two age groups of healthy volunteers, 23±3 (n = 14) and 66±7 years old (n = 9), respectively.

Results: An increased global LV torsion rate (peak systolic torsion rate 20.6±2.0 versus 14.5±1.0 degrees/sec/cm, peak diastolic torsion rate -25.2±1.8 versus -14.1±1.3 degrees/sec/cm) and a significant decrease in longitudinal LV motion (peak systolic values at midventricle 5.9±0.5 versus 8.5±0.8 cm/sec, peak diastolic values -10.7±0.7 versus -15.2±0.9 cm/sec) in the older age group were the most prominent findings. A paradoxical increase in peak radial velocities was detected at the LV apex, consistent with an increased ejection fraction with aging. Decreased and delayed LV rotational motions were found in older subjects. Of note, the peak counter-clockwise velocity at the LV base (Figure 1, solid line) in younger subjects was represented by the initial wave of counter-clockwise rotation of the entire ventricle at the commencement of systole (arrow a), whilst in the older age group it was represented by a recoil wave of ventricular untwisting in diastole (arrow b), showing alterations of the entire pattern of LV rotation. LV apical rotation (Figure 1, dotted line) in the older age group was affected even to a higher degree, altering also the undulating pattern of recoil motions in diastole.

Figure 1 Detection of myocardial ischemia

Figure 1. MOLLI T1 vs. IR-SE T1

-8-1022 Novel imaging techniques
color encoded (AMC) perfusion maps with visual qualitative analysis of adenosine stress CMR in symptomatic patients for detection of flow-limiting stenoses.

**Materials and Methods:** Adenosine stress myocardial perfusion was performed in 25 patients (21 men, age 68 ± 7.5 years) using the 3.0 Tesla Magnetom Skyra. Perfusion studies were analyzed with qualitative visual analysis and AMC perfusion maps. Angiographically detected coronary artery stenoses > 75% or ≥ 50% with a myocardial perfusion reserve index (MPRI) > 1.5 were considered as hemodynamically relevant. Diagnostic performance, inter- and intraobserver reliability as well as time requirement for both methods were compared.

**Results:** Sensitivity (90.8% vs 87.5%), specificity (100% vs 77.8%), positive predictive value (PPV) (100% vs 87.5%), negative predictive value (NPV) (90% vs 77.8%) and accuracy (96% vs 84%) for detection of ischemia on a per-patient basis was slightly superior using AMC perfusion maps compared to visual analysis. On a per-coronary artery territory basis, AMC perfusion maps facilitated the attribution of an ischemia to the respective vessel. The inter- and intraobserver reliability was better for the AMC perfusion maps (CCC 0.94 and 0.93, respectively) compared to the visual analysis (CCC 0.73 and 0.79, respectively). Additionally, in comparison to the visual analysis, AMC perfusion maps allowed a faster analysis (7.7 ± 1 minutes to 3.2 ± 1.9 hours, p < 0.0001). Figure 1 demonstrates a patient example for the diagnosis of ischemia using AMC perfusion maps and visual analysis.

**Conclusion:** AMC perfusion maps seem to represent a feasible and fast method to detect myocardial ischemia on a per-patient and on a per-coronary artery territory basis in our pilot study.

**P5519**

**LV mass volumes and ejection fraction estimation by novel semi-automated software, Feature Tracking, “FT” (TomTec, Germany) to traditional contouring methods**

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**Purpose:** Quantification of left ventricular (LV) mass (LVM), end systolic (ESV), end diastolic volume (EDV) and ejection fraction (EF) by CMR traditionally involves manual contouring of endocardial borders at end systole and diastole as well as the epicardial border at end diastole. We compare LV EF, LVM, volumes and fractional area of change (FAC) assessed by novel semi-automated software, Feature Tracking, “FT” (TomTec, Germany) to traditional contouring methods.

**Methods:** 259 adults (mean age 28 ± 6.3, range 20-49 years, 105 male) underwent CMR imaging (1.5T) to obtain SSFP horizontal long axis (HLA) and short axis (base, mid and apical levels). LVM, ESV, EDV and EF were measured by manual contouring using Argus and then estimated using FT software by delineating the end diastolic and end systolic border from the HLA view. FAC was estimated after contouring the endocardial border from the short axis views.

**Results:** Estimate of LVM, ESV, EDV and EF by FT was significantly quicker than the manual method (time 213 ± 202 seconds vs. 702 ± 145 seconds, p < 0.05). Correlations were excellent when comparing FT and CMR results for LVM (r=0.81, p < 0.001) and ESV (r=0.82, p < 0.001) and acceptable when comparing EDV (r=0.68, p < 0.001). Correlations were poor for EF (r=0.27, p < 0.001) and FAC provided better correlations with EF for both CMR (r=0.48, p < 0.001) and FT (r=0.51, p < 0.001). The novel estimation of FAC using the semi-automated software showed moderate correlations with EF as estimated by both CMR (r=0.48, p < 0.001) and FT (r=0.51, p < 0.001).

**Conclusions:** FT allows assessment of LV volumes, mass and systolic function using semi-automated software which is quicker than traditional methods and good agreement for LVM and LV volumes. Further modifications algorithms may be needed to improve estimation of EF.

**P5520**

**Quantification of coronary wall enhancement by cardiovascular magnetic resonance imaging:**

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**Purpose:** High-resolution contrast enhanced cardiac magnetic resonance (CE-CMR) imaging is a novel modality for the non-invasive visualization of contrast uptake within the coronary vessel walls. As quantification of enhancement may inform clinical decisions, the aim of the study was to assess the reproducibility of proposed methods of quantification.

**Methods:** Analysis of a 14-subject rich data-set, obtained in a 3 Tesla MRI scanner, was performed by two independent observers for intra and inter-observer reproducibility. Three methods of quantification were applied to each subject’s dataset. Methods 1 and 2 generated a contrast to noise ratio(CNR) in proximal, mid- and distal segments using coronary signal intensity and differed in the extraction of values to generate the ratio. Method 1 only included the visually detectable enhancement, whereas method 2 used complete segment (lumen and wall). Method 3 used all segments to quantify “total area of enhancement”.

**Results:** Method 1 showed an excellent intra and inter observer agreement for CNR (intra: r=0.98, P<0.01; MD±SD = 1.3±1.2, range 0.3-3.1); inter: r=0.97, P<0.01; MD±SD = 2.1±1.4) for mid-segment, whereas for total coronary length the intraobserver agreement was r=0.98, p<0.01 (MD±SD = 0.9±2.3). The best-obtained agreement for Method 2 was intraobserver (r=0.96, p<0.05) comparing the distal coronary wall segment enhancement. Method 3 for quantification of “total area” showed a good intra- and interobserver observer agreement (intra: r=0.92, p<0.01; MD±SD (mm²) = 0±1.6; inter: r=0.87, p<0.05, MD±SD (mm²) = 0.8±1.6).

**Conclusion:** We demonstrate an excellent intra- and interobserver reproducibility for quantification of coronary wall enhancement by CNR using the signal of visualized coronary enhancement only.

**P5521**

**Cardiac magnetic resonance feature tracking: a novel method to assess myocardial strain: comparison with echo speckle tracking in healthy volunteers and patients with left ventricular hypertrophy**

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**Purpose:** To compare a new 2-dimensional (2D) cardiac magnetic resonance (CMR) cine sequence-based technique (feature tracking, FT) to 2D speckle-tracking echocardiography for strain analysis in healthy volunteers and in patients with left ventricular hypertrophy and to evaluate interobserver variability.

**Methods:** Overall, 20 healthy volunteers (10 male, mean age 24±3 years) and 20 consecutive patients with hypertrophic cardiomyopathy (12male, mean age 47±19 years) were included. Longitudinal and circumferential strain and strain rate of the left (LV) and right ventricle (RV) were measured on CMR and speckle-tracking echocardiography.
Late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) can detect different patterns of reversible (by T2-weighted) and irreversible (by DE-CMR) cardiac involvement. In patients with extracardiac sarcoidosis, the extent of LGE by CMR predicts major adverse cardiovascular events (MACE) in patients with HCM and with gray-scale threshold of LGE >2 standard deviation (SD) or >6SD reflects mortality and morbidity more precisely in such patients. We systematically reviewed the extent of LGE in 86 consecutive HCM patients who underwent CMR (59 males, mean age 58±16 years). Two gray-scale thresholds of >2SD and >6SD exceeding the mean signal intensity for normal remote myocardium were used to define areas of LGE. The relationship between baseline clinical and CMR parameters and the development of MACE were examined.

Results: During mean follow-up period of 822±547 days, 24 (28%) patients developed MACE such as unplanned heart failure hospitalization (n=20), ventricular fibrillation (n=1), stroke due to cardiac emboly (n=2) and implantation of left ventricular assist device (n=1). Among them, 2 patients died of heart failure and 1 underwent heart transplantation. The extent of LGE defined as >2SD and >6SD were independent predictors of MACE (odds ratio=1.10, 95% confidence interval 1.02 to 1.20, p=0.007 and odds ratio=1.18, 95% confidence interval 1.07 to 1.35, p<0.001 respectively). Receiver operating characteristic curve analysis indicated good predictive performance of the extent of LGE defined as >2SD and >6SD with respect to MACE (area under the curve=0.856 and 0.926 respectively). When patients were divided into two groups by cut-off value of 19.9% defined from receiver operating characteristic curve analysis of the extent of LGE defined as >6SD, the initial onset of MACE was significantly earlier in LGE >19.9% group (n=36) than those of LGE <19.9% group (n=50) (log-rank test, p=0.001).

Conclusions: Subclinical cardiac involvement is relatively frequent in SSc. CMR can detect different patterns of reversible (by T2-weighted) and irreversible (by DE) cardiac involvement. Elevated E/E’ at echocardiography may raise the suspicion of myocardial fibrosis.
Quantitative NMR imaging in acute benign myocarditis: T1 and extracellular volume fraction measured with MOLLI at 3T

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Purpose: Myocardial T1 and extracellular volume fraction (EVF) have been previously quantified in patients with ischemic heart disease using modified Look-Locker sequences (MOLLI). The extent of late gadolinium enhancement (LGE) has been shown to be a strong predictor of adverse events after myocardial infarction (MI) and in cardiomyopathies. Quantitative measurements of T1 and EVF might potentially improve the LGE predictive value. In this study, we determined T1 and EVF in patients with acute myocarditis and we compared the results with those obtained in patients with chronic MI.

Methods: In 6 patients with myocarditis (32.2 year-old, sub-epicardial LGE) and 15 patients with MI (52.5 year-old, sub-endocardial/transmural LGE) myocardial T1 was determined using the MOLLI protocol at 3 tesla. MOLLI consists of 3 inversion blocks generating 3-3-3 single-shot True-FISP images. Pre- and post-Gd (15 min after injection) short-axis T1 maps were acquired within single-breathholds. The T1 values were compared in LGE and normal regions of the myocardium. The myocardial T1 values were normalized to the T1 of blood and the EVF was calculated from T1 values of myocardium (myo) and blood pre- and post-GD. Results: Adjusting for each patient weight, and recorded by mCi, Becquerel’s units and utilized for attenuation correction. The radiation doses of technetium 99m were measured with MOLLI at 3T. The software used the modified Syntax segmentation for defining the L-A left ventricular region in the 17 segment model. Background: Cadmium zinc telluride (CZT) solid-state detectors have been recently introduced in MPI. We prospectively compared diagnostic performances of the CZT ultrafast SPECT camera (Discovery NM 530c, GE Healthcare) with a standard three-head gamma camera (PRISM 3000XP or PRISM IRIX, Picker) in the same patient.

Aims: To generate an algorithm about the concordance between the individual epicalendary coronaries and the left ventricular segments on the basis of the coronary angiography, and to compare the overlap between the FFR-predicted ischemic segments and the segments with reversible perfusion defect on the SPECT according to the assignment in our algorithm and on the basis of the guideline.

Results: Of 29 patients with at least one angiographically significant lesion (<50% diameter stenosis) and with FFR measurements by intracoronary pressure wire and stress perfusion studies were analyzed. The distribution of the ischemia defined by reversible reversibility score/segment (RSc) on the perfusion polar map was correlated with the individual lesion-associated (L-A) left ventricular segments. Results: The software used the modified Syntax segmentation for defining the L-A left ventricular region in the 17 segment model. Results: In the HCC program 2:1 left ventricular segments (altogether 87) were assigned to the 14 FFR positive (<0.80) stenoses on the basis of the coronary angiography. Out of these segments 56 showed reversible perfusion defect. From these data the per-vessel analysis using the regional ischemia criteria (≥2 RSc) showed 65% sensitivity and 100% specificity for the prediction of ischaemia by the standard alignment. Per-segment analysis revealed 78% sensitivity and 84% specificity for the prediction of ischaemia by the standard alignment, respectively.

Conclusion: The myocardial segments affected by significant epicardial lesions can be defined higher sensitivity by the HCC program than on the basis of the standard alignment.

Comparison of myocardial perfusion imaging between ultrafast and standard single-photon emission computed tomography


Background: According to the current guideline the 17 myocardial segments can be assigned to the 3 major coronary arteries. However, the individual coronary artery variation can differ significantly from the standardized assignment. This can explain the recently published disagreements between the results of the fractional flow reserve (FFR) and the perfusion abnormality on the sцинtigrams (SPECT).

Aims: To generate an algorithm about the concordance between the individual epicalendary coronaries and the left ventricular segments on the basis of the coronary angiography, and to compare the overlap between the FFR-predicted ischemic segments and the segments with reversible perfusion defect on the SPECT according to the assignment in our algorithm and on the basis of the guideline.

Methods: The study group comprised of 15 consecutive patients who underwent a 1-day stress/rest Tc-99m sestamibi or tetrofosmin imaging protocol. Tc-99m tracer was injected 370 MBq after exercise and 740 MBq at rest. Image acquisition of 360° arcs was performed first on a standard gamma camera with the radiation dose in obese patients (weight ≥100kg) and above who were referred for stress perfusion imaging. Out of these segments 56 showed reversible perfusion defect. From these data the per-vessel analysis using the regional ischemia criteria (≥2 RSc) showed 65% sensitivity and 100% specificity for the prediction of ischaemia by the standard alignment. Per-segment analysis revealed 78% sensitivity and 84% specificity for the prediction of ischaemia by the standard alignment, respectively.

Conclusion: The myocardial segments affected by significant epicardial lesions can be defined higher sensitivity by the HCC program than on the basis of the standard alignment.
Fusion of multidetector coronary CT angiography and stress myocardial perfusion imaging in coronary lesions—a comparison with fractional flow reserve


Background: Stress myocardial perfusion imaging (MPI) may underestimate in patients with moderate stenosis and multi-vessel disease. Accuracy of detecting myocardial ischemia with fusion of multislice coronary CT angiography (MSCT) and MPI in these patients is still unclear.

Methods: We studied 51 stenosis with moderate angiographic severity (50-75% stenosis) in 35 patients (20 male, 73±8 years). FFR was measured in each moderate stenosis. Significant stenosis was labelled if FFR ≤ 0.75.

Results: 18 lesions showed significant ischemia by FFR. Fusion analysis showed a considerable improvement in sensitivity (83.3% vs 50.0%, p<0.05) and NPV (90.0% vs 76.3%, P<0.05) without significant changes in specificity (81.8% vs. 87.8%) and PPV (69.2% vs. 71.4%) compared to MPI alone.

Diagnostic accuracy in MPI and Fusion

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tr>
<td>MPI</td>
<td>50.0</td>
<td>83.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion</td>
<td>87.9</td>
<td>81.8</td>
<td>71.4</td>
<td>90.0</td>
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Conclusions: Fusion imaging can better identify significant coronary stenosis as compared to MPI alone.

Diagnostic usefulness of cardiac hybrid imaging of myocardial perfusion imaging and 64-slice computed tomography coronary angiography in post-CABG patients

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Background: The purpose of this study is to evaluate the incremental clinical value of hybrid imaging in the diagnosis of coronary artery disease for post-CABG patients. Reading myocardial perfusion image (MPI) in post-CABG patients is often equivocal because coronary blood flow is complex especially when complete sequential bypass technique is used.

Method: Enrolled were consecutive post-CABG patients (n=21) who had perfusion defect on stress Ti-201 MPI and the side-by-side assessment of MPI and 64-slice computed tomography coronary angiography (CTA) appeared equivocal on the myocardial ischemia and its culprit vessel. The side-by-side analysis and the analysis with hybrid imaging of CTA and MPI were compared.

Results: In 10 of 21 patients, the result of hybrid imaging analysis was different and confirmed the result of side-by-side analysis. In 11 of 21 patients, hybrid imaging provided additional diagnostic information. In 4 patients, postero-lateral myocardial ischemia corresponding to unprotected left circumflex artery was identified as the left marginal artery was grafted (Figure). In 3 patients, small inferior myocardial ischemia was detected and its culprit vessel was identified as unprotected branch of right coronary artery as the other branches were grafted.

Figure 1. Hybrid imaging of post-CABG patient

Conclusion: In post-CABG patients, hybrid imaging provides clear information on myocardial ischemia and the corresponding culprit coronary vessel.

Novel nuclear scan strategy with stress Adenosine-SPECT implements diagnosis of myocardial ischemia in chest pain patients presenting nondiagnostic ECG and troponin

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Aim: The aim of this study is to update the diagnostic scan strategy with the novel pharmacological stress agent Adenosine in chest pain patients presenting normal ECG and troponin.

Methods: Two consecutive non-randomized series of patients with chest pain and a negative first-line work-up including serial ECGs and serial troponins underwent myocardial perfusion imaging (SPECT). The first series was subjected to Dipyridamole-SPECT (year 2008) and the latter to Adenosine-SPECT (year 2009-2010). Those patients with perfusion defects underwent angiography, whereas others were discharged and followed up. The endpoint was the composite of coronary stenosis greater than 50% at angiography or cardiovascular death, myocardial infarction, unstable angina, and revascularization at follow-up.

Results: Out of 161 patients enrolled, 45 underwent Dipyridamole-SPECT and 116 Adenosine-SPECT. At univariate and multivariate analysis the presence of perfusion defects and basal nonischemic ECG or nonischemic echocardiography alterations were independent predictors of the endpoint. Areas under the ROC curve of Dipyridamole-SPECT and Adenosine-SPECT were comparable. Sensitivity and negative predictive value were significantly higher in patients subjected to Adenosine-SPECT vs Dipyridamole-SPECT (sensitivity 95% vs 56%, respectively, p=0.03, yield 70%; negative predictive value 99% vs 88%, respectively, p=0.02, yield 13%). Patients with basal nonischemic ECG or nonischemic echocardiography alterations (n=15) compared to patients without (n=101) when subjected to Adenosine-SPECT showed a yield in positive predictive value up to 84% avoiding unnecessary angiograms.

Conclusion: In chest pain patients presenting normal ECG and troponin the novel nuclear scan strategy with stress Adenosine-SPECT added incremental diagnostic and prognostic value over Dipyridamole-SPECT.

Reproducibility of delayed heart to mediastinum ratio on planar 123I-metaiodobenzylguanidine (123I-MIBG) myocardial scintigraphy in patients with heart failure

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Background: 123Iodine-meta-iodobenzylguanidine (123I-MIBG) myocardial scintigraphy provides important prognostic information in heart failure (HF) patients. However, widespread clinical implementation is hampered due to lack of validation and standardization. Therefore, the purpose of this study was to assess the reproducibility of delayed H/M ratio on planar 123I-MIBG myocardial scintigraphy.

Methods: Planar myocardial 123I-MIBG images of 70 HF patients were analyzed on two consecutive occasions by two experienced observers. Interobserver reproducibility of delayed H/M ratios was assessed using the Intraclass Correlation Coefficients (ICC) and the Bland-Altman analysis. Additionally, analysis was performed to assess the H/M ratio using a fixed size oval and circular cardiac region of interest (ROI). Results: In 10 of 21 patients, the result of hybrid imaging analysis was different and confirmed the result of side-by-side analysis. In 11 of 21 patients, hybrid imaging provided additional diagnostic information. In 4 patients, postero-lateral myocardial ischemia corresponding to unprotected left circumflex artery was identified as the left marginal artery was grafted (Figure). In 3 patients, small inferior myocardial ischemia was detected and its culprit vessel was identified as unprotected branch of right coronary artery as the other branches were grafted.

Figure 1. Agreements between observers

Conclusions: The present study showed that delayed H/M ratios in 123I-MIBG myocardial scintigraphy is highly reproducible in HF patients, confirming that 123I-MIBG myocardial scintigraphy can be implemented easily at large scale for clinical risk stratification in HF.
tigate valvular 18F-NaF activity in patients with aortic stenosis by assessing its distribution in relation to established calcium and by comparison with histology. **Methods:** 18F-NaF PET/CT scans were performed in 118 patients with a range of aortic stenosis. Regions of interest were drawn around the valve, and each voxel was assessed for the presence of calcium (>130 HU) and increased 18F-NaF activity (TBMax<1.97). Voxels were then categorised in to normal (CT-PET); inactive calcium (CT-PET+); novel calcification (CT+PET-); and calcium remodelling (CT+PET+). Five patients underwent aortic valve replacement. PET/CT was repeated on excised valves after incubation with 18F-NaF for 60mins at 37°C, followed by immunohistochemistry (CD68, osteocalcin and alkaline phosphatase). **Results:** In stenotic aortic valves 96% of voxels were normal, 3% showed inactive calcium, 32% showed novel calcification, and 10% showed calcium remodelling. With increasing disease severity the % of normal voxels decreased whilst the % of the other categories increased (Figure 1). In all severities of aortic stenosis, increased 18F-NaF was more commonly observed in the absence rather than presence of calcification on CT (p=0.001; moderate p=0.001; severe p=0.008). 18F-NaF activity closely matched the pattern of staining for osteocalcin and alkaline phosphatase which were frequently remote from calcific nodule formation.

**Conclusion:** 18F-NaF is a marker of active calcification in the valves of patients with aortic stenosis and provides complementary information to CT calcium scoring.

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**Table 1. Cardiac masses study**

<table>
<thead>
<tr>
<th>Masses</th>
<th>ECHO diagnosis</th>
<th>CMR diagnosis</th>
<th>Histopathological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus</td>
<td>4</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Myxoma</td>
<td>8</td>
<td>9</td>
<td>10</td>
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<tr>
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<td>2</td>
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<tr>
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<td>2</td>
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<tr>
<td>Total</td>
<td>34</td>
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</tbody>
</table>

**ECHO:** echocardiogram; **CMR:** cardiovascular magnetic resonance.

**Conclusion:** CMR strongly provides extra information about intracardiac masses above those provided by ECHO, such as tissue, morphological and functional characteristics.

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**ARRHYTHMIAS AND PACING IN CONGENITAL HEART DISEASE**

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**Children with spontaneous supraventricular tachycardia and normal ECG in sinus rhythm require a complete evaluation**

| B. Brembilla-Perrot, A. Moulin-Zinsch, G. Cismaru, M. Rodermann, G. Goudotte, J.P. Lethor, J.L. Cloez, G. Marchal, A. Tissierand, F. Marcon, University Hospital of Nancy - Hospital Brabois, Vandoeuvre les Nancy, France |

**Purpose of the study:** The interests of electrophysiological study (EPS) were evaluated in children or teenagers with supraventricular tachycardia (SVT) and a normal ECG in sinus rhythm. EPS is generally performed only before paroxysmal SVT ablation in children with a normal ECG in sinus rhythm. SVT is considered as benign and treatment is rarely indicated.

**Methods:** 124 children and teenagers aged from 5 to 19 years (mean 15±3) with a normal ECG in sinus rhythm were studied for spontaneous SVT by transesophageal route. Programmed atrial stimulation using atrial pacing and pro-
Recurrent atrial tachyarrhythmias and the RA function in adult patients with congenital heart disease under postoperative MAZE procedure.

A. Y. Shinya, T. Matsuyama, S. Y. Ho, H. Uemura, M. A. Gatzoulis, W. Li.
Royal Brompton National Heart & Lung Hospital, London, United Kingdom

Purpose: To assess the factors for recurrent atrial tachyarrhythmias after surgical MAZE procedure in adult patients with congenital heart disease (CHD).

Methods: We studied 37 CHD pts (age 41.5±13.0 years, range 17-68) who underwent surgical repair + surgical MAZE procedure (full MAZE: 6 pts and right atrial [RA] MAZE: 31 pts. TOF 3pts, ASD 8 pts, VSD 3pts, DCRV 1pt, iVSD 1pt, TA Fontan 1pt, TA Glenn 1 pt). The resected RA tissues were histologically assessed. The RA function was evaluated using Doppler before and 6 months after surgery. Follow-up period of arrhythmia events was 2.6±1.7 years. Comparisons were made among the subgroups depending on the pre- and post-operative RA function subgroup.

Conclusions: EPS is recommended in children with paroxysmal supraventricular tachycardia and apparently normal ECG in sinus rhythm. The data are helpful to guide the medical treatment, the follow-up and the indications of ablation. VT was misdiagnosed in children presenting a tachycardia with a right bundle branch block. Masked preexcitation syndrome with anterograde conduction through an accessory pathway was present in 13% of our population and 2 (1.6%) had a malignant form of preexcitation syndrome.

Recurrent atrial tachyarrhythmias and the RA function in adult patients with congenital heart disease under postoperative MAZE procedure.

Y. Shinya, T. Matsuyama, S. Y. Ho, H. Uemura, M. A. Gatzoulis, W. Li.
Royal Brompton National Heart & Lung Hospital, London, United Kingdom

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Conclusions: EPS is recommended in children with paroxysmal supraventricular tachycardia and apparently normal ECG in sinus rhythm. The data are helpful to guide the medical treatment, the follow-up and the indications of ablation. VT was misdiagnosed in children presenting a tachycardia with a right bundle branch block. Masked preexcitation syndrome with anterograde conduction through an accessory pathway was present in 13% of our population and 2 (1.6%) had a malignant form of preexcitation syndrome.

New arrhythmias predictor factors in adults with repaired tachyarrhythmia of fallot.

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2Unit, London, United Kingdom; 3Royal Brompton Hospital, London, United Kingdom

Purposes: repaired TAF of rTOF patients are at risk of both atrial and ventricular arrhythmia, right ventricular (RV) dilatation and dysfunction, and sudden death during long-term follow-up. We aimed to examine potential predictors of arrhythmias.

Methods: CMR and contemporaneous clinical data were prospectively collected and analysed for atrial size on cine 4-chamber view at end-systole. Endpoints were new onset of documented atrial arrhythmia (AA) and sustained ventricular tachycardia or ventricular fibrillation (VT) during follow-up.

Results: Of 154 patients (mean age 31.7 years [SD12.7]), median follow-up 5.6 years (4.6, 7.12) 12 new onset AA and 9 new onset VT occurred. New onset AA was correlated with maximal right atrial area indexed to body surface area (RAAmax) (ROC analysis, AUC0.74[0.66-0.81], P<0.003) (Figure), with a cut-off value of 16cm2/m2. On survival curve with this cut-off value, there was a significant difference in new onset atrial arrhythmia (P<0.004). RV outflow tract (RVOT) akinetie area length and decrease RV ejection fraction were predictor of new onset sustained VT (HR1.19[1.01-1.09], P=0.005 and HR5.9 [87-98], P=0.03 respectively). Patients with RV restrictive physiology were older (P<0.04) had a higher RAARmax (P=0.02) and a more important tricuspid regurgitation (P<0.002) with tilted RV.

Conclusions: RAARmax is a predictor of arrhythmia and the length of the RVOT akinetie area is a predictor of VT in rTOF. Right atrial area and RVOT akine tic area length measurement are feasible and widely available to inform clinical decision making. There is a new presentation of RV restrictive physiology in rTOF ageing patients, with predisposing factors to arrhythmias.

Does physiologic pacing prevent arrhythmias in adults with congenital heart disease?

P. Opic1, S.C. Yap1, M. Kranenburg1, A.P.J. Van Dijk2, W. Buds3, H.W. Vliegen1, L. Van Erven1, A. Cain1, M. Wilsenbreg1.
1J.W. Roos-Hesselink, 1Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands; 2Radboud University Nijmegen Medical Centre, Department of Cardiology, Nijmegen, Netherlands; 3Catharina University of Leuven, Department of Cardiology, Leuven, Belgium; 4Leiden University Medical Center, Department of Cardiology, Leiden, Netherlands

Purpose: to investigate the effect of physiologic pacing on the occurrence of atrial arrhythmias in adults with congenital heart disease (CHD).

Methods: All adult CHD patients who had a pacemaker implantation in one of the four participating tertiary referral centers were retrospectively identified. Patients with persistent/permanent atrial arrhythmias and patients who received a pacemaker for treatment of drug refractory atrial arrhythmias were excluded.

Results: Two-hundred and seventeen patients (54% male, 36% complex CHD) were identified with a mean age at implant of 26.1±7 years. A history of paroxysmal atrial arrhythmia was present in 46 patients (21%). The indication for pacing...
Permanent cardiac pacing in children - choosing the optimal pacing-site: a multi-centre study

J. Janousek1, I. Van Geldorp2, S. Krupickova2, E. Rosenthal2, M. Fruska2, M. Fruska2, J. Elders2, A. Hippla2, F.W. Prinzl3, T. Delhaas3 on behalf of the Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Pediatric Cardiology, 1Children’s Heart Centre, University Hospital Motol, Prague, Czech Republic; 2Pediatric Cardiology, Cardiovascular Research Institute Maastricht, Maastricht University Medical C, Maastricht, Netherlands; 3Evelina Children’s Hospital, London, United Kingdom; 4University Children’s Hospital, Department of Cardiology, Zurich, Switzerland; 5Oslo University Hospital, Oslo, Norway; 6Radboud University Nijmegen Medical Centre, Department of Cardiology, Nijmegen, Netherlands; 7Department of Pediatric Cardiology, Children’s Hospital, Helsinki University Central Hospital, Helsinki, Finland; 8Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, Netherlands; 9Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht, Maastricht Univ., Maastricht, Netherlands

Purpose: We evaluated the effects of pacing-site on left ventricular (LV) synchrony and function in children requiring permanent pacing.

Methods: We included children (age ≤18 years) from 21 centers with complete AV block and a structurally normal heart undergoing permanent pacing were cross-sectionally studied. Median age at evaluation was 11.2 (inter-quartile range (IQR) 6.3–15.0) years. Median pacing duration was 5.4 (IQR 3.1–8.8) years. Data were analyzed in a core lab. Pacing-sites were the free wall of the right ventricular (RV) outflow tract (RVOT, N=8), lateral RV (RVLat, N=44), RV apex (RVa, N=61), RV septum (RVs, N=29), LV apex (LVA, N=12), LV mid-lateral wall (LVLat, N=17) and LV base (LVB, N=7).

Results: LV synchrony, pump function (ejection fraction (EF), end-systolic volume index and change in shortening fraction as compared to pre-implantation values) and contraction efficiency were significantly affected by pacing-site and were superior in children paced at LVA/LVLat. LV dys synchrony assessed by radial strain correlated inversely with LV EF (R=0.80, P=0.001). Pacing from RVOT/RVLat predicted decreased LV function (LV EF >45%, OR 5.19 CI 1.74-15.50, P=0.003) whereas LVA/LVLat pacing was associated with preserved LV function (LV EF >55%, OR 6.97, CI 2.21-22.00, P=0.001). Age at implantation, pre-implantation LV size and function, duration of pacing, DDD mode, ORS duration and presence of maternal auto-antibodies had no significant impact in a multivariable analysis.

Conclusions: LV mechanical synchrony, pump function and contraction efficiency may significantly deteriorate with RVOT/RVLat pacing and are best preserved with LVA/LVLat pacing.

Arrhythmias and pacing in congenital heart disease / Congenital heart disease and pediatric cardiology – miscellaneous

The prevalence of adult congenital heart disease, a systematic review

T. Van Der Bom1, B.J. Bouma2, F.J. Meijboom2, A.H. Zwingerden1, B.J.M. Mulder1, 1Academic Medical Center, University of Amsterdam, Department of Cardiology, Amsterdam, Netherlands; 2University Medical Center Utrecht, Department of Cardiology, Utrecht, Netherlands; 3Academic Medical Center, Department of Clinical Epidemiology, Biostatistics & Bioinformatics, Amsterdam, Netherlands

Purpose: The reported prevalence of adult patients with congenital heart disease is variable. Basically two methods are applied. ACHD prevalence is either calculated from birth rates, documented birth prevalence and likely survival estimates, or estimated within large population wide databases. In order to come to a more robust figure, we performed a systematic review on the prevalence of CHD in adults.

Methods: A systematic search in Medline and Embase was performed to identify reports on the prevalence of ACHD. CHD was defined to exclude bicuspid aortic valve, mitral valve prolapse, Marfan syndrome, cardiomyopathy, congenital arrhythmia and spontaneously closed defects. Both calculated and empirical estimates were included in the review.

Results: Our search yielded ten publications on the prevalence of ACHD. Mean prevalence estimated with calculations (6 studies) was 3546 per million adults. Both birth prevalence and survival estimates varied widely between studies. Weighted mean prevalence of four observational studies was 3562 per million adults. Estimation of 36 percent of CHD cases that could not be specified, mean prevalence was 2297 per million adults. Taking these uncertainties into account, we estimated there were approximately 3000 CHD patients per million adults.

CONGENITAL HEART DISEASE AND PEDIATRIC CARDIOLOGY – MISCELLANEOUS

Lack of continuity of care may be a cause of morbidity in adults with moderate congenital heart disease

I. Mendez Santos, B. Munoz Calero, L. Gonzalez Torres, R. Gomez Dominguez, S. Rodriguez De Leiras, M. Chaparro, C. Caparros, M. Gonzalez Valdayo, J.M. Cruz Fernandez, P. Gallego Garcia De Viruésa, Virgen Macarena University Hospital, Sevilla, Spain

We sought to evaluate clinical impact of lack of continuity in specialized health-care in adults with a CHD diagnosed in infancy.

Methods: In 212 patients with CHD referred for first evaluation at our adult CHD outpatient clinic since 2004 to 2010 we analyzed length of time from leaving care at a pediatric institution to receiving attention at any adult congenital cardiac facility. Delay was defined as a duration since last visit < 2 years. Symptoms, new or evolving cardiac problems and need for intervention, defined as a surgical or catheter-based intervention within 6 months after the initial evaluation, were compared between patients with or without delay.

Results: Diagnostic categories: tetralogy of Fallot (ToF, 47), coarctation (39), transposition (TGA, 17), atrioventricular septal defect (22), single ventricle physiology (12). Eisenmenger syndrome (11), Ebstein anomaly (12), right ventricular (RVOTO, 24) or left ventricular outflow tract obstruction (13), sinus venosus defect (8), other CHD (6). 70% p had delay (mean duration of delay of 19±12 years; range 3-69 years). At first evaluation a new hemodynamically significant diagnosis was made in 107 p (50%); valvar regurgitation (30%), obstructive lesions (19%), subaortic or subpulmonary ventricular dysfunction (10%), aortic dilatation (8%), new anatomical lesions (3%) and arrhythmias (14%). A new intervention was indicated in 29% of p; 24.5% surgery; 10% catheter based intervention for vascular stenosis; 5%; ablation; 6% pacemaker implantation; 2% percutaneous closure of shunts and 4% balloon dilatation. The frequency of new diagnoses was higher in repaired ToF, RVOTO and TGA (84%, 81% and 75% of p, respectively; p<0.001).
and a new intervention in repaired TOF (42%), RVOTO (42%), TGA (27%) and coarctation (16%) (p < 0.001). Patients with delay were older (41±14 vs. 35±17 years, p < 0.01), had a higher prevalence of new or evolving cardiac lesions (68% vs. 16%, p < 0.001) and were more severely symptomatic at presentation (59% NYHA functional class I, 26% class II 14% class III vs. 70% class I, 24% class II vs 5% class III; p < 0.05). Delay (odd ratio 3.7 ± 0.95 1.8-7.3; p < 0.001) and age (odd ratio 1.04 CI 95% 1.021-1.07; p < 0.001) were significant in multivariate analyses to predict complications.

Conclusions: The prevalence of new or evolving cardiac complications in moderate CHD at late follow-up is as high as in complex CHD. Despite this, the lack of continuity of specialized care is still common and associated with cardiovascular morbidity. Our data support consideration of formal transitioning programs for these patients.

P5545 Retrograde single catheter closure of VSDs in children and young infants using the Amplatzer duct occluder II device

N. Sreeram, R. Penumatsa, S. Arramraju, V. Karunaraj, N.R. Koneti. University Hospital, Cologne, Germany

Objectives: To describe a new technique of transcatheter closure of VSDs in children. Antegrade transcatheter closure of VSDs is well established, but requires the formation of an arteriovenous loop. We describe the retrograde single catheter approach. Methods: Seventy seven symptomatic children (42 males, median age 46 months, range 0.6 to 240 months, median weight 14 kg, range 4.8 to 38 kg) with various types of perimembranous (n=41) or muscular defects were selected for VSD closure. The VSD diameter was planned to be > 6.5 mm, as this is the maximum available waist diameter of the Amplatzer Duct Occluder II (ADO II). An ADO II device was chosen with a waist diameter equal to or 1mm greater than the minimum VSD diameter of the Amplatzer Duct Occluder II (ADO II). The ADO II device was placed via the femoral artery, and the appropriate ADO II device delivered. The distal (RV) disc was initially deployed, followed by the waist and LV disc, under transthoracic (n=26) or transesophageal echocardiography (n=51). Results: The median VSD diameter was 4.5 mm (4 to 6.5 mm). The mean fluoroscopic time was 11±8 minutes. Two devices embolized, but were successfully retrieved, and the VSD closed with a larger device. Preexisting tricuspid regurgitation in children with perimembranous VSDs invariably improved. At a median follow-up of 14 months, 3 patients had a right nodule branch block; complete closure rate was 90%.

Conclusions: Retrograde VSD closure using a single standard guiding catheter is safe, feasible and simplifies the procedure. It should be considered in young, symptomatic patients.

P5546 Predictors of residual functional tricuspid regurgitation after transcatheter Attrial Septal Defect closure: importance of pre-closure tricuspid valve anatomy

F. Fang, X.X. Luo, Q.S. Lin, Y.C. Zhang, J.S.W. Kwong, X. Jiang, X. Mu, Y.V. Lam. The Chinese University of HK, Li Ka Shing Institute of Health Sciences, Inst. of Vascular Medicine, Hong Kong, Hong Kong SAR, People’s Republic of China

Introduction: Although chronic right heart volume overloading is relieved by de-closure of atrial septal defect (ASD), the change of functional tricuspid regurgitation (TR) remains unclear.

Methods: Echocardiography was done in 61 consecutive secundum ASD patients (46±17 yrs, 16 males) shortly before and at 3 months after device closure. Tricuspid annulus diameter (TAD), tenting area, tenting height, distal tricuspid septal leaflet angle (TSLA), right and left ventricular volumes were quantified. Persistent TR was defined as vena constrictor of TR ≥ 0.5 cm at 3-month follow-up. The pulmonary arterial systolic pressure was measured with standard fluid filled catheters and the ratio of pulmonary to systemic flow was calculated with oximetry by use of Fick’s principle.

Results: TR was significantly reduced after ASD device closure at 3-month (TR vena constrictor: 0.4±0.3 vs. 0.3±0.2 cm, p=0.005). However, persistent TR was detected in 30 patients (49%). At baseline, these patients had larger right ventricle, greater tricuspid tenting height, tenting area and TSLA as well as more dilated TAD compared to those without (Table). Multivariate logistic regression revealed that TAD (odds ratio (OR): 10.6±8, p=0.026) and TSLA (OR: 1.19, p=0.026) were independent predictors for the persistent TR. From the receiver operating characteristic curve, TAD of 3.4 cm (sensitivity 97%, specificity 84%, AUC 0.86, p<0.001) and an TSLA of 0.3 (sensitivity 100%, specificity 71%, AUC 0.83, p<0.001) were associated with post-closure persistent functional TR. Assessment of TSLA showed an incremental value over TAD for predicting persistent TR (OR:16.6 vs 12.3, p<0.001).

Conclusions: Around half of adult subjects have persistent TR at mid-term after ASD closure. TAD and TSLA independently predict persistent TR. Tricuspid structural changes are believed to play a pivotal role in this phenomenon.

P5547 Hemodynamic and genetic analysis in children with idiopathic/heritable and congenital heart disease associated pulmonary arterial hypertension

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Purpose: Idiopathic (I) pulmonary arterial hypertension (PAH) is rare in childhood and can be heritable (HPAH) caused by defects in transforming growth factor (TGF) signalling genes. The genetic background of congenital heart defects associated with PAH (CHD-PAH) is less clear. The aim of this prospective study was to compare clinical and genetic findings in children with HPAH and CHD-PAH.

Methods: Prospectively included were consecutive children with invasively confirmed diagnosis of HPAH or CHD-PAH. Assessment of family members, pedigree analysis and systematic screening for mutations in the genes bone morphogenetic protein receptor 2 (BMPR2), ACVRL1, endoglin, SMAD1, SMAD5, and SMAD9 were performed.

Results: We included 19 children with HPAH (6.3±4.7 years) and 11 with CHD-PAH (7.2±4.5 years). Two Mutations in BMPR2 and ACVRL1, respectively, and 3 not yet described unclassified sequence variants (ACVRL1 n=1; SMAD9 n=2) were found in HPAH children. One ACVRL1 mutation has not been described before. In CHD-PAH patients 1 BMPR2 mutation and 2 unclassified sequence variants (1 endoglin n=1, BMPR2 n=1) were found. Carriers of genetic mutations and sequence variants with pathologic functional impact had a significantly lower PVR (92.66±25.50, p<0.003) than patients with no mutation or silent sequence variants.

Conclusion: Mutations and unclassified variants with functional impact in different TFG signalling genes occurred in 21% of HPAH patients and 27.3% of patients with CHD-PAH and may influence the clinical status of the disease. Therefore, genetic analysis in children with various forms of PAH is important.
Prevalence and the long-term coronary risks of patients with Kawasaki disease in a general population aged younger than 40 years: a national database study

M.H. Wu. National Taiwan University Hospital, Taipei, Taiwan

Background: Patients with Kawasaki disease (KD) may develop coronary arterial lesions and subsequent coronary events. In Taiwan, the first patient was in 1976 and the annual incidence was 66/100,000 children - 5 years in 2000s. A population study from Taiwan, a country with high incidence of KD and easily accessible medical care, would reflect adequately the long-term risk.

Methods and Results: We retrieved the data of KD patients from national health insurance 2000-2010 database of Taiwan, a country with national health insurance and child health index similar to those in US. The occurrence of coronary events and interventions were identified by the respective ICD-9 codes. The prevalence of KD in population aged <40 years and <5 years was 15.68/100,000 (male:female=4.47) and 10.79/100,000, respectively. Coronary events occurred in 1254 patients (5.37%, male:female=2.19), i.e., an average annual risk of 2.4%. Among them, acute myocardial infarction occurred in 19 patients (0.081%, 18 male and 1 female) and one-third was within age 10-14 (median 15.7) years. Coronary intervention was performed by catheterization in 18 patients and by surgery in 10, with mortality at discharge being 0% and 25%, respectively.

Results: One patient developed myocarditis was performed SPE+CHDF using a combination of high-dose methylprednisolone after performing SPE+CHDF, because of refractory fraction of the subaortic ventricle, and the ascending aortic distensibility. Cardiac MRI for measurement of ejection fraction and aortic distensibility was performed before 3 months of the index event. Results: The mean age of adults with repaired TOF was 29±10.6 years and 23±4.7 years in adults with d-TGA (p=0.026). Absolute exercise capacity expressed as peakVO2 (ml/min/kg) did not differ between both groups (27.9±10.5 and 29.1±10.7, p=0.673), nor the percentage of predicted peakVO2 (76±27% and 73±20%, p=0.638). In a multivariate regression analysis with age, gender, type of congenital defect, body surface area, subaortic ejection fraction and aortic distensibility as predictors of peakVO2, the only independent predictors of exercise capacity were gender and aortic distensibility (table 1).

Table 1. Age distribution of the age at admission for cardiac catheterization, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG)

<table>
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<th>Age group (years)</th>
<th>No.</th>
<th>Percentage</th>
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<tbody>
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<td>6-10</td>
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<td>28%</td>
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<td>11-15</td>
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<tr>
<td>16-20</td>
<td>11</td>
<td>3.5%</td>
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<tr>
<td>21-25</td>
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<td>0.3%</td>
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<tr>
<td>26-30</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>31-35</td>
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<td>0.6%</td>
</tr>
<tr>
<td>36-40</td>
<td>1</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Conclusion: This population study gave estimates that there would be one KD patient per 6000. They, particularly the males, carry long-term coronary risks since young ages.

The efficacy of plasma exchange in refractory Kawasaki disease

K. Kozumi, H. Kise, N. Katsumata, Y. Hasebe, K. Sugita, M. Hoshiai. Department of Pediatrics, University of Yamashita, Faculty of Medicine, Chuo, Yamashita, Japan, Japan

Background: Kawasaki disease (KD) is a generalized vasculitis of unknown etiology that occurs predominantly in infant and children. The important feature of this disease is coronary arterial lesions (CALs) such as dilatation, aneurysm and stenosis. The inflammatory index of KD is intravenous immunoglobulin (IVIg). However, some patients do not respond to IVIg therapy and have a high incidence of CALs. To such patients, it is important to suppress inflammation in the early phase. We examined the efficacy and safety of slow plasma exchange (SPE) pulse continuous hemodiafiltration (CHDF) for refractory KD to IVIg therapy.

Patients: Between August 2005 and October 2012, eight KD patients refractory to IVIg underwent SPE-CHDF. The median age and body weight were 2.2 years (range, 0.5 to 5.5 years) and 12.7kg (range, 6.6 to 27kg), respectively. The treatment before SPE-CHDF were as follows; second course of IVIg (2g/kg/dose) in 2 patients, second course of IVIG pulse infliximab (3mg/kg/dose) in 3 patients, initial course of IVIG pulse infliximab in one patient, initial course of IVIg pulse high-dose methylprednisolone (30mg/kg/dose) in one patient.

Methods: Daily SPE with CHDF was performed for three days. SPE was performed over six hours, using 1.2 times the circulating plasma volume of fresh frozen plasma.

Results: SPE-CHDF was performed in 8 to 15 day after onset of KD. One patient who developed myocarditis was performed SPE-CHDF using a combination of high-dose methylprednisolone after performing SPE-CHDF, because of refractory fraction of the subaortic ventricle, and the ascending aortic distensibility. Cardiac MRI for measurement of ejection fraction and aortic distensibility was performed before 3 months of the index event. Results: The mean age of adults with repaired TOF was 29±10.6 years and 23±4.7 years in adults with d-TGA (p=0.026). Absolute exercise capacity expressed as peakVO2 (ml/min/kg) did not differ between both groups (27.9±10.5 and 29.1±10.7, p=0.673), nor the percentage of predicted peakVO2 (76±27% and 73±20%, p=0.638). In a multivariate regression analysis with age, gender, type of congenital defect, body surface area, subaortic ejection fraction and aortic distensibility as predictors of peakVO2, the only independent predictors of exercise capacity were gender and aortic distensibility (table 1).

Table 1

<table>
<thead>
<tr>
<th>PeakVO2</th>
<th>Coefficient</th>
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<td>1.31</td>
<td>0.055</td>
<td>4.52</td>
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<tr>
<td>-0.21</td>
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</tr>
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<td>-0.30</td>
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<td>0.06</td>
</tr>
<tr>
<td>0.02</td>
<td>0.000</td>
<td>0.56</td>
</tr>
<tr>
<td>2.3</td>
<td>0.000</td>
<td>1.67</td>
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</table>

Conclusion: Impaired aortic distensibility and its impact of ventriculo-arterial coupling predicts exercise capacity in adults with repaired congenital defects, independent of the ejection fraction of the underlying ventricle.
Exercise capacity and quality of life in congenital heart disease / Aortic valve disease: basic

P5553 Exercise capacity in adult patients with Fontan circulation is not limited by myocardial performance

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Purpose: The specific cardioregulatory mechanisms limiting exercise performance in the Fontan circulation are not well understood. Our study investigates a mixed group of adults with Fontan circulation as a result of different congenital heart malformations.

Methods: Thirtythree adults with Fontan type palliation were investigated by echocardiography at rest and during recumbent bicycle exercise until exhaustion. Tissue Doppler analysis was performed from recordings of the ventricular free wall and AV-anulus. The following parameters were analyzed: peak diastolic flow velocity through the AV-valve (E), Tei index, ratio of systole/diastole duration, NYHA class, peak systolic AV-anulus velocity (SV2), peak early diastolic AV-anulus velocity (E'), E/E'. A correlation analysis between these parameters (as baseline/maximal/increase percentage) and measurements from the echocardiography (SV, SV2, SV3, SV4, SV5, SV6, SV7) were varied. Tei index and NYHA class were also measured. All data is shown as "% of reference".

Results: VO2peak was predicted as percentage of defined reference, and the respiratory equivalent at aerobic threshold (VE/VO2) index.

Conclusions: Exercise capacity was low in all individuals. Respiratory efficiency (VE/VO2) was abnormal for all individuals, consistent with high dead space ventilation or abnormal pulmonary vascular function. Exercise capacity and respiratory efficiency were not correlated to systolic or diastolic cardiac function. Diastolic response was more heterogeneous than systolic.

P5554 Declining health related quality of life with age in 2076 patients with congenital heart disease

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Objective: Health-related quality of life in patients with congenital heart disease (CHD) is good or even better than in comparison to healthy peers. However, this was shown in younger patient groups and data from older patients are lacking. This cross-sectional study examined the health-related quality of life of older patients with CHD and compared them with younger age groups.

Patients and Methods: From July 2001 to December 2011, 2076 patients (916 female, 28.2±10.4 years, range 14-75 years) with various kinds of CHD underwent a quality of life assessment with the SF-36 questionnaire in our Institution as part of their routine follow-up examination. As quality of life declines with age in healthy subjects, all data is shown as % of reference.

Results: Self-reported quality of life was good, but with worse results in females. 104% ± 15% vs. 100% ± 18% (p < 0.001) and mental component summary (MCS) 104% ± 17% vs. 99% ± 20% (p < 0.001). MCS declines from 104% in patients younger 20 years, to 105% in patients age 20 to 30 years, 99% in patients aged 30 to 40 years, 97% in patients 40 to 50 years, and 84% in patients older than 50 years. Whereas the decline in the more mental domains of quality of life (MCS) was minor from 104% in patients younger 20 years, to 101%, 99%, 97% and 96% respectively.

Conclusions: Health-related quality of life in patients with CHD declines continuously with age. That decline was more prominent in the physical domains of health related quality of life. Preserving exercise performance in older patients with CHD remains a challenge to obtain good quality of life in those patients.
Hypofibrinolysis and aortic stenosis progression in human stenotic aortic valves as a source of fibroblasts and macrophages. The aim of the study was to investigate whether hypofibrinolysis might be involved in AS progression.

Methods: A total of 74 patients with AS (43M, 31F; aged 62.7±10.7 years, mean transvalvular gradient, 59.4±21 mmHg) scheduled for isolated valve replacement were studied. Transcutaneous fibrin clot lysis time (CLT) as a measure of fibrinolytic activity. These factors were present in the tissue, which at least in part, may be linked to increased sclerostin serum levels. IHC and PCR data demonstrated an association between the presence of AVC and aortic valve sclerosis production and deposition indicating a role of the valve in the calcification process.

Results: In AS patients CLT was positively correlated with the aortic valve leaflet thickness (r=0.47, p=0.003) and the degree of valve calcification (r=0.65, p<0.00001). Positive correlations of both circulating and locally expressed PAI-1 with CLT (r=0.42, p=0.04; r=0.39, p=0.03, respectively) were observed. Unexpectedly, we found that AS patients treated with statins on a long-term basis (n=21, 27%) when compared to those not taking these agents (n=53, 72%) had shorter CLT indicating accelerated fibrinolysis, measured by CLT (100 [IQR 54-147] vs 120 [IQR 70-154] min, p<0.041). There were positive correlations of valvular Fn, prothrombin and PAI-1 expression with CLT (r=0.36, p=0.008; r=0.32, p=0.01, r=0.4, p=0.047, respectively).

Conclusions: In patients with advanced AS, CLT is positively correlated with large Fn amounts, present within the valve leaflets and the levels of plasma and valvular PAI-1. We speculate that hypofibrinolysis may contribute to the development and/or progression of AS in humans. This study is the first to show that impaired efficiency of fibrin clot lysis typical of atherosclerotic vascular disease is associated with pathologic valvular abnormalities observed in AS.

Hypofibrinolysis and aortic stenosis progression in humans: associations with plasminogen activator inhibitor-1

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Purpose: A role of fibrinolysis in the pathogenesis of aortic stenosis (AS) is unknown, although fibroinolysis proteins have been detected in aortic stenotic valves. The aim of this study was to investigate whether hypofibrinolysis might be involved in AS valves.

Methods: A total of 74 patients with AS (43M, 31F; aged 62.7±10.7 years, mean transvalvular gradient, 59.4±21 mmHg) scheduled for isolated valve replacement were studied. Transcutaneous fibrin clot lysis time (CLT) as a measure of fibrinolytic activity. These factors were present in the tissue, which at least in part, may be linked to increased sclerostin serum levels. IHC and PCR data demonstrated an association between the presence of AVC and aortic valve sclerosis production and deposition indicating a role of the valve in the calcification process.

Results: In AS patients CLT was positively correlated with the aortic valve leaflet thickness (r=0.47, p=0.003) and the degree of valve calcification (r=0.65, p<0.00001). Positive correlations of both circulating and locally expressed PAI-1 with CLT (r=0.42, p=0.04; r=0.39, p=0.03, respectively) were observed. Unexpectedly, we found that AS patients treated with statins on a long-term basis (n=21, 27%) when compared to those not taking these agents (n=53, 72%) had shorter CLT indicating accelerated fibrinolysis, measured by CLT (100 [IQR 54-147] vs 120 [IQR 70-154] min, p<0.041). There were positive correlations of valvular Fn, prothrombin and PAI-1 expression with CLT (r=0.36, p=0.008; r=0.32, p=0.01, r=0.4, p=0.047, respectively).

Conclusions: In patients with advanced AS, CLT is positively correlated with large Fn amounts, present within the valve leaflets and the levels of plasma and valvular PAI-1. We speculate that hypofibrinolysis may contribute to the development and/or progression of AS in humans. This study is the first to show that impaired efficiency of fibrin clot lysis typical of atherosclerotic vascular disease is associated with pathologic valvular abnormalities observed in AS.

Enhanced osteoclast-burden and its correlation to the stenosis severity in end-stage human aortic valve stenosis

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Purpose: Several studies have described osteogenic signaling cascades in aortic stenosis. For example, BMP-related pathway have been observed in calcified regions of excised human aortic valves. In contrast, there is a little conclusive information on the osteoclasts activity, their relation to stenosis severity and the interplay between osteoblasts and osteoclasts. The bone remodeling in calcified aortic valves has its origin in microfractures at multiple sites of the valve, at which osteoclasts are the first cells recruited followed by osteoblasts, together building up a complex system: a bone multicellular unit. To date, no previous study assessed the spatial distribution of bone turnover containing genes with osteoinductive and osteoresorptive potentials obtained from different parts of calcified aortic valve tissue and their relation to the clinical stenosis severity.

Methods: Human stenotic aortic valves were obtained from 46 patients undergoing aortic valve replacement after macroscopic dissection to divide topographically normal, thickened and calcified parts of the valves. mRNA was extracted followed by quantitative real-time PCR to correlate the transcript levels of genes with osteoclast activity (BMP-2, BMP-6, Runt2, osteocalcin) and those with osteoresorptive functions (TRAP, RANKL, RANK, OPG, MMP-9, osteopontin=OPN) in a multivariate analysis to the stenosis severity.

Results: Firstly, the transcript levels of the genes taking part in osteoclast differentiation and activity exhibited significantly elevated levels in the calcified part of the valvular tissue such as TRAP: 5.08±1.6-fold, p<0.001; RANKL: 8.6±4.2-fold, p<0.001; RANK: 1.98±0.78-fold, p<0.015; OCN: 21.7±4.6-fold, p<0.001. Secondly, multiple regression analysis in the thickened part of the valvular tissue showed a significant influence of the linear combination of the mRNA levels of osteoclast-related genes as independent variables: TRAP (P=0.008), RANKL (P=0.002), RANK (P=0.001) and OCN (P=0.028) which remained significantly correlated with the dependent variable: the aortic valve area indexed for the body surface area.

Conclusions: Collectively, these findings suggest that in the end-stage disease the osteoclast-burden is more pronounced with its structural, compositional and clinical consequences, than the active bone formation.

Calcification begets calcification of the aortic valve, independent of vitamin D or parathormone level

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Purpose: In calcific aortic valve disease, the early lesion is similar to the atherosclerotic plaque, but further active calcification with features of skeletal bone formation prevails. Parathormone (PTH) and vitamin D-endocrine system are the principal regulators of the calcium pool and bone mineral turnover. We aimed to assess the association of vitamin D and PTH plasma and serum levels, respectively, with rate of aortic valve calcification in patients with initially normal or sclerotic aortic valve and significant coronary artery disease.

Methods: In prospectively enrolled consecutive patients with angiographically significant coronary artery disease and nonstenotic, normal or sclerotic aortic valve, we assessed calcium metabolism parameters including fasting serum intact (i) PTH, vitamin D level, and using multidetector computed tomography, aortic valve calcium (AVC) score at baseline and after 3-years follow-up. Annualized AVC score change was calculated in each patient, and independent predictors of this parameter were sought.

Results: We included 115 patients (91 males, age 66±6 years) who completed the follow-up (36±2 months). The baseline AVC score was zero in 40 patients and 0.185±0.1 in the remaining 75 patients. Between these groups there were no significant differences in the age, levels of iPTH (39±18 pg/ml), vitamin D (44±18 nmol/l), serum calcium (2.39±0.11 mmol/l), phosphorus (1.14±0.2 mmol/l), creatinine (95±19 mg/dl), high sensitivity C-reactive protein (4.6±4.4), body mass index (29.3±3.9 kg/m²), occurrence of hypertension, smoking, diabetes, or dyslipidemia. The annualized AVC score change was higher in those with baseline AVC score>0 than in those with baseline AVC score=0 (18.35 vs 4.10 mm²/year, p=0.011).

Only the baseline AVC score independently predicted the annualized AVC score change (p=0.04, 95% CI 0.02-0.05, p<0.001).

Conclusion: Baseline AVC score was the only independent predictor of the rate...
Decreased NOX4 levels associate with cardiac remodeling and impaired function in human aortic stenosis

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Purpose: The NADPH oxidases are a key family of reactive oxygen species (ROS)-producing enzymes. Depending on the NOX subunit, the NADPH oxidases may differentially contribute to pathophysiology. Recent animal studies suggest a protective role of NOX4 on the cardiac histomorphological and functional changes associated with pressure overload. Data on human myocardial NOX4 is lacking. We aim to evaluate NOX4 in the heart of patients with aortic stenosis and its association with the histomorphological profile and cardiac function.

Methods: Left ventricular biopsies from 34 patients with aortic stenosis were obtained during surgery for valve replacement. Cardiac function was assessed by echocardiography. Cardiac samples from 9 subjects deceased of non-cardiovascular diseases were also analysed. NOX4 localization was evaluated by immunohistochemistry and quantified by western blot. Myocardial capillary density (von Willebrand staining), fibrosis (Sirius red), apoptosis (TUNEL) and cardiomyocyte diameters and area (Masson’s Trichrome) were also assessed. Endothelial nitric oxide synthase (eNOS) messenger RNA was quantified by real time PCR.

Results: NOX4 was highly expressed in cardiomyocytes and also in endothelial cells. NOX4 levels were 5-fold reduced in patients compared to controls (N=91, p<0.004). In patients, NOX4 levels correlated with parameters of cardiac function (ejection fraction r=0.353, P=0.041; midwall fractional shortening r=0.355, P=0.046) and deceleration time (r=-0.345, P=0.046). Capillary density was reduced in patients compared to controls (r=0.856, P<0.001). Interestingly, in patients, NOX4 levels directly correlated with capillary density (r=0.389, P=0.023), which in turn associated with cardiac function. NOX4 levels directly correlated with eNOS expression (r=0.424, P=0.002). Decreased NOX4 levels also associated with greater apoptosis severity (-2.261, P=0.023) and cardiomyocyte transversal diameter (r=0.406, P=0.019), but not with fibrosis.

Conclusions: NOX4 levels seem to be reduced in cardiac chronic pressure overload in humans. The deficiency of NOX4 may have a negative impact in cardiac function. This may be in part due to changes in cardiac histomorphology, including reduced capillarization, reduced cardiomyocyte size and increased cardiomyocyte death.

Aortic valve disease: basic / Infective endocarditis

ApoA-1 mimetic peptide infusions induce aortic valve stenosis in ApoE−/− and Wrn delta hel/delta hel mice

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Purpose: We have previously shown that apolipoprotein A-I (Apo-A-I) infusions promote regression of aortic valve stenosis (AVS) in a rabbit model. The aim of the present study was to determine the effects of Apo-A-I mimetic peptide infusions in mice models of AVS and explore the underlying mechanisms for the benefits.

Methods: Fifty-seven hypercholesterolemic apolipoprotein E-deficient (ApoE−/−) mice and 19 mice with a deletion in the Werner progeria syndrome gene (Wrn Δhel/Δhel) received high-fat diets (and vitamin D2 for ApoE−/− mice) only during 20 weeks. Mice were randomized to receive saline (placebo group, n=29 for ApoE−/− and n=9 for Wrn Δhel/Δhel mice) or ApoA-I mimetic peptide infusions (ApoA-I treated group, 100 mg/kg, n=28 for ApoE−/− and 50 mg/kg, n=10 for Wrn Δhel/Δhel mice), 3 times per week for 4 weeks. Serial echocardiograms and post mortem valve histology were performed to evaluate the effects of ApoA-I mimetic peptide infusions on aortic valve stenosis.

Results: Aortic valve area (AVA) was improved at the end of treatment in both ApoE−/− and Wrn Δhel/Δhel mice treated with ApoA-I mimetic peptide infusions compared to placebo (ApoE−/−: 0.624 [0.606-0.641] vs 0.587 [0.569-0.605] mm², p=0.0039; Wrn Δhel/Δhel: 0.664 [0.640-0.686] vs 0.597 [0.574-0.621] mm², p=0.0002). Histological analysis revealed that the maximal thickness of aortic sinus walls was lower in valves from ApoA-I treated ApoE−/− mice (61.5±7.3 vs 69.1±11.8 μm for placebo, p=0.016). In ApoE−/− mice, type I collagen content was lower in the ApoA-I mimetic peptide treated mice compared to placebo (74.4±8.2 vs 81.5±7.5%, p=0.011). This finding was consistent with reduced total collagen content in aortic valves of ApoA-I treated Wrn Δhel/Δhel mice compared to placebo (89.4±3.2 vs 90.6±4.2%, p=0.023). AVA values from ApoE−/− mice calculated with our 3D computer model were similar to those observed with echocardiography (respectively 0.572 and 0.587 mm² for placebo and 0.609 and 0.624 mm² for ApoA-I treated mice).

Conclusions: ApoA-I mimetic peptide infusions lead to regression of AVS in murine models. Treatment is associated with reduced aortic valve fibrosis and decreased aortic root thickening leading to improved aortic valve opening. The potential benefits of HDL-based therapies should be evaluated in patients with AVS.

INFECTIVE ENDocardITIS

Prognostic role of positive blood cultures after 48-72 hours from the initiation of the antibiotic treatment in left-sided infective endocarditis

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Introduction: Persistent infection, one of the most feared complications of left-sided infective endocarditis (LSIE) is defined in the new European guidelines as persistent fever and positive blood cultures after 7-10 days of antibiotic treatment. This cut-off point is arbitrary, and probably too long. It would be very important to anticipate the development of persistent infection. In this regard, blood cultures after 48-72 hours from the initiation of the antibiotic treatment might play a role. Our objectives are to analyze the prognostic importance of persistent positive blood cultures after 47-72 hours from the initiation of the antibiotics in patients with LSIE and study its relationship with persistent infection.

Patients and methods: We repeated blood cultures after 47-72 hours of the initiation of the antibiotic treatment in 407 patients with LSIE of a total of 692 episodes considered as isolated LSIE from 1996 to 2011. We performed a logistic regression model to determine the risk factors of in-hospital mortality in these 407 patients.

Results: Half of the patients with positive blood cultures after 48-72 hours from the initiation of the antibiotic treatment developed persistent infection and their mortality was very high (45%). Patients with non viridans Streptococci prosthetic valve endocarditis in the left position had a higher risk of developing this situation. We found age (OR: 1.026; 95% CI: 1.007-1.046), Staphylococcus aureus and methicillin-resistant coagulase-negative staphylococci infection (OR: 10.2; 95% CI: 3.5-30), community-acquired infection in the subject (OR: 5.6; 95% CI: 1.8-16), and the presence of a pacemaker (OR: 6.4; 95% CI: 2.1-18) as factors significantly associated with high in-hospital mortality.

Conclusions: The presence of positive blood cultures after 48-72 hours from the initiation of the antibiotic treatment is an independent risk factor for in-hospital mortality in patients with LSIE. Patient with this condition have two-fold more risk of death than the rest of the patients. This additional information might be very useful in the early risk stratification of patients with LSIE.
Dramatic improvement of prognosis with surgery in patients with endocarditis and septic shock

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Objectives: To describe the clinical characteristics, and evolution of patients with infective endocarditis (IE) and septic shock (SS), and to analyze if surgery improves their prognosis.

Methods: We studied 894 consecutive episodes of IE that were recruited prospectively at three tertiary referral centers between 1996 and 2011. They were classified into 2 groups: Group I (N=156), episodes of IE that had SS, and Group II (N=738), those who did not.

Results: Age (61±16) and gender distribution were similar in both groups. Mortality was more frequent in patients from Group I: diabetes mellitus (29.5% vs 17.6%; p=0.001), chronic renal failure (15.4% vs 9.3%; p=0.023), cancer (15.4% vs 8.3%; p=0.006), and chronic obstructive pulmonary disease (12.2% vs 7.1%; p=0.033). Acute onset of symptoms (less than 15 days) was more common in patients with SS (63.2% vs 44.8%; p=0.001). The presence of vegetations (90.4% vs 79.7%; p=0.002) as well as perianural abscesses (25% vs 17.1%; p=0.020) were more frequently found in Group I. Location of infection was similar in both groups. S. aureus (42.5% vs 16.2%; p=0.001), and Gram negative bacilli (7.5% vs 3.7%; p=0.048) were more frequently isolated in Group I, while S. viridans (2.5% vs 4.0%; p=0.001), and Coagulase negative staphylococci (10.4% vs 18.4%; p=0.025) were more common in Group II. During hospitalization, development of heart failure (69.9% vs 49.7%; p=0.001), acute renal failure (30.1% vs 16.9%; p=0.001), and liver (1.8% vs 0.3%; p=0.040) and limb (12.2% vs 7.3%; p=0.044) emboli were more common in patients with SS. Patients from Group I underwent surgery less frequently (44.9% vs 57.9%; p=0.003) and had a high mortality rate (73.1% vs 11.9%; p=0.001). Among patients with SS, those who underwent surgery (n=70) had lower mortality than those who received medical treatment alone (n=86); (64.3% vs 80.2%; p=0.026).

Conclusions: Although in patients with IE and SS the presence of comorbidity. S.aureus infection, perianural complications, and mortality rates that remind that of left-sided IE. In patients with CRF, IE had a scarce clinical expression, and is understood disease which encompasses very different groups of patients: intravenous drug users (IDUs) (group 1), intra-cardiac devices carriercarr (pacemaker and defibrillator) (group 2) and patients without any of these conditions (group 3). Whether the profile of these groups is different has never been studied. The aim of this work is to describe and compare the clinical, microbiological, echocardigraphic and outcome features of right-sided IE in these three groups.

Methods: Among 866 episodes of IE consecutively diagnosed in three tertiary centers from 1996 to 2011, 135 were right-sided (15.5%). Of them, 39 (29%) appeared in group 1, 59 (44%) in group 2 and 77 (27%) in group 3. An analysis of 85 clinical, epidemiological, microbiological, echocardiographic and outcome variables has been performed.

Results: Differences in the most relevant variables are specified in the table.

Conclusions: Right-sided IE can be classified into three types (IDUs, intracardiac devices carriers and non-IDUs non intracardiac devices carriers), as there are relevant clinical, microbiological, echocardiographic and outcome differences between them. The worse prognosis is that of non-IDUs patients without intracardiac devices, with mortality rates that remind that of left-sided IE.

Pacemaker and ICD device related infections with lead and/or valve vegetations in the TEE - Diagnosis and treatment of a serious problem


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Introduction: With the increasing number of device implantations in patients with...
high comorbidity the number of device-related infections has been growing in the last few years. The device related Infection is a serious and life threatening complication after pacemaker and ICD implantation. Both the diagnosis and optimal treatment of such infections pose a big problem in tertiary care centers.

Methods: We examined retrospectively 327 consecutive patients (≥68.7 years, 252 (77.5%) who were referred to us with a device-related infection treated between January 2004 and December 2011. The diagnosis was based on either pocket erythema, erosion, abscess, persistent bacteremia and/ or positive blood culture or endocarditis with or without vegetation on the lead and/or cardiac valve.

Results: Of 327 patients with proven device-related infection, 203 patients had a pacemaker (4 biventricular systems), 122 patients an ICD (31 biventricular systems) and 2 patients had an OPTIMIZER®. 215 of these patients (66%) underwent a prior replacement. The average delay after replacement was 18 months. Only 112 (34%) patients had an infection after initial implantation. The average delay was 11 months. Valvular or lead vegetations were detected by transesophageal echocardiography to differentiate between vegetation, thrombus or scar tissue to identify an infection in order to choose the appropriate explantation technique and to avoid risky open heart surgery.

Conclusions: "True" versus "aborted" culture-negative infective endocarditis

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Purpose: To analyze the impact of antibiotic treatment prior to blood culture extraction in infective endocarditis (IE) and to point out the differences in epidemiology, clinical features, diagnosis and prognosis between "true negative" (TN) and "aborted" (A) IE.

Methods: We analyzed 106 consecutive cases of IE with negative blood cultures recruited prospectively at three tertiary hospitals between 1996 and 2011. These patients were divided in two groups: Group I (N=36) cases of IE with negative blood cultures who did receive antibiotic treatment during the 15 days before blood culture extraction (A); and Group II (N=54) cases who did not TN. Sixteen episodes were excluded because they did not receive any antibiotic treatment. 74.5% of all cases had "definite endocarditis" according to Li criteria, and 25.5% (n=21) were "possible endocarditis" (24 had 1 major and 1 minor criteria, and 5 had three minor criteria).

Results: Age, gender distribution and comorbidities were similar in both groups. We found a greater number of community acquired IE (57.1% vs. 79.2%, p=0.026) and diabetics (5.6% vs. 24.1%, p=0.021) in Group II. Time from symptoms to diagnosis was similar in both groups (average 33.4 days (±33.4) vs. 39.7 days (±35), p=0.661). There were no differences upon the portal of entry and clinical presentation. The presence of fever prior to admission was more frequent in Group I (7.8% vs. 54%, p=0.021). Attending to echocardiographic features, vegetation size (14.7mm vs 14.6mm, p=0.93) and presence of perianular complications were similar in both groups. During hospitalization, complications (heart failure, renal failure, persistent sepsis) occurred similarly in both groups. There were no differences in the need of surgery and mortality in the two groups.

Conclusions: The use of previous antibiotic therapy does not imply a delay in diagnosis neither a worse prognosis in culture-negative IE with respect to those who do not receive antibiotic treatment previous to blood culture extraction. Regarding to clinical profile, diagnosis and prognosis, there were no differences between TNIE and AIE.

The value of FDG-PET/CT in the diagnostic work-up of extra cardiac infectious manifestations in infectious endocarditis

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Purpose: Infectious Endocarditis (IE) is a serious condition with a high morbidity and mortality. The optimal management of IE depends not only on correct antibiotic therapy, but involves identification of the portal of entry and detection of extracardiac infectious manifestations. To discover the latter a 18F-FDG-PET/CT examination has been proposed. However, the diagnostic value of a PET/CT in this setting remains unresolved, thus, we wish to assess the usefulness of a PET/CT study in patients with IE as a supplemental method to standard work-up in evaluating IE.

Methods: A retrospective cohort study of IE patients admitted to our Department from 2008 to 2010, which were exposed to a 18F-FDG-PET/CT scan. Findings were assessed in relation to the routine work-up, which simultaneously served as the "gold standard".

Results: 72 patients were included, average age was 63 years and 71% were males. Staphylococci (40%) and streptococci (29%) were the most frequent pre-putative microorganisms. Patients from Group II (N=575), those without this complication. In-hospital mortality was 15%. Overall, 18F-FDG-PET/CT had a sensitivity, specificity, PPV, NPV, and accuracy of 66%, 95%, 53%, 97% and 90%, respectively, reflecting both cardiac and extracardiac complications. High positive predictive value, high high physiological uptake, and organs with presumable small lesion beyond the limit of PET detection (the brain, heart, intestinal, kidneys, eyes and teeth), the corresponding values increased to 90%, 94%, 47%, 99%, and 93%, respectively. By only focusing on the aforementioned organs the values decrease to 41%, 98, 70%, 93%, and 91%, respectively. Subgroup analysis comparing 18F-FDG-PET/CT scans performed early (n=37) and late (n=35) in the diagnostic work-up showed no significant difference.

Conclusion: 18F-FDG-PET/CT may be an important diagnostic tool in detecting extra cardiac infections but must be evaluated carefully, particularly when considering organs with a known high physiological uptake of glucose.

Clinical profile of patients with endocarditis and central nervous system embolisms

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Objectives: To describe epidemiological, clinical, microbiological, and prognostic characteristics of episodes of left-sided infective endocarditis (IE) complicated with symptomatic central nervous system (CNS) embolisms.

Methods: We analyzed 724 consecutive episodes of left-sided IE that were re- cruited prospectively at three tertiary referral centers between 1996 and 2011. They were classified into 2 groups: Group I (N=149), episodes of IE complicated with CNS embolisms, and Group II (N=575), those without this complication.

Results: Age (62±15) and gender distribution were similar in both groups. Re- lative to portal of entry, CNS embolism was more frequent in Group I (4% vs 1.6%; p=0.090), while chronic obstructive pulmonary disease (3.4% vs 9.8%; p=0.012) and previous cardiac disease (59.1% vs 69.2%; p=0.05) were more common in Group II. Patients from Group I had more CNS complications prior to admission (69.1% of episodes from Group I, CNS embolisms were already present at admission). The percentage of patients that underwent anticoagulation was higher in Group I (54.7% vs 45.4%; p=0.005) in Group II (N=575), those without this complication. Periannular complications and vegetation size were similar in both groups. No differences were found in the development of heart failure, acute renal failure, and septic shock during hospitalization. Spleen (20.8% vs 5.9%; p<0.001), kidney (5.4% vs 1.2%; p=0.005) and limb (20.6% vs 6.6%; p<0.001) emboli were more frequent in Group II. The percentage of patients that underwent cardiac surgery was similar in both groups. Mortality (37.6% vs 27.1%; p=0.012) was higher in Group II.

Conclusions: Patients with IE complicated with CNS embolisms have a more virulent microbiological profile. These patients had more systemic embolisms and in-hospital mortality was higher.
In-hospital and long-term outcome of left-sided infective endocarditis (LSIE). A prospective observational study in a 12-year contemporary cohort of patients

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Purpose: Despite improvements in medical and surgical treatment, LSIE continue to be associated with high rates of morbidity and mortality. The aim of this study was to describe in-hospital mortality and long-term outcome of LSIE patients.

Methods: Prospective observational cohort study in a referral hospital between January 2000 and December 2011. Patients with isolated right-sided endocarditis were excluded. Only the first episode of LSIE recorded for an individual patient was included in the analysis. This cohort consisted in 337 cases of infection on native valves (NVIE), and 101 on prosthetic valves (PVIE). Patients were followed-up until death, relapse, or recurrence.

Results: The median age was 66 years (IQR 52-75 years), 65% were male, 39% had been transferred from different community hospitals, and 31% acquired the infection in the healthcare setting. The median Charlson index was 2 points (IQR 0-3 points). Aetiology: streptococci 37%, staphylococci 33% (23 out of 99 S. aureus strains were methicillin-resistant), enterococci 14%, and other microorganisms 16%. At least one complication was observed in 83% of cases, being congestive heart failure the most common (47%). Although cardiac surgery was indicated in 73%, it was only performed in 49%. Overall in-hospital mortality was 29% (26% NVIE, and 39% PVIE), 80% due to causes directly related to infection. The median length of follow-up in patients alive at discharge was 3.2 years (IQR 1.4-5.8 years). For the overall series, the actuarial survival at 1 year was 60% (64% NVIE, 49% PVIE), and at 2 years 56% (59% NVIE, 43% PVIE). For those alive, the actuarial survival at 1 year was 86% (87% NVIE, 83% PVIE), at 2 years 79% (81% NVIE, 72% PVIE), and at 5 years 68% (71% NVIE, 51% PVIE). Relapse occurred in 2.2% (95CI 1.3-3.5%), a median of 25 days after finishing treatment (IQR 7-42 days). Eight patients (2.6%, 95CI 1.3-5.5%) suffered a recurrence during follow-up, with an incidence density of 0.0067 episodes per patient-year (95CI 0.0029-0.0133).

Conclusions: LSIE is a disease with a high rate of in-hospital and long-term mortality, especially when affecting prosthetic valves. However, relapse and recurrence are uncommon complications.

E- and P-selectins and haemathologic parameters in patients with clinically silent and overt cerebral embolism in the course of infective endocarditis

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Strokes are common complication of infective endocarditis (IE). Usually they are clinically overt. Sometimes embolism causes small focal brain damage not enough to develop clinical symptoms-silent embolism. They can be identified by CT/MRI scan. Haematology variables and inflammation-induced procoagulation activity changes in IE may play an important role in thromboembolic complications.

Aim: To correlate haematological parameters, CRP, E-, P-selectins levels with cerebral embolism in the course of IE.

Material and Methods: The study group: 65 pts (44 male), mean age 52 yrs (range 17-81 yrs) with IE diagnosed according to Duke criteria. There were 39 pts with native, 26 pts with prosthetic valve IE. In 29 pts IE was localized on aortic valve, 24 - mitral, 7 - both, 2 - tricuspid, 3 - other localisation. Neurological state assessment and brain imaging (MRI/CT) were performed. After MRI/CT brain imaging the study group was divided into 3 subgroups: with overt cerebral embolism (OCE) - 13 pts, with silent cerebral embolism (SCE) - 24 pts, without cerebral embolism (WCE) - 28 pts. Blood samples for CBC, levels of CRP E- and P-selectins evaluation were drawn 3-times: on the 1st (establishment of the diagnosis of IE), 2nd, 5th day.

Results: There were no differences in platelet count in pts with cerebral embolism (CE=OCE+SCE) and WCE (257±107G/l vs 243±80G/l, p=NS) as well as in SCE and OCE pts (259±110G/l vs 253±107G/l, p=NS). There were elevated CRP levels in pts with CE=OCE compared to WCE pts (7.6±5.8mg/dl vs. 4.6±2.9mg/dl, p=0.03), but in the univariate logistic regression model CRP was not an independent risk factor for risk of embolism. No differences between CRP level in SCE and OCE pts were found (7.3±5.5mg/dl vs. 8.1±5.5mg/dl, p=NS). Concentrations of P-selectin were elevated in pts with CE as compared to WCE pts (27-280 ng/ml, mean 71.33±44.69 vs. 17.8-119 ng/ml, mean 50.94±22.05, p=0.01) as well as in SCE vs WCE pts (29-148 ng/ml, mean 67.83±30.2 vs 17.8-119 ng/ml, mean 50.94±22.05, p=0.02). There were no differences in E-selectin levels in CE and WCE pts (15-194ng/ml, mean 72.19±44.28 vs 20-138 ng/ml, mean 56.69±33.87, p=NS), and in SCE and WCE pts (22-180ng/ml, mean 66.31±39.02 vs 20-138 ng/ml, mean 58.69±33.87, p=NS).

Conclusions: Elevated P-selectin levels can determine patients with high thromboembolic risk, both clinically overt and silent. Higher CRP level may indicate a more severe inflammatory reaction. CRP has an inhibitory effect on platelet aggregation. Supposedly high levels of CRP could affect the balance of coagulation and platelet aggregation in vegetations, making them more fragile.

Native valve infective endocarditis. The healthier the valve, the worse the prognosis

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Objectives: To describe epidemiological, clinical, echocardiographic, microbiological, and prognostic differences between patients with left-sided infective endocarditis (IE) and apparently normal valves, and those with native pathological valves.

Methods: We analyzed 895 consecutive episodes of IE, 424 of whom isolated left-sided non-prosthetic IE. They were recruited prospectively at three tertiary referral centers between 1996 and 2011 and classified into 2 groups: Group I (N=179), episodes of IE in ‘apparently’ normal valves, and Group II (N=245), episodes in pathological valves.

Results: Patients in Group I were younger (56±15 vs 64±15, p=0.001), without differences in gender. Comorbidity: alcoholism (12.8% vs 8.6%, p=0.028) was more frequent in Group I versus chronic anemia (15.6% vs 23.6%, p=0.040) was more common in Group II. The most frequent clinical presentations in Group I were fever (83.2%), cardiac symptoms (40.8%), and constitutional syndrome (35.2%). Electrocardiographic findings: new 2nd and 3rd degree atrio-ventricular block (0% vs 2.5%, p=0.043) and left bundle-branch block (1.1% vs 4.9%, p=0.034) were more common in Group II. The presence of vegetations (90.9% vs 86.5%; p=0.015) was more frequently found in Group I. Microbiological profile: S. aureus (25.3% vs 15%; p=0.009), and S. bovis (8.4% vs 2.9%; p=0.011) were more frequently isolated in Group I, while Coagulase Negative Staphylococcus (6.7% vs 13.5%; p=0.027) were more common in Group II. The development of septic shock (25% vs 16.5%; p=0.031) was more frequent in patients with ‘apparently’ normal valves, and a trend towards a higher incidence of heart failure (63.7% vs 55.1%; p=0.076) was noted in this group. In addition, patients in Group I underwent surgery (58.7% vs 48.6%; p=0.040) more frequently. No clear-cut differences were found regarding in-hospital mortality.

Conclusions: Patients with IE and ‘apparently’ normal valves, were younger and had a more virulent microbiologic profile than those with IE on pathologic native valves. Although there were no statistically significant differences in in-hospital mortality, heart failure, septic shock development, and the need for surgery were higher in these patients.

New prognostic score in patients with infectious endocarditis


Purpose: Infectious endocarditis (IE) is a condition with high morbidity and mortality. Several studies have evaluated risk-predicting factors in this population; however, there are no widely accepted prognostic criteria. This study aimed to evaluate the long-term prognosis of patients with IE and determine risk-predicting factors.

Methods: Longitudinal observational study including patients with IE. Clinical and echocardiographic variables were characterized, and their association with long-term prognosis was determined.

Results: Eighty-one patients were enrolled (72% male; age 64±14 years; follow-up 22±28 months). The most common etiologic agents were Staphylococcus spp
Radiolabeled leukocyte scintigraphy in patients with a suspicion of prosthetic valve endocarditis

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Objectives: Scintigraphic with radiolabeled leukocytes has demonstrated a good accuracy for the diagnosis of prosthetic material infection in several locations. Diagnosis of prosthetic valve endocarditis (PVE) can be difficult based only on morphological aspects detected by echocardiography. The aims of this retrospective study were to test the performances of leukocyte scintigraphy (LS) for the diagnosis of PVE, the grading of extent of infection, and the evaluation of clinical outcome in patients admitted for a clinical suspicion of PVE.

Methods: LS was performed in 43 patients admitted for a clinical suspicion of PVE. Results of LS were classified as positive, with either intense or mild accumulation of radiolabeled leukocyte in the prostatic material region, or negative in absence of radiolabeled leukocyte in the prostatic region. Morphological aspects and bacteriological culture were obtained from patients who underwent cardiac surgery (n = 10). Clinical outcome was collected in patients treated medically (n = 33).

Results: From the patients with an intense signal with LS who underwent surgery (n = 6), five had an abscess confirmed during intervention. Post-operative cardiac echography of the remaining patient confirmed the presence of an abscess, which had not been visualized pre-operatively. Patients with an intense accumulation of radiolabeled leukocytes with scintigraphy and treated medically (n = 3) had a poor outcome: death (n = 1); prosthetic valve dehiscence (n = 1); recurrent endocarditis (n = 1). From the patients with a mild activity with LS (n = 5), one patient developed prosthetic valve dehiscence during follow-up with the presence of a draining abscess confirmed during surgery. None of the patients LS who underwent surgery (n = 4) had an abscess evidenced during intervention. From patients with negative LS (n = 25), none presented recurrent endocarditis after a mean follow-up of 19.9 months.

Conclusions: This retrospective study suggests that LS can help to identify cardiac abscesses and evaluate clinical outcome in patients with a suspicion of PVE.
mode of anticoagulation is challenging given the differences in risks of valve thrombosis, haemorrhage and fetal complications. Our aim is to investigate pregnancy outcome in women with mechanical heart valves treated with different anticoagulant regimens.

Methods: The European Registry on Pregnancy and Heart disease is a prospective observational registry; 60 hospitals in 28 countries enrolled 1321 patients between January 2007 and June 2011, 52 pregnant women had at least one mechanical valve.

Results: Maternal mortality occurred in 2% (1 patient) due to bronchopneumonia. Hospital admission was necessary in 48% (25 patients). Mechanical valve thrombosis found to be present in 2 patients and was suspected in 2 other patients (total 8%). Heart failure occurred in 8% and hemorrhagic complications in 15% (6% major, 9% minor). In table 1 the distribution of complications observed with each anticoagulation regimen is shown. Caesarean section was performed in 42% of the patients, in 72% this was for cardiac reasons. Fetal mortality occurred in 6% (3 pregnancies) mean pregnancy duration was 37 weeks and birth weight was 2750g, an APGAR score of lower than 7 occurred in 31% of cases.

Table 1. E’ and left atrial volumes in women with CHD with and without cardiovascular complications

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No (%)</th>
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<tr>
<td>no CVC</td>
<td>25</td>
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<tr>
<td>CVC</td>
<td>45</td>
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Results: Women with CVC had lower E’ at 20 weeks gestation and higher LAV before and during pregnancy compared to women without CVC (table 1). E’ at 20 weeks gestation was associated with CVC ((OR 1.05, 95% CI 1.02-1.08, p=0.018) respectively).

Conclusions: Congenital heart disease has become the single most common indication for referral as more women with congenital heart disease reach childbearing age. Maternal complications and hospitalisation are common. Neonatal risk is also increased, mostly due to prematurity and associated complications.

P5581 Diastolic left ventricular function predicts cardiovascular outcome in pregnant women with congenital heart disease

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Purpose: Cardiovascular complications occur during pregnancy in women with congenital heart disease (CHD) and are related to left ventricular (LV) systolic function, but diastolic LV function has not been investigated.

Methods: We compared echocardiographic LV diastolic parameters (average of septal and lateral mitral annulus early diastolic velocity (E’) and left atrial volume (LAV)) between pregnant women with CHD and healthy pregnant women and related E’ and LAV to the occurrence of cardiovascular complications (CVC) in women with CHD. CVC were defined as need for urgent invasive cardiovascular procedure, heart failure, pulmonary edema, NYHA class deterioration ≥ 2 classes, arrhythmia, trumbo-embolic events, myocardial infarction, cardiac arrest, cardiac death and endocarditis. Women with twin pregnancies were excluded from analyses.

Results: We observed 213 pregnancies in 203 women with CHD and 70 pregnancies in 76 healthy women. CVC occurred in 25 (11.7%) women with CHD and did not occur in healthy women. E’ was lower in women with CHD at 20 weeks gestation compared to healthy women (10.6±1.6 cm/s, p<0.0001). LAV did not differ significantly between both groups. Women with CVC had lower E’ at 20 weeks and higher LAV before and during pregnancy compared to women without CVC (table 1). E’ at 20 weeks gestation was associated with CVC ((OR 1.05, 95% CI 1.02-1.08, p<0.0005); (OR 1.05, 95% CI 1.01-1.09, p=0.025) and (OR 1.01, 95% CI 1.01-1.08, p=0.018) respectively).

Conclusions: Different regimens of anticoagulation are still in use in pregnant patients with a mechanical heart valve. In this contemporary cohort of pregnant women with a mechanical heart valve, maternal and fetal complications occurred in almost half of the patients.

P5582 Pregnancy in women with mechanical valves: the European Registry on pregnancy and heart disease

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Background: Heart disease is an important cause of maternal mortality and morbidity in pregnancy. The use of medication during pregnancy may influence fetal outcome.

Methods: The European Registry on Pregnancy and Heart disease is a prospective observational registry; 60 hospitals in 28 countries enrolled 1321 patients between January 2007 and June 2011. We used WHO classification to stratify patients into different risk groups, with WHO class 1 indicating low risk, WHO class 2 indicating intermediate risk, WHO class 3 indicating high risk and WHO class 4 indicating a contraindication for pregnancy.

Results: Medication was used by 32% (424 patients) at some time during their pregnancy. LV pro-motion blockers (291 patients) were most frequently used followed by antitplatelet agents (155 patients), duretics (94 patients) and anti arrhythmic drugs (55 patients). The use of medication was associated with a higher WHO class. Class 2 and 3 patients had a fetal adverse event rate (combined endpoint of fetal death, birth weight < 2500 gram, APGAR score < 7 and preterm birth < 37 weeks) is shown in patients with and without medication for the total group and divided by WHO class. In patients using ACE inhibitors and angiotension II receptor blockers fetal death rate was 3%, 0%, respectively.

Conclusions: In pregnant patients with heart disease needing medication fetal death was higher, birth weight was lower and pregnancy duration was shorter possibly reflecting the greater severity of heart disease, although an interaction with the medication cannot be excluded.

P5583 Medication during pregnancy in women with heart disease: the European registry on pregnancy and heart disease

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Background: Coronary artery disease 6 (5) Congenital: Transposition (5), Tetralogy (10), Shunts (15), Coarctation (4), Cardiomyopathy: Hypertrophic (4), Dilated (12), Myocarditis (1) 17 (14) Other Other 3 0 0 33 0 33

Results: Medication was used by 32% (424 patients) at some time during their pregnancy. LV pro-motion blockers (291 patients) were most frequently used followed by antitplatelet agents (155 patients), duretics (94 patients) and anti arrhythmic drugs (55 patients). The use of medication was associated with a higher WHO class. Class 2 and 3 patients had a fetal adverse event rate (combined endpoint of fetal death, birth weight < 2500 gram, APGAR score < 7 and preterm birth < 37 weeks) is shown in patients with and without medication for the total group and divided by WHO class. In patients using ACE inhibitors and angiotension II receptor blockers fetal death rate was 3%, 0%, respectively.

Conclusions: In pregnant patients with heart disease needing medication fetal death was higher, birth weight was lower and pregnancy duration was shorter possibly reflecting the greater severity of heart disease, although an interaction with the medication cannot be excluded.
CVD Development, anatomy and Pathology

P5584 Identification and characterization of the novel human ether-a-go-go-related gene (hERG) R744P mutant linked to hereditary long QT syndrome 2


Purpose: Mutations of the cyclic nucleotide binding domain (CNBD) may disrupt human ether-a-go-go-related gene (hERG) Kþ channel function and lead to hereditary long QT syndrome (LQTS). We identified a novel missense mutation located in close proximity to the CNBD, hERG R744P, in a patient presenting with recurrent syncope and aborted cardiac death triggered by sudden auditory stimuli.

Methods: Functional properties of wild type (WT) and mutant hERG R744P subunits were studied in Xenopus laevis oocytes using two-electrode voltage clamp electrophysiology and Western blot analysis.

Results: hERG R744P channels exhibited reduced activating currents compared to hERG WT (1.48 ± 0.26 μA versus 3.40 ± 0.29 μA; n = 40). These findings were confirmed by tail current analysis (hERG R744P: 0.53 ± 0.07 μA; hERG WT, 0.88 ± 0.06 μA; n = 40). Cell surface trafficking of hERG R744P protein subunits was not impaired. To simulate the autosomal-dominant inheritance associated with LQTS, WT and R744P subunits were co-expressed in equimolar ratio. Mean activating and tail currents were reduced by 32% and 25% compared to hERG WT (n = 40), indicating that R744P protein did not exert dominant-negative effects on WT channels. The half-maximal activation voltage was not significantly affected by the R744P mutation.

Conclusions: This study highlights the significance of in vitro testing to provide mechanistic evidence for pathogenicity of mutations identified in LQTS. The functional defect associated with hERG R744P serves as molecular basis for cardiac repolarization.

P5585 Angiotensin II regulates cardiac L-type Ca channels and ryanodine receptors via NADPH oxidase

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Angiotensin II (Ang II) signaling has been implicated in arrhythmogenesis possibly by reactive oxygen species (ROS)-dependent regulation of L-type Ca current (ICa) and cardiac ryanodine receptors (RYR2). To test, if Ang II regulates ICa via ROS generated by NADPH oxidase 2 (Nox2), ICa was measured via whole-cell patch clamp in mouse ventricular myocytes. In wildtype (WT) myocytes, Ang II (1 μmol/L) significantly enhanced peak ICa († P < 0.05 vs. vehicle, N=20 vs. 10). PKA inhibition with H89, however, could not reverse the Ang II-induced increase in ICa (2.37 ± 0.06 μmol/L) but not significantly to hERG WT (1.48 ± 0.26 μmol/L) in WT+Ang II). To test, if Ang II regulates diastolic RyR2 activity, spontaneous Ca spark frequency (CaSpF) in 100 μmol/L) but not knock-out of CaMII (CaMII-/-) could completely reverse the Ang II-induced increase in peak ICa (P < 0.05 vs. Ang II). To test, if Ang II regulates CaMII, we used a novel CaMII inhibitor, PKA inhibition with H89, however, could not reverse the Ang II-induced increase in CaSpF (15% vs. 20% for Ang II vs. vehicle, N=20 vs. 10).

In conclusion, Ang II regulates ICa and RyR2 via two different mechanisms, the former involves Nox2-dependent activation of PKA, the latter requires Nox2-dependent activation of CaMII. Both these mechanisms can contribute to generation of EADs and DADs. This may be of relevance for the treatment of Ang II-induced arrhythmias.

P5586 Development of an effective cellular model for human endothelial mesenchmal transition in studying bicuspid valve malformations and cardioagenesis


Purpose: Endothelial mesenchmal transition (EndoMT) is an important process for cardiac outflow tract and aortic valve formation. It is proposed that Notch signaling is involved in this process and as shown in our as well as other studies, patients with defects of LOV may have mutations in Notch1 gene and other genes of Notch pathway. Notch1 is known as one of the regulators of EndoMT in development but its role in regulation of human heart development remains obscure due to difficulties of studying human development. The purpose of this study was to develop an effective in vitro system in order to study EndoMT and Notch-pathway using primary human cells from patients with the defects of LOV.

Methods: Two types of endothelial cells were used: HAEC (human aortic endothelial cells) from patients with aortic aneurisms and from healthy donors and HUVEC (human umbilical cord blood cells). EndoMT induced by different stimuli: 1) TGFβ; 2) NICD (activated domain of Notch1; 3) Notch ligands – Dll1, Dll4, Jag2. Effectiveness of EndoMT was estimated by loss of endothelial and gain of mesenchmal markers by three different methods: immunocytochemistry, RT-PCR, qPCR.

Results: TGFβ effectively induced EndoMT in HAEC, but to a much lesser extent in HUVEC. In contrast, NICD induced GM-CSF in HUVEC, but not in HAEC. Co-culture of cells expressing one of the Notch ligands (DII1, DII4 or Jag2) with either HAEC or HUVEC induced EndoMT with the most effect of DII4. We have checked different cellular markers to mark EndoMT by qPCR and Western blot analysis. The most effective marker for EndoMT estimation by immunostaining appeared to be the gain of mesenchmal marker SMA. In contrast, the loss of endothelial markers von Willebrandt factor and CD31/PECAM1 was less visible and countable. We have checked 20 markers previously described for EMT in literature by RT-PCR and revealed the most informative in our cellular system (FSP1, SLUG, TWIST, SMA). By qPCR the most effective markers were SMA, and also targets of NICD – Hes and Hey.

Conclusions: We have developed an effective in vitro system which allows studying EndoMT directly on the patients’ primary cells (HAEC) thus recapitulating processes seen in early cardiogenesis. Our results show that HUVEC and HAEC differ significantly in their sensitivity to EndoMT induction by various stimuli. Data obtained using one of these cell types should be interpreted carefully in condu- tion to endothelial cell properties of various vascular bases.

P5587 Induction of MesP1 by Brachyury(T) generates common cardiovascular precursor cells, which can be purified by MACS

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The proliferative potential of pluripotent stem cell derived cardiomyocytes is limited and necropaeic yields for novel vascular cells remain small. In a first attempt of such “cardiovascular forward programming” using pluripo- tent stem cells, we have previously shown that MesP1 represents a master reg- ulation sufficient to induce cardiovascular progenitor cells (David R., Nat Cell Biol, 2008). In ES cells MesP1 overexpression resulted in significantly increased numbers of beating cardiomyocytes and of endothelial cells. Our experiments revealed a prominent function of MesP1 within a gene regulatory cascade causing Dkk-1 mediated blockage of canonical anti-signalling. We thereby defined the Dkk-1 promoter as a direct target, activated by MesP1 protein. Patch clamping analyses showed electrophysiological characteristics corresponding to all cardiac subtypes in Nkx2.5 as well as MesP1 programmed ES cells with distinct characteris- tics: MesP1 forced the appearance of early/intermediate type cardiomyocytes (~60%) compared to control cells whereas Nkx2.5 led to differentiated ventric- ular cells (~85%) (David R., Cardio Res, 2009). Recently, we have analysed Eomes and Brachyury(T) as potential inducers of MesP1. We demonstrate that the MesP1 positive cell population is derived from the Brachyury(T) positive fraction in embryos and ES cells. Loss of Brachyury(T) decreases MesP1 expression in embryos and ES cells. Using EMSA, ChIP and reporter assays we found a 3.4 kb proximal MesP1 promoter fragment, directly bound and activated by Brachyury(T). We then used this promoter fragment for isolating MesP1 positive cells from differentiating ES cells via magnetic cell sorting. This yielded a highly pure common cardiovascular progenitor population with the potential to form cardi- omyocytes, endothelial cells and smooth muscle cells. Electrophysiological and pharmacological parameters of the cardiomyocytes affirm the role of MesP1 dur- ing the earliest cardiovasculargenic events: most of the cardiomyocytes (~94%) corresponded to the desirable multipotent early/intermediate type exceeding the numbers shown for Brachyury(T). Both programming via MesP1 (~40%). No ventricular or pacemaker like cells were found. Our work contributes to the understanding of the early cardiogenesis and may become an important prerequisite for cell therapy, tissue engineering and pharmacological testing in the culture dish us-
Cyclin-dependent kinase 9 inhibition impacts on cardiomyocyte proliferation in the developing zebrafish heart


Pathological cardiac hypertrophy is characterized by an increase in RNA transcription in cardiac cells. Cyclin-dependent kinase 9 (CDK9) is a key component of the Positive Transcription Elongation Factor b (P-TEFb) and is known to be increased in mammalian cardiomyocyte hypertrophy. We have pharmacologically reduced CDK9 activity in the zebrafish embryo (Dario rerio) to investigate its role in cardiomyocyte proliferation and ventricular function during normal development and recovery from laser-induced injury to the heart.

Methods: Tg(cmkl2:EGFP) zebrafish embryos (n=12-2, experiments) were exposed to flavopiridol, a selective inhibitor of CDK9, (3μM) from 24 to 120 hours post fertilization (hpf). At 72hpf, embryos underwent heart ventricle laser injury. Before, 2, 24 and 48hour post-laser injury, whole ventricle cardiomyocyte number (VCM) was assessed by counting DAPI stained nuclei following lysis injury hearts under confocal microscopy. Ventricle ejection fraction (EF) was measured by video image analysis of beating hearts.

Results: Data are means±sem and analysed by ANOVA. Flavopiridol had no effect on EF but reduced significantly VCM prior to laser. Laser injury alone reduced both EF (-29%, p<0.001) and VCM (-18%, p=0.078) at 2 hours, recovering to control levels at 24 and 48 hours post-laser. In embryos pre-treated with flavopiridol, laser injury further reduced EF (-46%, p<0.001) without any additional reduction in VCM (-11%, p=0.17).

Conclusions: Inhibition of CDK9 using flavopiridol reduces cardiomyocyte proliferation in the developing zebrafish ventricle resulting in globally reduced contractile function. Flavopiridol further inhibits functional recovery following laser injury probably due to other effects of CDK9 inhibition which are unrelated to cardiomyocyte proliferation.

It was the aim of the present study to identify targets and effects of muscarinic signalling in early (E9.5-E11.5 post coitum) and late developmental stages (LDS, E15.5-E20.5) of the murine embryonic heart. Using extracellular field potentials and intracellular measurements of action potentials on the single cell level, we identified in EDS NO and in LDS IKACh as important mediators of muscarinic response. The reduction of beating frequency by carbachol (CCh, 10 μM), was significantly lower in EDS (57.7±4.2%, n=15) than in LDS hearts (89.3±3.2%, n=20, p<0.001). This was at least in part mediated by the transient reduction of heart rate with spontaneous self-recovery in EDS hearts pointing to an involvement of a self-limiting signalling cascade. This assumption was corroborated by the application of blockers of the nitric oxide cascade: ODQ, a selective inhibitor of the nitric oxide-sensitive guanylyl cyclase and L-NMMA, a specific blocker of nitric oxide synthases, reduced the CCh-mediated effect by 80.2±4% (n=26, P<0.001) in EDS but not in LDS hearts. In contrast, Terlip, a blocker of the IKACh, diminishes CCh effects only in LDS. The latter observation was corroborated in LDS hearts of IKACh (-/-) mice where a residual CCh-induced reduction of heart rate by 18.7±3% (n=7, P<0.02) was found without control conditions and by 22.6±13% (n=4, P<0.04) after pretreatment with isoproterenol (10 μM) was observed. In summary, our data indicate a switch from NO to IKACh-mediated muscarinic signalling during embryonic heart development.

Muscarrnic regulation of the early embryonic heart: switch from NO to IKACh-mediated signalling

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A powerful system controlling negative chronotropy in the adult heart is the parasympathetic nervous system which interacts with muscarinic receptors. The development of muscarinic response during embryonic heart development, however, is only partially understood.

Unique left ventricular geometry and function of young adults born preterm: impact of prematurity and preeclampsia exposure

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Purpose: Ten percent of people are born preterm, during a critical phase of their left ventricular development, which would normally occur in utero in the third trimester of pregnancy. In animal models, exposure to postnatal haemodynamic flow patterns during this period leads to a distinct cardiac structure. We sought to determine, for the first time in humans, whether left ventricular geometry and function in young adulthood differs in those born preterm.

Methods: We studied 234 young adults, of which 102 had been followed prospectively since very preterm birth (mean gestational age = 30.3±2.5 weeks and mean birth weight = 1.3±0.3 kg) and 132 had been born at term to uncomplicated pregnancies. We quantified left ventricular structure and function by cardiovascular magnetic resonance on a 1.5T Siemens scanner using Angus and Tomtec Diogenes post-processing software of SSFP cine images. We then studied variation in ventricular parameters according to other pregnancy and later-life factors.

Results: Young adults born preterm have a reduced left ventricular long axis length (9.3±0.8 vs 9.8±0.7 cm, P<0.001) with increased mass (LVMi: 62.1±10.8 vs 55.6±11.4 g/m², P<0.001) and wall thickness (8.4±1.3 vs 6.8±1.2 mm, P<0.001) as well as smaller end diastolic (P<0.001) and systolic (P<0.02), and stroke volumes (P<0.002). Preterm-born young adults also have higher blood pressure but the geometric left ventricular changes differed from those we characterised in young adults born at term with equivalent blood pressure levels. Ejection fraction is preserved (P=0.75) but both peak systolic and diastolic longitudinal strain rates and velocities (P<0.001) are reduced, as well as peak longitudinal systolic strain (-14.8±3.2 vs -17.3±6.0%, P<0.001). Rotational movement of the left ventricle also differs from those observed in adults born at term with equivalent blood pressure levels. Since this study is performed on a large cohort, the impact of these changes on cardiac function remains to be determined.

Conclusions: Young adults born preterm have a unique left ventricular geometry and function. Furthermore, preeclampsia exposure in utero appears to have an additional specific long-term impact on left ventricular systolic function independent to the changes associated with prematurity.

Deviation from Murray law is associated with a higher degree of calcification in coronary bifurcations

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Background: Atherosclerotic plaque formation frequently occurs at locations near vascular bifurcations which is probably explained by inconstant shear stress near bifurcations. Murray’s law describes the optimal branching anatomy of vascular bifurcations and, if Murray’s law is obeyed, shear stress is constant over the bifurcation. This study therefore investigated associations between Murray’s law and intravascular ultrasound (IVUS) assessed plaque composition near coronary bifurcations.
Methods: In 253 patients plaque components (fibrous, fibro-fatty, necrotic core, and dense calcium) were identified by IVUS in segments proximal and distal to the bifurcation of a coronary side branch. The ratio of mother to daughter vessels was calculated according to Murray’s law (Murray ratio) with a high Murray ratio indicating low shear stress. Analysis of variance was used to detect independent associations of Murray ratio and plaque composition.

Results: Patients with a high Murray ratio exhibited a higher relative amount of dense calcium and a lower amount of fibrous and fibro-fatty tissue than those with a low Murray ratio. After adjustment for age, sex, cardiovascular risk factors or concomitant medications, the Murray ratio remained significantly associated with fibrous volume distal (F-ratio 4.90, P = 0.028) to the bifurcation, fibro-fatty volume distal (F-ratio 4.76, P = 0.030) to the bifurcation, and dense calcium volume proximal (F-ratio 5.93, P = 0.016) and distal (F-ratio 5.16, P = 0.024) to the bifurcation.

Conclusion: This study shows that deviation from Murray’s law is associated with a high degree of calcification near coronary bifurcations. Individual deviations from Murray’s law may explain why some patients are prone to plaque formation near vessel bifurcations.

Non coronary vascularization of the heart atria in men
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The investigated group comprised 103 persons (78 male and 25 female) suffering from coronary heart disease after CABG commonly with ligation of one of the internal thoracic arteries. All of these subjects underwent contrast spiral computed tomography (CT) for diagnostic purposes during the period of 1 to 15 years after the CABG procedure. On the basis of the CT angiograms, we noticed the existence of a “non-coronary atrial artery” (ncaa), its shape and its outlet into the coronary sinus. Several figures demonstrate images of the ncaa’s and the ncaa originated in the upper part of the descending aorta and had a common trunk with the intercostal artery and the bronchial artery. Some of the CT pictures also revealed single atrial veins, which ran either into the superior caval vein or into the coronary sinus. Several figures demonstrate images of the ncaa’s and the atrial veins.

The observation was independent of the mutation status of the ARVC cases (only man ARVC ventricular samples in our study. Cadherin decrease thus appears that DSG2 and DSG2 transcript levels were similar in ARVC and DCM controls, however a slight decrease in desmosomal length and adhesive strength. We thus hypothesized that a decrease in desmosomal protein expression at intercellated disks could be a general feature triggering ARVC.

Methods: We compared DSG2, DSC2, JUP and PKP2 protein levels from seven independent ARVC hearts samples, using desmosomal proteins from normal human heart samples as controls. Ventricular sections were examined by immunofluorescence, and proteins extracts were used for immunoblot analysis.

Results: Desmosomal proteins were localised at the intercalated disks in all patient samples as expected by immunohistochemistry, however a slight decrease in labelling intensity was observed in three of the patient samples. Immunoblotting demonstrated a marked decrease of DSG2 (74% ± sem) and DSC2 (43% ± sem) standardised to the cardiac specific protein actin-2, in all ARVC patients. This observation was independent of the mutation status of the ARVC cases (only three patients were carriers of a mutation in the DSG2 gene).

Conclusion: Despite correction of desmosomal cadherin at intercalated disks, we observed a strong decrease in DSG2 and DSG2 in all human ARVC ventricular samples in our study. Cadherin decrease thus appears
Changes in PPARalpha expression in relation to substrates of atrial arrhythmias: Histological insights

Conclusions:

- At the subpulmonary level.
- The PF subendocardial network penetrates the ventricular wall of the RVOT, contributing to a better outcome.
- The distribution of subendocardial and intramyocardial RVOT Purkinje fibers is spatially heterogeneous at the subpulmonary level.

Results:

- Seventy-three patients were enrolled over 18 years of age. Right atrial tissues resected during surgery were sectioned at 7 microns and stained with Goldner trichrome. Additionally, we validated the hypothesis that atherosclerotic progression in vivo mice can be assessed morphometrically.
- The profile of PPARalpha expression in LV tissue in Tgα mice in comparison to FVB mice changed significantly during lifetime.
- The PF subendocardial network penetrates the ventricular wall of the RVOT, ending at a distance of 3.5±1.5 mm from the epicardium. Endocardial and intramyocardial networks are surrounded by a connective tissue sheath. Throughout its course, the intramural PF loses this sheath and connect with myocytes of the RVOT with no transitional cells between them. These connections are scarce at the subpulmonary level.

Methods:

- Twenty-one mice were cross-bred with apolipoprotein E-deficient (E-/-) mice and formation of atherosclerotic lesions was analyzed.
- The PF subendocardial network penetrates the ventricular wall of the RVOT, ending at a distance of 3.5±1.5 mm from the epicardium. Endocardial and intramyocardial networks are surrounded by a connective tissue sheath. Throughout its course, the intramural PF loses this sheath and connect with myocytes of the RVOT with no transitional cells between them. These connections are scarce at the subpulmonary level.

Conclusions: The distribution of subendocardial and intramyocardial RVOT Purkinje fibers is spatially heterogeneous at the subpulmonary level. This anatomical finding suggests electrical discontinuities in the RVOT, essential for initiation of reentrant activity and may be a mechanism for focal excitations and ventricular tachycardia.
ter 16 weeks or 32 weeks consumption of a normal chow diet. Two different age groups (16 and 32 weeks) of IL-1Ra−/−/ApoE−/− mice (n=11) and IL-1Ra+/+/ApoE−/− mice (n=8) were used as atherosclerotic models. Another group of age-matched ApoE−/−/IL-1Ra−/−/ mice (n=8) were used as normal control group. Atherosclerotic models and control mice were imaged at the level of the aorta by UBM. The intima-media thickness (IMT) or plaque thickness was delineated in the ascending aorta short-axis images, and compared with corresponding histological measurements in the same vascular section. Plaque area was delineated in the aortic sinus short-axis of pathological images.

Results: 1. There were various degrees of atherosclerosis in atherosclerotic group in the aortic sinus and ascending aorta visualized by UBM and histology. Not any atherosclerotic lesion was found in control group. Plaque thickness in the ascending aorta (AAO) short-axis images, and compared with corresponding histological measurements in the same vascular section. Plaque area was delineated in the aortic sinus short-axis of pathological images.

Conclusions: 1. Ultrasound biomicroscopy provides a non-invasive, accurate way to detect atherosclerotic progression in mice in vivo. By measuring maximum IMT or plaque thickness in the ascending aorta, UBM is capable of following progression of atherosclerosis in As models mice. 2. Plaque thickness in the ascending aorta measured by UBM in atherosclerotic models was correlated with histological measurements from the same vascular region (r=0.79, P<0.01). And plaque area measured by histology in the aortic sinus of IL-1Ra+/+/ApoE−/− mice was increased compared with IL-1Ra−/−/ApoE−/− mice by UBM and histology (P<0.01). At 32 weeks, the differences of plaque thickness and plaque area between atherosclerotic models failed to achieve statistical significance by UBM and histology (P>0.05).

2. Plaque thickness in the ascending aorta measured by UBM in atherosclerotic models was correlated with histological measurements from the same vascular region (r=0.79, P<0.01). And plaque area measured by histology in the aortic sinus of IL-1Ra+/+/ApoE−/− mice was increased compared with IL-1Ra−/−/ApoE−/− mice by UBM and histology (P<0.01). At 32 weeks, the differences of plaque thickness and plaque area between atherosclerotic models failed to achieve statistical significance by UBM and histology (P>0.05).

EXCITATION-CONTRACTION COUPLING AND ARRHYTHMIAS

P5599 Secretoneurin, a peptide from the chromogranin-secretogranin family, regulates cardiomyocyte calcium homeostasis

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Purpose: To assess the functional role of secretoneurin (SN), a peptide from the chromogranin-secretogranin family, that is increased in the left ventricle in heart failure (HF), we explored functional aspects of SN in isolated cardiomyocytes by immunoblotting, real-time PCR, confocal microscopy, and Ca²⁺-dependent flux results.

Results: We found endogenous SN to be distributed throughout the cytoplasm of cardiomyocytes and labeled SN to be taken up from the suspension to cardiomyocytes by confluent microscopy. Uptake of SN was also verified by immunoblotting, where we found intracellular SN levels to increase in proportion to SN concentration in the cell suspension. SN increased cardiomyocyte contraction by 53% versus control cells (P=0.01) and reduced time to peak by 16% (P=0.01). Ca²⁺ transient amplitude was increased by 21% (P=0.002) and the time to half decay decreased by 14% (P=0.02). The sarcoplasmic reticulum Ca²⁺ content was increased by 21% after SN stimulation (P=0.001), but we did not observe altered Ca²⁺ uptake into the SR or extrusion from the cell. SN stimulation reduced Ca²⁺ spark magnitude by 4% (P=0.05), with a corresponding reduction in width (12%), and duration (16%) of Ca²⁺ sparks (P=0.001 for both), indicating reduced ryanodine receptor opening. Bioinformatics identified a calmodulin (CaM) binding motif for SN. Treatment of isolated cardiomyocytes with SN reduced autophosphorylation of CaM/CaM-dependent protein kinase II (CaM(KII)) at T286, which may account for observed effects of SN on ryanodine receptor function. There was no effect of SN on cardiomyocyte hypertrophy as assessed by transcriptional alterations in genes involved in this process.

Conclusions: SN is robustly taken up and distributed throughout the cytoplasm of cardiomyocytes, and regulates cardiomyocyte Ca²⁺ homeostasis. This action may be mediated via CaM and downstream effects on the ryanodine receptor. The effect of SN on Ca²⁺ homeostasis could be clinically important as patients with HF and elevated SN levels seem to have a poor prognosis.

P5600 Redox-dead protein kinase A disturbs excitation-contraction coupling

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In summary, myocytes with redox-dead PKA show reduced SERCA but increased ICa function. Thus, redox-dead PKA may be involved in the regulation of excitation-contraction coupling.

Figure 1

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Elemental SR Ca2+ release in failing human cardiomyocytes - a comparison with failing rat cardiomyocytes and inhibition by flecainide

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Ca2+ Sparks have been observed frequently in rat cardiomyocytes but less commonly in other species, calling the relevance of these elemental Ca2+ release events in humans into question. The aim of this study was to compare sarcoplasmic reticulum (SR) Ca2+ release events in human heart failure with those in a model of heart failure. In addition, we have previously observed a reduction in spark amplitude with the acute application of flecainide to rat cardiomyocytes and thus went on to assess whether there would be a similar effect in failing human cardiomyocytes.

Failing human ventricular cardiomyocytes were isolated from explanted hearts of heart transplant recipients. Rats underwent a surgical ligation of the proximal left coronary artery and ventricular cardiomyocytes were isolated from these animals 20 weeks later. Confocal microscopy of cells loaded with the Ca2+-sensitive indicator fluo-4 was performed in the presence of 1 μM isoprenaline and 5 μM flecainide. Data below is presented as mean ±SEM, statistical testing was performed using Mann-Whitney/Student’s t-test.

Both rat and human failing ventricular myocytes exhibited Ca2+ sparks. Within this data set, rat sparks (n=85 sparks from 11 cells) were imaged under the same conditions as human sparks (n=250 sparks from 19 cells). Spark frequency and amplitude were not significantly different in rat and human myocytes. Human sparks were significantly larger (4.2 ± 0.1 vs. 3.7 ± 0.1 pA, p<0.02), full-duration at half-maximum (86.8 ± 3.6 vs. 141.1 ± 4.6 ms, p<0.001) and spark mass (100.9 ± 12.8 vs. 14.2 ± 4.2 μm², p<0.02) compared with rat sparks. Spark frequency was significantly lower in human than rat cardiomyocytes (0.03 ± 0.01 vs. 0.00 ± 0.007 waves/second, p=0.0001). Application of flecainide for 5 minutes to human cardiomyocytes (n=9) produced a reduction in spark frequency (1.4 ± 0.3 reduced to 0.52 ± 0.2 sparks/100 μm²/second, p=0.03), amplitude in terms of F/F0 (0.49 ± 0.12 reduced to 0.15 ± 0.04, p=0.02) and spark-mediated SR leak (2.2 ± 1.3 reduced to 0.6 ± 0.4 μm²/s, p<0.008).

Conclusion: Failing cardiomyocytes exhibit spontaneous SR Ca2+ release events in the presence of isoprenaline that are of similar amplitude but have greater width and duration in comparison to failing rat cardiomyocytes. Despite their increased dimensions, human sparks are less likely to result in Ca2+ waves. The response of Ca2+ sparks to flecainide therapy in human cells is similar to that previously reported in rat cardiomyocytes with a reduction in amplitude, frequency and spark-mediated SR leak.

Inhibition of KCa2/3 leading to calcium influx via Cav1 (L) channels affords a rationale for adenosine A1 receptor chronoselectivity in the rat spontaneously beating atria


Purpose: Adenosine (ADO) is a well-known antiarrhythmic agent that is commonly used for prompt conversion of paroxysmal supraventricular tachycardia. The A1R-mediated negative chronotropic, dromotropic and inotropic effects of ADO are dependent on the increase in K+ efflux through G protein-coupled inward rectifying K+ channels (GIRK or KIR3.1/3.4). Yet, in contrast with muscarinic M2 receptors (M2R), the negative chronotropic effect caused by A1R is evoked at lower concentrations than the negative inotropic action (unpublished observations). Here, we investigated the rationale for ADO “chronoselectivity” testing its effect in the absence and in the presence of Ca2+ and K+.

Methods: Functional experiments were performed on spontaneously beating isolated atria from Wistar rats, continuously superfused with gassed (95% O2 + 5% CO2) Tyrode’s solution (37°C). Isometric muscle tension was monitored via a PowerLab data acquisition system. The distribution of A1R, M2R and Ca2+ and K+ channels in the sinoatrial (SA) node was compared with the surrounding cardiomyocytes by confocal microscopy. Ryanodine (1 μM) and R-PIA (0.001-1 μM) concentration-dependently decreased the rate and the force of spontaneous atrial contractions; their effects were prevented by blocking M2Rs with AF-DX 116 (10 μM) and A1Rs with DPCPX (100 nM), respectively. Both agonists were equipotent in decreasing the rate of contraction, but Oxo was more potent than R-PIA upon reducing the force of contractions. Inhibition of Kir3.1/3.4 with tertiapin-G (300 nM) prevented the negative chronotropic and inotropic actions of both agonists. Blockade of KCa2/3 was performed with apamin (30 nM) and of Cav1 (L-type) channels with verapamil (1 μM) sensitized atria to the negative inotropic action of R-PIA; therefore, these results failed to support the effect of Oxo. A1R and M2R were co-imaged both in SA node and in surrounding cardiomyocytes. Immunolabeling of Kir3.1, KCa2.2, KCa2.3 and Cav1.2 was also observed throughout the right atria.

Conclusions: Data indicate that ADO acting via A1R is a “chronoselective” atrial depressant as compared with the M2R agonist, Oxo. Differences in the expression of A1R between the SA node and surrounding cardiomyocytes do not afford a rationale for ADO chronoselectivity. While both A1R and M2R promote the opening of tertiapin Q-sensitive Kir3.1/3.4 channels modulating SA node automatism, adenosine A1R may prevent KCa2/3 activation increasing the time available for Ca2+ influx through Cav1 (L-type) channels.

Type II Ca2+ channel antagonists attenuated aldosterone induces endothelin-1-Rho-Rho-kinase-interleukin-18 pathway in cardiomyocytes

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Purpose: Interleukin-18 (IL-18), a member of the IL-1 family, is a proinflammatory cytokine with multiple biological functions. IL-18 induces myocardial hypertrophy, loss of contractility of cardiomyocytes and apoptosis leading myocardial dysfunction. Increased levels of circulating IL-18 are thought to be one of risk factors for heart failure. We previously reported that IL-18 expression was induced by aldosterone via the Rho/Rho-kinase pathway through endothelin-1 (ET-1) and angiotensin II (ANG II) production in cardiomyocytes. Ca2+ channel antagonists may be effective in preventing progressive cardiac dysfunction. However, interaction of IL-18 and Ca2+ channel antagonist is not clear. In the present study, we aimed to clarify the role of the Rho/Rho-kinase pathway and Ca2+ channel antagonists with respect to aldosterone induced IL-18 expression in rat neonatal cardiac myocytes.

Methods: We examined the effect of L- and Type II Ca2+ channel antagonists on aldosterone-, ET-1, and ANG II-induced IL-18 expression in rat neonatal cardiac myocytes.

Results: Aldosterone, ET-1, and ANG II induced IL-18 mRNA and protein expression. Addition of Type II Ca2+ channel antagonists, mibefradil and efonidipine, to cardiomyocytes led to a significant reduction in aldosterone-, ET-1, and ANG II-induced IL-18 expression. By contrast, L-Type Ca2+ channel antagonist, nifedipine did not inhibit these effects. Aldosterone-, ET-1, and ANG II-induced IL-18 expressions were inhibited by ET-1 receptor antagonist, BO2123 and ANG II receptor antagonist, olmesartan, and also by RhoA inhibitor, C3 toxin and Rho-kinase inhibitor, fasudil. Aldosterone, ET-1 and ANG II reduced Rho-kinase activity in cardiomyocytes. Western blots showed Aldosterone, ET-1, and ANG II-induced Rho-kinase activities were inhibited by mibefradil and efonidipine but not by nifedipine. These results indicate that mibefradil and efonidipine attenuated aldosterone-, ET-1, and ANG II-induced IL-18 expressions at a level in this pathway that lies between ET-1 or ANG II receptor and Rho-kinase.

Conclusions: These results suggest a novel mechanism for the beneficial effects of Type Ca2+ channel antagonists in cardiovascular disease through reductions in aldosterone-induced IL-18 expression.
Acute left atrial regional ischemia causes shortening of pan-atrial action potential duration and acceleration of drivers of atrial fibrillation

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Purpose: Acute atrial ischemia is a pathophysiological factor of atrial fibrillation (AF). As to the electrophysiological and metabolic mechanisms for the proarrhythmia, however, much remains to be clarified. We hypothesized that palmitic acid, a saturated fatty acid released from the ischemic myocardium may play an important role.

Methods: In 16 isolated sheep hearts (group 1), acute left atrial ischemia (ALI) was created by injection of microspheres (40-100 μm, 1.5 ml) into the left anterior atrial artery. In 5 other hearts (group 2), the whole atria were perfused with palmitic acid (20 μM) without creation of ALI. Optical action potential signals were recorded from the whole epicardial surface of both atria by 2 CCD cameras.

Results: ALI (for 90 min.) caused shortening of action potential duration (APD) not only in the left atrial ischemic zone (IZ, by 21.1 ± 0.9 ms, n=26 and 18.8 ± 0.8 ms, n=17 vs. vehicle, (P<0.05 vs. vehicle) but these changes were blunted with TXL (ICD, 525 ± 231, n=26 and 467 ± 26.6, n=22, P>0.05 vs. ISO: TT, 185 ± 4.7, n=26 and 158 ± 8.0, n=22, P<0.05 vs. ISO). In conclusion, ISO increased activity of CaMKII resulting in increased Nav1.5 phosphorylation and enhanced late INa. Polymerization of tubulin disrupts the ISO-induced CaMKII activation as well as phosphorylation of Nav1.5 and late INa enhancement.

Conclusions: ALI causes pan-atrial APD shortening and acceleration of drivers of AF. Palmitic acid released from the ischemic myocardium may play an important role in the initiation and perpetuation of AF.

CaMKII-dependent late INa and cardiac Na channel phosphorylation are disturbed by tubulin polymerization

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In heart failure, persistent current through Na channels (late INa) is enhanced leading to arrhythmias. We have shown that Ca/CaM-dependent kinase II (CaMKII) increases late INa but the mechanism was unclear. To test, whether ion channel trafficking is involved, isolated mouse ventricular myocytes were exposed to taxol for 24 hours followed by preincubation with taxol for another 24 hours. In the absence of inhibitors of PI3-K or SGK, polymerization of tubulin disrupted the CaMKII activation as well as phosphorylation of Nav1.5 and late INa. Polymerization of tubulin disrupts the ISO-induced CaMKII activation as well as phosphorylation of Nav1.5 and late INa enhancement.

Role of the serum-and-glucocorticoid-induced protein kinase (SGK) in the regulation of the cardiac ICaL by insulin and corticosteroids

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Purpose: Corticosteroids have been shown to increase the L-type Ca2+ current (ICaL) in cardiomyocytes in vitro by activation of the mineralocorticoid receptor (MR). The signal transduction pathways involved, however, are incompletely understood. Here we demonstrate that the upregulation of ICaL depends on the presence of insulin or IGF-1 and is sensitive to inhibition of the phosphatidylinositol 3-kinase (PI3-K) or the serum-and-glucocorticoid-induced protein kinase (SGK).

Methods: Left ventricular cardiomyocytes were isolated from female Wistar rats and investigated by the whole-cell patch-clamp technique after 24 hours incubation with corticosteroids alone, in combination with insulin or IGF-1 and/or the presence of inhibitors of PI3-K or SGK-1.

Results: In the presence of 100nM insulin, dexamethasone (1μM) increased ICaL (at ΔVm by 49%) from -8.2 ± 0.7 pApF-1 (n=11) to -12.2 ± 0.9 pApF-1 (n=15, P<0.001), while dexamethasone alone had no effect (-8.2 ± 0.7 pApF-1, n=11). Co-incubation with 1μM dexamethasone and 10nM IGF-1 increased ICaL by 42% (p<0.01). Insulin or IGF-1 alone did not affect ICaL after 24h. Concentration-response relations revealed an EC50 of 0.43 mM and 4.7nM for IGF-1 and insulin, respectively. Similarly, incubation with aldosterone increased ICaL in the presence of insulin but not in its absence. Coincubation with the PI3-K inhibitors PI-103 (0.5μM) or LY294002 (50μM) as well as co-incubation with the SGK inhibitor GSK650394 (10μM) abrogated the dexamethasone/insulin-induced effect on ICaL, while in the absence of dexamethasone/insulin, the inhibitors did not alter ICaL. GSK650394 (10μM) did not affect the activity of PKB/Akt in isolated

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cardiomyocytes incubated with dexamethasone/insulin after 24h as assessed by the degree of phosphorylation of the PKB/Akt specific substrate filamin-C.

**Conclusions:** We conclude that corticosteroids and insulin/GF-1 synergistically induce the increase in ICaL and may constitute important effectors in the regulation of cardiac function under physiological and pathophysiological conditions.

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**P5610**

**Junction between pulmonary veins and left atrial posterior wall** plays a substrate for wavebreaks and anchoring of short-lived scroll waves during stretch-related atrial fibrillation

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**Purpose:** The mechanisms that maintain atrial fibrillation (AF) are incompletely understood. Recently, we demonstrated in sheep hearts that transmural scroll waves (SWs) during persistent AF form at the junction between pulmonary veins and left atrial posterior wall and play a more important role in AF perpetuation.

**Methods:** In 12 isolated sheep hearts under increased intra-atrial pressure (12 cmH2O), AF was induced in the absence of acetylcholine. Optical action potential signals were recorded simultaneously from epicardial and endocardial surface of the left atrium by two CCD cameras and a cardio-endoscope. Electrodes were placed at the PVJ, LAA and right atrial appendage (RAA).

**Results:** The minimum dominant frequency of ventricular electrograms was 8.5±1.4 Hz at PVJ, 6.9±0.9 Hz at LAA, and 5.5±1.2 Hz at RAA (means±SD). In 16 of 16 transmural SWs recognized during a total 46 activations of SRAf, their filaments were found at PVJ with trajectories circumnavigating the PV ostia (Figure). 3-D numerical simulation suggests that transition from thin to thick region at PVJ favors the SW anchoring via modification of excitability by stretch-activated ion channel conductance.

**Conclusion:** PVJ plays a pivotal role to maintain SRAf by providing substrates for anchoring transmural SWs and for formation of wavebreaks.

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**P5611**

**An experimental model of atrial fibrillation showed increased interstitial conduction time and atrial postrepolarization refractoriness as antiarrhythmic effects of simvastatin and docosahexaenoic acid**

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**Purpose:** Previous studies showed that simvastatin (SIM) and docosahexaenoic acid (DHA) have therapeutic potential in primary and secondary prevention of atrial fibrillation (AF) and recent data demonstrated that SIM and DHA can help to prevent AF in patients after cardiac surgery. The objective of the present study was to investigate the effects of SIM and DHA on atrial electrophysiology in an intact whole-heart rabbit model of AF.

**Methods:** Monophasic action potentials (MAPs) and ECGs were recorded from 20 isolated Langendorff-perfused rabbit hearts at baseline and after subsequent drug administration (DHA 10 μM, n=10; SIM 500 nM, 1 μM, n=10). AF was induced by burst pacing and resulting arrhythmia episodes were studied concerning number and length and defined as “non-sustained” (< 1 s) and sustained (> 1 s).

**Results:** Atrial action potential duration (aAPD) was decreased moderately by DHA and SIM (αAPD; 10 μM DHA: -10 ms, SIM 500 nM: -1 ms, 1 μM: -10 ms; p<0.01). Administration of DHA and SIM led to significant increase in interatrial conduction time. The ΔHCAV was increased moderately by DHA (12 ms; p<0.05, 500 nM SIM: +5 ms, 1 μM SIM: +13 ms; p<0.05). Both drugs did not affect atrial effective refractory period (aERP).

**Conclusions:** Moderate increase in atrial post-repolarization refractoriness (aPRR) was found for DHA (+9 ms) and SIM (1 μM, +8 ms; p<0.05) as a consequence of stable aERP and decreased aAPD. Burst pacing induced reproducible occurrence of AF at baseline (6 of 10 hearts for both groups). DHA led to reduced number of hearts with inducible AF (4 of 10 hearts) and reduced number of single episodes of AF (28 to 16 AF episodes).

**P5612**

**Tpeak-Tend determined across multiple leads represents global not transmural dispersion of repolarization**

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**Purpose:** The Tpeak-Tend interval (TpT e) is supposed to reflect dispersion of ventricular repolarization. A prolonged TpT e has been shown to predict ventricular arrhythmias and sudden cardiac death (SCD). However, the exact determinants of the TpT e are unknown. Because TpT e differs considerably among the 12 standard ECG leads, interpretation of the TpT e might not be feasible. Therefore, we aimed to clarify the meaning of TpT e using multiple leads in relation to repolarization patterns.

**Methods:** Isolated pig hearts (n=7) were submerged in a blood-filled bucket and retrogradely perfused according to Langendorff. Intramural electrograms were simultaneously recorded to estimate repolarization times (RTs) during atrial pacing at a cycle length of 650 ms. At the same time a standard 12-lead pseudo ECG was recorded. Recordings revealing ST-elevation or a flat T-wave were excluded from analysis. RT-dispersion was calculated as the minimum minus maximum RT. Transmural RT-dispersion was determined in the left ventricle and global RT-dispersion in the whole heart. Tend was measured using the tangent-method. TpT e intervals in all 12 ECG leads are summarized by the minimum, maximum and mean TpT e (TpT e_min, TpT e_max, TpT e_mean). Finally, TpT e_total was defined as the interval of the minimum Tpeak in any of the 12 leads to the maximum Tend in any of the 12 leads.

**Results:** No indication for a M-cell layer was found in transmural recordings. Transmural RT-dispersion was 13±4.0 ms (mean ± sd, endocardial later than epicardial) and global RT-dispersion was 84±16.1 ms (p<0.05). The averaged TpT e_min (30±4.5 ms), TpT e_mean (44±5.9 ms) and TpT e_max (74±8.0 ms) were all significantly larger than transmural RT-dispersion and significantly smaller than global RT-dispersion. TpT e_total (87±17.2 ms) was statistically equal to global RT-dispersion, and significantly larger than transmural RT-dispersion (p<0.01).

**Conclusions:** TpT e total reflects global RT-dispersion, whereas TpT e_min, TpT e_mean and TpT e_max are poor estimates of global or transmural RT-dispersion. Whether TpT e determined across multiple leads, as a measure for global dispersion, is also a better predictor for arrhythmias in the in vivo human heart remains to be elucidated.

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**P5613**

**Torsemide but not furosemide positively influences structural remodeling during atrial fibrillation in mice**

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**Introduction:** Loop diuretics are used for fluid control in patients with cardiac diseases but their prognostic effect remains a matter of debate. Early reports have suggested that torsemide, but not furosemide, may prevent fibrosis in the left ventricle. The role of torsemide and furosemide for structural remodeling during atrial fibrillation is unknown.

**Methods and Results:** Transgenic mice with cardiac overexpression of Rac1 GT-Pase (RacET) develop spontaneous AF at higher age and are characterized by increased atrial fibrosis compared to wildtype (WT). 8 months of RacET showed increased protein expression of the profibrotic cytokine connective tissue growth factor (CTGF, 368±28%), the key enzyme of collagen crosslinking lysyl-oxidase (LOX, 187±77%) and the fibrosis-related microRNA-21 (mir-21) expression. Reduced expression of the mir-21 target spouty1 (Spry1). Treatment with torsemide (10mg/kg/day) but not with furosemide (40mg/kg/day) or vehicle for 8 months prevented atrial fibrosis in RacET as well as the upregulation of CTGF, LOX and mir-21 and downregulation of Spry1. The effects of torsemides were independent of Rac1 GT-Pase activity. Importantly, torsemide treated RacET exhibited a reduced prevalence of atrial fibrillation (38% RacET+Toras vs. 70% RacET).

In order to test the underlying mechanism, primary neonatal cardiac fibroblasts were treated with torsemide or furosemide. Torsemide (50 μM, 24 h) but not furosemide (500 μM, 24 h) reduced the expression of CTGF, LOX and mir-21 whereas Rac1 expression and activity was unaffected. Interestingly, in vitro
studies showed that torsemide but not furosemide inhibited aldosterone synthase (CYP11B2) activity by 75±1.8%. Mineralocorticoid receptor expression was not altered by both loop diuretics. All effects are significant with p<0.05.

Conclusions: Torsemide but not furosemide prevents atrial fibrillation and reduced the prevalence of atrial fibrillation in RacET mice. This is associated with inhibition of CYP11B2 activity and reduced expression of the profibrotic regulators CTGF, LOX and miR-51.

LGE-MRI detected structural remodeling in a 12-month canine model of chronic AF
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Background: LGE-MRI techniques to quantify atrial structural changes during chronic AF have been shown to be predictive of stroke and AF recurrence following ablation procedures. The timecourse of structural changes in chronic AF is unknown. Patients with chronic AF are not typically scanned until after substantial structural remodeling has occurred. An animal model of chronic AF provides the opportunity to study the structural remodeling from normal hearts as AT progresses from paroxysmal to persistent and finally to permanent AF.

Methods and Results: Measurements of the Rapsod target atrial pacing induced AF was established for 12 months in 3 dogs. Monthly LGE-MRI scans were conducted to evaluate structural remodeling. Results: Mean fibrosis levels during 0-3 months, 4-7 months, and 8-12 months demonstrated progressive structural remodeling as overall LA fibrosis increased from 1.2%, to 2.4%, and finally to 4.4%, respectively. An example of this progression is shown in the figure, with normal tissue shown in blue and fibrotic tissue shown in green.

Conclusions: While electrical remodeling in AF takes place over days to weeks, LGE-MRI detected fibrosis develops over a period of months to years. The extent of structural remodeling detected by LGE-MRI techniques provides a noninvasive means for monitoring the longitudinal progression of structural remodeling in chronic AF patients. To the best of our knowledge, this is the longest duration of sustained AF in a large animal model in the literature.

CARDIAC BIOLOGY

Interaction of S100A4 with p53 in fibroblasts modulates cardiac fibrosis through two distinct mechanisms
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Purpose: The metastasis-associated protein, S100A4 is reported to be involved in fibroblast activation and fibrosis in several organs. Tumor suppressor p53 is one of the known targets of S100A4. Although accumulation of p53 in cardiac myocytes is reported to cause left ventricular dysfunction, the role of p53 in cardiac fibroblasts remains unclear. Thus, we explored the role and relationship of S100A4 and p53 in cardiac fibroblasts. Methods and Results: To investigate the role of S100A4 in vivo, transverse aortic constriction (TAC) was performed in S100A4 knockout (KO) mice, which showed a similar baseline-phenotype to wild type (WT) mice. S100A4 knockdown increased fibrosis by 3.7-fold in WT mice at one week after TAC. Although there was no difference in hypertrophic response, KO mice showed reduced interstitial fibrosis (fibrotic area, 2.7% in KO vs. 7.4% in WT; p<0.05) and decreased number of myofibroblasts in the left ventricle. The expressions of collagen and profibrotic cytokines such as TGF-β1 and connective tissue growth factor were significantly suppressed in KO mice. In vivo cardiac fibroblasts, the knockdown of S100A4 significantly suppressed collagen expression and cell proliferation. S100A4 co-localized and interacted with p53 in the nucleus. S100A4 knockdown increased the expression of p53 downstream genes such as p21 and mdm2, and downregulated the expression of Proliferating Cell Nuclear Antigen (PCNA). Thus S100A4 promotes cell cycle progression through inhibition of p21. On the other hand, mdm2 inhibitor, rutin-3 increased the protein level of p53 and decreased collagen expression. Knockdown of p53 enhanced the collagen expression induced by TGF-β. S100A4 directly promotes collagen expression (p<0.05) by inhibiting p53. Concomitant knockdown of p53 recovered both collagen expression and cell proliferation reduced by S100A4 knockdown.

Conclusions: These findings suggest that S100A4 modulates p53 function in fibroblasts and thereby mediates myocardial interstitial fibroses through two distinct mechanisms; cell proliferation and collagen expression. Blockade of S100A4 may have therapeutic potential in cardiac hypertrophy and heart failure by attenuating cardiac fibrosis.

MicroRNA-1 downregulation modulates gap junction levels of expression and induces ventricular tachyarrhythmias in rat hypertrophied hearts
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Purpose: During left ventricular hypertrophy (LVH), gap junctions and connexin 43 (Cx43) dysfunction cause an important electrical disarray leading to ventricular tachyarrhythmias and ventricular fibrillation (VF). The role of miR-1 in LVH has not been fully elucidated. Therefore, the aim of this study was to investigate whether a reduction in the extent of LVH, obtained through valsartan (VAL) administration, could limit the electrical remodeling and the onset of VF by modulating miR-1 and Cx43 expression.

Materials and Methods: Twenty Wistar male rats (90-120 g weight) were randomly assigned to receive either 10 mg/kg VAL or placebo for 12 weeks after inducing aortic constriction (BAN+VAL, n=12; BAN, n=12). Additional rats were used as sham (n=20). Serial echocardiographic assessments were performed, together with hemodynamic measurements and electrophysiological studies (EPS) at the end of the protocol. Moreover, in order to test gap junctions regulation, cultured cardiomyocytes were challenged with Angiotensin II (AngII) 5 μM/mL alone or in combination with VAL 10 μg/mL for three hours.

Results: VAL significantly reduced LV echocardiographic mass 12 weeks after banding. Programmed ventricular stimulation conducted with standard protocol (100 ms basal cycle length followed by three extrastimuli) was associated to an increased susceptibility to VF in BAN group as indicated by induction of fibrillation and torsade de points compared to BAN+VAL in which only premature ventricular contractions were induced. AngII determined higher transcript levels of Cx43 compared to unstimulated cardiomyocytes and reduced miR-1, whereas VAL administration to cultured cells reverted miR-1 and reduced Cx43 levels. Similarly, a significant decrease of miR-1 levels in BAN rats compared to sham rats was observed (2.3 fold, p<0.03), which was associated to a significant increase of Cx43 (3 fold, p<0.03). Interestingly, in banded rats prevented miR-1 down-regulation (1.7 fold, p<0.03) and Cx43 up-regulation (1.3 fold, p<0.03) therefore leading to a dramatic reduction of VF induction at EPS. Finally, immunoblotting analysis displayed increased phosphorylation of Cx43 on Ser368 after banding in vivo and after AngII treatment in vitro, and both phenomena were markedly prevented by VAL administration (1.9 fold, p<0.001, and 3.8 fold, p<0.001, respectively).

Conclusions: Angiotensin receptor antagonization diminished LVH and improved cardiac function 12 weeks after aortic banding. Reduced hypertrophy by VAL was associated with a significant miR-1 up-regulation and Cx43 remodulation after pressure overload, hence decreasing susceptibility to VF.

Arginase inhibition retards the development of doxorubicin-induced heart failure in mice
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Purpose: Growing evidence suggests that increased arginase activity (AA) contributes to vascular dysfunction by competing with NO synthase (NOS) for a common substrate L-arginine, causing decreased NO production and increased superoxide production due to NOS uncoupling. However, the pathophysiological role of arginase in heart failure (HF) remains unknown. We investigated whether increase in AA plays an important role in the development of doxorubicin (Dox) induced cardiomyopathy and whether arginase blockade protects from Dox cardiotoxicity in mice.

Methods and Results: (1) HF was induced in 6 male mice by Dox administration at a dose of 5 mg kg-1 week-1 for 5 weeks. Arginase 1 expression assessed by Western blot was increased in heart tissue comparing to control mice (n=6, PBS), but not arginase 2 expression. AA measured by colorimetric assay was increased by 4.4-fold in the serum and 1.3-fold in the left ventricle (LV) of the Dox group. Immunohistochemical analysis revealed abundant expression of arginase 1 primarily in the cardiomyocytes in the Dox group. (2) To assess cardioprotective effect of arginase inhibition, mice were treated either with PBS, Dox, or Dox plus an arginase inhibitor nor-NOHA (40 mg day for 5 weeks). The LV ejection fraction (EF) assessed by echocardiography was decreased in the Dox group compared
to control group (50.9±2.9% vs. 59.3±3.6%), whereas treatment with non-NOHA almost completely reversed Dox-induced LV systolic dysfunction (62±4.2±9%). Quantitative PCR showed 39.1% reduction in the level of BNP expression after non-NOHA treatment compared to Dox group. (3) To further elucidate extracardiac organs of the major target for arginase inhibition, we analyzed Dox-induced changes in expression levels of arginase mRNA and protein and AA in various organs. Quantitative PCR revealed that expression of hepatic arginase 1 and renal arginase 2 was significantly decreased, whereas pulmonary arginase 1 and 2 was markedly increased by Dox administration. AA changed 1.8-fold, 1.2-fold and 9.8-fold compared to control in the liver, lung and kidney, respectively. (4) The sera of HF patients from various causes were collected (n = 25), and the ratio of arginine to ornithine, which inversely correlates with AA, was determined. Interestingly, the ratio of arginine to ornithine significantly correlated with both BNP and LVEF (correlation coefficient r = -0.28 and 0.42, respectively).

Conclusions: Arginase activity is increased in HF in mice and humans, and arginase inhibition strikingly ameliorates Dox-induced HF in mice. Arginase may provide a novel therapeutic target for HF.

P5618 Potential role of miR-122 in myocardial fibrosis of human aortic valve stenosis through transforming growth factor-beta1 regulation
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Purpose: Transforming growth factor-beta type 1 (TGF-β1) may play a role in the development of myocardial fibrosis in aortic valve stenosis (AS). Some microRNAs have been described to be involved in myocardial fibrosis in different cardiac pathologies. The aim of this study was to analyze the role of microRNAs in myocardial fibrosis through TGF-β1 regulation, in AS patients.

Methods: Endomyocardial biopsies were obtained from 28 patients with AS, and from 16 controls of 10 control subjects. As compared to controls, AS patients presented myocardial fibrosis, as assessed by a significant increase in collagen volume fraction (CVF). Patients were divided in two groups by cluster analysis according to CVF values: Group 1 (CVF>15%, n=13) and group 2 (CVF≤15%, n=15). MicroRNA expression profile was analyzed in 4 patients from group 1 and 6 patients from group 2 using TDA, and those microRNAs differentially expressed between both groups that could potentially target TGF-β1 were validated by real-time RT-PCR in all 28 patients.

Results: TDA analysis showed that 99 microRNAs were downregulated and 19 upregulated in group 2 patients compared to group 1 patients. Real-time RT-PCR corroborated that miR-122 and miR-18b were downregulated in group 2 patients compared to group 1 patients and controls. The expression of miR-122 and miR-18b was inversely correlated with TGF-β1 regulation, in AS patients.

Conclusions: Our data suggest that downregulation of miR-122 is associated with myocardial fibrosis through TGF-β1 stimulation, in patients with AS.

P5619 Investigating novel regulators and inhibitors of aortic valve calcification
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Objective: Activation and transformation of aortic valvar interstitial cells (VICs) are implicated in the pathogenesis of severe calcific aortic stenosis (CAS). We aimed to characterise gene expression pathways of CAS in porcine VICs and to determine the in vitro effects of a novel inhibitor of calcification.

Methodology: In vitro calcification studies were undertaken using porcine aortic VICs. Calcification was induced by 3 Mm sodium phosphate (Na3PO4), pH 7.4, and the effect of denosumab (an inhibitor of Receptor Activator of Nuclear factor KB Ligand, RANKL; 50g/ml) was analysed. mRNA expression of osteoblast and myofibroblast markers were measured by quantitative polymerase chain reaction (qPCR). Calcification was determined by alizarin red staining and alkaline phosphatase (ALP) activity.

Results: Initial studies demonstrated that porcine VICs calcify spontaneously with demonstrable calcium deposition by day 14 (36.7% increase; p<0.001) associated with a progressively 3 fold increase in ALP activity (p<0.05). Expression of the osteoblast markers Runx2 (1.3 fold; P<0.05) and TGFβ (3.2 fold; P<0.05) were also increased at day 14 with similar increases seen in a number of myofibroblast markers including α-actin (1.7 fold; P<0.05), RhOα (4.6 fold; P<0.001) and TGFβ. RANKL mRNA expression remained unchanged. Treatment of porcine VICs with Na3PO4 led to a marked increase in calcium deposition (50±13%). Denosumab dramatically inhibited this Na3PO4 induced calcification to baseline levels (P<0.05).

Conclusions: This study has demonstrated the upregulation of key molecules during the calcification of VICs and has identified a potential inhibitor of this pathological process. A fuller understanding of the actions of denosumab may identify a novel therapeutic strategy for clinical intervention against aortic valve calcification and aortic stenosis.

P5621 Quantitative gene expression analysis of endothelial and mesenchymal markers in microdissected neoplastic cells of cardiac myxomas in comparison with the overall cell population
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Purpose: Cardiac myxomas, although rare, represent the most frequent primary cardiac neoplasia. They have an uncertain histogenesis and previous studies investigating their overall heterogeneous cellular population suggest an origin from pluripotential stem cells. The aim of this study is: a) to investigate the gene expression pattern in microdissected properly neoplastic myxoma cells (MCs), and in particular the presence of endothelial markers and of myocyte antigens, by quantitative (Real-Time PCR) analysis as compared to overall cellular population; b) to verify whether RT-PCR analysis on RNA extracted from the overall tumour tissue could be a source of subcellular heterogeneity.

Methods: The transcript amounts of several genes were investigated on formalin-fixed and paraffin-embedded (FFPE) samples of 7 cardiac myxomas. The following genes were analyzed: uSMA, CD31, alpha-cardiac actin (>CA), calretinin (CALB2), matrix metallopeptidase 2 (MMP2), Tissue inhibitor of metalloproteinases 1 (TIMP1) and Notch1. In each case, MCs were microdissected by laser capture, and reverse transcription RT-PCR was performed on RNA extracted from either microdissected MCs and adjacent whole paraffin sections. All cases were also immunohistochemically characterized by using specific antisera raised against uSMA, CD31, CALB2, by using immunoperoxidase technique.

Results: By quantitative RT-PCR, we found a lower expression of Cab2, CD31 and Notch1 genes in microdissected cells as compared to the whole myxoma sections in most cases (Cab2: 1.7; CD31: 6.7; Notch1: 6.7). TIMP1, uSMA and MMP2 genes showed a variable expression. We did not find co-expression of uSMA and CD31 in all cases. Finally, >CA was not expressed in any case according to the Literature. MCs were Cab2+/negative in all cases by immunoperoxidase staining.

Conclusions: We detected a different gene expression pattern in MCs as compared to whole cardiac myxomas sections. So far, this is the first study comparing gene expression of microdissected cells with the whole heterogeneous cell population of the same tumor. The results of the present study may give novel insights as to CM origin and differentiation.

P5622 Has anti-apoptotic bag3 protein mutation a possible role in the pathogenesis of Tako-tsubo cardiomyopathy?
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Background and aim: Tako-tsubo cardiomyopathy (TTC) is a stress-related acute cardiac condition characterized by transient myocardial stunning/induction of left ventricular systolic dysfunction in absence of obstructive coronary artery disease. The pathogenesis of TTC is still unclear. BAG3 is an anti-apoptotic protein produced in myocardial cells whose expression can be increased by stressful stimuli. The relationship between a mutated BAG3 protein and an higher susceptibility to myocardial apoptosis induced by stressful triggers has been hypothesized. Aim of this study is verify the presence of BAG3 mutations in patients with TTC.

Methods: Mutationanalyses with genomic DNA were performed in 16 patients (15 females; age 61±13.2 years) enrolled according to theMayo Clinic diagnostic criteria for TTC and in 10 sex and age matched healthy donors. Quantitative polymerase chain reaction (PCR) primers were designed to analyze all exons and flanking non-coding region of BAG3 gene. PCR products were then sequenced by reaction with Big Dye (ABI). Sequencing data were analyzed using bioinformatics software for the detection of mutations in coding exons and introns of the whole translated region (3UTR) of BAG3 mRNA.

Results: A mutation in coding region or in the 3’UTR of BAG3 has been detected in 12 patients (75%) with TTC and in none of controls (p=0.0009). Among TTC patients those with BAG3 mutation are younger (57.8±13.2 vs 71.2±8.9 years; p=0.026) and have a significantly higher incidence of trigger events (11 vs 1; p = 0.045). Furthermore there is a trend for an higher rate of acute heart failure in this subgroup (9vs 1; p = 0.079).

Conclusions: Our data suggest that a reduced anti apoptotic action of mutated BAG3 protein could play a role in the occurrence of stress induced myocardial stunning in TTC patients.
Aldehyde dehydrogenase-2 deficiency aggravates cardiac dysfunction elicited by endoplasmic reticulum stress induction

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Mitochondrial aldehyde dehydrogenase-2 (ALDH2) has been characterized as an important regulator of endogenous cytoprotection in the heart. This study was designed to examine the role of aldehyde dehydrogenase-2 knockout (KO) in the pathogenesis of heart underwnten endoplasmic reticulum (ER) stress induction. Wild-type (WT) and ALDH2 KO mice were subjected to tunicamycin challenge and echocardiographic examination was performed. Protein levels of GRP78, p-eIF2α, CHOP, phosphorylation of Akt, p47phox NADPH oxidase and 4-hydroxyproren were determined by Western blot analysis. Cytotoxicity and apoptosis were estimated by MIT assay and caspase-3 activity respectively. ALDH2 deficiency exacerbated cardiac dysfunction and increased the protein levels of ER stress markers after ER stress induction characterized by the changes of ejection fraction and fractional shortening, when compared with WT mice. In vitro, tunicamycin significantly increased the levels of GRP78, p-eIF2β, CHOP and p47phox NADPH oxidase, the effect of which was exacerbated by ALDH2 knockout but was abolished by ALDH2 overexpression. Overexpression of ALDH2 abrogated tunicamycin-induced dephosphorylation of Akt. Inhibition of PI3-K with LY294002 did not negatively affect the inhibition of ER stress markers conferred by ALDH2, but reversed the anti-apoptotic role of ALDH2, which may be associated with p47phox NADPH oxidase. These results suggest that ALDH2 was implicated in the regulation of ER stress and ER-stress-induced apoptosis. The protective role of ALDH2 against cell death induced by ER stress was probably mediated by Akt signaling via p47phox NADPH oxidase. These findings indicate a critical role of ALDH2 in the pathogenesis mediated by ER stress in heart.

Docosahexaenoic acid (DHA) prevents activation of oxidation-sensitive nuclear transcription factor (NF)κB and attenuates pressure overload induced cardiac dysfunction and hypertrophy

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Intake of fish oil containing both omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) prevents development of heart failure. This effect could be linked to decrease the activity of oxidation-sensitive nuclear transcription factor (NF)κB. We previously showed that DHA has more potent and beneficial effect than EPA. Here we assessed the effect of DHA on oxidative status and activity of NF-κB and the development of left ventricle pathology in response to chronic arterial pressure overload.

Methods: Rats were fed standard chow or diets supplemented with EPA or DHA at 3% of the total energy intake, underwent either sham or abdominal aorta banding, and were maintained for 12 ws. Left ventricular (LV) function was assessed by echocardiography. Western blot analysis was performed for NADPH and NF-κB. Peroxides and NF-κBα activity were measured by ELISA.

Results: On the standard diet aortic banding increased LV mass by 39%, LV end diastolic volume by 51% and end systolic volume by 148%, compared to sham condition (p<0.05). These detrimental effects were attenuated by the DHA supplementation. DHA inhibited myocardial reactive oxygen species production evidenced by decrease of peroxides content (figure). NADPH oxidase activity has emerged as major reactive oxygen species source in the heart, and without supplemented pressure overload increased NOX2 and NOX4 (figure) isoforms activity. DHA also decreased nuclear translocation NF κB-κBp65 and NF-κBp65-binding activity (figure) in myocardium.

Conclusion: Dietary supplementation with DHA suppressed NADPH oxidase, decreased reactive oxygen species, inhibited NF-κBα activity and prevented pressure overload-induced LV hypertrophy, LB remodeling and contractile dysfunction.

Repetitive hyperthermia attenuates progression of left ventricular hypertrophy and increases telomerase activity in hypertensive rats

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Hypertension causes cardiac remodeling and diastolic dysfunction that may lead to diastolic heart failure. We investigated the hypothesis that repetitive hyperthermia attenuates the progression of cardiac hypertrophy and delays the transition from hypertrophic cardiomyopathy to heart failure in Dahl salt-sensitive (DS) hypertensive rats. Six-week-old DS rats were divided into the following three groups: a normal-salt diet (0.4% NaCl) (NS group, n=8), a high-salt diet (8% NaCl) (HS group, n=8), and a high-salt diet (8% NaCl) plus repetitive hyperthermia by daily immersion for 10 min in 40°C water (HS-RHT group, n=8). All rats were sacrificed at 10 weeks. Cardiac hypertrophy and fibrosis were noted in the HS group, whereas hyperthermia attenuated salt-induced cardiac hypertrophy, myocardial and perivascular fibrosis and blood pressure elevation. The phosphorylation of endothelial nitric oxide synthase (eNOS) and Akt was decreased in the HS group compared with the NS group, but these changes were not observed in the HS-RHT group. The protein levels of HSP 60, 70 and 90 were elevated in the HS group, whereas hyperthermia attenuated salt-induced hypertrophy. Moreover, the increased protein levels of iNOS, nitrotyrosine, toll-like receptor-4, BNP, PTX3 and TBARS in the HS group were inhibited by hyperthermia. Telomeric DNA length, telomerase activity and telomere reverse transcriptase (TERT) were reduced in the HS group; however, these changes were partially prevented by hyperthermia. In conclusion, repetitive hyperthermia attenuates the development of cardiac hypertrophy and fibrosis in salt-induced hypertensive rats through activation of eNOS and induction of HSPs. Furthermore, hyperthermia preserves telomerase, TERT activity and the length of telomere DNA.

Genotype-phenotype correlation in HCM patients with TNNT2 mutation. A pilot study

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Background: Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited cardiovascular disorder. Sudden cardiac death (SCD) can be the most serious complication of the disease. Mutations in the gene encoding cardiac troponin T gene are generally considered to have the worst prognosis and higher incidence of SCD. There is evidence from clinical studies about the malig variants of cardiac troponin T gene mutations, which carry a high risk of SCD despite only mild hypertrophy.

Aim of the study was to compare therapeutic strategies in TNNT2 homozyous and heterozygous patients. Adverse prognostic sign was considered the necessity of cardioverter-defibrillator (ICD) implantation in primary or secondary prevention of SCD.

Patients and methods: Prospectively were examined 40 HCM patients (16M/24F, mean age 54.5±2.4years), in whom complete cardiac evaluation as well as DNA analysis was performed. DNA was extracted from whole blood samples using a commercial DNA extraction kit. Exon 9 from the locus TNNT2 was sequenced, genotype 318CtoT (cytosin to thymin substitution at position 318) in heterozygous and homozygous form were identified.

Results: Heterozygous genotype 318CtoT was found in 42.5% (17/40) patients; homozygous genotype 318CtoT was found in further 42.5% (17/40) patients. No mutation was detected in 15% (6/40) patients. Out of all, 5 (12.5%) patients had ICD implanted due to non-sustained ventricular tachycardia and aborted/sustained SCD. Analysis showed, that in 23.5% (4/17) of TNNT2 homozygous were in implanted compared with only 5.8% (17/4) heterozygous patients (P=0.05).

Conclusion: The study results implicate that TNNT2 HCM patients have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous mutation carriers. It is supposed that significant cardiomyocytes undergo endoplasmic reticulum (ER) stress in the context of such mutations. However this is a pilot study, further follow-up studies for the prognostic value evaluation of genotype-phenotype correlation in the population of TNNT2 mutation carriers are needed.

Cardiogenic characteristics and long-term outcome in Andersen-Tawil syndrome patients related to KCNJ2 mutation

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Introduction/Purpose: Andersen-Tawil syndrome (ATS) is an uncommon form of long QT syndrome (LQTS). We investigated linked to mutations in the KCNJ2 gene. Currently, few is known on the long term arrhythmic prognosis of this disease.

Methods: We have conducted a retrospective multicenter study in 9 French hospitals. Patients were recruited only if they were carrier of a KCNJ2 mutation.

Results: Thirty-five patients (female n=21) were included with a mean follow-up of 6.4 years. The mean age at diagnosis was 30±19 years. Fourteen patients (40%) experienced syncope and one patient was resuscitated from a cardiac arrest before inclusion. The mean QTc interval was 441±56 ms
Nitrite influences proliferation of myoblasts via its reduction to nitric oxide in skeletal muscle tissue

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The nitrate-nitrite-NO pathway is an accepted source for NO formation. Nitrate- and/or nitrite reducing proteins like myoglobin and xanthine-oxidoreductase (XOR) have been identified. Little is known about the nitrate- and nitrite reductase capacity of skeletal muscle tissue. In our ex vivo analysis, we considered the role of myoglobin, XOR, and low pH as in exercise. As it is unclear whether the nitrate metabolism plays a role in MTOR regulated muscle growth, we investigated the influence of nitrite and NO on myoblast proliferation in vitro.

Muscle homogenates were prepared from NMRI-wildtype (WT) and myoglobin-knockout-mice (Myo-/-) hindlimb tissue. Nitrate reductase capacity was measured by incubating muscle homogenate in PBS + 500 μM nitrate at pH 6.0, 37°C, 0% oxygen, with its nitrite content analyzed in samples via HPLC. Nitrite reductase capacity was measured by incubating muscle homogenates in PBS + 100 μM nitrate at pH 6.0, 37°C, 0% oxygen, in line with a CLD. The influence of nitrite, ODQ, DETA-NONOate, or rapamycin (RY) on C2C12 myoblast proliferation was observed in cultures grown in DMEM + 10% FCS at 37°C/5% CO2.

Muscle tissue consumed nitrate at a rate of 0.65±0.02 mmol/mg tissue. In parallel, nitrite was formed (0.21±0.04 mmol/mg tissue). Alloupinid affected neither nitrate consumption (0.63±0.01 mmol/mg tissue) nor nitrite formation (0.21±0.01 mmol/mg tissue). Under anaoxia at pH 7.3, muscle tissue formed NO from nitrate at a rate of 37±15 pmol/s/mg protein. pH 6.5 accelerated the conversion to 110±18 pmol/s/mg protein (p<0.001). Myo--/--tissue generated less NO at pH 6.5 (80±14 pmol/s/mg protein; vs. WT-tissue; p=0.018). Alloupinid had no effect on NO formation (106±6 pmol/s/mg protein; n=3 in all groups).

Myoblast proliferation increased using nitrite (0.2 μM; 0.26±0.01; 2.0 μM; 0.27±0.01; 20 μM; 0.29±0.01; 200 μM; 0.30±0.01 Δ O.D.; vs. control 0.23±0.01 Δ O.D.; p<0.001) but partially reversed by 2.0 μM nitrite alone (0.16±0.01 Δ O.D.; vs. RY; p<0.001), and reversed by 2.0 μM nitrite and 10 μM ODQ (0.15±0.01 Δ O.D.; vs. RY; p<0.001; n=5 in all groups).

We showed nitrate- and nitrite-reduction capacity of skeletal muscle tissue and the stimulation of myoblast proliferation by nitrite and NO. This might implicate a role of the nitrite-NO metabolism in the regulation of muscle growth.
Subtotal nephrectomy accelerates pathological cardiac remodeling post myocardial infarction: implications for the cardiorenal syndrome

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Purpose: To understand the nature of concomitant cardiac and renal dysfunction, we investiigated the pathological changes that occur when a kidney insult (induced by 5/6 nephrectomy – STNx) follows that of myocardial infarction (MI) on heart and kidney function and structure.

Methods: Male Sprague Dawley rats (n=43) were randomized into four groups: Sham-operated MI + Sham-operated STNx (Sham+Sham), MI + Sham-operated STNx (MI+Sham), Sham-operated MI + STNx (Sham+STNx) and MI+STNx. MI/Sham surgery (left anterior descending coronary artery ligation) was induced initially and STNx/Sham surgery performed 4 weeks later. Echocardiography, glomerular filtration rate and blood pressure were assessed prior to the second surgery and 10 weeks thereafter. Thereafter, hemodynamic parameters were measured and tissues collected for analysis.

Results: Survival rate was 100%, 59.7%, 91.7% and 44.1% in Sham+Sham, MI+Sham, Sham+STNx and MI+STNx animals, respectively. Left ventricular ejection fraction was further decreased from 39.7±1.8% in MI+Sham to 31.2±1.3% in MI+STNx animals (p<0.01) at week 14, despite no difference in infarct size (34.6±2.2% and 33.7±1.5% respectively). Tau logistic; the time constant of relaxation, was further increased from 12.3±0.7 msec in MI+Sham to 17.0±1.4 msec in MI+STNx animals (p<0.01). Heart weight/body weight (BW) and lung weight/BW ratios were greater in MI+STNx compared to MI+Sham animals (p<0.01 and p<0.01 respectively). In the non-infarct zone of the myocardium, MI+STNx animals demonstrated greater myocyte cross-sectional area, as well as increased interstitial cardiac fibrosis and collagen I compared to MI+Sham animals (p<0.01, p<0.01 and p<0.01 respectively).

Conclusions: This study demonstrated STNx accelerates cardiac hypertrophy, fibrosis and cardiac dysfunction post-MI whilst MI accelerates STNx-induced renal dysfunction (p<0.01). Left ventricular systolic function post MI+STNx was significantly impaired compared to MI+Sham (p<0.01). MI+STNx animals showed greater renal interstitial fibrosis in the non-infarct zone compared to MI+Sham animals (p<0.01). These findings introduce the hypothesis that PA ameliorates the devastating effects of ageing on endothelial function in elderly subjects, suggesting another cardioprotective effect of habitual exercise on atherosclerosis progression.

Physical activity: novelty benefits in second subsets


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Background: Physical activity (PA) protects against heart failure partly by reducing risk factors such as diabetes, hypertension and myocardial infarction, but also by unknown mechanisms.

Objective: By use of directed acyclic graphs, we identified the most appropriate models to investigate total (adjusting for education and previous MI) and direct (multivariable-adjusted) effects of total and leisure time PA on risk of heart failure of any and non-ischemic origin, respectively.

Design: Cohort study

Participants: Of the participants in the two events the National March in September 1997, 39,813 agreed to fill in a questionnaire of lifestyle factors and medical history.

Main outcome measures: We investigated non-linear relations of self-reported total daily PA assessed using a novel Energy Expenditure Questionnaire, and perceived health status (SF-36). All variables were corrected for multiple testing. Following variables were investigated: demographic characteristics, clinical characteristics, educational level, employment status, marital status and all fields of perceived health.

Results: Patients were significantly less active compared to the general population (p<0.05). Fifty five percent of all patients reported to be involved in sports activities, most often fitness, swimming, jogging, cycling and football. Of this group, 7 patients (10%) were involved in competition (3 x football, 1 x tennis, 1x skateboarding, 1x dressing, 1x fishing). However, when also exercise intensity was taken into account, 55% of all patients were sedentary, 27% had an active or moderately active lifestyle and 18% of the group had a vigorously active lifestyle. Peak oxygen uptake (71±16%, p<0.001) was significantly reduced and related to reduced physical activity levels (r=0.43, p<0.01) and perceived physical functioning (r=0.361; p=0.002). Out of all investigated determinants of physical activity, only BMI was weakly correlated with the volume of health-related sports per week (r=0.0263; p=0.008).

Impact of physical activity on endothelial function in middle-aged and elderly inhabitants in an area with increased rates of longevity: Ikaria study

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Purpose: Physical activity (PA) has substantial vascular and cardiac health benefits and can ameliorate cardiac risk. Measurement of endothelial function is well validated in large populations as strong predictors of adverse cardiovascular outcomes. In the present study we evaluated the effect of physical inactivity on endothelial function in middle aged and elderly inhabitants of Ikaria Island; as the inhabitants of this island show increased longevity and low rates of cardiovascular mortality.

Methods: The study was conducted on a subgroup population of Ikaria study consisted of 185 middle aged (40-65 years) and 142 elderly subjects (66-91 years) who were permanent inhabitants of Ikaria Island. Endothelial function was evaluated by ultrasound measurement of flow-mediated dilatation (FMD). We evaluated PA using the shortened version of the self-reported International Physical Activity Questionnaire (IPAQ). Overall the study sample was divided in three groups according to the categorical score achieved in IPAQ questionnaire: low PA (n=75), moderate PA (n=200) and vigorous PA (n=48). Subjects in the low PA group were recorded as physically inactive and the rest as physically active.

Results: In the middle aged group, 24% of the participants were classified as physically inactive and in the elderly group, 22% were classified as inactive. Mean FMD (5.79±3.19%) was inversely associated with age (r=-0.242, p<0.001) and accordingly, middle aged subjects had higher FMD compared with the elderly (6.26±3.31% vs. 5.21±2.95%, p=0.003). Age-specific analysis revealed that middle aged physically active subjects had higher FMD compared with the elderly physically active participants (5.64±3.24% vs. 5.34±3.07%, p<0.008) while, there was no difference in FMD values between middle aged physical inactive subjects and elderly physically active (5.04±3.32% vs. 5.34±3.07%, p=0.99).

Conclusions: These findings introduce the hypothesis that PA ameliorates the devastating effects of ageing on endothelial function in elderly subjects, suggesting another cardioprotective effect of habitual exercise on atherosclerosis progression.

Dietary determinants of physical activity in young adults with tetralogy of Fallot

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Introduction: Although sports participation is allowed to most adult patients with correctly tetralogy of Fallot (TOF), a reduced exercise tolerance and reduced perceived physical functioning is often present in these patients. We aimed to investigate daily physical activity in adults with TOF and to investigate the underlying determinants of physical activity in daily life.

Methods: We studied 73 TOF patients (53 male: mean age 27±3.7 years) who underwent echocardiography and cardopulmonary exercise testing, and who completed questionnaires about physical activity (Flemish Physical Activity Computerized Questionnaire) and perceived health status (SF-36). All variables were compared with data from a general population. Determining of physical activity level was studied by Pearson or Spearman correlation coefficients with correction for multiple testing. Following variables were investigated: demographic characteristics, clinical characteristics, educational level, employment status, marital status and all fields of perceived health.

Results: Patients were significantly less active compared to the general population (p<0.05). Fifty five percent of all patients reported to be involved in sports activities, most often fitness, swimming, jogging, cycling and football. Of this group, 7 patients (10%) were involved in competition (3 x football, 1 x tennis, 1x skateboarding, 1x dressing, 1x fishing). However, when also exercise intensity was taken into account, 55% of all patients were sedentary, 27% had an active or moderately active lifestyle and 18% of the group had a vigorously active lifestyle. Peak oxygen uptake (71±16%, p<0.001) was significantly reduced and related to reduced physical activity levels (r=0.43, p<0.01) and perceived physical functioning (r=0.361; p=0.002). Out of all investigated determinants of physical activity, only BMI was weakly correlated with the volume of health-related sports per week (r=0.0263; p=0.008).
Conclusions: Adult patients with TOF have a sedentary lifestyle and are less active than the general population. Inactivity significantly contributes to reduced exercise capacity of adult patients with TOF, in addition to the impairment based on the cardiac condition. Moreover, reduced exercise capacity and the intensity of sports performed in daily life are related with perceived physical functioning. Individual patient counselling on physical activity might be a low cost, high benefit measure to be taken in this patient population.

P5635

Effects of exercise training on inflammation and endothelial function
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Background: Physical activity is associated with the lower risk of cardiovascular disease, but the mechanism underlying this association is unclear. The beneficial role of physical activity might result from its effects on the inflammatory process and endothelial function.

Aim: We investigated whether physical fitness and the level of physical activity are associated with biomarkers of atherosclerosis in athletes and nonathletes.

Methods: Forty six athletes and 46 age- and sex-matched subjects, who had no practice of regular exercise, were recruited. All subjects underwent anthropometric measurements and maximal cardiopulmonary exercise treadmill tests. Physical activity level was assessed by a short version of International Physical Activity Questionnaire (IPAQ). Blood samples were taken before and immediately after exercise. Plasma interleukin-6 (IL-6), soluble CD40 ligand (sCD40 L) and soluble Soluble intracellular adhesion molecule-1 (sICAM-1) concentrations were estimated using LUMIA method.

Results: The resting IL-6 and sCD40 L concentrations were lower in athletes as compared with nonathletes (0.76±0.92 vs. 1.88±3.52 pg/ml, p<0.003, 88.87±892.99 vs. 2367.73±8743.44 pg/ml, p<0.005, respectively), while sICAM-1 level did not differed both groups. The concentration of IL-6 was increased significantly after the exercise as compared to baseline measurement (1.46±1.35 pg/ml, p<0.001). While IL-6 levels were correlated negatively with VO2peak (r= -0.25, p=0.03) and IPAQ score (r= -0.26, p=0.02), CD40 L concentration correlated negatively with IPAQ score (r= -0.4, p=0.004).

Conclusions: Intensive exercise training and high exercise capacity are related to lower IL-6 and CD40 L plasma levels. This may be an important factor that decreases atherosclerosis progression.

P5636

Physical fitness improvement ameliorates arterial stiffness, myocardial hypertrophy and inflammation in patients with Chronic Kidney Disease

Chronic kidney disease (CKD) patients usually presents exercise intolerance, cardiovascular and vascular stiffness and hypertension and poor prognostic. The hypothesis of this prospective study is to prove the beneficial effect of an exercise program in CKD patients.

Patients were selected from the ambulatory of CKD in conservatice treatment. After a treadmill test to exclude CAD patients were submitted to basal evaluation. Central blood pressure and arterial stiffness were performed by Sphygmocor device. ECHO Doppler evaluates arterial and cardiac measurements. Aerobic capacity was measured by estimated VO2max according to Bruce protocol. Complete laboratory tests was used to establish the renal and inflammation degree. Patients were included in a program of exercise consisting of warm up, aerobic and strength training during 1h, 3 times a week, during four months. All evaluations were repeated after the end of training program. Paired student "t" test was applied and results were presented as Mean ± SD. Our results showed an improvement in the aerobic capacity followed by arterial stiffness and cardiolit and cardacular hypertrophy and inflammation.

Subjects characteristics and outcomes

<table>
<thead>
<tr>
<th></th>
<th>Before (n=7)</th>
<th>After (n=7)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56±11.2</td>
<td>55±11.2</td>
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<tr>
<td>Central Systolic BP (mm Hg)</td>
<td>110.7±6.9</td>
<td>106.3±12.4</td>
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<tr>
<td>Central Diastolic BP (mm Hg)</td>
<td>71.9±12.0</td>
<td>67.9±9.10</td>
<td>0.024</td>
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<tr>
<td>Central Pulse Pressure (mm Hg)</td>
<td>39.1+5.36</td>
<td>38.4±10.86</td>
<td>0.850</td>
</tr>
<tr>
<td>VO2 max (ml/kg/min)</td>
<td>26±0.16</td>
<td>30±2.70</td>
<td>0.009*</td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>8.2±0.73</td>
<td>7.4±1.02</td>
<td>0.040*</td>
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<tr>
<td>IRT Lmt (mm)</td>
<td>0.03±0.16</td>
<td>0.01±0.188</td>
<td>0.835</td>
</tr>
<tr>
<td>IRT Right (mm)</td>
<td>0.92±0.28</td>
<td>0.81±0.233</td>
<td>0.07**</td>
</tr>
<tr>
<td>LV mass/height surface area (g/m²)</td>
<td>47.7±13.63</td>
<td>58.9±12.07</td>
<td>0.044*</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>5.0±3.26</td>
<td>2.6±2.04</td>
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<tr>
<td>Creatinine (mg/d)</td>
<td>2.2±0.95</td>
<td>2.2±0.74</td>
<td>0.796</td>
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</tbody>
</table>

In conclusion we found that an exercise program has a beneficial effect in patients with CKD. Also, for the first time, we documented a regression of cardiac hypertrophy with exercise protocol training in CKD.

P5637

A physical active lifestyle seems to have beneficial impact on cognitive status in elderly individuals.
Ilika study

Introduction: Physical activity has long been related with cardiovascular and overall health. Cognitive status is one of the main components of having successful aging. The purpose of this study was to evaluate the role of physical activity on cognitive status in elderly permanent inhabitants of Ikaria Island, an area that has been recognized as having the greatest percentage of people living above the age of 90 years old.

Methods: From June to October of 2009, we studied 343 men and 330 women, aged 65 to 100 years, permanent inhabitants of Ikaria Island; of them 282 (mean age 74±6 years old, 42% males), fulfilled the Mini Mental State Examination (MMSE) for the evaluation of their cognitive status. Among several lifestyle and biochemical characteristics, cardiovascular disease (CVD) factors and anthropometric indices, physical activity was evaluated using the validated IPAQ; while education status was evaluating according to school years and depression status using the Geriatric Depression Scale (GDS).

Results: CVD was evident in 21% of the participants; while 43% of those participants who succeeded to fulfil the IPAQ were defined as obese (38% as, 42% of them as diabetics, 42% of them as hypertensives (HTN) and 58% of them as having hypercholesterolemia. Those in the higher tertile of IPAQ were younger in age (72.46±2.07 vs. 70.2±0.7, p=0.02), more males (68% vs. 43%, p=0.02), less CVD (33% vs. 33%, p=0.05), lower HTN (p=0.02), higher creatinine clearance (77±15 vs. 69±22, p<0.05), less HTN (55% vs 62%, p=0.06), lower BMI (p=0.05) and with higher MMSE (27±3 vs. 25±4, p=0.01). Logistic regression analysis using the value of 24 as a cut-off point of intact cognitive function, after controlling for age, gender, HTN, creatinine, BMI, education years, hypercholesterolemia, diabetes melitus and GDS, revealed that those elderly individuals who were physical active showed a 8-fold probability of having normal cognitive function (OR=8.223, p-value=0.002).

Conclusions: Physical activity seems to have protective effect on cognitive function, independent of cardiovascular risk factors, lifestyle habits, depression and education status, of elderly individuals. It seems that a physical active life may reduce the progression of age-related cognitive decline in advanced age individuals.

P5638

The interplay between inflammation, physical activity, and metabolic syndrome in a remote geriatric community
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Background: Metabolic syndrome (MetS) increases the risk of cardiovascular disease and diabetes mellitus. Obesity, physical activity, and inflammation may be most important in the pathophysiology of MetS. Because it is unclear whether this is true in an aging Asian population, we thus explored the association between physical activity, MetS, physical activity, and inflammation markers in elderly (≥65 years old) Asian men.

Methods: We enrolled 404 elderly residents (mean age:74.64±6.14 years) in a remote Asian community. Each underwent a structured questionnaire interview on their level of physical activity. Those subjects with high-sensitivity C-reactive protein (hsCRP) level >0.9mg/L were referred as a high inflammatory status.

Results: The total prevalence rate of MetS was 27.8%, lower than previously reported Caucasian data. The average hsCRP level was significantly higher in the MetS group (1.60±0.69 vs. 1.00±0.31 mg/L, p<0.01), the frequency was significantly higher in the MetS group (39.3 ±18.8%, p = 0.03), and the risk of elevated hsCRP increased with escalating MetS components (p for trend <0.001). Interestingly, the non-MetS group had a higher average weekly physical activity than the MetS group (7842.25±664.16 vs. 4929.34±468.26 kcal/wk, p = 0.02), which was also true for those with lower hsCRP levels (4844.50±6.16 vs. 4891.68±0.08 kcal/wk, p = 0.03). Risk factors (higher triglycerides, greater waist circumference, lower weekly physical activity, and lower HDL-C level), however, were all independent for hsCRP (p<0.05 for all factors). Multivariate analysis showed that instead of the importance of central obesity in Caucasian MetS populations, only lower HDL-C levels and lower weekly physical activity were independent predictors of inflammation and hsCRP levels in this geriatric Asian MetS population.

Conclusions: We found that, instead of obesity, low HDL-C levels, reduced physical activity, and inflammation were the major pathological MetS factors in our Asian participants.
Carotid-ventricular coupling during exercise

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**Purpose:** The assessment of vascular performance and its relationship with cardiac parameters in exercise remains unsettled. Therefore, we evaluated carotid cross-sectional distensibility coefficient (DC) and left-ventricular elastance (ElvI) during graded bicycle semi-supine exercise test.

**Methods:** 36 consecutive patients with known or suspected CAD, 20 men, 61±8 years, and 18 healthy volunteers (9 men, 34±3 years) were recruited. Cardiac volumes were estimated from 2D transthoracic echocardiography, right carotid diameter and distension by an automatic system applied to ultrasound B-mode image sequences and central pressures by applanation tonometry; in addition, from these direct measurements, carotid cross-sectional distensibility coefficient (DC) and left-ventricular elastance (ElvI) were obtained. All measurements were performed at rest and at 60%, 70% and peak of the age-dependent maximal heart rate.

**Results:** At exercise peak DC was decreased (from 59.7±20.6 to 39.7±14.5 10-3/kPa) and ElvI increased (from 8.4±3.0 to 13.7±5.8 mmHg/ml*m2) in healthy subjects (p<0.05 vs baseline for all), but not in patients. (DC from 22.1±8.5 to 21.2±7.9 10-3/kPa, ElvI from 3.8±2.2 to 5.4±3.7 mmHg/ml*m2, p=n.s. for all). In the global univariate analysis an inverse correlation of DC in exercise with diameter, age and central pulse pressure (p<0.05; r = -0.32, r = -0.53 and r = -0.43, respectively) was found; in addition, no significant association was observed between DC and ElvI. A significant positive correlation (r=0.28, p=0.02) was observed between DC and ElvI in healthy subjects (r=0.28, p=0.02) but not in patients (r=0.06, p=0.55). In the former group, after adjusting for carotid diameter, mean blood pressure, age, sex and exercise step, DC and ElvI were still significantly associated (full model, r²=0.67).

**Conclusions:** Carotid distensibility was increased and ventricular elastance was reduced during exercise in healthy volunteers but not in patients with known or suspected CAD. The relationship between the two parameters were inversely related during exercise in healthy volunteers, but not in patients with known or suspected CAD.
Effects of advanced school sport course on arterial stiffness and fitness - a pilot trial

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Purpose: Controversial data exist on central hemodynamics and arterial stiffness in young high school students. Our study is therefore aimed to evaluate two different groups of high school students, i.e. one group attending, and the other not attending advanced sport courses. We performed a physical performance test and measured central hemodynamics and arterial stiffness.

Methods: We studied 62 physical healthy pupils [40 attending advanced sport courses, 19 men and 21 women] and 22 pupils not attending sports courses [9 men and 13 women] with a total age 18.9±1.3 years. Both groups were matched for age, body composition and metabolic risk factors. The two groups were observed hemodynamically at rest with a blood pressure meter. Additionally, a standard PHQ test, social behavior evaluation and mental tests, such as retenivity tests were performed.

Results: Fitness measured by a 3000m run was significant different between the two groups [sports group 12.7±1.5 min vs. 16.9±3.5 min; p<0.001]. Subgroup analysis revealed highest differences between females [sports group: 13.2±2.1 min vs. controls: 18.9±2.6 sec; p<0.001]. There were no differences between the two groups regarding peripheral systolic and central systolic blood pressure, aortic pulse pressure, pulse wave velocity and Augmentation Index (AIX) brachial, neither between the different courses nor between men and women. However, we found typical gender-dependent differences regarding peripheral diastolic blood pressure [male 65±9 vs. female 70±8.2 mmHg; p=0.05], peripheral pulse pressure [63±12.4 vs. 52±7.7 mmHg; p=0.05] and AIX aortic [5.1±6.1 vs. 15±11; p=0.05].

Summary and Conclusion: High school students attending sport courses had a significantly higher fitness compared to controls. We could not observe significant differences regarding peripheral or central blood pressures and aortic stiffness. The normal values of the controls cannot be improved by better cardiorespiratory fitness levels in young high school students. However, gender-dependent differences were observed. As consequence, future studies in sportmen should analyze the long-term development of aortic stiffness and central hemodynamics with respect to (i) age, (ii) different cardiorespiratory fitness levels, (iii) type of sports, and (iv) gender.

Effect of chronic physical exercise on the inducibility of ventricular fibrillation in a model of isolated rabbit heart

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Purpose: It has been reported that physical training may protect against sudden death, which in most cases is due to ventricular fibrillation (VF), and it has also been proposed as a nonpharmacological antiarrhythmic intervention. The onset and maintenance of VF are related to the electrophysiological heterogeneity of myocardium. Moreover, several investigators have shown the antifibrillatory effect of physical training in different in vivo models. We have investigated the effect of chronic exercise on electrophysiological heterogeneity of ventricular myocardium and the inducibility of VF in a model of isolated and perfused heart from trained rabbits. Our hypothesis was that chronic physical exercise decreases myocardial heterogeneity and prevents against the triggering of VF by pacing.

Methods: Fifteen NZW rabbits were submitted to a training protocol on treadmill for 6 weeks and seventeen control animals were housed. After this time, animals were anesthetized, killed and their hearts excised and isolated in a Langendorff system. A pacing electrode and a plaque with 256 recording electrodes were located on the left ventricle. VF was induced at increasing frequencies. Inducibility of ventricular at the first attempt was determined. In the hearts in which VF was not triggered additional attempts were used to induce this arrhythmia to analyze it. Four minutes after the onset of VF, the mean dominant frequency (DF) of the arrhythmia and its standard deviation (SD) were obtained, by a spectral analysis. DF and its SD were determined in multiple points of the ventricle, in each experiment, to obtain the coefficient of variation (CV) of DF (SD X 100/DF) as a heterogeneity index. To compare VF inducibility between groups, a "chi-square" test was applied, and for comparisons of CV of DF an Unpaired Student t test was used.

Results: The table shows the inducibility (number of cases, and percentage values) of VF, CV of the DF in percentage and its standard deviation is also showed.

<table>
<thead>
<tr>
<th></th>
<th>VF triggering</th>
<th>No VF triggering</th>
<th>CV of DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL 7 (44%)</td>
<td>9 (56%)</td>
<td>12.98±4.28</td>
<td>0.0001</td>
</tr>
<tr>
<td>TREATED 1* (7%)</td>
<td>13 (93%)</td>
<td>7.78±2.20</td>
<td>0.006 respect to control group.</td>
</tr>
</tbody>
</table>

Conclusions: Physical training exerts protection against VF triggering and this can be related with its effect on the myocardial electrophysiological heterogeneity.

Effect of physical training and IKATP blockade on the energy to reverse ventricular fibrillation in the regional myocardial ischemia. An experimental study

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Purpose: It has been reported that chronic physical exercise exhibits an antiarrhythmic effect in ischemic myocardium and this effect may be related to a blocking effect of IKATP current. Conversely, authors suggest that the opening of this channel protects ischemic myocardium. In the present study we have investigated the energy required to revert ventricular fibrillation (VF) in isolated rabbit hearts from trained and treated with the IKATP blocker glibenclamide, animals, in order to assess both the similarity between the training and the IKATP blockade effects on ischemic myocardium. Our hypothesis was that both training and IKATP blockade reduce the energy required to revert VF, in a quantitatively similar manner, respect to control hearts.

Material and method: Ten NZW rabbits were submitted to a six-week endurance exercise training program, ten rabbits (glibenclamide group) and ten rabbits (control group) were not trained. When the exercise program was finished, rabbits were anaesthetized (ketamine, 10 mg/kg i.v.), killed and the hearts excised, isolated and perfused in a Langendorff System. A pacing electrode and a plaque with 256 recording electrodes were positioned on the left ventricle. Without to interrupt the perfusion of the isolated heart, VF was induced at increasing frequencies and recordings were performed. In the treated group, glibenclamide (10 micromol) was infused throughout the aortic root. We have used a defibrillatory technique based on a bipolar wave method. Five minutes after VF triggering, the circumflex coronary artery was occluded. Ten minutes after it, attempts to defibrillation were applied using increasing levels of energy (in joules). An ANOVA (one factor) test and a LSD post hoc test were used to comparisons between groups.Differences were significant when p<0.05.

Results: Mean energy to defibrilate in the control tended to be higher (p=0.059) than in the trained group (0.17±0.09; n=10, vs. 0.11±0.05; n=10), and also (p=0.059) than in the glibenclamide group (0.17±0.09; n=10, vs. 0.11±0.05; n=10). The values of trained and glibenclamide groups were identical, p=1 (0.11±0.05; n=10, vs. 0.11±0.05; n=10).

Conclusion: Physical training and IKATP blockade seem to reduce the energy required to revert VF, in a quantitatively similar manner. These results could reinforce the idea that the antiarrhythmic effect of chronic physical exercise on ischemic myocardium could be related with a IKATP blockade effect.
Cardiac rehabilitation: need of a global program for full recovery

**Cardiac Rehabilitation: Need of a Global Program for Full Recovery**

**Prevalence of sleep apnea in cardiac rehabilitation facilities in Germany, results of the Reha-Sleep registry**

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**Background:** Sleep apnea (SA) is a risk factor for cardiovascular disease, disease progression and mortality.

**Aim:** The aim of this prospective cohort study was to determine the prevalence of SA in patients undergoing cardiac rehabilitation (CR) after myocardial infarction (MI), bypass surgery (CABG), valve replacement, and 2% following device implementation. Moderate to severe SA (AH1 ≥ 15) was present in 35% of the patients (mean AH1 of 35.1±17). Of the SA patients 58% suffered from moderate AH1 (< 30) and 42% from severe SA (AH1 ≥ 30). A periodic breathing pattern indicating the risk for Cheyne-Stokes respiration was present in 15% of the patients. Patients with sleep apnea were older (66±10 vs. 55±13, p<0.001, t-test) and BMI was higher (28±4 vs. 26±4, p=0.007). In patients with SA cardiac surgery was performed (24% vs. 8%), hypertension (80% vs. 68%) and diabetes II (28% vs. 11%) were more frequent. Furthermore in SA we see lower exercise load (84±40 vs. 108±55 watts, p<0.001), and a trend to towards higher Epworth score (6.2±3 vs 5.8±4, p=0.05) and as well as reduced sleep quality (5.7±2 vs. 6.2±2, p=0.07). There was no significant difference in walking-distance (277±215 vs 242±217 m, p=0.27), SF-12-scores (PCS 35±9 vs. 36±10, p=0.2, MCS 47±11 vs. 47±12, p=0.8) or EF (56±11 vs. 55±10, p=0.6) between the two groups.

**Conclusions:** Sleep apnea is highly prevalent in patients undergoing cardiac rehabilitation in Germany. Patients with SA were older, had a higher BMI, and more often had cardiac surgery and suffered more often from hypertension and dia-betes. Therefore routine screening for SA in CR should be recommended.

**Benefits of cardiac rehabilitation programmes in high-risk patients with symptomatic chronic heart failure and low left ventricular ejection fraction**


**Purpose:** Cardiac rehabilitation (CR) is recommended for patients with symptomatic chronic heart failure (CHF). However, a very low percentage, specially those with low left ventricular ejection fraction (LVEF) or non-ischemic etiology, is referred to CR by the different patient. We aim to investigate the potential immediate and long-term benefits of CR in this high-risk population.

**Methods:** 92 patients (pts) followed in our CHF Unit, were assigned to participate in a CR programme (50%) or not (50%), depending on their city of residence. Eligible patients were those with New York Heart Association functional class (NYHA-FC)<II within the last year, LVEF<45%, and without any exclusion criteria: recent myocardial infarction, NYHA-FC IV, severe valvular heart disease, CR programme adhered to the current European guidelines, clinical, echocardiographic, biological and peak-oxygen consumption were prospectively recorded at baseline, 6 and 9 months. Follow-up was carried out at 12 month visits.

**Results:** Mean age was 59.2±11.9 years and 23.1% were females. The only baseline difference was the percentage of implantable cardioverter-defibrillator (ICD) (43.5% vs those in the programme vs 65.2%, p=0.036). Any cardiovascular event occurred during the CR programme. 65.2% of pts presented an improvement in NYHA-FC after CR vs 22.9%(p<0.001); as reflected also by a mean increase of NYHA-FC ≥ II vs 2.2%(p<0.001). Also, LVEF(%) increased from 39±9 to 33±9.8±0.01. LV telediastolic diameter and mitral regurgitation degree significantly decreased after CR (p<0.001). Also, peakBNP decreased after CR in 290 (IR: 215-40.5) while it raised 578 (IR:106-681) in the usual care group (p<0.001). Peak-oxygen consumption increased in 0.86±0.33 mL/kg/min after CR, decreasing 2.20±4.48 in the other group (p<0.001). At a mean follow-up of 8.8±2 months, 13 patients were admitted for acute CHF (p=0.012). The combined endpoint of death/ICD appropriate shock and re-admission occurred in 6.5% of the pts who had undergone CR vs 34.8% in the other group (p<0.001). The inclusion in the CR programme was the only factor associated with a reduction in the incidence of the combined endpoint (OR: 1.75, 95%CI:0.05-0.603, p=0.006).

**Conclusions:** CR for pts with symptomatic CHF and reduced LVEF promotes an improvement in NYHA-FC, echocardiographic parameters, peak-oxygen consumption and proBNP. Furthermore, CR was an independent predictor of a lower rate of cardiovascular events in the follow-up for this high-risk population.

**Inspiratory muscle work capacity is more severely depressed than inspiratory muscle strength in patients with chronic heart failure**


**Purpose:** To investigate whether a respiratory endurance index such as the inspiratory muscle strength (PImax) is a stronger determinant of functional status compared to inspiratory strength (PIs) in chronic heart failure (CHF).

**Methods:** We prospectively studied 60 patients, age 56±10.6 yrs, LVEF 26.7±8% of NYHA I (n=19/II (n=28)/III (n=7)/IV (n=6) vs normal values reported every 1 sec, us- ing an electronic manometer and computer software (Trainair). Patients also underwent cardiopulmonary exercise testing, 6 minute walk test (6MWT) and eval-

**Results:** Mean peakVO2 was 15.9±3.7 mL/kg/min and 6MWT was 359±80 m. In CR, PImax and PIs were at 54% and 77% of the normal measured val-

**Conclusions:** Both Pimax and Stpmax were associated with lower functional status in patients with CHF. Pimax was more severely depressed compared to strength and may represent a better determinant of enhanced exercise tolerance while pa-

**Ventricular and autonomic benefits of exercise training in myocardial infarction persists after detraining**


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**Purpose:** The aim of this study was evaluate the impact of detraining (DTG) on the ventricular and autonomic benefits obtained by exercise training (ET) after myocardial infarction (MI) in rats.

**Methods:** Male Wistar rats were divided in to (n=8, each group): control (C), MI + ET (MT), MI + ET (DI). One week after MI, the two MI groups were submitted to aerobic ET (3 months; 1 hour/day; 45-75% of maximal running speed). After ET, ID group was followed during 1 month of DTG. At the end of ET and/or DTG protocol the animals were submitted to echocardiographic evaluation and arterial pressure measurement in order to better study the baroreflex sensitivity (BRS), by vasoactive drugs infusion and pulse interval variability (RIV, Fast Fourier Transform).

**Results:** MI area, that was similar in the groups at the initial evaluation.
Remote ischemic postconditioning improves coronary microcirculation in healthy subjects and in patients with heart failure


Background: Remote ischemic postconditioning (RIPC) offers a non-invasive and simple procedure to provide protective effects on organs at risk of ischemic injury. The mechanisms of RIPC include suppressed inflammation and improved endothelial function that are potentially involved in the pathogenesis of heart failure. This study therefore aimed to investigate the effect of 1-week RIPC treatment on coronary microvascular function in healthy subjects and in patients with heart failure. Coronary flow reserve (CFR) was used as a physiological index of coronary microcirculation, and was measured by transthoracic Doppler echocardiography (TTDE).

Methods: This study consisted of 10 patients with heart failure (64 ± 19 years, 9 men) and 8 healthy volunteers (29 ± 7 years, 8 men). They were received with RIPC treatment (intermittent arm ischemia through four cycles of 5 min-inflation and 5 min-deflation of a blood-pressure cuff for one week at a time in a morning and the evening). All subjects underwent TTDE examination for CFR measurements in the left anterior descending coronary artery before and after RIPC procedure.

Results: RIPC treatments were completed and well-tolerated in all patients. RIPC provided increased CFR from 4.0 ± 1.0 to 4.7 ± 1.4 in healthy subjects, and from 1.9 ± 0.4 to 2.3 ± 0.7 in patients with heart failure, respectively (both p < 0.05) (Figure 1). No significant hemodynamic or mechanical complications were observed during the procedure or follow-up.

Conclusions: This TTDE study demonstrated that 1-week RIPC treatment improved the status of coronary microcirculation in healthy subjects and in patients with heart failure, supporting the widespread use of RIPC in clinical practice.

Methods: 249 consecutive patients were enrolled. Admission serum albumin measurements were collected. FC was measured in metabolic equivalents (METs) achieved during the initial and the final exercise sessions of the CRP. Improved exercise fraction was through the METS difference. Post-discharge follow-up was performed to determine the occurrence of a composite outcome (all cause mortality and new hospital admission for ACS, stroke and congestive heart failure).

Results: 222 (89.2%) patients were patients and mean age was 53.9 ± 9.9 years. Mean serum albumin was 39.2 ± 7.5 and 56 (22.5%) patients had hypoalbuminemia ( < 37mg/dL). Patients with hypoalbuminemia were older (56.7 ± 10.4% vs. 52.9 ± 9.6%, p < 0.012), more often women (19.6% vs. 7.9%, p = 0.014) and diabetic (30.4% vs. 16.5%, p = 0.023). There were no differences in other cardiovascular risk factors prevalence, admission diagnosis, left ventricular systolic function and severity of the coronary disease. Hypoalbuminemic patients had lower hemoglobin (13.2 ± 2.3 vs. 14.5 ± 1.3 g/dL, p = 0.0001) and a higher maximum BNP level (294.5 ± 298.2 vs. 155.6 ± 159.9 pg/mL, p < 0.0001).

The CRP FC improved significantly in both groups: from 5.1 ± 1.4 METS to 6.3 ± 2.0 METS (p = 0.0001) in hypoalbuminemia group, and from 5.6 ± 1.4 to 9.5 ± 1.8 METS (p = 0.0001) in normalalbuminemia group. However, the degree of improvement was lower in the hypoalbumin group (3.2 ± 1.9 METS vs. 3.8 ± 1.6 METS, p = 0.033).

Follow-up was possible in 235 (94.4%) patients, for a mean time 24 ± 8.3 months. Composite outcome occurred in 23 (9.2%) patients at a mean time of 11.4 ± 6.8 months. After Cox-regression multivariate analysis, adjusted for relevant covariates, hypoalbuminemia was a strong and independent predictor of the composite outcome (HR 6.0, CI 2.5:14.0, p < 0.0001).

Conclusions: Admission hypoalbuminemia associates with poorer FC recovery and worse outcome in ACS undergoing CRP. A new, inexpensive, functional and prognostic marker might have been found.

Hypoalbuminemia as a predictor of worst functional capacity recovery in patients attending cardiac rehabilitation after ACS


Background: Hypoalbuminemia is a negative acute phase protein and a marker of poor prognosis in heart failure and acute coronary syndrome (ACS).

There are no data addressing the relation between hypoalbuminemia and functional capacity (FC).

This study aimed to evaluate the effect of admission serum albumin on the improvement of FC in ACS patients undergoing a cardiac rehabilitation program (CRP), as well as to access the prognostic impact of hypoalbuminemia in this population.

Methods: 123 patients with a hospital-diagnosed myocardial infarction (MI) occurring 3 months before inclusion were included. Traditional cardiovascular risk factors were measured and the Minor Symptoms Evaluation Profile (MSEP) was used to evaluate self-estimated quality of life at entry of the study. Mean follow-up period was 6.0 ± 1.4 yr. The combined end-point consisted of cardiovascular
Introduction: Diabetes mellitus is one of the modifiable coronary risk factors of main focus in cardiac rehabilitation (CR) after an acute coronary syndrome (ACS). The pre-discharge six-minute walking test (6mWT) is frequently used to prescribe exercise training intensity at entry of a cardiac rehabilitation (CR) program early after cardiac surgery. Changes in physical functional capacity at discharge represent an outcome measure of CR. However, there are no data on the value of a pre-discharge 6mWT on long-term prognosis after cardiac surgery.

Methods: We analyzed data from 304 patients (mean age 66.1 ± 11 years, 22% females). LVEF ≥ 52.1 ± 11%, BMI 26.9 ± 4.9, Hb 10.5 ± 1.4 g/dl, serum albumin 3.9 ± 0.4 mg/dl) who were admitted to our rehabilitation institute following cardiac surgery. A 6mWT was performed at entry and at discharge and expressed as % of theoretical equivalents (METS) achieved and total time (TTPE) to peak exercise at standard exercise testing. We used independent sample t-test and paired sample t-test for between-group and intra-group differences. Survival analysis was done using cox-regression method.

Results: Two-hundred and forty-nine patients were evaluated, mean age was 54 ± 10 years and 222 (89.2%) were men. Forty-nine (19.7%) were diabetic of which were 9 (18.4%) women. Diabetics were older, more frequently women, and showed worse cardiovascular risk profile with higher proportion of smokers, overweight patients and unfavorable body composition. Moreover, the diabetics had more extensive coronary heart disease and had higher proportions of CABGs. Only the non-diabetic patients showed significant improvement in FC (0.8 ± 1.7 ± 0.001 vs. 0.3 ± 1.2, p = 0.15) and in TTPE (55.9 ± 7 p = 0.001 vs 16 ± 92 p = 0.39). These patients were followed for 11.4 ± 6.6 months. Using cox-regression analysis Diabetes mellitus was associated with a higher probability of suffering and adverse cardiovascular outcome (16.7% vs 8%), although significance failed to be demonstrated possibly due to short follow-up duration.

Conclusions: Even though diabetics improve their FC and TTPE they do not show statistical significance improvement. Diabetics show a higher tendency for events throughout follow-up. This suggests that a longer follow-up might be needed to better assess these patients.
Lucrative effects of cardiac rehabilitation on exercise capacity and quality of life in anxious depressed women undergoing coronary artery bypass grafting

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Purpose: Considering supportive strategies such as cardiac rehabilitation program may lead to reducing worse physical and psychological burden especially in women. Current study came to address the beneficial influence of cardiac rehabilitation (CR) schedule on improving cardiovascular parameters as well as depression and anxiety status in Iranian women who attended a complete CR program.

Methods: Of 2834 women who referred to the CR clinic between June 2008 and June 2010, 88 women completed their 24-session CR program and were included into our study. The main outcome was changes of cardiovascular parameters, health related quality of life (QOL); measured using the Medical Outcomes Study Short Form Health Survey (SF-36) and depression and anxiety status assessed using the Costello-Conrey Depression and Anxiety Scale (CCDAS). Study patients were dichotomized into two groups with CCDAS score < 60 (n = 41) and with CCDAS score ≥ 60 (n = 47) via determination of the cut-off point 60 based on the median scores for total CCDAS score.

Results: Regarding changes of cardiovascular parameters after attending a CR program, the participants in the two subgroups similarly experienced significant improvement in METs value and Peak O2 exercise index after attending CR programs. Those with CCDAS score more than 60 had notably lower scores in all baseline QOL components. QOL domains scores significantly improved only in the patients with CCDAS score more than 60 following complete CR sessions. Physical and mental summary scores as well as total score of SE-36 were significantly raised numerically in the two groups, while were significantly increased in the group with CCDAS score more than 60 after CR completing.

Conclusions: Cardiovascular parameters similarly improved in women with and without high anxiety-depression score following CR program. However, improvement of different components of QOL can be more appeared in those who experience psychological impairment.
Reclassification of cardiovascular risk in Europe: application of the updated Systematic Coronary Risk Evaluation (SCORE) algorithm incorporating high-density lipoprotein levels

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Purpose: Cardiovascular disease (CVD) imposes a significant health burden throughout the European Union. Cardiovascular risk can be assessed using validated risk prediction models, such as the European Systematic Coronary Risk Evaluation (SCORE) algorithm that assesses 10-year risk of cardiovascular mortality. This is increasingly relevant for guiding treatment options. Recently, the SCORE algorithm has been updated to incorporate high-density lipoprotein cholesterol (HDL-C) levels (SCORE-HDL), thus providing a more accurate estimate of risk. We have investigated the proportion of patients who would have their risk classification changed with the SCORE-HDL algorithm when compared to the original SCORE.

Methods: The European Study on Cardiovascular Risk Prevention and Management in Daily Practice (EURIKI) (NCT00882336) was a cross-sectional study conducted simultaneously in 12 European countries, recruiting 7641 patients aged ≥ 50 years who were free of clinical CVD but had at least one cardiovascular risk factor (dyslipidaemia, hypertension, diabetes mellitus, smoking or obesity). We calculated risk using international SCORE and SCORE-HDL algorithms in patients aged 50–55 years without diabetes and not receiving lipid-lowering therapy.

Results: In total, risk was assessed in 2321 patients. According to SCORE, 447 were at low risk (LR), 1409 were at intermediate risk (IR) and 465 were at high risk (HR) of CVD mortality (LR: < 1%, IR: 1–5%, HR: ≥ 5% 10-year risk). According to SCORE-HDL, 597 were at LR, 1328 were at IR and 396 were at HR. Of the 447 patients at LR according to SCORE, 11.9% were reclassified by SCORE-HDL as IR and none as HR. Of the 1409 patients at IR according to SCORE, 14.3% and 2.9% were reclassified as LR and HR, respectively. Of the 465 patients at HR according to SCORE, 23.4% and 0.2% were reclassified as IR and LR, respectively. Comparable proportions of males and females at IR according to SCORE were reclassified as HR by SCORE-HDL (3.6 and 2.4%, respectively). However, only 1.9% of males were reclassified from LR to IR, in contrast to 24.9% of females.

Conclusions: Assessment of CVD risk using SCORE-HDL in our patient population (aged 50–55 years, with at least one cardiovascular risk factor but no history of CVD, without diabetes and not receiving lipid-lowering therapy) often resulted in cardiovascular risk reclassification when compared with the original SCORE.

Reclassification into a lower risk category was more common than into a higher risk category, especially amongst females at IR according to SCORE. Most of our study cohort were categorized as LR or IR by both algorithms.

P5664 Persistent impairment of arterial stiffness is associated with future cardiovascular outcome in patients with Coronary Artery Disease

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Purpose: Arterial stiffness is a strong predictor of cardiovascular disease (CVD). The medications for atherosclerotic risk factors and lifestyle changes may modify arterial stiffness. Measurement of cardio-vascular index (CAVI) provides information of the overall arterial stiffness from the origin of the aorta to the ankle independent of blood pressure. This study investigates the impact of improved CAVI in response to optimize therapy for atherosclerotic risk factors on future CVD events.

Methods: This study consisted of 273 patients (87.9 years, 153 men) with suspected coronary artery disease (CAD) who underwent CAVI examinations at study enrollment and 6 month later. In addition, 100 healthy subjects (66±8 years, 55 men) were served as controls in order to estimate normal value of CAVI. All subjects were followed for more than 1 year or until the occurrence of CVD events. Results: Impaired CAVI was defined as ≥8.7 (mean plus 1 standard deviation of thrombosis). Of the 273 CAD patients, 202 patients were followed and in 6 (6%) patients with impaired CAVI and in 6 (6%) patients with impaired CAVI (p < 0.05). Age (p=0.05), multi-vascular disease (p=0.01) and persistent impaired CAVI (p=0.05) were independent predictors for future CVD outcomes. Conclusion: Improved CAVI had worse CVD outcomes as compared to those with improved CAVI (p<0.05) (Figure B).
Primary prevention: new markers and interventions in the field

AF centres, 709 (36%) patients had AF - either described in their clinical history (n=426; 22%) or new onset AF (n=257; 14%) - of these, 683 (96%) had CHADS2=0 and 209 (29%) were not taking OAC. ANGELS of AF reports were then added to the database for altering antithrombotic therapy in 24 patients. Specifically, appropriate OAC therapy was prescribed in 22/209 (10.5%) patients, antplatelet therapy was started in 2 (1.0%) patients. In 158 patients (75.6%) antplatelet therapy was stopped as the best therapeutic choice and in 27 (12.9%) patients no antithrombotic therapy was prescribed. The percentage of patients on OAC therapy, as indicated by guidelines, increased during follow-up from 46.1%, at baseline, to 69.4% at stroke risk evaluation stage, and up to 72.6% at the end of the observation period. In control centres, corresponding figures were 46.9% at baseline and 56.8% at the end of the observation period (p<0.001 vs ANGELS AF group).

Conclusions: The ANGELS of AF project demonstrates the possibility to improve OAC use in accordance with available guidelines for stroke risk reduction in AF by supplying attending physicians with reports about patients risk factors and AF information from continuous device monitoring.
nique. Large elastic artery stiffness was determined in vivo by pulse wave velocity (PWV). Vascular function was measured in isolated aortic rings using pharmacological agents to test constriction and vasodilation. Ex vivo coronary and cardiac function was determined in isolated perfused hearts. In vivo diastolic dysfunction was assessed by mitral inflow (early (E) and late (A)) and annulus (E' and A') velocity pattern through pulsed wave (PW) and tissue doppler (TD) high-resolution ultrasound imaging.

**Results:** Dietary nitrate supplementation increased nitrate intake in plasma (YC 30.3 ± μmol to YN 100.1 ± μmol. OC 38.3 ± μmol to OC 162.3 ± μmol, both p <0.05). Coronary endothelium dependent vasodilation was lower in old compared to young mice and nitrate treatment reversed this dysfunction, but had no effect on young animals (YC 76.3±% vs OC 60.2±% vs ON 74±4%, p<0.05). Coronary endothelium dependent flow responses revealed a diminished repayment flow, which was reversed after treatment (Jc Flow: YC 517±40% vs OC 370±28% vs OC 494±28%, both p<0.05). PW and TD imaging revealed an aging-related "pseudo-normal" diastolic pattern depicted with normal E/A and reduced E′/A′, which was reduced with dietary nitrate supplementation (E/A: YC 1.62±0.1 vs OC 1.43±0.1, p=NS; E′/A′: YC 1.48±0.1 vs OC 1.06±0.1 vs OC 2.14±0.1, both p<0.05). The diastolic dysfunction was confirmed in isolated hearts and reversed by dietary nitrate treatment (dp/dt min [mmHg/s]: YC 28% ± 22% vs ON 49.4% ± 20.2%, p<0.05). Coronary endothelium dependent flow responses revealed a diminished repayment flow, which was reversed after treatment (Jc Flow: YC 517±40% vs OC 370±28% vs OC 494±28%, both p<0.05).

**Conclusion:** We observed an altered age-related cardiovascular phenotype, which was reversed by dietary nitrate supplementation. Nitrate could be a promising agent against senescence associated diastolic and vascular dysfunction.

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**P5671**

mPrevention: Content analysis of iOS and Android smartphone applications in regard to primary cardiovascular risk factor prevention

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**Purpose:** With the increasing access to and popularity of smart phones, a great pool of applications (apps) has been developed rapidly concerning health issues, including cardiovascular diseases and risk factors. We analyzed the content of "health and fitness" apps from the two fastest-growing platforms (namely, Apple's iOS and Google's Android) distributed through their official online stores (itunes.com and market.android.com respectively). We sought to see how many apps are relevant to controlling for modifiable cardiovascular risk factors.

**Methods:** We examined popular apps on iTunes and Android Market. Two reviewers analyzed the information provided in specific web-pages for each app, and coded it independently for their (1) primary and secondary subject focus areas; (2) language; (3) price; and (4) relevance to the category ("Health and Fitness"). Because of the dynamic nature of popular apps list, we took the final list on January 25, 2012.

**Results:** A total of 240 popular apps on iTunes and 24 on Android Market were assessed. Fifty-four (22.5%) iOS apps declared the "fitness" as their primary focus areas; (2) language; (3) price; and (4) relevance to the category ("Health and Fitness""). Because of the dynamic nature of popular apps list, we took the final list on January 25, 2012.

**Conclusion:** It seems that the most prevalent apps that deliberately gather information about heart rates were apps or less popularity of other cardiovascular risk factors from developers' perspective. We could not find a comparable bulk of popular apps which consider this condition (P=0.001). The difference in IMT and prevalence of plaque was also significant even in patients without MetS as well as those with MetS (all P<0.05).

**Nafld-associated adjusted odds ratio of carotid plaque was 1.583 (95% CI, 1.309-1.857, P=0.024) without MetS and 1.536 (95% CI, 0.512-4.604, P=0.444) with MetS.

**Conclusion:** NAFLD is significantly associated with carotid atherosclerosis in non-diabetic outpatients even without MetS. Carotid screening for NAFLD might be beneficial for assessment of future atherosclerotic complications.

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**P5674**

Abdominal aorta vascular wall changes in healthy term neonates induced by their own and mothers cardiovascular risk factors

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**Purpose:** Prematurity and birth weight influence adulthood cardiovascular risk profile. Nevertheless, other mothers’ and infants’ parameters can be considered as early determinants of adult cardiovascular risk. Study aim was to evaluate the influence of maternal cardiovascular risk factors, pregnancy lifestyle habits, serum levels of lipids and proinflammatory markers of healthy term neonates at birth, on antero-posterior abdominal aorta diameter (APAO) (a well-established early marker of atherosclerosis).

**Methods:** We studied 97 neonates and their mothers (mean age: 32±2 years). We evaluated: gestational age, birth weight, length and head circumference, fasting glucose, total, HDL-, and LDL-cholesterol, triglycerides, fibrinogen, D-dimers and APAO within 24 hours after birth. Cardiovascular risk profiles of mothers considered: diabetes, gestational hypertension, smoking and prepregnancy body mass index (BMI).

**Results:** Maternal BMI showed an inverse relationship with infants D-dimers levels (r= -0.36, p=0.007). Mothers who smoked before and during the first...
primary prevention: new markers and interventions in the field of primary prevention

Objective: To evaluate the effect of 5-years cardiovascular preventive program in primary care of Russian Federation, depending on the baseline educational level and blood pressure levels.

Methods: In 1977-1990 in Moscow a large prevention project was realized. The project was realized in two primary care areas of Moscow and included men with baseline age 40-59. One primary care area was intervention area where cardiovascular prevention program was realized during the 5 years, other area was control. Participants of intervention (n=3488) and control primary care areas (n=3168) had the similar age, education and cardiovascular morbidity. The cardiovascular prevention program was realized during the 5 years, other area was control. Participants of intervention (n=3488) and control primary care areas (n=3168) had the similar age, education and cardiovascular morbidity.

Results: A total of 1019 participants were screened and 298 (29%) were randomised to usual care or a nurse-led primary prevention program for such individuals who would not normally be subject to pro-active primary prevention.

Conclusion: The IMPRESS study is investigating an innovative, nurse-led screening and primary prevention program for such individuals who would not normally be subject to pro-active primary prevention.

Purpose: Individuals with a family history of premature cardiovascular disease (CVD) have greater risk for similar development of CVD that is not quantified by traditional risk tools such as the Framingham Risk Score (FRS). The IMPRESS study is investigating an innovative, nurse-led screening and primary prevention program for such individuals who would not normally be subject to pro-active primary prevention.

Methods: Intima Media thickness guidance of Primary prevention in Relatives of individuals with Early onset atherosclerosis (Study IMPRESS) is a 3 year nurse-led, multicentre, randomised control study for individuals aged 40-65 years with a family history of premature CVD to determine if they are at low or intermediate FRS with or without evidence of increased carotid intima media thickness (CIMT). Eligible individuals are randomised to usual care or a nurse-led primary prevention clinic (comprising a combination of clinic visits, telephone and electronic communication) to implement an adaptable traffic-light system in order to systematically perform individual risk and need delineation to "nurture" the intensity and frequency of health care intervention for the reduction of cardiovascular risk factors. We report on the risk profile after a short term 3 month follow up of the first 60 high intensity (red) intervention participants.

Results: A total of 1019 participants were screened and 298 (29%) were randomised into the study (aged 53±7 years and 42% male) based on: low FRS and increased CIMT (74%), intermediate FRS without (17%) or with increased CIMT (7%), or the presence of atherosclerotic plaque (2%). Of these, 142 were randomised to the Intervention Group with 83% requiring high risk (red) management. Comprehensive reports and clinical recommendations were sent to each individual's primary care physician. After 3 months of initial nurse-led management, compared to baseline, there have been clinically significant improvements in the following: i) total cholesterol from 5.38±1.04 to 4.73±1.12 mmol/L (Δ -0.65 mmol/L); ii) LDL cholesterol from 3.60±0.89 to 2.84±0.95 mmol/L (Δ -0.73 mmol/L); iii) triglycerides from 1.67±1.08 to 1.29±1.09 mmol/L (Δ -0.38 mmol/L); iv) FMD (mm) from 5.6±2.5 to 7.0±2.0 (Δ 1.4); v) blood pressure (138±19/85±11 to 135±16/84±10 mmHg) (Δ -3/5 mmHg). There was also a small reduction in mean BMI from 29.2±5.8 to 29.0±5.7 kg/m² (Δ 0.2 kg/m²).

Conclusions: Early results show potential for the innovative IMPRESS intervention study, utilising diet and lifestyle modification in conjunction with statin therapy (if needed) to better identify adults with a family history of CVD and reduce their risk of the same fate.
Impact of supplemental treatment with ezetimibe in patients with coronary artery disease on statin therapy; Coherence Tomography Study


Background: Although lipid lowering therapy by statin and ezetimibe has been reported to provide greater reduction in low-density lipoprotein cholesterol (LDL-C) level than statin monotherapy, it is unknown whether the supplementary therapy could affect plaque stabilization. The change in fibroblast growth factor is a major determinant of vulnerable plaques and optical coherence tomatography (OCT) has been an imaging modality for assessing such micro-structural changes due to the resolution (10–20 μm). The primary objective of this study is to evaluate the effect of ezetimibe addition on OCT estimation on progression of coronary atherosclerotic plaque evaluated by OCT.

Methods: A total of 90 angiographic pectin patients with intermediate non-culprit lesions were enrolled and divided into two groups; OCT estimation group (statin group; n=45) or ezetimibe-OCT estimation group (ezetimibe group; n=45). OCT analysis was performed at baseline and 9-month follow-up.

Results: Lipid rich plaque was detected in 57 patients (statin group n=26, ezetimibe group n=31) at baseline OCT examination. Therefore, follow-up OCT analysis was performed for those patients. The LDL-C level was similar at the two groups. Although the lumina area was not significantly changed, fibrous-cap thickness was significantly increased and angle of the lipid laden was significantly decreased in both groups. The change in the fibrous-cap thickness was significantly greater in the ezetimibe group than in the statin group, although the change of the lumina area and lipid laden angle were similar.

Conclusion: The lipid lowering therapy by statin and ezetimibe could increase the fibrous-cap thickness of lipid-rich plaque than statin therapy.

The centralized pan-levant survey on the under-treatment of hypercholesterolemia CEPHEUS-levant1, analysis of predictors of cholesterol goal attainment

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Purpose: The primary objective was to establish the proportion of dyslipidemic patients on lipid lowering drugs (LLDs) reaching their target LDL-C goals according to Updated 2004 Current National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) guidelines. Secondary objectives targeted subgroups including primary/secondary prevention, metabolic syndrome, and goals achieved according to The Third Joint European Task Force (TJETF) guidelines and identified determinants of under-treatment.

Methods: This multi-center, cross-sectional survey enrolled 1022 consecutive dyslipidemic patients in an urban out-patient clinic setting, in Jordan and Lebanon (August 2010-January 2011) on LLDs for ≤3 months with stable doses for ≥6 weeks. Physicians and patients filled out dyslipidemia diagnosis and treatment questionnaires, then clinical data and fasting blood samples were collected during one visit.

Results: Patients included were in the full analysis set. According to the TJETF guidelines 57% of patients achieved their target LDL-C goal, 50% in primary prevention, 63% in secondary prevention and 48% in patients with metabolic syndrome (Met S). Compliance with the total number of participants (n=22) were (a) absence of metabolic syndrome (b) statin mono-therapy (c) age <55yrs (d) lower waist circumference (e) lower pre-treatment LDL-C level and (f) patient compliance, among others. In the multivariate analysis the predictors were: (a) type of LDL therapy (b) patient compliance and (c) lower pre-treatment LDL-C level.

Conclusion: CEPHEUS-Levant reports sub optimal attainment of LDL-C goals for patients on LLDs. Significant predictors of goal attainment were the lower risk categories (absence of diabetes mellitus, Met S or coronary heart disease) lowest pre-treatment LDL-C levels, statin mono-therapy and patient compliance. Aggressive awareness campaigns and other initiatives targeting lifestyle changes and treatment adherence are indicated with special attention to the highest risk groups.

The interplay between sense of coherence and perceived health in adolescents with congenital heart disease

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Purpose: Life expectancy in patients with congenital heart disease (CHD) has increased substantially. In general, patients perceive their health as good, even in case of complex CHD. It is hypothesized that sense of coherence (SOC) plays a role in the perception of health. However, the interplay between SOC and perceived health has not been thoroughly investigated yet. Therefore, we examined the direction of relationships between SOC and domains of perceived health in adolescents with CHD.

Methods: In this longitudinal study, we assessed 429 adolescents with CHD at two points in time with a nine month interval. The median age was 16 years, and the sample comprised 535 boys. Subjects were recruited from the database of paediatric and congenital cardiology of our hospital, and were eligible if they had confirmed CHD; were 14-18 years of age at the start of the study; had a last cardiac consult ≤5 years ago; were able to read and write Dutch; and valid contact details were available. Patients were excluded if they had cognitive or physical limitations inhibiting filling out the questionnaires; had prior heart transplantation; and if they did not consent. Participants were asked to complete the 13-item orientation to life questionnaire to measure SOC, and the generic and cardiac module of the PedsQL to measure generic and disease-specific perceived health. Cross-lagged path analysis using structural equation modelling was conducted, controlling for age, sex and disease complexity.

Results: SOC at time 1 negatively predicted all domains of generic perceived health (physical problems p<0.01; emotional problems p<0.001; social problems p<0.05; school problems p<0.001) and three out of five domains of disease-specific perceived health (symptoms p<0.05; physical appearance p<0.001; cognitive problems p<0.001 at time 1) and (c) lower pre-treatment LDL-C level.

Conclusions: Evidence was obtained for reciprocal pathways between SOC and the domains of perceived health, although the predominant direction of effects was from SOC to perceived health. Hence, SOC could be an important individual characteristic to focus on in interventional and prevention efforts.
Sexual concerns of cardiac patients: a psychometric analysis

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Purpose: Cardiac patients often report fears and concerns, symptoms interfering with sexual activity, and changes in sexual interest and function, but validated instruments are lacking. This study validated the Sterneke Sexual Concerns Inventory – General Cardiac Version (SSCI-GCV).

Methods: Questionnaires were mailed to patients hospitalized over a 1-year period with CAD, ACS, angina, MI, HF, or CABG, with 336 respondents. The SSCI-GCV was revised from a similar instrument used in HF, adding 1 item for sexual fear of MI, a prevalent concern among cardiac patients. Questions related to erectile dysfunction (ED) were revised for improved clarity. The 14 items represented: change in the sexual relationship (1 item), sexual fears (5 items), change in interest (1 item), symptoms with sexual activity (3 items), sexual dysfunction (3 items), other sexual concerns (1 open-ended item). Items were rated on a Likert scale from “never” (0) to “frequently” (3), with a higher score indicating greater sexual concerns. Item analysis included correlation matrices to assessing items representing underlying factors for sexual concerns. Construct validity was assessed with confirmatory factor analysis and known groups, comparing sexually active to non-active using t-tests.

Results: After item analysis of Likert scaled items, 12 of 13 items were retained; amount of change in the sexual relationship poorly correlated with other items (r = 0.30) and was removed. Two items on ED, one in the count of partner, were combined as one variable for ED; therefore analyses were computed on 11 items. Cronbach’s alpha for the revised instrument was 0.86 (N=205). Using confirmatory factor analysis, factor loadings showed items were appropriate for the combined scale. For sexual concerns, sexual interest, and symptoms with sexual activity, all loadings were above 0.50; two items were < 0.50, ED and partner overprotectiveness, but both retained, consistent with the literature and patient and partner self-report. There were no differences in the total score between those sexually active and not active, indicating that those not sexually active may also have sexual concerns.

Conclusions: The SSCI-GCV is a reliable and valid instrument for measuring sexual concerns of cardiac patients, and may be useful in both research and clinical settings. The study further illustrates the need to assess all cardiac patients, including those not currently sexually active for which sexual concerns may present a barrier to sexual activity, and the instrument may serve to facilitate discussion of sexual quality of life.

Implementing a European curriculum for clinical expertise and delegated responsibilities in heart failure nursing: an educational initiative from the HFA and CCNAP

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There is an increasing role for heart failure (HF) nurses with extended clinical expertise and delegated responsibilities in many European countries. Further, many nurses seek an academic accreditation for their experience, skills and knowledge.

Objectives: To describe the experiences of implementing a European curriculum for clinical expertise in HF nursing that was developed by the Heart Failure Association and the Council for Cardiovascular Nurses and Allied Professionals of the European Society of Cardiology.

Methods: Data on implementation were collected from 5 educational programmes in 4 countries: Sweden, Norway, Germany (2) and Spain. Data collection included methods of teaching and assessment, and that their new education is a career opportunity to more advanced tasks and responsibilities.

Results: Both in Norway and Sweden 25 nurses underwent the programme. In Germany 8 courses were held including 74 nurses. In Spain, 84 nurses are currently involved in an online course. The course extent varies between 200-400 hours in total. In Norway the course is part of a post graduate specialization in cardiovascular nursing on a master degree level. In Sweden the course can be part of a master degree. The clinical learning methods were supervised consultations, practical opportunities for skill acquisition, case presentations and multi-disciplinary group work. The theory based were tutorials, lectures, seminars and self-tuition. Sweden used a web-based tool for the anatomy/physiology sections. In Spain, the whole course is given online allowing the students to connect to the platform at their convenience. This also applies to the teachers from different geographical areas in Spain thus allowing to operate on lower cost. In one of the German sites an evidence-based telephone-monitoring is taught as part of post-discharge management. Examinations consist of individual written (often multiple choice) and oral exams, group exams and case presentation. Course evaluations were consistently high, and students perceived that the syllabus sufficiently covered the HF area and was relevant for clinical practice.

Conclusions: The challenges of implementing the curriculum for HF nursing in Europe were met. Entry requirements for the nurses, the organization of the training, requirements and role of educational supervisor and training centers as well as a regular update on the content are important areas for ongoing improvement. Further, it is important that the specialised HF nurses contribute to HF care and that their new education is a career opportunity to more advanced tasks and responsibilities.

Depression disorder in administration patients with CAD is stronger independent risk factors for cardiovascular events than other psychosocial disorders

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Aim: Although recent attention has focused on the role of psychosocial factors in the acute precipitation of myocardial infarction and sudden cardiac death, it is not clarified which psychosocial factor contributes to aggravation of most. So our aims of present study were to evaluate depression, anxiety and anger symptoms in patients with coronary artery disease (CAD) and investigate their relationship to prognosis.

Method/Result: We prospectively enrolled 226 of consecutive patients (male: 174, age: 65.7±10.8) who admitted to our hospital because of CAD. Depression disorder was estimated by questionnaire of PHQ-9 (the Patient Health Questionnaire), anxiety disorder was by GAD-7 (Generalised Anxiety Disorder) and anger was by TAS (Trait anger scale). We defined depression as high PHQ-9 score (>10), anxiety disorder as high GAD-7 score (>10) and anger as high TAS score (>22). A comparison was made on a new cardiovascular event (myocardial infarction, stroke, transient ischemic attack, or congestive heart failure) or cardiac death (Mean follow-up duration 13.8±6.9 months) on the basis of depression symptoms and anxiety symptoms and anger symptoms. The patients with depression symptoms had significantly higher survival rate from cardiovascular death (p = 0.05) or composite endpoint (cardiovascular death and hospitalization), as well as those with anxiety or anger symptoms. Moreover, the patients with depression was more sensitive than anxiety or anger (HR 3.76 vs 3.64 or 1.22).

Evidence for reversibility of cocaine cardiotoxicity. Follow-up study with cardiovascular magnetic resonance at 3T

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We have previously evaluated with cardiovascular magnetic resonance at 3T (3CMR) a cohort of 98 consecutive cocaine addicts and observed cardiovascular pathology in a high percentage of them, mainly decreased biventricular systolic function (LVF, RVF) and increased left ventricular mass (LVM). Our aim now was to follow up with 3CMR the first 30 subjects of this cohort found to have cardiovascular pathology, after 1 year of a rehabilitation program.

Methods: Of the 50 subjects initially scanned before December 2010 (7 females, age-range: 26-53, years of addiction: 7,8), 30 were found to have some degree of cardiovascular pathology. They were scheduled for a 1 year follow-up 3CMR scan after their rehabilitation program. 3CMR protocol included TrueFISP cine sequences in the usual planes, STIR sequences, myocardial late gadolinium enhancement (LGE) study after gadolinium-DTPA (0.1mmol/kg), and T2TSE study of the aorta. Images were analyzed by 2 blinded, independent observers.

Results: Mean follow-up was 13±3,9 months. 12 patients were lost for follow-up (1 patient died, 1 was in prison, 2 denied consent and 8 had lost contact with the Unit). Of the remaining 18 patients, only 11 had achieved complete rehabilita-
tion and quit cocaine (group A). Group A showed a significant decrease in both end-diastolic and end-systolic volumes (LVEDV,LVESV, RVEDV, RVESV) and increase in LVEF and RVEF with a mild, non-significant decrease in LVM (±1.4 g). Patients who had not quit cocaine (group B) showed non-significant increases in volumes and LVM and decreases in LVEF, RVEF. The table shows the initial parameters for all subjects and their variation on follow-up.

<table>
<thead>
<tr>
<th>Initial (all subjects)</th>
<th>Mean ± SD</th>
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<tr>
<td>RVEF (%)</td>
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- **Conclusion**: These preliminary results show that 1 year of cocaine abstinence leads to a significant decrease in ventricular volumes and increase in biventricular systolic function, pointing towards the reversibility of cocaine cardiotoxicity.

### P5688

**Relation between poor sleep quality and resistant hypertension**

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**Purpose**: Both insomnia and short sleep duration have been associated with increased incidence of new-onset hypertension. However, the relationship between sleep loss and hypertension severity, and in particular resistant hypertension, has not been ascertained yet.

**Methods**: 270 patients at first access to an Excellence Hypertension Outpatient Unit were enrolled. Medical and pharmacological history, anthropometric parameters, office blood pressure (BP) values were collected. Resistant hypertension was defined according as BP values >140/90 mmHg with ≥3 or more antihypertensive drugs, or controlled BP with 4 or more drugs, including a diuretic. Pittsburgh Sleep Quality Index (PSQI), and Beck Depression Inventory (BDI) were assessed.

**Results**: Complete data were available for 252 patients (51.1%), mean age 57±12 years, BMI 27.5±5 kg/m², current antihypertensive treatment 86%, previous CV events 11%, diabetes 8%, current smoking 15%, hypercholesterolemia 61%. Mean sleep duration was 6.4±1.6 hours, with a 49% prevalence of short sleep duration (<6 hours) and similar in both sexes (4.6±1.6 in females, 6.5±1.6 hours in males, p=0.99). Conversely, women had higher PSQI (6 vs 4, p=0.03) and higher BDI scores (6 vs 3, p=0.008). Resistant hypertensive patients (15% of the total population) had higher PSQI than the remaining population (7 vs 5, p=0.02). However, this association was present in women (8 vs 5, p=0.01) but not in men (5 vs 4, p=0.49), as well as the association between BDI score and resistant hypertension (women 8 vs 5, p=0.02; men 3 vs 3, p=0.63). In a multiple logistic regression analysis, the presence of poor sleep quality (defined as PSQI≥5) was independently associated with resistant hypertension (OR 2.1, CI95% 1.1-5.4), sex and presence of depressive symptoms, even after adjustment for age, obesity, previous cardiovascular events, sleep duration, use of hypnotic drugs. The insertion of independently associated with resistant hypertension (OR 2.1, CI95% 1.1-5.4), sex and presence of depressive symptoms, even after adjustment for age, obesity, previous cardiovascular events, sleep duration, use of hypnotic drugs. The insertion of

**Conclusion**: Short sleep duration is highly prevalent in hypertensive patients. This condition is accompanied by poor sleep quality and depressive symptoms, especially in hypertensive women. Poor sleep quality is associated with a 2.1-fold higher probability of having a diagnosis of resistant hypertension. This association could be mediated by the presence of diabetes mellitus.

### P5689

**Improving adherence to antihypertensive agents in chronic kidney disease**

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**Background**: Hypertension is a modifiable and very important risk factor in chronic renal disease (CKD), and medication adherence (MA) is critical in reaching treatment goals. Improvement of MA for antihypertensive agents and its impact on blood pressure (BP) in CKD practice settings are not well studied.

**Methods**: In a prospective, controlled-open-label studies, the authors have evaluated the three-year MA for antihypertensive agents on progress of renal disease and risk of development of cardiovascular disease in 546 hypertension patients with CKD from 2006 to 2010 with targeted nurse-physician intervention. Before randomization Outpatient BP measurements were averaged as high (>140/90 mm Hg). Blood pressure, serum creatinine(Cr) and potassium were monitored every 14 days in the period of follow-up by physician and healthcare nurse so that every patient is able to perform self-monitoring BP at home and medication possession ratio(MPR) of target systolic blood pressure<130/80 mmHg is more than 90% in observation groups. MA was calculated using medication possession ratio (MPR = actual treatment days/total possible treatment days). Good versus Poor MA (MPR ≥ 0.9 vs. <0.9) groups were compared for differences in outcome and laboratory variables.

**Results**: By the end of three year,MPR in observation group is 94% and in other is 38%, mean blood pressure in good MA group was 126±9/7±6 mmHg and in control was 146±8±19/12±6 mmHg. Cr clearance increased from 51±2.0 to 64±3.0 ml/min (p<0.001) in the group of good MA MA, By contrast, Cr clearance decreased significantly from 52.1±9.1 to 40±3.6 ml/min (P<0.001) in the controls. During this time, urine protein excretion decreased from 1.4±0.9 to 0.7±0.4 g every 24 hours(P<0.0001) in the treatment group, but urine protein excretion decreased slightly (from 1.3±0.4 to 1.2±0.7) in the controls. 20 patients had got ACS, 28 patients stroke,38 patients had got pneumonia, 11 patients renal dialysis and in the treatment group, but incidence of hyperkalaemia was similar between two groups.

**Conclusion**: Good MA is associated with a greater controlled hypertension, reduced protection of heart and kidney and may decrease mortality than the poor MA.
medication, were referred to our hospital. Only 53 patients were eligible for renal denervation. Main reason for exclusion was white coat hypertension (n=18; 25%), but also secondary causes of hypertension were revealed, which were not described during previous screening (see table).

Main reasons for excluding patients:

- White coat hypertension 18 (25%)
- Primary hyperaldosteronism 6 (8%)
- Significant renal artery stenosis 4 (5%)
- Primary hyperparathyroidism 1 (1%)
- Glycinemic acidosis 1 (1%)
- Comorbidity 8 (11%)
- Multiple main arteries 1 (1%)
- Prior renal artery stenting 4 (3%)
- Other (i.e. single kidney, patient refusal, non-compliance) 31 (42.5%)

Conclusion: Extensive screening for secondary causes of hypertension can elucidate the reason for hypertension in an essential part of patients with resistant hypertension. More importantly, this prevents treatment with an invasive treatment modality, which can be anticipated not to be effective in these patients.

P5690 Characteristics of target organ damage in hypertensive patients being treated with renin-angiotensin system inhibitors versus calcium channel blockers

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Purpose: Protective effects of renin-angiotensin system inhibitors (RASIs) against target organ damage have been reported to be greater than those expected from their blood pressure (BP) lowering effect. Characteristics of hypertensive patients treated with RASIs and calcium channel blockers (CCBs) were investigated.

Methods: Hypertensive patients under a monotherapy with RASIs (n=175, RA-Sis group) and CCBs (n=261, CCBs group) were recruited from 9,288 participants in our health checkup program. Their brachial BP, central BP (CBP), electrocardiogram (ECG), and ambulatory BP monitoring (ABPM) were performed in all patients. Echocardiographic examination, and urinary albumin excretion were measured. Untreated hypertensive patients (n=671, no medication group) were used as a reference. Patients treated with anti-diabetic or anti-dyslipidemic medication were excluded from the study.

Results: Brachial BP and CBP were similarly reduced in RASIs and CCBs groups as compared to no medication group. In contrast, the urine albumin level was lower in RASIs than in no medication group, while the level was not different in CCBs and no medication groups. eGFR was not different in RASIs and CCBs groups.

Conclusions: Although RASIs are more often prescribed than CCBs in patients with albuminuria, urine albumin was smaller in RASIs group than in CCBs group. This suggests that RASIs strongly reduces urinary excretion of albumin and may prevent the development of chronic kidney disease.

P5692 Women with at least one child, compared to nulliparous, have almost three-fold risk of early hypertension during menopausal transition

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Purpose: Pregnancy produces marked alterations in cardiovascular physiology and it is still debated if it may result in permanent detrimental effects on the body. Particularly, studies regarding the relationship between parity and blood pressure are in later life have produced conflicting results. The aim of our study is to analyze whether parity influences the prevalence of hypertension in a population of perimenopausal women.

Methods: We prospectively enrolled a population of 1000 perimenopausal women, (mean age of 55.2±5.4 years), with a median follow-up of 63.0 months (25th-75th percentiles: 42.7-104.0 months). The study sample consisted of patients who self-referred, between November 2008 and February 2009, to the BenEssere Donna Clinic, dedicated to menopause-related disorders. Results: 122 (12.2%) women were nulliparous and 878 (87.8%) have had at least one child. 34 (27.9%) women among nulliparous and 326 (37.1%) women among parous were hypertensive at baseline (p=0.046) and 812 women (81.2%) were in their postmenopausal period. Univariate analysis showed that women with one or more children were at higher risk of being hypertensive (Odds-Ratio (OR): 1.529; 95% Confidence Interval (CI): 1.068-2.184; p=0.047). Likewise, multivariate analysis revealed that parity (OR: 2.72; 95% CI: 1.20-6.17; p=0.001) and family history of hypertension (OR: 3.82; 95% CI: 2.31-5.83; p<0.001) were independently related to hypertension at baseline. In a subanalysis of 640 (64.0%) initially normotensive women, 109 (10.9%) subjects developed hypertension after follow-up, without a statistically significant relation with parity (13.6% in nulliparous versus 17.6% in parous; p=0.362). Consistently, parity showed no relationship with the incidence of hypertension during follow-up (OR: 1.35; 95% CI: 0.707-2.757; p=0.363 at univariate analysis).

Conclusions: Our study, for the first time in a population of caucasian perimenopausal women, demonstrated that parity is an independent risk factor for early hypertension during menopausal transition. Consistently, hypertension that develops after menopause appeared not to be related with parity.

P5693 Metabolic abnormalities in patients with resistant hypertension - relation to blood pressure levels and obstructive sleep apnea severity - the RESIST-POL study

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Purpose: To evaluate metabolic abnormalities in patients with true resistant hypertension in relation to blood pressure levels and the severity of obstructive sleep apnea (OSA).

Methods: From the group of 204 patients included in the RESIST-POL study with true resistant hypertension (clinic BP: >140/90 and ambulatory daytime mean 24-hour BP: >135/85 mmHg staying on 3 antihypertensive drugs including renin-angiotensin), with eGFR-60ml/min/1.73m² and without previously recognized diabetes mellitus (DM) we included for this analysis 155 patients (93M, 62F, mean age 47.5, range 19-69yrs) without secondary causes of hypertension. Ambulatory blood pressure monitoring (ABPM) was performed and mean 24h BP values as well as dipping status were evaluated. All patients underwent full night polysomnography – apnea/hypopnea index (AHI) was assessed. OSA was defined as AHI >2 events/h. Metabolic syndrome (MS) components, including oral glucose tol-

Results: Genotype distribution for non-HT and HT was GG: 50.9%, GA: 41.8%, AA: 7.9% and GG: 51.5%, GA: 37.6%, AA: 10.9% respectively. There was no significant difference in fibrinogen levels (mg/dl) between 455A homozygotes and 455G allele carriers in non HT patients (448±34.6 vs 433±28.9, p=NS). Importantly, 455A genotype presented with significantly more fibrinogen compared to GG-GA in HT patients (535±42.5 vs 414±28.0, p<0.001). Moreover, HT 455A homozygotes had significantly increased D-dimers levels (µg/l) compared to 455G allele carriers (640±33.6 vs 485±5.27, p<0.05). No difference was observed for non-HT regarding D-dimers between the 455A genotype and GG-GA (477±6.7 vs 450±4.07, p=NS). Interestingly, 455A genotype presented with higher IV% (X%) and IX% levels compared to GG-GA in HT patients (133.6±5.8 vs 117.8±3.3, p<0.05, for IV) and (101.9±4.6 vs 92.2±2.4, p<0.05, for IX). However, no difference was observed in IV and IX levels between 455A and GG-GA (105.8±11.6 vs 118.7±4.4, p=NS for IV and 95.8±8.0 vs 119.4±29.1, p=NS for IX) in non-HT respectively.

Conclusions: We have shown that the G455A fibrinogen genetic polymorphism has a remarkable impact on prothrombotic profile of patients with hypertension, by affecting fibrinogen, D-dimers, factor V and factor X levels. These findings provide evidence that this polymorphism modifies further the atherosclerotic effects of hypertension via alterations in the coagulation cascade.

Clinical aspects in hypertension 1067
ebrance test (OGTT) were assessed. The subcutaneous fat volume (SVF) and intra-abdominal visceral fat volume (VFV) were measured at L4-L5 disc space level using a computed tomography scan.

Results: Metabolic syndrome was diagnosed in 99 patients (63.9%). The most frequent MS component was abdominal obesity (72.3%), followed by increased fasting glucose (51.6%), increased triglyceride plasma levels (34.2%) and decreased HDL cholesterol plasma levels (32.9%). On OGTT impaired glucose tolerance was found in 27.1% patients and previously unrecognized DM was found in 11.6% patients. Patients with MS were characterized by higher frequency of OSA (58.9%, p < 0.01). There were no difference in 24 h breathing and sleepiness status between patients with and without MS. There were significant correlations between AHI and glucose plasma levels on OGTT, the presence of abdominal obesity, SVF (r = 0.25, p < 0.01) and VFV (r = 0.43, p < 0.01). Patients with newly recognized DM and patients with increased fasting glucose were characterized by higher VFV as compared with patients without these abnormalities.

In a multivariate model including age, sex, MS components, 24 h BP levels, SVF and VFV, AHI was independently related with male gender (β = 0,31; p < 0,001) and VFV (β = 0,27; p < 0,01).

Conclusions: In our studied group of patients with resistant hypertension abdominal obesity and glucose metabolism abnormalities were relatively frequent and were related to severity of OSA but not to BP levels. Among factors characterizing metabolic abnormalities the volume of visceral fat seems to be a dominant feature related to the severity of OSA.
and inflammation on the urinary levels of this marker in hypertension has never been performed. Urinary 8-OHdG and plasma TNF-alpha, sTNF-R1, sTNF-R2 and IL-6 were determined.

Results: 8-OHdG/creatinine were higher in hypertensive patients (p < 0.001) and correlated with left ventricular mass index (p < 0.01). When 8-OHdG/creatinine was compared according to obesity and diabetes in our hypertensive subjects, no significant differences were found. 8-OHdG/creatinine was increased in hypertensive smokers (p < 0.002) and women (p < 0.006). Furthermore, 8-OHdG/creatinine correlated with TNF-alpha, sTNF-R1, sTNF-R2 (< 0.0001) and with IL-6 (p < 0.05). A multivariate linear regression analysis showed that gender, smoking and TNF-alpha were independent factors of 8-OHdG/creatinine.

Conclusions: Urinary 8-OHdG was increased in hypertensive patients with hypotropy even under medical treatment. The presence of other cardiovascular risk factors on top of hypertension do not alter the concentrations of this oxidative stress marker, only smoking increases its levels. TNF-alpha is an independent factor of 8-OHdG. These data suggest that this urinary marker gives specific additional information, further than blood pressure control alone when evaluating hypertensive patients and its calculation may contribute to optimize medical treatment.

Table 1

<table>
<thead>
<tr>
<th>Group A (n=46)</th>
<th>Group B (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>120 ± 12</td>
<td>112 ± 9.5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>73 ± 8</td>
<td>73 ± 6</td>
</tr>
<tr>
<td>Apelin pg/ml</td>
<td>240 ± 130</td>
<td>400 ± 160</td>
</tr>
<tr>
<td>Relaxin pg/ml</td>
<td>50 ± 12.5</td>
<td>65 ± 42.5</td>
</tr>
</tbody>
</table>

Table 5700 T-lymphocyte renin-angiotensin system activation is modulated by low-grade inflammation in hypertensives and obeses

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Purpose: In these last years human T-lymphocytes were shown to be endowed with a functional active renin-angiotensin system (RAS), independent to the circulating system, and to have a role in the development of hypertensive target organ damage. T-lymphocyte RAS could be activated in hypertensive patients with low-grade inflammation. Low-grade inflammation is reported to mediate cardiovascular risk also in obeses. The aim of this study is to assess the activation of T-lymphocytes RAS in hypertensives and/or obeses and the possible correlation with low-grade inflammation.

Methods: T-lymphocytes were obtained from peripheral blood samples of 8 obeses, of stage I and II (BMI ≥ 30, 7M,42 years old, 3F, 29 years old, respectively) and 9 hypertensive subjects with BMI ≥ 29 (7M,52 ± 10 years) and 7 hypertensives with BMI ≥ 29 (7M,52 ± 10 years). No patient was affected by diabetes mellitus or glucose intolerance, and was not in therapy with ACE-inhibitors and/or Angiotensin receptor blockers. Seven healthy subjects formed the age and sex-matched control group. After isolation, T-lymphocytes were put in culture and at 6 hours mRNA for ACE was quantified by RT-PCR. Presence of low-grade inflammation was defined by serum levels of high sensitive CRP (hsCRP) > 2 mg/L.

Results: hsCRP showed a large distribution in groups, with mean values significantly higher than controls. All hypertensives with BMI ≥ 29 presented hsCRP levels > 2 mg/L. ACE mRNA levels showed a large distribution inside the three groups, with mean values significantly higher than controls. ACE mRNA levels were linearly related to hsCRP levels (R=0.79, p<0.0001). There was a positive correlation between hsCRP levels and BMI. No significant correlation was found between ACE mRNA levels and BMI. In the three groups, ACE mRNA levels were significantly higher than controls only in patients with low-grade inflammation.

Conclusion: Circulating T-cells ACE gene expression is modulated in presence of low-grade inflammation. In hypertensive and/or obese patients, a selective T-lymphocytes RAS activation can occur. If these results will be confirmed, T-cells RAS activation could be considered as a new marker for the optimization of both cardiovascular risk definition and antihypertensive therapy management.

P5701 Variability of NT-proBNP and its relationship with inflammatory status in patients with stable essential hypertension: a one-year follow-up study

E. Rosello Lleti1, P. Morillas2, J.R. Calabuig1, L. Grigorian3, L. Martinez Dolz1, L. Almenar4, M.J. Sancho Tell4, M. Portoles4, V. Bentoméu5, M. Rivera Otero1. 1Hospital La Fe, Valencia, Spain; 2Hospital de San Juan de Alicante, Alicante, Spain; 3University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, Spain

Purpose: The variability of NT-proBNP levels has been studied in heart failure, yet no data exist on these changes over time in hypertensive patients. Furthermore, studies on the relationship between natriuretic peptides and inflammatory status are limited.

Methods: 220 clinically and functionally asymptomatic stable patients (age 59 ± 13, 120 male) out of 252 patients with essential hypertension were followed up. NT-proBNP was measured at baseline, 12 and 24 months.

Results: No differences in NT-proBNP were found with respect to the basal stage in the hypertrophic group, but significant changes were found in non-hypertrophic subjects. The reproducibility of NT-proBNP measurements was better in patients with hypertrophy than in the non-hypertrophic group for the three intervals (stage I-basal; stage II-basal; stage II-basal) with a reference change value of 34%, 35% and 41%, respectively, in the hypertrophic group. A more elevated coefficient of correlation was obtained in the hypertrophic group than in patients without hypertrophy: basal versus stage I (r=0.79, p<0.0001 and r=0.59, p<0.0001) and stage I versus stage II (r=0.86, p<0.0001 and r=0.82, p<0.0001). Finally, levels of NT-proBNP significantly correlated with sTNF-R1 (p<0.0001) and IL-6 (p<0.01) during follow-up. A multivariate linear regression analysis showed that sTNF-R1 is an independent factor of NT-proBNP.

Conclusions: This work shows that there is good stability in NT-proBNP levels in a follow-up study of asymptomatic patients with stable hypertension and left ventricular hypertrophy. As a consequence, assessment of NT-proBNP concentrations may be a useful tool for monitoring the follow-up of hypertensive patients.
Impact of plasma aldosterone level on coronary plaque regression in hypertensive patients with stable coronary artery disease

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Renin-angiotensin-aldosterone system (RAAS) has been associated with coronary artery disease (CAD). RAAS plays a crucial role on an increased risk of cardiovascular events in hypertensive patients. However, little data exists regarding the correlation between RAAS and changes of plaque volume. Therefore, we assessed the correlation between RAAS and plaque change in hypertensive patients with stable CAD who underwent percutaneous coronary intervention treated with almidione 5mg/d or azele-nine 5mg/d for 10 months. Non-culprit coronary lesions associated with mild-to-moderate stenosis were evaluated by volumetric IVUS at baseline and 10 month after PCI. A total of 100 IVUS images were recorded at an interval of 0.1 mm for a length of 10 mm in each plaque. For each patient, aldosterone, ren- nin, and other biomarkers (CRP, TNF-alpha, IL-6) at baseline and follow-up were measured.

Results: Blood pressure significantly decreased from 138.74 mmHg at baseline to 129.69 mmHg at 10 months follow-up (p=0.003). Aldosterone was decreased during follow-up period (69 pg/ml to 65 pg/ml) whereas rennin increased (16.8 pg/ml to 18.7 pg/ml). The decrease in aldosterone was not associated with a decrease of blood pressure. Blood pressure was not associated with the change of plaque volume. Patients in the lowest quartiles (Q1) of aldosterone at the follow-up had a significantly greater reduction of plaque volume than did patients in the three higher quartiles (Q2-4) (-6.3% versus -3.9%, -3.5%, -2.9%). A multiple logistic regression analysis identified level of follow-up aldosterone as a significant independent predictor of the regression of plaque volume. There were no significant correlation between aldosterone and change of plaque volume.

Conclusions: Decreased aldosterone is likely to contribute to plaque regression in hypertensive patients with stable CAD.

Clinical application of real-time elastography for evaluation of renal function in patients with hypertension

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Background: Real-time elastography (RTE) is a useful modality for evaluating organ elasticity. However renal elasticity has not been estimated. The aim of this study was to assess the performance of RTE in depicting renal elasticity in hypertensive patients with and without chronic kidney disease (CKD).

Methods: In 73 treated hypertensive patients, RTE of kidney was performed using a HV900 (Hitachi Medico, Tokyo, Japan) to calculate the central echo complex volume by intravascular ultrasound (IVUS) in patients with CAD. 115 patients with stable CAD who underwent percutaneous coronary intervention treated with almidione 5mg/d or azele-nine 5mg/d for 10 months. Non-culprit coronary lesions associated with mild-to-moderate stenosis were evaluated by volumetric IVUS at baseline and 10 month after PCI. A total of 100 IVUS images were recorded at an interval of 0.1 mm for a length of 10 mm in each plaque. For each patient, aldosterone, rennin, and other biomarkers (CRP, TNF-alpha, IL-6) at baseline and follow-up were measured.

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K. Miyazaki1, S.S. Suzuki2, T.M. Miyazaki1, H.D. Daida1, Juntendo University School of Medicine, Tokyo, Japan; 2Juntendo University, Shizuoka Hospital, Shizuoka, Japan

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Conclusions: Decreased aldosterone is likely to contribute to plaque regression in hypertensive patients with stable CAD.

C-reactive protein is associated with deteriorated health related quality of life in hypertensive subjects

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Purpose: The association between essential hypertension (EH) and low scores of health-related quality of life (H-QoL) is well established, while inflammation is emerging as a precursor and predictor of cardiovascular disease. We assessed the hypothesis that there might be a possible association between high sensitivity C-reactive protein (hs-CRP), a time-honored marker of inflammation and H-QoL, in the setting of EH.

Methods: We studied 154 consecutive subjects (aged 58±17 years, male:78), with stage I-III untreated uncomplicated EH (office blood pressure=150/98 mm Hg). In all participants venous blood samples were drawn for evaluation of hs-CRP levels. To assess the H-QoL, the widely validated Short Form 36 (SF-36) General Health Survey questionnaire was administered. The SF-36 is a generic H-QoL instrument that includes eight subscales. These subscales were further grouped into two summary scales, the physical component summary (PCS) and the mental component summary (MCS).

Results: There was a significant negative correlation between hs-CRP levels and scores in six dimensions of SF-36, thus with the total score. (Table)

Conclusions: In conclusion, there is an intriguing link between inflammation and low scores of health-related quality of life in the setting of essential hypertension. The pathophysiological substrate of these interrelationships needs further investigation through large scale prospective studies.

High-salt intake induces cardiac damage in spontaneously hypertensive rats, and handle region peptide prevents this damage without blood pressure reduction

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Objective: This study aimed to examine the effect of high-salt loading on plasma and cardiac tissue renin angiotensin system and cardiac damage at an early stage of hypertension in spontaneously hypertensive rats.

Method: Spontaneously hypertensive rats (SHR) and Wister Kyoto rats (WKY) 8 week age received regular chow (normal-salt diet) and high-salt diet (8% NaCl chow) for 6 weeks from 6 to 12 weeks. Systolic blood pressure was measured every week during the course. At the end of the experiment, plasma renin activity (PRA), plasma level of angiotensin II concentration were measured and the expression of renin and (pro)renin receptor in the myocardium was evaluated by western blot analysis.

Results: High-salt diet increased systolic blood pressure compared to normal-salt diet both in WKY's and SHR's. High-salt diet for 6weeks decreased PRA and plasma angiotensin II concentration both in SHR's and WKY's. Prorenin decay peptide did not affect blood pressure, PRA, plasma levels of angiotensin II or expression of renin and (pro)renin receptors, but decreased the development of cardiac damage such as perivascular fibrosis and cardiomyocyte hypertrophy.

Conclusion: High-salt diet did not supress cardiac tissue renin and cardiac (pro)renin receptors, despite plasma RAS activity was decreased at an early stage of hypertension. The blockade of cardiac (pro)renin receptors play an important role in preventing cardiac damage induced by high-salt diet.
Effects of cilnidipine on carotid sinus baroreflex in rats

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Purpose: Cilnidipine is a unique calcium channel blocker with inhibitory action on both L-type and N-type calcium channels. The present study aimed to sepa-

rately evaluate the central and peripheral actions of intravenous cilnidipine in its effects on the sympathetic arterial pressure (AP) regulation by the carotid sinus baroreflex.

Methods: We isolated carotid sinus baroreceptor regions of anesthetized and vagotomized Wistar Kyoto rats, and measured electrical sympathetic nerve ac-
tivity (SNA), AP and heart rate (HR) in response to stepwise changes in carotid sinus pressure (CSP). Effects of intravenous cilnidipine administration (30 μg/kg bolus + 100 μg/kg/h, n = 6) and an N-type calcium channel blocker ω-conotoxin GVIA (50 μg/kg bolus, n = 5) were examined.

Results: The baroreflex neural arc from CSP to SNA showed a sigmoidal re-

sponse, and the baroreflex peripheral arc from SNA to AP approximated a straight line. The neural arc was not affected by cilnidipine or ω-conotoxin GVIA. The slope of the peripheral arc was significantly decreased by cilnidipine (0.73±0.07 to 0.40±0.04 μg/mmHg, P <0.01) and by ω-conotoxin (0.88±0.14 to 0.11±0.05 μg/mmHg, P <0.01). The intersection between the neural and peripheral arcs on a pressure-SNA plane provided an estimate of the operating-point AP under baroreflex conditions. Cilnidipine significantly decreased the operating-point AP (110±7 to 85±4 mmHg, P <0.01), which reduced the neural arc gain at the operating point (1.45±0.31 to 0.39±0.16 mmHg, P <0.05). After chronic administration of cilnidipine, the sensitivity was also significantly reduced. In contrast, the neural arc gain was not altered, the neural arc gain at the operating point was decreased, and the neural arc slope was significantly decreased by cilnidipine, suggesting that cilnidipine, at the doses used, was not as potent as ω-conotoxin GVIA but not by methods. This trend was statistically significant in ED 8 embryos injected with 200 μg/kg metoprolol (61% metoprolol, 36% controls).

Conclusions: Both cilnidipine and ω-conotoxin GVIA decreased the slope of the peripheral arc, which reduced the operating-point AP. While the neural arc charac-
teristics were not altered, the neural arc gain at the operating point was decreased with the decrease in the operating-point AP due to the nonlinearity of the neural arc. The HR response was not significantly affected by cilnidipine, but the response range of HR was significantly reduced by ω-conotoxin GVIA but not by methods. This suggests that cilnidipine, at the doses used, was not as potent as ω-conotoxin GVIA to block N-type calcium channels.

Antioxidant effects of farnesyl pyrophosphate synthase inhibitor ibandronate in spontaneously hypertensive rats vivo and vitro

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Reactive oxygen species (ROS), originating mainly from vascular smooth muscle cells (VSMCs), lead to vascular damage and endothelial dysfunction in hyper-
tension. The downstream signal pathways of Farnesyl pyrophosphate (FPP) synthase, Rac1 and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mediated the ROS generation. We investigated the effect of FPP synthase inhi-

bition, on ROS production, potential beneficial influence on endothelial function in spontaneously hypertensive rats (SHR) and the underlying mechanisms. SHR rats were treated with ibandronate for 30 days. Endothelium-
dependent and independent vasorelaxation were measured in isolated aortic rings. Additionally, VSMCs from SHR and Wistar-Kyoto rats (WKY) were cultured. The ROS production and NADPH oxidase activation were determined by fluores-
cence and chemiluminescence, respectively, in vivo or in vitro. Angiotensin II (Ang II) concentration dependently increased ROS production in cultured VSMCs from WKY and SHR. The Ang II-induced responses were greater in SHR VSMCs, but significantly reduced by ibandronate pretreatment. Treatment with ibandronate significantly decreased the production of ROS, translocation of NADPH oxidase subunit p47phox, NADPH oxidase and Rac1 GTP-binding activity in aortas and VSMCs, and improved the impaired endothelium-dependent vasodilation in SHR. Addition of geranylglycerol, but not farnesol or mevalonate reversed the inhibitory effects of ibandronate. Moreover, inhibition of geranylglycerol-transferase mim-

icked the effect of ibandronate on this excessive oxidative response. FPP syn-

thase inhibitor ibandronate exerts anti-oxidative effects in cultured VSMCs and in the vasculature of SHR mediated by Rac1/NADPH oxidase pathway. These effects of ibandronate may contribute to the vasoprotective effects for impaired endothelium in SHR.

Heart rate changes mediate the embryotoxic effects of antiarrhythmic drugs in the chick embryo

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Background: A significant increase of cardiovascular medication use during preg-

nancy has been reported in recent years. Only a limited evidence on safety pro-

files is available and very little is known about mechanisms of adverse effect on the fetus. We hypothesized that drug-induced bradycardia is the leading mecha-
nism. We focused our investigation on agents with negative chronotropic effect.

Methods: ED4 and ED8 chick embryos were studied by video microscopy and 

ultrasound microscopic imaging ex vivo after intraamniotic injection of 200 μl of meto-

prol, Ibradibavine, 50 μl of carvedilol or 200 μl of normal saline for a period of 30 minutes. Stroke volume was calculated by Simpson’s method in ED 4 embryos and pic systolic ellipsoid formula in video recordings (ED4). Cardiac output was calculated from equation CO(μl/min)=SV(μl)/HR(BPM). Embryotoxicity was tested in vivo after administration of various doses of studied drugs between ED3-ED8. Using digital camera, we describe heart rate in ED 4 embryo after administration of metoprolol (33%), carvedilol (27%) and Ibradibavine (55%) compare to controls (8%). In more mature ED 8 embryos this effect was more pronounced (metoprolol 71%, carvedilol 54%, Ibradibavine 53%, controls). Decreasing trend of CO in ED 4 embryos was not statistically significant for all three tested drugs. This trend was statistically significant in ED 8 embryos injected with metoprolol (61% metoprolol, 36% controls).

No significant mortality was observed in ED 4 embryos injected by different doses of metoprolol and mortality was 39% in ED 8 embryos injected by 200 μl of meto-

prol. A significant mortality was achieved in ED4 embryos injected by 200 μl of carvedilol (86%) and by 200 μl of Ibradibavine (80%).

Conclusion: Sensitivity to negative chronotropic effect of metoprolol, carvedilol and Ibradibavine increases with development. The embryonic heart has limited po-
tential to vary stroke volume and significant bradycardia is followed by a sig-

ificant decrease in cardiac output, likely leading to embryonic death. Metoprolol in usual doses appears to be relatively safe in pregnancy whereas carvedilol and Ibradibavine might have a potential adverse effect on fetus.
Anti-hypertensive effects of heat shock protein inducer geranylgeranyl acetone via suppression of aortic smooth muscle cell migration and contraction

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Purpose: In hypertension, the chronic activation of the rennin-angiotensin system (RAS) leads to dysfunctions of the vasculature, including increased vascular tone, inflammation, fibrosis and thrombosis. Angiotensin (Ang) II exerts its myriad effects in modulating cardiovascular physiology and pathology by smooth muscle cell growth, migration, apoptosis, fibrosis, hyper-contractility and calcification. Heat shock proteins (HSPs) are involved in the protection against different cellular stress and vascular remodeling. The purpose of this study was to determine whether HSPs induce geranylgeranyl acetone (GGA) attenuates vascular remodeling such as migration and contraction of smooth muscle cells.

Methods: To investigate the anti-migration effects of GGA, we performed wound healing assay and transwell invasion assay in 1 μM Ang II-stimulated rat (SD rat, male, 6 weeks old) aortic smooth muscle cells (RASMCs). In addition, we evaluated effects of GGA on phenylephrine (PE)-induced vasoconstriction in rat thoracic aorta. The thoracic aorta was isolated from SD rat (male, 6 week old). We assessed effects of acetylcholine (Ach) on 1 μM PE-induced contraction in 3 mm aorta rings, and it was compared with 10 μM GGA pretreatment.

Results: As a result of wound healing assay, 1 μM Ang II significantly increased migration compared with vehicle, whereas markedly inhibited by 10 μM GGA in RASMCs. In addition, GGA also dramatically inhibited Ang II-mediated RASMCs invasion from transwell assay. Furthermore, GGA significantly increased 139.86 ± 18.22% of Ach-induced relaxation in PE-stimulated rat thoracic aorta (p < 0.005, n=5).

Conclusion: Based on this result, HSPs inducer GGA has anti-hypertensive effects via anti-remodeling of vascular smooth muscle cells and contraction of rat thoracic aorta.

Bilateral: Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule-1 (KIM-1) as markers for acute kidney damage after renal denervation

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Background: RENALdenervation (RDN) is one possible treatment option of therapy resistant arterial hypertension. Besides therapeutical success, procedural complications like functional and structural kidney injury are of major clinical interest. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) represent sensitive, specific and highly-predictive biomarker for acute kidney injury (AKI). Therefore, in the present study we aimed to examine whether changes of urinary NGAL, KIM-1 and creatinine predict subsequent AKI after RDN.

Material and Methods: We analyzed the changes of urinary NGAL, KIM-1 levels as well as creatinine levels in patients with resistant arterial hypertension undergoing RDN. 30 consecutive patients were included to this study from July until November 2011. RD was performed according to standard clinical practice. Serum and urine samples were collected prior to and at 2 days as well as 4 weeks after RD. The blood and urine specimens were sent to the laboratory for evaluation effects of GGA on phenylephrine (PE)–induced vasocontraction in rat thoracic aorta. The thoracic aorta was isolated from SD rat (male, 6 week old). We assessed effects of acetylcholine (Ach) on 1 μM PE-induced contraction in 3 mm aorta rings, and it was compared with 10 μM GGA pretreatment.

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Conclusion: Based on this result, HSPs inducer GGA has anti-hypertensive effects via anti-remodeling of vascular smooth muscle cells and contraction of rat thoracic aorta.

Coronary blood flow is slow in prediabetic and diabetic patients with normal coronary arteries when compared to non-diabetics

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Purpose: To evaluate coronary blood flow in patients with normal coronary arteries in 3 groups: Diabetic, pre-diabetic and non-diabetic patients.

Methods: In this retrospective study, 759 patients with normal coronary arteries were included in the study. The angiograms of the eligible patients were reviewed again for TIMI frame counting. Patients were then grouped according to their status of DM: Group 1: Non-diabetic patients, group 2: prediabetic patients, group 3: patients with DM.

Results: TIMI frame counts for each of 3 coronary arteries were found to be significantly different between groups (Corrected TIMI frame counts for left anterior descending artery and TIMI frame counts for left circumflex and right coronary arteries are given respectively in 3 groups: Group 1: 19 (16-21), 20 (17-24), 20 (17-23); Group 2: 20 (17-24), 19 (16-23), 20 (17-24); Group 3: 20 (17-23), 19 (16-22), 20 (17-23); p<0.01 for each coronary artery). When the groups were compared to each other with post-hoc tests, group 2 and group 3 had similar TIMI frame counts for all 3 coronary arteries but both of these groups had significantly higher TIMI frame counts than group 1 (p values for each comparison were<0.017).

Conclusions: We have revealed for the first time that patients with prediabetes have slow coronary flow measured by TIMI frame count just like diabetic patients when compared to non-diabetics. This may show the endothelial dysfunction in the coronary arteries which develops in the prediabetic phase before overt DM arises.

The relationship between glycaemic variability and cardiovascular complications in patients with acute myocardial infarction and type 2 diabetes

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Purpose: Patients with type 2 diabetes (T2DM) and acute myocardial infarction (AMI) have a poor prognosis. Hyperglycemia during hospitalization is a risk predictor, but attempts to improve prognosis by insulin-based glucose control have hitherto not been consistently successful. Increased glycaemic variability, a potential effect of insulin treatment, has been linked to a worse prognosis in critically ill patients. To our knowledge the possibility of such relation has not been studied in patients with T2DM and AMI, which was the objective of the present study.

Methods: We studied 578 T2DM patients participating in the DIGAMI 2 trial (male 69%; mean age 68±11 years; diabetes duration 7.5±8 years), who had glucose levels measured hourly while receiving an insulin-glucose infusion during the first 48 hours of hospitalization for AMI. Mean glucose and three measures of glycaemic variability: Root Mean Square Error (RMSE), range and slope were calculated.

Results: During 12 months of follow-up 82 patients died and 150 experienced the composite endpoint. In unadjusted analyses the mean level of glycaemic variability did not differ between patients who died compared to those who survived. In a
Temporal mortality reductions after myocardial infarction between 1985 and 2008 were observed with in-hospital and 20 year follow-up. Ten-year mortality decreased equally in patients with diabetes from 53% in 1985-90 to 39% in 2000-8 (adjusted HR 0.56, 95%CI: 0.43-0.73) and in those without diabetes from 38% in 1985-90 to 29% in 2000-8 (adjusted HR 0.66, 95%CI: 0.60-0.73). There was a 1.5-fold increased risk of mortality at 20 year follow-up. In-hospital mortality was lower in diabetic patients with previous myocardial infarction (31.9 vs. 27.5%, p=0.017), had more patients with previous diabetes mellitus (53.3 vs. 45.4%, p<0.001), β-blockers (44.9 vs. 31.3%, p<0.001), and statins (54.6 vs. 43.6%, p<0.001). Mean left ventricle ejection fraction (LVEF) was 54.7±9.9 vs. 51.2±11.6% (p<0.001), respectively. In the group B, the B2 had more women (38.8 vs. 30.2%, p=0.007), similar age and lower prevalence of stress and familiar history. The group B1 was more treated with aspirin (56.7 vs. 48.6%, p<0.01), and β-blockers (45.9 vs. 31.5, p<0.001). Mean LVEF was 52.6±10.2 vs. 48.7±11.9% (p<0.001), respectively. CVD occurred in 8.1% and 9.5% in groups A1 and A2 (Log Rank 0.411), and 7.8% and 13.6% in groups B1 and B2 (Log Rank 0.029), respectively.

Conclusion: In our population, heart rate at admission was only a CVD predictor in diabetics, clearly showing the close relationship between diabetes, autonomic dysfunction and post-CDES outcome. This result emphasizes the importance of optimal heart rate control post-CDES, namely in high-risk subsets.
The prognostic significance of HbA1c in patients with newly detected glucose abnormalities and acute myocardial infarction treated invasively

J. Kowalczyk1, M. Mazurek1, T. Zielinska1, R. Lenarczyk1, D. Siedowska1, A. Swiatkowski2, W. Strab1, K. Strojec3, L. Polonski2, Z. Kalauza1. 1Dept of Cardiology, Congenital Heart Diseases & Electrocardiography, SChD, Medical University of Silesia, Zabrze, Poland; 2Dept of Internal Medicine, Diabetology&Cardiometabolic Diseases, SChD, Medical University of Silesia, Zabrze, Poland; 33rd Department of Cardiology, Medical University of Silesia, Silesian Centre for Heart Diseases, Zabrze, Poland

Background: Glucose abnormalities (GA), especially diabetes mellitus (DM), are frequent and significant comorbidities influencing prognosis in patients (pts) with cardiovascular diseases. The objective of this study was to evaluate prognostic role of HbA1c in pts with newly detected glucose abnormalities treated invasively due to acute myocardial infarction (AMI).

Methods: Single-centre prospective study encompassed 2146 consecutive survivors of acute AMI phase. In all patients without diagnosed diabetes mellitus standard oral glucose tolerance test was performed during stable condition before hospital discharge and interpreted according to the guidelines. From the study population 2 major groups with defined new glucose abnormalities and established diagnosis of AMI were selected: 457 pts with impaired glucose tolerance (IGT) and 306 pts with newly detected DM – newDM. In each of these groups the median value of HbA1c was calculated and established as the cut-point for further analysis. The major indication for comparison between study groups with log-rank test and independent risk factors were selected with multivariate Cox-regression analysis.

Results: The median HbA1c for IGT group was 5.9% and 7.0% for newDM. Patients with IGT and HbA1c>5.9% had significantly lower post-hospital mortality (4.6%) than those with HbA1c>5.9% (25.0%; p<0.001). Similarly, pts with newDM and HbA1c>7.0% had lower mortality (6.1%) than those with HbA1c>7.0% (14.2%; p<0.05). Additionally, analysis revealed that increase of HbA1c of one of the strongest independent risk factors of death in pts with IGT (HR 3.39, 95%CI 3.19-3.59; p<0.001) and newDM (HR 1.52, 95%CI 1.48-1.66; p<0.001).

Conclusions: Increase of HbA1c above the estimated cut-points in patients with newly detected glucose abnormalities was associated with significantly reduced long-term survival after AMI treated invasively. Moreover, increase of HbA1c in IGT and newDM was one of the strongest independent risk factors of death in these study populations.

The prognostic significance of HbA1c in patients with newly detected glucose abnormalities and acute myocardial infarction treated invasively

J. Kowalczyk1, M. Mazurek1, T. Zielinska1, R. Lenarczyk1, D. Siedowska1, A. Swiatkowski2, W. Strab1, K. Strojec3, L. Polonski2, Z. Kalauza1. 1Dept of Cardiology, Congenital Heart Diseases & Electrocardiography, SChD, Medical University of Silesia, Zabrze, Poland; 2Dept of Internal Medicine, Diabetology&Cardiometabolic Diseases, SChD, Medical University of Silesia, Zabrze, Poland; 33rd Department of Cardiology, Medical University of Silesia, Silesian Centre for Heart Diseases, Zabrze, Poland

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A comparative study of circulating endothelial progenitor cells and endothelium function in type 2 diabetes and type 2 diabetes with coronary heart disease patients

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Objective: The purpose is to compare a study circulating EPCs, endothelial dysfunction and their relationships between type 2 diabetes(T2DM) patients and type 2 diabetes with coronary heart disease (T2DM-CAD) patients.

Methods: The study subjects were recruited between 2010-2011, consisted of 88 consecutive healthy subjects, 73 T2DM patients and 79 T2DM-CAD patients. Circulating EPCs was determined by flow cytometry and detail echocardiography was performed to assess brachial artery responses of endothelium-dependent flow-mediated dilation(FMD) and endothelium-independent glyceryl trinitrate-mediated vasodilation(GTN).

Results: Circulating EPCs percentage declined obviously in T2DM patients and T2DM-CAD patients, circulating CD133/KDR(+)% and CD34/KDR(+)% in T2DM patients were higher than in T2DM-CAD patients (0.51±0.288 vs. 0.39±0.157, P=0.042, and 0.36±0.125% vs. 0.67±0.220%, P=0.028, respectively), brachial artery FMD was no significant difference between T2DM patients and T2DM-CAD patients (6.62±2.86% vs. 6.13±2.51%, P=0.335). However, GTN was significant difference between T2DM patients and T2DM-CAD patients (16.80±6.47% vs. 13.26±4.49%, P=0.017). There were high relation-ship between circulating CD133/KDR(+)% and CD34/KDR(+)% and brachial artery FMD in T2DM patients, T2DM-CAD patients and healthy subjects. Circulating CD133/KDR(+)% and CD34/KDR(+)% were strong predictors of artery endothelial dysfunction.

Conclusions: Hypoglycemia could reduce circulating EPCs percentage and weaken endothelial function in diabetic subjects. The damages of artery smooth muscle in T2DM-CAD patients were more serious than in T2DM patients.

Glycation gap for estimating the risk of death in diabetic and non-diabetic patients with acute coronary syndrome

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Purpose: Recent studies have reported that the glycation gap (GG) predicts the progression of nephropathy in diabetic patients. Chronic glucose dysregulation is associated with worse outcomes in patients hospitalized for acute coronary syndrome (ACS). In the present study, we examined the relationship between the GG and the risk of death in a prospective cohort of diabetic and non-diabetic patients with acute coronary syndrome (ACS).

Methods: The study involved 1137 consecutive patients admitted to our center with a diagnosis of ACS. The GG was calculated as the difference between measured HbA1c values and the HbA1c values predicted from fructosamine based on the HbA1c-fructosamine regression equation. Patients were classified as having diabetes and by GG-tertiles. The primary end point was all-cause mortality.

Results: The median age of the patients was 66±13 years; 26% were women, and 35% had a history of diabetes. The primary end point was observed in 247 patients (22%). Kaplan Meier curves in Figure 1 show the cumulative survival among patients in the high, medium, and low-GG groups according to diabetes status. The influence of the GG on mortality was highly significant in both diabetic and non-diabetic patients (p<0.001). In a multivariate analysis, after controlling for potential confounding risk factors, we found that higher GG values were associated with a significantly higher risk of death in both diabetic [HR IC 95%: 1.31 (1.04;1.64), p=0.000] and non-diabetic patients [HR IC 95%: 1.30 (1.04-1.64), p=0.018].

In hospital complications

<table>
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<th>Treatment</th>
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<th>p Value</th>
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</tbody>
</table>

Conclusions: The GG was a strong, independent predictor of long-term all-cause mortality in hospitalized patients with ACS, regardless of diabetes status.
diabetes mellitus is associated with more severe depression and higher levels of subclinical inflammation markers.

**LIPIDS AND CARDIOVASCULAR DISEASE**

**P5726**

Evaluation of mipomersen, an ApoB synthesis inhibitor, for potential to control LDL-C in patients with severe heterozygous familial hypercholesterolemia who may be eligible for apheresis

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Introduction: When maximum lipid lowering therapy fails to lower LDL-C to target levels, weekly or biweekly LDL-apheresis is currently the only available treatment option in patients with severe heterozygous familial hypercholesterolemia (severe HeFH). Although extremely expensive and limited by access, in the United States LDL-apheresis is generally deemed appropriate if, despite maximum lipid lowering therapy, LDL-C remains above 200 mg/dL in persons with coronary heart disease (CHD) or above 300 mg/dL in the absence of CHD. Certain countries (i.e. Japan and Germany) have adopted much lower thresholds for apheresis eligibility (such as 100 mg/dL). Mipomersen (MIPO), an ApoB synthesis inhibitor, reduces LDL-C significantly when added to maximally tolerated lipid-lowering therapy. We hypothesise that MIPO may prevent the necessity for apheresis by reducing LDL-C such that apheresis no longer is indicated, even in countries with significantly lower thresholds.

Methods: Data from a study in patients with severe HeFH (LDL-C >300 mg/dL or ≥200 mg/dL plus coronary artery disease (CAD), on maximally tolerated statin therapy (clinical-trials NCT00734664) were used to determine in what percentage of patients the addition of MIPO resulted in a LDL-C level below the thresholds for apheresis eligibility (using cut-offs of <300, <200, and <100 mg/dL, compared to placebo (PBO)). Fifty-eight patients were randomized (29 MIPO, 19 PBO); median age 51 years, 43% male; baseline LDL-C 267 mg/dL.

Results: LDL-C fell by ≥36% in the MIPO group, and rose by 13% in the PBO group. 41% (7/17) of MIPO patients with baseline LDL-C >300 mg/dL and 61% (22/36) with baseline LDL-C >200 mg/dL achieved levels lower than 200 mg/dL at the primary efficacy time point (2 weeks after last dose), compared to 0% (0/3) and 14% (1/7) in PBO, respectively. Overall 15% (6/39) of MIPO patients and 0 PBO reached a LDL-C level <100 mg/dL. MIPO-treated patients had a higher incidence of injection site reactions and flu-like symptoms, but most were mild or moderate in severity. Elevations in ALT and AST occurred more frequently in MIPO than in placebo patients; these were temporarily associated with the LDL-C lowering response to treatment.

Summary: When added to maximally tolerated lipid lowering therapy, MIPO may eliminate the need for apheresis in a significant number of patients with severe HeFH. Further studies are warranted to evaluate whether patients who qualify for apheresis could be adequately controlled with MIPO.

**P5727**

Plasma triglyceride level may not predict the clinical outcomes in patients with controlled plasma low-density lipoprotein cholesterol level after percutaneous coronary intervention

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Background: Few data are available in the association of triglyceride (TG) level and cardiovascular risk factors in patients with controlled plasma low-density lipoprotein (LDL) cholesterol level less than 100 mg/dL. We assessed whether hypertriglyceridemia is associated with major cardiovascular events (MACE) in patients with controlled LDL cholesterol level, who underwent percutaneous coronary intervention (PCI) in drug eluting stent (DES) era.

Methods: The need for hypertriglyceridemia is associated with major cardiovascular events (MACE) in patients with controlled LDL cholesterol level, who underwent percutaneous coronary intervention (PCI) in drug eluting stent (DES) era.

Summary: We measured at baseline Lp-PLA2 mass and activity (with an ELISA and a colorimetric method) in 727 randomly selected Caucasian patients who underwent coronary angiography and were followed-up for incident CV events (acute coronary syndromes, stroke, CV death). Based on a threshold value (Youden index) determined January 2004 and December 2009, a total of 9,929 consecutive patients who underwent PCI with DES were enrolled. Among those, we analyzed 2,704 patients who had been kept on statin after PCI and whose LDL-C was less than 100 mg/dL. We defined a MACC as the composite of all-cause death, nonfatal myocardial infarction, and revascularization of any cause.

Results: After adjusting multiple variables, Multivariate Cox proportional hazard analysis revealed that multivariate disease and the presence of coronary angiographic B2C lesion were associated with increased hazard ratios (HR). (HR=1.213, 95% CI 1.010–1.456, p=0.039, HR=1.483, 95% CI 1.162–1.962, p=0.001, respectively). However, follow-up TG level above 300 mg/dL was not statistically significant inter groups of MACC (HR=0.891, 95% CI 0.695–1.148, p=0.372).

Conclusions: Plasma TG level was not closely associated with MACCEs in patients with well controlled LDL-C level under 100 mg/dL who underwent PCI with DES.

**P5728**

Two rare variants explain association with acute myocardial infarction in an extended genomic region including the apolipoprotein(a) gene

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Purpose: Relatively low numbers of kringe 4 type 2 repeats in apolipoprotein(a), also known as lipoprotein(a) (Lp(a)), are associated with increased risk of cardiovascular disease (CVD). However, the underlying genetic basis is far from clear. We aimed to identify risk associated markers: specific nucleotides in LPA instead of standard haplotypes.

Methods: The study population comprised 2136 cases with acute myocardial infarction and 1211 controls. The rs3798220-G (frequency 2%) and rs10455872-G (frequency 7%) alleles of LPA were associated with increased risks of acute myocardial infarction (P<0.0001). None of nine polymorphisms included in a haplotype analysis of the SLC22A3-LPAL2-LPA region were significantly related to disease, whereas specific haplotypes were associated. Risk haplotypes (CTCTGTGT (P=0.0022) and CTCCTGTAC (P=0.0074)) were correlated with the rs3798220-C (r2=0.77) and rs10455872-G (r2=0.28) alleles, respectively.

Conclusions: Considerable proportions of the effects of the CTCTGTGTG and CTCCTGTAC haplotypes could be explained by linkage disequilibrium with rs3798220-C and rs10455872-G. The findings allowed for a more precise definition of risk-associated markers: specific nucleotides in LPA instead of standard haplotypes defined by non-effective variants from the extensive SLC22A3-LPAL2-LPA region.

**P5729**

Lipoprotein-associated phospholipase A2 and cardiovascular events in high risk coronary artery disease patients

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Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a Ca2+-dependent lipase, mostly produced by monocytes/macrophages, which circulates in plasma associated to LDL, and to a much lesser extent to HDL. By hydrolyzing oxidized phospholipids on LDLs surface it generates oxidized fatty acids and lysophosphatidylcholine, two triggers of the inflammation cascade that could elicit pro-atherogenic effects. Since it remained controversial if Lp-PLA2 plays a role in atherogenesis, we investigated if Lp-PLA2 mass and activity predicted cardiovascular (CV) events in high-risk coronary artery disease patients using a prospective cohort study design.

Methods: We measured at baseline Lp-PLA2 mass and activity (with an ELISA and a colorimetric method) in 727 randomly selected Caucasian patients who underwent coronary angiography and were followed-up for incident CV events (acute coronary syndromes, stroke, CV death). Based on a threshold value (Youden index) determined January 2004 and December 2009, a total of 9,929 consecutive patients who underwent PCI with DES were enrolled. Among those, we analyzed 2,704 patients who had been kept on statin after PCI and whose LDL-C was less than 100 mg/dL. We defined a MACC as the composite of all-cause death, nonfatal myocardial infarction, and revascularization of any cause.

Results: After adjusting multiple variables, Multivariate Cox proportional hazard analysis revealed that multivariate disease and the presence of coronary angiographic B2C lesion were associated with increased hazard ratios (HR). (HR=1.213, 95% CI 1.010–1.456, p=0.039, HR=1.483, 95% CI 1.162–1.962, p=0.001, respectively). However, follow-up TG level above 300 mg/dL was not statistically significant inter groups of MACC (HR=0.891, 95% CI 0.695–1.148, p=0.372).

Conclusions: Plasma TG level was not closely associated with MACCEs in patients with well controlled LDL-C level under 100 mg/dL who underwent PCI with DES.
Lipoprotein-associated phospholipase A2 (LpPLA2), cardiovascular events and mortality in patients with type 2 diabetes mellitus on hemodialysis

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Purpose: We previously reported the intensive lipid-lowering therapy for 12 months with rosuvastatin is more effective than the conventional therapy with pravastatin in slowing progression of carotid intima-media thickness (IMT) in the JART (Justification for Atherosclerosis Regression Treatment) study. This multi-center study, which enrolled 348 adult Japanese with hypercholesterolemia who had a maximum IMT >1.1 mm was stopped according to the recommendation by the data and safety monitoring committee, because the interim 12 months results showed the superiority of the rosuvastatin group (ROS). We conducted the Extension study to examine whether 24 months intensive lipid-lowering therapy with rosuvastatin can regress the carotid IMT.

Methods: In this Extension study, ROS was followed-up for 24 months as scheduled in the original study (primary prevention; target LDL-C <80 mg/dL, secondary prevention; <70 mg/dL) and measured the change of the mean-IMT from baseline.

Results: One hundred eighteen patients were followed-up for 24 months. The mean change of ROS was 7.78±2.45 (SD) mg. LDL-C was 86.0±19.7 mg/dL. Reverted no deaths in the JART study (83.7±23.9 mg/dL). The mean change of the mean-IMT from baseline was -0.005±0.104 mm at 24 months though it was 0.012±0.093 mm at 12 months in the JART study (Figure). Additional analysis of plaque characterization using the gray-scale median (GSM) at baseline and 24 months in some typical high-risk patients.

Conclusions: The JART Extension provides the first evidence that long-term intensive therapy with standard rosuvastatin dosing can regress atherosclerosis in a Japanese population. The GSM method used as a score of echogenicity is useful for the evaluation of atherosclerotic plaque stability.

Background: High-density lipoprotein (HDL) has a major role in reducing oxidative and inflammatory processes, contributing to a decrease in atherosclerotic burden. However, there is no evidence concerning the role of HDL functional- ity during acute stress. Therefore, we aimed to investigate the association between HDL-cholesterol (HDL-c) levels and variations in oxidative and inflammatory markers between admission and fifth day following ST-elevation myocardial infarction (STEMI).

Methods: Consecutive STEMI patients (n=180) were selected from the Brasilia Heart Study for this investigation. HDL-c, triglycerides, C-reactive protein (CRP), interleukin-2 (IL2), tumor necrosis factor α (TNFα) and 8-isoprostaglandin F2α (8-isoprostane) levels were measured in the first 24 hours and at the fifth day after MI onset. Patients were divided into 3 groups according to HDL-c tertiles at admission: <33, 33-42 and >42mg/dL.

Results: On admission, no differences were found between groups in plasma 8-isoprostane (p=0.77), IL-2 (p=0.46), TNFα (p=0.06) and CRP (p=0.2). On an analysis of the variation between admission and fifth day, there was a more intense decrease of 8-isoprostane levels in patients with higher HDL-c levels at admission (2.9±0.012–2.9±0.012 vs. 2.4±0.012–2.9±0.012 mg/mL, p<0.0001). TNFα (8.0±1.9–12.6 vs. 6.2±1.3–11.9 mg/mL, 5.2±1.2–15.0 mg/mL, p<0.0001) and CRP (9.2±2.9–11.4 vs. 4.8±3.1–6.5 mg/mL, p<0.0001) between admission and fifth day. Furthermore, in a multivariate analysis model, HDL-c levels were independently associated with a higher decrease in 8-isoprostane (Exp(B)=0.962; 95% confidence interval: 0.928–0.996; p=0.028).

Conclusion: This study is the first evidence that high HDL-c levels are independently associated with an accelerated recovery of oxidative stress in acute phase...
of STEMI and this finding may explain the observation of an attenuated inflammatory response in those patients.

**P5734**
The non-HDL cholesterol to HDL cholesterol ratio is an independent predictor for poor long-term clinical outcomes in patients with target LDL cholesterol in the drug eluting stent era


**Purpose:** Higher non-HDL-C/HDL-C ratio has a strong correlation with poor long-term clinical outcome in patients on statin within target LDL cholesterol level after PCI with drug eluting stents (DES).

**Methods:** A total of 9,292 consecutive patients who underwent PCI with DES in COMCT (CathOlic medical center percutaneous Coronary Invention) registry from January 2004 to December 2009 were enrolled. Among these, we analyzed 2,704 patients with follow up lipid panel who had been kept on statin and attained low LDL-C (LDL-C < 100 mg/dL). Based on the follow-up non-HDL-C/HDL-C ratio, they were divided into quartiles. We defined a major adverse cardiac event (MACE) as the composite of all-cause death, non-fatal myocardial infarction, and revascularization of any cause.

**Results:** The median follow up period was 19.8 months (IQR 6.3-33.3 months). Multivariate Cox proportional hazards regression analysis indicated that the presence of multivessel disease, angiographic ACC/AHA B2 lesion, non-LDL-C/HDL-C ratio was significantly associated with increased incidence of MACE after adjusting multiple variables (adjusted HR =1.470, 1.248, 1.433, respectively).

**Conclusions:** Non-HDL-C/HDL-C ratio can be a potential risk predictor in patients on statin with target LDL-C in the drug eluting stent era.

**P5735**
Human cardiac microvascular endothelial cells are less sensitive to VEGF165A than HUVECs

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**P5735**
**Purpose:** We analyzed 2057 patients (pts) with ACS (median age 64 years, 68% men) included prospectively in a data bank from a tertiary cardiology hospital. The role of statins on mortality was analyzed for the global population, and also according to the first LDL level at hospitalization (group I LDL < 70 mg/dL, N=384; group II LDL 70-130 mg/dL, N=1145; group III LDL >130 mg/dL, N=326; group IV LDL >160 mg/dL, N=202). Chi-square (with Fisher exact test when indicated) was utilized for categorical variable comparisons, and the Mann-Whitney U-test was applied for continuous variable comparisons. Different adjusted models (logistic regression) were developed, taking into account in-hospital mortality as dependent variable and baseline variables (including LDL as a continuous variable) as independent ones.

**Methods:** Study patients were divided into quartiles. We defined a major adverse cardiac event (MACE) as the composite of all-cause death, non-fatal myocardial infarction, and revascularization of any cause.

**Results:** The median follow up period was 19.8 months (IQR 6.3-33.3 months). Multivariate Cox proportional hazards regression analysis indicated that the presence of multivessel disease, angiographic ACC/AHA B2 lesion, non-LDL-C/HDL-C ratio was significantly associated with increased incidence of MACE after adjusting multiple variables (adjusted HR =1.470, 1.248, 1.433, respectively).

**Conclusions:** Non-HDL-C/HDL-C ratio can be a potential risk predictor in patients on statin with target LDL-C in the drug eluting stent era.

**P5736**
**Conclusions:** Administration of omega-3 PUFAs can improve the long-term outcome in patients after PCI with drug eluting stents.


**Purpose:** Statins improve outcome in the long-term after acute coronary syndromes (ACS). However, little is known about its relationship with in-hospital mortality in patients with ACS. The main purpose of this study was to analyze the role of statins, started in the first 24 hours post-hospitalization, regarding in-hospital mortality.

**Methods:** We analyzed 2057 patients (pts) with ACS (median age 64 years, 68% men) included prospectively in a data bank from a tertiary cardiology hospital. The role of statins on mortality was analyzed for the global population, and also according to the first LDL level at hospitalization (group I LDL < 70 mg/dL, N=384; group II LDL 70-130 mg/dL, N=1145; group III LDL >130 mg/dL, N=326; group IV LDL >160 mg/dL, N=202). Chi-square (with Fisher exact test when indicated) was utilized for categorical variable comparisons, and the Mann-Whitney U-test was applied for continuous variable comparisons. Different adjusted models (logistic regression) were developed, taking into account in-hospital mortality as dependent variable and baseline variables (including LDL as a continuous variable) as independent ones.

**Results:** 1) For the overall population, the use of statins in the first 24 hours of hospitalization (70.8% of the pts) correlated significantly with decreased mortality (Odds Ratio (OR)=0.663, P=0.024). However, the benefit was not uni-
form among the LDL-level groups, being restricted to those groups with lower LDL levels: OR=0.425, P=0.021 for group I, OR=0.497, P=0.003 for group II, OR=1.541, P=0.470 for group III, and OR=1.418, P=0.147 for group IV (chi-square for trend 0.40, P=0.001). 2) The adjusted model for the whole population showed that the use of statin correlated significantly and independently with mortality (OR=0.607, P<0.010). The P-values for statin utilization remained significant after the inclusion of the time of between pain beginning and hospitalization (OR=0.564, P=0.008), myocardial infarction (MI)/unstable angina (OR=0.610, P=0.011), and ST-elevation MI/Non-ST-elevation MI (OR=0.623, P=0.016). As in the univariate analyses, the impact of statin utilization was different according to the LDL level: OR=0.348, P=0.016; OR=0.460, P=0.003; OR=1.793, P=0.380 and OR=0.573, P=0.213, respectively, for groups I, II, III and IV. In conclusion, the early beginning of statin utilization after hospital arrival decreases in-hospital mortality in patients with ACS, especially in those with lower levels of LDL. These findings reinforce the hypothesis that the beneficial pleiotropic effects of the statins is more evident in the early phase post-ACS.

Effect of statins on venous thromboembolic events: a meta-analysis of published and unpublished evidence from randomised controlled trials

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Background: It has been suggested that statins substantially reduce the risk of venous thromboembolic events. We sought to test this hypothesis by performing a meta-analysis of both published and unpublished results from randomised trials of statins.

Methods: We searched MEDLINE, EMBASE and the Cochrane’s CENTRAL up to October 2010 for randomised controlled trials comparing statin with no statin, or comparing high dose versus standard dose statin, with 100 or more randomised participants and at least 6 months’ follow-up. Investigators were contacted for unpublished information about venous thromboembolic events.

Findings: Twenty one trials of statin versus control (105,627 participants) and seven trials of an intensive versus a standard dose statin regimen (40,594 participants) were included. In trials of statin versus control, allocation to statin therapy did not significantly reduce the risk of venous thromboembolic events (464 statin vs 520 control, odds ratio [OR]=0.89, 95% confidence interval [CI] 0.78 to 1.01, P=0.07) with no evidence of heterogeneity between effects on deep vein thrombosis (266 vs 310, OR=0.86, 99% CI 0.69–1.07, P=0.32 among the other 20 trials). There was no evidence that higher doses of statin therapy (204 vs 222, OR 0.92, 99% CI 0.71-1.19) or exclusion of the trial result that provided the motivation for our meta-analysis (JUPITER) had little impact on thrombosis (266 vs 310, OR 0.86, 99% CI 0.69–1.07) and effects on pulmonary embolism (54 vs 68, OR 0.79, 99% CI 0.56–1.13). Exclusion of the size of the study (OR=1.01, P=0.07) with no evidence of heterogeneity between effects on deep vein thrombosis (266 vs 310, OR=0.86, 99% CI 0.69–1.07) and effects on pulmonary embolism (54 vs 68, OR 0.79, 99% CI 0.56–1.13) and other unmeasured events. There was no evidence of a difference in the effect of statin on outcomes according to the LDL level: OR=0.348, P=0.016; OR=0.460, P=0.003; OR=1.793, P=0.380 and OR=0.573, P=0.213, respectively, for groups I, II, III and IV.

Conclusions: The findings from this meta-analysis do not support the previous suggestion of a large protective effect of statins (or higher dose statins) on venous thromboembolic events. However, a more modest reduction in venous thromboembolic events cannot be ruled out.

Statin treatment is associated with lower risk of recurrent venous thromboembolism in patients not receiving aspirin. A nationwide cohort study

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Purpose: The risk of primary venous thromboembolism (VTE) and pulmonary embolism (PE) associated with statin therapy is well established in the literature. However the effect of statin in recurrent VTE and PE has not been established. Therefore the aim of our study was to investigate the effect of statin in the long-term prevention of VTE and PE.

Methods: All patients discharged from first VTE or PE during 1997-2009 as well as all prescription claims for statin and other medications before and after discharge were identified through Danish nationwide registers. Patients were followed until in-hospital discharge or 31 December 2009. The risk of recurrent VTE or PE associated with statin-use was studied by multivariable Cox proportional-hazards models.

Results: A total of 38,893 individuals were included, mean age 63(±17) years, 49% males and 3982 (10%) used statin. The crude incidence rate of recurrent VTE/PE was 35.0 per 1000 person-years. Adjusted hazard ratio of recurrent VTE/PE for statin use was 0.88 (0.80-0.96). Interaction was seen between statin use and aspirin-use in the relative risk of recurrent VTE/PE, p=0.04. Adjusted hazard ratio for statin use with vs. without aspirin use was 0.84 (0.76-0.92) vs. 1.02 (0.85-1.23). See table 1.

Conclusions: Statins were associated with lower risk of recurrent VTE/PE in patients not receiving aspirin. Further studies on the effect of statins on prevention of recurrent VTE/PE episodes are warranted.

Lipoprotein(a) is an important factor to determine coronary artery plaque morphology in patients with acute myocardial infarction

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Background: Lipoprotein(a) [Lp(a)] can influence the development and disruption of atherosclerotic plaques through its effect on lipid accumulation. The purpose of this study is to evaluate relationship between serum Lp(a) levels and coronary artery plaque morphology of an infarct-related and non-infarct-related lesions of coronary artery in acute myocardial infarction (AMI)

Methods and Results: Coronary plaque morphology was evaluated in 54 patients (age 62±11 yrs, mean±SD, men n=39, women n=15) with AMI using intravascular ultrasound with radiofrequency data analysis (IVUS-VH) before coronary intervention and using 64-slice computed tomography angiography (64-CTA) within 2 weeks. Patients were divided into the group with Lp(a)>25mg/dl (n=17) and the group with Lp(a)<25mg/dl (n=37). IVUS-VH identified four types...
of plaque component at the infarct-related lesion: fibrous, fibro-fatty, dense calcium, and necrotic core. Necrotic core component was significantly greater in the Lp(a)-25mg/dl group than in the Lp(a)-25mg/dl (27.8±6.2 mm² versus 15.7±1.0 mm², p<0.005). Histological changes in CTA were classified as calcified plaque (NCP), mixed (calcification-50%). The 64-CTA indicated that the Lp(a)-25mg/dl group had a greater number of total plaques, NCPs and vulnerable plaque (CT-density ≤ 130 HU) than the whole coronary arteries than the Lp(a)-25mg/dl (5.3±1.9 vs. 3.7±2.2, p=0.04, 4.0±1.2 vs 1.2±1.3, p<0.002, 2.2±2.2 vs 0.5±0.7, p<0.002, respectively).

Conclusions: Serum Lp(a) is associated with the number of plaques and plaque morphology. With high Lp(a) level in AAA need more intensive treatment of plaque stabilization.

High density lipoprotein levels are strongly associated with the recovery rate of insulin sensitivity during acute phase of myocardial infarction: a study by eugycemic hyperinsulinemic clamp

P5744

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Background: The loss of insulin sensitivity (IS) during myocardial infarction (MI) is strongly associated with increased morbidity and mortality. Recent data suggest that in stable conditions, HDL may improve IS. To date, the role of HDL in the modulation of IS in acute stress conditions such as MI is unknown.

Aim: We explored the influence of plasma levels of HDL-c on the change in IS during the acute phase of MI.

Methods: Consecutive non-diabetic patients with ST-elevation MI (n=20) underwent eugycemic hyperinsulinemic clamp (EHC) on the first morning and on the fifth day after onset of MI. Patients were grouped according to HDL-c levels at admission above and below median value (35mg/dl).

Results: No admission, there was no significant difference in baseline IS index, clinical, anthropometric or treatment characteristics between Low and High HDL groups. Between admission and fifth day, there was a decrease of 8% in IS index in the Low HDL group and an 11% increase in the high HDL group (p<0.001 for intergroup and p<0.012 for intergroup difference). This difference remained significant after controlling for the gender, age, waist circumference, triglycerides and statin dosing during hospitalization.

Conclusions: Based on the gold standard method for evaluation of IS, this study provides evidence that serum levels of HDL-c are strongly associated with the recovery rate of IS during the acute phase of MI.

Cholesterol ester transfer protein role during acute phase of myocardial infarction

P5743

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Introduction and aim: The HDL phenotype induced by enhanced cholesterol ester transfer protein (CETP) activity is considered pro-atherogenic. But recent findings have linked increased CETP activity in sepsis-related acute stress to reduced inflammatory response and there is no information regarding CETP activity impact in ST-elevation myocardial infarction (STEMI). We evaluated the role of CETP on HDL phenotype and inflammatory response in patients with STEMI.

Methods: Consecutive STEMI patients (n=61) were selected from the Brasilia Heart Study. HDL-c, C-reactive protein (CRP), IL-2, TNF-α, 8-isoprostanes levels, CETP % activity and HDL size by laser scattering were measured in the first 24 hours (D1) and at the 3rd (D3), 5th (D5) and 30th (D30) days after MI onset. ANOVA analysis indicated the differences in CETP activity and HDL particle size between days, while ANCOVA analysis were performed to evaluate the impact of CETP on HDL phenotype and inflammatory response in patients with STEMI.

Results: We observed a decrease in CETP activity between D1 and D3/D5, followed by a recovery by the D30 (14.6±10.3; 11.0±5.0; 10.4±8; 14.9±5%, respectively; p<0.001). Consistently, HDL size increased between D1 and D5, but reduced D30 (7.7±3.4; 6.7±5.9; 7.7±6.3; at D1, D5 and D30, respectively; p<0.001). In parallel, patients with higher decrease in CETP activity between D1 and D5 (ΔCETP below median) experienced a higher reduction in HDL-c levels [-4.0 (1.4; -1.5) vs. -5.0 (-1.2; -2.5) mg/dl] and above median 8-isoprostanes levels [22 (16; 27) vs. 16 (8; 23) μg/mL, p<0.001] and a reduction 8-isoprostane levels (-5.3 (3.2; 12) μg/mL vs D1 and D5. Meanwhile, those with ΔCETP above median showed an increase in 8-isoprostanes levels in the period (6.6 (2.2; 13) μg/mL, p<0.001). However, ΔCETP did not influence the change in CRP. IL-2, TNF-α levels following MI.

Conclusions: This is the first study to demonstrate a marked reduction in CETP activity following STEMI. This finding may explain the observed increased HDL size and contributes to a better understand of CETP role during acutephase of STEMI. Further investigation may be necessary to unveil the impact of CETP inhibitors during acute stress.

Relation between creatinine clearance (MDRD) and mortality in intensive care unit patients with STEMI


Background: Current ESC STEMI guidelines do not emphasize significance of renal dysfunction to a degree seen in guidelines for NSTEMI-ACS patients. In previous ACOs-registries, patients with STEMI and impaired renal function were included as a high risk population.

The aim of the present study was to investigate the impact of admission estimated glomerular filtration rate (GFR) on clinical outcomes of patients undergoing primary PCI and percutaneous coronary intervention (PCI) or thrombosis for ST-segment elevation myocardial infarction (STEMI).

Methods: 1138 consecutive STEMI patients were enrolled from 01/2007 to 10/2016. CRP IL-2, TNF-α, 8-isoprostanes were measured by commercial assay using the Mitrolight Instrument (CMA). GFR was calculated using the abbreviated MDRD formula. We examined the impact of impaired renal function (GFR<60mL/min/1.73 m²) on treatment and hospital mortality. Patients were divided into two groups according to creatinine clearance: group I: GFR<60mL/min/m², group II: GFR≥60mL/min/m².

Results: In hospital mortality was 5.3%. In hospital mortality rate was significantly higher in group I as compared to group II (16.2% vs 2.3%, p<0.001).

Patients in group I were older, had more cardiovascular comorbidities and more
Does clinically relevant non-major bleeding in acute STEMI have a higher risk of MACE?


Background: In developing countries, fibriolysis is the commonest choice of reperfusion for STEMI patients. Outcomes improved with the addition of aspirin and further improved with the addition of clopidogrel and LMWHs. However, aggressive therapy is associated with increased risk of both minor and major bleeds, but we noted an increase in clinically relevant non-major bleeds. When such bleeding occurs in the immediate post-STEMI period, all anti-platelets and LMWH have to be stopped during this critical phase. Are these patients at a higher risk of MACE?

Objective: To determine the bleeding risk in STEMI patients who received aspirin, clopidogrel and LMWH prior to STK and the outcome in such patients who developed clinically relevant non-major bleeds.

Method: 423 consecutive STEMI patients admitted to the CCU, Hospital Kuala Lumpur over 18 months (January 2009 till June 2010), were analyzed. Before being admitted to the CCU, in the Emergency Department, all STEMI patients are given a stat dose of 300mg aspirin PO, 300mg clopidogrel PO and an equivalent of 0.6 ml of eparioparin sc, followed by 1.5 mega of STK iv. Patients who bled were classified as minor, clinically relevant non-major (CRNM) and major bleeding, based on the ISTH classification.

Results: 80 out of the 423 patients (19.96%) developed bleeding. CRNM bleeding was the commonest, 48% (39) followed by minor 30% and major bleeding 21%. Patients with CRNM bleeding had higher mortality compared to minor bleeding (12.82% vs 0%, p = 0.0675) during the index hospitalization. Patients who received < 48 hours of anti-platelet and LMWH post STEMI showed a higher mortality when compared with those who received > 48 hours. (22% vs 0%, p = 0.007). Patients on fondaparin bled earlier compared to those on eparioparin (median 4hrs vs 9.5 hrs), but was not statistically significant.

Conclusion: These findings show that aggressive anti-platelet and LMWH pre-treatment before STK results in significant CRNM bleeding in the post STK period, which resulted in a significantly higher mortality during the index hospitalization. It also showed that those who received < 48 hours of post STK anti-platelet and LMWH treatment had a significantly higher morbidity.

CRITICAL ROLE OF COMORBIDITIES IN CORONARY DISEASE

P5747

Prevalence of coronary artery disease in patients with paroxysmal or persistent atrial fibrillation studied by 64-slice computed tomography coronary angiography

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Purpose: AF is considered to be associated with and maybe even caused by CAD. To date this assumption has not been validated by imaging methods in large scale. Therefore the prevalence of coronary artery disease (CAD) in patients with paroxysmal or persistent atrial fibrillation (AF) scheduled for pulmonary vein isolation was assessed by 64-slice computed tomography coronary angiography.

Methods: TOR: Prior to pulmonary vein isolation we performed 64-slice computed tomography on 314 patients with paroxysmal or persistent AF. Diagnostic findings with regard to normal, nonobstructive CAD and obstructive CAD (luminal stenosis > 50%) were recorded. Patients with obstructive CAD were put to further diagnostics. Those with luminal stenoses of 70-75% were referred to stress testing and if positive subjected to cardiac catheterization. Patients with luminal stenoses ≥ 70% were, as well as those with typical angina, directly referred to cardiac catheterization.

Results: In computed tomography coronary angiography 40% of the patients had normal coronary findings, while 38% showed nonobstructive and 22% obstructive CAD. Interestingly a correlation between type of AF (i.e. paroxysmal or persistent) and degree of stenosis could not be found.

Conclusions: Our results confirm a high prevalence of CAD in patients with paroxysmal or persistent AF. To our notion this rather represents a coincidence due to similar risk factors than a relation of cause and effect. However CAD might account for the increased mortality of patients with AF and depending on the patients individual cardiovascular risk profile coronary intervention seems to be reasonable.

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Antithrombotic therapy for stroke prevention in patients with newly diagnosed atrial fibrillation and a history of acute coronary syndrome: The Global Anticoagulant Registry in the FIELD (GARFIELD)

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Little is known about stroke incidence and outcomes in atrial fibrillation (AF) patients with an acute coronary syndrome (ACS). Following ACS with or without PCI in AF patients, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term (3-6 months), or for longer in selected patients at low bleeding risk, followed by long-term therapy with VKA plus clopidogrel or aspirin. We describe how baseline characteristics and use of antithrombotics in ACS patients with AF from the GARFIELD registry.

Methods: The aim of this registry is to enroll 55,000 patients in 5 sequential prospective cohorts at 12000 randomly selected sites in 50 countries. Patient eligibility included age ≥ 18 years, newly diagnosed non-valvular AF, and a 1-day investigator-determined stroke risk factor. This analysis describes the use of antithrombotic agents in patients with a history of ACS in cohort 1.

Results: Of 5,151 AF patients enrolled in cohort 1, 1,048 had a history of ACS. Mean age 71.2±9.5 years, 72.2% were men, median body mass index 27.3 kg/m2; 33.9% had a history of diabetes, 82.4% hypertension, 17.5% prior stroke or transient ischaemic attack, and 38.8% congestive heart failure. OAC alone was used in 31.4% of all ACS patients; OAC plus one or more antiplatelet (AP) agent was more frequently used among patients with stenting (Table).

Conclusion: Antithrombotic use in patients with a history of ACS (n=1048). BMS, bare-metal stent; DAPT, aspirin + ADP receptor/P2Y12 inhibitor; DES, drug-eluting stent.

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Presence of atrial fibrillation in patients with acute myocardial infarction undergoing percutaneous coronary intervention predicts contrast-induced nephropathy


Purpose: Atrial fibrillation (AF) is known as one of factors that negatively influence kidney function. Contrast-induced nephropathy (CIN) is associated with poor clinical outcomes in patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI). We investigated whether AF could predict CIN in AMI patients treated with PCI.

Methods: We analyzed clinical data from 1041 AMI patients treated with PCI, of whom 1037 patients fulfilled the inclusion criteria. CIN was defined as an increase in serum creatinine level (>25% or >0.5 mg/dL) within 48 hours after PCI. CIN was divided into AF with prior history or new-onset AF developed during AMI without previous history.

Results: Atrial fibrillation was observed in 71 patients (6.7%) and CIN in 148 patients (14.2%). Patients with AF exhibited higher incidence of CIN than those without AF (31.4 vs 13.0%, p < 0.001). Multivariate analysis showed that AF was the second most significant independent predictor of CIN [odds ratio (OR) 3.48, 95% confidence interval (CI) 1.69 - 7.15, p = 0.001], following impaired renal function (serum creatinine level >1.5 mg/dL) at baseline (OR 3.50, 95% CI 1.89 - 6.49, p = 0.001). Each new-onset AF (OR 3.94, 95% CI 1.55 - 9.99, p = 0.004) and AF with prior history (OR 2.98, 95% CI 1.04 - 8.57, p = 0.043) was also a
Incidence and prognosis of new-onset atrial fibrillation in acute coronary syndrome: observations from Taiwan ACS Full Spectrum Registry

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Purpose: Data about new-onset atrial fibrillation (AF) in acute coronary syndrome (ACS) in Asia is scarce. We analyze the prognostic impact of new-onset AF in ACS patients hospitalized in Taiwan, from ACS Full Spectrum Registry.

Methods: Patients with ACS complicated with new-onset AF (n=60) and those without AF (n=2632) were followed for 12-month outcomes.

Results: The incidence of new-onset AF in patients with ACS in Taiwan was 2.5%. In medical history, the patients with new-onset AF were older (69 vs. 62.5%, p<0.05), higher rate of DM (47.5% vs 35.6%) and dialysis (8.8% vs. 3.6%) than those without AF. In presenting features, patients with new onset AF have higher heart rate (93 vs. 82/min), TnI (29.7 vs. 13.7ng/mL), Cr (2.5 vs. 1.6mg/dL), Killip class and lower systolic blood pressure (140 vs 131mmHg) than patients without AF. AF in hospital events, the patients with new-onset AF have higher rate of LM lesion (7.5% vs. 3.2%) and receiving CABG (8.8% vs. 3.2%) than patients without AF. In discharge medication, patients with new onset AF have less rate of taking aspirin (61.0% vs. 82.9%), clopidogrel (72.7% vs. 87.5%) and ACEi/ARB (48% vs. 87.5%) than without AF. The adjusted 12month mortality (OR 1.03) were significantly higher in patients with new-onset AF than those without AF. (all p<0.05)

Conclusions: Despite low incidence, our study suggested that new onset AF is associated with a worse predictor of one-year stroke and mortality in patients with ACS.

Prognostic impact of atrial fibrillation in acute coronary syndrome patients with and without ST segment elevation

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Background: Atrial fibrillation (AF) is the most common sustained arrhythmia in acute coronary syndrome patients, but the long term impact of both the presence and time of onset of AF are unknown.

Goal: To assess the impact of previous vs new onset AF on the 5-year mortality in acute coronary syndrome patients, with (ST) and without (NSTE) segment elevation.

Methods: 676 patients were studied (mean age 61.6±1.4 years old, 79.6% males), 33.6% having STE. New onset AF was defined as AF diagnosed during hospital stay with sinus rhythm at admission. The basal demographic and clinical characteristics were analysed using a multivariable model (Cox regression) to determine the independent predictors of 5-year mortality.

Results: AF was found in 39 pts (5.8%), comprising known (2.2%) and new-onset AF (3.6%). The 5-year mortality was 13.6%, AF was independently associated with greater 5-year mortality (HR 2.28 CI 95% 1.23-4.18, p=0.009). Both AF and ACS type did not significantly influence the 5-year mortality (Figure 1).

Figure 1. 5-year mortality (%) according to type of AF and ACS

Conclusions: In our ACS patient population, AF was associated with greater 5-year mortality, regardless of AF or ACS type.
Obstructive sleep apnoea is highly frequent in consecutive patients with refractory angina

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Purpose: Obstructive sleep apnea (OSA) is common among patients with stable coronary artery disease and may contribute to poor cardiovascular outcome. OSA has not been investigated in patients with refractory angina, a debilitating condition characterized by persistent symptoms despite optimized medical therapy. Methods: Consecutive patients with multi-vessel coronary disease by angiography and refractory angina (severe ischemic symptoms that persist despite optimal medical therapy and whom coronary revascularization procedures are no longer feasible or helpful) were recruited from a specialized out patient clinic. Regardless of sleep complaints, all patients were evaluated by standard overnight polysomnography, symptoms of excessive daytime sleepiness by Epworth Sleepiness Scale (ESS) and one week diary of angina. Results: We evaluated 31 patients (16 males, age: 62±10y, body mass index: 28.9±4.5kg/m²). Co-morbidities were common (dyslipidemia 100%, hypertension 93% and diabetes 61%) and all patients presented persistent angina despite optimal an- ischemic medical therapy and preserved systolic function (ejection fraction on echocardiography: 53±11%). Patients were assessed for sleep quality, poor sleep efficiency (60.16%) and the prevalence of OSA (AHI>15) and severe OSA (AHI>30) was 71 and 55%, respectively. As compared with patients without OSA, patients with OSA group 1 (AHI<5) had a similar age, gender, BMI (23.5±4.5kg/m², p=0.26) similar ESS (10.6±11.6), non-significant trend to higher frequency of diurnal (66 vs. 91%, p=0.13) and nocturnal angina (45 vs. 77%, p=0.08).

Conclusions: This preliminary study showed a high frequency of OSA in con-secutive patients with refractory angina. Traditional risk factors for OSA, including age, male gender and BMI did not discriminate patients with OSA. Non-significant trends to higher frequency of diurnal and nocturnal angina suggest that OSA may contribute to trigger angina symptoms.

Obstructive sleep apnea: more insights on the subclinical cardiovascular alterations and the effect of treatment with continuous positive airway pressure

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Purpose: The mechanisms underlying the increased risk of cardiovascular dis- ease (CVD) in obstructive sleep apnea (OSA) remain poorly understood. The present study aimed to assess: 1. the occurrence of subclinical CV alterations in newly diagnosed OSA, and 2. the effect of treatment with continuous positive airway pressure (CPAP) on these parameters.

Methods: We conducted a prospective cohort study including OSA patients (n = 117; age: 49.6±9.8 years; BMI: 29.8±4.5) and age and BMI matched non-OSA controls (n=18; age: 46.9±8 years; BMI: 29.7±9.3) without known CVD. The pa- tients received a 2-D Doppler and Doppyramol-stress myocardial contrast echocar- diography (MCE using Sonovue echoc contrast; Philips, IE 33), non contrast echoc- agatson score and contrast enhanced cardiac CT scan (13 coronary segments assessed for degree of stenosis; 64-slice GE, Cardiol artery intima media thick- ness (IMT) measurement and Brachial artery vascular reactivity assessment by flow mediated dilatation (FMD). Patients with AHI >15 were eligible for CPAP, and those adhering to 5 hours daily use of CPAP were assessed after 6 months (n=65).

Results: Patients were divided into 3 groups: control group 1 (n = 18; AHI 9.5±3.5), group 2 with mild to moderate OSA (15 < AHI < 35; n = 33; AHI 27.3±4.5) and group 3 with severe OSA (AHI > 35; n = 84; AHI 63.4±19.9). All patients had diastolic dysfunction grade I or II, and normal systolic BP (124±16 min/Hg, p = ns between groups). There was significant increase in resting heart rate (HR), interventricular septum (IVS) thickness, IVT, fibrinogen, C-reactive protein, triglyceride levels and coronary plaque from group 1 to group 3 (p < 0.05 for all). Similarly, the FMD was lower, the arterial oxymeglogobin saturation (Sao2) nadir and FMD were the best predictors for presence of coronary plaque (p < 0.04). At 6 months after CPAP treatment there was no change in the BMI but improvement of the resting HR, IVS thickness, IMT, FMD and LDL-cholesterol levels (p<0.05), with some patients showing improved myocardial contractile reserve. Conclusion: Newly diagnosed OSA patients without clinical CVD show signifi- cant graded alterations in IMT, FMD, coronary plaque, IVS thickness and myocar- dial contractile and perfusion reserve with worsening AHI. Treatment with CPAP reverses some of these alterations at 6 months.

Obstructive sleep apnea syndrome is an independent predictor for cardiovascular disease in obstructive sleep apnea syndrome

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Gamma glutamyl transferase (GGT) is a new marker for predicting myocardial infarction, stroke, cardiac death and inflammation. There is an association between Obstructive Sleep Apnea Syndrome (OSAS) and cardiovascu- lar disease. This study was designed to investigate the association between serum GGT levels and cardiovascular disease in patients with OSAS, and re- lationship between severity of OSAS and serum GGT level. We evaluated the medical records of 166 subjects who were admitted for sleep study. OSAS was diagnosed by polysomnography if Apnea-Hypopnea Index (AHI) > 5. According to AHI, individuals in whom AHI > 5 were recruited as group 1 (OSAS negative group), AHI = 5-15; group 2 (mild OSAS group), AHI = 15-30; group 3 (moderate OSAS group), AHI >30; group 4 (severe OSAS group). Cardiovascular disease was defined if the patients had heart failure, coronary artery disease or arhyth- mia. Of the subjects, 112 (67.5%) were male and the mean age was 54.3±12.2 years. There were 22 patients (13.2%), 17 patients (10.2%), 34 patients (20.4%) and 93 patients (56.2%) in group 1, 2, 3 and 4, respectively. There was significant increase in serum GGT levels while AHI score increases (group 1 = 28.0±10.1, group 2 = 33.6±13.2, group 3 = 35.2±8.5, group 4 = 40.0±22.0, p for trend < 0.05). Higher serum GGT levels and apoA-I, C-reactive protein and aspartate aminotransferase levels were similar in all groups (p > 0.05). There was a significant independent association between serum GGT levels and the sever- ity of OSAS. Moreover, serum GGT levels were significantly high in patients with cardiovascular disease compared with patients without cardiovascular disease in severe-moderate-mild OSAS (p < 0.05) and OSAS negative groups while CRP levels were not. This was a significant independent association. The present study suggests that high serum GGT level, regardless of the other traditional risk fac- tors, is an independent predictor of cardiovascular disease in patients with OSAS. The results should be confirmed with other randomized prospective studies.

Significance of nonalcoholic fatty liver disease in patients with acute coronary syndrome and stable angina pectoris


Background: Nonalcoholic fatty liver disease (NAFLD) frequently occurs with features of the metabolic syndrome including obesity, type 2 diabetes mellitus (DM), dyslipidemia (DL) and hypertension (HT). Recent evidence suggests that NAFLD is a novel predictor of coronary artery disease (CAD) independent of such features of metabolic syndrome. However, the causal relation between NAFLD and CAD remains poorly understood. We sought to clarify the clinical significance of NAFLD in CAD by comparing demographic factors between acute coronary syndrome (ACS) such as acute myocardial infarction (AMI) and unstable angina (UA), and stable angina pectoris (SAP).

Method: We performed a retrospective analysis of prospectively collected data obtained from consecutive patients with ACS or SAP who were admitted to our hospital from 2009 to 2009. The data included conventional risk factors such as smoking, DM, DL, HT and hyperuricemia. Prevalence of NAFLD was confirmed by reviewing medical chart or discharge summary. We used SYNTAX scoring system to assess coronary artery complexity and plaque burden in those patients with ACS and SAP.

Results: The study included 1570 patients (age 69.8±10 years, 75.2% male, range 29 to 92 years), of whom 31.2% had SAP, 23.7% had UA and 45.1% had AMI. NAFLD was present in 14.7% of SAP, in 12.9% of UA and in 9.0% of AMI. The prevalence of NAFLD was significantly higher in patients with SAP than those with ACS (AMI-UA) (14.7% vs 10.4%, p<0.017). Moreover, the SYNTAX score was also significantly higher in patients with SAP than ACS (20.5±10.3 vs 17.4±9.5, p<0.002). There was no significant difference in any other demographic factors between ACS and SAP groups.

Conclusions: Patients with stable coronary artery disease appeared to have higher prevalence of NAFLD with greater coronary artery complexity than those with ACS. This finding may help us to understand the causal relation between NAFLD and CAD in terms of epicardial fat, which frequently occurs under hyperinsulinemia accompanied with metabolic syndrome.

Ibradine protects autonomic homeostasis of heart rate after salbutamol inhalation in patients with chronic obstructive pulmonary disease and coronary heart disease

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Background: Patients with COPD demonstrate severe alteration of autonomic heart rate regulation. Bronchodilator therapy with β2-agonists may potentially in-
Pulmonary hypertension in acute coronary syndrome: prevalence and implications

Introduction: Pulmonary hypertension (PHT) is defined as a pathophysiological and hemodynamic state that may be present in multiple clinical conditions. Its prevalence and its impact on prognosis in patients hospitalized with acute coronary syndrome (ACS) are not well established.

Purpose: To evaluate the prevalence of PHT in patients admitted with ACS and its impact on prognosis.

Population and methods: This study included 902 patients with ACS consecutively admitted to a coronary care unit over 2 years. In the first 48 hours of admission, a transthoracic echocardiography was performed in all patients. PHT was defined as a pulmonary artery systolic pressure (PASP) ≥ 36 mmHg estimated by transthoracic echocardiography. The patients were grouped according to presence of PHT: Group (G): 1. patients with PHT, G2: patients without PHT (PSAP < 36). This diagnosis was confirmed with the presence of indirect signs of HTP. Primary endpoint was major adverse cardiac events (MACE) in the follow-up at 6 months. Results: 154 (17.1%) of the 902 patients had HTP. These patients were older (p < 0.001), had higher prevalence of hypertension (p = 0.007) and diabetes (p = 0.001) and lower prevalence of smoking (p = 0.012). They had history of myocardial infarction (p = 0.01), stroke (p = 0.038), peripheral arterial disease (p < 0.0001) and coronary artery bypass grafting in 10% more often. At admission, they had a lower mean hemoglobin levels (p < 0.001) and higher mean values of cystatin C and B type natriuretic peptide (p = 0.001 and p = 0.047 respectively). Tree vessels disease was more common in these patients (p = 0.005). Death and MACE at 6 months were higher in G1 (p = 0.028 and p < 0.001 respectively). The presence of PHT on admission was an independent predictor of MACE at 6 months in multivariate analysis (OR = 1.7, 95% CI. 1.1 to 2.7, p = 0.025).

Conclusion: In this population, the presence of PHT on admission was associated with a worse prognosis at 6 months after ACS. Thus, it can complement the risk assessment of these patients. The underlying mechanisms of this relationship deserves further studies with a higher number of patients.

P5760 Impact of in-hospital timi bleeding and chronic kidney disease on one-year cardiovascular events in patients with acute coronary syndrome
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Background: In-hospital bleeding (IHB) have been recently reported to increase the risk of subsequent cardiovascular events (CVE) in patients with acute coronary syndrome (ACS). Whether the association is influenced by the presence of chronic kidney disease (CKD), a known risk factor of bleeding or CVE, or both have independently detrimental effects on CVE is unknown.

Methods: In a Taiwan nationwide registry, 2819 ACS patients were enrolled. CKD was defined as an estimated glomerular filtration rate of less than 60 ml/min per 1.73 m² using the Modification of Diet in Renal Disease Study equation. The IHB is defined as the presence of Thrombosis In Myocardial Infarction (TIMI) bleeding. The primary end point was the composite CVE of death, non-fatal myocardial infarction and non-fatal stroke at one year.

Results: Both IHB and CKD are independently associated with an increased risk of the primary end point (OR 2.17, 95% CI: 1.63 to 2.87 and OR 2.39, 95% CI: 1.28 to 4.50, both p < 0.01) after adjusting by age, sex and medication at discharge. Patients with IHB and CKD have 10.5 fold risk to suffer from the primary end point compared with those without IHB and CKD (OR 10.53, 95% CI: 4.84 to 22.89, p < 0.01). The Kaplan–Meier curves showed significantly higher event rates during one-year follow-up among those with IHB and CKD both in the ST elevation and non-ST elevation ACS populations (both p < 0.01).

Conclusions: IHB or CKD is independently associated with poor outcome and patients with both IHB and CKD have the worst outcome in the ACS.

P5761 Isolated coronary surgery - associated acute kidney injury: a comparison with RIFLE criteria
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Purpose: The consensus statement RIFLE (risk, injury, failure, loss, and end-stage kidney disease) indicates criteria to define the type and consequence of acute kidney injury (AKI). In the RIFLE criteria of AKI, the threshold given for serum creatinine (cCr) increase and glomerular filtration rate (eGFR) decrease do not correspond (Table). We sought to estimate the ability of both criteria to predict the risk of in-hospital mortality in patients undergoing isolated CABG.

Methods: Data on 4,576 consecutive patients undergoing isolated CABG from Jar89-Dece08, excluding 31 on preoperative dialysis. AKI was defined by using either largest cCr increase or greater eGFR decrease, postoperative compared to baseline. In all patients, aperoperative baseline cCr was available. We compared the diagnostic properties of both RIFLE criteria and calculated the areas under the receiver operating characteristic (ROC) curve.

Results: Global mortality was 0.6% (31 patients). 22.5% patients were diagnosed AKI.

RIFLE classes by creatinine and estimate

<table>
<thead>
<tr>
<th>RIFLE stage by creatinine thresholds</th>
<th>No-AKI</th>
<th>Class I</th>
<th>Class II</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-AKI</td>
<td>2,380</td>
<td>0</td>
<td>0</td>
<td>2,380</td>
</tr>
<tr>
<td>Class II (risk)</td>
<td>1,165</td>
<td>744</td>
<td>61</td>
<td>1,980</td>
</tr>
<tr>
<td>Class III (injury)</td>
<td>0</td>
<td>86 (1.6%)</td>
<td>165 (3.6%)</td>
<td>251 (5.5%)</td>
</tr>
<tr>
<td>&lt;cCr threshold</td>
<td>0</td>
<td>0</td>
<td>22 (0.4%)</td>
<td>22 (0.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>3,545</td>
<td>830 (18.1%)</td>
<td>165 (3.6%)</td>
<td>36 (0.8%)</td>
</tr>
</tbody>
</table>
as having postoperative AKI by the sCr criteria versus 48.0% with eGFR criteria. The largest disagreement was detected in class R. Overall, the diagnosis of AKI using eGFR thresholds was more sensitive than sCr changes, and this was also true for staging of patients in RIFLE classes R and I. However, for patients staged in the highest AKI class F, sensitivity was higher for sCr criteria. The areas under the ROC curve for sCr and eGFR were 0.86 (95% confidence interval: 0.79 to 0.92) and 0.89 (95% confidence interval: 0.80 to 0.93), respectively.

Conclusions: Both RIFLE criteria (sCr and eGFR) are accurate predictors of mortality after CABG. The high incidence of postoperative AKI should prompt the use of either sCr or eGFR RIFLE criteria to identify patients at risk and to stimulate measures that target AKI as an issue for quality improvement.

**P5763** Prognostic value of occult renal failure in patients with acute myocardial infarction

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Purpose: Occult renal failure is frequently under diagnosed on clinical practice. However, the prevalence and prognosis impact on acute myocardial infarction (AMI) is not well established.

Methods: Between November 2005 and January 2010, 8,213 eligible patients (5,870 men; mean age = 61 ± 12.4 years-old) were analyzed from the Korea AMI Registry. Occult renal failure was defined as creatinine clearance <60 mL/min using Modification of Diet in Renal Disease Study equation and normal creatinine levels (<1.5 mg/dL in men and <1.3 mg/dL in women) in post-MI patients. The 12-month major adverse cardiac events (MACEs) were defined as death, recurrent MI, and revascularizations.

Results: Prevalence of occult renal failure was 13.1% (n = 1,079). Patients with occult renal failure were older with higher inferior MI, more prior coronary heart disease, more hypertension, more diabetes mellitus, and higher Killip class. Kaplan-Meier survival curve showed that 12-month MACEs (23.8% versus 12.4%, p < 0.001) and 12-month mortality (17.8% versus 5.5%, p < 0.001) were significantly higher in patients with occult renal failure compared with patients without occult renal failure. In Cox proportional hazards model, occult renal failure (crude hazard ratio [HR] 2.12, 95% confidence interval [CI] 1.84 – 2.43; p < 0.001) was independent predictor of 12-month MACEs (adjusted HR 1.24, 95% CI 1.01 – 1.53; p=0.040) and 12-month mortality (adjusted HR 1.52, 95% CI 1.12 – 2.06; p=0.007) after adjustment for confounding variables.

Conclusions: In patients with AMI with normal creatinine levels, occult renal failure should not be underestimated in clinical practice.

**P5764** Preventive effect of the PRetreatment with Intravenous Nicorandil on Contrast-Induced nephropathy in Patients with renal dysfunction undergoing coronary angiography (PRINCIPLE Study)

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Background: Renal hypoxia plays an important role in the development of contrast-induced nephropathy (CIN). We investigated the effect of pretreatment with intravenous nicorandil on the incidence of CIN in patients with renal insufficiency undergoing coronary angiography.

Methods: The present randomized controlled multicenter study enrolled a total of 166 patients (nicorandil n=81, control n=85) with estimated glomerular filtration rate (eGFR) <60 mL/min. Nicorandil 0.5 mg was dissolved in 0.5% saline 100 ml was administered intravenously for 30 minute just prior to coronary angiography in the nicorandil group, whereas same volume of saline was given to the control group. Increase in serum creatinine (ΔScr) > 0.5 mg/dL or an absolute increase of >0.5 mg/dl was defined as CIN.

Results: Baseline characteristics were similar between the nicorandil and the control group. Baseline Scr (1.67 ± 1.37 vs. 1.56 ± 0.45 mg/dL, p=0.173) and eGFR (38.3 ± 13.7 vs. 40.6 ± 13.7 mL/min, p=0.253) did not differ. There was no difference between nicorandil and control in mean peak increase in serum creatinine measured within 48 hours after coronary angiography (0.12 ± 0.29 vs. 0.14 ± 0.25 mg/L respectively, P = 0.621). The incidence of CIN was also similar between the two groups (7.8% vs. 6.8%, p=0.810).

Conclusion: Prophylactic intravenous infusion of nicorandil did not decrease the incidence of CIN in renal failure patients undergoing coronary angiography.
Methods: We studied 2726 pts with AMI included in a national multicenter reg-
istry. We considered two groups: pts with CKD and pts without CKD. The pres-
ence of CKD was defined by creatinine ≥2mg/dl (n=101) or on dialysis (n=14). We compared age, gender, cardiovascular risk factors, electrocardio-
graphic presentation of AMI, acute therapy and invasive strategy adopted. De-
fined as the primary end-point hospital mortality and secondary end-point as the
prevalence of one of the following complications (major bleeding, need for blood
transfusion, mechanical ventilation, congestive heart failure, reinfarction) and the
combined presence of death and complications.

Results: The prevalence of CKD has been found in 115 pts (4.2%). Pts with CKD
were older (75.9±8.7 vs 65.0±13.4 years, p=0.001), had higher prevalence of
hypertension (93.0% vs 67.3%, p=0.001), diabetes mellitus (52.6% vs 26.6%,
p=0.001), history of bleeding (3.6% vs 1.2%, p=0.048) and less smoking (8.7%
vs 30.5%, p=0.001). The AMI non-ST elevation and undetermined location of
AMI were more frequent in pts with CKD (68.7% vs 43.0%, p<0.001 and 7.8%
vs 3.2%, p=0.015), respectively. Pts with CKD received less beta-blocker therapy
(70.4% vs 79.7%, p=0.016), inhibitor of angiotensin converting enzyme (74.8%
vs 83.2%, p=0.019), statins (91.3% vs 95.9%, p=0.031), fondaparinux (6.1%
vs 15.2%, p=0.007), glycoprotein IIb/IIIa inhibitors (7.0 vs 25.7%, p=0.001),
and more therapy with enoxaparin (77.4% vs 65.0%, p=0.006). Pts with CKD had
less coronary angiography (65.2% vs 90.3%, p<0.001) and there were no differences
in the severity of coronary artery disease. The primary endpoint was more fre-
quent in pts with CKD (8.7% vs 3.3%, p<0.001), as well as each of the secondary
end-points: the presence of a complication (41.7% vs 21.8%, p=0.001) and the
combined presence of death and complications (43.5% vs 22.1%, p<0.001).
After multivariable adjustment CKD per se was not an independent predictor for
each end-points.

Conclusions: Our results suggest that pts with CKD and AMI have less cardio-
vascular risk factors and have more in-hospital complications and mortality. How-
ever, CKD in these patients was not an independent factor of mortality.
Investigations for Iron Deficiency Anemia (IDA) in patients admitted with Acute Coronary Syndrome: how good are cardiologists?

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Background: Anaemia is associated with increased risk of morbidity and mortality in patients with ischaemic heart disease (IHD) and heart failure. Incidental anaemia in patients awaiting coronary interventions is common particularly in elderly populations. Currently there are no clear guidelines how to investigate these patients. The elderly patients have a higher relative risk of having occult GI malignancy and endoscopy is the gold standard to identify early disease. Endoscopic investigations are however not without complications and generally contraindicated during acute coronary syndrome.

Aim: To assess the management of anaemia in patients awaiting percutaneous coronary interventions.

Material and Methods: This is a retrospective analysis of patients with anaemia admitted with acute coronary syndrome in a tertiary cardiac centre. Information was collected from patient records and endoscopy reporting database over a period of two years (January 2009 – December 2010). Standard statistical methods were used to analyse the data.

Results: A total of 230 patients who were admitted with an acute coronary syndrome (ACS) were identified with anaemia and over a period of 24 months. Only 61 (26.5%) patients were referred to gastroenterologists for the investigation of anaemia. The mean age was 70±19 years with 77% (47/61) were more than 60 years of age. Seven patients was checked only in 50% (31/61) of these patients and 71% (22/31) had low levels. Coeliac serology was done in only 5% (3/61) patients, which was normal. Among these, 92% (56/61) patients were on aspirin, 50% (31/61) on clopidogrel while 11% (7) on warfarin. Oesophago-gastro-duodenoscopy (OGD) was performed in 75.5% (46/61) of the referred patients, with 13.04% (6/46) had nonerosive/gastritis, 8.69% had peptic ulcer disease while angiodysplasia, gastric erosions, gastric polys and hiatus hernia in 4.3% each. OGD was normal in the rest; none had cancer or active bleeding. Colonoscopy was performed in 54.09% (33/61) patients and CT colonogram in 5%. Colorectal cancer was found in 8.33% (3/36) patients, benign polyps in 5.55% and diverticulosis in 22%. Less than 1% patient had proctitis, haemorrhoids and pseudomembranous colitis.

Conclusion: A large number (73%, 169/230) of the anaemic patients with ACS/HHD were not referred to rule out gastrointestinal cause of anaemia. Coeliac serology is not checked routinely. The prevalence of colorectal cancer was high in the small proportion of those referred. Referral to Gastroenterology and appropriate investigations are required in this patient group.

Small abdominal aortic aneurysm is associated with death and cardiovascular events during a 2-year follow-up after an acute coronary syndrome

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Background: Abdominal aortic aneurysm (AAA) is associated with peripheral and coronary artery disease, however little is known about the prognosis of patients who experienced an acute coronary syndrome and have an abdominal aortic aneurysm. The aim of this study was to assess the prevalence of AAA in patients hospitalised for acute coronary syndrome and to evaluate if it was associated with an increased cardiovascular (CV) risk during follow up.

Methods: Between February 1, 2009 and March 30, 2009, randomised patients hospitalised for acute coronary syndrome with significant (>50% stenosis) coronary lesions underwent echocardiography to check for the presence of AAA. An AAA was defined as a dilation of infrarenal aorta with a maximum anteroposterior diameter ≥ 30 mm. During a 2-year follow-up we recorded all-cause deaths, cardiovascular deaths and non-fatal cardiovascular events. The combination of cardiovascular death and cardiovascular non-fatal events was defined as the primary endpoint.

Results: Among 305 patients, 20 AAs (6.6%) were diagnosed, of average (±SD) diameter 33±3.7 mm, with a maximum diameter of 45 mm, none requiring surgery. Follow-up available in 259 patients (85.7%). During follow-up, 49 patients (25.5%) experienced an event (all-cause death or nonfatal CV event): 23 deaths (7.6%), of which 16 were from cardiovascular cause, and 55 non-fatal CV events (18.2%). No event was due to the AAA.

Conclusion: Our results show that in patients with coronary artery disease, the presence of small, non-surgical AAA is associated with worse CV prognosis and higher mortality at 2 years.

Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy

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1University of Turin, San Giovanni Battista ‘Molinette’ Hospital, Cardiology Department 1, Turin, Italy. 2Department of Medical-Surgical Sciences and Biotechnologies Sapienza University of Rome, Rome, Italy

Aims: Highly active antiretroviral therapy (HAART) dramatically reduces human immunodeficiency virus (HIV)-associated morbidity and mortality, but adverse effects of HAART are becoming an increasing challenge, especially in the setting of acute coronary syndromes (ACS). We thus performed a comprehensive review of studies focusing on ACS in HIV patients.

Methods and results: MEDLINE/PubMed was systematically screened for studies reporting on ACS in HIV patients. Baseline, treatment, and outcome data were appraised and pooled with random-effect methods computing summary estimates (95% confidence intervals [CI]). A total of 11 studies including 2442 patients were identified, with a notably low prevalence of diabetes (10.86 4.11, 17.6; 95% CI). Rates of in-hospital death were 8.00% (2.8, 12.5; 95% CI), ascribable to cardiovascular events for 7.90% (2.43, 13.37; 95% CI), with 2.31% (0.40, 4.01; 95% CI) developing cardiogenic shock. At a median follow-up of 25.90 months (11.25, 42; 95% CI), no deaths were recorded, with an incidence of 9.42% of acute myocardial infarction (2.68, 16.17; 95% CI) and of 20.16% (9.84, 30.51; 95% CI) of percutaneous coronary revascularization. Moreover, pooled analysis of the studies reporting incidence of acute myocardial infarction in patients exposed to protease inhibitors showed an overall significant risk of 2.68 (odds ratio 1.89, 3.89; 95% CI).

Conclusions: Human immunodeficiency virus patients admitted for ACS face a substantially short-term risk of death and a significant long-term risk of coronary revascularization and myocardial infarction, especially if receiving protease inhibitors.

Peripheral arterial disease and long-term mortality following acute coronary syndromes: insights from a large registry of unselected patients


Previous studies have shown that short-term prognosis of patients with acute coronary syndromes (ACS) is affected by the presence of peripheral arterial disease (PAD). However its effect on long-term outcomes is less well understood.

Purpose: To evaluate the impact of the presence of PAD on long-term outcome of a large cohort of unselected patients hospitalized for ACS.

Methods: In 2004 and 2005, 2446 consecutive patients were hospitalized at our institution for ACS (896 STE-ACS and 1150 NSTE-ACS). They were followed up for 5 years after discharge. The whole population was divided into two groups according to the presence of PAD. PAD was defined as a history of any of the following conditions: claudication, amputation due to arterial insufficiency, bypass surgery or percutaneous intervention to the extremities or documented aortic aneurysm. The main study endpoint was 5-year overall mortality. The Kaplan-Meier method was used to analyze the occurrence of death in the two study groups and Log-rank Cox Mantelli Test was used for comparison. Multivariable Cox regression analysis was then performed.

Results: PAD had been diagnosed in 312 (15.3%) of the 2,046 patients. Patients with PAD had higher prevalence of diabetes mellitus, Kilip class III-IV and chronic kidney disease and were significantly less likely to undergo PCI. 5-year mortality rate was significantly greater among the patients with PAD compared to those without PAD (62.2% vs 38.1%, p <0.001). After adjusting for baseline
Association of family history of premature cardiovascular disease with traditional cardiovascular risk factors and coronary heart disease in an Indian industrial population

P. Jeemon,1 D. Prabhakaran,2 A. Roy,3 L. Ramakrishnan3

S. Pardey,4 K. S. Reddy4 by behalf of Sentinel Surveillance Study in Indian Industrial Population (SSISP) Investigators.1 Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom;2Centre for Chronic Disease Control, New Delhi, India;3All India Institute of Medical Sciences (AIIMS), New Delhi, India;4Public Health Foundation of India, New Delhi, India

Background: A positive family history (PFH) is known to be associated with coronary heart disease (CHD) and is an important variable for investigating the roles of nature and nurture in promoting cardiovascular health. We studied the association between PFH and CHD in an Indian industrial population.

Methods: Data on CHD risks and prevalent CHD were captured from 19,973 individuals in the SSISP study conducted in ten industrial centres spread across India. Information on PFH of CHD and stroke (before age 60 years) in parents and siblings was obtained. Individuals with PFH were compared with age, sex and centre matched control subject without PFH. Additionally, this study evaluated whether PFH and stroke were compared with age, sex and centre matched control subjects.

Results: A total of 2181 individuals had PFH (10.9%). The BMI, waist circumference, SBP, DBP, total cholesterol, triglycerides and current tobacco use were higher in individuals with PFH (Table 1). Short term Framingham CHD risk of >10% was present commonly in subjects with PFH (27.3% vs. 19.9%, p<0.001). The multiple logistic regression analysis of CHD cases and controls revealed a strong association of PFH and CHD with an odds ratio of 2.60 (90% CI 1.60-3.75), even after adjustment for all traditional risk factors of CHD.

Conclusion: Despite the clustering of risk factors, PFH emerged as a variable associated with CHD independent of the traditional risk factors. PFH should be therefore used as an indicator of high cardiovascular risk early in life and such individuals and families should be aggressively targeted by known CVD risk prevention strategies.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFH</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs), Mean (SD)</td>
<td>39.92 (10.20)</td>
<td>39.92 (10.20)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m²), Mean (SD)</td>
<td>24.79 (3.37)</td>
<td>23.71 (4.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WC (cm), Mean (SD)</td>
<td>86.82 (10.47)</td>
<td>84.28 (11.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg), Mean (SD)</td>
<td>126.16 (16.33)</td>
<td>124.76 (16.92)</td>
<td>0.007</td>
</tr>
<tr>
<td>DBP (mmHg), Mean (SD)</td>
<td>79.79 (10.41)</td>
<td>78.11 (10.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl), Mean (SD)</td>
<td>184.76 (38.65)</td>
<td>173.95 (40.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl), Mean (SD)</td>
<td>136.92 (71.77)</td>
<td>129.73 (76.28)</td>
<td>0.005</td>
</tr>
<tr>
<td>Current tobacco use, N (%)</td>
<td>562 (25.77)</td>
<td>467 (21.41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Framingham Risk Score - 10%, (%)</td>
<td>27.26%</td>
<td>19.89%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusion: Although obesity seems to be a real phenomenon in our patients after acute coronary syndrome. Mid-term prognosis for overweight and obese patients is better in this setting, compared to the normal weight individuals.

Aortic valve sclerosis is associated with the presence and degree of coronary artery disease independently of clinical risk factors in a large population of patients with flail mitral leaflet

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Although the link between aortic valve sclerosis (AVS) and coronary artery disease (CAD) is well known, there are no studies analyzing this association in a large and multicenter low risk population. We hypothesized that AVS could predict the presence and degree of CAD in patients with severe organic mitral regurgitation.

Methods: We retrospectively analyzed consecutive patients with flail mitral leaflet due to rupture cordae who had coronary angiography for pre-surgical screening and not because suspect of CAD. Clinical end points were considered: 1) presence of any degree of CAD (stenosis >20%) and 2) presence of obstructive CAD (stenosis >75% of at least one coronary artery). AVS was defined as focal areas of increased echogenicity and thickening of the leaflets. Traditional clinical risk factors were considered: age, sex, hypertension, hypercholesterolemia (total cholesterol >200 mg/dl or statin), diabetes, family history of CAD and smoking habit.

Results: 538 patients (mean age: 64.61, 62.2% male) formed the study population. Any degree of CAD was present in 117 patients (26%) and obstructive CAD in 69 patients (15%). AVS was associated with a 9.3 fold increased risk of any degree of CAD (95% CI 4.5 19.2 p<0.0001) and with a 6.4 fold increased risk of obstructive CAD (95% CI 2.7 14.8 p<0.0001) after adjustment for clinical risk factors. In the subgroup of patients with <2 risk factors, AVS was associated with a 10 fold increased risk (95% CI 2.9 37.9 p<0.0001) and in those with >3 risk factors with a 16 fold increased risk of any degree of CAD (95% CI 7.2 35.8; p<0.0001).

Conclusion: In a large and multicenter sample of patient with flail mitral leaflet, AVS was strongly associated with the presence and degree of CAD independently of clinical risk factors.
The value of 2D longitudinal strain for detection of significant coronary artery disease in patients without visual segmental wall motion abnormalities

D. Cing, Q. Zhou, R.Q. Guo, Renmin Hospital of Wuhan University, Wuhan, China, People’s Republic of

Background: To investigate the value of two dimensional longitudinal strain (LS) for detecting significant coronary artery disease (CAD) in patients without visual segmental wall motion abnormalities (SWMA) by speckle tracking imaging (STI).

Methods: 168 patients under suspicion of CAD were recruited in this study. Conventional 2D echocardiography and STI were performed in all subjects to obtain the conventional echocardiographic parameters and LS of each segment before coronary angiography. LSa, LS5m and LSb-m were calculated as the mean LS of the 6 segments in apical, middle and basal level respectively, LSa and LSb-m were calculated as the mean LS of the 12 segments in apical-middle level and basal-middle level respectively, and GLS (global longitudinal strain) was the mean LS of all 18 segments.

Results: According to coronary angiography results, patients were divided into three groups: severe stenosis group, mild stenosis group and control group. Compared with the other 2 groups, segmental LS and the mean LS parameters were significantly decreased in severe stenosis group. However, there were not significant differences between the mild stenosis group and the control group. The ROC curves analysis demonstrated that LSb-m had the highest accuracy and LSa had the lowest accuracy for detecting severe CAD (areas under the curve were 0.843 and 0.721, respectively). Using ~18.1% as a cutoff point of LSb-m to diagnose severe CAD had high sensitivity and specificity (81.3% and 84.1%, respectively).

Conclusion: LS might be helpful for detecting severe CAD in patients without visual SWMA, and LSb-m is the most effective parameter.

The use of beta-blockers is associated with a well-developed collateral circulation in patients with a chronic total occlusion

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A well-developed collateral circulation provides a survival benefit in patients with coronary artery disease but a large heterogeneity exists in extent of the collateral circulation. Studies aiming to detect clinical parameters related to this heterogeneity show controversial results. The varying degree of stenoses has been a potential confounder. Most of these studies applied angiographic assessment of the collateral circulation which is less accurate than intracoronary derived collateral flow index (CFI). We present data from a unique patient group with a chronic total occlusion (CTO) in which CFI was measured directly upon opening of the CTO.

Data from 109 patients from a Swiss and Dutch center that were successfully treated by percutaneous coronary intervention after collecting clinical parameters and lab values were pooled. During a 1 minute balloon-inflation CFI was measured noninvasively by transthoracic echo and visual SWMA, and LSb-m is the most effective parameter.

Conclusion: The scaling law exponent B depends on the truncation level of inclusion vessels diameters while its value is paramount for correct estimation of hyperemic blood flow.

Non-invasively measured coronary flow reserve of the infarct related artery is predictor of midterm outcome in STEMI patients treated with primary PCI

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Coronary flow reserve (CFR) of the infarct related artery (IRA) after primary PCI reflects the anatomical and functional status of coronary microcirculation in the infarct zone. IRA-CFR can be assessed non-invasively by transthoracic echo and...
Influence of age on the clinical characteristics, Impact of acute myocardial infarction redefinition.

Conclusion: Non-invasively assessed coronary flow reserve of the infarct related artery 7 days after primary PCI in STEMI patients is independent predictor of clinical events during mid-term follow-up.

Purpose: Age is powerfully associated with cardiovascular (CV) event rates, but limited contemporary data are available on outcomes in patients with stable coronary artery disease (CAD) in different age groups. We sought to assess age-specific differences in 1-year outcomes in patients enrolled in the CLARIFY registry.

Methods: CLARIFY is an international, prospective, observational, longitudinal registry in outpatients with proven stable CAD. We divided 30,978 participants from 45 countries (Nov 2009-Jul 2010) into 3 age groups (<65, 65-74, and ≥75 years), to evaluate differences in clinical characteristics, management, and 1-year outcomes.

Results: Compared with those <65 years, elderly patients more often had comorbidities such as hypertension, peripheral artery disease, asthma or chronic obstructive pulmonary disease, and were less likely to be treated with aspirin, beta-blockers and lipid-lowering agents. Elderly patients had markedly higher proportions of 1-year all-cause and CV deaths. (See Table 1).

Conclusion: Across the broad spectrum of outpatients with stable CAD, elderly patients received fewer CV medications and had worse outcomes. Our findings emphasize the need to focus on elderly patients with CAD and optimize their therapeutic regimen.

Table 1

<table>
<thead>
<tr>
<th>&lt;65 years (n=16,068)</th>
<th>65-74 years (n=11,120)</th>
<th>≥75 years (n=7,590)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>82.5</td>
<td>76.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>66.6</td>
<td>76.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>26.4</td>
<td>31.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma/OPOD, %</td>
<td>5.0</td>
<td>10.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean resting heart rate, bpm</td>
<td>69.6</td>
<td>67.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral artery disease, %</td>
<td>7</td>
<td>12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean systolic BP (mm Hg)</td>
<td>129</td>
<td>132</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>91.3</td>
<td>86.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>78.3</td>
<td>73.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering agent, %</td>
<td>94</td>
<td>91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-year all-cause death, %</td>
<td>0.9</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td>1-year cardiovascular death, %</td>
<td>0.5</td>
<td>0.8</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Prognostic value of geriatric syndromes in patients hospitalized for acute coronary syndrome

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Objective: To determine the prognostic value of geriatric syndromes in patients older than 65 years admitted with an acute coronary syndrome (ACS). Methods: A prospective registry of 167 consecutive patients admitted to a single center from November 2010 to March 2011, with diagnosis of acute coronary syndrome and older than 65 years. We excluded patients who required coronary artery bypass grafting during hospitalization. A predischarge questionnaire was conducted to assess the 5 Fried criteria of frailty syndrome, cognitive impairment (Pfeiffer test), physical dependency (Barthel test) and comorbidities (simple comorbidity index). The primary endpoint was death or readmission for any cause at 3 months follow-up.

Results: Mean age was 77±9 years, 60% were male and 22% had ST-segment elevation ACS. During hospitalization, coronary angiography was carried out in 81% of cases. Overall, the prevalence of frail (Fried criteria ≥3) was 59%, cognitive impairment (Pfeiffer’s 3) 11%, and comorbidity (simple index ≥2) 35%. During follow-up there were 13 deaths, 34 readmissions and 42 total events. In univariate analysis, geriatric syndromes were associated with events: frailty (RR=4.3, 95% CI 1.4 to 13.0, cognitive impairment (RR=4.2, 95% CI 1.6-10.8), physical dependency (RR=2.3, 95% CI 1.1-5.6) and comorbidity (RR=2.1, 95% CI 1.0 to 4.5). In the multivariate analysis, after adjusting for known prognostic variables in ACS, cognitive impairment was the geriatric syndrome with prognostic value (HR=2.5, 95% CI 1.1 to 5.7) with hemodynamic data (systolic blood pressure on admission, Killip class ≥2 and left ventricular ejection fraction). In the subgroup of patients with cognitive impairment, the frequency of other geriatric syndromes was high: 95% frailty, 76% physical dependence and 100% comorbidity.

Conclusion: Cognitive impairment is the geriatric syndrome with the greatest prognostic value in patients admitted for ACS, and includes a large number of other geriatric syndromes.

Impact of acute myocardial infarction redefinition. Should we consider the differences or are all types the same?

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Acute myocardial infarction(MI) redefinition changed the classification of the ischemic event and the type M1 (1) and M2 (II) are considered the most relevant ischemic events. The differences about clinical expression and prognostic are not fully understood, since M1 had a generally weak representation in the majority of the clinical trials. We aimed to determine any potential differences between M1 and M2. 744 patients admitted with MI (68.6 ±13.4%) were included in M1, 45.3% in M2. Primary outcomes were in-hospital (IH) and 24-months mortality (24M).

Results: 580 cases were classified as M1 (78.3%) and 161 (21.7%) as MII. The following variables are shown in the Table. M1 patients were older, higher heart rate, NT-proBNP and creatinine values and lower admission haemoglobin values. M1 had higher proportion of diabetes and STEMI and higher troponin values. Grace score values were higher in the M2, however no difference in NIH was found, between the MI type [N=60 (8.6%) vs. 17 (10.5%), p=0.422]. The 24M was higher in the M2 group [N=79 (13.6%) vs. 45 (28.0%), p<0.001, OR 2.639, 95%CI 1.70-4.10]. In the follow-up, M2 group had higher proportion of heart failure readmissions (N=58 (10%) vs. 26 (14.1%), p=0.026, OR 1.788, 95%CI 1.07-2.99) and re-infarctions (N=57 (9.8%) vs. 24 (14.9%), p=0.069) than M1.

Conclusion: Distinction between MI1 and MI2 appears to have clinical significance, suggesting distinct pathological mechanisms. It seems that it would be of interest to clarify the MI2 differences in future studies, and discussed if long term medical management should be the same as in MI1, or should we consider MI2 particularities.

Prognostic significance of long-term period heart rate rhythms in chronic heart failure

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Purpose: Abnormalities in autonomic control are a feature of neuroendocrine activation in HF and are responsible to dysregulation of biological rhythms. The
Early administration of aldosterone blocker improves cardiac remodeling and myocardial function in spontaneously hypertensive rats.

**Methods:** We enrolled seventy-nine HF patients (age 53±14 years and left ventricular ejection fraction [LVEF] 37±10%). A rhymotonic analysis was used to assess the HR rhythms in 7-days (7D) Holter recordings corresponding to 24 hours (24H), 6 hours (6H) and 7D. Rhythms properties were quantified by mesor and amplitude, in beats per minute (bpm) and by acrophase, in hours. Standard deviation of all normal RR intervals ([SDNN]) and percentage of adjacent normal RR intervals (~0.0-ms different (pNN50)) were chosen as representative indexes of sinus arrhythmia. Short and long heart rhythms during the first day of the monitoring period. Cardiac death or HF decompensation were registered.

**Results:** All patients had 24H rhythm. 61 patients (77%) had 8H rhythm and 66 patients (83%) had 7D rhythm. During the follow-up (31±13 months), 15% patients experienced events. Neither SDNN nor pNN50 indexes differed significantly with regard to the presence of events. Among long-period HR rhythm parameters only 7D median amplitude was different between patients with or without events: 1.1 bpm [0.5-1.5] vs 2.0 bpm [0.0-3.9]; p=0.049 respectively. After multivariate adjustment, LVEF [per %], Hazard Ratio 0.92, 95% CI 0.87 to 0.98; p=0.01), NT-proBNP (per 100pg/ml, Hazard Ratio 1.036, 95% CI 1.005 to 1.069; p<0.022) and 7D amplitude of the HR, 1.71 bpm (Hazard Ratio 5.4, 95% CI 1.2 to 34.4, p=0.047) were independent predictors of events.

**Conclusions:** A 7D HR rhythm is present in most patients with HF, and has prognostic significance.

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Soluble ST2 reflects hemodynamic stress in heart failure

**Methods:** Soluble ST2 (sST2) is a promising biomarker in heart failure (HF). sST2 is a potential target for drug therapy, since elevated levels of sST2 are associated with worsening HF and increased mortality. In experimental studies, ST2 expression is induced by myocardial stress and inflammatory stimuli. The determinants of sST2 levels in vivo are not well described. We aimed to assess the association between sST2 levels and prespecified hemodynamic parameters reflecting right and left ventricular pre- and afterload, as well as clinical characteristics and laboratory values.

**Results:** 92 patients aged 51±14 years were included. Baseline left ventricular ejection fraction (LVEF) by echocardiography was 27±10%. Median duration of symptoms was 209 (105-438) days and pharmacological treatment duration 81 (18-158) days. In 10 patients (11%) a probable disease-causing mutation was detected. In 1689 patients (18%), viral RNA-DNA was detected in the endomyocardium. Soluble ST2 was significantly associated with low systolic blood pressure, elevated heart rate at rest, low LVEF, elevated right atrial pressure (RAP), elevated pulmonary capillary wedge pressure, decreased cardiac output (CO), male gender, shorter time on pharmacological treatment, and with NT-proBNP and CRP. After adjusting for LVEF and CO, levels of sST2 were higher in patients with severe symptoms (NYHA class III/IV) and in patients with a monogenetic cause (p<0.05), but not in patients with viral persistence. On multiple regression analysis, only HR and RAP remained independent predictors of sST2.

**Conclusion:** Soluble ST2 levels are higher in patients with HF and elevated right and left ventricular filling pressures and severe symptoms; even after adjusting for
LVEF and CO. Hemodynamic parameters, unlike CRP and NT-proBNP, are independently associated with stST2. Our results imply that in dilated cardiomyopathy, stST2 reflects hemodynamic decompensation.

**P5788**

**Relationship between high sensitivity ST2 levels and renal function in heart failure**

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**Background:** ST2 is a novel biomarker that provides important prognostic information in patients with heart failure (HF), together with NT-proBNP. It is well known that NT-proBNP is substantially influenced by renal function.

**Aim:** To examine whether soluble ST2 levels are related to renal function, comparing the results obtained with those of NT-proBNP to analyze the prognostic value of the association of the two markers according to renal function.

**Patients:** 891 patients (71.6% men, age 70.2 years [IQR 65.0-77.2]) were studied. LVEF was 34% [IQR 26-43%]. Most patients were in NYHA class II (65.5%) or III (28.1%). Median follow-up was 41.3 months [IQR 22.0-60.4].

**Results:** Both NT-proBNP (r = -0.46, p < 0.001) and ST2 (r = -0.18, p < 0.001) inversely correlated with eGFR. Although statistically significant, the degree of correlation between ST2 and eGFR was weaker. Patients were divided according to eGFR in 3 subgroups: ≥ 60 ml/min/1.73 m², 30-60 ml/min/1.73 m², ≤ 30 ml/min/1.73 m². Levels of both markers significantly increased as eGFR worsened (p < 0.001). However, in the sickest patients (NYHA functional class III-IV), only NT-proBNP levels significantly raised at worsening eGFR strata (p < 0.001), whereas ST2 levels remained similar in the three studied subgroups (p = NS).

**Conclusions:** ST2 appeared less influenced by renal function than NT-proBNP. In combination with NT-proBNP, ST2 improved the long-term prognostic accuracy even in patients with renal insufficiency. In these patients however, if only a marker was abnormally elevated, ST2 tended to better discriminate survival than NT-proBNP.

**P5790**

**Changes of physical function (QoL) after 1-year-follow-up are independently associated with changes of MR-proADM in patients with preserved left ventricular function**

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**Background:** There is limited evidence in patients at cardiovascular risk about factors that are associated with a progressive reduction of physical function. The aim of this analysis was to investigate whether neurohumoral activation as well as parameters of diastolic function are associated with changes in physical function measured as quality of life questionnaire (QoL) in after 1 year (1-FU).

**Methods:** In the DIAST-CHF observational study n=1937 patients (±50 years) with risk factors for heart failure or previously confirmed diagnosis of heart failure were prospectively followed. NT-proANP (n=855) and MR-proADM (n=1082) and Log NT-proBNP (n=1082) were measured at baseline and at 1-year FU. The combination of the two biomarkers according to cut-off classification in AHI ≥ 30 ml/min/1.73 m² was not significantly different between patients with or without worsened PHF. Log NT-proBNP, log MR-proADM and log MR-proANP at baseline were significantly associated with changes of physical function after one year (p < 0.001). Multiple Regression analyses revealed that in addition to age (p < 0.001), logMR-proANP at baseline (p < 0.004) was independently associated with worsening of physical function after one year.

**Conclusion:** In patients with cardiovascular risk factors and reduced physical function after one year parameters of neurohumoral activation were higher when compared to patients with unchanged or improved physical function. Since the association of MR-proANP was independent of other parameters such as diastolic function, our data suggest that neurohumoral activation is a major determinant regarding the physical impairment in these patients.

**P5791**

**Angiotensin II-dependent osteoprotegerin production in murine and human heart**

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**Purpose:** Osteoclastogenesis inhibitor factor, osteoprotegerin (OPG) is present in the heart. However, it remains unknown the pathophysiological roles of OPG interacted with vasoactive peptide, angiotensin II (Ang II). This study aimed to elucidate whether Ang II influences the OPG production in murine and human heart.

**Methods and Results:** Blood samples of 56 patients (67±10 years old, male 57%) were collected simultaneously from the orifice of left coronary artery and the great cardiac vein after coronary angiography, and measured the OPG concentration by ELISA. The OPG concentration was significantly higher in the left coronary artery than in the orifice of left coronary artery (7.7±4.4 vs. 6.7±3.6 pg/ml, p < 0.0001). The gradient of OPG concentration throughout the heart was significantly decreased in subjects taking either angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor blocker (ARB) (1.5±0.3 vs. 0.45±0.3 pg/ml, p < 0.019). In addition, subcutaneous infusion of Ang II (250 ng/kg/min) to 7-week-old male Wistar rats for 14 days significantly (p < 0.01) up-regulated the OPG mRNA by 4-folds in the left ventricle. Immunoreactivity of OPG was widely distributed in the myocardium and intramuscular vessels in wall controls, whereas it increased to distribute in the interstitial cells in Ang II-induced hypertrophied rat heart. In cultured neonatal rat cardiac fibroblasts, but not in myocytes, Ang II (10-7 mol/L) raised the OPG mRNA by 2-folds for the first hour compared to controls; whereas it was blunted by the pretreatment of ARB, RHN-6270 (10-6 and 10-7 mol/L), but not by Ang II type 2 receptor antagonist, PD-125,319 (10-6 and 10-7 mol/L).
Overnight beneficial impacts of adaptive servo ventilation on cardiac overload, sympathetic nervous activity, and myocardial damage in chronic heart failure patients with chronic obstructive sleep apnea

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Background: Sympathetic nervous activation and ongoing myocardial damage play critical roles in the progression of chronic heart failure (CHF). The purposes of the present study were to 1) examine effects of adaptive servo ventilation (ASV) on the improvement of Chronic Obstructive Sleep Apnea (COPD) ventilation on cardiac overload, sympathetic nervous activation, and myocardial damage, and 2) to determine whether ASV or oxygen therapy (O2) was more effective in suppressing CSR in CHF and the development of neurohumoral abnormalities.

Methods and Results: Forty two patients with CHF and CR (mean LVEF 34.6%) were enrolled. We performed polysomnography (baseline, O2, and ASV) for three consecutive days, and measured levels of ANP, BNP, norepinephrine, high-sensitive troponin T, and urinary catecholamines. Both O2 and ASV reduced AHI, high-sensitive troponin T, and urinary catecholamine excretion. However, only ASV decreased ANP, BNP, and plasma norepinephrine. In addition, the decreasing degree of AHI, BNP, and high-sensitive troponin T by ASV was greater than O2.

Polysonomographic, blood and urinary data

<table>
<thead>
<tr>
<th>Baseline</th>
<th>O2</th>
<th>ASV</th>
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<tr>
<td>AHI (events/h)</td>
<td>22.5</td>
<td>10.7</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>165.5 (205.7)</td>
<td>152.4 (233.1)</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>245.8 (517.5)</td>
<td>214.8 (477.8)</td>
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<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>84.8 (947.1)</td>
<td>76.5 (40.8)</td>
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<tr>
<td>Urinary norepinephrine (mg/day)</td>
<td>0.450 (1.061)</td>
<td>0.382 (0.131)</td>
</tr>
<tr>
<td>High-sensitive troponin T (ng/ml)</td>
<td>0.018 (0.017)</td>
<td>0.016 (0.006)</td>
</tr>
</tbody>
</table>

1 Data are presented as median (interquartile range). *P<0.05, †P<0.01 vs. Baseline; ‡P<0.05, §P<0.01 vs. O2.

Conclusions: ASV has multiple effects of not only improving CSR but also attenuating sympathetic nervous activity, reducing cardiac overload and myocardial damage. ASV might be a promising useful tool for CHF, and for patients who cannot use O2, ASV to some extent is effective for CSR.

Copeptin in hyponatremia and its relation to steroid sensitivity troponin T and renal function in heart failure

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Purpose: Vasopressin (AVP) regulates volume and osmotic homeostasis via free water resorption and is liberated by different stimuli. Whereas osmotic stimuli are well recognized, non-osmotic stimuli have not yet been elucidated and the interplay between both functions and their effect on volume regulation and vasoactivity is largely unknown. Copeptin, the analytically accessible C-terminal fragment of AVP, was reported to indicate a worse prognosis in heart failure, but its interaction with hyponatremia, hypovolemia, arterial underfilling and the renin-angiotensin-aldosterone system (RAAS) is unknown, as its dependency on renal function. We investigated copeptin levels and hyponatremia, and their relationship to aldosterone and cortisol levels, medication patterns and mortality.

Methods: Data from n=926 patients from the Interdisciplinary Network Heart Failure Study (ISRCTN23325295) was analyzed. Heart failure patients after an acute decompensation episode were included prior to hospital discharge after best possible recompensation. All patients exhibited a left ventricular ejection fraction (LVEF) ≤40. Comprehensive clinical characterization, blood sampling, and echocardiography were performed. Hyponatremia was defined as serum sodium <135 mmol/l, according to the standards at our hospital.

Results: The mean age was 68±12 years, and 71% were men. 92 patients (10%) were hyponatremic, and 473 (51%) had chronic renal failure of KDOQI stage 3 or higher. Independent correlates of hyponatremia at baseline were serum aldosterone (OR 1.003/mg 0.95% CI 1.001-1.005, p=0.01), serum copeptin (OR 1.040/g/dl 95% CI 1.004-1.077 P=0.003), serum urea (OR 1.009/mg/dl 95% CI 1.004-1.014 P=0.0001) and systolic blood pressure (OR 0.986/mmHg 95% CI 0.979-0.99 P=0.004), while copeptin, LVEF and therapy with RAAS inhibitors or beta-blockers were not. Copeptin levels correlated strongly with serum urea (Spearman r=0.540, P<0.0001) and showed a linear inverse association with diastolic blood pressure (β=−0.081/mmHg, P=0.01).

Conclusions: Copeptin did not predict hyponatremia, but correlated with indicators of renal dysfunction and displayed an inverse relation to diastolic blood pressure. While this might support the arterial underfilling hypothesis for non-osmotic AVP release, the actual impact of AVP levels on sodium homeostasis in the interrelationship of hormonal regulation remains uncertain. In contrast aldosterone and cortisol levels, renal function parameters and systolic blood pressure were associated with hyponatremia and might exert a strong role in sodium homeostasis in patients with heart failure, independent from AVP.
Methods: 151 subjects with LV systolic dysfunction were followed over 10 months for a total of 908 visits and sST2, GDF-15 and hsTnT were measured at each visit. Clinical and laboratory characteristics, remodelling parameters by echocardiography and combined total CV events were recorded.

Results: Table 1 summarizes the results. Single values of sST2, GDF-15 and hsTnT predicted time to first CV event (p = 0.01, 0.01, and 0.001, respectively), even adjusted for clinical variables and NT-proBNP: time spent above prognostic cut-off for each was also predictive of CV events (p = 0.002, 0.002, and < 0.001, respectively). Only serial sST2 measurement added prognostic value beyond baseline levels (p = 0.006). Several medication classes had independent effects on concentrations of sST2, GDF-15, and hsTnT. No clear link between each marker and LV remodeling was found.

Conclusions: In chronic HF patients, single measures of sST2, GDF-15, or hsTnT add independent prognostic information to clinical variables and NT-proBNP. Serial sST2 measurement adds prognostic information to baseline concentrations. HF therapies may lead to changes in the levels of these prognostically important biomarkers.

P5796 New insights into the role of thyroid hormones in the severity of right ventricular dysfunction
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Background: Thyroid hormones play an important role in the regulation of cardiac muscle function. However, questions are remained to be answered regarding the thyroid hormones’ profile in patients with right ventricular (RV) dysfunction. The aim of the present study was to investigate the association between the severity of RV dysfunction and the serum levels of thyroid hormones.

Methods: This case series study was conducted on 263 patients with RV dysfunction during 2008 and 2011. All patients underwent Two-dimensional and in-suit Doppler echocardiographic examination. Consequently, based on the severity of the RV dysfunction patients were divided into 5 groups (mild; mild to moderate; moderate; moderate to severe and severe right ventricular dysfunction). Thyroid function was assessed by serum total T3 (TT3), total T4 (TT4), free T3 (FT3), free T4 (FT4) and thyroid stimulating hormone (TSH) levels.

Results: 263 patients including 1486 (56.5%) male and 1145 (30.5%) female with the mean age of 61.97 (SD=15.81) yr were enrolled in this study. Mean serum TT3, TT4 and TSH levels were 1.22 (SD=0.55), 82.79 (SD=39.82) and 3.21 (SD=4.76), respectively. No statistically significant difference was found between patients with various severities of RV dysfunction with regard to age, gender, body mass index, heart rate and blood pressure. A significant correlation was seen between the severity of RV dysfunction and serum FT4 and TSH levels (r= -0.081 and p=0.001, respectively). Noncorrelation was seen between serum TT4 level and the severity of RV impairment. Serum total and free T3 levels were conversely correlated with severity of RV dysfunction (r=- 0.109 and p<0.001, respectively).

Conclusion: With the increasing severity of RV dysfunction, thyroid dysfunction in the patients show a trend toward hypothyroidism. This is manifested by an increase in TSH level and reduction in total and free T3 levels. Interestingly, it seems that in patients with RV dysfunction serum FT4 level is affected less commonly than T3.

P5797 Uptake, utilisation and referral patterns following introduction of primary care BNP testing for patients with suspected heart failure
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Purpose: Recent guidance from the UK National Institute for Clinical Excellence (NICE) and the European Society for Cardiology recommends B-type natriuretic peptide (BNP) testing in primary care for patients with suspected heart failure (HF). NICE guidance also requires that patients with a highly raised BNP (> 116 pg/mL) are referred for specialist cardiology assessment within a two week wait (2WW). Our aim was to study local uptake, utilisation and referral patterns following introduction of BNP testing at a UK teaching hospital.

Methods: Our institution provides secondary care cardiology services to a population of 550,000, in addition to tertiary level care to 1.2 million. Following introduction of BNP/2WW referral pathway in October 2011 we analysed the number of BNP requests from 86 referring GP practices, clinical indications and proportion of abnormal results over an initial three-month period. Referral patterns to cardiology in patients with elevated BNP were studied, in particular to the 2WW HF clinic. The final diagnoses after specialist assessment and echocardiography were recorded.

Results: Over a three-month period 212 patients underwent BNP testing, from 67/68 (78%) of GP surgeries in the region. Of these 11 (5.2%) were high (BNP > 116pg/mL), 47 (22%) were raised (29-116pg/mL), 147 (69%) were normal (< 29pg/mL). Dyspnoea was the commonest clinical indication (78 patients, 37%), followed by possible HF symptoms (29 patients, 14%) and peripheral oedema (27 patients, 13%). 29 requests (14%) were clinically inappropriate based on the information supplied by the GP surgery. Of the 11 patients with highly raised BNP, one was correctly referred to the 2WW HF clinic, but was admitted as an emergency before being seen. Another 3 (27%) were sent to general cardiology outpatient. In the first month 24 patients were seen in the 2WW HF clinic, all without BNP testing, where a diagnosis of HF was confirmed in 16 (67%). There was no significant change in the number of HF acute admissions over the time period studied.

Conclusions: Uptake of BNP testing in primary care has occurred rapidly and the majority of requests are clinically appropriate. BNP testing has predominantly been used in patients where there is diagnostic uncertainty. Patient referral to the 2WW HF clinic has occurred without BNP testing, in patients where clinical suspicion of HF is high. Interpretation of results and use of the 2WW HF referral pathway requires specific education to ensure that patients with elevated BNP are reviewed in the timescale advised by NICE.

P5798 The prognostic role of brain natriuretic and N-terminal pro-B-type natriuretic peptides changes in heart failure. A meta-regression study of 25 randomized trials in 15,722 patients

Purpose: The relationship between brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels and risk of cardiovascular events in patients with heart failure (HF) has been demonstrated in previous studies. However, it is unclear whether changes of BNP and NT-proBNP predict clinical events in HF patients. The aim of the current study was to verify whether changes in neuro-hormonal peptides reflect incidence of clinical events in HF patients.

Methods: The MEDLINE, Cochrane, ISI Web of Science and SCOPUS database were searched for articles about HF treatment until November 2011. Study inclusion criteria were: report of BNP and/or NT-proBNP at baseline and at end of follow-up, and of clinical endpoints (all-cause death and hospitalization for HF); randomized protocol design. Meta-regression analysis was performed to test the relationship between BNP and NT-proBNP changes and outcomes. The influence of potential effect modifiers and the presence of publication bias were also explored.

Results: 25 trials enrolling 15,722 participants were included. In meta-regression analysis, no relationship between BNP changes from baseline to end of follow-up and outcomes was detected (all-cause death: t= -0.87, p=0.39; HF hospitalization: t=1.95, p=0.09). Similarly, NT-proBNP changes did not correlate to all-cause death and HF hospitalization (t=0.38, p=0.08 and t=1.34, p=0.31, respectively). No publication bias was detected.

Figure 1. Meta-regression analysis.

Conclusions: In HF patients, changes of BNP and NT-proBNP levels do not reflect the effects of therapies on mortality and hospitalization.

P5799 Combination of brain natriuretic peptide and pro B-type natriuretic peptide has incremental prognostic value in patients with acute myocardial infarction
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Objective: Cardiac biomarkers, such as brain natriuretic peptide (BNP) and high sensitivity C-reactive protein (CRP), have been associated with an adverse out-
First evidence of increased serotonin activity in Takо-Tsubo cardiomyopathy

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Background: Takо-Tsubo cardiomyopathy (TTC) or stress-induced cardiomyopathy is a transient cardiac dysfunction that mimics myocardial infarction (MI). Catecholamine-induced myocardial stunning has been postulated as a central mechanism of TTC and transient increase of sympathetic nervous activity with increase of noradrenalin from the heart was suggested to participate to the TTC pathophysiology. If a case reports a serotonin syndrome as an indirect cause of TTC, there is no data about the serotoninergic activity during the acute phase of TTC.

Objective: To investigate evidence of serotonin release from patients with TTC in comparison with patients with blood aldosteronism and their associates.

Methods and results: Plasma serotonin levels in 14 consecutive patients with TTC according to the “MyoClinic” diagnostic criteria were compared with those in 14 patients with MI and 14 healthy controls subjects. The median age of patients with TTC was 64 years and 12 (86%) were women. Clinical presentation was chest pain for 13 (93%) patients with TTC and 6 (43%), 3 (21%) 2 (14%) and 1 (7%) patients had T-wave inversion, ST elevation, Q wave and new left bundle branch block at ECG respectively. Two (14%) patients with TTC had no ECG modifications. Troponin levels were higher in patients with MI than in patients with TTC (median Troponin level, 92.6 ng/ml [interquartile range, 11.2 to 216.2] vs. 2.4 ng/ml [interquartile range, 1.2 to 5.4] respectively; P<0.005) but there was no difference for left ventricular ejection fraction (LVEF) at presentation (median LVEF, 45% [interquartile range, 40 to 49] vs. 49% [interquartile range, 38 to 45] respectively; P=0.52). Troponin and serotonin levels at admission were markedly higher in patients with TTC and MI than among healthy controls subjects (median serotonin level, 3.0 pg/ml [interquartile range, 0.8 to 4.9] vs. 3.4 pg/ml [interquartile range, 2.0 to 7.3] vs. 9.6 pg/ml [interquartile range, 0.7 to 1.2] respectively; P=0.001). There was no difference for serotonin levels between patients with TTC and those with MI (P=0.36).

Conclusion: Plasma serotonin levels are increased during the acute phase of TTC in the same range than patients with MI. This finding suggests that serotonin could participate to the pathophysiology of TTC.
might be a target for the prevention of progression to HF. Finally, MRI seems to be more sensitive than PWV or CIMT measurements to detect early arterial remodeling.

**P5803 NT-proBNP-guided preemptive treatment of outpatients with chronic heart failure followed in a hospital clinic**


**Background:** Prevention of decompensation in patients suffering of chronic heart failure (CHF) is a difficult task. Recognition of imminent decompensation requires an easily measurable parameter which may predict this impending complication at an early stage, thus allowing preventive therapy. We used NT-proBNP testing to monitor CHF patients in a heart failure clinic and to guide therapy.

**Aim:** We evaluated the ability of NT-proBNP-guided therapy to improve the clinical care and outcome of CHF patients.

**Methods:** In this randomized double-controlled prospective study, patients were clinically evaluated and their NT-proBNP level measured at each clinic visit (every 45±19 days). Patients were divided into conventionally treated (Gr1) and conventionally plus NT-proBNP-guided treated (Gr2) groups. NT-proBNP level was measured within 48-hours and treatment was immediately intensified if NT-proBNP concentration was higher by more than 30% from previous measured level.

**Results:** 121 CHF patients at NYHA III/IV (60/55/6) were followed for 16.1±1 months in an outpatient clinic. Gr1 (60 patients) and Gr2 (61 patients) were well matched (age 69.4±10.5 versus 70.2±11 years, and LVEF and NT-proBNP at the beginning 23±7%, 5860±2434 pg/ml versus 22±6% and 5866±2032 pg/ml respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (χ²=0.403), cardiovascular mortality (χ²=0.39), and in all-cause hospitalizations (p=0.45). However, hospitalizations for acute decompensated heart failure (ADHF) were significantly reduced in Gr2 (NT-proBNP-guided therapy) by 55% (p=0.047).

**Conclusions:** NT-proBNP-guided preemptive treatment of patients with CHF did not result in reduced overall and cardiovascular mortality, and did not decrease all-cause hospitalizations but significantly prevented admissions for ADHF. In our opinion, the main reasons for the relatively low efficiency of NT-proBNP-guided treatment were: (1) Inability to perform an NT-proBNP test every 1-2 weeks. (2) Significant effect of other non-AHF disease and conditions on NT-proBNP level. (3) Lack of clear-cut criteria for NT-proBNP changes signifying ADHF and triggering intensification of treatment.

**P5804 Apelin potentiates B-type natriuretic peptide-mediated vasodilatation in health but not in heart failure**

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**Purpose:** The novel peptide apelin has vasodilator and inotropic actions and antagonises angiotensin-II. There is interest therefore in the therapeutic potential of apelin in heart failure (HF), especially as plasma apelin levels are reduced in heart failure with reduced ejection fraction (HFrEF) compared to age matched healthy controls.

**Methods:** MA segments of canine aorta were mounted in a 4-channel myograph under continuous 3% CO₂ and 97% O₂ and were preincubated with 1µM apelin for 30 minutes. Segments of MA were mounted on a 4-channel myograph under 3% CO₂ and 97% O₂. Response curves were constructed for BNP (1x10⁻⁹M - 3x10⁻⁶M) in the presence and absence of 30 minutes of preincubation with 1µM of apelin.

**Results:**

1. Apelin (1µM) pre-treatment increases BNP-mediated concentration-dependent relaxation in control MAs (max relaxation 14.3±6% in control MAs vs 14.0±8% in MAs pre-treated with apelin, p<0.05).

2. 10.5 versus 23.6 pg/ml, versus 22.6±6% and 5866±2032 pg/ml respectively (p=NS). (P5803)

3. 0.403). (P5803)

4. 23.6±6% and 5866±2032 pg/ml respectively (p=NS). (P5803)

5. 0.047). (P5803)

**Conclusions:** NT-proBNP-guided preemptive treatment of patients with CHF did not result in reduced overall and cardiovascular mortality, and did not decrease all-cause hospitalizations but significantly prevented admissions for ADHF. In our opinion, the main reasons for the relatively low efficiency of NT-proBNP-guided treatment were: (1) Inability to perform an NT-proBNP test every 1-2 weeks. (2) Significant effect of other non-AHF disease and conditions on NT-proBNP level. (3) Lack of clear-cut criteria for NT-proBNP changes signifying ADHF and triggering intensification of treatment.

**P5805 NT-proBNP for detection of sunitinib-induced cardiac toxicity in renal cell carcinoma**

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**Aim:** Metastatic renal cell carcinoma (mRCC), the most common kidney cancer, is associated with poor 5-year survival. Targeted treatment with the tyrosine kinase inhibitor sunitinib significantly improves outcome, but frequently induces cardiac toxicity, especially severe hypertension, LV dysfunction, ischemia or arrhythmias. Repeated assessment of cardiac function is essential. Frequent echocardiograms are often not feasible in routine practice. Electrocardiograms (ECG) may show unspecific changes, requiring interdisciplinary cardiology- oncology teamwork. Easily available biomarkers for cardiac toxicity are desirable to support the treatment continuation decision. N-terminal pro-B type natriuretic peptide (NT-proBNP) has been shown to increase in chemotherapy cardiotoxicity. The aim was to investigate the role of NT-proBNP as possible early indicator for sunitinib-induced cardiac toxicity.

**Methods:** Prospective pts with mRCC assigned for first-line treatment with sunitinib were analyzed for cardiac history. Monitoring included assessment of symptoms, ECG and echocardiography at baseline, every 3 months and at increase of biomarkers. NT-proBNP (Roche Elecsys) and Troponin T (TnT) were obtained at baseline and every 4 weeks, and routine laboratory. Significant findings indicating cardiac damage were defined as newly pathological echo, cardiac symptoms, new changes in ECG or increased TnT.

**Results:** 46 pts (median age 66 y, 40-82) were included, 98% had undergone nephrectomy. After median treatment of 15 weeks (2-101), 34 (76%) pts experienced an increase of NT-proBNP compared to baseline. New changes in ECG and echo were observed in 7 (21%) and 6 (18%) pts. Echocardiography detected new regional wall motion disturbances (n=4), progression of diastolic dysfunction (n=2) and severe heart failure in 1 patient. NT-proBNP levels without increase from baseline were always associated with complete absence of findings for cardiac toxicity. Higher NT-proBNP (median 1584 pg/ml; IQR 998-4474) during sunitinib was more often associated with development of symptoms, cardiac events or TnT increase (p=0.001) vs none (526; 243-978). A wide range of NT-proBNP was observed during sunitinib, with events occurring mainly in NT-proBNP > 1000. With cardiac toxicity all but 1 pt could continue sunitinib without dose reduction, the pt with heart failure recovered on discontinuation.

**Conclusions:** NT-proBNP is an easily assessed marker of cardiac toxicity. Low NT-proBNP may rule out cardiotoxicity in specific scenarios. An interdisciplinary approach between cardiologists and oncologists is essential for continuation of tumor-treatment.

**SURGICAL OPTIONS**

**P5806 Heart rate reduction for 36 months with ivabradine reduces left ventricular mass in cardiac allograft recipients**

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**Background:** Grf denervation in heart transplant recipients causes sinus tachycardia, occasionally requiring pharmacologic heart rate reduction. Currently, no long term data regarding effects of the novel β channel antagonist ivabradine on heart rate control, effects on left ventricular (LV) mass, tolerability, and safety are available in patients after heart transplantation (HTX).

**Methods:** Resting heart rate, left ventricular mass indexed to body surface area (LVMI), tolerability, and safety of ivabradine therapy were evaluated at baseline and available in 36 months HTX recipients with marked sinus tachycardia.

**Results:** In three patients (10.0% of total) ivabradine medication was discontinued. Further analysis was based on 27 patients with 36-month drug exposure. Mean patient age was 53.9±11.3 years and mean time after HTX was 5.0±4.8 years. Mean ivabradine dose was 12.0 mg/day (±3.4 mg). Resting heart rate was reduced from 91.0±10.7 beats per minute (bpm) at baseline to 81.2±8.6 bpm at follow-up (p<0.0006). A statistically significant effect of heart rate re-
How to assess risk in advanced heart failure - a new strategy that utilizes well-known markers

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Process of patient assessment before heart transplantation (OHT) - the optimal treatment for refractory heart failure (HF) - is based on several parameters, but practice shows that it still requires improvement. In our study we focus on evaluation of prognostic value of hsCRP and NT-proBNP in a group of patients with severe HF. The goal is to find a new way of using old, easily available tests for better identification of highest-risk patients with the greatest need for heart transplantation in this most severely ill population and to reduce pre- and perioperative mortality.

Materials and Methods: We studied a sample of 632 patients referred for OHT from POLCARD-HF register (2003-2007). First, we stratified five main factors influencing end points (EP, i.e. death or need for urgent OHT) in the entire group. Then, we divided our sample into four subgroups based on hsCRP and NT-proBNP elevation: (1) both markers not elevated, (3) isolated hsCRP elevation, (4) elevation of both markers and analysed survival/need for urgent OHT in those subgroups. Finally, we analyzed predictive value of the risk factors mentioned above in subgroups. Results: In routine clinical evaluation the whole group presented the following characteristics: mean NYHA class 3.2±0.6, HR 77±15 bpm, SAP/DDBP 103/67±31/15 mmHg, LVEF 22±8%, serum Na 136±4 mmol/l, NTproBNP 3942±5637 pg/ml, hsCRP 9.52±mg/l. AUC of ROC analysis was <0.80. Then, we divided our sample into subgroups based on the cut-offs for NT-proBNP and hsCRP revealed by ROC analysis. Using univariate analysis we found that the above three variables significantly affected the EP. NT-proBNP was a significant predictor of EP regardless of the presence of hsCRP elevation. In subgroup (1) both markers were below the cut-offs, and subgroup (3) had an isolated elevation of hsCRP. Subgroup (2) had elevated hsCRP and NT-proBNP, subgroup (4) had elevated both markers and all patients had a stiff thoracic aorta (PWV 7±0.6 m/s).

Conclusions: Our study confirms the role of both markers in identification of 1-year risk of EP in OHT candidates. The highest risk subgroup included patients with both markers elevated. Further studies on larger samples are needed to confirm our findings and to evaluate the role of these markers in OHT candidates.

Thoracic aorta compliance a determinant of survival in patients with MVR and severance of subvalvular apparatus

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Purpose: Mitral valve replacement with severance of subvalvular apparatus (MVRsssa) is associated with a still high operative mortality and with a long term follow-up with a high morbidity and a poor quality of life. Aortic compliance is an important determinant of ventricular afterload. An inverse relationship has been demonstrated between arterial compliance and wave velocity. An echocardiographic doppler method has been used for the measurement of thoracic aortic compliance and we have measured this parameter in conjunction with post op echocardiographic evaluation of patients with MVR.

Methods: Fifty-six (56) patients who had successfully undergone MVRsssa were studied. Rheumatic mitral disease accounted for 35 patients. In 38 patients a mechanical prosthesis was inserted. Follow-up varied between 0.4 and 30 years.

Results: Patients were divided into 2 groups: Group A: Follow up more than 10 years (mean age 56.6, SD 5.9) and Group B: Follow up less than 10 years (mean age 56.7, SD 10.2).

Conclusions: Aortic compliance (PWV) in patients with MVRsssa is lower than in patients with MVR, with a significant difference between the two groups. This finding is consistent with the lower risk of MVRsssa patients compared to MVR patients. Aortic compliance is a reliable parameter in the evaluation of thoracic aorta compliance and is a promising tool for the follow-up of MVRsssa patients.
Results: Thirty-one patients (69%) inducible for scar related VT underwent LVR with concomitant EEC (Group 1) and 14 non-inducible patients (31%) underwent only LVR (Group 2). Twenty-eight patients in Group 1 (90%) and 11 patients in Group 2 (91%) were discharged alive. All 38 patients in Group 1 and 7 patients in Group 2 received an ICD including 2 additional implantations for primary prevention 4 and 11 months after discharge. During 30±18 months follow up 4 patients died (1 cancer and 1 heart failure in each group). In Group 1, 11 patients (39%) experienced VT during follow-up, as compared to only 1 patient (9%) in Group 2. The patients without ICD did not experience syncope or palpitations and were considered free from VT. The negative predictive value of EP testing prior to LVR on the primary occurrence of VT after LVR was 91%. Conclusion: Electrophysiological testing prior to LVR can identify patients at low risk for occurrence of VT after surgery. Concomitant EEC did not prevent VT occurrence in 39% of patients inducible for scar related VT prior to surgery and EEC.

**PS511**

Assessment of left ventricular volume, shape and function after surgical restoration of dyskinetic anteroapical left ventricular aneurysm with multi-slice computed tomography

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Purpose: Surgical ventricular reconstruction is an established treatment option in patients with advanced heart failure due to postinfarct left ventricular aneurysms. In this study we evaluated the potential of dual-source multi-slice computed tomography (MSCT) in the measurement of essential parameters of LV volume, shape and function for the planning of the surgical procedure and assessment of volumetric and functional changes after surgical restoration.

Methods: Between June 2006 and July 2009 a total of 35 patients (mean±SD: 61±11 years, 17 males, 18 females; mean age, 62.7±11.5 years) with anterolateral left ventricular aneurysm underwent ventricular restoration and were assessed by two-dimensional strain echocardiography and MSCT (Somatom Definition, Siemens) before and a short time after surgery (3 to 5, median 7 days). Sphericity index (SI) as short to long axis ratio, apical conicity index (ACI) as the ratio between apical and short axis length, LV end diastolic and end systolic volume as well as aneurysm end diastolic and end systolic volume were measured semi automatically and indexed to the body surface area (LV-EDVI and LV-ESVI, A-EDVI and A-ESVI, respectively). LV ejection fraction (LVEF), cardiac output (CO) and cardiac index (CI) were calculated before and after surgery on the basis of MSCT data.

Results: After surgical repair there were statistically significant reductions of absolute volumes (LVEDV from 310.4±130.1 to 228.4±79.0 ml, LVESV from 228.4±117.0 ml to 135.3±79.0 ml) and indexed LV volumes (LV-EDVI from 159.5±117.0 ml/m² to 103.2±63.8 ml/m², mean change: -33.7±17.0%; LV-ESVI from 115.6±56.0 ml/m² to 68.9±37.0 ml/m², mean change -39.0±20.0%). Absolute mean diastolic aneurysm volume was 68.6±57.0 ml with slight systolic increase to 72.1±80.0 ml, demonstrating adverse volume shift. Indexed aneurysm volume showed the same tendency, with A-EDVI 34.4±27.0 ml/m² > A-ESVI 14.3±9.9 ml/m² (p<0.001). Between March 2010 and July 2011, 1015 patients (Logistic EuroSCORE 20.1±13.3%) with severe aortic stenosis were included in the study, of which 966 had a procedure. LA and GA were used in 547 (55%) and 449 (45%) patients, respectively. LA and GA did not differ with regard to age (81.4±6.4 vs. 81.5±6.4 years, p=0.5), gender (77% vs. 76% female, p=0.6), body mass index (27.6±5.2 vs. 27.4±5.2 kg/m², p=0.6), preoperative creatinine (1.1±0.4 vs. 1.1±0.5 mg/dl, p=0.7) and systolic blood pressure (153±18 vs. 153±19 mmHg, p=0.9). The GA and LA groups did not differ with regard to age, gender and body mass index.

Conclusions: With its capabilities MSCT demonstrates significant LV volume reduction after surgical left ventricular restoration. This leads to improvement of LV function and geometric improvements towards more physiological LV shape.

**PS512**

Cardio-hypertrophic syndrome in cardiovascular surgery; an old but still unresolved problem

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Objectives: Despite recent advances in surgical techniques and perioperative management, liver dysfunction (LD) after open heart surgery remains common, and its characterization and importance are unclear. We speculated that LD is closely related to cardiac status and aimed to clarify the significance of cardio-hypertrophic syndrome in cardiac surgery patients.

Methods: Postoperative LD was defined as serum total bilirubin (T-bil) concentration >2 mg/dl during the period after surgery. (1) First, we evaluated the prevalence and risk factors of postoperative LD in 704 cardiac surgery patients (479 males, 225 females; mean age, 62.7±16.1 years) who underwent open heart surgery since 2007. (2) Next, to determine factors affecting recovery from LD, 95 patients who survived postoperative LD who underwent a ventricular assist device (VAD) implantation from 1992 to 2010 were assessed.

Results: (1) Postoperative LD developed in 85 patients (12.1%), and was associated with greater in-hospital mortality (LD group vs. non-LD group: 34.1% vs. 21.1%, p<0.01), postoperative renal failure (25.9% vs. 4.0%, p<0.01), and respiratory complications (40.0% vs. 8.9%, p<0.01). Multivariate analyses revealed postoperative NYHA status (odds ratio=2.68; II vs. III/IV, p<0.01), preoperative LD (odds ratio=10.47; p<0.01), preoperative renal dysfunction (odds ratio=1.91; p<0.05), and longer cardiopulmonary bypass time (odds ratio=1.01; p<0.05) as independent predictors for postoperative LD. (2) Seventy-two percent of the patients with postoperative LD were treated with LA and recovered from liver dysfunction. Univariate analysis showed that postoperative T-bil, body weight, creatinine, hemodialysis, preoperative mechanical support, and right VAD, as well as postoperative total creatine index, central venous pressure (CVP) prior to LVR (odds ratio= (vs. <): 9.5±3.7 vs. 12.4±4.5 mmHg, p<0.05), and T-bil on day 3 (9.2±6.4 vs. 15.1±9.7 mg/dl, p<0.05) were higher in patients with unremitting LD. Multivariate analysis demonstrated that CVP on postoperative day 3 (odds ratio=1.32; p<0.05) and T-bil on day 3 (odds ratio=1.17; p<0.05) were predictive of a lack of recovery from postoperative LD.

Conclusions: Cardio-hepatic syndrome, which is associated with higher rates of in-hospital mortality, remains common in this modern era and is significantly related to postoperative heart failure. Key factors for outcome of patients with cardio-hepatic syndrome were found to be preoperative renal dysfunction and postoperative liver congestion with a high CVP level. It is important to be aware of this syndrome in cardiac surgery patients and establish appropriate management strategies.
CPB, we investigated the plasma levels of RAGE and its ligands pre- and post- surgery and determined a possible association with the apoptotic proteins Bcl 2 (anti) and BAX (pro) in left ventricular biopsies. Plasma levels of S100 proteins and RAGE were detected by ELISA. Bcl 2 and BAX protein and mRNA levels were measured by Western blot and quantitative PCR respectively. We performed Student’s t-test, linear regression analysis and Pearson’s correlation to define these associations. Significant increased were detected in plasma levels of S100B (p = 0.027) and RAGE (p = 0.026) pre- versus post-surgery. A significant decrease was seen in plasma levels of S100A6 post-surgery (p = 0.003) and no change was detected in S100A1 plasma levels. There was a positive correlation between plasma levels of S100B post surgery and the ventricular BAX/Bcl 2 mRNA expression ratio (n = 12, p = 0.0057, r = 0.742). Also, a negative correlation was detected between the plasma levels of S100A6 post surgery and the ventricular BAX/Bcl 2 mRNA expression ratio (n = 12, p = 0.036, r = 0.608).

In CABG surgery with CPB, plasma levels of S100B and RAGE increased post surgery with a concomitant decrease in S100A6. There is a positive correlation between S100B and a negative correlation between S100A6 post surgery and the ventricular BAX/Bcl 2 ratio indicating a potential apoptotic state in the ventricle. In conclusion, these findings suggest a positive correlation between S100B, RAGE and the apoptotic markers Bcl 2 and BAX, in a population of patients undergoing CABG surgery with CPB.

**PS815**

**Totally epicardial cardiac resynchronization therapy in patients with heart failure undergoing CABG:**

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Purpose: totally epicardial cardiac resynchronization therapy (CRT) system implantation is a novel treatment option for patients with heart failure (HF) and dysynchrony undergoing coronary artery bypass grafting (CABG). The long-term results of this treatment strategy are unknown.

We performed a 5-year follow-up of patients with HF who underwent epicardial CRT system implantation.

Methods: Twenty-six patients underwent totally epicardial CRT pacing system implantation during CABG. In the short-term follow-up (6 months) we observed improvement in clinical (NYHA, walk-test distance, quality of life) and echocardiographic (LVEF, LVESD, mitral regurgitation) parameters in comparison to baseline. Twenty five patients were further followed-up prospectively for 5 years.

Results: There were 5 (20%) deaths: 4 (16%) cardiac (2 because of worsening of HF, and 2 of myocardial infarction) and one (4%) noncardiac. The comparison of clinical short and long-term results in 20 patients who completed the 5-year follow up revealed no significant differences in 16 pts (80%), further improvement in 2 (10%) and worsening in 2 (10%) pts. In relation to short-term follow up, at 5 years LVEF and ESV remained unchanged in 9 (45%) pts, improved in 1 (5%) pt, and deteriorated in 10 (50%) - pts in 9 pts slightly deteriorated by less than 10% in LVEF and 15% in ESV. Mitral regurgitation didn’t change in 14 (70%) pts, increased by one grade in 6 (30%) pts. There were 2 (8%) device-related adverse events: one patient had a new ventricular lead implanted transvenously because of exit block and 1 patient had a new atrial implanted transvenously because of lead fracture. Rest of the patients had good pacing and sensing parameters, no PM replacement had to be performed.

Conclusion: The benefits of CRT delivered by a totally epicardial system implanted during CABG persist in the long-term follow-up and are associated with a low complication rate.

**PS816**

**Fluid overload as a biomarker of morbidity and mortality after cardiac surgery**

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Purpose: To evaluate fluid overload and serum creatinine changes as predictors of cardiovascular morbidity and mortality after cardiac surgery.

Design: Prospective cohort study with patients submitted to cardiac surgery followed by postoperative Intensive Care Unit admission, from September/2010 through August/2011.

Methods: Clinical and laboratory data of each patient was collected at preoperative and trans-operative moments and fluid overload and creatinine levels were measured. Fluid overload was calculated as follows: (Sum of daily fluid received (L) - total fluid output (L))/body weight (kg) x 100.

Results: From 502 patients, 62,4±13.3 years old, 61,4% male and 38,6% female, 1 patients had good pacing and sensing parameters, no PM replacement had to be performed.

Conclusion: The frequency of AT1 1166AC and CC genotypes and C allele was higher in CAD patients with advanced LV dysfunction. It represents a genetic marker that identifies CAD patients at higher risk for heart failure.
Hypertrophy and impaired cardiac function of CD36 knockout mice in a pressure overload condition

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Background: CD36 is an important transporter of long-chain fatty acids (LCFA) in the myocardium. Previously, we have reported that CD36-deficient patients demonstrate a marked reduction of myocardial uptake of LCFA, while myocardial glucose uptake is compensatorily increased in KO mice, which may demonstrate a marked reduction of myocardial uptake of LCFA, while myocardial glucose uptake is compensatorily increased in KO mice, which may be a possible mechanism of their impaired cardiac function.

Methods: Using wild type (WT) and KO mice at 7–10 weeks (wks) old, we performed transverse aortic constriction (TAC) to generate pressure overload and measured cardiac function by echocardiography. To assess cardiac hypertrophy and fibrosis, histological and molecular analyses were performed.

Results: At the baseline, there were no significant differences in left ventricular wall thickness and left ventricular fractional shortening (LVFS) between KO and WT mice. By applying a TAC for 4 wks, the survival rate was significantly lower in KO mice (30.0% vs 85.7%, P=0.0018). At 2 wks after TAC, KO showed significantly higher heart weight (HW) toibia length (TL) ratio than that of WT (HW/TL mg/mg,10.4±1.0 vs 8.4±0.8, P<0.003). We also observed significantly larger cross-sectional area of cardiomyocytes in KO than that of WT, suggesting that hypertrophic response of KO mice was more marked than WT. KO with TAC showed increased lung weight (LW) to TL ratio and significantly reduced LVFS rather than WT with TAC (LW/TL mg/mg,13.9±5.7 vs 9.2±2.0, P=0.0069, FS%,24±1.1 vs 34.9±3.0, P=0.00007), suggesting that pressure overload induced early systolic dysfunction in KO mice even at 2 wks after TAC, when WT mice showed compensated cardiac hypertrophy. In the basal condition, glucose uptake in myocardium of KO was significantly increased as compared with WT. At 1wk after TAC, myocardial glucose uptake was enhanced in both KO and WT mice. The phosphorylation level of AMPK was also higher in KO than WT mice. Correlation of AMPK phosphorylation level with inflammatory markers (IL-6, TNF-α, IL-1β) and TGF-β1 in KO mice suggested that AMPK may have a role in the regulation of inflammatory responses.

Conclusion: The LFCA transporter CD36 plays important roles regulating cardiac hypertrophy and function.

Direct renin inhibitor prevents ventricular remodeling and sudden arrhythmic death in mice with dilated cardiomyopathy

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Purpose: Progression of left ventricular (LV) remodeling including fibrosis contributes to the occurrence of lethal ventricular arrhythmias and sudden cardiac death. Further detailed understanding of molecular mechanism underlying a substrate for arrhythmogenicity in chronic heart failure (CHF) has been desired. To evaluate the contribution of renin-angiotensin system (RAS) for generation of this substrate, we administered direct renin inhibitor aliskiren to cardiac-specific, dominant-negative form of renin-restrictive silencer transgenic mice (dnNRSF-Tg), which exhibit progressive dilated cardiomyopathy with lethal arrhythmias beginning at 12 weeks of age and 60% of which die suddenly by 30 weeks.

Methods: Aliskiren 22 mg/kg/day was administered via osmotic mini-pumps to dnNRSF-Tg of two groups: Early stage of CHF (from 12 to 18 weeks of age) and late stage of CHF (from 16 to 28 weeks of age). We measured heart rate and blood pressure, and performed echocardiographic analyses in both stages. In late stage, we analyzed survival rate, fibrosis in histological sections, ventricular expression of remodeling-related genes, hemodynamic LV parameters with a catheter-tip micromanometer and arrhythmogenicity by performing in vivo intracardiac electrophysiological study.

Results: Aliskiren reduced blood pressure in wild-type mice (108±3 mmHg to 94±4 mmHg, p<0.001) but not significantly in dnNRSF-Tg (95±4 mmHg to 89±3 mmHg, p>0.05). Nor did it affect heart rate. In both stages aliskiren improved LV ejection fraction in dnNRSF-Tg (41±2% to 52±4% in early stage, p<0.03; 35±4% to 56±4% in late stage, p<0.005). In late stage aliskiren improved survival rate (vs. vehicle; p=0.05) and attenuated the increase in ventricular mRNA expression of atrial natriuretic peptide, β-myosin heavy chain, transforming growth factor (TGF)-β1, TGF-β3, TGF-β type II receptors, myocardial infarction and fibrosis (vs. vehicle; p<0.05). In dnNRSF-Tg, aliskiren also increased the maximal rate of LV pressure change (dP/dt) (vs. vehicle; p<0.05), tended to normalize LV and diastolic pressure, and furthermore repressed incidence of ventricular arrhythmias during electrophysiological study in dnNRSF-Tg.

Conclusion: Inhibition of RAS by aliskiren significantly suppressed fibrosis, remodeling and increased susceptibility to ventricular arrhythmias, and thereby improved the survival rate without changing blood pressure in dnNRSF-Tg. These results demonstrate the potential contribution of RAS to the arrhythmogenic substrate during the progression of CHF.
used eNOS deficient mice (eNOS−/−) and L-NNAME-treated rats (L-NNAME treat-
ment, 4 weeks). Steady state mRNA levels of genes were analyzed by qRT-PCR.
Results: eNOS deficiency in mice and L-NNAME administration in rats caused decreased
expression of genes in blood pressure (L-NNAME: −42 mmHg; eNOS−/−: −31 mmHg) and cardiac hypertrophy eNOS−/−: (n=13); HW/BW (mg/g) 6.23±1.10 vs. eNOS+/+ (n=14); 5.26±0.66 and eNOS−/−: (n=4; p<0.05) 5.19±0.62; L-NNAME: 4.43±0.43 (n=10) vs. 3.93±0.53 (n=14). Among all genes under investigation only ANF was found to be commonly up-regulated in eNOS deficient mice and L-NNAME treated rats. Administration of captopril or hydralazine attenuated some of the gene and cardiac hypertrophy indicating that the up-regulation was related to pressure overload rather than NO deficiency. However, TGF-β1 (eNOS−/−: −38%; L-NNAME: −32%) and the pro-apoptotic gene bax (eNOS−/−: −73%; L-
NNAME: −27%) were significantly down-regulated in both models of NO deficiency
study support a species-independent regulatory mechanism, by which this
Conclusions: In conditions of heart failure, eNOS expression is reduced. The data of this
study supports a species-independent regulatory mechanism, by which this
cost of decreased antioxidative capacity. This represents a novel mechanism how
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Purpose: Cell-specific conditional gene manipulation models have revealed different roles of cardiomyocyte (CM) and non-CM signaling in maladaptive cardiac remodeling. A major factor involved in such cross talk is transforming growth factor-beta (TGFβ), which exists in CM and non-CMs. Recently, we showed a key role of CM-TGFβ signaling in cardiac pressure-overload (TAC). Besides pressure-overload, myocardial ischemia or catecholamine stimulation frequently precipitate pathological remodeling in the heart. Here, we tested the role of cell-specific TGFβ signaling in these models, contrasting antibody-based inhibition versus CM-specific gene suppression of TGFβ receptor 2 (TgfbR2) in mice.

Methods: Mice with cardiac-specific conditional knockdown of TgfbR2 (AMH-driven tamoxifen-inducible Cre (MCM) TgfbR2 floxed mice) or with systemic injection of TGFβ-neutralizing antibody (NAB) were subjected to proximal LAD ligation (MI) or isoproterenol administration (ISO) in C57Bl/6j mice. Outcome was assessed by echocardiography, staining for myocardial fibrosis, gene- and protein expression (qRT-PCR, immunoblot) and immunohistochemistry (SMAD3).

Results: Chronic ISO induced mild cardiac hypertrophy with moderate fibrosis. NAB treatment significantly inhibited fibrosis, yet cardiac function and hypertrophy were not improved. Unlike with the TAC model, where CM-TgfbR2 knockdown strikingly inhibited fibrosis and ameliorated function, with ISO CM-TgfbR2 knockdown rather worsened function and fibrosis. Myocardial SMAD3 activation was not suppressed with dominant non-CM SMAD3 phosphorylation. TGFβ-activating kinase (TAK1), which is critical in pressure-overload, was not activated by ISO. Myocyte-derived TGFβ was not increased, while the fibroblast-specific marker periostin was significantly up-regulated with ISO.

While myocardial function and dilation were worse in the MI model compared to TAC and ISO, fibrosis in the remote area was virtually absent, as was SMAD3 or TAK1 activation. Likewise, TGFβ or periostin expression was not changed. CM-TgfbR2 knockdown did not alter function or fibrosis in this model.

Conclusions: ISO-induced myocardial fibrosis and mild hypertrophy. Here, unlike in the TAC model, CM-specific TgfbR2 suppression did not reduce fibrosis but NAB therapy did, suggesting that ISO-induced myocardial fibrosis is mainly triggered by non-CM sources. The chronic maladaptive remodeling of viable myocardium upon MI involves substantially less fibrosis and CM-related TGFβ signaling seems to play a minor role.

Heart failure remodeling - could the failing myocytes be the additional source of endogenous erythropoietin? P. Leszek1, B. Sochanowicz2, K. Brzozka3, E. Komuda-Leszrek3, M. Kusmierczyk4, W. Piotrowski5, T. Rywik1, J. Rozanski1, M. Kruszewski1. 1Institute of Cardiology, Warsaw, Poland; 2Institute of Nuclear Chemistry & Technology, Dept. Radiobiology & Health Protection, Warsaw, Poland; 3Department of Transplantation Medicine and Nephrology, Medical University of Warsaw, Warsaw, Poland.

Erythropoietin (EPO), predominantly produced in a kidney, activates the erythropoietin receptor (EPOR) and maintains myeloid erythropoiesis by preventing apoptosis and stimulating proliferation/differentiation of erythroid progenitors. Moreover, in a failing heart (HF), EPO exerts cytoprotective, antiapoptotic, proangiogenic effects what was confirmed in clinical setting by exogenous EPO supplementation. Thus, the purpose of our study was to assess myocardial EPO expression and also whether EPO is produced in human heart.

Methods and Results: Study group of 33 patients: left/right ventricle (LV/RV) (LV - EF 22±11%, RV 32±10 mm), CrCl 68±13 mL/min/m², NTproBNP (5464±4825 pg/mL), TGFβ (15.8±9.7 pg/mL), hCRP (0.72±0.9 mg/dl). Serum iron homeostasis: iron (62±32 μg/dl), ferritin (156±120 μg/ml), transferrin receptor (3.8±2.6 mg/L), EPO (29.5±4.4 μg/mL) and hCRP (39.8±5.3%), Hb (13.2±1.7 g/dl), creatinine clearance (Cl Cr 68±23 mL/min). We demonstrated expression and functionality of erythropoietin receptor in myocardium. What is still under investigation is the possible mechanisms related to M-EPO/M-EPOR expression and functionality what was confirmed in clinical setting by exogenous EPO supplementation.

Purpose: The presence of anemia (A), commonly seen in heart failure (HF) patients (pts), stimulates the kidney erythropoietin (EPO) production. Endogenous EPO, a major hormone stimulating the production and differentiation of erythroid progenitors, acts by erythropoietin receptor (EPOR). Recently we proved that EPO/EPO-R are also synthesized locally in human myocardium (EPM-EPOM-EPOR), however the exact mechanisms of stimulation are still unknown. Thus, the purpose of our study was to elucidate the possible mechanisms related to M-EPO/EPO expression.

Methods and Results: Study group of 33 patients: left/right ventricle (LV/RV) (LV - EF 22±11%; RV 32±10 mm), Cl 68±13 mL/min/m², mPWP (23±9 mmHg), mPWP (23±9 mmHg), NTproBNP (5464±4825 pg/mL), TGFβ (15.8±9.7 pg/mL), hCRP (0.72±0.9 mg/dl). Serum iron homeostasis: iron (62±32 μg/dl), EPO (29.5±4.4 μg/mL), Hb (39.8±5.3%), Hb (13.2±1.7 g/dl), creatinine clearance (Cl Cr 68±23 mL/min). We demonstrated expression and functionality of erythropoietin receptor in myocardium. What is still under investigation is the possible mechanisms related to M-EPO/EPO expression.
The effect of short term changes in circulating free fatty acids on myocardial and skeletal muscle lipid content: a randomized trial in heart failure patients with type 2 diabetes

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Background: Myocardial lipid content (MYLC) and left ventricular ejection fraction (LVEF) are inversely correlated in heart failure patients with type 2 diabetes (HTF2D). Measuring MYLC as opposed to skeletal muscle lipid content (SMLC) is technically more complicated and time consuming. It is unknown whether SMLC could be used as a marker of changes in MYLC.

Methods: Fifteen HTF2D patients (EF<45%) underwent 8 hours of high (intralipid/heparin) and low (hyposulinaemic euclergic clamp) circulating free fatty acids (FFA) in a randomized cross-over designed trial. MR-proton-spectroscopy (MRS) was used to measure MYLC and SMLC expressed as percentage of water content.

Results: Circulating FFA levels differed between study arms (0.05±0.01 SEM mmol/L (low FFA) vs. 1.07±0.07 mmol/L (high FFA), p<0.001). Thirteen patients completed MYLC measurements and ten patients completed SMLC measurements in both study arms. MYLC was significantly higher during the high FFA arm (0.78±0.23% vs. 1.16±0.19%, p<0.01) (figure 1A) whereas SMLC (0.80±0.09% vs. 0.84±0.10%, p=0.12) (figure 1B) did not differ between study arms. No association was found between MYLC and SMLC in either study arm (p=0.93 (low FFA); p=0.03 (high FFA)). SMLC and the level of insulin resistance (HOMA-IR) correlated positively in both study arms (differences: p<0.02, (low FFA); 0.30, p=0.01, (high FFA)) whereas no association was found between MYLC and HOMA-IR.

Conclusion: In HTF2D patients MYLC and SMLC respond differently to short term changes in circulating FFA, suggesting different regulatory mechanisms of lipid content in heart and skeletal muscle. Our findings show that SMLC cannot be used to assess content of and changes in MYLC.

Lack osteopontin is associated with an early compensation of left ventricular systolic function in a streptozotocin-induced model of diabetic cardiomyopathy

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Myocardial expression of osteopontin (OPN) has been linked to myocardial fibrosis in different models of heart failure. The objective of the present study was to evaluate the role of osteopontin in the progression of myocardial dysfunction using a model of streptozocin induced diabetic cardiomyopathy in OPN knockout (KO) mice.

Methods: Diabetes was induced by intraperitoneal injections of STZ (50 mg/kg) for 5 consecutive days in a group of wild type (WT) and OPN KO mice. Diabetes mellitus was confirmed (plasma glucose > 200 mg/dl) in both groups. We performed an echocardiogram at baseline and every 2 weeks thereafter up to 8 weeks, while ECGs were obtained 3 and 6 weeks after diabetes induction, after the observation period of 8 weeks; mice were sacrificed and macroscopic and histologic examination of the hearts was performed to estimate myocyte area, apoptosis and fibrosis. T test or one way ANOVA were used for continuous variables, a P<0.05 were considered significant.

Results: There was a reduction in the ejection fraction (EF) in echocardiograms performed at 2 weeks, in WT-diabetic (WT-D)=51.3±7.2 p=0.003 and OPN KO mice=48.2±5.2, p=0.003 compared to WT non-diabetic (WT=50.05±0.07). EF decreased significantly faster in WT-D compared to WT non-diabetic and in OPN KO mice compared to WT-D (P=0.021). In contrast, K-D and OPN KO-D EFs were not different compared to WT=53.3±4.6, (P=0.46). A trend towards higher EFs was observed in the OPN KO group at 2 weeks (P=0.05). EFs were similar in WT-D and OPN KO-D at 8 weeks (P>0.05). EF differences were preserved in WT-D and OPN KO-D mice, whereas OPN KO-D EFs were significantly lower than WT=51.4±4.6 versus WT-D=53.3±4.6, (P=0.05). No significant differences were observed in EFs between WT-D and OPN KO-D groups in 4 weeks, whereas OPN KO-D EFs were significantly lower than WT-D EFs in 8 weeks (P=0.05).

Conclusion: Lack of osteopontin expression is associated with an earlier recovery of systolic dysfunction in a diabetic cardiomyopathy model.

Long-term therapy with a partial adenosine A1-receptor agonist up-regulates mRNA and protein expression of glucose transporters in left ventricular myocardium of dogs with chronic heart failure

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Background: Recruitment of glucose transport proteins GLUT-1 and GLUT-4 is a cellular mechanism by which the heart increases glucose transport for metabolism in response to increased energy demands. In the failing left ventricle, mRNA and protein levels of the transporters GLUT-1 and GLUT-4 are down-regulated and energy demands are increased therefore increased dependence on fatty acid oxidation. We previously showed that long-term treatment with the partial adenosine A1-receptor agonist capadenoson (CAP) improves left ventricular (LV) systolic function in dogs with advanced heart failure (HF). In this study we examined the effects of CAP on the regulation of GLUT-1 and GLUT-4 in LV myocardium of dogs with chronic HF.

Methods: Studies were performed in LV myocardium of 12 HF dogs randomized to 3 months oral monotherapy with the CAP (7.5 mg twice daily, n=6) or to no therapy at all (Control, n=6). LV myocardium from 6 normal (NL) dogs was used for comparison. mRNA expression of GLUT-1 and GLUT-4 was measured in LV tissue homogenate using reverse transcription (RT-PCR).

Results: Compared to NL dogs, Control HF dogs showed a 3.6 fold decrease in mRNA expression of GLUT-1 and a 2.7 fold decrease in GLUT-4. Treatment with CAP increased mRNA expression of GLUT-1 to 1.38 fold decrease from 0.64±0.04 vs. 0.26±0.04, p<0.05 and GLUT-4 to 1.42±0.06 vs. 0.40±0.05, p<0.05. CAP treatment significantly increased tissue levels of both GLUT-1 (1.49±0.03 vs. 0.30±0.03) and GLUT-4 (0.82±0.03) compared to Control HF dogs. mRNA levels were essentially unchanged between NL dogs, untreated HF Controls and CAP-treated dogs.

Conclusion: In dogs with chronic HF, long-term therapy with CAP improves mRNA and protein expression of GLUT-1 and GLUT-4. This improvement in expression of glucose transport proteins is likely to restore partial dependency of the failing heart to more efficient glucose metabolism, and therefore, lead to improved myocardial energetics and pump function.
**ARNI, combined nephrilysin and angiotensin receptor inhibition augments anti-fibrotic and anti-hypertrophic effects in vitro**

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**Background:** A novel strategy combining the angiotensin receptor blocker (ARB) Valsartan (VAL) with a nephrilysin inhibitor (NEP) to augment beneficial endogenous natriuretic peptide activity has produced superior antihypertensive effects in patients with resistant hypertension compared to VAL alone. We investigated the effects of combined ARB and NEP on cardiac fibrosis and hypertrophy.

**Methods:** Neonatal rat cardiac fibroblasts (NCF) and cardiomyocytes (NCM) were stimulated with 100 nM of angiotensin II (AngII) and co-cultured with increasing doses of VAL, the inactive NEP pro-drug AHU-377 (AHU), and its active metabo-

**Results:**[Table not shown.]

**Conclusions:**[Additional text not shown.]

**Cardiac effects of combined ARB+NEP**

<table>
<thead>
<tr>
<th>NCM stimulated with 100 μM AngII</th>
<th>VAL dose (mM)</th>
<th>Effect on NR3C2 mRNA expression (95% CI)</th>
<th>Effect on collagen (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAL alone</strong></td>
<td>0.0</td>
<td>1.26 (1.06-2.40)</td>
<td>110.6 (107.4-113.8)</td>
</tr>
<tr>
<td><strong>VAL+10μM LBO</strong></td>
<td>0.0</td>
<td>1.12 (1.00-1.25)</td>
<td>106.9 (104.7-109.2)</td>
</tr>
<tr>
<td><strong>NCF stimulated with 100 μM AngII</strong></td>
<td>0.0</td>
<td>1.30 (1.10-1.70)</td>
<td>104.2 (101.9-106.6)</td>
</tr>
<tr>
<td><strong>VAL alone</strong></td>
<td>0.0</td>
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</tr>
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</table>

Data displayed as % of unstimulated control (=100%). ***p < 0.001, **p < 0.01, ##p < 0.05 vs unstimulated control.

**Conclusions:** Our data show that the combination of ARB and NEP inhibits the anti-fibrotic and anti-hypertrophic effects mediated by ARB alone. These novel findings and recent promising clinical data further support the study of combined ARB and NEP inhibition (ARNI) in cardiovascular disease.

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**Nucleocytoplasmic transport and gene expression in patients with heart failure**

E. Rosollo Lied1, M. Pastoriza2, M. Rivera Otero1, E. Tarazon1, I. Sanchez Lazaro1, J.R. Gonzalez Juanatey2, A. Salvador2, I. Sanchez Lazaro1, F. Lagó2, I. Azorín1, V. Bertomeu1, A. Salvador1, A. Kompa1, H. Krum1, 1Monash Centre of Cardiovascular Research & Education in Therapeutics, Melbourne, Australia; 2Novartis Institutes for BioMedical Research, Translational Sciences, Basel, Switzerland

**Purpose:** We have previously shown alterations in nucleocytoplasmic transport (NCT) in patients with heart failure (HF). In particular increased protein levels and different distribution of importins, exportins and Ran regulators were found in ischemic and dilated human hearts, compared with healthy controls. Furthermore we found significant relationships between exportin and importin levels, markers of NCT, and left ventricular function parameters. However the origin of such alterations remains unknown. Therefore we wanted to explore if changes in gene expression are associated with heart failure (HF).

**Methods:** We studied 36 Caucasian patients undergoing heart transplant (mean age 50±10 years). Fifteen were diagnosed with dilated cardiomyopathy (DCM), 15 with ischemic cardiomyopathy (ICM) and six were normal control hearts (CNT). Genome-wide gene expression was determined using Affymetrix Human Gene 1.0 ST arrays. Background correction, normalization, probe summarization and data analysis was done with Partek Genomics Suite software using RMA techniques.

**Results:** When we compared human CNT with DCM patients we found changes (FDR<0.1, change> 2 folds) in 54 genes (35 up and 19 down regulated). When we compared human CNT with ICM patients we found changes in 13 genes (5 up and 8 down regulated). Eight genes where differentially expressed in both DCM and ICM when compared with human CNT. XP01 (exportin-1 gene) was up regulated in both groups of patients in accordance with previously found exportin-1 protein levels.

**Conclusions:** In this study we found significant changes in gene expression of human explanted hearts of patients with DCM and ICM when compared to CNT. XP01, related to nucleocytoplasmic transport was up regulated in both cardiomyopathies in accordance with previously described exportin-1 protein levels. This fact may be closely related with the cardiomyocyte capability of repair and may open new therapeutic expectations in patients with heart failure.

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** Influence of heart failure on nucleor organization and protein expression in human hearts**

E. Rosollo Liedi, M. Rivera Oteroi, R. Cortesi, L. Martinez Dolzi, L. Almenara, F. Lagói, I. Azorín1, V. Bertomeu1, A. Salvador1, A. Kompa1, H. Krumi, 1Monash Centre of Cardiovascular Research & Education in Therapeutics, Melbourne, Australia; 2Novartis Institutes for BioMedical Research, Translational Sciences, Basel, Switzerland

**Purpose:** The nucleolus represents a dynamic structure involved in important cellular processes, but its role in development of heart failure (HF) has not been studied.

**Methods:** We investigate for the first time the influence of HF on nucleolar organization and protein expression in patients with ischemic (ICM) or dilated cardiomyopathies (DCM). A total of 71 human hearts from ICM (n=38) and DCM (n=27) patients, undergoing heart transplantation and control donors (n=6), were analysed by western-blotting and gene expression methods.

**Results:** When we compared protein levels according to HF etiology, nucleoli was increased in both ICM (117%, p<0.05) and DCM (141%, p<0.01). Moreover, mRNA expression was also upregulated in ICM (1.46-fold, p<0.05) and DCM (1.70-fold, p<0.05). Fibulinrin, B23 and MDM2 were not different when compared with control donors. Immunofluorescence studies showed that the highest intensity of nucleoli was into nucleoli (p<0.0001), and it was increased in pathological conditions (p<0.0001).

**Conclusions:** The present study demonstrates that HF influences on morphology and organization of nucleolar components, revealing changes in the expression and in the levels of nucleolin protein. In addition we performed a new way for future studies that analyze other factors involved in the nucleolar activity that could alter several nucleolar processes, and that can be potential drug targets in human HF hearts.

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**Hepcidin: a key regulator of iron homeostasis in advanced heart failure**

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Correcting iron deficiency with the use of iv iron supplementation in patients with heart failure (HF) with/without anemia seem to produce promising results. However, the harmless application of iv iron is limited by the gaps in our knowledge of iron homeostasis. Hepcidin a peptide hormone produced by the liver, appears to be a key regulator of iron homeostasis in humans. Its production is regulated by iron (IR) load, inflammation and erythropoiesis levels. Thus, the purpose of our study was to elucidate the role of hepcidin in advanced HF.

**Methods and Study:** Group 33 patients, left/right ventricle (L/RV) (LVEDV 245±84 ml; LVESS 198±85 ml; LV EF 22±11%; RVD 32±10 mm), NT-proBNP (4204±4265 pg/ml), TNF-alpha (15±1±3 ng/ml), hsCRP (0.7±0.9 mg/dl). Serum iron homeostasis assessment: iron, FR, TRx, TSAT, sTfR, sTfR/logTfR, UIBC, UIBC, EPO, Proteocidin (HEP), McCord Myocardial In (Instrumental Neuron Activation Analysis, μg/ml), FR, M, sTfR-M (ELISA – ng/ml protein) in the explanted failing hearts (HF), compared to non-failing hearts (NHF n=11).

In the whole group out of all serum and myocardial variables Pearson correlation found HEP to correlate with TRx (r=0.40, p=0.0238), UIBC (r=0.40, p=0.0203), TNF-alpha (r=0.42, p=0.0344) and creatinine (r=0.42, p=0.0246).

**Conclusions:** In HF patients HEP levels are related to inflammation (TNF alpha) and renal function (creatinine). HEP is associated with serum IR transportation (TfR M) in HB patients.
Mechanisms of blunted muscle vasodilation during peripheral chemoreceptor stimulation in heart failure patients

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**Purpose:** We recently described that systemic hypoxia provokes vasoconstriction in HF patients. Which might due to augmented sympathetic nerve activity to muscle (MSNA), in this study, we tested the hypothesis that either the exaggerated MSNA and/or blunted endothelial dysfunction mediate the blunted vasodilation during hypoxia in HF patients.

**Methods:** Twenty seven HF patients and 23 age-matched healthy controls were studied. MSNA was assessed by microneurography and forearm blood flow (FBF) by venous occlusion plethysmography. Peripheral chemoreflex control was evaluated through the inhaling of a hypoxic gas mixture (10% O\(_2\) and 90% N\(_2\)).

**Results:** MSNA (P=0.001) were greater and basal FBF levels (P=0.003) were lower in HF patients versus controls. During hypoxia, MSNA responses were greater in HF patients (P=0.02), and forearm vasodilation was blunted in HF compared to controls (P=0.002). In the presence of phentolamine, hypoxia significantly increased FBF responses in both groups, but the increase was lower in HF patients versus controls (P=0.003). Phentolamine + L-NMMA infusion during hypoxia did not change FBF responses in HF, but markedly blunted the vasodilation in controls (P<0.06). FBF responses to hypoxia in the presence of vitamin C, an antioxidant that promotes NO availability, were unchanged when compared with saline infusion, and remained lower in HF patients versus controls.

**Conclusions:** Muscle vasoconstriction in response to hypoxia in HF patients is due to exaggerated reflex sympathetic nerve activation and blunted endothelial function (NO activity). We were unable to identify a role for oxidative stress in these studies.

Alteration of the nuclear pore complex in patients diagnosed with heart failure

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**Purpose:** We have recently reported alterations in different transporters that orchestrate the nucleocyttoplasmic transport, such as increased importin and exportin levels in patients diagnosed with heart failure (HF). We asked whether we could also find any alteration in the nuclear pore complex (NPC) structure, the gateways connecting the nucleoplasm and cytoplasm. Therefore, we quantified several representative proteins that compose the different parts of NPCs, named nucleoporins (Nup), in this syndrome.

**Methods:** A total of 84 human heart samples from ischemic (ICM, n=45) and dilated (DCM, n=30) patients undergoing heart transplant and control donors (CNT, n=9), were analyzed by Western-blotting. Subcellular distribution of proteins was analyzed by immunocytochemistry, fluorescence and electron microscopy.

**Results:** When we compared nucleoporin protein levels according to etiology, ICM showed significant higher levels of linker Nup93 (42%, p<0.0001), FG Nup153 (139%, p<0.01) and transmembrane ring Nup NDC1 (65%, p<0.0001) than those of the CNT group. Furthermore, DCM also showed significant differences for Nup93 (88%, p<0.0001), Nup153 (157%, p<0.01) and NCD1 (41%, p<0.0001). However, the nucleoporins Nup155, Nup160 and translocated promoter region (TPR) did not show significant differences. Furthermore, subcellular distribution of nucleoporins was not altered in pathological hearts, although we observed an increase in the fluorescence intensity in ICM and DCM samples of those Nup with high protein levels.

**Conclusions:** This study shows alterations in specific proteins that compose NPCs, overall those that are directly exposed to cargo undergoing transport (Nup93 and Nup153) and those that surround the core (NDC1), in hearts from patients with ICM and DCM and could be the base for a new HF treatment.