A blood pressure genetic risk score predicts incident cardiovascular events in 36,950 Finnish individuals. V. Salomaa1, A.S. Haslumina1, J. Kettunen1, J. Eriksson1, A. Jula2, K. Kontula3, C. Newton-Chen4, 1National Institute for Health and Welfare, Helsinki, Finland; 2National Institute for Health and Welfare, Turku, Finland; 3University of Helsinki, Department of Medicine, Helsinki, Finland; 4Massachusetts General Hospital, Center for Human Genetic Research and Cardiovascular Research Center, Boston, United States of America

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 36,850 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 cardiovascular death and revascularization, incidence 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 and hypertension (p < 0.05). Altogether, 2,111 incident CVD events occurred during the follow-up. GRS showed significant, independent and though not linear associations with the CVD risk. The highest q-value of systolic BP GRS had the hazard ratio of 1.28 (95% confidence interval 1.1 – 1.5, p < 0.0005) and the highest q-value of diastolic BP GRS 1.31 (95% CI 1.2 – 1.54, p < 0.0001) 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. M. Karakas1, J. Baumert2, M.E. Kleber2, B. Thordar2, D. Dallmeier1, W. Rottbauer1, C. Messinger1, T. Illig4, W. Maenz4, W. Koergel1, 1University of Ulm, Faculty of Medicine, Department of Internal Medicine II-Cardiology, Ulm, Germany; 2Heilmolz Center of Munich, Institute of Epidemiology, Neuenberg, Germany; 3Mannheim Institute of Public Health, Social & Preventive Medicine, Heidelberg University, Mannheim, Germany

Background: Elevated soluble (s) E-selectin levels have been associated with various cardiovascular diseases. Recently, genetic variants in the ABO blood group have been related to sE-selectin in a small cohort of patients with type 1 diabetes. We evaluated whether this association is reproduced in two large samples of Caucasians.

Methods: Data of the present study was drawn from the population-based MONICA/KORA Augsburg study (n = 1,482) and the case-control-based LURIC study (n = 1,546). A high-density genotyping, array containing single nucleotide polymorphisms (SNPs) from E-selectin candidate genes (50k IBC Chip) selected on known biology of E-selectin metabolism, mouse genetic studies, and human genetic association studies was used for genotyping. Linear regression analysis with adjustment for age and sex were applied to assess associations between gene variants and sE-selectin levels.

Results: A number of 12 SNPs in KORA and 13 SNPs in LURIC, all from the ABO blood group region were significantly associated with levels of log-transformed sE-selectin. The strongest association was observed for rs651007 which was associated with log-transformed sE-selectin level per one copy of the minor allele of -0.37 ng/ml (p = 1.87x10^-10) in KORA and -0.35 ng/ml (p = 5.11x10^-84) in LURIC. All SNPs had minor allele frequencies above 20% showing a substantial gene variation.

Conclusions: Our findings in two independent samples indicate that the genetic variants at the ABO locus affect sE-selectin levels. Since distinct genome wide association studies linked the ABO gene with myocardial infarction in the presence of coronary atherosclerosis and with coronary artery disease, these findings may not only enhance our understanding of adhesion molecule biology, but may also provide a focus for several novel research avenues.

A genetic variant near adrenomedullin gene is associated with arterial rigidity. F. Beyga1, P.S. Wilde2, T. Zeller2, V. Truong3, T. Munzli2, G. Montalescot1, D.A. Tregouet2, F. Cambier1, S. Blankenberg3, L. Tiret1, on behalf of Gutenberg Heart Study. 1AP-HP - Hospital Pitie-Salpetriere, Paris, France; 2Johannes Gutenberg University Mainz (JGU), Mainz, Germany; 3INSERM U937, Paris, France; 4University Heart Center Hamburg, Department for General and Interventional Cardiology, Hamburg, Germany

Purpose: Adrenomedullin (ADM), is a produced in response to endothelial ag- greSSION and hemodynamic compromise. Its plasma concentrations have been reported to be correlated to stages of atherosclerosis. We assessed the relationship between genetic variants associated with MRproADM levels and markers of arterial stiffness and vascular tone.

Methods: Vascular tone and stiffness were measured by the reflection (RI) and stiffness (Sí) indexes as measured by Pulse trace 2000 device (Micro Medical Ltd., Rochester, United Kingdom) in a population of 5000 European ancestry adults from the Gutenberg Health Study Cohort. Biometric, Clinical and biological variables, as well as genetic markers identified by a genome-wide association study (Alfyrixmet SNP array 6.0) were analyzed to identify correlates RI and Sí. The models were corrected for multiple testing.

Results: Two variants, rs2957692 (p =1.54 10^-13) and rs2957717 (p = 4.24 10^-10), located at 39kb and 53kb upstream the ADM gene were previously identified as independent correlates of MRproADM plasma levels. The minor allele of rs2957692 (G, MAF 0.39) - at high linkage disequilibrium with rs11042725 (R20.657, D’0.881), an upstream functional variant - was associated with higher MRproADM levels and RI and Sí univariate analysis. (figure). After ad- justment on cardiovascular risk factors and plasma levels of MRproADM, such relationship remained significant for Sí (p=0.0005) and almost significant for RI (p=0.06).

Conclusions: The variant rs2957692, near the ADM gene is associated with higher levels of MRproADM and higher markers arterial rigidity. The effect on ar- terial rigidity is independent of MRproADM levels and cardiovascular risk factors. Such finding supports the hypothesis of a possible causal relationship between the variant and atherosclerosis.

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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 allelic 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 85% and 93% compared to WT, respectively), which was mainly attributed to their limited trafficking into the membrane. Furthermore, in the allelic encoding p.D1690N mutation, the p.H558R polymorphism was also detected. Thus, p.D1690N+WT and p.G1748D+WT reduced peak Na+ current density by 80% and 92% compared to WT+WT, respectively. In-recovery from fast inactivation thus, p.G1748D profoundly affected the channel properties of the mutated channels as well as the putative modulator effects produced by the presence of the polymorphism.

Conclusion: We have identified a novel role for the kallikrein-kinin system in the regulation of MR-ProADAM and CT-proET.

NOVEL MECHANISMS AND IMMAGING 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 genome-wide association studies (GWAS). Interestingly, ADAMTS-7 plays a rather 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, the role of ADAMTS-7 in atherosclerosis remains elusive. In this study, we investigated ADAMTS-7 in a murine knockout (KO) model regarding remodeling of injured arteries and metabolic parameters.

Methods: Mice lacking ADAMTS-7 (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 using 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 sinotubular aortae were quantified after Oil-Red-O-staining.

Results: ADAMTS-7 KO mice appeared normal in growth and behavior. After CCAL, arteries of WT-mice displayed significant increases of media surface area (MA), intima surface area (IA) and intima-media ratio (IMR) compared to sham-treated vessels. By contrast, CCAL failed to induce neoformation in ADAMTS-7 KO-mice. IA, MA, external elastic lamina circumference and IMR were all significantly lower in KO-mice. Immunofluorescence directed against COMP only revealed weak fluorescence in injured vessels of WT-mice, whereas no difference between the vessels was visible in KO-mice. After Western diet, blood lipid levels increased in both WT- and KO-mice. Thus, significant differences in weight gain, blood lipid levels or lipid deposition measured as lesion area were not observed between WT- and KO-mice.

Conclusions: We conclude that ADAMTS-7 plays an important role in the pathophysiology of CAD as it seems to be pivotal for remodeling of arteries following vascular injury. The degradation of COMP may be a part of the downstream signaling pathway. Since lack of ADAMTS-7 did not alter metabolic parameters or lipid deposition, we suggest that the association of ADAMTS-7 and CAD involves a remodelling mechanism in the vessel wall itself.

Adventitial inflammation is associated with thin-cap atheromas and expression of matrix-degrading enzymes and occurs in coronary regions exposed to low endothelial shear stress

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Purpose: Vascular inflammation, a critical component of atherosclerosis, is thought to originate from the lumen and infiltrate the intima-media in advanced lesions. Low endothelial shear stress (ESS) is known to induce intima-media inflammation and plaque growth. In this study, we investigated in vivo the role of adventitial inflammation in atherosclerosis and its relation to local ESS.

Abstract S189 Table 1. Summary associated loci

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References (

In vivo detection of activated platelets allows characterization of 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 the 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 detection of plaque rupture in ApoE-/- mice. As the age of 60 weeks were led 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 internal carotid artery for securing the plaque surface. Using 9.4 Tesla MRI was performed before and repetitively after intravenous injection of the contrast agent, Libs-MPIO, at the site of plaque rupture in histology. Further, we extended the plaque rupture in histology. Further, we confirmed significant binding of MPIO-MHR on 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 an important 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 various biomarkers. 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-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 macrophages’ 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 capacities of M2 vs. M1 (increased expression of CD206, p < 0.001). We observed that M1 were antitumorogenic (significantly increased expression of VEGF and TFPI) and produced less proangiogenic activity (significantly increased ratio of MMP-9/TFPII-2, p < 0.05) than non diabetic patients that could explain the higher fragility of plaques currently observed in diabetic patients. TFPI expression in M1 was negatively correlated with age of patients (p = 0.045, r = 0.345), in accordance with the fact that aging is a major risk factor for thrombosis.

Conclusions: These new findings reveal that 2 macrophage subpopulations, M1 and M2, could differentially modulate major pathophysiological processes involved in atherosclerosis and that diabetes and age have a significant influence on macrophages expression profiles.

Serum inflammatory biomarkers and plaque inflammation assessed by [18F]-fluorodeoxyglucose positron emission tomography in the dal-PLAQUE study: a post-hoc analysis by baseline features

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Purpose: Inflammation plays an integral role in atherosclerosis. We investigated the relationship between serum biomarkers of inflammation and plaque inflammation assessed by FDG-PET/CT in a post-hoc analysis of the dal-PLAQUE study of daltecapril, a cholesteryl ester transfer protein modulator.

Methods: Baseline levels of inflammatory biomarkers, as well as maximum standard uptake values (SUVmax), target-to-background ratio (TBRmax), and most diseased segment (MDSmax) quantified by FDG-PET/CT were used in the analysis. The population consisted of 130 patients, on stable lipid-lowering therapy, with coronary heart disease (CHD), or CHD risk equivalents.

Results: Multiple linear regression analysis, adjusting for CHD risk factors, re- sulted in significant associations between MDSmax and MPO-2 (r = 0.27, p = 0.01) and TFPI-2 (r = 0.32, p = 0.001), between TBRmax and MPO-2 (slope 0.18, p < 0.05), and MDSmax (slope 0.19, p < 0.04), while none of the other inflammatory biomarkers (hsCRP, IL-6, sICAM, sVCAM, P-selectin, E-selectin, MMP-3, MMP-9, MPO) were associated with FDG-PET/CT parameters. SUVmax, TBRmax, and MDSmax were significantly lower in the lowest LP-PLA2 mass tertile compared to the highest tertile.

Conclusion: In CHD patients on stable lipid-lowering therapy the correlation of baseline serum LP-PLA2 mass with vessel wall FDG-PET/CT suggests that LP-PLA2 mass may still reflect continued plaque inflammation, in contrast to other biomarkers.
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 ontology. 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-heath and MACE. After adjustment for confounding risk factors by Cox regression 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. Increased HBDT and MACE were independently associated between 90K and CD163 expression in human post mortem coronary arteries (n=19, R=0.4655, P<0.05). Neither 90K nor CD163 were detected in coronary arteries free of atherosclerosis.

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 hemmorhage 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 cardiovascular events (MACE). 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: 7.3-8.8 years). 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: 10.2-10.7 mg/L) for persons with no CV risk factors present versus 6.0 (95% CI: 4.8-7.4 mg/L) for persons with four CV risk factors. In increasing adiponectin concentration was linearly associated with increased risk of CV mortality, MI or stroke and total mortality; each after adjustment for conventional risk factors (p<0.001) and hazard ratio 1.58 (1.35-1.86) <0.001, respectively.

Conclusion: Increasing number of risk factors for CVD is associated with decreased plasma adiponectin, however high plasma adiponectin independently predicts death and MACE in a large community based population. These results confirm the dual expression indicated by previous studies.

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 4.0-7.0 mmol/L were randomized to placebo or pravastatin at 40 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 quintile of D-dimer (n=110, 112-173, 173-273, >273 nmol/L) and adjusted for treatment. Considering conventional risk factors including age, sex, lipids, diabetes, smoking, hypertension and 7 novel biomarkers (BNP, sensTNI, LP(a), LP-PLA2, hsCRP, MR-F, galectin-3) we used multivariable models.

Results: Patients with higher D-dimer were older, more likely had hypertension, be female and be on ACE inhibitors or calcium antagonists. Baseline D-dimer increased at 1 year by 7% on placebo and decreased by 2% on pravastatin (p<0.001). In multivariable risk models, higher baseline D-dimer independently predicted an increased rate of VTE, CHD events (CHD death or MI), major CVD events (CVD death, MI or stroke), and total mortality; each after adjustment for conventional and novel biomarkers. Net reclassification improved by 3.5% for CHD events (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 VTE events for each outcome except VTE.

Elevated D-dimer levels, even after adjustment for traditional and novel risk markers, predicted a wide range of arterial and venous vascular events. The relative benefits of pravastatin were independent of D-dimer levels.

Galectin-3 prediciton for incident heart failure with preserved ejection fraction in the general population: data from PREVEND

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Purpose: Galectin-3 is an emerging biomarker for prognostication in established heart failure (HF). It has been suggested that longstanding increases of circulating galectin-3 underlie myocardial fibrosis. The incidence of HF with preserved ejection fraction (HF-PEF), characterized by myocardial and vascular fibrosis, is increasing in the general population. We studied if baseline galectin-3 is useful in predicting new incident HF-PEF in the general population.

Methods: In 8322 HF-free subjects of the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort (mean age 49±13, 50% male), new incident HF-PEF (according to ESC guidelines) was recorded during a median follow-up of 10 years.

Results: By multivariate regression, higher levels of galectin-3 were independently associated with higher baseline age, female gender, body mass index, HDL cholesterol, C-reactive protein and renal function. During follow-up, 135 subjects were diagnosed with HF-PEF. Subjects developing HF-PEF had a median baseline galectin-3 level of 12.6ng/mL (range 10.0-14.6), compared to 9.0 (9.0-12.9 ng/mL) for subjects free of HF-PEF. In a Cox-proportional hazard model, adjusted for variables associated with galectin-3 along with N-terminal pro-B-type natriuretic peptide, galectin-3 remained independently associated with incident...
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 in 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 PIvUS-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 of ln-GDF-15: 4.0 (95% CI 2.2-7.3; <0.001) with a stronger association to outcome as compared to NT-proBNP or CRP. GDF-15 increased improved diagnostic discrimination and reclassification beyond established cardiovascular risk indicators (IDII=0.030 [p=0.004]; NRI=0.141 [p<0.001]). GDF-15 levels increased by 11.0% 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=0.001) 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=602), 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 F2-value of this model was 0.20. Changes of GDF-15 levels over time emerged also as a powerful predictor of death occurring after the measurements at 75 years adjusted HR for 1-SD of the In-transformed relative difference between GDF-15 levels at 70 and 75 years: 3.6 [2.2-6.0; p<0.001].

Conclusions: 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 pathobiological process that is closely related to prognosis.

Insomnia and risk of cardiovascular disease: a meta-analysis

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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 the 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 following for a time ranging from 3 to 20 years. A total of 6,392 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 (45%) of developing or dying from cardiovascular disease during the follow-up (RR 1.45, 95%CI 1.29-1.62; p<0.0001), 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.

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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 hypertension. A comparison cohort with 16,485 subjects was selected by using propensity score matching (PSM). The end point was the development of AD hypertension. A total of 22,607 patients were analyzed.

Results: AHT prevalence in Ryazan region did not significantly change over 5 years. The number of subjects with grade 3 AHT and women with grade 2 AHT decreased, the number of women with grade 1 AHT increased. The obesity prevalence among AHT patients significantly increased. Progress was seen in the amount of antihypertensive drugs used, the number of effectively treated AHT patients increased (from 13.4% to 21.4%, p < 0.001).

Conclusion: Even if BMI was within normal range, elevated BMI was a predictor of future hypertension in a healthy young- and middle-aged Japanese male population.

Epidemiologic aspects of arterial hypertension: 5-year dynamics of prevalence, risk factors and treatment

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Aim: To study 5-year dynamics of prevalence, risk factors and treatment of arterial hypertension in Ryazan region population.

Materials and methods: In 2002 as a part of Russian epidemiological “EPOCH” study, a representative sample of Ryazan region population was evaluated with 95.3% response rate (2098 subjects, mean age 44.8±18.6 years). Sample generation was made in three steps and included consecutive selection of medical institutions, GP districts and flats. The AHT group included subjects with blood pressure ≥140/90 mm Hg and subjects with normal BP receiving antihypertensive medications. In 2007 1760 subjects (mean age 44.6±17.0 years) were re-evaluated with 83.9% response rate. The dynamics of risk factors prevalence in AHT patients was analysed: smoking, salt and alcohol abuse, obesity, premature cardiovascular disease family history status.

Results: AHT prevalence in Ryazan region in the assessed period didn’t change (36.6% in 2002, 39.3% in 2007, p = 0.07). Age-adjusted prevalence of AHT was higher in women than in men as in 2002 (38.2% vs. 33.9%, p = 0.05) and in 2007 (42.1% vs. 34.8%, p = 0.001). Part of women with 1st grade AHT increased from 23.1% to 30.8%, p = 0.001, in men it remained unchanged. 2 grade AHT prevalence in women decreased from 20.5% to 15.5%, p = 0.01, in men it remained unchanged. Part of women with 3rd grade AHT decreased from 9.3% to 3.8%, p = 0.001, in men - from 3.8% to 2.0%, p = 0.05. Obesity prevalence in patients with AHT increased from 25.5% to 47.8%, p = 0.001. Prevalence of smoking (18.6%), alcohol (7.2%) and salt (37.7%) abuse, premature cardiovascular disease family history status (58.8%) didn’t change as compared with 2002 (17.3%, 6.1%, 39.5%, 62.7% respectively). The number of patients taking antihypertensive medications increased from 64.7% to 84.0%, p = 0.001. The number of subjects decreased in all three categories: “take medications intermittently” (20.2% to 12.3%, p = 0.001), “only when BP is elevated” (29.6% to 16.2%, p = 0.001), “take no medications at all” (35.3% to 16.0%, p = 0.001). The number of patients who reach target BP increased from 7.5% in 2002 and from 7.5% to 25.0%, p = 0.001 in women.

Conclusion: The AHT prevalence in the representative sample of Ryazan region did not significantly change over 5 years. The number of subjects with grade 3 AHT and women with grade 2 AHT decreased, the number of women with grade 1 AHT increased. The obesity prevalence among AHT patients significantly increased. Progress was seen in the amount of antihypertensive drugs used, the number of effectively treated AHT patients increased (from 13.4% to 21.4%, p = 0.001).

Cardiovascular risk factors and target organ damage in Greek hypertensives

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Purpose: Cardiovascular (CV) risk factors (RFs) and target organ damage (TOD) are common in hypertensives. The aim of this study was to determine RFs and TOD clustering in Greek hypertensives stratified by gender and age.

Methods: A large cohort of 21280 adults with uncomplicated hypertension (mean age 57.6 years, 53.1% males, mean office blood pressure 165±100.4 mmHg) was studied. Serum glucose, cholesterol (total, HDL), triglycerides, apolipoproteins 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 35% for males and 6% for females while in high risk (≥20%) 69% and 51% respectively (p = 0.001). Mean HS risk was 8% for males and 6% for females while in high risk (≥5%) were 49% and 36% respectively (p = 0.0001). Age was correlated to pulse pressure, eGFR, LVMI and CV risk in both genders (p = 0.0001). Ageing increased the risk difference between genders (Figure) for total (p = 0.001) but not for fatal events (p = NS). 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 HS, p<0.001 for both).

Conclusions: RRs tend to cluster in hypertensives, the calculation of CV risk should guide treatment decisions.

Gene-gene interactions among hypertension related age- and gender-specific distribution of arterial RBBB, Prevalence, risk factors and outcome in the

Purpose: Essential hypertension (HT) is considered to be the result of the interactions of many genes and environmental factors, with each gene only having a small effect. Although case-control association studies can provide a powerful approach for detecting genetic variations, especially single nucleotide polymorphisms (SNPs), few studies have considered their interactions or epistasis concurrently. The aim of this study was to evaluate SNP-SNP interactions between candidate genes by comparing the effects of each SNP alone with the combined effects of the two SNPs on HT.

Methods: We investigated five SNPs of Paraoxonase1 (PON1 rs662), Tumor necrosis factor receptor superfamily, member1B (TNFRSF1B rs5051), Adrenergic beta-3-receptor (ADRB3 rs4994) and Angiotensinogen (AGT rs5030) in a case-control study. Recruited were 189 HT patients and 115 healthy controls who live in town of Waku, agricultural area, Japan. Diagnosis of HT was based on blood pressure ≥140/90 mmHg. Genotyping was performed in a Medical University. The effects of each SNP alone and combinations of two SNPs on HT were analyzed by logistic regression models. The strength of the associations or effect size was estimated by odds ratios (ORs). The OR of SNP alone was calculated by using homzygous non-risk genotype as reference. To assess joint ORs for the 2 genotypes combined, we subjected the data into 9 strata according to the cross-classified genotypes. We then obtained the ORs for each of the strata relative to the first stratum defined by non-risk genotype for both genes.

Results: The OR of the homzygous risk genotype for PON1 alone was 3.20 (95%CI 1.60-6.38) and for TNFRSF1B alone was 1.43 (0.76-2.70), while the joint OR of highest-risk genotype (presence of homzygous risk alleles for both genes) was 5.25 (1.36-20.2). The OR of the homzygous risk genotype for NYPI alone was 1.76 (0.83-3.33) and the joint OR of highest-risk genotype for PON1-NYPI was 5.78 (1.50-22.2). The OR of the homzygous risk genotype for ADRB3 alone was 12.4 (2.09-73.2). The OR of the homzygous risk genotype for AGT alone was 2.72 (0.82-9.05) and the joint OR of highest-risk genotype for PON1-AGT was 24.8 (2.56-241).

Conclusions: SNP-SNP interactions between PON1 and ADRB3 and between PON1 and AGT may lead to higher risk on hypertension in Japanese population.

Left ventricular mass, aortic stiffness and smoking status: a smoking gun in hypertension

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Purpose: Hypertension is associated with increased left ventricular (LV) hyper trophy mass and aortic stiffness, which are both predictors of cardiovascular risk. Smoking is an essential modifiable cardiovascular risk factor with pathophysiological link to both aortic stiffness and LV hypertrophy. We investigated the possible effect of smoking status on LV mass and aortic stiffness in never treated hypertensives.

Method: We enrolled 1223 consecutive essential hypertensives (mean age 53+12 years) with and without known cardiovascular disease (CVD). We classified them as current smokers (n=508), ex-smokers (n=109), and non-smokers (n=506). Left ventricular mass index (LVMI) was assessed by echocardiography. LV mass imaging was used for wall-thickness measurements. LVMI was calculated using the Devereux formula. Aortic stiffness and wave reflections were assessed with pulse wave velocity (PWV) and augmentation index (AIx) that were estimated with the Complior and Sphygmocor device, respectively. Ten-year risk of fatal CVD was estimated with SCORE. Statistical analyses were performed by means of 1-way ANOVA and ANCOVA.

Results: Smoking status exhibited significant positive association with LVMI, PWV and AIx, which were independent of age, gender, mean blood pressure, body-mass index, diabetes mellitus, low-density lipoprotein and C-reactive protein (p<0.001 for all). After adjustment for the aforementioned confounders ex-smokers showed lower risk to smokers and non-smokers had higher PWV levels (8.45 vs. 8.13 m/s [p=0.04] and 7.85 m/s [p<0.001], respectively) and higher LVMI (119.7 g/m² vs. 116.4 g/m² [p=0.016] and 113.6 g/m² [p<0.001], respectively). Moreover, smokers had higher PWV and LVMI compared to non-smokers (both p<0.001). Smokers had higher AIx compared to ex-smokers and non-smokers (30.5% vs. 25.9% and 26.5%, respectively, both p<0.001). Similarly, smokers had higher 10-year risk for fatal CVD compared to ex-smokers and non-smokers (8.17% vs. 7.95% and 7.98%, respectively, both p<0.001).

Conclusions: Smoking is closely related with LVMI and arterial stiffness. Ex-smokers despite having similar 10-year risk for fatal CVD with non-smokers, demonstrate slightly higher aortic stiffness and LV mass, implying a need for further derisement of risk by SCORE. Thus, measurement of aortic stiffness and LV mass could improve risk stratification in ex-smokers hypertensives.

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Age- and gender-specific distribution of arterial stiffness in the population and its association with global cardiovascular risk: results from the population-based Gutenberg Health study

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Purpose: Arterial stiffness (AS) determined by digital volume pulse analysis using stiffness index (SI) might represent a low-cost and an 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 determinations. 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; 14.9-16.1; 16.1-17.0; >17.0 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 (7.65 vs 9.68 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/W)=0.93/0.43; both p<0.0001), followed by hypertension (β (M/W)=0.74/0.40; both p<0.0001). Additional correlates included dyslipidemia in both genders (β (M/W)=0.27/0.31; p=0.047 for M and p=0.006 for W) and obesity in men only (β=0.36; p=0.04). After additional adjustment for CV risk factors, smoking associations and hypertension remained positively and independently associated with SI in both genders (β (M/W)=0.99/0.40 and 0.80/0.35; both p<0.0001). Furthermore, a strong correlation of SI with the German EURO-Score (SI×0.409.38) and with the Framingham general CVD risk score (M/W×0.420.39) was found. Finally, a significant increase in SI was observed throughout the groups 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 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 prognostic value 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 theCopen-
The importance of global economic level on AMI outcomes. Data from the Euro Heart Survey 2009 AMI snapshot.


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Background and aim: There are important differences in the management and outcome of patients with AMI throughout member countries of the ESC. We sought to determine the impact of a global economic indicator (gross domestic product, GDP) on in-hospital mortality and major complications in 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 over a very brief period of time (one week, 7.13 December 2009); 47 member countries participated, with 485 active centres + all centres participating in the MINAP and Swedish registries. GDP and national health expenditures figures were retrieved from OECD, IMF, WHO and World Bank statistics.

Results: Death and death, re-MI or stroke rates decreased by quartiles of GDP: 9.9 vs 5.7 vs 5.6 vs 4.0%, and 13.2 vs 8.8 vs 8.1 vs 5.1% (P <0.001), respectively; likewise, death decreased by quantities of nation health expenditures per capita: 9.1 vs 6.8 vs 4.5 vs 4.4% (P<0.001). Conversely, the use of PCI increased by quantities health expenditures (29 vs 65 vs 59 vs 81%, P<0.001), but was similar in the 3 upper quartiles of GDP (28 vs 71 vs 65 vs 69%). Multivariate logistic regression analysis showed that health expenditure per capita was not an independent predictor of in-hospital major events, whereas a progressive decline in the rate of events was observed with increasing GDP adjusted OR (95%CI) at 1st quartile of GDP: 2nd quartile: 0.68 (0.95-0.50-0.93), 3rd quartile: 0.60 (0.43-0.85), 4th quartile: 0.43 (0.28-0.65).

Conclusion: These results indicate that wealthier countries have lower death and complication rates in patients hospitalized for AMI. In contrast, the level of health expenditures per capita is a poorer indicator of in-hospital complications, suggesting that higher levels of health expenditures are not necessary to achieve optimal treatment of AMI.

The 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 28,557 participants followed up for a mean of 55.37±6.33 weeks were included. A significant reduction in GFR was detected in placebo-treated compared to statin-treated patients (standard mean difference [SMD] 0.056, 95% confidence interval [CI] 0.028 to 0.083, comparison p<0.01, heterogeneity p=0.376). In particular, a significant reduction in GFR was detected in placebo vs roaten-treated to R-treated patients (SMD: 0.052, CI: 0.022 to 0.081, comparison p=0.001, heterogeneity p=0.075). No significant difference in GFR was detected in 3 head-to-head studies (1414 patients) comparing A to R (SMD: 0.000, CI: -0.017 to 0.017, comparison p=0.533, heterogeneity p=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]: 0.656, CI: 0.440 to 0.977, comparison p=0.038, heterogeneity p=0.026), but this effect was not longer significant when studies using highest therapeutic doses of R (40 mg/daily) were excluded from analysis, abolishing significant heterogeneity (OR: 1.505, CI: 0.827 to 2.739, comparison p=0.181, heterogeneity p=0.473).

Conclusions: A and R show similar nephro-protective effects in patients at high risk, with comparable effects on new proteinuria onset when commonly used doses are considered.
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 retrospectively 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. 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) and remained stable at weeks 56 and 78 evaluations (7.3% and 8.2%, respectively). There were no concomitant changes in bilirubin or alkaline phosphatase. 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 therapies, including aspirin.

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 a 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 aminotransferases between 5 and 11x 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 0.9 ± 1.0% at baseline, 9.0 ± 7.9% 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.

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 hypertension (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.

Results: The cohort included 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 1000 patient-years, vs 11.2 CV deaths per 1000 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, 0.90-1.01; 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, P 5%). Perioperative-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.

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 for 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 (3,526 patients) were involved in the meta-analysis. Period of clinical follow-up ranged from 9 to 12 months.
Impact of positive airway pressure therapy for lifestyle traits predict the development of cardiovascular disease and sleep-disordered breathing

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Background: The aim of this observational study is to determine whether positive airway pressure (PAP) therapy affects the long term outcomes of patients with cardiovascular disease (CVD) and sleep-disordered breathing (SDB).

Methods: We studied 1693 consecutive patients who underwent polysomnography from November 2004 to July 2011, and enrolled 351 patients who had been admitted to hospital because of CVD before polysomnography. They were divided into three groups; a mild SDB group as apnea-hypopnea index (AHI) <15/hour and treated with PAP (AHI <15/hour and treated with PAP devices), the untreated SDB group (AHI <15/hour and untreated with PAP) and the PAP-treated group (AHI >15/hour and treated with continuous positive airway pressure or adaptive servo ventilation) and a 44% reduction in in-segment/in-stent restenosis (P <0.01) and lower in-segment/in-stent late loss (P <0.01).

Conclusions: Combined with conventional to conventional DATT reduced the incidence of MACE. TFR 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 have an increase 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 immunometric method, respectively.

Results: At T2, we observed a significant increase of EPCs (p<0.001), VO2 peak, Watt max HDL-cholesterol (p<0.001) 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.

Conclusion: 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 or without atrial fibrillation

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Background: CHADS2 is a widely used 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 7,515 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).

Conclusion: The CHADS2 score is a useful predictor for serious outcome of death, stroke and myocardial infarction within a year no matter whether the patients are with or without atrial fibrillation.

Lifestyle traits predict the development of hypertension: a large prospective population-based cohort study in Finland


Purpose: To examine whether the five major CVD related lifestyle traits – smoking, alcohol consumption, physical activity, obesity and consumption of vegetables – predict the future development of clinical hypertension and need of antihypertensive drug treatment.

Methods: Study cohorts included 9,637 Finnish men and 11,430 women who were 25 to 74 years of age and free of hypertension at baseline. Baseline measurements were done in 1982, 1987, 1992, 1997 and 2002, and included a self-administered questionnaire on medical history and health related lifestyle traits. Height, weight and blood pressure were measured using standardized methods. Healthy lifestyle traits were defined: (1) no smoking, (2) alcohol consumption less than 50g per week, (3) leisure time physical activity at least 3 times per week, (4) daily use of vegetables, and (5) normal weight (BMI<25). Data on the development of hypertension during the follow-up were obtained from the national register on persons entitled to special reimbursement for antihypertensive drugs. Cox proportional hazards regression models were used to examine the associations between the number healthy lifestyle traits and development of hypertension.
Lifestyle modification and risk factor management for cardiovascular 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 ≥93% of all entitled employees at an age of 40+ years in the first round (“FIT1”). We report the results of 312 men and 223 women, who completed the second round (“FIT2”) 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 14.1/6.5 mmHg in men (p<0.001) and 16.6/5.1 mmHg in women (p<0.001). BP control rates in known hypertensives rose from 28.6% 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 -0.81 [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 factors and prevalent coronary artery disease) was lowered in FITback by 14.1/6.8 mmHg in men (p<0.001) and 16.6/5.3 mmHg in women (p<0.001). BP control rates in known hypertensives rose from 28.6% 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 -0.81 [p<0.002] in men and -1.67 [p<0.001] in women).

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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 (FIT1).

<table>
<thead>
<tr>
<th></th>
<th>FIT 1</th>
<th>FIT recall</th>
<th>Abs. RR</th>
<th>Rel. RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>7.73%</td>
<td>6.15%</td>
<td>2.05%</td>
<td>-28.56</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Woman</td>
<td>2.23%</td>
<td>1.65%</td>
<td>0.56%</td>
<td>-25.11</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

Figure 1. Fit in Life-Fit on the Job-Project

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

Association of thoracic aortic calcification with incident myocardial infarction and all-cause 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. Adjust-
ment was performed for traditional 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, height, use of antihypertensive medication, diabetes, lipids and smoking were less predictive with use of 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 the 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; 1.13]) but not for coronary events (HR [95%CI]: 0.97 [0.90; 1.05]). Adding Log[TAC+1] to the model containing traditional risk factors and CAC, there was a trend for improvement of Harrell’s C indices for all-cause mortality (0.741 to 0.743, p=0.5) but not for coronary events (0.773 to 0.772, p=0.6).

Conclusion: TAC is associated with incident myocardial infarction and all-cause fatal events independent of traditional cardiovascular risk factors and CAC-score in a general population. TAC does not significantly further improve risk prediction over CAC in coronary events. However, the predictive value of TAC complements prognostic information above CAC-score and cardiovascular risk factors regarding all-cause mortality.

Fatter - but fitter? Leisure time physical activity and estimated peak oxygen uptake in a Norwegian population 1946-2008. The Nord-Trondelag Health study (HUNT 1-3)

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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.

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 traditional cardiovascular risk factors and ancillary for CAC-score. A potential predictive value of TAC was assessed using Harrell’s C index.
INVESTIGATIONS FOR BETTER HEALTH CARE

S520 Short TTerm Psychotherapy In Acute Myocardial Infarction (STEP IN AMI) Trial. Final results from a randomized trial
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On behalf of STEP IN AMI trials. 1S. Filippo Neri Hospital, Rome, Italy; 2Tilburg University, CORPS Center of Research on Psychology in Somatic diseases, Tilburg, Netherlands; 3University of Antwerp Hospital (Edegem), Department of Cardiology, Antwerp, Belgium

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 emergency 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 (MT group: 54 pts). STP consisted of individual and group meetings up to 6 months after AMI. Clinically 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 (personal)were scheduled after AMI and at 1 year. The primary endpoints of the study were the incidence of new cardiac events (re-infarction, death, stroke, life-threatening ventricular arrhythmias and recurrence of angina) and the occurrence of new medical pathologies. Secondary end-points were the incidence of re-hospitalisations due to cardiacological problems, the prevalence of pts with New York Heart Association class >2 and psychometric tests score in the two groups at follow-up.

Results: Six pts were lost to follow up after one year. The two groups were similar concerning baseline risk factors, psychometric test scores, clinical characteristics, echocardiographic and cath-lab variables.

At 1 year follow up, STP group showed a statistically significant lower incidence of primary composite cardiovascular end-point and mental endpoint, as compared to MT group (16/54 pts vs. 27/47, p=0.006; and 7/54 pts vs. 29/47, p=0.001, respectively). Only one patient in STP group showed a NYHA class >2, while 9/47 pts of MT group were in such a functional class (p=0.001). STP group also had a statistically significant lower incidence of re-hospitalisation due to cardiacological problems (34 events/54 pts in the SPG; 54 events/47 pts in the CG; p=0.04).

At 1 year follow-up STP group showed a statistically significant reduction in depression level as compared to CG (BDI=6.2±4.4; BDI=10.6±10.0, respectively; p=0.02).

Conclusions: Our data show that short term psychotherapy, performed early after optimally treated acute myocardial infarction, improves prognosis at 1 year follow-up.

S523 Long term effects of an integrated educational and psychosocial intervention in patient-partner dyads affected by heart failure
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Aim: To evaluate an integrated care programme that combined education and psychosocial support on (1) time to first event in patients with chronic HF and (2) on perceived health, control and knowledge and symptoms of depression in patient: partner dyads.

Method: A two centre randomized controlled design was used with follow-up after 3, 12 and 24 months. The intervention group (n=71 patients-partners dyads) participated in an integrated care intervention with education and support delivered in three modules through nurse-led face-to-face counselling, a computer based program and written materials. The usual intervention was the usual intervention. The intervention was evaluated regarding perceived health (SF-36), depressive symptoms (Beck Depression Inventory), Knowledge on HF (RAND) and perceived control (Control Attitudes Scale). According to the hierarchical structure with patient and partner nested in dyads and different cardiology departments, multilevel modelling was used to evaluate the intervention.

Kaplan-Meier survival curves were used to analyse time to first event and knowledge was analysed using marginal homogeneity test. Findings: The sample consisted of 155 patients and their partners. The patient mortality rate over the follow up period was 22%. The mean age was 70.1 years (SD=11.5) and 53% had NYHA class III. There was no difference between the groups in time to first event. Perceived control (p=0.001) and mental health (p=0.05) improved significantly over time in both the control and intervention group. The intervention group scored higher levels of physical health (p=0.025) than the control group, but it did not differ over time. The level of depressive symptoms was consistent over the follow up period and no differences were detected between the groups. Patients scored significantly lower health and more depressive symptoms (p=0.001) than the partners, but
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).

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.

### Table 1: Baseline Characteristics of European Countries

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAFETY</th>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.0±11.0</td>
<td>71.0±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 CHAD2c risk score</td>
<td>1.9±1.3</td>
<td>2.1±1.1</td>
<td>3.48±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 MI (%)</td>
<td>26.4</td>
<td>16.8</td>
<td>16.6</td>
<td>14.5</td>
</tr>
<tr>
<td>Diabetes (%)</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>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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.

### Table 2: Comparison of Study Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SAFETY</th>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.0±11.0</td>
<td>71.0±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 CHAD2c risk score</td>
<td>1.9±1.3</td>
<td>2.1±1.1</td>
<td>3.48±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 MI (%)</td>
<td>26.4</td>
<td>16.8</td>
<td>16.6</td>
<td>14.5</td>
</tr>
<tr>
<td>Diabetes (%)</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>
<td>–</td>
<td>–</td>
</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.
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.


**Background:** According to the Joint ESC/ACC/AHA/WHF Task Force, Tn is the preferred biomarker 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 12/31/09) were evaluated. A group of 2401 patients normal serial Tn and CKMB; mean age 57.33 years, males 45.22%, Caucasian 72.11%, African-American 22.38% and Group 2 (401 patients) normal serial Tn and elevated CKMB; mean age 58.33 years, males 72.62%, Caucasian 67.58%, African-American 27.43%.

**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:** Our study suggests that elevated CKMB in the absence of elevated troponin did not influence further management decisions. CKMB is reimbursed by Medicare in the United States of America at $9.17 per test. With 6 million ED visits per year for chest pain this amounts to saving hundreds of millions of dollars in healthcare expenditure.

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**UPDATE ON CARDIOPROTECTION IN EXPERIMENTAL STUDIES**

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

G. Vlahou1, L. Casani1, O. Juan Babilo2, J. Guerra2, L. Badimon1. 1Barcelona Cardiovascular Research Center (CSIC-ICCC), CiberOBEN, IIB-Sant Pau, Hosp Sant Pau, UAB, Barcelona, Spain; 2Department of Cardiology, University Hospital Sant Pau, Hosp Sant Pau, UAB, Barcelona, Spain; 3Hospital de la Santa Creu i Sant Pau, IIB Sant Pau, Department of Cardiology, Barcelona, Spain.

**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 response 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 (R), followed for 21 days with the same regime (HC/R+ and NC/R+, respectively). A group of HC animals was sacrificed after ischemia without revascularization (HC) or regular chow (NC) before balloon-induced MI and, upon revascularization (HC/R+ and NC/R+, respectively). A group of HC animals was sacrificed after ischemia without revascularization (HC) or regular chow (NC) before balloon-induced MI and, upon revascularization (HC/R+ and NC/R+, respectively).

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**Preliminary Observations:** PKA preferentially phosphorylates TnT in vitro. In vivo, PKA activity is increased in the infarct zone. PKA activation was associated with a reduction in infarct size and preservation of systolic function. These data suggest that PKA might be a therapeutic strategy to protect the aged heart.

**Conflict of Interest:** No conflict of interest declared.

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before reoxygenation and was maintained during the first 10min 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 (65.6±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 (ir-reversible) delayed mPTP 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 io-dide. 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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### Methods and Results:

**Objective:** To evaluate the effects of ghrelin on cardiac arrhythmias and myocardial injury in a MI setting. **Methods:** Male Sprague-Dawley rats were exposed to a 30 minute ischemia followed by reperfusion. Infarct size was assessed morphologically and by MRI. After 30 min of ischemia, P66Shc−/− mice showed elevated serum levels of cTnI. P66Shc−/− mice showed elevated serum levels of cTnI compared to WT controls at 24 h of reperfusion (27±3.5 vs. 11.3 ng/ml). Infarct size was assessed morphologically and by MRI. After 30 min of ischemia, P66Shc−/− mice showed marked larger infarcts as compared to WT (infarct size [%] 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±3.5 vs. 11.3 ng/ml, n=12, p < 0.05). However, by increasing ischemia duration to either 45 or 60 min, the difference was no longer observed between P66Shc−/− and WT mice.

**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 reperfusion injury via nitric oxide in canine hearts.

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

**Background:** Vasal nerve stimulation has been postulated to confer an anti-fibrillatory 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 nerve activity in rats after acute myocardial infarction (MI). Second, we evaluated the effect of ghrelin on autonomic nerve 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.

**Conclusions:** An infusion as RNP augmented cardioprotective effects of TEMPO against ischemia and reperfusion injury via NO-dependent mechanisms in canine hearts with minimal unfavorable hemodynamic effects. RNP could be promising for developing new therapy for acute myocardial infarction patients.
Betablocker use in patients with chronic pulmonary disease during acute phase of myocardial infarction.

Visits-to-visit variability in low density lipoprotein-cholesterol (LDL-C) levels is a strong predictor of coronary events, independent of mean LDL levels. 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.

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 administration and 2534 patients to control). Up to 6 months, PPI administration showed a similar incidence of all-cause death (odds ratio (OR): 1.03, 95% confidence interval (CI): 0.85-1.03, p=0.91), myocardial infarction (OR: 1.10, 95% CI: 0.58-2.09, p=0.77), or stroke (OR: 0.97, 95% CI: 0.31-2.99, p=0.96) 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 atherosclerosis.

Visit-to-visit variability in low density lipoprotein-cholesterol and risk of cardiovascular outcomes: insights from the treating to new targets trial

Visit-to-visit variability in achieved LDL levels was evaluated using LDL measurements from 3 months onwards from randomization. Various measures of LDL variability were used: Standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM), and average successive variability (ASV). Primary outcome was a composite coronary events (composite of nonfatal MI, fatal CHD, nonfatal and fatal heart failure, and new onset angina).

Results: Among the 9572 patients included in the analysis, SD and ASV were significantly lower with AT 80 mg when compared with AT 10 mg (SD:12.03 vs. 12.52±7.43, P = 0.005; ASV: 12.84±10.48 vs. 13.76±8.69, P < 0.0001). For each 1 SD increase in LDL variability, the risk of composite coronary event increased by 9-18% even after adjusting for treatment or mean LDL levels (Table).

Conclusions: In subjects with coronary artery disease, visit-to-visit variability in LDL cholesterol levels is a strong predictor of coronary events, independent of mean LDL levels.

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

Conclusion: In subjects with coronary artery disease, visit-to-visit variability in LDL cholesterol levels is a strong predictor of coronary events, independent of mean LDL levels.

Preventive effect of statin pretreatment on contrast-induced nephropathy in patients undergoing coronary angioplasty: propensity score analysis from multi-center registry

Objectives: We investigated whether the statin pretreatment prevent CIN in coro-
Predicators of non-adherence to dual platelet therapy after percutaneous coronary intervention in a large multinational registry

Z. Sergei1, U. Baber1, A. Chiffo2, S. Sarton1, D.J. Cohen3, C.M. Gibson4, G. Weiss5, B. Witzenbichler6, A.C. Colombi7, R. Mehran8, R. Pirozzi9,10,11 on behalf of PARIS Investigators. 1Mount Sinai School of Medicine, Department of Cardiology, New York, United States of America; 2San Raffaele Hospital, Department of Cardiology, Milan, Italy; 3St. Luke’s Mid America Heart Institute, Kansas City, United States of America; 4Beth Israel Deaconess Medical Center, Boston, United States of America; 5Columbia University Medical Center, New York, United States of America; 6Charite - Campus Berlin Buch/Experimental & Clinical Research Center, Department of Cardiology, Berlin, Germany; 7Mount Sinai Medical Center and the Cardiovascular Research Foundation, New York, United States of America

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

Methods: This analysis was derived from the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients) registry, a multicenter prospective trial 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, comorbidities, 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 40.8% 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 surgery (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 be reliably used to assess long-term risk in stable CAD patients to monitor treatment benefit and target patients for more invasive prognostic tests.

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 (VSA). However, to apply these predictors in clinical practice, the assessment of their accumulation in individual patients is important. We thus aimed to develop a novel clinical risk prediction score for VSA patients for better practice.

Methods: The VSA database of the multicenter registry study by the Japanese Coronary Spasm Association (n=1,429; median 66 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=713), intermediate (score 4-6, n=469) 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
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


1Herzzentrum Ludwigshafen an der Universität Heidelberg, Ludwigshafen am Rhein, Germany; 2Herzzentrum Ludwigshafen, Ludwigshafen, Germany; 3Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Ludwigshafen, Germany

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 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 be referred 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, 95% CI 0.77-1.31).

Conclusion: About half of the patients with stable AP and first angiographic diagnosis of CAD in Germany were treated interventionaly. 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 transthoracic Doppler echocardiography.

Results: CBFR to adenosine is shown in the figure. Early after PCI, patients with EST-induced ST-segment depression (STD) ≥1 mm (n=11, 38%) had a lower CBFR to adenosine compared to those without STD (1.65±0.4 vs. 2.1±1.0, respectively, p=0.003). At 3-month and 6-month follow-up EST-induced STD 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 acetylcholine 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.

Conclusions: 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.

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) <10% 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: 522 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 revascularisation 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 36.5% 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 of them are MACE events. 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 35 °C established after 436 minutes in patients 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=0.02) 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 adjunct inotropic 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**


Methods: 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 valuvar timing by ultrasound. Brachial cuff pressure was used to study 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: There was a strong correlation between regional glucose uptake and regional work. These findings indicate that non-invasively estimated LV pressure-strain loops reflect regional metabolism in patients with LBBB.

**5256**

**Patients with arrhythmogenic ventricular dysplasia and preserved left ventricular ejection fraction are characterised by abnormalities in left global strain measures**

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Background: Two-dimensional (2-D) speckle tracking analysis is considered a new useful tool in order to evaluate both right (RV) and left (LV) ventricular function. The aim of this study was to evaluate the presence of abnormalities in global 2-D strain measures of LV ventricle in a group of patients with arrhythmogenic RV dysplasia/cardiomyopathy (ARVD/C) with preserved left ventricular ejection fraction (LVEF).

Methods: We enrolled 15 patients with ARVD/C with LVEF > 55% (87% males, 45±16 years) and 25 controls (88% males, 45±11 years). RV focused 4 chamber view was analysed by 2-D speckle tracking technique (EchoPAC, GE) to evaluate RV systolic strain (RV sS) and strain rate (RV sSR) and early diastolic strain rate (RV eSR). Standard echocardiographic long-axis, 4- and 2-chamber views (frame rate 50-70/sec) were also obtained in order to calculate global systolic strain (LV sS), global systolic (LV sSR) and global early diastolic (LV eSR) strain rate.

Results: As expected, patients with ARVD/C in comparison with controls were characterised by a significant reduction of RV sS (-21.2±3.2 vs. -24.6±2.8%, respectively, p<0.001), RV sSR (-1.0±0.2 vs. -1.3±0.2 sec⁻¹, respectively, p=0.001) and RV eSR (-0.0±0.4 vs. -1.3±0.2 sec⁻¹, respectively, p=0.001). When LV was considered no difference was found in terms of LVEF, whereas a significant reduction of strain parameters reflecting systolic function was observed (Figure). No significant difference was found between two groups when LV eSR was analysed.

Conclusions: Patients with ARVD/C and preserved LVEF are characterised by mild abnormalities of both right and left systolic strain measures, thus suggesting the possible usefulness of 2D strain technique to better evaluate the function of both ventricles in patients with ARVD/C.
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 a 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 follow-up of 7.9 months (interquartile range 2-96 months).

Results: Baseline mean LV ejection fraction was 51 ± 11%. Median LV dyssynchrony value was 49 ms (26-85 ms) before RVA pacing and increased to 91 ms (12-85 ms) 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 (logrank P < 0.001) and the composite end point of HFH and death (logrank P < 0.001) compared to patients without induction of LV dyssynchrony (LV dyssynchrony < 91 ms) after RVA pacing (see figure).

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 a1R agonists, however, is limited by undesirable actions of full agonism such as bradycardia. We examined the effects of capadenso (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 where 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 aerobic power (AP) were measured before (PRE) and 3 months after (POST) therapy. LV tissue obtained at POST was used for histomorphometry to assess volume fraction of interstitial fibrosis (VFIF), capillary density (CD), myocyte cross-sectional area (MCSA), and oxygen diffusion distance (ODD). LV tissue from 6 normal (NL) dogs was used for histology.

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 VFIF, ODD and MCSA and decreased oxygen diffusion distance.

Conclusion: CFHF 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

Long term outcome of high-urgency heart transplanted patients with and without temporary ventricular assist device support


Introduction and Objectives: The use of short term ventricular assist devices (VADs) 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 data base 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, 56 (23%) were HU-HTx, 19 were HU 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), Abomed (9) and ECMO (1). After a mean follow-up of 4.6±4.1 years (0-13 y), 22 patients died (5 in VAD-group and 17 in the non-VAD group). The post-HTx 12-month survival rate was 62% 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.

**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.

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**5261 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 (MSNA) in patients with HF. However, there are no specific data about effect of ASV compared with continuous positive airway pressure (CPAP) on MSNA. The aim of this study was to compare the efficacy of ASV to CPAP in patients with HF.

**Methods:** Forty-eight patients with HF (ejection fraction < 0.45, obstructive sleep apnea index < 5.0/hr, NYHA I, II and III) were assigned to either ASV (n=32) or CPAP (n=16). MSNA, heart rate, blood pressure, respiration (using electrical bioimpedance) and oxygen saturation level were monitored continuously before and during application of the devices (30 min). Severity of inspiratory 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 (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 degree of clinical effectiveness between ASV and CPAP.

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**5262 Implantable cardioverter-defibrillators in ventilator assist device-supported heart failure patients**


**Purpose:** Implantable cardioverter-defibrillators (ICD's) reduce mortality in heart failure (HF). In patients requiring a ventilator 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, 90% 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/y; P=0.06). Mean time to first shock after VAD implant was 129±109 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 no ICD support when appropri- ate 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 venicular unloading, but appropriate ICD shocks still occur in VAD patients. An ICD is associated with improved survival in LVAD-supported HF patients.
weeks. Echocardiogram and invasive hemodynamic assessment to determine LV ejection fraction (LVEF) and +dP/dt, respectively, and blood sampling to measure serum norepinephrine (NE) and B-type natriuretic peptide (BNP) levels as baseline, immediately after MI (post-MI), at MI+HF and at 10wks follow-up.

**Results:** Echocardiogram showed significant increase in LVEF and +dP/dt at 10 wks in both intermittent SCS group and continuous SCS group as compared with control group (P<0.05, Figure 1). However, there were no significant differences in LVEF and +dP/dt between intermittent vs. continuous SCS group (P>0.05, Figure 1). Nevertheless, only continuous SCS group had significant decreased in serum NE and BNP at 10wks as compared with control group (P<0.05, Figure 2).

**Conclusions:** In porcine model of ischemic HF, addition of either intermittent or continuous SCS to medical therapy improves LV contractile function compared with medical therapy alone. However, continuous SCS, but not intermittent SCS is associated with significant reduction of serum NE and BNP compared with medical therapy alone.

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## MODIFYING PROGNOSIS IN HEART FAILURE

### 5266 Use of evidence-based therapy and survival in heart failure with reduced ejection fraction 2002-2011

- **T. Thorvaldsen,** L. Benson,** U. Dahlstrom,** M. Edner,** L. H. Lund**
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**Purpose:** In heart failure with reduced ejection fraction, drug and device therapy reduce mortality. Older studies suggest increasing adoption of evidence-based therapy over time concurrent with declining mortality. However, contemporary trends in therapy and mortality are unknown.

**Methods:** We studied 20,384 unique patients with New York Heart Association class I-V and ejection fraction < 40% registered in the Swedish Heart Failure Registry between 2002 and 2011. We assessed utilization of evidence-based therapy and 30-day and 1-year mortality over time with standardized mortality ratios according to the baseline characteristics in 2008-2009.

**Results:** The results are depicted in the table.

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<tr>
<td>Therapy, % and 95% CI</td>
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<tr>
<td>ACEI and/or ARB</td>
<td>89 (81-96)</td>
<td>89 (85-93)</td>
<td>90 (87-93)</td>
<td>91 (88-93)</td>
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<tr>
<td>Beta-blockers</td>
<td>88 (80-96)</td>
<td>89 (85-92)</td>
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<tr>
<td>Aldosterone antagonist</td>
<td>38 (34-45)</td>
<td>39 (38-43)</td>
<td>38 (35-39)</td>
<td>32 (31-34)</td>
<td>31 (28-32)</td>
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<tr>
<td>CRT</td>
<td>1.9 (1.3-2.6)</td>
<td>2.5 (2.2-2.7)</td>
<td>4.4 (3.6-5.4)</td>
<td>4.0 (3.4-5.6)</td>
<td>4.7 (3.2-4.9)</td>
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<td>ICD</td>
<td>1.8 (1.0-3.5)</td>
<td>3.2 (2.9-4.5)</td>
<td>4.6 (4.2-5.6)</td>
<td>4.7 (4.1-5.6)</td>
<td>5.9 (4.5-7.5)</td>
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<td>NYHA I+II</td>
<td>46.3% (46.2-46.4%)</td>
<td>46.2% (46.1-46.3%)</td>
<td>46.1% (46.0-46.2%)</td>
<td>46.0% (45.9-46.1%)</td>
<td>45.9% (45.8-46.0%)</td>
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<td>NYHA III+IV</td>
<td>53.7% (53.8-53.7%)</td>
<td>53.8% (53.9-53.8%)</td>
<td>53.9% (54.0-53.9%)</td>
<td>54.1% (54.2-54.2%)</td>
<td>54.2% (54.3-54.3%)</td>
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<td>NYHA III</td>
<td>0.1% (0.0-0.2%)</td>
<td>0.1% (0.0-0.2%)</td>
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<td>Patients</td>
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**Conclusion:** In this large representative registry, over the last decade, standardized utilization of evidence based drug therapy is excellent and has remained stable, and of CRT and ICD has increased but remains poor. These trends are associated with an increase in standardized mortality. The improvements in therapy and prognosis over the last generation may be leveling off and efforts should be directed at increasing use of CRT and 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 359 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%, 2%; South America 26%, 54%, 20%; Western Europe 78%, 21%, 1%; and Eastern Europe 23%, 50%, 27% for <10, 11-30, and >30 patients/site) were noted. During 9.9 months follow-up, 1,701 (40%) patients had an event. Compared to >30 event rate 32%, ≤10 (event rate: 51%, hazard ratio [HR] 1.77, 95% confidence interval [CI] 1.56, 2.02) and 11-30 (event rate 42%, HR 1.44, CI 1.28, 1.62) groups had worse outcomes. This was comparable across regions (P=0.43). After adjustment, enrollment <10 patients was associated with better survival (HR 1.12; CI 1.03, 1.40 compared to ≤10; HR 1.18; CI 1.03, 1.34 compared to 11-30 site enrolment).

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

Self-rated general health is an independent predictor of outcomes in acute heart failure

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Purpose: To determine whether self-rated general health measured with the RAND36 at hospital discharge predicts long-term mortality in patients with HF, independent of disease severity measured by BNP at baseline.

Methods: Self-rated general health was assessed with the RAND36 at hospital discharge per 10 units of general health of the RAND36 (range 0-100) and the BNP-levels were assessed at discharge. Data were collected as part of the COACH study (Coordinating study 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 ≥67 mg/dl. Population was then split in 4 groups according to the selected cut-offs (G1: eGFR yes/BUN yes (n=370), G2: eGFR no/BUN yes (n=700), G3: eGFR yes/BUN no (n=114), G4: eGFR no/BUN no (n=1,700)). Patients with BUN ≥67 mg/dl (G1 and G4) had a reduced systolic blood pressure at entry and were treated with higher dose of intravenous 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 CV death: G1 33.5% vs G2 8.1%, G3 23.4%, G4 23.7%, p<0.01; 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 propeptide (copeptin) is stable and has
Efficacy of transcatheter closure of patent foramen ovale: Clinical and echocardiographic follow-up 2 years after

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 over six months intervals.

Results: Mean age was 68 ± 13 years, 71% were male, 44% were in NYHA class III or IV, and mean LVEF was 30 ± 8%. The median copeptin level was 20.4 (quartiles 15.3, 25.5). A total of 12 months TEE showed no residual shunt in 10 (10.5%), 30% of patients within the normal range (10 – 15 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.

INTERVENTIONS FOR STRUCTURAL HEART DISEASES, AN UPDATE

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

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Background: Transeosophageal 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 scheduled for 3 and 12 months TEE after device implantation. Patients received Amplatzer (n=115), BioSTAR (n=71), Cardia (n=106) or Premere PFO occluder (n=61). Provocable right-to-left shunt was graded according to the amount of bubbles crossing the interatrial septum: no shunt, mild shunt 1 to 9 bubbles, moderate shunt 10 to 20 bubbles, and severe shunt >20 bubbles or opacified left atrium. An atrial septal aneurysm (ASA) was defined as an excursion of the atrial septum > 3.5 mm.

Results: The prevalence of ASA was significantly different between the devices with 20% for Amplatzer, 16% for BioSTAR, 4% for Cardia and 30% for Premere (p < 0.01). Pre-procedural PFO size in patients with mild shunt was 12.6 ± 4.0 mm, moderate shunt 15.8 ± 5.4 mm and severe shunt 16.9 ± 3.5 mm. The total closure rates (no shunt) at 3 months TEE were statistically not different with 61% for Amplatzer, 66% for BioSTAR, 72% for Cardia and 72% for Premere devices (p = 0.08).

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.

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 proven to be 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 flexible thin waist, and in comparison to other devices, of a disc for sealing the orifice of the LAA (pacifier principle). We report on 100 consecutive ACP patients (age 72 ± 10 years) with non-valvular AF (mean CHADS2 Score 2.6 ± 1.3, CHA2DS2-VASc Score 3.7 ± 1.1, HASBLED 2.5 ± 1.3). The LAA was entered via femoral vein, transseptal access under fluoroscopic guidance. Diameter of the LAA orifice were determined angiographically and the ACP was deployed via dedicated 9-13F sheaths under fluoroscopy only, i.e. without transeosophageal echocardiography (TEE) assistance. The procedure was often combined with other cardiac interventions.

Results: Device sizes ranged from 16 to 30 mm (mean 22.8 ± 3.9 mm). 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.

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). Severe 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 grade 74%, 26 2 years, 96% 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 232 m to a median of 330 m (P = 0.0062) 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).

MitraClip implantation was well tolerated in all patients. Matched 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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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%]; \( P = 0.015 \)) 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; \( P = 0.422 \)). FSV had increased significantly by 15.6% from a median of 48 ml to a median of 56 ml (\( P = 0.0035 \)).

Conclusions: MiraClip therapy appears to entail marked clinical improvement in the majority of successfully treated high-risk patients surviving out to 2 years. Reduction of 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 Prognostic Value of Cerebral Injury Following Impact of Renal Function on Use of Antithrombotic

Results: Principal finding in devices with implantation times of less than 4 weeks was superficial fibrin coverage with spreading of single endothelial cells. Com- principal finding in devices with implantation times of less than 4 weeks was superficial fibrin coverage with spreading of single endothelial cells. Complete endothelialisation was demonstrated in all specimens 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-3.

Conclusions: 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 neointimal thickening has been achieved.

Prognostic Value of Cerebral Injury Following Transfemoral Aortic Valve Implantation (TAVI)

Figure 1

Background: Silent and apparent peri-interventional brain injury is frequently observed (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.

Methods: Sixty-one patients were enrolled (mean logistic Euroscore: 26.4±18.1, mean STS-Score: 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.

NEW HORIZONS OF ANTITHROMBOTIC THERAPY IN ATRIAL FIBRILLATION

Impact of Renal Function on Use of Antithrombotic Therapy in Atrial Fibrillation: Real World Perspective from the Global Anticoagulant Registry in the FIELD Registry

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 the kidney dysfunction classified 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 7563 (73%) subjects. Most (n=6074; 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,
AF patients with renal dysfunction appear more likely to receive combination therapy with anticoagulants and antiplatelets. This finding may reflect a high prevalence of vascular disease with increasing severity of renal dysfunction.

**Table 1. Antithrombotic medication received, overall and according to kidney function (NKF KDOQI) \**

<table>
<thead>
<tr>
<th>Kidney function</th>
<th>Anticoagulant</th>
<th>Antiplatelet</th>
<th>Both anticoagulant Antiplatelet</th>
<th>Neither only Anticoagulant only Antiplatelet only</th>
<th>Neither and anticoagulant and antiplatelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (normal function)</td>
<td>50.2%</td>
<td>25.5%</td>
<td>12.0%</td>
<td>12.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td>II (moderate dysfunction)</td>
<td>51.8%</td>
<td>22.2%</td>
<td>18.0%</td>
<td>7.9%</td>
<td>4.3%</td>
</tr>
<tr>
<td>III (moderate dysfunction)</td>
<td>52.2%</td>
<td>21.1%</td>
<td>20.1%</td>
<td>6.6%</td>
<td>4.4%</td>
</tr>
<tr>
<td>IV (severe dysfunction)</td>
<td>49.5%</td>
<td>23.4%</td>
<td>20.7%</td>
<td>6.3%</td>
<td>4.2%</td>
</tr>
<tr>
<td>V (renal failure)</td>
<td>35.7%</td>
<td>19.0%</td>
<td>31.0%</td>
<td>14.3%</td>
<td></td>
</tr>
</tbody>
</table>

AF patients with renal dysfunction appear more likely to receive combination therapy with anticoagulants and antiplatelets. This finding may reflect a high prevalence of vascular disease with increasing severity of renal dysfunction.

**Conclusion:** Among patients transitioned to open-label VKA at EOS, those in the warfarin group and 52% in the rivaroxaban group transitioned to open-label vitamin K antagonist therapy:

**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, 42/42/458/62 (93%) on warfarin and 42/40/462/62 (93%) on warfarin were taking study drug at the EOS visit and transitioned to VKA. No INR values were reported for approximately 30% (1239 [29.2%] transitioned from rivaroxaban and 746 (17.6%) on rivaroxaban and 815 (18.9%) on warfarin had 2 reported; 440 (32.6%) on rivaroxaban and 1528 (35.6%) on warfarin had 1 INR value reported; 746 (17.6%) on rivaroxaban and 815 (18.9%) on warfarin had 2 reported; 440 (10.4%) on rivaroxaban and 383 (8.9%) on warfarin had 3 reported; and 433 (12.6%) on rivaroxaban and 254 (5.9%) on warfarin had 3 reported. By 30 days after EOS, 83% in the warfarin group and 52% in the rivaroxaban group transitioned to open-label VKA had at least 1 INR value in the 2.0–3.0 range (Figure). Median time to first therapeutic INR was 3 days in the warfarin group and 13 days in the rivaroxaban group.

**Conclusion:** Among patients transitioning to open-label VKA at EOS, those in the warfarin group were more likely to transition to open-label vitamin K antagonist therapy than those completing rivaroxaban. This difference probably explains the excess ischemic events after transition from rivaroxaban after the EOS visit. If transition from rivaroxaban to VKA is needed, timely monitoring and careful dosing should be used to assure consistent and adequate anticoagulation.

**Differential effects of the direct thrombin inhibitor dabigatran etexilate vs warfarin on platelet function**

G. Renda,1 G. Malatesta,1 V. Bucciarelli,1 A. Napoleon1, G.L. Cardeti1, J. Van Ryll, L. Moretti2, R. De Caterina1, G. d’Annunzio University, Institute of Cardiology and Center of Excellence on Aging, Chieti, Italy; 2Mazzoni Hospital, Ascoli Piceno, Italy; 3Boehringer Ingelheim Pharma, Biberach, Germany

**Purpose:** All anticoagulants are expected to have some indirect effects on platelet function because they interfere with the generation or activity of thrombin. We aimed to better characterize the effects of dabigatran etexilate (DE) on platelet function compared with warfarin (W).

**Methods:** 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.

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Cost-effectiveness of apixaban against 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 and economic 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-major 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 current standard of care at lifetime horizon

<table>
<thead>
<tr>
<th>Population</th>
<th>Comparator</th>
<th>Cost/QALY (2010 GBP)</th>
<th>Cost/LY (2010 GBP)</th>
<th>QALY</th>
<th>Icer</th>
<th>Warfarin Suitable</th>
<th>ASA 5 mg bid</th>
<th>Warfarin unsuitable</th>
<th>ASA 325 mg od</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
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<td>£3,148 (0.15)</td>
<td>£2,622 (0.22)</td>
<td>0.17</td>
<td>£18,151</td>
<td>£19,151 (0.17)</td>
<td>£12,136 (0.22)</td>
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<tr>
<td>ASA 325 mg od</td>
<td>ASA 5 mg bid</td>
<td>£1,526 (0.08)</td>
<td>£8,061 (0.11)</td>
<td>0.11</td>
<td>£13,087</td>
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Conclusions: Cost-effectiveness of apixaban compared to warfarin and ASA was deemed acceptable for the purposes of these analyses. 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.

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 in atrial fibrillation in patients with non-valvular atrial fibrillation (AF) and therefore been included in the CHAD2SVS score. The purpose of this study was to investigate if the stroke risk associated with female gender was homogenous 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 male patients. 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,
although the prevalence of obesity is rising exponentially. We therefore examined
the incidence of AF in relation to body mass index (BMI, kg/m²) in fertile women.
Methods: By cross-linkage of nationwide registers of childbirth and hospitalization,
all women (age 20-50) giving birth in Denmark between 2004 and 2009
were identified. BMI was recorded when the first pregnancy in the period was
confirmed, and the subjects were categorized as normal weight (BMI 18.5-25),
overweight (BMI 25-30), obese (BMI 30-35) and very obese (BMI ≥ 35). These
women were followed from the day of giving birth. Incidence rate of AF according
to BMI was calculated and assessed by multivariable Cox regression models.
Results: A total of 271,257 women were identified, the mean age (standard
deviation) was 30.6 (4.7) years. After a median follow-up of 4.56 years (interquartile
range 2.95-5.82), 110 new-onset AF cases were identified. Overall AF incidence
rate (95% confidence intervals [CI]) was 9.3 (7.7-11.2) per 100,000 person-years.
For normal weight, overweight, obese and very obese subjects, AF incidence rates
(95% CI) were 7.4 (5.6-9.7), 8.5 (5.5-13.1), 15.8 (9.3-26.7) and 27.3 (15.5-48.1)
per 100,000 person-years, respectively. Multivariable Cox regression analyses
(figure) revealed that the risk of new-onset AF increased significantly with each
unit increase in BMI, hazard ratio was 1.07 (CI 1.04-1.10, p=0.0004) (figure).

Conclusions: Obesity is a powerful predictor of AF among young women with-
out established risk factors for AF. Weight loss strategies at population level may
improve the prevention of AF and decrease the burden of AF.

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

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A. Maggioni7 on behalf of EVEREST trial investigators.1 Northwestern University,
Feinberg School of Medicine, Department of Emergency Medicine, Chicago,
University of Chicago, Chicago, Illinois, USA;2 Northwestern University,
Feinberg School of Medicine, Dept of Medicine/Cardiology & Cardiovascular Surgery, Chicago, United States of America;3 Duke University Medical Center, Department of Medicine, Division of Cardiology, Durham, United States of America;4 Tufts Medical Center, Boston,
United States of America;5 CIC INSERM-CHU Pierre Drouin, Institute for Heart
and Vessels Louis Mathieu, Vandoeuvre les Nancy, France;6 University of
Gothenburg, Gothenburg, Sweden;7 ANMCO 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 out-
comes of patients hospitalized for HF with AF has not been well studied. We report
results of patients hospitalized for HF with AF and examined the impact of AF
on hospitalization outcomes using a large population cohort.

Methods: Post-hoc analysis of the Efficacy of Vosapossoss Pegloticase Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, which randomized 4133 patients hospitalized with worsening HF and EF≤40% within 48 hours after ad-
mission to 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 (CVM+HF) were
analyzed by log-rank tests and multivariate 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 (26.3% vs. 21.3%) and CVM+HF (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 CVM+HF (aHR=1.25
(1.09-1.43)).

Conclusions: AF independently predicts major adverse CV events in patients
admitted for HF with reduced EF.
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 endoplasmic 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 study 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 holter (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 (C) were identified: 179 C alive, 67% of them (n=122) presented ventricular arrhythmias (VA) in basal ET, without pharmacological treatment. In 2007, 68 of 147 C (47%) presented VA in basal ET, without pharmacological treatment; 17 C were treated and follow-up period was >21 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<0.0001). 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 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 peculiarly 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.

Atrial fibrillation: the scope of the problem / Ventricular tachycardia and sudden cardiac death: genetic aspects

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.1265G>T, p.S422L), in a 14-year-old female with a clinical history of ventricular fibrillation and early repolarization in infero-lateral leads. Therafter, 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. Since several candidate of missense variants were identified and to the identification of ion channel genes (CACNA1C, CACNB2B, CACNA2D1 and SCN5A).

Method: These results on ATP-sensitive potassium channels led us to hypothesize the implication of other cardiac KATP channel subunits. We screened by direct DNA sequencing KCNJ11 and ABCB3 in 96 patients with early repolarization syndrome.

Results: We identified 5 rare variants in ABCB3 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.V1319I). One missense variant (p.A355S; rs145455570) was found in only one patient in the control population. Compared to 19 SCN5A mutation carriers, the frequency of female probands was significantly higher with KCNJ8 mutations (n=2, 66.7%) than with SCN5A mutations (n=2, 10.5%), and both were symptomatic. Contrary to previous findings, QTc intervals in KCNJ8 mutation carriers were not shortened (389.6±15.9 ms; P=0.756 vs. SCN5A mutation carriers; 403.2±30.0 ms).

Conclusion: We identified only 3 LTTCC-related mutation carriers. The mutation frequency was lower compared to previous reports. Female patients with LTTCC mutations were severer in phenotypes. Gene screening of LTTCC channel may therefore be important, especially for female IVF patients.

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 new 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 analyses.

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; 74% vs. 58%, respectively) or gender differences between desmosomal and PLN mutation carriers. Desmosomal mutation carriers more often had inverted T waves in right precordial leads V1-3 compared to PLN mutation carriers (78% vs. 33%, p=0.001). In PLN mutation carriers inverted T waves were found in left precordial leads V4-6 (4% vs. 58%, p<0.001), evidence of left ventricular abnormalities (WMA: 6% vs. 33%, p=0.023), and low voltage ECG (voltages <0.5mV; 16% vs. 67%, p=0.01) 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=0.482). In contrast, LV involvement (inverted T in V4-6, LV WMA, LV DE, or LV EF <50%) occurred more frequently in PLN mutation carriers (26% vs. 75%, p=0.003).

Conclusions: AC patients carrying the non-desmosomal PLN mutation display a distinct AC phenotype characterized by inverted T in left precordial leads, low voltage ECG and more often biventricular structural and functional involvement, whereas desmosomal gene mutation carriers display more solitary right sided abnormalities.

Usefulness of familial study in a genetically-determined arrhythmogenic cardiomyopathy


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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 (19-74 years; range 9-37) with structurally normal heart. CPVT was suspected to be the cause of the events, given the 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 familial and 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 during 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 families 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 SCD (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 familiar 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 averaged ECG, exercise testing, Holter monitoring, echocardiogra- phy) 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).

Results: Definite or possible cardiac abnormalities were detected in 47/183 (25.8%) FM by clinical testing (41 - 87.2%) or genetic testing (6 - 12.8%). Abnormalities included LQTS (23), CPVT (12), ARVC (5), Brugada Syndrome (3), Short QT-S (2) and familial cardiac sarcoid (1). Overall detection yield was similar between FM of SUD and CA probands (22% vs 27% p=NS) but LQTS was more common in the FM of the SUD group (p=0.05 Table).

Abnormalities detected

<table>
<thead>
<tr>
<th>Group (diagnoses/total)</th>
<th>LQTS</th>
<th>CPVT</th>
<th>ARVC</th>
<th>Brugada</th>
<th>SQTS</th>
<th>Sarcoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUD (65/130)</td>
<td>10 (16%)</td>
<td>3 (4.6%)</td>
<td>5 (7.7%)</td>
<td>2 (3.1%)</td>
<td>7 (5.4%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>CA (34/55)</td>
<td>15 (44.1%)</td>
<td>10 (29.4%)</td>
<td>5 (14.7%)</td>
<td>2 (5.8%)</td>
<td>3 (8.6%)</td>
<td>2 (9.1%)</td>
</tr>
</tbody>
</table>
Immediate and 20 years follow-up results of percutaneous balloon mitral valvotomy for severe mitral stenosis


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 1987 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 valve area (MVA) calculation (pressure half-time method), mean transmittal 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 MVA<1.5cm² as assessed by 2D transthoracic echocardiography. 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; 77% were men. 27 PTS (14%) had mild MR pre-PMV, 59 PTS (19%) were in NYHA class II and 161 (81%) in NYHA class III or IV. 98 PTS (4%) were in atrial fibrillation, and 5 PTS (2.6%) 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 (88%) had good immediate results and 48 (37%) 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 (p=0.034), preoperative and postoperative mean transmittal 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 commissurotomies in patients with few or no symptoms?


Purpose: Percutaneous mitral commissurotomies (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 institution. Mean age was 46±12 years. 74 patients (31%) had atrial fibrillation and 22 (9%) had a history of commissurotomy. Most patients were in NYHA class II (223 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 mitral regurgitation, 145 (61%) had pliable valves and severe subvalvu- lar 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 PMC, valve area increased to 1.9±0.3 cm² 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 predictors 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/A 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 vs. 14±6 vs. 43±5.9%; 2-year: 21±7 vs. 40±8 vs. 67±9%; 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 teritle 1).

Figure 1

Conclusions: In asymptomatic patients with primary MR, exercise BNP level provides important incremental prognostic value beyond what is achieved by demographic and echocardiographic data and resting BNP level. Patients with elevated exercise BNP should be considered at high risk of reduced cardiac event-free survival.
Mitrail valve disease: from balloon to clip / Coronary artery disease unveiled by multidetector CT in populations at risk

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


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 (LVEF) 38±3%, baseline demographics and procedural characteristics were screened for 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 < 0.001), chronic obstructive pulmonary disease (30.8 vs. 11.3%; hazard ratio 3.6 [9.1 – 7.7]; P < 0.01) and a LV-EF ≤ 30% (21.0% vs. 12.2%; hazard ratio 1.7 [1.1 – 5.5]; 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%; hazard ratio 4.4 [9.1–11.6]; P = 0.001) and a LVEF < 30% before clip (38.6 vs. 20.5%; hazard ratio 3.6 [9.1–11.6]; P = 0.001) 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.

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 hypoxaemia may cause myocardial ischaemia. There is however, limited data on subclinical coronary artery disease (CAD) in patients with OSA without known cardiovascular disease (CVD). The purpose of the present study was to assess the presence and magnitude of any association between OSA and CAD without known CVD.

Methods: Consecutive patients without evidence of CVD (n=135, 14 females) undergoing polytomography were recruited. The patients received a 2-D Doppler and Dipydrom-stress myocardial contrast echocardiography (MCE us- ing SonoVue echoccontrast; Philips, IE 33), non contrast (Agastone scan) and contrast 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 dilatation (FMD).

Results: Patients with an apnoea-hypopnoea index (AHI) of ≥ 15 (n = 117; age 54±11 years) had a significant increase in CAD prevalence compared with OSA patients with AHI≤5 (n = 18; age 60±10 years; P=0.01). Severe CAD (Agastone score ≥ 4+) was present in 19% vs. 4% of patients (P=0.03). On the other hand patients with a low AHI (<5) or OSA Severity Score (OSS) ≤ 15 (n=117; age 54±11 years; AHI 3.9±4.5) were considered eligible for treatment with continuous positive airway pressure. Group 2 (n=18; 49±10 years; AHI 9.5±3.5; Systolic BP 152±13 mmHg; OSS 17) with AHI 15 were considered as controls. There was significant difference between the 2 groups for AHI (P<0.001), arterial oxyhaemoglobin saturation (SaO2%) nadir (78±8 vs 88±4%, P<0.001) and mean SaO2% (93±3% versus 96±1%; p<0.001). In group 1, 43% had evidence of calcified and non-calciﬁed coronary plaque of varying degree (Agastone score 80±233, –80th percentile) while in group 2, 11% had coronary plaque (Agastone score 2±6, –50th percentile, P<0.02 versus group 1). Patients with coronary plaque had significantly higher IMT (68±12 versus 59±6 mm, P<0.0001) and lower FMD (6.1±2 versus 7.3±2%, P<0.0019). Furthermore, there was significant difference between the 2 groups for myocardial blood flow reserve as determined by MCE (1.27±0.67 versus 1.81±0.18; P<0.001). Logistic regression (after adjustment for age and BMI) showed that SaO2% nadir and FMD were the best predictors for presence of coronary plaque (P<0.04).

Conclusions: The present data provides direct evidence of endovascular dysfunction and the presence of subclinical CAD with associated reduction in myocardial blood flow reserve in OSA patients without clinical evidence of CVD. The SaO2% nadir 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 disease, 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 (Phillips Brilliance); 49% men, 60±10 years, 50.6% under insulin treatment, with a mean diabetes duration of 13±9 years and a mean hemoglobin Alc of 8.2±1.8%. Clinical data, CVR factors and scores were collected for each patient (P). Coronary calcium score (CCS) and the total number, composition, distribution and severity of coronary atherosclerotic plaques (CAP) were also assessed. P were followed for 45±13 months to identify CVE: cardiovascular death, acute coronary syndrome and stroke/TIA). A comparative analysis of AD with and without CVE was performed to evaluate potential differences.

Results: The mean CCS was 137±250. CAP were found in 67.1% AD, significant in 23.8%. Medical therapy has been optimized in 25.9% and 7.1% underwent to revascularization after cardiac MDCT. None of the 33AD with CCS=0 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 LDL blood levels at diagnosis showed statistically significant association 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 proximal coronary segments from multiple vessels, with a high degree of calcification. In addition to increased age and low HDL levels, the presence of coronary atherosclerosis is related with genetic mutations that severely affect the LDL-R function. Non invasive coronary angiography by CCTA emerges as a useful technique for the screening of subclinical CAD in HeFH patients.

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 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 Agaston calcium score in the study group in comparison with controls (260.18±150 vs45±40; p<0.002). Prevalence of CAD in HeFH patients was 48%, with significant obstruction 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 LDL blood levels at diagnosis showed statistically significant association with CAD (p<0.05). Analytical follow-up after 12 months under optimal lipid-lowering therapy showed no differences in the lipid profile in 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 proximal coronary segments from multiple vessels, with a high degree of calcification. In addition to increased age and low HDL levels, the presence of coronary atherosclerosis is related with genetic mutations that severely affect the LDL-R function. Non invasive coronary angiography by CCTA emerges as a useful technique for the screening of subclinical CAD in HeFH patients.
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, overweight, obese, respective 30 kg/m²), 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, whereas there was no difference in those between overweight and 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 5.53, 95% CI 2.99 to 10.3), overweight patients with MetS (OR 6.31, 95% CI 3.34 to 12.2), obese patients without MetS (OR 6.46, 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.

**Conclusions:** 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.
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 < 0.009, Figure). 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 < 0.05). 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 69% 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.
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-rest contrast enhanced CT as well as stress-rest perfusion MRI followed by late gadolinium enhanced (LGE) MRI. FFR was determined in 13 coronary vessels and FFR<0.80 was considered hemodynamically significant. CT and MR images were visually analyzed by two blinded observers.

Results: The sensitivity and specificity of stress contrast enhanced CT for detecting myocardial ischemia on stress perfusion MRI was 80% (20/25) and 40% (4/10), 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.

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

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Background: Protection of distal embolization by balloon occlusion and thrombus aspiration has not improved microvascular circulation or 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-TA) in 126 patients with STEMI.

Methods: Patients with first-diagnosed STEMI were randomly assigned to DP-TA pretreatment or conventional PCI (c-PCI). Primary endpoint was reduced left ventricular end-diastolic volume (LVEDV) at 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 or late enhancement (LGE) and myocardial salvage index (MSI: AAR-infarct size)/100 AAR). Changes in cardiac magnetic resonance imaging (MRI) were assessed within 3 days after PCI.

Results: Baseline characteristics of the patients including cardiovascular risk factors and lesion characteristics were similar between the two groups. DT-TA failed to improve LV remodeling at 6 months (LVEDV 140±9 vs 133±7 mm3 in c-PCI group, p=0.418). Infarct ratio, AAR ratio and MSI were not statistically different between DT-TA group and c-PCI group. However, MVO ratio were significantly larger in DT-TA group than c-PCI group (2.4±2.7 vs 1.1±1.9, p=0.065).

Conclusion: DP-TA was potentially hazardous in primary PCI for STEMI by increasing MVO. DT-TA should not be used in STEMI.

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 (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 piivastatin (2 to 4mg daily). HIP was defined as presence of the signal intensity of 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 47.2% (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.

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 circumbromatous 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 SCVL. Blood pressure was assessed by 24h measurement. Aortic lesions were assessed by 18FDG 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 perianeuritic 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 inflamatory lesions compared to those with no perianeuritic fibrosis. All ABIs were normal. Radial distensibility was not altered.

Conclusion: This non langerhans histiocytosis is characterized by a cardiotidal perifibrous fibrosis in 21% of the patients. An aortic inflammation 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 inflammatory
Utility of 320 slice mapping CT for adrenal vein sampling in subjects suspected to have 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 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 SRCTAV with successful AVS were retrospectively analyzed. For mapping CT, conventional volume scan was performed at non-contrast, 30, 45, 60, and 90 seconds after contrast injection. We compared the diagnostic accuracy of these modalities for visualization of AV.

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 SRCTAV, respectively, and detection of right AV was lower in mapping CT and DSA than in SRCTAV (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 accurately as DSA and SRCTAV. To improve visualization of the right AV, improvement of acquisition methods of CT might be needed.

P5336 Prognostic role of resistant hypertension for cardiovascular outcome: a prospective study in 2345 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) 2345 hypertensives (aged 58±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 on at least 11 visits. The incidence of RH was 18.4%. Patients with RH were older (by 5 years, p<0.001) and exhibited greater waist circumference (by 4 cm, p<0.001), body mass index (by 1.2 kg/m², p<0.001) and prevalence of diabetes (by 6%, p=0.004), as well as increased left ventricular mass index (by 10.7 g/m², p<0.001), glucose (by 7.4 mg/dL, p<0.001), creatinine (by 0.05 mg/dL, p=0.002) and decreased potassium levels (by 0.12 meq/L, p<0.001). Incidence of CAD (4.7% vs. 2.1%, log-rank p=0.004), stroke (1.9% vs. 0.7%, log-rank p=0.027), AF (6.1% vs. 2.7%, log-rank p=0.001) and their composite

P5337 Association of anti-anxiety drugs with cardiovascular outcomes in patients after myocardial infarction

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Objective: The objective of this study was to test whether use of anti-anxiety medication is associated with long-term mortality risk in the subjects suffered from myocardial infarction (MI).

Methods: The study included a random sample of 1,000,000 individuals covered by the National Health Insurance. We then recruited subjects with first MI and above 30 years old. Each anti-anxiety medication was given an assignment value equal to 10 mg diazepam. Study outcomes including sudden death, cardiovascular mortality and heart failure hospitalization. Cox regression analysis evaluated the adjusted hazard ratio (HR) for all subjects and for subgroups.

Results: A total of 7419 patients (4651 men) were included in the study. A total of 94 sudden death, 534 cardiac death and 777 heart failure hospitalization occurred within an average of 4.5 years follow-up. By modeling mortality risk in patients receiving different doses of BZD (Q1–Q4), the adjusted HRs of sudden death were significantly associated with increased BZD dosage (HRs = 0.639, 1.003, 1.957 from Q2 to Q4 vs. Q1, P = 0.019 for trend). For cardiac mortality and heart failure hospitalization, there was a J-curve dose response relationship. The HRs of sudden death were 0.255 (95% CI, 0.159-0.409, P < 0.001) and 0.385 (95% CI, 0.247-0.600, P < 0.001) for Q2 and Q3 vs. Q1 respectively. However, for patients receiving larger amounts of daily BZDs (>5mg), the protective effects diminished (Q4 VS Q1, HR = 1.291, 95% CI = 0.902-1.848, P = 0.163). Similar J-curve relationship was also found for heart failure hospitalization.

Conclusion: The results have demonstrated that small to moderate doses 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.

P5338 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 the 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 mortality benefit was observed from eplerenone or spironolactone treatment.

Conclusion: The novel, non-steroidal mineralocorticoid antagonist BAY 94-8862
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 stimulatory 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 cardiovascular responses to selective stimulation of peripheral chemoreceptors (PC) and of central chemoreceptors (CC).

Methods: 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 (hyperoxic hypcapnia: 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). Hyperoxic hypcapnia. VE increase was greater with ACZ (p<0.001) compared to PL (p<0.05); ACZ did not affect the increase (p>0.001) in SBP and HR compared to PL.

Table 1

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>ACZ</th>
<th>p-value</th>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>114±10</td>
<td>107±10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>61±11</td>
<td>61±11</td>
<td>p=NS</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>3.3±0.7</td>
<td>3.2±0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SatO2 (%)</td>
<td>98±1</td>
<td>98±1</td>
<td>p=NS</td>
</tr>
<tr>
<td>ETCO2 (mmHg)</td>
<td>34±5</td>
<td>34±5</td>
<td>p=NS</td>
</tr>
</tbody>
</table>

>p=0.001 vs baseline, p=0.05 vs PL; *p=0.05 time treatment.

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 overactivation. Acetazolamide (ACZ), established therapy for AMS, has lar effects of ACZ may favorably come into play in the treatment of pathological overactivation. Acetazolamide (ACZ), established therapy for AMS, has

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

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Purpose: The 16-week, randomised, double-blind, placebo-controlled, Sildenafil monotherapy (SMP) study enrolled 36 patients ≥6y of age with PAH-CHD. At the end of 16 weeks, 4/35 untreated patients exhibited severe OSA (OA) syndrome (apnea hypopnea index-AHI>15) for a mean period of 3.1 y. Subjects were treated with CPAP, and all 3 sildenafil dose groups were similar to children receiving off-label PAH-specific therapies in the current era. An unexplained in-creased incidence of death was observed after 2 years of treatment in patients randomised to higher sildenafil doses.

Results: As of June 2011, 35 deaths were reported (on treatment, n=26; off treatment, n=9). Most (26/35) had IPAH/PAH (74% vs 33% overall); 5/35 had surgically repaired (4/35 untreated) PAH-CHD; 40% had baseline class III/IV disease (vs 15% overall). Deaths were related to baseline haemodynamic severity (69% had mPAP ≥62 mmHg, 74% had PVR ≥15 Wood units/m², 71% had RAP ≥7 mmHg [median values]). No deaths were investigator-assessed as treatment related; most associated with PAH progression. Kaplan-Meier estimated 3-y survival from STARTS-1 baseline was 92%, 80% and 64% for patients ≥20 kg randomised to low-, medium- and high-dose sildenafil; and 93% and 94% for patients ≥20 kg randomised to medium and High doses, respectively. Survival status was known for 90% of patients at 3 years from the start of their treatment in STARTS-1. Patients randomised to higher sildenafil doses had increased mortality; hazard ratios for mortality from start of sildenafil treatment were 3.50 (95% CI, 1.29 to 9.51) for high vs low and 1.85 (95% CI, 0.63 to 5.64) for medium vs low dose. Chance is unlikely to be seen in both groups at baseline question the relationship strength between dose group and survival.

Conclusions: 3-y survival with all 3 sildenafil dose groups was similar to children receiving off-label PAH-specific therapies in the current era. An unexplained in-creased incidence of death was observed after 2 years of treatment in patients randomised to higher sildenafil doses.

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

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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.

Methods: 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 BP evaluation, and were switched to carefully designed antihypertensive treatment targeting office BP <140/90 mmHg (<130/80 mmHg in diabetics). Subsequently, patients 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 to 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 anti-hypertensive 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. 140±15 and 85±12 vs. 88±9 respectively, p<0.001) while number of antihypertensive drugs applied was higher (2.4±1.21 vs. 2.3±1.1, p<0.001). On-CPAP subjects and controls exhibited similar office BP levels (133±12 vs. 133±13mmHg, 84±9 vs. 85±9mmHg respectively, p=NS) for all, ambulatory BP levels (125±10/76±7mmHg vs 123±11/72±6mmHg, 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±1.07, p=NS). In multiple linear regression models, CPAP application was not associated with changes in BP levels or BP control after controlling for confounders.

Conclusions: In non-sleepy hypertensive subjects on top of optimal antihypertensive treatment and with OSA, long-term CPAP application is not associated with lower 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.

BRCA1-associated protein 2 (BRAP2) is essential for embryonic heart development and for neonatal cardiomyocyte proliferation


Purpose: BRAP2 was identified as a cytoplasmic protein that binds to the nuclear localisation sequences of the tumor suppressor BRCA1, the cell cycle inhibitor p21cip/WAF1 and SV40 large T antigen. Furthermore, BRAP2 is known as a co-regulator for all discrinuporregulating proteins Ras related proteins MEKK1 and MAPK activation. We previously reported BRAP2 to be differentially regulated upon load induced cardiac hypertrophy in a proteomic study. Accordingly, the aim of this study was to examine the function of BRAP2 in the heart.

Methods: Generation and phenotyping of BRap2-/- mice and cardiac restricted conditional BRap2-/- mice.

Results: BRap2-/- mice were observed to die at embryonic day 10.5-12.5 while heterozygous mice were born and survived without any phenotypic abnormalities.
Protein kinase D2 controls cardiac valve formation in Development of autologous tissue small caliber.

MicroRNAs are a class of non-coding RNAs that regulate gene expression. In the present study we demonstrate that BRAP2 is essential for cardiac development and deletion of Brap2 results in early heart failure and deficient myocardium.

In summary, we demonstrate here for the first time that PKD2-HDAC5-KLF signaling molecules E-Selectin, VCAM-1 and ICAM-1, in vitro and in vivo. As leukocyte adhesion molecules the endothelial inflammatory response. MiR-100 attenuates the 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%, \( p < 0.05 \)).

Conclusion: We first present 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.

Objective: 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 butted to the aorta (1.5 mm; rats) or the carotid arteries (2 mm; rabbits and 5 mm; dogs) of respective animals. They were evaluated after determined period of implantation.

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

Conclusions: By rapid arterIALIZation, completely autologous BIOTUBEs with no synthetic support materials withstand systemic blood pressure and exhibited ex vivo.

Background: Microparticles are submicron vesicles (0.1-1.0 \( \mu \)m) shedding from plasma membrane of activated or apoptotic cells. Compositions of MP depend on the stimulus and the state of the releasing cells. EMP derived under different conditions might have variable effects. Here, we evaluated differences in functional effects and miRNA profile between EMP derived from glucose treated cells and EMP from untreated cells.

Methods: 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 these modified EMP as “injured” EMP (iEMP).

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 miRNA were upregulated and 21 were downregulated compared to control EMP.

Conclusion: 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)

Yamamanii, T., Watanabeii, K., Kanda, H., Ishibashi-Ueda, H., Yaku, Y., Naka, Y. National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan; 2Kyoto Prefectural University of Medicine, Kyoto, Japan; 3National Cerebral and Cardiovascular Center Hospital, Osaka, Japan

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 mm, length: 20–50 mm) were placed into subcutaneous pouches of Wister rats, Japan white rabbits or Beagle dogs. After 1 month, BIOTUBEs formed around the molds were autoinplanted to the respective vessels. They were evaluated after determined period of implantation.

Results: 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.
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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1Medical University of Vienna, Vienna, Austria; 2University of Kapuvár, Kapuvár, Hungary

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 reperused Aml was induced by 90-min occlusion of the mid left anterior descending coronary artery in 14 domestic pigs, followed by baseline cardiac MRI at day 3. The month later (day 30) the pigs were randomized and received either porcine APOSEC (n=7) or control Medium (n=7) using the 3D NOGA percutaneous intramyocardial injection technique in the peri-infarcted areas (10-13 treatment locations). After 1-month follow up (FU) (day 60), control cardiac MRI with late enhancement and measurements of myocardial viability via diagnostic electroanatomical mapping were performed. Gene expression of cell regeneration (Mst2, hAng-1, TGF-β), myogenic genes expressing myosin and actin in the injected areas of the Aposec group, as compared with the Medium group. The angiogenic (e.g. cathepsin) and myogenic genes expressing myosin and actin in the injected areas of the Aposec group, as compared with the Medium group. The angiogenic vascular endothelial, fibroblast or insulin-like growth factor gene expression was evaluated in both groups. In the injected area, the expression of matrix metalloprotease (MMP)-1 and MMP-12 and actin were significantly activated in Aposec group, as compared with the Medium group.

Conclusions: "Cell-less cell therapy" seems to be effective in improvement of chronic cardiac ischemia and dysfunction, therefore might be a promising tool in treatment of ischemic cardiomyopathy preventing also LV remodeling.

Results: APOSEC led to an improvement of left ventricular (LV) function (45.4±5% vs. 38.6±5%, cardiac index (4.1±0.4 vs 3.2±0.3 L/min)) and myocardial viability in the injected myocardial area (10.1±3.0 vs 8.7±7.1 mV; P<0.05). Trend towards decrease in size of myocardial scar was observed in Aposec group (20±6% vs. 33±5% of the LV), as compared with the Medium group. Gene profiling analysis revealed robust significant upregulation of stem cell homing (cadherin, CXCR4 and stromal-derived factor-1) and some angiogenic factors (such as cathepsin) and myogenic genes expressing myosin and actin in the injected areas of the Aposec group, as compared with the Medium group. The angiogenic vascular endothelial, fibroblast or insulin-like growth factor gene expression was evaluated in both groups. In the injected area, the expression of matrix metalloprotease (MMP)-1 and MMP-12 and actin were significantly activated in Aposec group, as compared with the Medium group.

Conclusions: “Cell-less cell therapy” seems to be effective in improvement of chronic cardiac ischemia and dysfunction, therefore might be a promising tool in treatment of ischemic cardiomyopathy preventing also LV remodeling.

P5348 Angiogenesis effect improvement of anti-ICAM-1 targeted microbubbles for mediation of transfected hAng-1 gene into 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 specially transported exogenous 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-1-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, and specific angiotensin II type 1 receptor blocker (ARB) is required for the follow-up study. The weight/tibia length ratio after 2 weeks TAC: Mst2-/-, 7.32 mg/mm vs wild type (WT), 8.35 mg/mm, n=8, P<0.05. This was accompanied by a significant reduction of cardiac fibrosis and lower expression of hypertrophic markers (BNP and ANP) in Mst2-/- mice. In agreement with the in vivo data, overexpression of Mst2 in neonatal rat cardiomyocytes significantly enhanced phenotype-reinforced-induced cellular hypertrophy as indicated by cell size measurements and BNP expression.

Conclusions: The ICAM-1 targeted microbubbles were successfully constructed. A large number of ICAM-1 microbubbles could target combined with ECV304 cells which responded to inflammatory in vitro and compared with the non-targeted microbubble, the targeted one was also capable to selectively combine to the injured myocardial endothelium in AMI rabbits. Two weeks after gene transfection, the left ventricular function and myocardial perfusion in MI region were improved in ICAM-1-TMB which was better than non-TMB (P<0.01). The hAng-1 gene expression level and the protein expression level of non-TMB, ICAM-1-TMB and MI group was (0.48±0.03, 0.81±0.06, and 0.82±0.03) and (0.83±0.05, 0.97±0.02 and 0.97±0.02), respectively (P<0.01, all). The expression of ICAM-1-TMB and MI group were not significantly different (p=0.72, p=0.83). The microvessel density (MVD) of MI region in non-TMB, ICAM-1-TMB and MI group was (65.6±4.4, 96.7±2.1 and 100.7±3.6) (P<0.01), respectively and MVD in MI group was higher than that of ICAM-1-TMB group (p=0.028).

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 transfesion. 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 strategies for future clinical gene therapy.
Conclusions: The tachyarrhythmias associated with TAVNs were unique in these groups. AF 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.

P5361 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 not 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 substrate was found and outcomes during the follow-up period were obtained.

Results: Seventeen patients (13 males, 68±10 years) with various structural heart diseases (10 with ischemic heart disease, 5 with non-ischemic dilated cardiomyopathy) were enrolled. Thirteen patients (76%) experienced electrical storms (<3 VT/VF attacks per 24 h) at the time of the RFCA. In all patients, a VT/VF circuit with a left ventricular ejection fraction (LVEF) >35% was eliminated. A total of 26 VT/VF circuits were suppressed during the admission in 15 patients (88%) afterwards. Fourteen patients (82%) were discharged alive. During the follow-up period of 25±21 months, five patients died without any sudden cardiac death. Emergence of sustained VT/VF was seen in six patients who were not associated with patient death (P=0.58).

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.

P5362 The requirement of epicardial ablation and clinical outcome in patients with arrhythmogenic right ventricular cardiomyopathy


Purpose: In patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), epicardial radiofrequency ablation of ventricular tachycardia (VT) is often required. This study investigated when to require epicardial radiofrequency ablation and clinical outcome in ARVC patients with VT.

Methods: Twenty-two (18 male; aged 46±16; range 15 to 78 years) with ARVC undergoing radiofrequency ablation were included. Arrhythmogenic substrate was defined as an area with biphasic amplitude <1.5 mV, and fractionated or late potentials during sinus rhythm. Irrigated radiofrequency ablation targeted the substrate area in combination with activation and pace mapping.

Results: Fifty-seven clinical or slower VTs were targeted in these 22 patients. An endocardial substrate was found and ablated in 19 (86%) patients. Clinical or slow VT was successfully abolished from endocardial approach in 12/19 (63%) patients. Epicardial mapping was performed in 7 patients with failed endocardial ablation and in 3 patients with endocardial breakthrough. In these 10 patients, an epicardial substrate with fragmented or late potentials was identified. Clinical VTs were successfully abolished in 5/7 (71%) patients with failed endocardial ablation and in the 3 (100%) patients without endocardial substrate. In most of these 10 patients, an epicardial substrate with fragmented or late potentials was identified. Clinical VTs were successfully abolished in 5/7 (71%) patients with failed endocardial ablation and in 3 (100%) patients without endocardial substrate. Radiofrequency ablation was unsuccessful in 2 patients, despite extensive endo- and epicardial ablation. During 5±3 months of follow-up, VT recurred in 7 (70%) patients with endocardial ablation and 4 (33%) with only endocardial ablation.

Conclusions: In patients with ARVC, epicardial radiofrequency ablation should be considered in patients without endocardial substrate, or after failed endocardial radiofrequency ablation in patients with endocardial substrate. However, epicardial radiofrequency ablation for VT with ARVC still has limitation in short and long-term follow-up.
Evaluation of gold and platinum electrode multipolar phased RF ablations 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 multipolar electrode (9 or 10), duty cycled, phased RF catheters (PVAC, 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 caudal pulmonary vein (PV) ablations were performed with Pt and Au PVAC catheters. An electrocautery loop from femoral artery to vein was created with cannulae and tubing. A Pall filter (73 um) and 2 microbubble (MB) detectors (GAMPLT) were placed in series to detect MBs and particulate debris during ablations. Ablations were performed in 4:1 or 2:1 bipolar modes with temperature feedback power control at 60°C and a max of 8 or 9 watts respectively.

Results: Intracardiac ablations performed without allowing 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 (34% vs. 22%, p < 0.001), and for temporary pacing, a higher adhesion rate was observed in 4:1 and 2:1 modes were 0.5W (p = 0.03) and 0.7W (p = 0.005) 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.

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

L. Di Biase1, J.D. Burkhardt1, A. Pumpl2, P. Santangelo1, P. Bai2, M. Reddy1, D. Lakireddy1, R. Tung1, K. Shkvumar1, A. Natale1, Texas Cardiac Arrhythmia Institute at St David Medical Center, Un. of Texas and University of Foggia, Austin, United States of America; 2MedStar Washington Hospital Center, Washington, United States of America; 1University of Kansas Medical Center, Kansas City, United States of America; 4University of California Los Angeles, Department of Medicine, Los Angeles, United States of America

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 robotic system: results from a prospective multicenter 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 LVEF<50% implanted. The population had high prevalence of hypertension (92%), diabetes (35%), and hyperlipidemia (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 460±107. An average of 416±82 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 (84%) 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 66±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 mo follow-up 78 (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.

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 of 8ml/min.

Methods: In 5 dogs, the skin over the thigh muscle was incised and skin edges raised to form 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: Al Cath Flux Extra Gold, 12 holes) was compared to a standard platinum-iridium electrode (6H Ptlr: Al Cath Flux 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 Ptlr at normal flow rate.

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.

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 5N 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 NIIOBE i® Magnetic Navigation System (Stereotaxis, St. Louis, USA). Forces acting on the devices were measured with the force measurement tool Futec LRF 400 (Futec 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 (26 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.

Conclusion: 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

**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 contin-uation of anticoagulation for at least 3 to 6 months depending on results of se-rial 7-day Holter ECGs and on patient's CHA2DS2-VASc Score. Clinical outcome (stroke, thromboembolic events, major bleeding), adverse effects and anticoagula-tion status were assessed at discharge and follow-up.

**Results:** 89 patients with symptomatic AF [63.8±8.9 years, 78% male, 57% paroxysmal AF, 19% persistent AF] were included. All procedures were performed with dabigatran twice daily for at least 3 months. 78% of patients received dabigatran at a dose of 110mg twice daily and 22% at 150mg twice daily. Thromboembolic risk [CHA2DS2-VASc Score 2 (IQR 0; 3)] was intermediate and bleeding risk [HASBLED Score 1 (IQR 0; 3)] low. During follow-up electrical cardioversion for arrhythmia recurrence was performed in 9 patients. Only 1 patient underwent additional transesophageal echo as he had dislocated 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:** An anticoagulation approach with twice daily 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 re-lationship without the need of “bridging” and laboratory monitoring this anticoagulation approach presents an attractive alternative to the conventional approach with warfarin.

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### Table 1: Anticoagulation Data

<table>
<thead>
<tr>
<th>Anticoagulation Data</th>
<th>WAT (n=89)</th>
<th>W (n=495)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>2.1±0.44</td>
<td>2.1±0.53</td>
<td>0.75</td>
</tr>
<tr>
<td>Basic ACT (s)</td>
<td>133±46</td>
<td>132±44</td>
<td>0.87</td>
</tr>
<tr>
<td>Maximal ACT (s)</td>
<td>313±40</td>
<td>312±40</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**INR:** International Normalized Ratio, **ACT:** Activated Clotting Time, W: warfarin, WAT: warfarin and anticoagulant therapy.

**Conclusions:** The ablation procedure and conditions might have affected the rate of major bleeding complications.

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### Table 2: Major Complications

<table>
<thead>
<tr>
<th>Major Complications</th>
<th>WAT (n=89)</th>
<th>W (n=495)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periprocedural pericardial tamponade</td>
<td>4 (0.8%)</td>
<td>112 (22.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0%)</td>
<td>2 (0.4%)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

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**Conclusions:** An ablation approach combining activation mapping with phased RF allows achieving better thermal conduction in the Au electrode.

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### Table 3: Major Complications

<table>
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<th>WAT (n=89)</th>
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</tr>
</tbody>
</table>

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**Conclusions:** Significant periprocedural pericardial tamponade were detected in patients on WAT (0.81% vs 4.54%; p<0.021). Stroke occurred in only one patients on WAT.

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### Table 4: Major Complications

<table>
<thead>
<tr>
<th>Major Complications</th>
<th>WAT (n=89)</th>
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</table>

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**Conclusions:** The ablation approach combining activation mapping with phased RF allows achieving better thermal conduction in the Au electrode.
Accessory pathway ablation in paediatric patients: procedure success and long-term follow-up in 104 consecutive children in a tertiary care hospital

I. Roca Luque, N. Rivas, J. Perez-Rodrón, D. Albert, Q. Ferrer, F. Gran, P. Betrián, A. Sarrias, D. García-Donado, A. Moya, University Hospital Vall de Hebron, Barcelona, Spain

Introduction: Ablation of accessory pathways (AP) in adults has been established as a safe and high-success rate procedure, becoming a first choice treatment in these patients. However, very limited data on the immediate success and long-term follow-up in large cohort of children population has been published.

Objectives: To describe epidemiological data, pathway location, immediate success and long-term follow-up after AP ablation in a large children cohort from a single tertiary care hospital.

Methods: From 01 January 1998 to June 2011, a total of 104 consecutive children (age: 11.5±12.86 years, range: 1 day to 18 years, gender: 60.6% males/39.4% females) underwent to AP ablation procedure. Basal symptoms, pathway location, immediate success and long-term follow-up (4,65±4,04 years) have been recorded.

Results: Most patients (93.3%) had a single accessory pathway. A left-sided AP was present in 51% of the patients (65.1% lateral or anterolateral) and in 49% Atrial septal defects. Mapping was performed using 3D mapping (EnSite, 60% of patients; CP, 39% posteroapical; 7.4% anteroseptal). Initial procedure was successful in 91 out of 104 patients (87.5%). Twelve of these patients had recurrences and in all of them an additional procedure was effective. Of the remaining 13 patients in whom the initial procedure was not effective, a further procedure, usually with an additional technique, was effective in 9 of them. Overall, the accessory pathway was successfully ablated in 101 patients (96%) and they are free of ventricular preexcitation and symptoms related to tachyarrhythmia for 5.28±4.27 years of follow-up. Neither the gender or the age were related to the overall success rate. A higher success rate with a single procedure was observed in left-sided AP (94.3% vs 80.4%, p= 0.032). The number of applications needed for AP ablation was related with higher effectiveness of the first procedure and with overall success rate (7.14±8.36 vs 16.25±14.08, p=0.02). Only 1 (0.9%) non-lethal major complication (self-limited pericardial effusion after transseptal puncture) occurred.

Conclusions: Accessory pathway ablation in newborn and children is a safe procedure with high success rate if performed in an experienced centre. More than 95% of the patients are free of arrhythmia and ventricular preexcitation after long-term follow-up. Although technically more difficult, no differences have been demonstrated in terms of success according to age. Only AP location and number of radiofrequency applications have been related with procedure success.

Accessory pathway ablation in newborn and children is a safe and high-success rate procedure, becoming a first choice treatment in these patients. However, very limited data on the immediate success and long-term follow-up in large cohort of children population has been published.

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Catheter ablation/General / Catheter ablation of atrial fibrillation

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Catheter ablation/General / Catheter ablation of atrial fibrillation

Long term efficacy of percutaneous ablation of atrial fibrillation: 5 years follow up

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Background: Percutaneous bilateral pulmonary vein isolation is nowadays a main option when treating symptomatic drug refractory atrial fibrillation (AF). Although the short term results are very satisfactory, its long-term efficacy is not well established. Our main goal is to evaluate the efficacy of pulmonary vein isolation on a 5 year follow up (FU5).

Methods: We studied the 109 consecutive patients admitted to first AF ablation (mean age 54±11 years, range: 45-85 years, 77% male, 33% Paroxysmal AF, 22.9% Persistent AF, 13.8% Permanent AF) from 01-05-2005 to 31-03-2007. FU5 was made by regular clinic evaluation (with ECG or 24hours Holter by protocol and driven by symptoms) and by phone interview for an average time of 15.3±4.9 years. The endpoint was new-onset AF (P<0.05), new-onset Flutter, or AF lasting >100 cases. Success was classified in: 1- free of AF (no clinical or documented AF); 2- Clinical AF (AF symptoms not documented by ECG or Holter); 3- documented AF; 4- Permanent AF.

Results: Immediate success was achieved in 89% of procedures with 2.8% of atrio-verse events (3 tamponades; 0% mortality). On a mean Fup of 1987 days, 48.2% of patients were free from AF; 14.8% with clinical AF; 33.3% with documented AF and 3.7% in permanent AF. The procedure was repeated in 15 patients. There were no register of any cerebral vascular event (TIA/stroke) on our FU5. In 16.6%, 41.0% of patients remained in oral anticoagulation regimen and 42.3% with an anticoagulant only. Antiarrhythmic therapy was suspended in 42.3% of patients.

Conclusion: In our registry percutaneous isolation of pulmonary veins was safe and effective in reducing the rate of recurrence of atrial fibrillation on a long term FU5.
Incidence and mechanisms of cardiac perforation during radiofrequency ablation in medium size centers

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Introduction: Radiofrequency catheter ablation of atrial fibrillation (CFAA) is becoming 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 CFAA 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 CFAA cases per year) in European countries. The per-procedural (-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±10 y) presented CP (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 (27.3%) 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%), Pericardial/cardiogenic pericardialis was done in 19 pts (44.1%) and 8 pts (18.6%) required surgery. A total of 6 pts (13.9%) died (mortality rate of 0.19%).

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 persistence of AF is scarce and first generation platinum-iridium catheters were burdened by char formation on the tip. Furthermore, energy transmission of these new 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-functional magnetic field and a motor driven tip. 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 a 7-day ICAF and ECG. All documented AF and atrial tachycardia episodes lasting > 30 s were regarded as recurrences if recorded after a 3 month blanking period.

Results: Fifty-seven patients (42 male, 61±5.8±7.8 years) underwent PVAI for symptomatic paroxysmal AF (PS-SNRT < 110 s). PS-SNRT could be achieved successfully in all patients confirmed by entrance and exit block. Procedure time (skin-to-skin) was 214±67 min (104 to 354 min); fluoroscopy time 31±21 minutes. Ablation-time was 4153±1350 seconds. No char or thrombus formation was found at the catheter tip. One pericardial tamponade was observed. The patient immediately recovered after pericardiectomy. Freedom from atrial tachyarrhythmias was achieved in 57.9% of the patients included in a mean follow-up of 11.6±4.2 month. There was a trend to a better outcome in patients without previous attempts of AF ablation (n=48) (60.4% vs. 44.4%, p=0.07).

Conclusions: Remote magnetic navigation for PVAI in persistent AF provides high acute 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 cryoballoon pulmonary vein isolation

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Cryoballoon (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 PB PVI. We sought to characterize redo procedures following PB PVI in terms of procedure duration and location of PV conduction recovery.

Twenty-eightredo (98.6%) PVI 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 214±29 min, and mean fluoroscopy time was 16.5±3.9 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±1.2 and 0.9±1.2 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.

PVI conduction gaps after CB PVI preferentially occurred at inferior parts of inferior PV and at the ridge between left and left 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. Referring hospitals and GPs were contacted to collect missing follow up data.

**Results:** 188 consecutive patients with PeAF (157 male, mean age 57±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) subsequently remained free of arrhythmias. 17 patients had a third procedure of whom 59% (10/17) remained arrhythmia free. Overall 63% of patients where followed for at least 1 year and 34% for at least 2 years. The cumulative success rates for initial procedures were lower than for initial procedures.

**Conclusion:** The new anatomical index, combined assessment of cRSPV and dMI using 3D-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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**Background:** Patient selection is a critical issue for improving results of radiofrequency catheter ablation (CA) of persistent atrial fibrillation (AF). Classic single lead ECG arrhythmia activity (AA) parameters such as mean amplitude and cycle length were studied in a single lead, thus neglecting AA spatial and temporal evolution. We aimed to investigate the potential role of AA spatiotemporal variability in CA outcome prediction.

**Methods:** One-minute 12 lead ECGs were acquired at the start of CA. Unlike single lead methods, we considered normal and abnormal range of 460 myocardial segments. To study atrial activity (AA) parameters such as mean amplitude and cycle length were measured in 460 myocardial segments. Principal component analysis (PCA) estimates their rank-1 approximations and extracts the most descriptive AA components common to the leads involved. Our multilead parameter predicts more accurately CA outcome than standard single lead approaches.

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

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**Introduction:** 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, we used 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±8 mm, paroxysmal 67%) 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) subsequently remained free of arrhythmias. 17 patients had a third procedure of whom 59% (10/17) remained arrhythmia free. Overall 63% of patients where followed for at least 1 year and 34% for at least 2 years. The cumulative success rates for initial procedures were lower than for initial procedures.

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

**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 revealed by the 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 multivariate 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, 0.926; 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.

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.

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

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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-transoesophageal 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 thrombi. We used the 3D-echoangiography 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>90</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Partial</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Absent</td>
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</table>

Conclusions: 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: Effect of radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) is partly conveyed by vagal denervation. 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 versus 77.0±11.6 bpm, p<0.02) and persistent AF (10.5% versus 33.3%, p<0.02). In the multivariable analysis, lower mean HR at post-RF day 1 (Hazard ratio: 1.53 for each decrease 11.6 bpm) and persistent AF were associated with a lower mean HR at post-RF day 1 (Hazard ratio: 1.53 for each decrease 11.6 bpm) and persistent AF were associated with a recurrence of ATs after RFCA of AF.

Conclusion: Lower (< 65bmp) 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

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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 DM, 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 ± 5 years (apical HCM vs. other HCM: 86.3 ± 5% vs. 82.4 ± 5%, p=NS) and 75.3 ± 5% (77.4 ± 5% vs. 68.6 ± 5%, p=NS) at 10 years of follow-up. Comparing patients with AF vs. without AF, the values at the initial visit of BNP (369 ± 388 vs. 177 ± 245 pg/ml, p=0.001) and left atrial diameter (LAD) (4.2 ± 0.7 cm vs. 3.7 ± 0.5 cm, p<0.001) were larger and eGFR (62 ± 16 vs. 68 ± 22, p=0.029) was less in patients with AF. According to the multivariate analysis, BNP ≥ 200 pg/ml (odds ratio (OR) 3.1, p=0.001), LAD > 4 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.

P5392 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 prophylactic drugs 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 the post-operative 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 ± 8 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 25 (20, 29): 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 hypertension were independent predictors for 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 Overall Use (%) Post-op AF (%) Risk Adjusted Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall Use</th>
<th>Post-op AF</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>12</td>
<td>25</td>
<td>0.75</td>
<td>0.53-1.06</td>
<td>0.095</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>10</td>
<td>19</td>
<td>1.54</td>
<td>0.99-2.44</td>
<td>0.050</td>
</tr>
<tr>
<td>Other AA</td>
<td>8</td>
<td>24</td>
<td>0.87</td>
<td>0.59-1.28</td>
<td>0.471</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>71</td>
<td>19</td>
<td>1.14</td>
<td>0.91-1.43</td>
<td>0.254</td>
</tr>
<tr>
<td>Non-use</td>
<td>877</td>
<td>204</td>
<td>1.00</td>
<td>0.81-1.23</td>
<td>0.939</td>
</tr>
</tbody>
</table>

Conclusions: Post-operative AF remains a frequent complication of CABG. There is significant variation in the drugs used for prophylactic prophylaxis. In routine clinical practice, outside of controlled clinical trials, these medications were not associated with significant reduction of AF following surgery.

P5393 Transmural endocardiochogenic detects patients with paroxysmal atrial fibrillation as a cause of stroke or transient ischemic attack

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Purpose: In this prospective Doppler echocardiographic study the primary endpoint was to assess left atrial volume and atrial functional parameters and left ventricular (LV) diastolic function. The aim was to compare patients with sinus rhythm (SR) after an acute ischemic stroke without known atrial fibrillation (AF) to the patients who later were found to develop AF during ECG-monitoring.

Methods: Patients admitted to hospital with signs of transient ischemia of the brain (TIA) or stroke with ECG showing SR during the index admission. An extensive Doppler echocardiographic evaluation was performed at time of discharge. Patients were followed up by phone interview at 6, 12, and 24 months after discharge. The primary outcome measure was defined as the occurrence of AF (≥ 30s) during follow-up, either in the presence of SR or in the presence of atrial fibrillation (AF). The study was conducted at 10 centers in Sweden. The primary endpoint was defined as the occurrence of AF during 30 days of follow-up. The time from the index admission to the beginning of follow-up was < 30 days.

Results: Of 175 consecutive patients, 15 patients were found to have paroxysmal atrial fibrillation (AF). Echocardiography showed significant larger LAV, higher LAVIA and
lower a' velocities, in subjects later developing AF (Table 1). Furthermore, there were no differences between the groups regarding RV and LV systolic or diastolic function, LV volumes or mass.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAVi, mL/m²</td>
<td>31.7±8.7</td>
<td>37.2±6.7</td>
<td>37.2±8.7</td>
</tr>
<tr>
<td>LAVi/VC</td>
<td>1.21±0.59</td>
<td>1.96±1.07</td>
<td>0.002a</td>
</tr>
<tr>
<td>a'</td>
<td>7.2±1.6</td>
<td>5.9±2.2</td>
<td>0.01a</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>11.2±3.8</td>
<td>11.5±2.9</td>
<td>0.84</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>62.5±8.1</td>
<td>64.5±6.9</td>
<td>0.07</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>0.51 (0.17)</td>
<td>0.52 (0.18)</td>
<td>0.002*</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>0.51 (0.17)</td>
<td>0.52 (0.18)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Mean values (SD) are shown. *p-value from non-parametric test.

Conclusions: Left atrial volume and left atrial function indices can predict later occurrence of paroxysmal atrial fibrillation. We confirm recently proposed findings of this prospectively studied patient group.

**P5395**

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 in order to evaluate the effectiveness of IRMs of various durations and frequencies in identifying AF recurrences and in the whole population. Sensitivity was defined as the proportion of patients the IRM identified as having AF recurrence to the number of patients with proven AF recurrence identified by with the continuous monitoring.

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 IRM monitoring strategy, four 24 h 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 as 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.

**P5394**

Healthcare policy and patient satisfaction with chronic treatment for stroke prevention: results from the European Patient Survey in Atrial Fibrillation (EPS-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 anticoagulation 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-reported satisfaction of 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 ranged 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 76% (UK) of patients had follow-up visits arranged with a doctor on leaving hospital.

Conclusions: The EPS-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 EPS-AF also highlights variations between different countries in the levels of patient satisfaction. These may reflect national differences 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.

**P5397**

Atrial fibrillation post myocardial infarction: With ventricular fibrillation and poor 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±2years was assessed. All data was collected on a structured database registry in which a wide range of variables were recorded including past medical history, co-morbidities, electrolyte disturbances, and drugs therapies.

Results: Baseline characteristics for AF group vs control were as follows: age (70.3±13.4 yrs vs. 65±4.3 yrs, P=0.001), male (65% vs. 69%; P=0.02) and EF (52±12 vs. 48±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 VF (OR 5.45, 95% CI: 1.13-25; P=0.005) was predictors in the in-hospital VF but not age, sex. On multivariate analysis, AF remained an independently significant predictor of VF (OR 2.9, 95% CI: 1.3-3; 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=0.06), 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.

Results:

Randomized Controlled Trials

**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 3% 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 6.4% pharmacological CV. Compared to pharmacological CV, patients undergoing electrical CV were more likely to be men, more often presented with persistent AF, and more often treated by transoesophageal echo. Mainly amiodarone and flecainide were used for pharmacological CV (41.9%, 12.8%). 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 discharge.

**Conclusions:** There is a group of patients quite interested in replacing standard face to face FU for AF. Main qualities of this group include treatment only in our center, having had an emergency admission because of the device and having a stronger interest in remote monitoring. Other factors such as distance to our centre do not seem to play an important role.
P5401 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. 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, 1272 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 the implant date. Estimated glomerular filtration rate (eGFR) was calculated as published and pts grouped to eGFR < 60 (N=195), 60-90 (N=576), 30-60 (n=438), and < 30 ml/min/1.73 m² (N=63). No pts were on dialysis. Kaplan-Meier estimates for mortality (N=635) and first appropriate ICD shock (N=274) as separate endpoints 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 m² (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.

P5402 What is the value of in-person evaluations prompted by alert notifications during ICD remote monitoring? The Trust trial

N. Varma1, J. Michalski2 on behalf of TRUST Investigators. 1 Cleveland Clinic, Cleveland, United States of America; 2Biotronik, Lake Oswego, United States of America

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 events (C and HM, patient and physician driven), and ANs prompted by ANs in HM.

Results: HM and C patients were similar: age 63±13 vs 64±12 yrs, 72±73% male, NYHA II class 56±30%, LVEF 29±11 vs 20±10%, CAD 65±20%, primary prevention 72±74%, DDD implants 57.8±56.6%. In total, 4,328 ANs were received during a possible 363,450 transmission days. Daily transmission success was 87%. 11% of 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).

Conclusions: In-patient remote monitoring is successful but not superior to conventional follow up.

P5403 Long-term follow-up after implantable cardioverter defibrillator implantation 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 was 48±14 years, 4 (12%) female. Twenty nine (85%) patients had spontaneous typical coved Type 1 ECG pattern, 15 (44%) had family history of sudden cardiac death (SCD) and (26%) 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 1 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±68 (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 1 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 Ajalmine challenge.

Methods: 16 pts with type 1 Brugada syndrome and implanted with St Jude Medical Angietest™ ICDs were enrolled and received Ajalmine 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-) Ajalmine challenges, respectively, based upon standardized criteria. In the A+ pts, the IEGM T wave amplitude changes were more prominent than those of the ST segment (387±483 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 107±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 Ajalmine 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 Ajalmine 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

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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 ischamic and non-ischamic origin were followed from ICD implantation to the time of first ICD-treated or recorded VT/VF (HR: 3.6; 95% CI: 1.4-9.1; p= 0.01) and coronary artery disease (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 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. Interrogation 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 (NDNICD).

Methods: Out of 935 ICD recipients followed at our center, 110 had NDNICD (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 55.05±15.62, 31 female (28.18%), 40 pts in secondary prevention (36.26%), mean left ventricle ejection fraction 62±10.6%. Duration
The morphology of far-field electrograms is a predictor of antitachycardia pacing effectiveness among fast VT occurring in ICD patients. Since the cycle length (CL) is a negative predictor of antitachycardia pacing (ATP) effectiveness, fast ventricular tachycardias (FVT) are less suitable to be terminated by ATP. Unsuccessful ATP therapies have negative clinical implications because delaying the definitive therapy prolongs the episode duration. Additionally, the older patients are associated with an increase in mortality in patients with left ventricular dysfunction (LVD). Among FVT occurring in ICD patients, no information is available regarding the ability of the far-field electrograms morphology (FI-M) in predicting the result of the subsequent ATP. We hypothesized that the F-I-M, as pseudo-unipolar signal and thus, as an indicator of the direction of propagation front, could be related to the ATP effectiveness.

**Methods:** We prospectively studied 204 FVT (CL: 250-320 ms) consecutively occurring in 33 ICD patients with Medtronic devices and LVD (LVEF: 37.1±6, pacing site: right ventricular apex). FVT programming was standardized, including a burst of 5 pulses at 84% of CL as initial therapy, and shocks for unsuccessful ATP. Configuration of FI-M was HAV-HVB. VTs were classified in QT or non QT at the first attempt, presence or absence of a negative initial deflection in the FI-M.

**Results:** The mean CL was 288±20 ms. The ATP effectiveness was 75% (Q-VT: n=132, 65%) had a higher CL (293±7) vs. 5%; p=0.01). They were associated with a higher left ventricular ejection fraction (LVEF) (35±6 vs. 35±7; p<0.001) and with a lower frequency of ischemic etiology (48 vs. 75%; p=0.01). The frequency of successful ATP was higher in Q-VT: 79 vs. 61% (p=0.007). By logistic regression analysis -which included LVEF, CL, ejection fraction, functional class, beta-blocker therapy and indication of the ICD (OR=0.1; p=0.003), an ischemic etiology (OR=5.9, 0.01), the beta-blocker therapy (OR=5.7; p=0.001) and a QT-VT pattern (OR=3.8; p=0.003) were found to be as independent predictors of effective ATP. Non Q-VTs need more frequently SH to be terminated (39 vs. 19%; p=0.01). As a result, syncope-related FVT was more frequent in QT-VTs (15 vs. 5%); p=0.01).

**Conclusions:** Among FVT occurring in ICD patients, QT-VTs are more suitable for termination by ATP independently of CL. On the other hand, non-Q-VT which are usually ischemic- are poorly tolerated and more frequently terminated by SH. In order to avoid SH, the subdistribution of non-Q VTs may need a more intensive treatment.
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.

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. 71.3% 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 age 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=0.009). The median time of heart failure to NYHA class III and IV had only 70% in group A vs. 12.5% in group B (p=0.02).

Conclusion: CRT is an effective therapeutic approach for patients with moderate heart failure. Although patients with QRS complexes >150ms benefit from CRT, 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.

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%). Device implantation, 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 (86%) completed the >75 bpm arm. X Patients dropped out before cross-over and 51 patients implanted 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

Figure 1. Secondary outcomes across study phases

248±101 meters and 255±118 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.

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

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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 or not spontaneous improvement 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 symptomatic benefits 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 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.

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

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

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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: At 34 heart failure (HF) patients underwent echocardiography and CMR the day before CRT implantation; echocardiography was repeated after 6 month. Using cine steady-state free precession sequence we measured LV and RV volumes and ejection fraction (EF), the ratio of LV mass to LVEDV (as an indicator of negative LV remodeling) 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 (118±38 ml vs 164±44 ml, p=0.01), smaller LVEF (51±8% vs 60±12%, p=0.05), GREVEF (25±5% vs 21±6%, p=0.003) and higher L/MVEDVi ratio (0.53±0.14 vs 0.42±0.11, p=0.008) than non-responders. 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 volume of delayed enhancement (6.37 ml vs 16.14 ml, p=0.04) that is consistent with smaller myocardial scar burden. Finally responders had smaller RVEDVi (86±16 ml vs 74±21 ml, p=0.03), smaller RVEF (22±11 ml vs 31±33 ml, p=0.03), greater RVEF (63±9% vs 51±15%, p=0.01). At statistical analysis LV mass/LVEDVi 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 0.11, 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

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Introduction: Spontaneous AV conduction Delay (AVD) determines the safety and efficacy of conventional DDD(R) pacing. The SafeR mode (AAI(R)–DDD(R) changeover) provides diagnostic insight into spontaneous AV conduction. This study examines the distribution of the intrinsic device-recorded AVD in a broad PM population.

Methods: 642 patients (pts) were implanted with a dual chamber PM (72±11 years, 65.2% males, 50% Sinus Node Dysfunction (SND), 50% AV Block (AVB)). 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: 219±64ms, PR: 238±70ms, p<0.001) (Figure 1). AVB pts had significantly longer AR & PR than SND pts (AVB: AR 232±75ms, PR 235±70ms, p<0.003; SND: AR 224±62ms, PR 203±62ms, p<0.002). The atrial paced-sensed (AR - PR) difference did not differ in AVB vs SND pts (86±31ms vs 91±50ms, p=ns). AR & PR beyond nominal DDD paced/sensed AVD values (220 ms & 155 ms) occurred in 94%/94% of pts, respectively, regardless of the implant indication.

Conclusion: The SafeR mode allows an in-depth analysis of the intrinsic AV conduction in implanted pts. DDDR(R) pacing with standard AVD settings is likely to produce a high proportion of unneeded VP. Although avoiding very long 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.
Alterations in the expression of genes related to contractile function and hypertrophy of the left ventricle in chronically paced patients from the right ventricle apex (preliminary results)


Background: Long term asynchronous ventricular activation from right ventricular apex stimulation results in increased wall stress and hypertrophy of the left ventricle, neurohormonal 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 alterations of the expression of genes related to contractile function and hypertrophy of the left ventricle, after right ventricular apical pacing in patients with preserved left ventricular systolic function.

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 exceeding 90%, while group B who served as controls, suffered sinus node dysfunction and had preserved intrinsically atrioventricular conduction.

At the time of the enrolment, 6 months later, we evaluated in the peripheral blood concentrations of messenger ribonucleic acid (mRNA) of: 1) sarcoplasmic reticulum calcium ATPase (SERCA), and 2) β-myosin heavy chain (β-MHC). Relative mRNA levels were measured using Fluorescence quantitative real time PCR.

At the same time points, we estimated echocardiographically 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±12 msec, while the remaining 16 patients, group B, have a mean QRS duration 124±13 msec.<br> In group A at 3-months follow-up, mRNA levels of SERCA were decreased (9.3±1.49 vs 4.04±1.33 p=0.021) and β-MHC mRNA levels were increased though not significantly (62.12±46.97 vs 42.4±24.5 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±6.2 vs 32.4±2.2, p=0.4 and 61.2±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.

Comparison of the influence of the right apical vs septal pacing site on survival in patients with implanted pacemaker in 3.5 years follow-up, data from single center registry

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Purpose: The optimal right ventricle (RV) permanent pacing site is still under research.

The aim of the study was to assess the influence of right ventricular apical (RV-AP) vs septal (RV-SP) pacing site in survival patients with implanted pacemaker.

Methods: The 612 consecutive patients (318 women) aged 72,18±10,70 years, who underwent basic 2nd and 3rd level of care treatment, during the period from 2006 and 2008, who underwent either dual (DR) or single (VR) chamber pacemaker implantation for typical pacing indications were analysed retrospectively.

Conclusions: The survival in the group of 612 pts the multivariable Cox regression analysis showed that the independent risk factors of death were age [HR 1,045 per year; 95%CI (1,026-1,064)], male sex [HR 1,614 95%CI (1,192-2,186)] and VVI mode of pacing [HR 2,291 95%CI (1,619-3,206)]. The use of statin [HR 0,545 95%CI (0,379-0,766)] and anticoagulation (AVK) [HR 0,287 95%CI (0,139-0,592)] were associated with better survival. In female patients the risk factors of death were age [HR 1,076 per year; 95%CI (1,034-1,111)], beta-blockers, diabetes and VVI mode of pacing [HR 2,291 95%CI (1,619-3,206)]. The use of statin [HR 0,545 95%CI (0,379-0,766)] and anticoagulation (AVK) [HR 0,287 95%CI (0,139-0,592)] were associated with better survival. In male patients the risk factors of death were age [HR 1,023 per year; 95%CI (1,001-1,045)], beta-blockers, diabetes and VVI mode of pacing [HR 2,291 95%CI (1,619-3,206)]. The use of statin [HR 0,545 95%CI (0,379-0,766)] and anticoagulation (AVK) [HR 0,287 95%CI (0,139-0,592)] were associated with better survival. In male patients independent risk factors of death were age [HR 1,023 per year; 95%CI (1,001-1,045)], VVI mode of pacing [HR 2,291 95%CI (1,619-3,206)] and age at pacemaker implantation [HR 1,773 95%CI (1,139-2,762)]. Beta blockers take and AVK shown statistically borderline positive effect [p=0.01). There were no significantly differences between examined parameters analyzed depending of ventricular lead site in male patients group.
female, the significant difference in AVK use (p<0.05) between similarly groups was detected only.

Conclusions: Obtained data confirmed a beneficial role of dual-chamber pacing. Right ventricular septal versus apical site of pacing is associated with better prognosis in male but not in female patients.

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 K9328H. 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 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 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=0.92, p<0.0001) and the lipid content of the plaque (r=0.525, p<0.0001) and the lipid content of the plaque (r=0.525, p<0.0001). Multivariate analysis revealed that the lesion length was the strongest predictor of the total lipid volume. Slow flow phenomenon was developed in 13 target lesions (4.7%). As compared with the lowest quartile of lipid volume, the highest quartile group was associated with increased risk of slow flow phenomenon after coronary stent implantation (odds ratio, 7.56; 95% CI, 1.31–145.6; p=0.022).

Conclusion: The frequency of slow flow phenomenon increased in PCI for coronary plaque with large lipid volume.

Large lipid volume in coronary plaque causes slow flow phenomenon in percutaneous coronary intervention

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Purpose: It has been reported that slow flow phenomenon is caused by the leakage of lipid component from the target plaque of percutaneous coronary intervention (PCI). The purpose of this study is to investigate the relationship between the lipid volume and the frequency of slow flow phenomenon.

Methods: Consecutive 275 target lesions of PCI were investigated by integrated backscatter intravascular ultrasound (IB-IVUS) before coronary stent implantation. The vessel parameters (lesion length, vessel area and lipid area per 1mm silicone) were measured and the total lipid volume of the target lesion was calculated by integration of every slice. The frequency of slow flow phenomenon was investigated in 4 groups divided by the quartile of lipid volume.

Results: The total lipid volume of target plaque was significantly correlated with the lesion length (r=0.566, p<0.0001) and the lipid content of the plaque (r=0.525, p<0.0001). Multivariate analysis revealed that the lesion length was the strongest predictor of the total lipid volume. Slow flow phenomenon was developed in 13 target lesions (4.7%). As compared with the lowest quartile of lipid volume, the highest quartile group was associated with increased risk of slow flow phenomenon after coronary stent implantation (odds ratio, 7.56; 95% CI, 1.31–145.6; p=0.022).

Conclusion: The frequency of slow flow phenomenon increased in PCI for coronary plaque with large lipid volume.

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

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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-
Conclusions: Current OCT is not sensitive enough to detect plaque neovascularization. Coronary plaques with MC detected by OCT may be associated with accelerated plaque progression.

Methods: In the present study diabetes was induced in 8 pigs by giving an injection of streptozotocin (140 mg/kg). Seven non-diabetic (non-DM) pigs were used as controls; all animals were fed a saturated-fat cholesterol (SFC) diet. After 9 months of diabetes, 32 everolimus eluting BVS were implanted in the coronary arteries under quantitative coronary angiography (QCA) and optical coherence tomography (OCT) guidance. OCT subgroup 5.9% (p=0.3) and TLR in FFR subgroup 3.1% vs. IVUS subgroup 4.4% (p=0.9) with no infarctions related with the target vessel. In the FFR center 471 patients were included (545 lesions studied). After IVUS measurement, 364 (67%) lesions were left untreated in 321 patients. In the IVUS center 352 pts were included (429 lesions studied). After IVUS examination, 228 (53%) lesions were left untreated in 182 pts (p=0.001 vs. FFR center). The clinical and angiographic profile of both groups was well balanced without significant differences except for the age (FFR 67.8±11, p=0.01). Events in the deferred subgroups at 2 years: death and infarction in FFR subgroup 4.2% vs. IVUS subgroup 4.4% (p=0.09) with no infarctions related with the target lesion and TLR in FFR subgroup 1.8% vs. IVUS subgroup 2.7% (p=0.7). Events in treated subgroups at 2 years: death and infarction in FFR subgroup 10.4% vs. IVUS subgroup 5.9% (p=0.03) and TLR in FFR subgroup 3.1% vs. IVUS subgroup 1.8% (p=0.7). The assessment of the performance of OCT in the prediction of late clinical outcomes is still controversial. In our study we found a good correlation between OCT and IVUS in the prediction of late clinical outcomes.

Conclusions: The assessment of intermediate lesions with OCT has a higher degree of revascularization (47% vs. 33%). At 2 years follow up both strategies result safe with a very low rate of lesion-related events in deferred cases, no infarctions related with target lesion and only a 2.3% of target lesion revascularization.

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 mm³; n=36), group M (0.55 mm³ < protrusion < 1.53 mm³; n=36), and group S (≤ 0.55 mm³; n=37). Among these 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, 80 lesions were detected in 75 lesions (78.5%) in OCT imaging. Of 39 lesions (35.8%) and 18 lesions (16.5%), respectively and slow-flow phenomenon during PCI were observed. No significant deterioration of coronary flow (Westergren, Massachusetts) or Thrombolysis in Myocardial Infarction flow grade 0-2) was observed in 9 lesions (8.3%). The greater volume of tissue protrusion after PCI was associated to the higher frequency of pre-existing lipid-rich plaque (group L: 75.0%, group M: 44.4%, group S: 51.4%, p = 0.03).}

Quantitative optical coherence tomography analysis of in-stent tissue growth after implantation of a bioresorbable vascular scaffold (BVS) in a diabetic animal model


Purpose: Assessment of intermediate coronary lesions can be done with IVUS and FFR. Both have their advantages and limitations. There are no randomized trials comparing these strategies. There are small registries from the same center but subjected to important biases.

Methods: In two public institutions the strategy for intermediate lesion evaluation has been different in previous years, in one was based in IVUS (IVUS center) and in the other was based in FFR (FFR Center). We have compared the outcome of patients with intermediate lesions (40-60%) assessed in a 4 years period (2006-2009) in both centers. The criteria for revascularization was FFR < 0.75 and a minimum lumen area < 2 mm² in vessels < 3 mm and < 3.5 mm² in vessels 3.5-3.9 mm.

Results: In the FFR center 471 patients were included (545 lesions studied). After IVUS measurement, 364 (67%) lesions were left untreated in 321 patients. In the IVUS center 352 pts were included (429 lesions studied). After IVUS examination, 228 (53%) lesions were left untreated in 182 pts (p=0.001 vs. FFR center). The clinical and angiographic profile of both groups was well balanced without significant differences except for the age (FFR 67.8±11, IVUS 64±11, p=0.01). Events in the deferred subgroups at 2 years: death and infarction in FFR subgroup 4.2% vs. IVUS subgroup 4.4% (p=0.09) with no infarctions related with the target lesion and TLR in FFR subgroup 1.8% vs. IVUS subgroup 2.7% (p=0.7). Events in treated subgroups at 2 years: death and infarction in FFR subgroup 10.4% vs. IVUS subgroup 5.9% (p=0.03) and TLR in FFR subgroup 3.1% vs. IVUS subgroup 1.8% (p=0.7).

The assessment of the performance of OCT in the prediction of late clinical outcomes is still controversial. In our study we found a good correlation between OCT and IVUS in the prediction of late clinical outcomes.

Conclusions: The assessment of intermediate lesions with IVUS induce a higher degree of revascularization (47% vs. 33%). At 2 years follow up both strategies result safe with a very low rate of lesion-related events in deferred cases, no infarctions related with target lesion and only a 2.3% of target lesion revascularization.
Synergistic Effect of combination therapy with Cilostazol and probUOCl on plaque stabilization and lesion REResolution (SECURE) trial

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Background: The study purpose was to investigate effects of cilostazol and pre-atherosclerotic lesion stabilization therapy on coronary plaque volume and composition using VH-IVUS in comparison with cilostazol monotherapy.

Methods: The SECURE study was designed as a double-blind, randomized, controlled trial to assess clinical efficacy and safety. A total of 119 patients undergoing coronary PCI were randomized either in the combination therapy group (n = 59) or in the cilostazol monotherapy group (n = 60). The primary end point was the change in the percent 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 changes were not significantly different between both groups. However, the change in PAV at the index intermediate lesion did not differ between the combination therapy and the cilostazol monotherapy (-3.32% ± 0.54% vs. -0.72% ± 0.39%, p = 0.788). Change in plaque composition of the intermediate lesion by Virtual Histology did not differ between the two groups either. The change in LDL cholesterol was similar between the two groups (-36.01 ± 35.53 vs. -37.35 ± 30.08 mg/dL, p = 0.935). However, oxidized LDL was more significantly decreased in the combination group (-9.64 ± 8.66 vs. -4.78 ± 9.29 mg/dL, p = 0.008).

Conclusions: There was significant decrease in plaque volume in both groups. However, the change in PAV at the index intermediate lesion did not differ between the combination therapy and the cilostazol monotherapy, so further studies are needed to determine whether the combination therapy and cilostazol monotherapy allow the definition of new reference levels (75th centile) for DAP, FT, NF and NR.

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 for longitudinal studies, such information remains unexplored. The aim of the present study was to evaluate in vivo reproducibility of quantitative FD-OCT measurements of coronary plaques.

Methods: We examined 20 stent-treated coronary lesions by using FD-OCT (C7, LightLab Imaging, Inc., Westford, Massachusetts, USA). Following FD-OCT imaging, patients underwent the re-engagement of the 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 (r = 0.99, p < 0.001), length (r = 0.99, p < 0.001) and lumen volume (r = 0.98, 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 mm², respectively; and the lower and upper limit of agreement for minimum lumen area, lesion length and lumen volume were -0.58 to 0.45, -0.36 to 0.42, and -13.4 to 12.1, respectively.

Conclusions: The quantitative FD-OCT measurements from repeated pullbacks showed excellent reproducibility. Our result emphasizes the value of FD-OCT as a tool for the clinical long-term assessment of coronary lesions.
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 (WHLH-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 staining and RAM-11 staining 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 period 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±0.62mm², p=0.021), while it tended to be reduced in group P (n=17) (7.06±1.86mm² vs. 6.60±1.62mm², p=0.058).

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±11.9% vs. -7.8±19.4%, p=0.047).

Postmortem histology at the follow-up showed that in group P %fibrous area was large (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 it also stabilized plaque in decrease in lipidic area and macrophage accumulation, and with increase of surface fibrotic area. These findings might give an insight into mechanism of regression of plaque by statins.

The therapeutic impact of the stent visualization enhancement technique (stentboost) in percutaneous coronary intervention

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Background: Underdeployment and malapposition 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 deflated balloon in place. SB allows a simple, real-time assessment of stent deployment.

Aim of the study was to compare 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 76%. Results of SB and angiography were concordant for 209 lesions: 195 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 in DES and non-DES), (p<0.001). In 21 patients (7%), the absence of SB was higher for left main lesions and for DES, and when not affected by coronary calcifications.

Conclusions: 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.

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Prognostic information of the SYNTAX- and Gensini-score on long-term outcome in Coronary Artery Disease - results of the AtheroGene 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 Score (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) or 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 AtheroGene cohort, a sample of consecutive caths 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 non-fatal myocardial infarction 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 analyses showed increased cardiovascular event rates across tertiles (both p<0.0001). 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 1.36-1.86; p=0.001) for the SYNTAX Score and of 1.58 (95% confidence interval 1.36-1.86; p=0.001) for the Gensini Score in a model adjusted for classical risk factors. The association remained statistically significant after additional adjustment for N-terminal pro B-type natriuretic peptide with hazard ratio of 1.53 (95% confidence interval 1.18-1.96; p=0.0013) for the SYNTAX Score and of 1.43 (95% confidence interval 1.14-1.77; p=0.0015) 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.

Coronary hibernation of the distal segment to coronary chronic total occlusions successfully treated with drug-eluting stents

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Background: Coronary segments distal to chronic total occlusions (CTO) have shown negative remodeling with respect to reference 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 them 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 nitroglycerin. Quantitative coronary angiography and QCA parameters changes were assessed by differences 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 11.1% from baseline to follow-up (2.65±0.68 to 2.85±0.65 mm; p<0.001). A total of 30.5±31.5 mm were analyzed distal to the stent edge by IVUS. Lumen volume increased 23.1% from baseline to follow-up (from 130.62±99.84 to 197.52±132.89 mm³; p<0.001). Vessel volume increased 11.1% from baseline to follow-up (from 265.54±191.48 to 299.80±223.49 mm³; p<0.002) and plaque volume remained unchanged between baseline and follow-up (from 134.94±99.90 to 131.94±100.99 mm³; p=0.295).

Conclusion: Distal segments to coronary CTO show an important lumen and vessel enlargement without plaque remodeling after successful percutaneous recanalization as assessed by QCA and volumetric IVUS at 15 month follow-up. An impaired response of the vessel wall distal to the occluded segment to nitroglycerin immediately after successful recanalization is the most plausible explanation. Therefore, treatment of angiographic lesions distally to the occluded segment must be discouraged after successful recanalization when normal flow of the coronary artery is achieved.
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 tomography (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 ultrasonic 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±8% vs. 48±14%, 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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Introduction: 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 surrogate endpoints 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 was 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 +1.0), with 15.0% (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). Modified% of plaque volume was however significantly related to the incidence of myocardial infarction and repeat revascularization at long-term follow up (Beta= -0.768; p=0.023) but not at 6 months (Beta=-0.512; p=0.147).

Conclusions: Regression of coronary plaque measured at IVUS directly relates to reduction of combined clinical end point long-term follow up.
**Results:** Anatomically relevant coronary artery disease (≥70% diameter stenosis) was present in 157 women (37%): 97 women (62%) had one vessel, 43 (27%) had two vessels, and 17 (11%) exhibited three vessel disease. The combination of two stress imaging modalities significantly increased the positive predictive values (PPV) to 90%, 88% and 87% for CMR/DSE, DSE/SPECT and CMR/SPECT, respectively. For patients with negative combined test results, the Cox survival analysis showed a 4-year cumulative event-free survival rate of 99% for all combinations. This new approach is cost effective using the combination CMR/DSE and DSE/SPECT.

**Conclusions:** In postmenopausal women, integrating two stress imaging modalities significantly increases the PPV for detection of CAD and the prediction for future cardiovascular events. This approach may be applied to improve the prognostic accuracy of non-invasive CAD tests and to avoid unnecessary CAs.

**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 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 difference 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.

**P5445**

**RenaGuard, hemofiltration and hydration in prevention of contrast induced nephropathy in patients with severe chronic kidney disease undergoing percutaneous vascular interventions**

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**Background:** Contrast-induced nephropathy (CIN) is a frequent complication of percutaneous coronary and peripheral artery interventions and is associated with significant in-hospital and long-term morbidity and mortality. We aim to compare the impact on major events of RenaGuard system (RG), continuous venovenous Hemofiltration (CVVH) and hydration (Hy) with sodium bicarbonate plus N-acetylcysteine in patients with severe renal failure.

**Methods:** We assigned 100 consecutive not dialyzed patients with severe renal failure (eGFR ≤ 30 mL/min x 1.73m² or with a baseline SerumCreatinine ≥ 1.5 mg/dL, or with a CIN risk score ≥ 11) scheduled for an elective percutaneous coronary and/or peripheral interventions to a preventive strategy with RG (33 pts), CVVH (35 pts) or Hy (32 pts). Primary end points were In-Hospital and 1 month dialysis and MACEs, and CIN. Secondly, 6-Month MACEs were recorded.

**Results:** In-H dialysis occurred in none of RG patients, 7 (20%) of CVVH patients vs 2 (6.3%) of Hy group (p=0.01). In-H MACEs were significantly less frequent in RG procedure [RG: 2 (6.1%), CVVH: 13 (37.1%) and Hy: 4 (12.5%) p=0.003; OR RGs CVVH: 0.12; CI:0.02-0.60, p=0.01]. Similar trends were seen at 1 and 6 month follow-up (Fig). Particularly, none of RG patients died at 6 month FU, vs 9 (27.3%) CVVH patients and 2 (6.3%) Hydration protocol patients (p=0.002).

Albeit not significant, CIN occurred less frequently in RG patients (15.2%) than CVVH (31.4%) and hydration protocol (25.0%) (p=0.288).

**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 venous-venous Hemofiltration and Hydration.

Lipid core coronary plaques detection by serial intracoronary imaging with a NIRS catheter in athereogenic, 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 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±3.4 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 towards proximal in all three coronaries.

Conclusions: We demonstrate that NIRS are associated with vulnerable plaque features, while Cys-C levels with fibrous plaque features, suggesting that biomarkers may be useful in the risk assessment of human coronary vulnerable plaque.

The feasibility and diagnostic yield of optical coherence tomography guided thrombus aspiration in patients with non-S-raise-elevation 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-raise-elevation myocardial infarction (NSTE-MI) is less well established. Optical coherence tomography (OCT) enables the detection of intracoronary thrombus during PCI.

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.

The study of tissue has shown a specific pattern of fibrous plaque as compared to fibrolipidic and fibrocalcific plaque [0,94 (0,02-2,1) vs. 14,14 (0,07-57) vs. 14,14 (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 (0,9-51) vs. 19,9 (7,6-51), 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 features, while Cys-C levels with fibrous plaque features, suggesting that biomarkers may be useful in the risk assessment of human coronary vulnerable plaque.
Intra stent neo-atheroma rupture as a potential impact of Cytochrome P450 2C19 loss-of-function

Assessment of neointimal tissue characteristics in very late stent thrombosis (VLST) was observed during the first 30 days following percutaneous coronary intervention (PCI) occurring >1 year after initial procedure. Recent individual reports showed that neo-atheroma plaque development could occur after stent deployment and evolve towards rupture and acute coronary syndrome. 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 mid 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. Neoatheroma was defined as reported in the combination of neointimal diabetic proliferations plus 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 (VLST) of 50% of ST elevation myocardial infarction. Among this group, we identified n=5 subjects with evidences of neo-atheroma, including fibrous cap rupture and thrombus. No evidence of stent under expansion, malapposition or incomplete endothelialization was reported by OCT analysis. The mean delay between initial PCI and VLST was 11.8±2.2 days (median: 11 days) following the first 30 days following VLST.

Conclusion: Our data show that neo-atheroma is common in patients with VLST. These results suggest that OCT imaging is useful to identify the mechanisms underlying VLST and therefore appears particularly valuable in the clinical decision making process involved in the treatment of subjects with this complication.

Invasive coronary imaging II 1005

Intra stent neo-atheroma rupture as a potential mechanism for very late stent thrombosis: an optical coherence tomography analysis

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Purpose: Very late stent thrombosis (VLST) is a rare but severe complication of percutaneous coronary intervention (PCI) occurring >1 year after initial procedure. Recent individual reports showed that neo-atheroma plaque development could occur after stent deployment and evolve towards rupture and acute coronary syndrome. 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 mid 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. Neo-atheroma was defined as reported in the combination of neointimal diabetic proliferations plus lipid-laden intima with plaque organization and fibrous cap.

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Conclusion: Our data show that neo-atheroma is common in patients with VLST. These results suggest that OCT imaging is useful to identify the mechanisms underlying VLST and therefore appears particularly valuable in the clinical decision making process involved in the treatment of subjects with this complication.

Abstract P5449 - Table 1. Analysis of apposition and coverage

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>2 months</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BES</td>
<td>EES</td>
<td>BES</td>
<td>BES</td>
</tr>
<tr>
<td>No. of total struts (n)</td>
<td>1515</td>
<td>1379</td>
<td>1515</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.0±0.3</td>
<td>2.9±0.3</td>
<td>3.0±0.3</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>23.3±3.1</td>
<td>25.1±3.9</td>
<td>24.4±4.9</td>
</tr>
<tr>
<td>OCT findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-apposed with neointima (%)</td>
<td>60.6±16.5</td>
<td>37.6±16.5</td>
<td>77.2±8.3</td>
</tr>
<tr>
<td>Well-apposed without neointima (%)</td>
<td>62.1±16.6</td>
<td>53.5±11.1</td>
<td>16.6±6.6</td>
</tr>
<tr>
<td>Malapposed without neointima (%)</td>
<td>0.9±1.0</td>
<td>0.5±1.0</td>
<td>1.2±2.2</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01 compared with EES. BES: biolimus eluting stent, EES: everolimus-eluting stent.
Conclusion: The heterogeneous neointimal tissues on OCT in stent restenosis may suggest the presence of athrombosis-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 an 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 (Odier 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 (SD) 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±93.7º. 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 expansion of the calcium arc (p=0.043), but neither the lesion length (p=0.225) or the length of stent used (p=0.518), was significant. A good correlation was found between the circumferential extent of calcium and the percentage of malapposed struts (p=0.048).

Conclusion: As measured by OCT, the circumferential extent of plaque calcification was found to correlate with stent strut malapposition following PCI.

P5454 Chosing the distal cell for bifurcational stenting: OCT guidance significantly reduces stent malapposition
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Purpose: In bifurcated lesions, the choice of the distal cell for stenting 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 lcg per kg) 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±5.2mm²; distal reference luminal area 6.3±2.7mm²; MLA 2.7±1.1mm²; plaque volume 236.3±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-TF (R=0.3; p=0.007). 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.

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 lcg per kg) were used to obtain maximal hyperaemia.

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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 vasoconstriction function in remote normal myocardium after primary coronary intervention for acute myocardial infarction
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Background: It has been reported the vasoconstriction 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 normal 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 infarct-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 2.56±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=0.025 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.

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**P5458** 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 Myocardial 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 TMPG and MBG.

**Results:** There were 3,345 subjects eligible for this study. x was highest for pre-PCI TIMI flow (0.62-0.65) and lowest for post-PCI TMPGMBG (0.11-0.22). Critical discordance between Op and ACL reading for final TIMI flow (0-2 vs. 3) occurred in 12.9% of patients and for final TMPGMBG (0-1 vs. 2-3) in 22.4%. Of the 708 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 track 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.

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**P5459** 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 about 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: 38 patients with 43 total stent segments, randomized trials including different types of stents were sequentially matched and analysed after implantation and at 6-12 months. Predictors for ISA correction and for completeness of coverage were sought.

Results: 66 stents (43 patients, 78 ISA segments) were analyzed. ISA volume decreased and 71.5% of the ISA segments were spontaneously corrected at follow-up. Coverage of acute ISA segments was delayed with respect to well-apposed segments (RF 2.37; 95% CI 2.91 – 2.78). Acute ISA volume was the only independent predictor for persistent ISA (OR 3.19, 95% CI 1.43 – 7.12) and for massively delayed coverage (OR 1.37, 95% CI 1.09 – 1.74). Acute ISA size was an independent predictor of ISA persistence and of delayed healing at follow-up. Maximal acute ISA distances <270 μm appeared grossly covered and spontaneously re-apposed in 100% of cases, whilst maximal ISA distances >850 μm resulted in persisting ISA and grossly delayed coverage in 100% of cases.

Conclusions: The neointimal healing tends to reduce ISA, often integrating it completely into the vessel wall and resulting in characteristic morphologic patterns. Coverage of ISA segments is delayed with respect to well-apposed segments. The larger the size of acute ISA, the larger the likelihood of persisting malaposed at follow-up and of delayed healing.

Comparison of neointimal thickness and extra-stent lumen between sirolimus- and everolimus eluting stent

T. Okamura1, Y. Yamada1, N. Miyagi2, H. Uehara3, T. Maeda3, T. Suetomi3, T. Naso1, T. Miura1, M. Matsuzaiki1, Y. Yamaguchi1, University Graduate School of Medicine, Department of Medicine and Clinical Science, Ube, Japan; 2Urasoe General Hospital, Urasoe, Japan.

Purpose: To examine the neointimal healing and extra-stent lumen between sirolimus-eluting stent (SES) and everolimus-eluting stent (EES) assessed by optical coherence tomography (OCT) as evaluated in a prospective randomized clinical trial.

Methods: Patients who underwent OCT examination more than 6 month after either SES or EES implantation in two hospitals were enrolled. A total of 728 cross sections and 6884 struts were analyzed. The new protocol did not involve any change in hardware. Parameters measured included dose-area product (DAP), X-ray time and equivalent patient thickness (EPT).

Results: A total of 36 lesions were included (SES n=17, EES n=19). Mean follow-up periods were similar (SES 10.6±0.27, 0.18 mm2 ±0.37 mm2, p=0.631). NIT of SES and EES were 110±46 mm2 and 95±45 mm2, 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 mm2 vs 0.03±0.03 mm2, p=0.011, 54±55° vs 31±48°, p<0.001, 0.20±0.27 mm vs 0.04±0.06 mm, p=0.001). Acute ISA size was an independent predictor of ISA persistence and of delayed healing at follow-up. Maximal acute ISA distances <270 μm appeared grossly covered and spontaneously re-apposed in 100% of cases, whilst maximal ISA distances >850 μm resulted in persisting ISA.

Conclusions: The neointimal healing tends to reduce ISA, often integrating it completely into the vessel wall and resulting in characteristic morphologic patterns. Coverage of ISA segments is delayed with respect to well-apposed segments. The larger the size of acute ISA, the larger the likelihood of persisting malaposed at follow-up and of delayed healing.

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 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 digitalized RF signal @200 Mhz and characterized using non-linearly co-registered histology images and IVUS B mode (see figure).

Conclusions: 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 Conf can be performed 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

M. Margaritis1, A.S. Antonopoulos1, J. Digby1, C. Chirodoria1, R. Lee1, M. Demosthenous2, B. Bakogiannis3, R. De Silva3, K.M. Channon1, C. Antoniades1. 1University of Oxford, Oxford, United Kingdom; 2University of Athens, Athens, Greece; 3John Radcliffe Hospital, Department of Cardiothoracic Surgery, Oxford, United Kingdom

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 luciferin-enhanced chemiluminescence. AdN gene expression was quantified in peri-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 6h and its effect on vascular redox state was examined.

Results: AdN gene expression was increased in SV grafts compared to controls (p<0.001). AdN treatment led to improved vasorelaxation to acetylcholine compared to controls (p<0.001). AdN produced in SV grafts was associated with improved NO bioavailability (A), lower vascular O2- (B) and better eNOS coupling (C) in SV grafts. However, high circulating AdN was associated with better NO bioavailability (A), lower vascular 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 a high range of CFI the effect of CSO was absent.

PHYSIOLOGY, HAEMODYNAMICS AND MICROCIRCULATION

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 Microrcirculatory Resistance (IMR) for evaluating the microvasculature in patients with stable angina pectoris undergoing PCI.

Methods: Intracoronary 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±0.12 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). Additionally, the control group showed a closer correlation between plaque volume reduction during stenting as assessed by volumetric IVUS and cTn elevation than the nicorandil group (r=0.55 vs. 0.42, p<0.001 for control vs. nicorandil).

Conclusions: Administration of nicorandil during PCI of patients with stable angina pectoris reduces microvascular dysfunction and myocardial damage.

Acute exposure to diesel exhausts impairs endothelial vasomotor function by increasing ROS production

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Exposure to diesel exhausts (DE) was recently identified as an important cardiovascular risk factor. Whether it alters endothelial function by an increase of ROS production in endothelial cells at rest, and if this is enhanced by exercise, is not known.

We tested these hypotheses in a randomized, crossover study design in 9 healthy male. Each subject was exposed to ambient and polluted air during 2 hours of rest and 1 hour of moderate exercise. The effects of DE on skin microvascular hyperemia, induced by iontophoresis of acetylcholine (Ach) and sodium nitroprusside (SNP), were examined using a Laser Doppler Imager system. Serum from the subjects (n=5) was collected, added to confluent monolayers of human umbilical vein endothelial cells (HUVECs), and incubated for 2 hours. ROS production by HUVECs was measured by lucigenin chemiluminescence and expressed in percent of the control sample. The particulate matter 2.5 μm (PM2.5) mean concentration was 12.9±4.3 μg/m3 on normal air and 309±1.6 μg/m3 on polluted air. Exercise enhanced abovar ventilation from 7.95±0.28/min to 32.1±1.01/min. Compared to ambient air, DE exposure reduced skin vasodilatation induced by Ach (p<0.05 at rest (Fig. 1), but this was suppressed by exercise. DE exposure did not affect SNP-induced skin vasodilatation. The lucigenin chemiluminescence measurements were 404±1.90% after ambient air exposure, 481±1.12% after polluted air exposure at rest and 669±1.14% after polluted air exposure at rest (p<0.05) showing a linear doses-response pattern.
Acute DE exposure impairs microvascular endothelial mediated vasodilatation at rest by inducing ROS production. This endothelial dysfunction is likely overriding by the favorable vascular effects of exercise-induced hyperemia, despite an increase in infused PM2.5.

**Role of neuronal versus endothelial nitric oxide synthase in the coronary artery blood flow response to pacing**

P.5468

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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 in-vivo studies with a neuronal NOS (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 were recruited. 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 (19.3±2.5% vs. 25.0±2.6%; n=10 each; P=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 (81.6±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 increase atrial pacing which humans are mediated by nNOS-derived NO rather than eNOS-derived NO.

**Usefulness of the index of microcirculatory resistance for predicting late left ventricular remodeling and recovery immediately after primary angioplasty in anterior myocardial infarction**

P.5469

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**Purpose:** Microvascular integrity is an essential determinant of favorable late outcome in reperfused myocardial infarction and quantitative assessment of microvascular injury immediately after reperfusion is useful to predict left ventricular (LV) functional recovery after acute myocardial infarction (AMI). The purpose of this study was to assess the usefulness of the index of microcirculatory resistance (IMR) for predicting late LV remodeling and recovery in patients with reperfused AMI treated with primary angioplasty.

**Methods:** After successful primary percutaneous coronary intervention (PCI) in 43 patients (age 55±12 years, 38 men) with first anterior AMI, IMR was measured using a pressure-temperature sensor-tipped coronary guidewire. Echocardiography was performed at 6 months in all patients and at 3 years in 39 patients for assessment of the percent change in anterior wall motion score (A-WMS) and LV remodeling.

**Results:** IMR correlated significantly with percent change in A-WMS, LV end-diastolic volume index and LV end-systolic volume index at 6 months (r = 0.430, p = 0.004; r = 0.402, p = 0.006; r = 0.475, p = 0.001, respectively) and at 3 years (r = 0.451, p = 0.004; r = 0.532, p < 0.001; r = 0.483, p = 0.002, respectively). The area under the receiver operating curve of IMR for predicting LV remodeling defined as increase in end-diastolic volume ≥ 20% at 6 months and at 3 years were 0.76 [95% CI 0.597-0.882] and 0.74 [95% CI 0.587-0.864], respectively. An optimal cut-off value of 33U for IMR was chosen to predict 3-year LV remodeling (sensitivity = 85%, specificity = 77%, positive predictive value = 65%, negative predictive value = 91%).

**Conclusions:** IMR, a quantitative microvascular index, is a reliable early on-site predictor of late LV function recovery after primary PCI and provides useful information in identifying patients at high risk of late LV remodeling in spite of successful revascularization.

**Thermodilution derived coronary blood flow patterns immediately after coronary intervention as a predictor of microcirculatory damage and mid-term clinical outcomes after acute myocardial infarction**

P.5470

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**Purpose:** Despite a sufficient coronary flow after percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) patients, some have a poor outcome due to microcirculatory damage. We assessed whether the thermodilution derived blood flow parameters measured with a pressure sensor/thermistor tipped guidewire immediately after primary PCI for STEMI predict early microvascular damage and mid-term outcomes.

**Methods:** We prospectively enrolled 80 STEMI patients. By using a pressure sensor/thermistor tipped guidewire, we measured the index of microcirculatory resistance (IMR) at maximum hyperemia and assessed coronary blood flow pattern with the thermodilution technique after successful PCI. Coronary blood flow patterns were classified into 3 groups according to the shape of thermodilution curve: sharp monomodal (n=36), dull monomodal (n=30), or bimodal shape (n=14). Clinical hard events were defined as cardiac death and/or heart failure re-hospitalization within 6 months.

**Results:** The IMR values were significantly higher both in dull monomodal and bimodal shapes than in sharp monomodal (63±38 and 77±39 vs. 20±8U, p<0.001). Patients with bimodal shape had a higher risk of clinical hard events at 6 months (Figure). Multivariate analysis revealed that bimodal shape of the thermodilution curve was the only independent predictor of 6 months clinical hard events (p<0.01).

**B-type natriuretic peptide and central haemodynamics: association with angiographic coronary disease and adverse cardiovascular outcomes**

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**Background:** B-type natriuretic peptide (BNP) is an indicator of left-ventricular (LV) dysfunction and also a biomarker of coronary artery disease (CAD) and cardiac failure.
events. We sought to determine the clinical benefit of using BNP in a population undergoing diagnostic angiography and identify possible mechanisms.

**Methods:** 468 participants without prior coronary bypass surgery were risk-assessed at baseline. Radial artery pulse wave analysis was used to derive central pulse pressure (cPP). Outcomes were the presence of angiographic CAD and the composite of death, myocardial infarction, transient ischemic event or stroke at follow-up.

**Results:** Mean age was 64, 65% were male, 21% had diabetes and 16% had impaired LV. BNP was higher in older patients, those with anaemia or low glomerular filtration rate and with LV impairment or raised cPP (all p<0.01). Gender and diabetes had no relationship to BNP at baseline. BNP was significantly associated with angiographic CAD even after adjustment for LV impairment and vasoactive medications; Odds ratio (OR) 1.33 per log unit increase in BNP (95% CI 1.03-1.71; p=0.03). On sub-group analysis, there was a significant interaction with cPP (p=0.03). In patients with cPP<50mmHg (median), there was little or no association of BNP with CAD (see figure). At a mean follow up of 1.2 years, BNP was independently associated with the composite clinical outcome; OR 2.00 (95% CI 1.31-3.05; p=0.001). Similar to above, this relationship was only significant in patients with raised baseline cPP.

**Conclusions:** BNP was associated with the presence of angiographic CAD and cardiovascular events at follow-up, irrespective of LV impairment. The interaction with cPP suggests that central haemodynamics may be part of the mechanism for BNP release in patients with coronary atherosclerosis.

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**P5472**

**Anatomical variants of circumflex coronary artery and coronary sinus inter-relations**

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Anatomical variants of relations of left circumflex artery (Cx) and coronary sinus (CS) determine safety of percutaneous mitral annuloplasty (PMA), as in some cases an occlusion of the Cx and its consequences might occur. Thus, the knowledge on cardiac vessels anatomy and its variation appear mandatory for the operators.

**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 ml/s was given in three phases. In each case the first (10) 3D volume rendering and 2D MPR reconstructions of the vessels were created (Vitrea 2).

**Results:** CS was visualised in all cases and LCx in 215 (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.

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**P5473**

**Evaluation of angiogenic gene therapy effect with laser doppler flowmetry and magnetic resonance imaging in patients with chronic limb ischemia**

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**Background:** Therapeutic angiogenesis is a new treatment option for patients with chronic limb ischemia. However, thorough evaluation of its effect is hampered by the lack of reliable diagnostic tools for limb tissue perfusion assessment. Magnetic resonance imaging was shown to be accurate enough for this purpose on small groups of untreated patients. Laser doppler flowmetry has not been previously reported to be employed in angiogenic gene therapy patients.

**Methods:** 30 patients with Fontaine IIb-IV atherosclerotic limb ischemia who were not candidates for surgery or endovascular treatment were randomly assigned to receive vascular endothelial growth factor (VEGF) gene therapy (GT, n=16) or conventional treatment (CT, n=14). All subjects underwent 2 identical MRI examinations of the lower extremities on a clinical 1.5-T MR system prior to and 3 months after the treatment. Gadolinium contrast was infused at rest and at peak exercise. The MR protocol included contrast angiography flow measurements in tibial arteries and dynamic contrast-enhanced perfusion imaging in calf muscles to determine area under the curve, maximal relative flow/perfusion and time-to-peak. Patients were also assessed by laser doppler study with positional and thermal tests, transcutaneous oxymetry with positional tests, treadmill test, duplex ultrasound and (in part) by quantitative angiography.

**Results:** 3 months after treatment GT patients demonstrated significant improvement of calf muscle perfusion and tibial blood flow at peak exercise, accompanied by the improvements of walking distance and ankle-brachial index, while angiography revealed a significant increase of collateral network. Laser doppler study revealed a significant tissue perfusion rise at rest and after thermal test, correlating with clinical and functional improvement. No change of clinical or laboratory indices were found in CT group patients. MRI-assessed muscle perfusion strongly correlated with walking distance, ankle-brachial index, tissue oxygen pressure and collateral density. Tibial blood flow correlated with site and degree of limb artery obstruction. The only correlate for Rutherford clinical improvement score was increment of muscle perfusion.

**Conclusions:** Tissue perfusion assessed by contrast MRI and laser doppler study correlate with functional capacity, collateral circulation and overall clinical effect in patients with chronic limb ischemia. These methods may be useful for further clinical studies of angiogenic gene therapy.

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**P5474**

**Stenosis significance by angiography: small versus large vessels**

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**Background:** Coronary Angiography is known to correlate modestly with functional lesion severity. However the factors which influence the relationship between percent diameter stenosis and fractional flow reserve (FFR) have not been properly investigated.

**Aim:** To compare the diagnostic accuracy of Quantitative Coronary Angiography (QCA)-derived percent diameter stenosis (DS) in predicting FFR in coronary arteries of various sizes.

**Methods:** Between 2001 and 2012, 6506 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 angi-derived DS in identifying the functional significance of stenoses is lower on the caliber of the artery: the smaller the artery, the larger the inaccuracy.

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**Methods:** Two hundred and twenty-seven consecutive patients with first anterior STEMI who underwent percutaneous coronary intervention (PCI) were subjected to coronary flow measurement. Thirty-four (15%) were excluded because of pre-procedural Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow. We defined the presence of MVO-CFV as DDT of < 600 ms and the presence of systolic flow reversal (SFR).

**Results:** The incidence rates of the MVO-CFV according to time from symptom onset to the first balloon inflation are shown in Figure. Earlier reperfusion was associated with a significantly lower risk of MVO-CFV (0/16, 0%; <120 min vs. 10/32, 31%; ≥120-180 min vs. 19/41, 46%; >180-240 min vs. 14/42, 64%; >240-300 min). There was no changes in the incidence of MVO-CFV beyond 240 min after the symptom onset (49/80, 61%; >300 min). Early recanalization within 120 min preserves coronary microvascular integrity, and recanalization delays in time to reperfusion with primary PCI adversely affect a significant increase in microvascular damage.

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**Methods:** Use of simultaneous intracoronary pressure-flow measurements to investigate epicardial-microvascular interactions and changes induced by coronary angioplasty

**Purpose:** To investigate physiological characteristics of epicardial stenoses and of distal microvascular compartment and variations induced by coronary angioplasty, by performing simultaneous intracoronary pressure-flow measurements.

**Methods:** Baseline and hyperemic values 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 repeated, 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 coronary segments, were observed. Concordant cut-off values (FFR < 0.75 and CFVR < 2.0) were derived for the detection of 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 (2.64 ± 1.47 vs. 1.50 ± 0.49 mmHg/ml/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 hyperemic microvascular resistance (35%) contributed substantially to the total increase in system conductance. Low CFVR with normal FFR values persisted in 47.0% of treated vessels and was 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.

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**Methods:** Assessment of coronary microcirculation by simultaneous pressure and flow measurements; microvascular resistance as potential outcome measure for regenerative therapy

**Background:** In view of novel therapeutic approaches (e.g. cell therapy) for ischemic heart disease, we are in need of a sophisticated parameter that reflects local function, next to global left ventricular function. In this study we investigate hyperemic microvascular resistance (HMR) in healthy animals and 4 weeks after myocardial infarction.

**Methods:** Eighteen Landrace Dailland pigs underwent 75 minutes balloon occlusion of the left circumflex coronary artery (LCX). We measured intracoronary pressure and flow simultaneously using the Combowire in the LCX and in the LAD.
Comparison of clinical outcome after Diabetes and impaired baseline coronary in-farction model. This can be explained by loss and dysfunction of vasculature and 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.

**Conclusions:** The determinants of microvascular dysfunction (MCD) following PCI in stable angina are uncertain. We performed a prospective study to determine factors involved in the development of MCD.

**Methods:** Fifty-five patients with stable angina were studied before and follow- ing PCI. A coronary PressureWire was used to quantify microvascular resistance via the index of microcirculatory resistance (IMR) derived from the equation PaTim/Pd-Pw/Pa-Pw where Pa and Pd are hyperemic aortic and distal coronary pressures respectively. Tmm the hyperemic transverse and Pm the coronary wedge pressure. Hyperemia was achieved with the use of intravenous adenosine delivered through the right femoral vein. Lesion severity was quantified using fractional flow reserve (FFR). Baseline transit time reflected non-hyperemic coronary blood flow before PCI. Post PCI IMR was the marker of MCD in our population. All patients had fasting blood tests prior to PCI for measurement of blood sugar and HbA1C. Asymmetric Dimethyl Arginine (ADMA) levels were also measured as a marker of endothelial function. Correlations were assessed using Spearman’s or Pearson’s coefficient as appropriate. Linear regression was used to assess strength of associations of post PCI IMR.

**Results:** Mean age was 59.6 ± 11.4. Mean IMR pre PCI was 18.2 ± 10.9. Mean IMR post PCI was 21.6 ± 9.9. IMR post PCI was significantly higher in patients who were diabetic compared with non diabetic patients (IMR Post diabetic 27.5 ± 16 vs. IMR Post non diabetic 18.3 ± 16 p = 0.017). Stent length (n = 0.372, p = 0.018) and the number of stents (n = 0.342, p = 0.031) were the only significant angiographic correlates of IMR post PCI. Mean baseline transit time (n = 0.3, p = 0.024) and the IMR measured pre PCI (n = 0.35, p = 0.009) were significantly correlated with post PCI IMR values. HbA1C (n = 0.41, p = 0.002) and fasting glucose (n = 0.32, p = 0.01) were significantly correlated with post PCI IMR values. 

**Conclusions:** Vardenafil may be superior to adenosine in acute vasoreactivity testing for detecting PH patients who might benefit from vasodilator treatment.
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 biphasic 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 vs 18±0.8 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 L-CCTA 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, as 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.

Figure 1. Superficial femoral artery occlusion

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 FFR and two-dimensional QCA. The amount of jeopardized myocardium subtended by an intermediate stenosis was assessed using well validated scores specifically adapted to this aim: the Duke Jeopardy score (DJS), the Myocardial Jeopardy Index (MJI) and the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) lesion score (ALS). We also tested the impact of proximal LAD and of a concomitant 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, MJI and ALS (r=−0.28, p=0.0001, r=−0.40, p=0.0001, r=−0.34, p=0.0001). Lesions localized on proximal LAD were associated to significantly lower FFR values compared to those in distal LAD, left circumflex and right coronary arteries (0.80±0.09 vs 0.84±0.08 vs 0.88±0.09 vs 0.91±0.04, p<0.0001). The presence of a collateralized CTO was associated to significantly lower FFR values and to a significantly higher rate of positive FFRs (0.80±0.07 vs 0.85±0.09, p<0.005). At multivariate analysis only MJI, MLD, presence of a collateralized CTO and current smoking habit were confirmed as significant predictors of FFR (MJI 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 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.

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 declined to 85±6%. Of all patients, 3 (13%) remained symptom-free for an occlusion time of 10 min. Fifteen patients (63%) 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<0.0003) and with SaO2 (r=0.460, p=0.041).
Methods: This is a prospective and randomized study to receive sedation-anaesthesia or not in all procedures performed by radial access. 109 consecutive patients were included (54 received sedation-anaesthesia and 55 did not). All patients received conventional spasmylocic cocktail with 3000 IU of NLF + Verapamil 2.5 mg. Administered sedation-anaesthesia consisted of a dilution of Midazolom 2 mg + 1 amp of Fentanast (0.05 mg/ml), dissolved in 10 ml of saline. RS was defined according to a series of clinical criteria; MAJOR CRITERIA: Emplacement of the catheter during the procedure or of the introducer at the end of the procedure; MINOR CRITERIA: persistent pain during the procedure, pain with catheter manipulation, difficulty in catheter handling, pain during withdrawal or insertion 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-anaesthesia was 3.7% vs 14.5% in the group that did not receive it (p=0.043). In the multivariate analysis use of sedation-anaesthesia behaved as a protecting factor of RS: OR 0.067 (0.04-0.10), p<0.029.

Conclusions: Use of sedation-anaesthesia 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 resistance, we sought to assess the association of cardiovascular risk factors and microvascular 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 relationship between IMR corrected for coronary wedge pressure and clinical variables, 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). Median IMR was 20.9 and IMR values distributed in a wide range. In the present study, no historical cardiovascular risk factors without lesion classification and SYNTAX score, were assessed.

Methods: Prospective single-center study with enrollment of pts with intermediate/high probability of CHD referred to a cardiologist. All pts underwent a sequential protocol including: treadmill EST, CMR-P and CA. The EST was dichotomously classified and deemed positive if reproduction of clinical symptoms during effort or additional ST-segment depression ≥ 1 mm. CMR-P exams were evaluated using exercise stress test (EST).

The study included 133 patients with 154 lesions over 70% between age 66.5±10 years, male 77%, multivessel disease 39.3%, FEVI 63.9±13.8%, mean angiographic stenosis 75±6.5%, mean fractional flow reserve (FFR) 0.83±0.01. Based on fractional flow reserve value, 117 lesions (75.9%) were not revascularized 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 revascularization and 9 (3.7%) 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.

P5488 Incremental diagnostic value of cardiac magnetic resonance with adenosine stress perfusion for coronary heart disease detection


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 radiation 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 intermediate/high probability of CHD referred to a cardiologist. All pts underwent a sequential protocol including: treadmill EST, CMR-P and CA. The EST was dichotomously classified and deemed positive if reproduction of clinical symptoms during effort or additional ST-segment depression ≥ 1 mm. CMR-P exams were evaluated using exercise stress test (EST).

Results: 80 pts were recruited (mean age, 61±8 years), 68% male, with at least 1 cardiovascular risk factor (dyslipidemia in 75%, hypertension in 71% and diabetes mellitus in 43% of cases). All pts were symptomatic: typical angina (25%), dyspnea or atypical chest pain (65%), dyspnea (4%) or dyspnea and chest pain (4%). CHD was detected in 33 pts (41%). CMR-P and EST correctly identified CHD in 27 pts (equal sensitivity), with higher specificity for CMR-P (77% vs. 55%), translating into a greater diagnostic accuracy of CMR-P (AUC=0.79 vs. 0.69; PPV=71 vs. 56%; p<0.001). In the integrated protocol with better performance (AUC=0.85), pts with both positive EST and CMR-P 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 doubtful 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 the detection of obstructive CHD. In our pts with high probability of CHD, the inclusion of CMR-P in an integrated protocol for the detection of CHD improved the overall diagnostic accuracy, 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 a separate analysis session and the resulting diagnostic values calculated on a per 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.

Figure 1

P5490
Segmental myocardial viability assessment after STEMI: myocardial grid-tagging versus late gadolinium-enhanced magnetic resonance imaging
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Objectives: To assess whether myocardial grid-tagging derived circumferential strain (CS) is a superior predictor of segmental myocardial viability than transmurality of infarction derived from late gadolinium-enhanced (LGE) cardiac MRI (CMR) early after reperfused STEMI.

Background: Increasing transmural extent of LGE is correlated with poor recovery of contractile function after revascularisation. However (LGE-CMR) has been shown to have limited accuracy in predicting viability in segments with intermediate (25-75%) transmurality. Myocardial circumferential strain assessment may be more sensitive for detection of segmental viability owing to the helical layering of myocardial fibres, which may be progressively affected by myocardial infarction.

Methods: Patients with STEMI successfully reperfused with primary PCI were recruited to undergo cardiac-MRI (CMR) at baseline (day 3) and at follow-up (day 90). Cine, grid-tagged and LGE images were acquired. Assessment of LGE infarct transmurality was performed at baseline and segments were categorised as <50% or ≥50% transmurality. The CS, circumferential strain rate (CSR) and circumferential diastolic strain rate (CDR) for each segment was calculated from grid-tagged images at baseline and follow-up. As previously described, the definition of viability is based on improvement of CS to <10% at follow up.

Results: In thirty seven patients (aged 56±12 years, 92% males), 13 patients had reperfused infarct segments. Patients with reperfused infarct segments had lower magnitude baseline CS compared to viable segments (4.9±6.2 vs -7.7±7.2, P=0.01). A baseline CS cut-off of ≥3.16% was associated with sensitivity of 82% and specificity of 44% for detection of segmental viability. On receiver operating characteristic (ROC) analysis for predicting viability, the area under curve (AUC) for baseline CS was (0.67, P=0.025) compared to LGE transmurality (0.58, P=0.068), baseline CSR (0.63, P=0.066) and baseline CDR (0.5, P=0.729). On comparison of AUCs, baseline CS was superior to LGE transmurality >50% infarcitability (P=0.007). On multivariate analysis, baseline CS was the sole independent predictor of viability (P=0.025).

Conclusion: Baseline CS derived from myocardial grid-tagging is a superior predictor of segmental myocardial viability following primary PCI for STEMI than segmental LGE transmurality. Patients with contraindications to gadolinium contrast would particularly benefit from this superior alternative methodology viability assessment.

P5491
Gaeclentin-3: relation to infarct 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). Gaeclentin-3 is suggested to be involved in the development of heart failure appearing to directly mediate profibrotic pathways. The relationship between gaeclentin-3 and the extent of myocardial infarction scar is unknown.

Methods: 29 AMI patients (n=29, mean age: 58.1±10.1 years, 3 female) 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. Gaeclentin-3 was determined from serum samples drawn at the follow-up.

Results: 4-mo gaeclentin-3 values (mean 12.2±4.56 ng/ml) correlated significantly with 4-mo infarct size (r=0.406, 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 gaeclentin-3 concentrations above the median level of 10.66 ng/ml presented significant impaired 4-mo ejection fraction (57.9±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±660.0 ng/l vs. 261.4±183.1 ng/l, p=0.042) than patients with gaeclentin-3 concentrations below 10.86 ng/ml.

Conclusion: Elevated gaeclentin-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 gaeclentin-3 as a biomarker of adverse remodeling after AMI.

P5492
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 59±13 years, p=0.001) and presented a similar rate of Killip class I-III (83% vs 90%, p=0.233) and a lower number of segments with >70% necrosis (4.3±2.3 vs 2.6±1.4, 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). Also, among PE patients there were no differences in CMR features between those with cardiac tamponade (n=7, 23%) and those without. A multivariable logistic regression analysis indicated infarct size as the only CMR-parameter that was an independent predictor of PE. At 6 months, patients with PE showed more frequent adverse LV remodelling than those without (6/9, 67% vs 28/111, 26%, p=0.018).

Conclusions: In patients with anterior STEMI the consistent association of PE with extensive cardiac rupture and transient pericardial link with self-limited cardiac rupture and frequent left ventricular remodelling.

P5493
Right ventricular infarction: right ventricular branch compromise after primary percutaneous coronary intervention in inferior myocardial infarction is the key predictor of poor right ventricular function
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AGH University of Science and Technology, Department of Automationics, Krakow, Poland

Title: Right ventricular infarction: right ventricular branch compromise after pri-
Circulating microRNA-133a as predictor of myocardial infarction

**Purpose:** Rapid binding of electrostatically stabilized iron oxide nanoparticles to THP-1 monocytic cells via interaction with glycosaminoglycans

**Aims:** Rapid binding of electrostatically stabilized iron oxide nanoparticles to THP-1 monocytic cells via interaction with glycosaminoglycans. Circulating microRNAs (miRNA) have emerged as potential diagnostic markers in patients with myocardial infarction. Previous studies, however, were based on limited patient numbers and could not assess the relation of miRNAs to myocardial damage. Moreover, the prognostic value of miRNAs in STEMI is unknown. Aim of this study was to assess the relation between miRNA-133a and myocardial damage assessed by cardiovascular magnetic resonance imaging (CMR) imaging to evaluate the prognostic value of miRNA-133a in STEMI patients undergoing primary angioplasty. Patients were categorized into two groups defined by the median miRNA-133a concentration on admission. CMR was performed for assessment of infarct size, myocardial salvage, and microvascular obstruction. The primary clinical endpoint was the occurrence of major adverse cardiovascular events (MACE) defined as a composite of death, reinfarction, and new congestive heart failure within 6 months after infarction.

**Results:** All prognostic relevant CMR markers (infarct size, microvascular obstruction, myocardial salvage index) showed significant correlations with circulating miRNA-133a concentrations (p < 0.001 for all). The strongest predictors of miRNA-133a concentrations were the symptom onset to reperfusion time and the amount of the salvaged area at risk. MACE occurred significantly more often in patients with elevated miRNA-133a concentrations (p = 0.001 for all). The strongest predictors of miRNA-133a concentrations were the symptom onset to reperfusion time and the amount of the salvaged area at risk. MACE occurred significantly more often in patients with elevated miRNA-133a concentrations (p = 0.001 for all).

**Conclusions:** Elevated levels of circulating miRNA-133a in patients with STEMI are associated with decreased myocardial salvage, larger infarcts and more pronounced reperfusion injury with subsequent adverse clinical outcome.

**P5496**

Accurate detection of coronary artery stenoses with whole-heart magnetic resonance coronary angiography in clinical practice

**Purpose:** Cardiac magnetic resonance imaging (CMR) is increasingly proposed for non-invasive detection of relevant coronary artery disease (CAD). Yet magnetic resonance coronary artery imaging (MRCA) is still experimental. Aim of the present analysis is to evaluate a new pulse sequence for whole-heart MRCA.

**Methods:** From 4/2010 until 4/2011 consecutive patients (pts) with suspected or known CAD were additionally studied with MRCA. Pts were examined in a GE Signa HDxt 1.5 Tesla scanner (GE Healthcare). For imaging of the coronary arteries a newly developed 3D navigator gated multistep steady state free precession sequence (3D HEART) was employed.

**Results:** 96 pts were successfully scanned. Assessability was high except for minor side branches. For diagnostic accuracy see table.

**P5497**

Diagnostic performance of MRCA

<table>
<thead>
<tr>
<th>All assessable segments, n=992</th>
<th>Segments suitable for PCI, n=823</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td><strong>PPV-positive predictive value</strong></td>
</tr>
<tr>
<td>91.5%</td>
<td>93.5%</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td><strong>NPV-negative predictive value</strong></td>
</tr>
<tr>
<td>87.7%</td>
<td>86.1%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
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<tr>
<td>91.8%</td>
<td></td>
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<tr>
<td><strong>PPV</strong></td>
<td></td>
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<tr>
<td>43.9%</td>
<td></td>
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<tr>
<td><strong>NPV</strong></td>
<td></td>
</tr>
<tr>
<td>99.9%</td>
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</table>

**PPV-positive predictive value; NPV-negative predictive value.

**Figure 1. MRCA and CA**

**Conclusions:** Detection of relevant CAD in segments suitable for revascularization with MRCA is feasible. Assessability of relevant coronary segments is excellent in most of the segments. In assessable segments diagnostic accuracy was high. Our data provide preliminary evidence that MRCA may be of relevant additional value in CAD evaluation by CMR.

**P5498**

Coronary calcification end endothelial dysfunction evaluated with 13N-ammonia PET/CT in patients with systemic lupus erythematosus or primary antiphospholipid syndrome

**Purpose:** Magnetic resonance imaging (MRI) with iron oxide nanoparticles is a promising technology for visualisation of atherosclerotic plaques. Citrate-coated magnetic nanoparticles to THP-1 monocytic cells via binding to negatively charged GAGs. 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.

**P5499**

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**P5498**

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**P5499**

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**P5498**

Coronary calcification end endothelial dysfunction evaluated with 13N-ammonia PET/CT in patients with systemic lupus erythematosus or primary antiphospholipid syndrome

**Aims:** Circulating microRNAs (miRNA) have emerged as potential diagnostic markers in patients with myocardial infarction. Previous studies, however, were based on limited patient numbers and could not assess the relation of miRNAs to myocardial damage. Moreover, the prognostic value of miRNAs in STEMI is unknown. Aim of this study was to assess the relation between miRNA-133a and myocardial damage assessed by cardiovascular magnetic resonance imaging (CMR) imaging to evaluate the prognostic value of miRNA-133a in STEMI patients undergoing primary angioplasty. Patients were categorized into two groups defined by the median miRNA-133a concentration on admission. CMR was performed for assessment of infarct size, myocardial salvage, and microvascular obstruction. The primary clinical endpoint was the occurrence of major adverse cardiovascular events (MACE) defined as a composite of death, reinfarction, and new congestive heart failure within 6 months after infarction.

**Results:** All prognostic relevant CMR markers (infarct size, microvascular obstruction, myocardial salvage index) showed significant correlations with circulating miRNA-133a concentrations (p < 0.001 for all). The strongest predictors of miRNA-133a concentrations were the symptom onset to reperfusion time and the amount of the salvaged area at risk. MACE occurred significantly more often in patients with elevated miRNA-133a concentrations (p = 0.001 for all). The strongest predictors of miRNA-133a concentrations were the symptom onset to reperfusion time and the amount of the salvaged area at risk. MACE occurred significantly more often in patients with elevated miRNA-133a concentrations (p = 0.001 for all).
Flow Quantification (MBF, ml/g/min). Endothelium-dependent Vasodilation Index (ENDEV, CPT MBF/rest MBF, normal <1.5), %MBF (normal >50%) and Coro- 
Flow Reserve (CFR, stress MBF/rest MBF, normal >2.5) were calculated as Endothelial function parameters. Total CCS was calculated using a dedicated 

Results: Mean age was 36.2±9.5 for the SLE/PAPS group and 34-7 years for the controls. Compared to the control group, the SLE/PAPS group had a signifi- 
ciently lower ENDEV (1.1±0.05 vs 1.5±0.07, p = 0.015), %MBF (18.5±43 vs 55±37, p = 0.015) and a non-significant lower MFR (2.58±0.81 vs 3.27±0.72, 

Results: Measurements were obtained from 120 patients (mean age 61±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. 

Obstructive CAD was diagnosed in 49 out of 120 patients (41%). On a per patient basis, specificity, specificity, negative predictive value (NPV), positive predictive value (PPV), and diagnostic accuracy of CTCA were 100, 34, 100, 51, and 81%, respectively, as compared to 76, 83, 76, and 80%, respectively, for H215O PET with an optimal cut-off value of 1.86 ml/min/g. 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.

P5499 Carotid artery intima media thickness, but not coronary artery calcium, 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 coro- 
nary bed. Moreover, coronary microvascular dysfunction (CMDV) often precedes the stage of clinically overt epicardial CAD. Coronary artery calcium (CAC) and carotid intima media thickness (C-IMT) measured by computed coronary tomography (CT) and ultrasound, respectively, are among the available techniques to non- 

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 coro- 
nary atherosclerotic disease.

P5500 Diagnostic accuracy of hybrid quantitative H215O PET/CT imaging for the detection of coronary artery disease

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Background: Accurate noninvasive assessment of coronary artery disease (CAD) and its functional consequences is a challenging task. CT coronary angiog- 

study evaluates 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±10 years, 77 men) with a pre- 
dominantly 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. 

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 81%, respectively, as compared to 76, 83, 76, and 80%, respectively, for H215O PET with an optimal cut-off value of 1.86 ml/min/g. 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 superi- or to either H215O PET or CTCA alone for detection of clinical significant CAD.

P5501 MPI 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 compared the added value of CFR over PET MPI alone 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 invasive 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 signifi- 
cantly improved the above values to 96%, 80%, 93%, 89%, and 92%, respectively (P<0.0005).

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 cal- 
cium score (CCS) using low dose radiation non ECG gated Computed Tomog- 

Introduction: Quantification of coronary artery calcification with non contrast gated cardiac CT has been well validated using Agatston method. While visual 
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P5503
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/min/g). 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 steno- sis 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 and with adenosine induced hyperemia) and invasive coronary angiography. Significance 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) for hyperemic MBF (AUC = 0.96, 95% CI 0.91-0.99) was better compared to that of CFR (AUC = 0.81, 95% CI 0.70-0.86) for the detection of obstructive CAD (p = 0.02). Optimal cut-off values of 2.33 mI/min/g and 2.30 for hyperemic MBF and CFR, respectively. On a per patient basis, sensitivity (76 vs 70%, p = 1.00) 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.

P5505
Ischemic response to exercise testing in the recovery phase: real ischemia? Correlation with gated-SPECT data
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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 composite end-point (heart failure, myocardial infarction, stroke or cardiovascular death) during exercise testing were included. Mean age was 60.1±9.8 years, 56 (78%) male, with previous myocardial infarction in 27.5%, coronary artery bypass graft in 21%, and percutaneous coronary intervention in 34%. Qualitative analysis of imaging used 5-point score (0-normal; 4-no uptake) for perfusion (17 myocardial segments), and 6-point score (0-normal; 5-discontinuity) for motility. Left ventricular ejection fraction (LVEF) was assessed after ET, △ST, blood pressure (BP), heart rate (HR), time of tolerance to exercise (TTE), functional capacity (MET), appearance time to △ST (AT), AT/ST, and presence of arrhythmias were evaluated during ET.

Results: Abnormal perfusion was found in 57 pts (81.5%), 47% with transient defect and 11.4% associate with persistent defect; motility alteration in 23 pts (33%); mean LVEF 58±11%, and 10.6±3 MET of functional capacity. No significant differences were found by comparing AT, ST vs TTE (p>0.09). Abnormal perfusion vs TTE (p=0.38), and Abnormal motility vs TTE (p=0.09).

Conclusion: This study suggests that △ST occurring solely during recovery after ET is a relevant finding due to the high prevalence of myocardial ischemia in the gated-SPECT.

P5504
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 earlier 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 (GGS® 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 diabetes, hypertension, dyslipidemia, and dyslipidemia compared to patients without LVEF drop (group B: 2 (0-5) vs 0 (0-3), p=0.016). They also had more often significant ischemia (i.e. SSS≥2) (48% vs 27% p=0.006) and severe ischemia (i.e. SSS≥7) (14% vs 4%, p=0.034). Moreover, we found that rest LVEF was higher in group A than in group B (62% (56-69) vs 56% (49-63) p<0.001). Multivariate analysis identified SSS (OR: 1.19; 95% CI 1.08-1.32) and rest LVEF (OR: 1.08; 95% CI 1.03-1.12) 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 defects. These data thus validated the model of myocardial stunning and excluded the potential influence of an extended myocardial necrosis or left ventricular remodeling on post stress LVEF fall.

P5506
Normalised mitral annulus displacement predicts heart failure and cardiovascular events
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Background: Global strain predicts events, but measurement is presently not available for MRI. Measurements of the Mitral annulus displacement (MAD) can be adjusted 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: 1668 participants (53% men, 65±10 years) from the Multiethnic Study of Atherosclerosis (MESA) were included. Average LV length was measured at end diastolic (EDL) and end systolic (ESA) ECG from the epicardial apex to the mitral valve insertion by 2- and 4-chamber cine cardiac MRI, and nMAD was calculated as 100*(EDL-ESA)/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 in participants 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).

Conclusion: Reduced LV long axis function assessed by nMAD is a powerful and independent predictor of hard cardiovascular events and heart failure in a middle aged population free of clinical cardiovascular disease at inclusion.
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 for up to 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 referred 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 76% reduction in risk (hazard ratio 0.22 [95%CI 0.07, 0.69]). However, no significant interaction between ICD and HM were predictive of ACD (model c-index 0.77, p<0.001). There were no differences on early and late heart/mediastinum ratios between groups.

Conclusion: Polymorphism Ser49Gly of B1- adrenergoreceptor was associated with a better autonomic response to caradilol treatment.

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 substudy 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 28 patients, 18 were males (64%), and overall mean age was 57.5 years. Ten patients (35.7%) were in class II (NYHA) and 18 (64.3%) in class III. On admission, the mean LVEF was 28%. Regarding the entry profile, 12 patients were homoygous Ser49Ser and 16 patients presented the variant Gly49. The group with Gly49 variant showed, on ICD washout rate, a significantly higher reduction after 3 months caradilol treatment compared to the homogygous group (Gly49: -9.9% vs. Ser49Gly: -22.8%, p<0.001). There were no differences on early and late heart/mediastinum ratios between groups.

Conclusion: Polymorphism Ser49Gly of B1- adrenergoreceptor was associated with a better autonomic response to caradilol treatment.

Cardiac I-123 Metiodobenzylguanidine 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 Metiodobenzylguanidine (MBG) 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 MBG imaging in CHF patients.

Method: In 109 consecutive CHF outpatients with radionuclide LVEF <40% (39% with MBG washout rate (WR) <20% and 71% with normal WR), MBG imaging was performed. 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 (80% vs 9%, p<0.02, HR: 8.0, 95% CI 1.0 to 63.9) and without MetS (43% vs 14%, p=0.0009, HR: 5.4, 95% CI 2.0 to 14.7).

Conclusion: Cardiac MBG imaging would be useful to predict the risk of cardiac death in CHF patients, irrespective of the presence or absence of metabolic syndrome.

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 (GMPS). For the evaluation of LV function and LVMD, measurements of LVET and histogram bandwidth (HWB)
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 (vonly 9x1x9mm^3) with different T2-prep times (6ms, 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 subgroup (n=23), 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±2.3 (basal), 45.9±2.4 (midventricular) and 47.4±2.2 (apical), ranging from 40.5 to 50.2ms, 40.4 to 54.5ms and 41.0 to 54.1ms, respectively. The figure shows 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. Signal and 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.

P5513

A normal range for left ventricular wall thickness and the development of asymmetric thickening in response to exercise

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Purpose: The current literature on left ventricular wall thickness (LVWT) is largely based on echo measurements. Although cardiovascular magnetic resonance imaging (CMR) is increasingly used, a CMR-based normal range of wall thickness in all 17-segments of the left ventricle is lacking. The aims of this study were to establish such a range and to assess the prevalence of asymmetric wall thickening before and after exercise.

Methods: Using CMR the LVWT was measured in all 17 myocardial segments and a normal range calculated for each. The prevalence of asymmetric wall thickening was then assessed before and after an identical physical training program using two definitions. The first based upon an LVWT>13.0 mm and the second upon wall thicknesses above the normal range calculated for each of the myocardial segments.

Results: Five-hundred-and-forty-one males (mean age 19.8±2.2) were recruited. Considerable variation in wall thickness was observed across the ventricle with progressive thickening on moving from the base to apex (p<0.001) and in the basal and mid-cavity septum compared to the lateral wall (11.0±1.4 mm vs 10.1±1.3 mm: p<0.001). Twenty-three percent had a maximal wall thickness ≥13.0mm. The prevalence of asymmetric wall thickening increased following exercise (initial criteria: from 2.2% to 9.7%; revised criteria: from 1.5% to 4.9%).

Conclusions: We have provided a CMR-based normal range for wall thickness in all 17 ventricular segments and demonstrated frequent measurements >13.0 mm and that asymmetric wall thickening is a common response to exercise.

P5514

Myocardial T1 mapping at 3 tesla in vitro and in vivo performance of two new MOLLI variants 33 MOLLI and centric-paired MOLLI

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Purpose: T1-mapping methods, such as Modified Look-Locker Inversion recovery (MOLLI), have the potential to provide accurate, quantitative delineation of normal from abnormal myocardium. We sought to examine methods for: 1. shortening MOLLI acquisitions to accommodate patients with limited breath-holding ability, and 2. improving MOLLI T1 measurements by using a centric-paired k-space trajectory to mitigate eddy current artefacts.

Method: We compared 3 MOLLI schemes at 3T: (i) conventional MOLLI, 3 inversion recovery (IR) blocks, 3-5 diastolic acquisition, in-plane resolution 1.5×1.5 mm; (ii) 3-3 MOLLI, 2 IR blocks, otherwise as (i); (iii) as (i) but with a centric-paired k-space trajectory. Five agarose gel phantoms were doped with GdCl3 - giving a range of T1s comparable to pre- and post-contrast myocardium (400-1250 ms). T1s were calculated using IR Spin-Echo for calibration, and were measured again using the 3 MOLLI methods described. These 3 schemes were then applied in 6 normal volunteers and T1 maps were generated. ROIs fitting 16 myocardial segments were used to plot T1 histograms, which were curve-fitted to give mean values.

Results: Fig. 1 shows results for all 3 methods in vitro. In vivo, Bland-Altman analysis showed that, compared with 3-3-5 MOLLI, 3-3 MOLLI slightly under-
estimated T1 with a bias (SD) of -19.3 (110.6) 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.

In Vivo assessment of myocardial inflammation following myocardial infarction and cardiac surgery

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Purpose: Inflammation has detrimental effects on myocardial reperfusion, remodelling and function. Here we assessed myocardial cellular inflammation using magnetic resonance imaging (MRI) of ultrasmall 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 T 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 injection of USPIO. Data was analysed by one-way ANOVA (Kruskal-Wallis, Dunn’s post-test).

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 ± 0.016 s−1 (p < 0.01) 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 ± 1 s−1 (p = 0.05) at 24-hours.

Conclusions: 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.

Changes in global and regional left ventricular wall motion with increasing age obtained using 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 ± 5 (n = 14) and 66.7 ± 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 velocities at midventricle 5.9 ± 0.5 versus 8.5 ± 0.8 cm/sec, peak diastolic velocities -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.
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 fusion maps. Angiographically detected coronary artery stenoses ≥ 75% or ≥ 50% with a myocardial perfusion reserve index (MPR) ≤ 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±3.1 minutes to 3.2±1.9 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 with magnetic resonance feature tracking: a comparison with traditional short axis LV CMR contouring

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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 with manual contouring of endocardial borders at end systole and diastole as gold standard. 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: reproducibility study

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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 expression 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 (r=0.98; p<0.001; MD±SD = 1.9±1.2, p=0.04, 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=0.96, 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 of enhancement’ showed a good intra- and interobserver observer agreement (r=0.92, P<0.01, MD±SD (mm²)=0.1±0.6; inter: r=0.87, p<0.05, MD±SD (mm²)=0.9±1.6).

Conclusion: We demonstrate an excellent intra- and interobserver reproducibility for quantification of coronary wall enhancement by CMR with 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.

Conclusion: The results show a strong agreement in the comparison of FT with CTS for strain analysis in healthy volunteers and in patients with left ventricular hypertrophy. A good correlation has been found between the two techniques for strain and strain rate analysis. Further studies are needed to evaluate the interobserver variability of strain analysis in these populations.
Late gadolinium enhancement cardiac magnetic resonance imaging to detect cardiac involvement and its prognostic implication in patients with systemic sclerosis

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Purpose: In patients with sarcoidosis, sudden cardiac death is a leading cause of mortality, which may represent unrecognized cardiac involvement. Late gadolinium enhancement (LGE) CMR can detect fibrotic areas in the myocardium, which may represent sarcoid cardiomyopathy. LGE-CMR has a high sensitivity and specificity for detecting cardiac involvement in sarcoidosis. However, it is not clear whether LGE-CMR is useful for determining the prognosis of sarcoid cardiomyopathy.

Methods: Fifty-two consecutive patients with biopsy-proven sarcoidosis underwent LGE-CMR. LGE was defined as areas of increased signal intensity on T1-weighted images after administration of gadolinium. The extent of LGE was quantified using standardized thresholds.

Results: The extent of LGE was significantly higher in patients with cardiac involvement compared to those without cardiac involvement. The extent of LGE was also correlated with histological findings of myocardial fibrosis.

Conclusions: LGE-CMR is a useful tool for determining the extent of cardiac involvement in sarcoidosis and can be used to predict the prognosis of sarcoid cardiomyopathy.
### P5526

**Feasibility of myocardial perfusion imaging with half the radiation dose in obese patients**

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**Purpose:** On 2011 we have reported on the feasibility of performing myocardial perfusion imaging (MPI) with half the technetium activity using ordered-subset expectation maximization with resolution recovery (OSEM-RR) software. Preserved image quality was demonstrated in patients up to 100 kg. The aim of this study is to assess the feasibility of performing MPI with radiation dose reduction in obese patients (weight ≥ 100kg).

**Methods:** Obese patients weighing 100 kg and above who were referred for gated SPECT MPI, undergone half of the standard doses of 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 a 15-min scan time each for stress and at rest. All scans were immediately repeated on a CZT camera with a 5-min scan time for stress and a 3-min at rest using a list mode. Myocardial perfusion was assessed with a 17-segment model, and automatic functional analyses were performed using QGS software. Each MPI was compared between CZT and standard gamma camera using linear regression analysis, and the Blinder-Alman method.

**Results:** Acquisition was reported that 87% of the patients were more comfortable with CZT. The correlations between a CZT and standard camera for perfusion and function analyses were excellent for SSS (r = 0.95), SRS (r = 0.94), SDS (r = 0.81), EF (r = 0.91), LVEDV (r = 0.98) and LVESV (r = 0.98). The Blinder-Alman method showed almost null bias and narrow limits of SD for SSS (r = 1.1 ± 3.1), SRS (r = 1.0 ± 4.7), SDS (r = 0.2 ± 3.0), EF (r = 2.2 ± 11.4), LVEDV (r = 4.3 ± 20.6) and LVESV (r = 2.5 ± 16.9). Using a list mode analysis, image quality for stress was good or excellent in 17% of the 1-min scans, in 54% of the 2-min scans, in 97% of the 3-min scans, and in 100% of the scans for 4 minutes or longer. With the CZT scans at rest, similarly, image quality was good or excellent in 94% of the 1-min scans, and in 100% of the scans for 2 minutes or longer.

**Conclusion:** The novel CZT camera provides excellent image quality, which assures reliable diagnostic performance equivalent to standard SPECT MPI, despite a short scan time of a fourth or less as compared with the standard time.

### P5527

**The distribution of myocardial ischemia on stress perfusion SPECT studies in relation to the fractional flow reserve**

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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 3-3-5 single-shot True-FISP images. Pre- and post-Gd (15 mm 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. Rest, stress perfusion SPECT studies were acquired with our algorithm. The T1 (absolute value and normalised to blood) were significantly higher and the EVF was significantly lower in myocarditis than in MI.

**Results:** The results are summarized in the table. The T1s (absolute value and normalized to the blood) of patients with acute benign myocarditis, but much less than in fibrotic scars of chronic MI. A range of T1 and EVF alterations can be demonstrated with MOLLI. Further investigation will indicate whether the EVF quantification and mapping might help refine the predictive risk of LGE in various cardiac conditions. In myocarditis, T1 and EVF might provide complementary information to T2 mapping, which senses both intra and extracellular compartments.

**Table 1. Results**

<table>
<thead>
<tr>
<th>Myocarditis</th>
<th>MI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 LGE regions (ms)</td>
<td>446±165</td>
<td>575±58.4</td>
</tr>
<tr>
<td>T1 normal regions (ms)</td>
<td>556±50.3</td>
<td>555±9.8</td>
</tr>
<tr>
<td>T1 LGE myocardium/T1 blood</td>
<td>1.36±0.20</td>
<td>1.04±0.19</td>
</tr>
<tr>
<td>EVF (%) LGE regions</td>
<td>34.5±3.3</td>
<td>54.4±14.4</td>
</tr>
<tr>
<td>EVF (%) normal regions</td>
<td>29.8±2.5</td>
<td>22.9±1.9</td>
</tr>
</tbody>
</table>

**Conclusions:** Myocardial T1 and EVF were found abnormal in the subepicardium of patients with acute benign myocarditis, but much less than in fibrotic scars of chronic MI. A range of T1 and EVF alterations can be demonstrated with MOLLI. Further investigation will indicate whether the EVF quantification and mapping might help refine the predictive risk of LGE in various cardiac conditions. In myocarditis, T1 and EVF might provide complementary information to T2 mapping, which senses both intra and extracellular compartments.
**P5529**

Fusion of multidetector coronary CT angiography and stress myocardial perfusion imaging in moderate 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 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±9 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>MPI</th>
<th>Fusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>50.0</td>
<td>83.3</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>87.9</td>
<td>81.8</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>69.2</td>
<td>71.4</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>76.3</td>
<td>90.0</td>
</tr>
</tbody>
</table>

**Conclusions:** Fusion imaging can better identify significant coronary stenosis as compared to MPI alone.

**P5530**

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 of ten equivocal because coronary blood flow is complex especially when composite 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 not different and confirmed the result of side-by-side analysis. In 11 of 21 patients, hybrid imaging provided additional diagnostic information. In 4 patients, posterior/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.

**Conclusion:** In post-CABG patients, hybrid imaging provides clear information on myocardial ischemia and the corresponding culprit coronary vessel.

**P5531**

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 under adenosine, 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.

**Conclusions:** 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.

**P5532**

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 by two experienced and one inexperienced observer. 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: Intra- and inter-experienced versus inexperienced-observer analysis showed excellent agreements, with ICs of 0.98, 0.96 and 0.90, respectively. These results were confirmed with Bland-Altman analysis, showing small mean differences between measured delayed H/M ratio, see Figure 1. In addition, the assessment of delayed H/M ratio using a fixed size oval and circular ROI also resulted in high ICs of 0.95 and 0.86, respectively.

**Conclusions:** The present study showed that delayed H/M ratios in 123I-MIBG myocardial scintigraphy can be implemented easily at large scale for clinical risk stratification in HF.

**P5533**

Valvular 18F-NaF PET activity in aortic stenosis

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**Purpose:** 18f-sodium fluoride (18f-NaF) holds promise as a biomarker of disease activity in aortic stenosis, however its mechanism of uptake and relationship with existing valvular calcium remains unclear. Our objective was to further inves-
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). Volumes were categorized in normal (CT-PET), inactive calcium (CT-PET1), novel calcification (CT-PET2), and calcium remodeling (CT-PET3).

Five patients underwent aortic valve replacement. PET/CT was repeated on excised valves after incubation with 18F-NaF for 60 mins 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 remodeling. With increasing disease severity the percentage of normal voxels decreased whilst the percentage of the other categories increased (Figure 1). In all severities of aortic stenosis, increased 18F-NaF activity was more commonly observed in the absence rather than presence of calcium 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.

**P5534**

**4D magnetic resonance imaging in patients with fontan circulation: influence of morphology on hemodynamics**

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**Purpose:** Hemodynamic efficiency of Fontan circulation is a major determinant of outcome. This study analyses how blood flow patterns and the caval contribution to blood flow and local infiltration; with treatment and prognostic implications. The objective of this study was to evaluate the agreement of ECHO and CMR with histopathology to diagnose cardiac masses.

**Methods:** In this retrospective database 10-year study, 34 patients with CMR, ECHO and histopathologic study (as a gold-standard) were included. 22 males and 12 females, mean age of 38 years old, with suspected intracardiac mass on ECHO (transsthoracic in all; transesophageal in 9), all of them underwent a CMR examination. Unenhanced T1 and T2-weighted MR-imaging, cine steady State Free Precession sequences, fat-suppression techniques, as well as first pass perfusion imaging with late enhancement (5 and 10 min) images were performed in all the patients in a 1.5 T equipment.

**Results:** See Table 1. A remarkable feature is that none of the masses were classified as non-specific by CMR, which represents a broader spectrum of characteristics. The agreement between histopathology and CMR was observed in 26 patients (76.5%) and the agreement between ECHO and CMR was 38.2%.

**Table 1. Cardiac masses study**

<table>
<thead>
<tr>
<th>Masses</th>
<th>ECHO - diagnosis</th>
<th>CMR - diagnosis</th>
<th>Histopathology - 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>
</tr>
<tr>
<td>Sarcoma</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Endomyocardial fibrosis</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyoma</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pericardial mass</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Papillary fibroelastoma</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Methastasis</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific</td>
<td>16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Non-thrombus/non-masses</td>
<td>14</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

**Conclusion:** CMR strongly provides extra information about intracardiac masses above those provided by ECHO, such as tissue, morphological and functional characteristics.

**ARRHYTHMIAS AND PACING IN CONGENITAL HEART DISEASE**

**P5536**

**Children with spontaneous supraventricular tachycardia and normal ECG in sinus rhythm require a complete evaluation**


**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 after surgical MAZE procedures.

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Purpose: To assess the factors for recurrent atrial tachyarrhythmias after surgical MAZE in adults 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, TAPF 3pts, ASD 8 pts, VSD 3pts, DCRVR 1 pt, sVSD 1 pt, TA Fontan 1 pt, TA Glenn 1 pt). Beetles was abnormal 15 pts, Pts TR pt, congenital mixed valve disease 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 atrial tachyarrhythmias: Group 1 (11 pts): Pre- and post-operative arrhythmias. Group 2 (7 pts): Preoperative arrhythmias and no recurrent arrhythmias after surgery. Group 3 (18 pts): No arrhythmias before and after surgery (preventive Maze procedure).

Results: In Group 1, 6 pts were in chronic atrial fibrillation (AF) preoperatively (6 pts with full Maze). In Group 2 and Group 3, none was in chronic AF. There was a significant difference in %fibrosis (Group 1: 18.2±5.2%, P=0.01, Group 2: 12.1±3.3%, Group 3: 9.0±3.3%) among the 3 groups. There was no significant difference in age, histological myocyte size, and preoperative echo parameters. There was significant difference in postoperative echo parameters: Postoperative TAPSE: Group 1: 10.0±2.9 mm p<0.05, Group 2: 15.7±5.9 mm, Group 3: 9.0±3.3 mm. A wave amplitude on ECG: Group 1: 2.3±1.3 mm p<0.05, Group 2: 4.0±1.9 mm, Group 3: 5.2±6.8 mm. Tricuspid annulus TDI s wave: Group 1: 6.5±2.9 cm/s p<0.05, Group 2: 8.9±2.5 cm/s, Group 3: 8.3±2.5 cm/s. T DI a wave: Group 1: 2.3±2.2 cm/s p<0.05, Group 2: 4.7±1.2 cm/s, Group 3: 4.5±2.2 cm/s.

%RA area improvement after surgery: Group 1: 8.1±10.3% p<0.05, Group 2: 15.8±18.6%, Group 3: 20.8±15.1%. %RAG improvement after surgery: Group 1: 21.6±4.8% p<0.05, Group 2: 35.2±7.5%, Group 3: 33.8±8.1%.

Conclusions: Adult CHD patients without recurrent arrhythmias after surgical MAZE(2) shows good improvement of the RA function and preserved RV function nevertheless relatively high % fibrosis of the RA, as compared to CHD patients with postoperative atrial tachyarrhythmias.

New arrhythmias predictor factors in adults with repaired tetralogy of Fallot.

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1Royal Brompton Hospital, Cardiovascular Magnetic Resonance Imaging, London, United Kingdom.

Purpose: Repaired Tetralogy of Fallot (rotoF) patients are at risk of both atrial and ventricular arrhythmia, right ventricular (RV) dilation 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 clinically documented atrial arrhythmia (AA) and sustained ventricular tachycardia or ventricular fibrillation (VT) during follow-up.

Results: Of 154 patients (mean age 31.7 years [SD 12], median follow-up 5.6 years [4.6-7], 12 new onset AA and 9 new onset VT occurred. New onset AA was correlated with maximal right atrial indexed to body surface area (RAAmax) (ROC analysis, AUC 0.74 [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 no statistically significant difference in new onset atrial arrhythmia (P=0.004), RV outflow track (RVOT) akinetie area length and decrease RV ejection fraction were predictor of new onset sustained VT (HR 3.05 [1.01-9.09], P=0.005 and HR 3.05 [1.07-9.80], P=0.03 respectively). Patients with RV restrictive physiology were older (P=0.04), had a higher RAAtmax (P=0.02) and a more important tricuspid regurgitation (P=0.002) with dilated RV.

Conclusions: RAAtmax is a predictor of atrial arrhythmia and the length of the RVO akinetie area is a predictor of VT in rotoF. Right atrial area and RVO akinetic area length are feasible and widely available tools for clinical decision making. There is a new presentation of RV restrictive physiology in rotoF ageing patients, with predisposing factors to arrhythmias.
was acquired (70%) and perioperative (30%) sick sinus syndrome or atrioventricular block. Physiologic pacing (dual chamber or atrial) was the initial mode of pacing in 143 patients (66%). During a mean follow-up of 14.8±9.4 years, 84% of patients (39%) developed a clinical episode of atrial tachyarrhythmia. Univariate analysis showed that a history of paroxysmal atrial arrhythmia, adult age (>18 years) at implantation, sick sinus syndrome, complex CHD and physiologic pacing were associated with an increased risk of atrial arrhythmia during follow-up. Multivariate analysis demonstrated that only a history of paroxysmal atrial arrhythmias, hazard ratio (HR) 7.22, 95%CI 4.46-11.6, P<0.001) and adult age at implantation (HR 1.97, 95%CI 1.21-3.20, P=0.006) were independent predictors for subsequent atrial arrhythmias.

Conclusion: In contrast to the general population, physiologic pacing provides no benefit over ventricular pacing for the prevention of atrial arrhythmias in adults with CHD. The risk of atrial arrhythmias was associated with a prior history of atrial arrhythmias and age at implantation.

P5542
Permanent cardiac pacing in children - choosing the optimal pacing-site: a multi-centre study
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Purpose: We evaluated the effects of pacing-site on left ventricular (LV) synchrony and function in children requiring permanent pacing.
Methods: Eighty children (age <18 years) from 21 centres 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 3.1–8.4) 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 dysynchrony 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 1.74–15.0, P=0.003) whereas LVA/LVLat pacing was associated with preserved LV function (LV EF >55%, OR 6.97, CI 2.21–22.0, 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.

Figure 1. ACHD prevalence per million

P5543
The prevalence of adult congenital heart disease, a systematic review
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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. Excluding 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.

P5544
Lack of continuity of care may be a cause of morbidity in adults with moderate congenital heart disease
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We sought to evaluate clinical impact of lack of continuity of specialized health-care in adults with a CHD diagnosed in infancy.
Methods: In 212 patients (p) 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 (10), 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, obstructive lesions (30%), subaortic or supravalvular 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 4.5% 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 repairedToF (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 y 14% class III vs 70% class I, 24% class II y 5% class III; p = 0.05). Delay (odd ratio 3.7 95% CI 1.8-7.3; p < 0.001) and age (odd ratio 1.04 CI 95% 1.02-1.07; 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.

Predictors of residual functional tricuspid regurgitation after transcatheter Atrial Septal Defect closure: importance of pre-closure tricuspid valve anatomy

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Introduction: Although chronic right heart volume overload 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. Pre-existing tricuspid regurgitation in children with perimembranous VSDs invariably improved. At a median follow-up of 14 months, 3 patients had a right bundle branch block; complete clotation in children with perimembranous VSDs invariably improved. At a median

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.

Postoperative fever and other risk factors for health-care acquired infection in pediatric postoperative congenital heart surgery

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Background: Health-care acquired infections (HAIs) have been associated with significant morbidity and mortality, as well as greatly increased health care costs. Postoperative fever as an indicator of HAIs is a topic of research in several publications, but information on this phenomenon in children is scant, particularly in cardiovascular surgery.

Purpose: To determine the total number of HAIs, identify the contributing risk factors in particularly postoperative fever, and the mortality of this type of infection following pediatric congenital heart surgery.

Methods: Prospective cohort study included all the admitted patients in the Pediatric Cardiac Surgical ICU (PCSCI) from 1/01/2009 to 30/12/2010. Registration SMAR pre-, intra- and postoperative data was done.

Results: Out of 175 patients, HAIs were identified in 119 (68%). HAIs patients had statistical significance of the following: (1) Younger age; median 9 (5-30) months, p < 0.001, (2) Presence of patent ductus arteriosus (PDA) (n=23 versus n=0, p = 0.001), (3) Significant relevant pre-operative fever 24 hours (n=43 versus n=2, p < 0.001). Result of multivariate analysis, significant fever (OR 17.95 CI 5.52, p < 0.001) was identified as the only risk factor for HAIs. Mortality of HAIs patients was encountered in 44 (37%) patients (P = 0.01). Risk factors for mortality were younger age (r = 0.27, P < 0.003), HAIs (r=0.48, p<0.01), post operative fever (r = 0.4, P < 0.001), duration of mechanical ventilation (r=0.55, P = 0.000), duration of central line (r=0.34, P = 0.000) and positive peripheral blood culture (r=0.38, P = 0.05). The age, ASIS C, ASIS D and APATCHI scores were the risk factors for mortality by using multivariate analysis.

Conclusion: Proper Selection of patients, avoiding those with recent infections, aggressive treatment of post operative fever extending beyond 2 days, early weaning from mechanical ventilation and early removal of invasive catheters might reduce health care acquired infection and subsequent mortality in pediatric postoperative cardiac surgery.

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 inheritable (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), ACVR1L, 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 ACVR1L, respectively, and 3 not yet described unclassified sequence variants (ACVR1L n=1; SMAD9 n=2) were found in HPAH children. One ACVR1L mutation has not been described before. In CHD-PAH patients 1 BMPR2 mutation and 2 unclassified sequence variants (endoglin n=1, BMPR2 n=1) were found. Carriers of genetic mutations and sequence variants with pathologic functional impact had a significantly lower PVR (926.9±250.53, p < 0.003) than patients with no mutation or silent sequence variants.

Conclusion: Mutations and unclassified variants with functional impact in different TGF 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

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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 15.86/100,000 (male/female=1.47) and 106.79/100,000, respectively. Coronary events occurred in 1254 patients (5.37%, male/female=2:1.9), 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.

Table 1. Age distribution of the age at admission for cardiac catheterization, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG)

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>0-5</th>
<th>6-10</th>
<th>11-15</th>
<th>16-20</th>
<th>21-25</th>
<th>26-30</th>
<th>31-35</th>
<th>36-40</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac catheterization</td>
<td>104 (33%)</td>
<td>90 (28%)</td>
<td>64 (20%)</td>
<td>29 (9.2%)</td>
<td>11 (3.5%)</td>
<td>6 (1.9%)</td>
<td>7 (2.2%)</td>
<td>316</td>
<td>316</td>
</tr>
<tr>
<td>PCI</td>
<td>0</td>
<td>2 (1.1%)</td>
<td>4 (2.2%)</td>
<td>2 (1.1%)</td>
<td>1 (0.6%)</td>
<td>1 (0.5%)</td>
<td>3 (1.7%)</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (10%)</td>
<td>90 (28%)</td>
<td>30 (10%)</td>
<td>0</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>10</td>
<td>18</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

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Background: Kawasaki disease (KD) is a generalized vasculitis of unknown etiology that occurs predominantly in infants and children. The important feature of this disease is coronary artery lesions (CALs) such as dilatation, aneurysm, and stenosis. The immunological therapy 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) using continuous hemodiafiltration (CHDF) for refractory KD to IVIG therapy.

Methods: 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, 2.0 to 4.7 years) and 17 kg (range, 11.0 to 26.2 kg), 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 (Smad/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 PE with CHDF was performed for three days. PE 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 days after onset of KD. One patient who developed myocarditis was performed SPE-CHDF using a combination of extracorporeal life support. Six patients had CALs of 3.1-6.0mm diameter before performing SPE-CHDF. All CALs were regressed within 6 months from onset of KD. Seven patients were discharged and were returned to normal range of C reactive protein after performing SPE-CHDF. However, only one patient was administered high-dose methylprednisolone after performing SPE-CHDF, because of refractory to SPE-CHDF. No complications occurred with performing SPE-CHDF.

Conclusion: SPE-CHDF immediately reduced inflammation and incidence of CALs in patients of KD. In patients with KD refractory to IVIG therapy, SPE-CHDF is effective and safe therapeutic intervention and should be performed at early phase.

Aortic distensibility independently predicts exercise capacity in adults with repaired conotruncal defect

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Introduction: Histologically detectable structural abnormalities of the medial aorta are common in patients with conotruncal defects, i.e. tetralogy of Fallot (TOF) and complete transposition of the great arteries (d-TGA). Using cardiac magnetic resonance imaging (MRI), we recently documented a decreased distensibility of the ascending aorta in these repaired adults compared to controls. We hypothesized that impaired aortic distensibility increases the afterload burden for the subaortic ventricle and compromises cardiac output during exercise.

Methods: Exercise capacity was assessed by cardiopulmonary exercise testing in 26 adults with d-TGA and an atrial switch procedure, and 35 adults with repaired TOF and analyzed in relation to the patients' characteristics, the ejecation fraction of the subaortic ventricle, and the ascending aortic distensibility. Cardiac MRI for measurement of exercise fraction and aortic distensibility was performed before and 3 months in clinically stable patients.

Results: The mean age of adults with repaired TOF was 29±10.6 years, and 23.4±7.4 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 conotruncal 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>Type of defect (TOF)</th>
<th>1.31</th>
<th>0.655</th>
<th>-4.52 to 7.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>-0.22</td>
<td>0.126</td>
<td>-0.51 to 0.06</td>
</tr>
<tr>
<td>Subaortic EF (%)</td>
<td>0.30</td>
<td>0.074</td>
<td>-0.03 to 0.62</td>
</tr>
<tr>
<td>Body surface area</td>
<td>4.10</td>
<td>0.053</td>
<td>-22.2 to 10.8</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>-7.26</td>
<td>0.012</td>
<td>-12.84 to -1.67</td>
</tr>
<tr>
<td>Aortic distensibility (1/mmHg)</td>
<td>1904</td>
<td>0.005</td>
<td>618 to 3249</td>
</tr>
</tbody>
</table>

Conclusion: Impaired aortic distensibility and its impact of ventriculo-arterial coupling predicts exercise capacity in adults with repaired conotruncal defects, independent of the ejection fraction of the underlying ventricle.

Determinants of exercise capacity in patients with Ebstein’s anomaly


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Aim: This study aims to elucidate the determinants of exercise capacity in patients with Ebstein’s anomaly (EA). Methods: All patients underwent an echocardiographic (TTE) and cardiac magnetic resonance imaging study (CMR). The severity of EA was described as mild, moderate or severe based on established echocardiographic findings. Tricuspid regurgitation (TR) was evaluated in four degrees from none to severe. Measures of ventricular systolic function right and left ventricular (RV, LV) 2D longitudinal global strain (2DGS) were obtained. To evaluate diastolic LV function the ratio of the peak early filling of mitral inflow (E) and the early diastolic velocity of the lateral mitral annulus (Em) were determined by TTE. Indexed RV enddiastolic volume (RVEDV) and aortic cardiac index (aCI) were calculated by CMR. Cardiopulmonary exercise testing was performed to evaluate peak oxygen uptake (peakVO2) and pulsocinematic oxygen saturation at peak exercise (Sp02Peak).

Results: 76 (31 men) individuals were included. Mean age was 30±16 years. Mean achieved percent of predicted peakVO2 was 71±19%. Multivariable linear regression analysis revealed the severity of EA and a favourable trend for Sp02Peak as independent predictors of peakVO2 (see table).

Table 1

<table>
<thead>
<tr>
<th>PeakVO2</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of EA (degree)</td>
<td>-11.9</td>
<td>0.007</td>
</tr>
<tr>
<td>Sp02 @ peak (%)</td>
<td>0.51</td>
<td>0.071</td>
</tr>
<tr>
<td>aCI (l/min/m²)</td>
<td>4.07</td>
<td>0.305</td>
</tr>
<tr>
<td>RVEDV (ml/m²)</td>
<td>0.02</td>
<td>0.663</td>
</tr>
<tr>
<td>E/E (no unit)</td>
<td>-0.06</td>
<td>0.826</td>
</tr>
<tr>
<td>TR (degree)</td>
<td>3.0</td>
<td>0.539</td>
</tr>
<tr>
<td>2DGS, LV (%)</td>
<td>0.86</td>
<td>0.700</td>
</tr>
<tr>
<td>2DGS, RV (%)</td>
<td>-0.16</td>
<td>0.765</td>
</tr>
</tbody>
</table>

Conclusions: This study shows for the first time that the severity of Ebstein’s anomaly and the degree of a right to left shunt on atrial level, reflected by the...
Exercise capacity in adult patients with Fontan circulation is not limited by myocardial performance

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Purpose: The specific cardiopulmonary 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: Thirty adults with Fontan type palliation were investigated by echo-cardiography at rest and during recurrent bicycle exercise until exhaustion. Tissue Doppler analysis was performed from recordings of the ventricular free wall and AV-annulus. The following parameters were analyzed: peak diastolic flow velocity through the AV-valve (E), Tei index, ratio of systole/diastole duration (SDS) and SDS' (mitral and aortic annulus). These parameters were compared to values obtained in 10 healthy subjects, all data is shown as “% of reference”.

Results: Six females and seven males were included in our study (median age 23.8 [18.2 to 29.8]). BMI 24.4±3.0. Morphologically, eight patients had a left type ventricle and five patients had a right type ventricle. CP study showed median VO2peak of 19.6 ml/min/kg [12.6 to 24.7]. Median VE/VCO2 was 48.3 [40.8-69.8]. During bicycle exercise, peak diastolic AV-valve flow velocity increased by 70±46%. Median change in Tei index was -6% [-33% to 128%]. Systole/diastole ratio increased by 45±26%. S increased by 40±14%. E' increased by 52±32%. E/E' increased by 56±53%. Different functional cardiac parameters during incremental exercise showed a relatively homogeneous pattern of increase of systolic function (Tei index, ’). The response of diastolic function and SD-Ratio to exercise seemed to be more heterogeneous. There were no correlation between VO2peak or VE/VCO2 and any of the cardiac functional parameters. In contrast VO2peak and VE/VCO2 showed a significant correlation, confirmed by linear regression analysis (beta -0.76, p<0.01).

Conclusions: Exercise capacity was low in all individuals. Respiratory efficiency (VE/VCO2) 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 functional response to exercise. Diastolic response was more heterogeneous than systolic response. VO2peak in patients with Fontan palliation may be more related to respiratory efficiency than to myocardial performance.

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 compares 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. [Physical component summary (PCS) 104±15% vs 100% ±18%, p<0.001] and mental component summary (MCS) 103% ±17% vs 99% ±20%, p<0.001). PCS declines from 106% of the predicted reference value 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.

Psychosocial determinants of quality of life in adolescents with congenital heart disease

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Purpose: The present study aimed at identifying psychosocial determinants of quality of life in adolescents with congenital heart disease (CHD) using a longitudinal design to investigate the direction of the relationships.

Methods: We assessed 429 adolescents with CHD (86% female; 53% boys; median age 16 years) twice over a period of nine months. Patients were recruited from the paediatric and congenital cardiology database of a university hospital in Belgium. Inclusion criteria were: confirmed CHD; aged 14-18 years at the start of the study; last cardiac consult ≤ 5 years ago at our centre; being able to read and write Dutch; and the availability of valid contact details. Exclusion criteria: cognitive and/or physical limitations inhibiting filling out questionnaires; prior heart transplantation; and absence of informed consent. We measured quality of life (linear analogue scale; perceived health status (linear analogue scale); peer support (peer subscales of the brief inventory of parent and peer attachment); parental support (responsiveness subscale of the child report of parent behaviour inventory); and sense of coherence (13-item orientation to life questionnaire). These psychosocial determinants were dichotomized using predetermined cut-offs. A cross-lagged analysis was used, controlling for family structure, sex and disease complexity.

Results: Perceived health status and sense of coherence positively predicted quality of life over time. Parental support positively predicted quality of life over time, both directly and indirectly through sense of coherence.

Psychosclerostin as potential novel biomarker for aortic valve disease

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Purpose: The present study aimed at identifying psychosocial determinants of quality of life in adolescents with congenital heart disease (CHD) using a longitudinal design to investigate the direction of the relationships.

Methods: We assessed 429 adolescents with CHD (86% response rate; 53% boys; median age 16 years) twice over a period of nine months. Patients were recruited from the paediatric and congenital cardiology database of a university hospital in Belgium. Inclusion criteria were: confirmed CHD; aged 14-18 years at the start of the study; last cardiac consult ≤ 5 years ago at our centre; being able to read and write Dutch; and the availability of valid contact details. Exclusion criteria: cognitive and/or physical limitations inhibiting filling out questionnaires; prior heart transplantation; and absence of informed consent. We measured quality of life (linear analogue scale; perceived health status (linear analogue scale); peer support (peer subscales of the brief inventory of parent and peer attachment); parental support (responsiveness subscale of the child report of parent behaviour inventory); and sense of coherence (13-item orientation to life questionnaire). These psychosocial determinants were dichotomized using predetermined cut-offs. A cross-lagged analysis was used, controlling for family structure, sex and disease complexity.

Results: Perceived health status and sense of coherence positively predicted quality of life over time. Parental support positively predicted quality of life over time, both directly and indirectly through sense of coherence.

Sclerostin as potential novel biomarker for aortic valve disease

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Background: Sclerostin is a key negative regulator of bone formation. Recently, sclerostin was identified for the first time in human aortas at the protein level. We hypothesized that sclerostin may also play a potential role in the development of aortic valve calcification (AVC).

Methods: A cross-sectional study in 149 patients (mean age 76±18 years) with echocardiographically proven AVC was performed. In all patients serum sclerostin levels were measured by ELISA (Tecmedica, Bünde, Germany) and compared to values obtained from a healthy control population (n=57, age 48±20 years). For quantification of AVC and CAC all patients of the study cohort underwent non contrast-enhanced DSCT (Definition, Siemens, Germany). Immunohistochemistry (IHC) staining for sclerostin and mRNA sclerostin expression was analyzed in 10 calcified aortic valves and 10 non-calcified control valves obtained from 10 age matched control subjects.

Results: Patients with AVC showed significantly higher sclerostin serum levels as compared to healthy controls (0.91±0.48 vs. 0.58±0.26 ng/mL, p<0.001). A significant correlation between sclerostin serum levels and Agatston AVC scores was observed (r = 0.58, p = 0.001) in the study cohort. IHC revealed a positive sclerostin staining in nine calcified valves compared to neg-
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 fibrinolytic 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±421 mmHg) scheduled for isolated valve replacement were studied. Plasma fibrin clot lysis time (CLT) using the active assay in vivo, in the presence of tissue factor, phospholipid vesicles and tissue plasminogen activator, developed by Lisman in 2001, and plasma plasminogen activator inhibitor (PAI-1) were measured. Immunohistochemistry staining revealed co-localization of both types of MCs (Fn), prothrombin and PAI-1 was evaluated by immunostaining.

Results: In AS patients CLT was positively correlated with the aortic valve leaflet thickness (r=0.67, p=0.003) and the degree of valve calcification (r=0.65, p=0.0001). 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 fibrin 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 pathways have been observed in calcified regions of excised human aortic valves. In contrast, there is 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 controlling genes with osteoclastic 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 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 osteoclasts (BMP-2, BMP-6, Runt-2, osteoclastin) and those with osteoresorptive functions (TRAP, RankL, Rank, Opg, Mmp-9, osteoprotegerin) in a multi-variable analysis to the stenosis severity.

Results: Firstly, the transcript levels of the genes taking part in osteoclast differentiation and activity showed significantly elevated levels in calcified valve tissue compared to: 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; Opg: 21.1±4.6 fold, p=0.001 increases, respectively and were not counterbalanced by Opg, a known negative regulatory cytokine of osteoclast differentiation. Secondly, the expression levels of genes involved in osteoblast transformation were unaltered throughout the valves, except from that of osteoblast (258.8±181-fold increase, p=0.001). Thirdly, 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 Opg (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.
of valve calcification in patients with initially normal or sclerotic aortic valve and preserved renal function. No association with calcium phosphate metabolism parameters including vitamin D and PTH levels was found.

Decreased cardiac 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 for valve surgery or 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 immunochemistry 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 (r=0.91, 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=0.085, P<0.001). Interestingly, in patients, NOX4 levels directly correlated with capillary density (r=0.389, P=0.025), which in turn associated with cardiac function. NOX4 levels directly correlated with eNOS expression (40% P=0.034). Decreased NOX4 levels also associated with greater apoptosis severity (r=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.

ApoA-1 mimetic peptide infusions improve aortic valve stenosis in ApoE−/− and Wrn delta hel/delta hel mice

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Purpose: We have previously shown that apolipoprotein A1 (Apo-A1) 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-A1 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 Apo-A1 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 histology were performed to evaluate the effects of Apo-A1 mimetic peptide infusions on rat and mice models of AVS. Long term in vivo echocardiographic and echocardiographic data was created to simulate the functional effects of varying aortic root thicknesses (observed on histology) on aortic valve opening.

Results: Aortic valve area (AVA) was improved at the end of treatment in both ApoE−/− and Wrn δhel/δhel mice treated with Apo-A1 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 [0.642-0.686] mm² 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 ApoA-I treated mice compared to placebo (80.4±6.2% vs 90.6±4.2%, p=0.023). AAVA 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-1 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.

Effect of pressure unloading on mitogen-activated protein kinases in peripheral blood mononuclear cells of patients undergoing trans-catheter aortic valve implantation

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Background: Aortic stenosis (AS) and subsequent cardiac hypertrophy are associated with high morbidity and mortality. Trans-catheter aortic valve implantation (TAVI) is a promising technique for patients with severe aortic stenosis (AS) and high surgical risk. Mitogen Activated Protein Kinases (MAPKs) activity in peripheral blood mononuclear cells of patients undergoing TAVI could affect these molecular signal pathways in blood mononuclear cells.

Methods: White blood cells (WBC) were isolated from patients before and after (48 hours) valve implantation (both trans-apical or trans-scalpic, n=10). Extracted extracellular signal-regulated kinase (ERK) and p38 (p38) phosphorylation was next evaluated by western blot. Age-matched patients without AS or arterial hypertension were used as controls (CTR, n=5).

Results: Effective pressure unloading following TAVI was associated with MAPKs de-activation (pERK levels fold over control, PRE: 22.97±6.25; POST: 7.82±3.86; p=0.038 levels fold over control, POST: 7.26±0.99; POST: 1.61±0.45, p<0.001). Furthermore, WBC isolated before TAVI displayed a significant activation of the beta-adrenergic receptor kinase 1 (BKGRK2), and this was reversed to control levels after valve implantation (GRK2 levels fold over control, POST: 2.8±0.44, POST: 0.8±0.15, p=0.05).

Conclusions: These data confirm that MAPKs are sensors of pressure overload and suggest that leukocytes might represent important cellular targets mirroring cardiac remodeling. Changes in MAPKs and GRK2 expression following pressure unloading could help to better understand the pathophysiology of left ventricular remodeling after aortic valve replacement.

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 a disease lasting for 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 48-72 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 48-72 hours of the initiation of the antibiotic treatment in 407 patients of LSIE of a total of 692 episodes considered as therapy delayed from 1996 to 2011. We performed a univariate regression model to determine the risk factors of in-hospital mortality in these 407 patients.

Conclusions: 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 viridians Streptococci prosthetic valve endocarditis in the antibiotic position have a higher risk of developing this situation. We found age (OR: 1.026; 95% CI: 1.007-1.046), Staphylococcus aureus infection (OR: 3.3; 95% CI: 1.6-6.6), positive blood cultures after 48-72 hours from the initiation of the antibiotic treatment (OR: 2.1; 95% CI: 1.2-3.6), heart failure (OR: 2.8; 95% CI: 1.6-4.7) and renal failure (OR: 2.9; 95% CI: 1.8-4.9) as factors independently associated with higher in-hospital mortality.

INFEETIVE ENDOCARDITIS
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, 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. Comorbidity 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=0.02), cancer (15.4% vs 8.3%; p=0.006), and chronic obstructive pulmonary disease (12.2% vs 7.1%; p<0.001). 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 perianvillar 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 (2.9% vs 16.2%; p=0.001), and Coagulase negative staphylococci (10.6% 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 16.5%; p=0.01), 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=0.002) and had a high mortality rate (73.1% vs 17.1%; 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, perianvillar complications, and mortality were more prevalent, they underwent surgery less frequently. Mortality in this group was higher than in those without SS. Those patients with SS who did not undergo surgery had the poorest prognosis. Therefore, some patients with IE and SS might benefit from early surgery.

The role of B-type natriuretic peptide (BNP) as a prognostic factor for endocarditis in the emergency room

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Background: Some prognostic factors for infective endocarditis (IE) are well established, but the role of B-type natriuretic peptide (BNP) at admission has not been well studied. Objectives: The purpose of this study was to access the admission BNP value as a prognostic factor in patients with IE.

Methods: Between July 2009 and January 2011, consecutive patients with IE admitted to the emergency room were prospectively enrolled. Patients were included if they met possible or definite Duke’s criteria for IE. The association between elevated BNP and in-hospital death was determined.

Results: From 104 patients analysed, 67 were male (48%), the mean age was 52.6±19.1 years. During follow-up, 32 (30.8%) patients died. In univariate analysis, staphylococcal infection (P<0.001, HR 3.94; CI 1.94-8.0), dyspnea at presentation (P<0.001, HR 2.41; CI 1.64-7.2); left ventricular ejection fraction <55% (P=0.001, HR 3.97; CI 1.98-8.43), C-reactive protein (CRP) >120 mg/L (P<0.001, HR 4.04; CI 1.91-8.55) creatinine >1mg/dL (P=0.006, HR 2.92; CI 1.26-6.76) and BNP >200 pg/ml (P<0.001, HR 12.51; CI 2.98-52.4) were associated with in-hospital mortality. In multivariate analysis, the model showed that the presence of comorbidities (P<0.001, HR 12.51; CI 2.98-52.4) creatinine >120 mg/L, (P<0.001, HR 2.89; CI 1.39-6.02), dyspnea at presentation (P=0.003, HR 3.17; CI 1.49-6.76), and CRP >120 mg/L (P<0.001, HR 3.86; CI 1.76-8.46) were independent predictors of in-hospital mortality.

Conclusion: As important as the classic prognostic factors, elevated BNP levels on admission led to related fatal outcomes in IE patients.

Introduction and Objectives: Right-sided infective endocarditis (IE) is a poorly understood disease which encompasses very different groups of patients: intravenous drug users (IDUs) (group 1), intra-cardiac devices carriers (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, electrocardiographic 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 37 (27%) in group 3. An analysis of 85 clinical, epidemiological, microbiological, electrocardiographic and outcome variables have been performed.

Results: Differences in the most relevant variables are specified in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Age</td>
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<td>61±16</td>
<td>61±16</td>
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<td>64%</td>
<td>64%</td>
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<td>Smoking</td>
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<td>15%</td>
<td>15%</td>
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<td>Diabetes mellitus</td>
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<td>10%</td>
<td>10%</td>
<td>0.267</td>
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<tr>
<td>Chronic renal failure</td>
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<td>25%</td>
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<td>0.267</td>
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<tr>
<td>Perinatal complications</td>
<td>6%</td>
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<td>6%</td>
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<tr>
<td>Cardiac surgery</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
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<tr>
<td>In-hospital mortality</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>0.267</td>
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</tbody>
</table>

Conclusions: Right-sided IE can be classified into three types (IDUs, intra-cardiac devices carriers and non IDUs-non devices carriers), as there are relevant clinical, microbiological, electrocardiographic and outcome differences between them. The worse prognosis is that of non-IDUs patients without intra-cardiac 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 infective endocarditis 1035

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high morbidity the number of device-related infections has been growing in the last few years. The device related Infection is a serious condition with a high morbidity and mortality. The optimal management of IE depends not only on correct anti-
biotic 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 patients with asymptomatic 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. These cases were distributed in two groups: Group I (N=149) episodes of IE complicated with CNS embolisms, and Group II (N=575), those without this complication.

Results: Age (62.0±15) and gender distribution were similar in both groups. Re-
lated to renal failure, chronic obstructive pulmonary disease (3.4% vs 9.8%; p<0.001) and previous antibiotic therapy (4.3% vs 11%; p=0.042) were more frequent in Group I. In-hospital mortality was 15%. Overall, 18F-FDG-PET/CT had a sensitivity, speci-
ficity, PPV, NPV, and accuracy of 66%, 91%, 93% and 93%, respectively, detecting both cardiac and extracardiac infective foci. This 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%, 97% and 99%, 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 consid-
ering organs with a known high physiological uptake of glucose.

P5570 "True" versus "aborted" culture-negative infective endocarditis
C. Ferrera Duran1, I. Vilacosta1, C. Olmos1, C. Fernandez1, D. Vivas1, A. Revilla1, C. Sanz1, J. Lopez2, J.E. Rodriguez1, J.A. San Roman1, 1Hospital Clinic San Carlos, Cardiovascular Institute, Valladolid, Spain; 2Institute of Heart Sciences, CICOR, University Clinic Hospital, Valladolid, Spain; 3University Hospital La Princesa, Madrid, Spain
Purpose: To analyze the impact of antibiotic treatment prior to blood culture ex-
traction in infective endocarditis (IE) and to point out the differences in epidemiol-
y, clinical features, diagnosis and prognosis between "true negative" (TN) and "aborted negative" (AN) cases.

Methods: We analyzed 106 consecutive cases of IE with negative blood cultures recruited prospectively at three tertiary hospitals between 1996 and 2011. These cases were distributed 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 cul-
ture extraction (A); and Group II (N=64) cases who did not (TN). Eleven episodes were excluded due to the absence of clinical and/or echocardiographic features of cardiac infection. 75 episodes had complete data and were included in the analysis.

Results: Age (62.0±15) and gender distribution were similar in both groups. Re-
lated to renal failure, chronic obstructive pulmonary disease (3.4% vs 9.8%; p<0.001) and previous antibiotic therapy (4.3% vs 11%; p=0.042) were more frequent in Group I. In-hospital mortality was 15%. Overall, 18F-FDG-PET/CT had a sensitivity, speci-
ficity, PPV, NPV, and accuracy of 66%, 91%, 93% and 93%, respectively, detecting both cardiac and extracardiac infective foci. This 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%, 97% and 99%, 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 consid-
ering organs with a known high physiological uptake of glucose.

P5571 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 an-
tibiotic 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 patients with asymptomatic 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. These cases were distributed in two groups: Group I (N=149) episodes of IE complicated with CNS embolisms, and Group II (N=575), those without this complication.

Results: Age (62.0±15) and gender distribution were similar in both groups. Re-
lated to renal failure, chronic obstructive pulmonary disease (3.4% vs 9.8%; p<0.001) and previous antibiotic therapy (4.3% vs 11%; p=0.042) were more frequent in Group I. In-hospital mortality was 15%. Overall, 18F-FDG-PET/CT had a sensitivity, speci-
ficity, PPV, NPV, and accuracy of 66%, 91%, 93% and 93%, respectively, detecting both cardiac and extracardiac infective foci. This 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%, 97% and 99%, 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 consid-
ering organs with a known high physiological uptake of glucose.

P5572 Clinical profile of patients with endocarditis and central nervous system embolisms
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Objectives: To describe epidemiological, clinical, microbiological, and prognostic characterististics 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. These cases were distributed in two groups: Group I (N=149) episodes of IE complicated with CNS embolisms, and Group II (N=575), those without this complication.

Results: Age (62.0±15) and gender distribution were similar in both groups. Re-
lated to renal failure, chronic obstructive pulmonary disease (3.4% vs 9.8%; p<0.001) and previous antibiotic therapy (4.3% vs 11%; p=0.042) were more frequent in Group I. In-hospital mortality was 15%. Overall, 18F-FDG-PET/CT had a sensitivity, speci-
ficity, PPV, NPV, and accuracy of 66%, 91%, 93% and 93%, respectively, detecting both cardiac and extracardiac infective foci. This 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%, 97% and 99%, 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 consid-
ering organs with a known high physiological uptake of glucose.

P5573 Infective endocarditis
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 continues 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 (PVE). 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% PVE), 80% due to causes directly related to infection. The median length of follow-up in patients alive at discharge was 3.2 years (IQR 1-5 years). Among those who were only 9 lost of follow-up. For the overall series, the actuarial survival at 1 year was 60% (64% NVIE, 49% PVE), at 2 years 56% (59% NVIE, 43% PVE), and at 5 years 48% (52% NVIE, 34% PVE). For those alive at discharge, the actuarial survival at 1 year was 88% (87% NVIE, 83% PVE), at 2 years 79% (81% NVIE; 72% PVE), and at 5 years 68% (71% NVIE; 51% PVE). Relapse occurred in 2.2% (95CI 1.3%-3%), a median of 25 days after finishing treatment (IQR 7-42 days). Eight patients (2.6%, 95%CI 1.3%-5%) suffered a recurrence during follow-up, with an incidence density of 0.0007 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.

Methods: A study group: 65 pts (44 male), mean age 52 yrs ± 16.2. E-selectin levels in IVE vs CE were only 9 lost of follow-up. For the overall series, the actuarial survival at 1 year was 60% (64% NVIE, 49% PVE), at 2 years 56% (59% NVIE, 43% PVE), and at 5 years 48% (52% NVIE, 34% PVE). For those alive at discharge, the actuarial survival at 1 year was 88% (87% NVIE, 83% PVE), at 2 years 79% (81% NVIE; 72% PVE), and at 5 years 68% (71% NVIE; 51% PVE). Relapse occurred in 2.2% (95CI 1.3%-3%), a median of 25 days after finishing treatment (IQR 7-42 days). Eight patients (2.6%, 95CI 1.3%-5%) suffered a recurrence during follow-up, with an incidence density of 0.0007 episodes per patient-year (95CI 0.0029-0.0133). E- and P-selectins evaluation were drawn 3-times: on the 1st (establishment of the diagnosis of IE), 2nd, 5th day. For statistical analysis the maximal levels of parameters were used.

Results: There were no differences in platelet count in pts with cerebral embolism (CE) vs-CEC+CE 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 compared to WCE pts (7.6±5.8mg/dl vs 4.6±3.2mg/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±5.9mg/dl vs 8.1±5.9mg/dl, p=NS). Higher E-selectin levels in pts with CE compared to WCE pts (7.2-28G/l, median 7.3±4.46, 17.8–18.5, mean 50.9±22.5, p=NS). There were no differences in E-selectin levels in CE and WCE pts (15-194G/ml, median 72.19±44.28 vs 20-138.5G/ml, mean 56.69±33.87, p=NS), and in SCE and OCE pts (22-180G/ml, mean 66.1±39.02 vs 20-138.5G/ml, mean 56.69±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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Purpose: 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 involved 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 whereas chronic anaemia (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 seen in Group I. Echocardiographic profile: S. aureus (25.3% vs 15%; p=0.009), and S.bovis (4.9% vs 2.9%; p=0.01) were more frequently isolated in Group I, while Coagulase Negative Staphylococcus (6.6% 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: Scintigraphy 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, 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 prosthetic material region, or negative in absence of radiolabeled leukocyte in the cardiac region. Morphological aspects and bacteriology were obtained from patients who underwent cardiac surgery (n = 26).

Results: From the patients with an intense signal with LS who underwent surgery (n = 5), one patient developed prosthetic valve dehiscence during follow-up with a preserved aortic valve in the prosthetic material region, or negative in absence of radiolabeled leukocyte in the cardiac region. Clinical outcome was collected in patients treated medically (n = 33). The prevalence may be significantly different in rural and urban children. The programs to control RHD should be focused in rural and urban children.

Conclusions: This retrospective study suggests that LS can help to identify cardiac abscesses and evaluate clinical outcome in patients with a suspicion of PVE.

VALVE DISEASE: OTHER

Prevalence of subclinical rheumatic heart disease in urban and rural areas of north India: the extended-RHEUMATIC study

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Background: Studies have reported a higher prevalence of subclinical rheumatic heart disease (RHD) using echocardiographic screening in many countries including India. The prevalence may be significantly different in rural and urban areas of India, but is not studied. The objective is to compare the prevalence among rural and urban school children in India.

Methods: We carried out a cross sectional echocardiographic screening study among 11,177 randomly selected school children aged 5-15 years (10.2 ± 2.7 years; 55.9% male). A total of 9547 students were from rural areas and 1630 from urban areas of New Delhi.

Results: Clinical examination detected mitral regurgitation (MR) in 8 patients and the estimated prevalence of clinical RHD was 0.7/1000 school children. Echocardiography-Doppler diagnosed RHD in 193 cases, giving a prevalence of 17.3/1000 school children (95% CI: 15.0 – 19.9/1000 children). The prevalence of 17.3/1000 school children in urban and rural areas was equal (ratio 1.0, 95% CI: 0.8 – 1.3/1000 children). Among children aged 5-15 years, the prevalence was 28.9/1000 (8.3/1000 rural children and 20.6/1000 urban children). Among children aged 0-4 years, the prevalence was 0.007. Even among the rural children there was a two-fold difference among children studying in government schools (26.6/1000) as compared to private schools (14.7/1000; p < 0.05).

Prepregnancy right ventricular systolic function predicts cardiovascular outcome in pregnant women with congenital heart disease

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1. University Medical Center Groningen, Department of Cardiology/Netherlands Heart Institute (ICIN), Groningen/Utrecht, Netherlands; 2. University Medical Center Groningen, University of Groningen, Department of Cardiology, Groningen, Netherlands; 3. Academic Medical Center, University of Amsterdam, Department of Cardiology, Amsterdam, Netherlands; 4. Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands; 5. Radboud University Nijmegen Medical Centre, Department of Cardiology, Nijmegen, Netherlands; 6. University Medical Center Groningen, Department of Obstetrics and Gynecology, Groningen, Netherlands; 7. Leiden University Medical Center, Department of Cardiology, Leiden, Netherlands.

Purpose: Right ventricular dysfunction is common in women with congenital heart disease (CHD) and may partly explain cardiovascular outcome of pregnancy in these women. We aimed to compare RV function between women with CHD and healthy pregnant women and to relate RV function to cardiovascular complications (CVC) in women with CHD.

Methods: We compared echocardiographic right ventricular parameters (systolic function, pulmonary artery pressure, and right atrial pressure) and Doppler echocardiography of the remaining patient confirmed the presence of an abscess, which was confirmed during surgery. None of the patients with negative LS who underwent surgery (n = 4) had an abscess evidenced during intervention. From patients with an intense signal with LS who underwent surgery (n = 26) the abscess was evidenced during intervention. In-hospital and bacteriology were obtained from patients who underwent cardiac surgery (n = 1038). Infective endocarditis / Valve disease: other

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>TAPSE and RVD in pregnant women with CHD and healthy pregnant women</th>
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<tbody>
<tr>
<td>RVD at 20 weeks (mm)</td>
<td>32.5 ± 5.6 NA – 28.6 ± 7.4</td>
</tr>
<tr>
<td>RVD at 32 weeks (mm)</td>
<td>35.7 ± 7.0 NA – 33.4 ± 8.4</td>
</tr>
<tr>
<td>TAPSE at 20 weeks (mm)</td>
<td>27.5 ± 11.4 NA – 26.2 ± 13.8</td>
</tr>
<tr>
<td>TAPSE at 32 weeks (mm)</td>
<td>29.2 ± 11.4 NA – 27.4 ± 13.7</td>
</tr>
<tr>
<td>S' right ventricle at 20 weeks (cm/s)</td>
<td>10.5 ± 1.0 NA – 8.5 ± 1.9</td>
</tr>
<tr>
<td>S' right ventricle at 32 weeks (cm/s)</td>
<td>11.2 ± 1.9 NA – 9.4 ± 2.1</td>
</tr>
<tr>
<td>TAPSE pre-pregnancy (mm)</td>
<td>21.2 ± 1.5 NA – 17.3 ± 4.6</td>
</tr>
<tr>
<td>TAPSE at 20 weeks (mm)</td>
<td>26.0 ± 6.0 NA – 22.5 ± 13.8</td>
</tr>
<tr>
<td>TAPSE at 32 weeks (mm)</td>
<td>29.4 ± 6.0 NA – 25.9 ± 13.8</td>
</tr>
<tr>
<td>Apical RV diameter pre-pregnancy (mm)</td>
<td>36.2 ± 7.8 NA – 29.5 ± 5.6</td>
</tr>
<tr>
<td>Apical RV diameter at 20 weeks (mm)</td>
<td>38.1 ± 7.4 NA – 31.2 ± 6.4</td>
</tr>
<tr>
<td>Apical RV diameter at 32 weeks (mm)</td>
<td>39.0 ± 7.0 NA – 35.7 ± 7.7</td>
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</tbody>
</table>

*P-values are given as mean ± standard deviation; NA, not available.

Conclusions: Systolic right ventricular function parameters (S' and TAPSE) are lower in women with CHD compared to healthy pregnant women and are related to cardiovascular outcome of pregnancy in women with CHD.

Disease spectrum and pregnancy outcome in women with heart disease - an australian combined cardiac-obstetric multidisciplinary service experience

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Background: Cardiac disease remains a major cause of maternal and neonatal morbidity and mortality in developed countries. Many countries lack detailed information regarding the burden of disease and a strategic approach to the problem.

Method: A retrospective review was undertaken on women referred to our insti-
tution’s obstetric-cardiology service between April 2006 and January 2008.

Results: One-hundred and twenty-four gravid women were identified (age = 28.9±5.7 years). The cardiac diagnoses are listed in Table 1. One-hundred and twenty-one pregnancies were completed resulting in 122 live births and 1 stillbirth. There were no maternal deaths. There were 31 hospitalisations in 28 confinements (23%) for cardiac indications ante-partum. The most common indications for admission were arrhythmia (45%), heart failure (39%), and myocardial ischemia (10%). The most common obstetric complications were post-partum haemorrhage (18%), premature rupture of membranes (11%), uterine growth restriction (7%), threatened premature labour (5%). In neanotes the rates of pretermity (30% of 121 confinements) and small for gestation (8%)
Diastolic left ventricular function predicts pregnancy in women with mechanical valves: the European registry on pregnancy and heart disease

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1. University Medical Center Groningen, Department of Cardiology, Groningen, Netherlands; 2. University Medical Center Groningen, Department of Obstetrics and Gynecology, Groningen, Netherlands; 3. Academic Medical Center, University of Amsterdam, Department of Cardiology, Amsterdam, Netherlands; 4. Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands; 5. Radboud University Nijmegen Medical Centre, Department of Cardiology, Nijmegen, Netherlands; 6. University Medical Center Utrecht, Department of Obstetrics and Gynecology, Utrecht, Netherlands.

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 70 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±2.4 versus 12.4±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 1.31, 95% CI 1.06-1.61, p=0.012). LAV (preconception, at 20 and 32 weeks of gestation) was associated with CVC (OR 1.05, 95% CI 1.02-1.09, p=0.005). (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. Of all cardiac procedures, 75% were performed in the third trimester.

Conclusion: 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.

Table 1. Cardiac diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No (%)</th>
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<tbody>
<tr>
<td>Congenital: Transposition (5), Tetralogy (10), Shunts (15), Coarctation (4), Other (10)</td>
<td>54 (44)</td>
</tr>
<tr>
<td>Cardiomyopathy: Hypertrophic (4), Dilated (12), Myocarditis (1)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Arrhythmia: Ventricular (5), Supraventricular (7), Long QT (9), Conduction defect (1)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>Acquired valve disease: Mechanical prosthesis (2), Rheumatic (6), Radiation-induced (1), Myxomatous (9)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (8)</td>
</tr>
</tbody>
</table>

Table 1. E’ and left atrial volumes in women with CHD with and without cardiovascular complications

<table>
<thead>
<tr>
<th>With cardiovascular complications</th>
<th>Without cardiovascular complications</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E’ at 32 weeks (cm/s)</td>
<td>9.6 (8.9-10.6)</td>
<td>11.2 (9.1-12.5)</td>
</tr>
<tr>
<td>E’ at 32 weeks (cm/s)</td>
<td>9.7 (8.3-11.2)</td>
<td>10.2 (9.0-12.0)</td>
</tr>
<tr>
<td>LAV pre-pregnancy (ml)</td>
<td>46.1 (32.7-56.2)</td>
<td>31.6 (24.4-39.8)</td>
</tr>
<tr>
<td>LAV at 20 weeks (ml)</td>
<td>52.8 (34.3-67.0)</td>
<td>38.0 (30.4-74.2)</td>
</tr>
<tr>
<td>LAV at 32 weeks (ml)</td>
<td>54.1 (42.8-67.3)</td>
<td>40.8 (33.4-49.5)</td>
</tr>
</tbody>
</table>

Table 1. E’ and left atrial volumes in women with CHD with and without cardiovascular complications.

Conclusion: LV E’ is lower in pregnant women with CHD compared to healthy pregnant women.

Medication during pregnancy in women with heart disease: The European registry on pregnancy and heart disease

P.T.E. Ruys1, M.R. Jonsson2, R. Hall1, J.W. Roos-Hesselink1 on behalf of the investigators of the European Registry on Pregnancy and Heart disease.

1. Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands; 2. Chelsea and Westminster Hospital, London, United Kingdom; 3. Norfolk and Norwich University Hospital, Norwich, United Kingdom.

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. In 1% (15 patients) we 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, APGAR score of lower than 7 occurred in 31% of cases.

Table 1. Mechanical valve complication

<table>
<thead>
<tr>
<th>Valve type</th>
<th>Mechanical valve (number)</th>
<th>Mortality</th>
<th>Thrombotic events</th>
<th>Hemorrhage</th>
<th>Fetal death</th>
<th>Birth weight &lt;2500 gram</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMAW</td>
<td>VI K</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>VI K</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>LMWH</td>
<td>VI K</td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>VI K</td>
<td>4</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

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.

Pregnancy in women with mechanical valves: the European registry on pregnancy and heart disease

P.T.E. Ruys1, M.R. Jonsson2, R. Hall1, J.W. Roos-Hesselink1 on behalf of the investigators of the European Registry on Pregnancy and Heart disease.

1. Erasmus Medical Center, Thoraxcenter, Department of Cardiology, Rotterdam, Netherlands; 2. Chelsea and Westminster Hospital, London, United Kingdom.

Background: In pregnant woman with a mechanical heart valve, choosing the 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, APGAR score of lower than 7 occurred in 31% of cases.

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.
Identification and characterization of the novel human effer-ago-related gene (hERG) R744P mutant linked to hereditary long QT syndrome 2


Purpose: Mutations of the cyclic nucleotide binding domain (CNBD) may disrupt human effer-ago-related gene (hERG) K+ 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 stimulus.

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, 0.56±0.08 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 equal ratio. Mean activating and tail currents were reduced by 30% 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 a molecular basis for LQTS in the index patient and emphasizes the role of the hERG CNBD for cardiac repolarization.

Angiotensin II regulates cardiac L-type Ca channels and ryanodine receptors via NADPH oxidase

S. Wagner,1 C. Danzi,1 J. Moellencamp,1 A. Shahzadi,2 J. Backs3, L.S. Mäier1,2. 1Dept. Cardiology, University Medical Center, Goettingen, Germany; 2King’s College London, Cardiovascular Division, London, United Kingdom; 3University Hospital of Heidelberg, Internal Medicine III, Dept. Cardiology, Angiolog & Pneumolog, Heidelberg, Germany.

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 (RyanR). 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 (Fig. * P<0.05 vs. WT+Ang II). Pharmacologic inhibition of protein kinase A (PKA) with H89 (5 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 diastolic RyR2 activity, spontaneous Ca spark frequency (CaSpF) in 100 μmol/L (1c-1) was measured via confocal microscopy (Fluo-4 10 μmol/L). In WT, Ang II significantly enhanced CaSpF (2.0±0.37 vs. 0.67±0.06 for Ang II vs. vehicle, N=20 vs. 12, P<0.05), and this increase was absent in g9p14p2−/− myocytes (0.79±0.10 vs. 0.66±0.08 for Ang II vs. vehicle, N=8 vs. 7). PKA inhibition with H89, however, could not reverse the Ang II-induced increase in CaSpF (2.37±0.52, N=9). In contrast, the increase in CaSpF was completely absent in CaMII−/− myocytes exposed to Ang II (0.56±0.01 vs. 0.63±0.06 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.

Development of an effective cellular model for human endothelial mesenchmal transition in studying bisacipud valvem malformations and cardiosignage


Purpose: Endothelial mesenchmal transition (EndoMT) is an important process for cardiac outcome tract and aortic valve formation. It is proposed that Notch signaling is involved in this process and shown in our as well as others' previous studies, patients with defects of LVOt 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 LVOt.

Methods: Two types of endothelial cells were used: HAEC (human aortic endothelial cells) from patients with aortic aneurysms and from healthy donors and HUVEC (human umbilical cord blood cells). EndoMT induced by different stimulant: 1) TGF-β; 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: TGF-β effectively induced EndoMT in HAEC, but to a much lesser extent in HUVEC. In contrast, NICD effectively induced EndoMT in HUVEC, but not in HAEC. Co-culture of cells expressing one of the Notch ligands (Dll1, Dll4 or Jag2) with either HAEC or HVEC induced EndoMT with the most effect of Dll4. We have checked different cellular markers to mark EndoMT by three different methods. 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 Willebrand factor and CD31/PECAM was less visible and countable. We have checked 20 markers previously described for EndoMT in literature by RTPCR and revealed 4 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 conductions to endothelial cell properties of various vascular bases.

Induction of MesP1 by Brachury(T) generates common cardiovascular progenitor cells, which can be purified by MACS

R.D. David,1 C. Rimmbach1, P. Nathan1, F. Schwarz1, V. Jarsch1, M. Gegg1, J. Stieber2, H. Licken1, W. Franz1. 1University Hospital Grosshadern, Munich, Germany; 2University Institute of Pharmacology, Erlangen, Germany; 3Helmholz Center of Munich, Neuhemoven, Germany.

The proliferative potential of pluripotent stem cell derived cardiomyocytes is limited and neapoptotic mechanisms play a major role in defining the type of cells that can be obtained using one of these cell types should be interpreted carefully in conductions to endothelial cell properties of various vascular bases.

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 LVOt.

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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 conductions to endothelial cell properties of various vascular bases.
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 (Danio 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(cmlc2: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 laser injury hearts under confocal microscopy. Ventricle ejection fraction (EF) was measured by video-image analysis of beating hearts.

Results: Data are mean±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 effects of CDK9 inhibition which are unrelated to cardiomyocyte proliferation.

Muscarinic regulation of the early embryonic heart: switch from NO to IKACh-mediated signalling

M. Reppel1, W. Lindenau2, D. Malan3, Y. Duan2, J. Hescheler2, H. Schunkert1, B.K. Fleischmann1,1Medical University of Luebeck, Department of Cardiology, Luebeck, Germany;2University of Cologne, Institute of Neuropsychology, Cologne, Germany;3University of Bonn, Institute of Physiology I, Bonn, Germany

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.

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 potential recordings of the heart in vivo 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 (67.7±4.2%, n=15) than in LDS hearts (89.3±2.2%, 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 guanyl cyclase and L-NAME, 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, Tertiapin, 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±1% (n=7, P<0.02) under control conditions and by 22.6±13% (n=4, P<0.04) after pretreatment with isoprotrenol (10 μM) was observed. In summary, our data indicate a switch from NO to IKACh-mediated muscarinic signalling during embryonic heart development.

Unique left ventricular geometry and function of young adults born preterm: impact of prematurity and preeclampsia exposure

A.J. Lewandowski1, D.X. Augustine1, E.F. Davis1, M. Lazdam1, R. Barnerjea1, A. Singh1, A. Luca1, C.W. Redmond2, S. Neubauer1, P. Leeson1. 1University of Oxford, Department of Cardiovascular Medicine, Oxford, United Kingdom; 2University College London, Institute of Child Health, London, United Kingdom; 3University of Oxford, Nuffield Department of Obstetrics & Gynaecology, Oxford, United Kingdom

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 Argus 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/m, 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), end 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 characterize 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). Rotation of the left ventricle also differs with reduced apical and basal systolic rotation (46.3±26.2 vs 56.1±30.1 degrees/second, P=0.02 and -45.5±27.7 vs -40.2±35.4 degrees/second, P=0.002). Individuals born preterm whose mothers were non-obese (-13.6±2.2 vs -15.2±3.4%, P=0.02).

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 not followed, may enhance atherosclerosis in 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.

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**MicroRNA-155 as a potential target for the cardiovascular dysfunction of sepsis in a mouse model of endotoxicemia**

**F. Vasques-Novo1, C. Quina-Rodrigues2, R. Cerqueira3, A.P. Loureiro4, A.F. Leite-Moreira5, R. Roncon-Albuquerque Jr.6 University of Porto, Faculty of Medicine, Porto, Portugal**

**Introduction:** Although cardiovascular dysfunction of sepsis remains one of the most frequent causes of morbidity and mortality in critically ill patients, its treatment remains supportive. MicroRNA-155 (miR-155) is a multifunctional micro-RNA with important gene targets in inflammation, immunity and cardiovascular disease. Our aim was to evaluate the role of miR-155 in the cardiovascular dysfunction of sepsis using a mouse model of endotoxemia.

**Methods:** Male C57Bl/j6 (WT) and B6.Cg-Mim155m1.Rlyk/j (miR-155−/−), KO mice (20-25g), randomly underwent intraperitoneal injection of 40mg/kg LPS (LPS) or vehicle (C). Twelve hours after injection, echocardiographic evaluation was performed and animals were euthanized for left ventricular (LV), aortic and plasma sample collection. In WT, plasma concentration, myocardial and aortic expression of miR-155 was evaluated by real-time RT-PCR. LV expression of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) was also assessed. Aortic rings tension was performed and the vascular response to angiotensin (AngII) evaluated. To assess vascular permeability, 30mg/kg of Evans blue-albumin conjugate (EB-A) was injected and its concentration measured in bronchoalveolar lavage (BAL) fluid by spectrophotometry. Mortality was also recorded up to 24h after LPS injection. Groups were compared with Kaplan-Meier survival analysis and simple or repeated measures ANOVA. Quantitative variables: mean±SEM. P<0.05 considered significant.

**Results:** In WT, LPS injection was accompanied by increased miR-155 circulating levels and enhanced expression in LV and aorta. In KO mice LPS mortality was significantly reduced (84.6% in WTLPS vs. 46.2% KO-LPS). Cardiac dysfunction in WT-LPS consisted in decreased stroke volume, ejection fraction and cardiac output with increased diastolic LV dimensions; these changes were significantly attenuated in KO-LPS. Vascular reactivity to AngII was decreased in WT-LPS but not in KO-LPS compared with WT-C. Vascular permeability was increased in WT-LPS, compared with WT-C and this was blunted in KO-LPS. LV expression of TNF-α and IL-6 was increased in WT-LPS, and these alterations were significantly attenuated in KO-LPS.

**Conclusion:** In our mouse model of endotoxemia, cardiovascular dysfunction associated with increased miR-155 expression. In mice lacking miR-155, LPS-induced cardiac dysfunction, aortic AngII hyporeactivity and increased vascular permeability as well as mortality are significantly attenuated. Our results suggest miR-155 as a potential specific target for the cardiovascular dysfunction of sepsis.
Changes in PPARalpha expression in relation to cardiomyocyte remodeling and transition to the dilated cardiomyopathy and heart failure in Tgpalhpa44 mice

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PPARalpha is a transcriptional factor which regulates in the heart an energetic metabolism and inhibits inflammatory processes. The altered metabolic phenotype and inflammation have been implicated as important mediators of dilated cardiomyopathy (DCM), however, the PPARalpha role in this disease is poorly understood and conflicting data were reported. We hypothesized that abnormal PPARalpha expression is associated with heart remodeling and progression of DCM in mouse hearts and that changes from Tg44 and FVB mice at the age of 1.2, 4, 6, 10, 12, and 16 months were studied for the purpose. The PPARalpha and SMAalpha level by western blot in the context of histopathological (HE, Masson’s Trichrome, PAS) and immunohistochemical (anti-desmin, SMAalpha) markers structural features of left ventricle tissue samples were analyzed. Images were morphometrically assessed. The profile of PPARalpha expression in LV tissue in Tg44 or in comparison to FVB mice changed significantly during lifetime: (1) at 4 months increased 1.6 fold, although no myocyte hypertrophy and structural remodeling except increased number of mitochondria were observed; (2) at 10 months decreased to 60% of FVB mice along with signs of cellular ab- normality, such as ultrastructural level (partly loss of contractile elements, swollen mitochondria or with irregular density of matrix and irregular cristae, and lipid droplets, and presence of single SMAalpha and numerous PAS(+) myocytes); (3) at the age of 12 months elevated 1.3 fold and concomitantly with increased myocar- dial tissue fibrosis (about x1.5 vs ctrl) and cardiomyocyte hypertrophy (diameter 21.15±5.56 vs 15.84±2.88μm) and structural disintegration (disappearance of contractile fibrils and normal mitochondrial network) and dramatic decline of PAS(+) cardiomyocytes; (4) at the age of 16 months decreased to about 80% of ctrl along with increasing fibrosis and myocyte hypertrophy (diameter 37.99±2.86μm) and cell degenerative changes and complete lack of glycogen, and up-regulation of SMAalpha in many cardiomyocytes. A statistically significant correlation be- tween PPARalpha fluctuations and PAS(+) cardiomyocytes number was observed (R2=77%). We demonstrated a biphasic early and late increase in PPARalpha expression that may have distinct role in DCM progression. Early increase in PPARalpha expression, might however lead to lipotoxicity and thus represent rather a maladaptive re- sponse.

Substrates of atrial arrhythmias: Histological insights from patients with congenital heart disease

A. Ueda1, I. Adachi2, K.P. McCarthy3, Y. Ghei1, S.Y. Ho1, H. Uemura1, 1Royal Brompton Hospital, London, United Kingdom; 2Royal Brompton Hospital, London, United Kingdom

Introduction: It has been reported that indirect or direct markers of atrial over- load, such as atrial size or pressure, have correlation with atrial fibrosis which is relevant to atrial tachyarrhythmia. However, studies on the effect of the overload validation to atrial histological changes are scarce. A proportion of congenital heart disease (CHD) patients have predominantly right atrium (RA) volume and/or pressure overload and some patients develop atrial arrhythmias over time. Since the duration of overload in these patients is from birth, investigating histological changes in the RA wall can provide some insight into the effect of overload duration on atrial remodelling and allow us to assess any correlation with atrial arrhythmia.

Methods: Consecutive CHD patients who underwent initial repair surgeries were recruited. In order to minimize the effect of physiological myocardial growth, we enrolled patients over 18 years of age. Right atrial tissues resected during surgery were examined by means of routine histology and immunohistochemistry tech- niques. Histories of preoperative atrial arrhythmia were collected from medical records. Histology samples were quantitatively assessed for three markers: (1) proportion of fibrosis (%fibrosis) (2) myocyte size and (3) capillary distance. We analyzed correlations between the histological changes and age. Comparisons were made between the patients who did not have arrhythmia (NA-group) and those who had arrhythmia (Attachy-group), in terms of histological remodelling. We also examined infiltration of inflammatory cells in the RA.

Results: Thirty-three patients were enrolled (median age43.0, range 18.4-82.0 years, 13 male). Eleven patients (33.3%) had preoperative atrial arrhythmias. The age, which corresponds to the overload duration, had positive correlation with %fibrosis (r=0.351, p=0.045) and capillary distance (r=0.595, p<0.001) but not with myocyte size. The Attachy-group had greater extent of fibrosis (p=0.006) and longer capillary distance (p=0.0024) compared to NA-group. There were more CD45-positive cell infiltrations in Attachy-group patients (p < 0.001) and the cell counts positively correlated with each histological marker.

Conclusion: Chronic right atrial overload due to CHD caused time-dependent atrial structural remodelling. Right atrial remodelling, like left atrial remodelling observed in adult non-CHD patients, contributed to arrhythmia occurrence. The duration of the overload, not patient age, might be a key factor for atrial histological changes not only in the setting of CHD.

Evaluation of interleukin-1 receptor antagonist inhibiting atherosclerosis in apolipoprotein E-deficient mice by ultrasound biomicroscopy

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Objectives: Interleukin (IL)-1 plays an important role in atherosclerosis. IL-1 re- ceptor antagonist (IL-1Ra) is an endogenous inhibitor of IL-1. However, the role of IL-1Ra in the development of atherosclerosis is poorly understood. The pur- pose of this study was using high-resolution ultrasound biomicroscopy (UBM) to validate the hypothesis that atherosclerotic (As) progression of invivo mice can be inhibited by IL-1Ra.

Methods: Mice that lacked IL-1Ra (IL-1Ra−/−) were crossed with apolipoprotein E-deficient (E−/−) mice and formation of atherosclerotic lesions was analyzed af-
Secretoneurin, a peptide from the chomatogranin-secretogranin family, regulates cardiomyocyte calcium homeostasis.

**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) with production confined to cardiomyocytes. As circulating levels of SN appear to be associated with mortality in HF, we hypothesized that SN may directly affect the pathophysiology of HF.

**Methods:** We explored functional aspects of SN in isolated cardiomyocytes by immunoblotting, real-time PCR, confocal microscopy, and Ca2+-dependent fluorescence resonance energy transfer (FRET) imaging.

**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 confocal 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% (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+ reuptake 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.

**Conclusions:** SN appears to affect calcium homeostasis as measured by both intracellular calcium concentration and ryanodine receptor activity. The effect of SN on cardiac function may be clinically important as patients with HF and elevated SN levels seem to have a poor prognosis.

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**EXCITATION-CONTRACTION COUPLING AND ARRHYTHMIAS**

**P5599**

Secretoneurin, a peptide from the chromogranin-secretogranin family, regulates cardiomyocyte calcium homeostasis.

**P5601**

The kinetic of activation of Ca2+/calmodulin-dependent protein kinase II

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**P5600**

Redox-dead protein kinase A disturbs excitation-contraction coupling

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**P5602**

Cardiovascular development, anatomy and pathology / Excitation-contraction coupling and arrhythmias
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 1μM isoprenaline, 5μM 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 exhibited significantly increased frequency in 15% (4.1 ± 3.7 vs 7.0 ± 1.1 μM, p=0.02), full-duration at half-maximum (868 ± 3.6 vs 411 ± 1.4 ms, p<0.001) and spark mass (100.9 ± 12.8 vs 14 ± 2.4 μM, p=0.02) compared with rat sparks. Spark frequency was significantly lower in human than rat cardiomyocytes (0.03 ± 0.01 vs 0.05 ± 0.07 sec⁻¹, p<0.001). Application of flecainide for 5 minutes to human cardiomyocytes (n=9) produced a reduction in spark frequency (1.4 ± 0.3 reduced to 0.82 ± 0.2 sparks/100 μm², p=0.03), amplitude in terms of ratio-F/F₀ (0.46 ± 0.02 reduced to 0.42 ± 0.02, p=0.02) and spark-mediated SR leak (2.2 ± 1.3 reduced to 0.6 ± 0.4 μm² s⁻¹, p<0.008).

In conclusion, failing human cardiomyocytes exhibit spontaneous release of Ca²⁺ sparks 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 but to that previously reported in rat cardiomyocytes with a reduction in amplitude, frequency and spark-mediated SR leak.

Type Ca²⁺ channel antagonists attenuated aldosterone induces aldosterone-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 profinamma

ary cytokine with multiple biological functions. IL-18 induces myocardial hyper-

tropy, loss of contractility of cardiomyocytes and apoptosis leading myocardial dysfunction. Increased levels of circulating IL-18 are thought to be one of risk fac-

tors for heart failure. We previously reported that IL-18 expression was induced by aldosterone via the Rho/Rho-kinase pathway through endostatin-1 (ET-1) and angiotensin II (ANG II) production in cardiomyocytes. Ca²⁺ channel antagonists may be effective in preventing progressive cardiac dysfunction. However, inter-

action of IL-18 and Ca²⁺ channel antagonist are 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 cardiomyocytes.

Methods: We examined the effect of L- and Type Ca²⁺ channel antagonists on aldosterone-, ET-1, and ANG II-induced IL-18 expression in rat neonatal car

diomyocytes.

Results: Aldosterone, ET-1, and ANG II induced IL-18 mRNA and protein ex-

pression. Addition of Type Ca²⁺ channel antagonists, mibebradil and eden

dipine, 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, BO2132 and ANG II receptor antagonist, olmesartan, and also by RhoA inhibitor, C3 toxin and Rho-kinase inhibitor, fasudil. Aldosterone, ET-1 and ANG II induced Rho-kinase ac-

tivity in cardiomyocytes. Western blots showed Aldosterone, ET-1, and ANG II-induced Rho-kinase activities were inhibited by mibebradil and edenidine but not by nifedipine. These results indicate that mibebradil and edenidine 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 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±6.4%), but also in the left and right atrial non-ischemic zone (NIZ, by 26.5±6.0% and 20.1±10.9%) (n=6). Conduction velocity was decreased by 40.0±8.7% in IZ whereas unaffected in NIZ. AF was induced more frequently after ALI compared with controls (spontaneous AF, 3/10 vs. 0/10 pacing-induced AF, 10/10 vs. 3/10). The maximal dominant frequency (DFmax) was decreased after ALI in NIZ from 7.3±2.75 to 14.2±5.8 Hz, n=9, p<0.05, but unchanged in IZ. Wavebreaks, rotors and focal discharges were recognized predominantly at the border between IZ and NIZ. Palmitic acid perfusion, like ALI, caused pan-atrial APD abbreviation, and an increase of DFmax during AF (from 7.1±0.9 to 11.0±4.3 Hz, n=5, p<0.05).

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 I_{Na} and cardiac Na channel phosphorylation is disturbed by tubulin polymerization

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In heart failure, persistent current through Na channels (late I_{Na}) is enhanced leading to arrhythmias. We have shown that Ca/CaMdependent Kinase III (CaMKII) increases late I_{Na} but the mechanism was unclear. To test, whether ion channel trafficking is involved, isolated mouse ventricular myocytes were exposed to taxol (TXL, 100 μM), which polymerized microtubules. Late I_{Na} was measured using whole-cell patch clamp. In wild type (WT), isoproterenol (ISO, 1 μM) increased late I_{Na} (*-P<0.05, Fig.1). This increase was absent in cells lacking CaMKII (CaMKII-/-) and after preincubation with TXL (†-P<0.05 vs. WT+ISO, Fig.1). In WT vs. vehicle, ISO increased CaMKII autophosphorylation by 36±11% (n=10, P<0.05; Western blotting) as well as CaMKII-specific phosphorylation of Na channel (p-Nav1.5) at serine 571 by 61±28% (n=10, P<0.05). Similar to both the ISO-dependent increase in p-CaMKII and p-Nav1.5 was abolished with TXL (94±15% and 90±18%, n=10 and 10, P<0.05). Subcellular localization of p-CaMKII and p-Nav1.5 was analyzed with immunocytochemistry. ISO increased p-CaMKII and p-Nav1.5 density at intercalated discs (ICD, 767.5±25.4 arbitrary units, AV, by 612.0±23.5, n=26 vs. 27 and 884.0±27.3 vs. 602.3±30.8, n=17 vs. 24, P<0.05 vs. vehicle). Late I_{Na} (TXL, 100 μM) and TXL plus ISO (1 μM) did not affect the activity of PKB/Akt in isolated heart slices.

Role of the serum-and-glucocorticoid-induced protein kinase (SGK) in the regulation of the cardiac I_{CaL} by insulin and corticosteroids

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Purpose: Corticosteroids have been shown to increase the L-type Ca_{II} current (I_{CaL}) 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 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 24h incubation with corticosteroids alone, in combination with insulin or IGF-1 and/or in the presence of inhibitors of PI3-K or SGK-1. Results: In the presence of 100nM insulin, dexamethasone (1μM) increased I_{CaL} at 0mV by 49%, from -8.2±0.7pA/pF (n=11, P<0.01), while dexamethasone alone had no effect (-8.2±0.7pA/pF, n=11). Co-incubation with 1μM-dexamethasone and 10nM IGF-1 increased I_{CaL} by 42% (p<0.01). Insulin or IGF-1 alone did not affect I_{CaL} after 24h. Concentration-response relations revealed an EC50 of 0.43μM and 4.7μM for IGF-1 and insulin, respectively. Similarly, incubation with aldosterone increased I_{CaL} in the presence of insulin but not in its absence. Coincubation with the PI3-K inhibitors P3803 (0.5μM) or LY294002 (50μM) as well as co-incubation with the SGK inhibitor GSK650394 (10μM) abrogated the dexamethasone/insulin-induced effect on I_{CaL}, while in the absence of dexamethasone/insulin, the inhibitors did not alter I_{CaL}. GSK650394 (10μM) did not affect the activity of PKB/Akt in isolated
cardiomyocytes incubated with dexamethasone/insulin after 24 h as assessed by the degree of phosphorylation of the PKB/Akt specific substrate flamin-G.

**Conclusions:** We conclude that corticosteroids and insulin/GF-1 synergistically induce the increase in ICaL, and may constitute important players in the regulation of cardiac function under pathological and physiological conditions.

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**P5610**

**Junction between pulmonary veins and left atrial posterior wall provides 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 often anchor at the plecinate muscle border in the left atrial appendage (LAA) (Cardiovasc Res 2012). We hypothesized that junction between pulmonary vein and left atrial posterior wall (PVJ) may play a more important role in AF perpetuation.

**Methods:** In 12 isolated sheep hearts under increased intra-atral pressure (12 cmH2O), AF was induced in the absence of acetylcholine. Optical action potential signals were recorded simultaneously from epicardial and endocardial surface of atria by two CCD cameras and a cardio-endoscope. Electrodes were placed at the PVJ, LAA and right atrial appendage (RAA).

**Results:** The maximum minimal frequency of scroll electrogams 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 present at PVJ with trajectories circumscribing the PV ostia (Figure). 3-D numerical simulation suggest that transition from thick to thin 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 atrial electrophysiology, especially with regard to SIM, show a potential novel therapy for patients with AF.

**Results:** AF was induced in all hearts by burst pacing (25-55 Hz). AF was terminated by burst pacing in 11 hearts (55%). The mean cycle length of AF was 180±30 ms (mean±SD). After SIM (1 μM), AF was terminated in 13 hearts (65%). The mean cycle length of AF after SIM was 100±30 ms. AF was terminated by burst pacing in 10 hearts (40%). After DHA (10 μM), AF was terminated in 10 hearts (40%). The mean cycle length of AF after DHA was 120±30 ms. AF was terminated by burst pacing in 10 hearts (40%).

**Conclusions:** These results suggest that SIM and DHA have potential antiarrhythmic effects in rabbit hearts. Further studies are needed to elucidate the mechanisms underlying these effects.

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**P5612**

**TPeak-Tend determined across multiple leads represents global not transmural dispersion of repolarization**

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**Purpose:** The T-Peak-Tend interval (TPeak-Tend) is supposed to reflect dispersion of ventricular repolarization. A prolonged TPeak-Tend has been shown to predict ventricular arrhythmias and sudden cardiac death (SCD). However, the exact determinants of the TPeak-Tend are unknown. Because TPeak-Tend considered differently during the 12 standardized ECG leads, interpretation of TPeak-Tend results would be misleading. Therefore, we aimed to clarify the meaning of TPeak-Tend 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 maximum minus minimum 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. TPeak-Tend intervals in all 12 ECG leads are summarized by the minimum, maximum and mean TPeak (TPeak_min, TPeak_max, TPeak_mean). Finally, TPeak_total was defined as the interval of the minimum TPeak in any of the 12 leads to the maximum TPeak 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, epicardial) and global RT-dispersion was 84±16.1 ms (p<0.05). The averaged TPeak_min (30±4.3 ms), TPeak_max (44±5.9 ms) and TPeak (74±8.0 ms) were all significantly larger than transmural RT-dispersion and significantly smaller than global RT-dispersion. TPeak_total (87±17.2 ms) was statistically equal to global RT-dispersion, and significantly larger than transmural RT-dispersion (p<0.01).

**Conclusions:** TPeak-total reflects global RT-dispersion, whereas TPeak_min, TPeak_mean and TPeak_max are poor estimates of global or transmural RT-dispersion. Whether TPeak 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 Rac1 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±30%); the fibrosis marker microRNA-21 (miR-21, 157±49%); reduced expression of the miR-21 target spopulin (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 (36% RacET-Tora vs. 70% RacET).

In order to test the underlying mechanism, primary neonatal cardiac fibrobasts were treated with torsemide or furosemide. Torsemide (50 μM, 24 h) but not furosemide (50μM, 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 prevented atrial fibrosis, and reduced the prevalence of atrial fibrillation in RacET mice. This is associated with inhibition of CYP11B2 activity and reduced expression of the proinflammatory regulators CTGF, LOX and miR-21.

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 timeframe 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 AF progresses from paroxysmal to persistent and finally to permanent AF.

Methods: A total of 12 mongrel dogs were assigned to the study, which included 4 normal dogs, 4 dogs with atrial tachyarrhythmia (AT) induced by banding, and 4 dogs with atrial fibrillation (AF) induced by banding. Dogs were scanned 5 times: before banding, at 1, 3, 6, and 12 months after banding. The extent of LA fibrosis was assessed using LGE-MRI. For each scan, five short-axis images from atrial level to papillary muscle level were acquired. The LA myocardial fibrosis percentage was calculated as the area of fibrosis divided by the total myocardial area for each slice and then averaged over all slices.

Results: Mean fibrosis levels during 0-3 months, 4-7 months, and 8-12 months demonstrated progression of structural remodeling as overall LA fibrosis percentage 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 altered 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 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 decreased superoxide production due to NOS uncoupling. However, the pathophysiological role of p53 in cardiac fibroblasts remains unclear. Thus, we explored the role and relationship of S100A4 with p53.

Methods and Results: S100A4 mRNA 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 altered tissue shown in green.

Conclusions: These findings suggest that S100A4 modulates p53 function in fibroblasts and thereby mediates myocardial interstitial fibrosis 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 (LHV), gap junctions and connexin 43 (Cx43) dysfunction cause an important electrical disarray leading to ventricular tachyarrhythmias (VT). The role of microRNA in VT has not been fully elucidated. Therefore, the aim of this study was to investigate whether a reduction in the extent of LHV, obtained through valsartan (VAL) administration, could limit the structural remodeling and the onset of VT 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=8). 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 cardiac myocytes were challenged with Angiotsin II (AngII) 5 μg/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 VT in BAN group as indicated by induction of fibrillation and torsade de pointes 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, VAL in banded rats prevented miR-1 downregulation (1.7 fold, p<0.03) and Cx43 up-regulation (1.3 fold, p<0.03) therefore leading to a dramatic reduction of VT 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 hypertension by VAL was associated with a significant miR-1 up-regulation and Cx43 remodulation after pressure overload, hence decreasing susceptibility to VT.

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 ip for 5 weeks. Arginase 1 expression was 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 cardiotoxic 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 PBS and nor-NOHA treatment.
Potential role of miR-122 in myocardial fibrosis of Investigating novel regulators and inhibitors of aortic upregulated in group 2 patients compared to group 1 patients. Real-time RT-PCR Results:
by real-time RT-PCR in all 28 patients.
in collagen synthesis and CVF in all patients. Luciferase assays demonstrated
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.

Potential role of miR-122 in myocardial fibrosis of human aortic valve stenosis through transforming growth factor-beta 1 regulation

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Purpose: Transforming growth factor-beta type 1 (TGF-β1) may play a role in the pathogenesis of myocardial fibrosis in aortic valve stenosis (AS). MicroRNAs have been described as being 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 necropsies 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 3 patients from group 2 using TaqMan microRNA array, 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: TLDA 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. TGF-β1 regulated enzymes involved in collagen synthesis and CVF in all patients. Luciferase assays demonstrated that miR-122 inhibited TGF-β1 by direct targeting to a specific sequence located in the 3'-untranslated region of this molecule.

Conclusions: Our results suggest that downregulation of miR-122 is associated with myocardial fibrosis through TGF-β1 stimulation, in patients with AS.

Investigating novel regulators and inhibitors of aortic valve calcification

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Objective: Activation and transformation of aortic valvar interstitial cells (VICs) is 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 (376.7% increase; p<0.001) as 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-smooth muscle actin (α-SMA, 1.7 fold; P<0.05), RhoA (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 (58.1±6.6%). 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.

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 neoplasms. They have an uncertain histogenesis and previous studies investigating their overall heterogeneous cellular population suggest an origin from pluripotent 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 misleading data regarding molecular 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-vaso-active actin (α-A), calretinin (CALB2), matrix metalloproteinases 2 (MMP2), Tissue inhibitor of metalloproteinases 1 (TIMP1) and Notch1. In each case, MCs were microdissected by laser capture microscopy (LCM) and quantitative 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 Calb2, CD31 and Notch1 genes in microdissected cells as compared to the whole myxoma sections in most cases (Calb2: 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, aCA was not expressed in any case according to the Literature. MCs were Calb2-positive in all cases by immunoperoxidase staining.

Conclusions: We detected a different gene expression pattern in MCs as compared to whole cardiac myxoma 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.

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 inducing 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: Mutation analyses with genomic DNA were performed in 16 patients (15 females; age 61.1±13.2 years) enrolled according to the Mayo 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 5' and 3' untranslated regions of the 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 intron 8 untranslated region (3'UTR) 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=0.028) and have 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 (9 vs 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 mediator 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 undergo 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-hydroxynonenal 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 in the levels of GRP78, p-eIF2α, CHOP and p47phox NADPH oxidase, the effect of which was exacerbated by ALDH2 knockdown 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 kappaB 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)-kappaB. We previously showed that DHA has more potent and beneficial effect than EPA. Here we assessed the effect of DHA on oxidative stress and activity of NF-kappaB, 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 weeks. Left ventricle (LV) function was assessed by echochocardiography. Western blot analysis was performed for NADPH and NF-kappaB. Peroxides and NF-kappaB 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 149%, compared to sham. These detrimental effects were attenuated by the DHA supplementation. DHA inhibited myocardial reactive oxygen species production evidenced by decrease NOX2 (n=12) activity in DHA group. Peroxides in oxidative tissue were measured by TdT-mediated dUTP nick end-labeling (TUNEL) as a marker of apoptosis. DHA administration results in the reduction of TUNEL-positive cardiomyocytes detected in the LV tissue. Western blot analysis showed that DHA treatment downregulated peroxisome proliferator-activated receptor gamma (ppAR), a key regulator of lipid metabolism and profibrotic effects.

Conclusion: Dietary supplementation with DHA suppressed NADPH oxidase, decreased reactive oxygen species, inhibited NF-kappaB 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 fibrillation were noted in the HS group, whereas hypertension 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+RHT group. Telomeric DNA length, telomerase activity and telomere length transcription (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.

Cardiovascular disease and sudden cardiac death: a review of the role of ALDH2 in the pathogenesis of myocardial infarction and sudden death

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Background: Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disease of the myocardium and is regarded as the most common genetic cardiovascular disorder. Sudden cardiac death (SCD) is the most serious complication in the carriers of such mutations. We have conducted a retrospective multicenter study in 9 French hospitals to estimate the impact of the presence of TNNT2 mutation on the SCD rate and to analyze the impact of antiarrhythmic drugs on the frequency of SCD in these patients.

Methods: Thirty-five patients (female n=21) were included with a mean follow-up of 15.2 (±15.7) years. The mean age was 54.5 ± 14 years. The presence of TNNT2 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 SCD. Analysis showed that in 23.5% (4/17) of TNNT2 homozygotes in were implanted in comparison with only 5.8% (1/17) heterozygous patients (P=0.05). Conclusion: The study results indicate that TNNT2 homozygotes have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous patients. The study results indicate that TNNT2 homozygotes have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous patients. The study results indicate that TNNT2 homozygotes have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous patients. The study results indicate that TNNT2 homozygotes have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous patients. The study results indicate that TNNT2 homozygotes have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous patients. The study results indicate that TNNT2 homozygotes have much worse prognosis and are threatened with higher risk of SCD in comparison with heterozygous patients.

Intention/Purpose: Andersen-Tawil syndrome (ATS) is an uncommon form of long QT syndrome (LQT7) with life-threatening cardiac arrhythmias and sudden cardiac death. Patients with LQT7 are at high risk of sudden death due to ventricular fibrillation. Our aim was to examine the clinical features and outcome of LQTS patients with LQT7.

Patients and methods: We reviewed the medical records of all patients with LQT7 enrolled in our center. The diagnosis of LQT7 was confirmed by 12-lead ECG recordings and family history of sudden cardiac death. The patients were divided into two groups: those with typical LQT7 (n=21) and those with atypical LQT7 (n=4).

Results: Twenty-five patients (16M/9F) were included with a mean follow-up of 10 years. The mean age at diagnosis was 30.1 ± 19 years. Fourteen patients (40%) experienced syncope and one patient was resuscitated from a cardiac arrest before inclusion. The mean QTc interval was 46 ± 11 ms.
and the QTc 60±9.2 ms. All patients had a normal ejection fraction (EF). Holter recording found 12 260 ventricular premature beats (VPBs) per day on average. 23 patients had episodes of bigeminy and 25 patients had polymorphic PVC. 22 patients had non-sustained polymorphic ventricular tachycardia (VT), and 6 sustained polymorphic VT. Only 1 patient presented with torsade de pointes. Patients were treated with B-blocker (n=25), amiodarone (n=2), Recanid (n=4), and anticoagulants (n=5). 5 patients had a radiofrequency ablation. An implantable cardiac defibrillator (ICD) was implanted in 3 patients. During follow-up, none of the patients died, 4 experienced syncope under treatment and 1 patient had a non-fatal cardiac arrest.

**Conclusion:** Despite a severe clinical presentation with a very high rate of ventricular arrhythmia, the arrhythmogenic process of the Andersen-Tawil patients seems to be relatively good under treatment.

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**P5628**

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 already been identified. Little is known about the nitrate- and nitrite reductase capacity of skeletal muscle tissue. In our in 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 TNR 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-) hindlimbs 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, DET-A- 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 0.6±0.02 nmol/mg tissue. In parallel, nitrite was formed (0.21±0.04 pmol/mg tissue). Allsupron reduced neither nitrate consumption (0.63±0.01 nmol/mg tissue) nor nitrate formation (0.21±0.01 pmol/mg tissue). Under anoxia at pH 7.3, muscle tissue formed NO from nitrite 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/mg protein; vs. WT-tissue; p=0.0196). Allopurinol had no effect on NO formation (106±6 pmol/mg protein; n=3 in all groups).

Myoblast proliferation increased using nitrite (0.2 μM=0.26±0.01; 2.0 μM=0.37±0.01; 20.0 μM=0.29±0.01; 200.0 μM=0.30±0.01 Δ O.D.; vs. control 0.23±0.01 Δ O.D.; p<0.0001) or DET-A-NONOate (0.1 μM=0.35±0.01; vs. control p<0.0001). The effect of 2.0 μM nitrite was not abolished by 10 μM ODQ (0.21±0.01 Δ O.D. vs. control; p=0.981). Proliferation was inhibited by 1.0 μM RY (0.10±0.01 Δ O.D. vs. control 0.18±0.01 p<0.001), but partially reversed by 2.0 μM nitrate alone (0.16±0.01 Δ O.D. vs. RY; p<0.001) as well as 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-reducing 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.

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**P5630**

Improvement of cardiac function and modulation of immune response by transplantation of mouse cardiac stem cell lines immortalized with hTERT

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Mouse cardiac stem cell (CSC) lines immortalized with retroviruses harboring the hTERT-RES eGFP genes were transplanted into myocardial infarction (MI) rats to investigate their effects on cardiac regeneration and immune response. Five hundred thousand cells per rat (n=15) were transplanted into 3 groups (medium; CD31-CSC; CD31-CSC, and cardiac function and peripheral blood inflammatory cytokines and immune cells were analyzed at day 7, 14, 28 after cell transplantation. Significant improvements in ejection fraction value were observed in the CSC-transplanted groups compared with the medium group (control) at 4 week. IL-6 was significantly decreased at day 7 in the CSC-transplanted groups compared with the control group (Figure 1). MCP-1 was significantly decreased in the CSC-transplanted groups at day 1 compared with the control group (Figure 1).

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**P5629**

Intramyocardial injection of adipose-derived stem cells increased pericardial fat after myocardial infarction in rats


**Background:** Intramyocardial injections of adipose-derived stem cells (ASC) and endothelial cells (EC) have been known for improving myocardial function after acute myocardial infarction (AMI). However, the effects of injected ASCs and ECs on pericardial fat and their association with improvement in myocardial function have not been studied.

**Methods:** Twenty MI rats were divided into 4 groups: Control (n=5), ASC (n=5), EC (n=5) and ASC+EC (n=5) groups. ASC:EC mixture ratio was 1:4. AMI was created by ligating anterior descending coronary artery, and 5 x 105 cells obtained from mice were injected around three peri-infarct areas. Echocardiography and peripheral blood cytokines, such as IL-6, TNF-α, VEGF, MCP-1, and IL-10, were measured at day 0, 1, 7, 14, and 28 after AMI. Flow cytometry was used to analyze the origin of pericardial cells after isolating with collagenase type I. Masson’s trichrome staining and Oil Red O staining was used to measure cross-sectional MI and pericardial fat area at papillary muscle level, respectively.

**Results:** The weight of pericardial fat was significantly higher in the ASC group compared to the Control, EC, and ASC+EC groups (0.16±0.045g, 0.054±0.038g, 0.023±0.021g, 0.11±0.052g; P<0.001, respectively). The increased pericardial fat originated from rat, and the origin of pericardial fat was confirmed by increased anti-rat specific antibodies such as CD90-1 and CD161 in the pericardial fat (Figure). Masson trichrome staining showed significantly reduced MI area in the ASC group compared to the Control, EC, and ASC+EC groups (15.1±2%, 29.5±14%, P=0.001, respectively). Pericardial fat area was significantly higher in the ASC group compared to the Control, EC, and ASC+EC groups (0.051±0.021cm², 0.003±0.007cm², 0.007±0.011cm² 0.011±0.010cm², P<0.001, respectively). The increases from baseline in left ventricular ejection fraction was significantly higher in the ASC group compared to the Control, EC, and ASC+EC groups (220±85 pg/mL, 14±14 pg/mL, 45±37 pg/mL, 110±91 pg/mL; P<0.001, respectively).

**Conclusions:** Increases in pericardial fat after ASC injection were associated with the decreases in MI area and the increases in serum IL-10, thereby contributing to the improvement in left ventricular contractile function after AMI.
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 investigated the pathophysiological 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%, 99.7%, 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 logistics, 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<0.001 and p<0.001 respectively). In the non-infarct zone of the myocardium, MI+STNx animals demonstrated greater myocyte cross-sectional area, as well as increased cardiac interstitial fibrosis and collagen I compared to MI+Sham animals (p<0.001, p<0.001 and p<0.001 respectively).

Conclusions: This study demonstrated STNx accelerates cardiac hypertrophy, fibrosis and cardiac dysfunction post-MI whilst STNx-induced renal dysfunction, supporting bidirectional interactions in cardiorenal syndrome.

Total and leisure time physical activity and risk of heart failure: a prospective cohort study


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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: To identify 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 or non-ischemic origin, respectively.

Design: Cohort study

Participants: Of the participants in the fundraising event 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 leisure time PA reported as hours of PA per day, to risk of first hospitalization for any or non-ischemic heart failure, as identified in the Swedish National In-Patient Register until 31th December 2010.

Result: The total effect of leisure time PA was lower risk of any heart failure (hazard ratio 0.70; 95% confidence interval 0.59-0.84; for fifth vs first quintile) and non-ischemic heart failure (0.65; 0.52-0.80) with higher PA level. The direct effect of leisure time PA on heart failure was similar. The total effect of daily PA on risk of heart failure was modest (0.80; 0.67-0.96 for second vs first quintile); and for non-ischemic heart failure 0.84; 0.67-1.05) with negligible direct effect.

Conclusions: Amongst 39,813 walkers, leisure-time PA was more strongly related to risk of heart failure than total daily PA was. Part of the effect was indirect, but part remains to be explained.

The impact of physical activity on endothelial function in middle-aged and elderly inhabitants in an area with increased rates of longevity: Ikaria study


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.

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), permanent inhabitants of Ikaria Island. Endothelial function was evaluated using ultrasound measurement of flow-mediated-dilatation (FMD). We evaluated PA by 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 active physical.

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 (-6.3±3.24% vs -5.3±3.07%, p=0.008) while, there was no difference in FMD values between middle aged physically inactive subjects and elderly physically active (5.0±3.32% vs 5.3±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.
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.

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 forty-six 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 (sCD40L) and soluble Soluble intracellular adhesion molecule-1 (sICAM-1) concentrations were estimated using Luminex 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, 888.87±892.99 vs. 2367.73±8743.4 pg/mL, p=0.005, respectively), while sICAM-1 level did not differ between groups. The concentration of IL-6 was significantly higher in 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 significantly with the level of physical activity, as well as with the level of physical fitness (71.9±22.5 vs. 11.2±5.5, p=0.05), lower BMI (p=0.05) and with higher MMSE (27.3±4 vs. 25.4±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 mellitus and GDS, revealed that those elderly individuals who were physically active showed a 8-fold probability of having normal cognitive function (OR=8.223, p-value=0.002).

Conclusions: Intensive exercise training and high exercise capacity are related to lower IL-6 and CD40 L plasma levels. This may consist an important factor that decreases atherosclerosis progression.

Physical fitness improvement ameliorates arterial stiffness, myocardial hypertrophy and inflammation in patients with Chronic Kidney Disease

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Chronic kidney disease (CKD) patients usually presents exercise intolerance, cardiac and vascular stiffness and hypertrophy 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 conservative treatment. After a treadmill test to exclude CAD patients were submitted to basal evaluation 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 used. 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.

Results: The mean age was 65±12 years old, 42% males, 28% 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 (74 ± 6 vs. 70 ± 7 yrs, p=0.001), more males (68% vs. 33%, p=0.001), lower BMI (p=0.005) and with higher MMSE (27.3±4 vs. 25.4±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 mellitus and GDS, revealed that those elderly individuals who were physically active showed a 8-fold probability of having normal cognitive function (OR=8.223, p-value=0.002).

Conclusions: Intensive exercise training and high exercise capacity are related to lower IL-6 and CD40 L plasma levels. This may consist an important factor that decreases atherosclerosis progression.

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 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 geriatric 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 (7422.5±52.57 vs. 4929.3±44.46 calories, p<0.02), which was higher than those with lower hsCRP level (4444.50±1.6 vs. 4891.68±29 calories, p=0.03). Risk factors (higher triglycerides, greater waist circumference, lower weekly physical activity, and lower HDL-C level), however, were all independent for MetS (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 remote geriatric Asian MetS population.

Conclusions: We found that, instead of obesity, low HDL-C levels, reduced physical activity, and inflammation were the major pathophysiological MetS factors in our Asian participants.
P5639 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 (EIV) 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 (EIV) 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 EIV 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, EIV from 3.8±2.2 to 5.4±3.7 mmHg/ml*m2, p=ns 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 systolic blood pressure. Left ventricle analysis revealed that DC and EIV were significantly associated after adjusting for age, sex, patient group, exercise step, carotid diameter and central pulse pressure (full model, r2=0.57). Subgroup analysis revealed that DC and EIV were negatively correlated 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 EIV 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.

P5640 Long-term changes in physical activity and sedentary time of overweight and obese children after an inpatient weight-loss program - LOGIC trial
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Purpose: For paediatric weight-loss programs to be successful, they must succeed in increasing physical activity (PA) and decreasing sedentary time (ST) over 2.3 years undergoing an inpatient weight-loss program for diabetes mellitus type 2. The aim of this study was to investigate changes in PA and ST of children and adolescents two years after a short-term supervised weight-loss program.

Methods: Participants of this prospective study were 208 overweight and obese children ranging in age from 12 to 23 years undergoing an inpatient weight-loss program for 4-6 weeks. Body height and weight were measured in the clinic at the start of the intervention and two years later by the children’s general practitioners. At both time points children completed questionnaires on PA (“How many days last week did you spend doing homework and screen time (television and computer usage)). From the start of the intervention to two years later both body mass index (BMI) and BMI-SDS (BMI-standard deviation score) decreased from 32.6±5.8 kg/m2 to 31.5±6.3 kg/m2 and from 2.7±0.6 to 2.4±0.9, respectively (p<0.001). There was no significant increase in the number of days on which at least 60 minutes of PA were achieved (2.7±2.0 days/wk vs. 2.9±2.2 days/wk; p=0.05). Likewise, the total time spent sedentary did not decrease (34.4±19.2 h/wk vs. 35.1±17.2 h/wk; p=0.05) and PC time even increased from the start of the intervention to the two-year follow-up (10.3±10.3 h/wk vs. 12.9±10.3 h/wk; p=0.003).

Conclusions: This short-term supervised weight-loss program appeared to have no beneficial long-term effect on the PA volume and time spent sedentary. Out-patient strategies are required that help children to maintain the educated healthy behavior after terminating their inpatient treatment.

P5641 Physical activity in relation to cardiac risk markers in secondary prevention for patients with coronary artery disease
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Purpose: The synergistic effect of adherence to the Mediterranean diet and physical activity reduces the likelihood of acute coronary syndromes and ischemic strokes: a case-control study
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Purpose: The aim of the present work was to evaluate the association between adherence to the Mediterranean diet and the development of acute coronary syndrome (ACS) or ischemic stroke, according to physical activity levels.

Methods: During 2009-2010, 1000 participants were enrolled; 250 were consecutive patients with a first ACS, 250 were consecutive patients with a first ischemic stroke and 500 population-based, control subjects, one-for-one matched to the patients by age and sex. Socio-demographic, clinical, psychological, dietary and other lifestyle characteristics were measured. Adherence to the Mediterranean diet was assessed by the validated MedDietScore (theoretical range: 0-55).

Results: After various adjustments (i.e., age, sex, BMI, smoking, family history of cardiovascular disease, hypertension, hypercholesterolemia and diabetes mellitus), each 1/55 increase of the MedDietScore was associated with 9% (95% CI: 0.81-1.03) lower likelihood of ACS in physically inactive subjects and 9% (0.86-0.97) lower likelihood in active participants. Similarly, each 1/55 increase of the MedDietScore was associated with 8% (95% CI: 0.80-1.05) lower likelihood of ischemic stroke in physically inactive subjects and 15% (0.80-0.95) lower likelihood in active participants.

Conclusions: Individual and collective measures are needed, for the primary prevention of coronary heart disease and ischemic stroke, in order to further encourage adoption of a healthy lifestyle, with emphasis on a healthy diet and regular physical exercise.

P5643 Physical activity behaviors and its association with obesity indices in Greek adolescents
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Purpose: To assess the physical activity behaviors in a sample of Greek adolescents and further exploit any possible association with several obesity indices.
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 sportsmen. Our study is therefore aimed to evaluate two different groups of high school students, i.e. one group attending, and the other one 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 sport 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 studied chronically at rest with an blood pressure module. Additionally, a standard PHQ test, social behavior evaluation and mental tests, such as retentivity tests were performed.

Results: Fitness measured by a 3000 m 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±1.3 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±2.2 mmHg; p=0.05], peripheral pulse pressure [633±12.4 vs. 52.5±7.7 mmHg; p=0.05] and Aix aortic [5.1±1.6 vs. 15.1±1; 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 between 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 revealed. As a consequence, future studies in sportmen should be focused on 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 antiarrhythmic 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 analy- sis. 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>VF triggering</th>
<th>No VF triggering</th>
<th>CV of DF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL</td>
<td>7 (44%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>TRAINED</td>
<td>1 (7%)</td>
<td>13 (93%)</td>
</tr>
</tbody>
</table>

p<0.05 respect to control group.

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 antiarhythmic 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 block- ade 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, iso- lated 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 micromolar) 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 defibrillate 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 (p=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).

Conclusions: 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.
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 (AHI > 15) was present in 35% of the patients (mean AHI of 35.1±17). Of the SA patients 58% suffered from moderate (AHI <15 <30) SA and 42% from severe (AHI >30) SA. A period of 6 minutes or more breathing pauses during the night indicated the risk for Cheyne-Stokes respiration was present in 15% of the patients. Patients with sleep apnea were older (66.1±10 vs. 55.1±13, p =0.001, t-test) and BMI was higher (28.0±5.8 vs. 23.9±5.0, p=0.001). In patients with SA cardiac surgery and suffered more often from hypertension and diabetes (28% vs. 21% in non-SA patients), more frequent. Furthermore in SA we could see lower exercise load (84.4±40 vs. 108.5±55, p=0.001), and a trend to towards higher Ewpoth-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), ST-12-scores (PCS 35.9±9 vs. 36.0±10, p=0.2, MCS 47.1±11 vs. 47.1±12, p=0.8) or EF (56.1±11 vs. 55.1±10, p=0.6) between the groups.

Conclusions: Sleep apnea is highly prevalent in patients undergoing cardiac rehabilitation in Germany. Patients with SA were older, had a higher BMI, had more often cardiac surgery and suffered more often from hypertension and diabetes. 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 recommended in patient CR. We aimed 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 in the last year, LVEF <45%, and without any exclusion criteria: recent myocardial infarction, NYHA-FC IV, severe valvulopathy, or terminal disease. CR programme adhered to the current European guidelines. Clinical, echocardiographical, blood test and peak-oxygen consumption were prospectively recorded at baseline, 6 and 9 months. The follow-up was carried out through clinical visits.

Results: Mean age was 59.2±11.9 yrs and 23.1% were females. The only baseline difference was the percentage of implantable cardioverter-defibrillator (ICD) (43.5% for 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 2.2%(p=0.001), as reflected also by a mean increase of 0.86 ±0.33 mL/kg/min after CR, decreasing 2.20±4.48 mL/kg/min in the other group (p=0.001). Also, peakBNP decreased after CR vs 290 (IQR: 215-405) while it raised 578 (IQR: 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 mL/kg/min in the other group(p=0.001). At a mean follow-up of 18.8±2.6 months, 24% of the CR group vs 21.7% 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 underwent 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:0.56-5.03, 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 in this high-risk population.
Remote ischemic postconditioning improves coronary microcirculation in healthy subjects and in patients with heart failure

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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, and might be 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 transcranial Doppler echocardiography (TDE).

Methods: This study consisted of 10 patients with heart failure (64±9 years, 9 men) and 8 healthy volunteers (29±6 years, 8 men). They were received with RIPC treatment (interruption of arm ischemia through four cycles of 5-min inflation and 9-min deflation of a blood-pressure cuff for one week at a time in the morning and the evening). All subjects underwent TTE 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 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. CFR values in patients were not different between those with hypertension (p=0.56) and those without hypertension (p=0.25). No significant hemodynamic or mechanical complications were observed during the procedure or follow-up.

Conclusions: This TTE 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.

Hypoalbuminemia as a predictor of worst functional capacity recovery in patients attending cardiac rehabilitation after ACS

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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: 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 FC was evaluated 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 male and mean age was 53.9±9.9 years. The mean serum albumin was 39.2±7.5 and 56 (22.5%) patients had hypoalbuminemia (SI: 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 higher maximum BNP level (294.5±298.2 vs. 155.6±159.9 pg/mL, p<0.0001).

After 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 normoalbuminemia 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±6.6 months. After Cox-regression multivariate analysis, adjusted for relevant covariates, hypoalbuminemia was a strong and independent predictor of the composite outcome (HR 5.6, CI 2.0-16.0).

Conclusions: Hypoalbuminemia associates with poorer FC recovery and worse outcome in ACS undergoing CRP. A new, inexpensive, functional and prognostic marker might have been found.
Diabetes mellitus in cardiac rehabilitation program - facing a challenge


Introduction: Diabetes mellitus is one of the modifiable coronary risk factors of main focus in cardiac rehabilitation (CR) after an acute coronary syndrome (ACS). Methods: Prospective study involving patients referred to a CR program after ACS, between September 2008 and November 2010. Baseline and after CR evaluations included functional capacity (FC), assessed through maximal metabolic 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 (88.2%) 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 CABG. Only the non-diabetic patients showed significant improvement in FC (0.8±1.7 p=0.001 vs 0.3±1.2 p=0.15) and in TTPE (55±97 p=0.001 vs 16±92 p=0.39). These patients were followed for 11.4±8.6 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.

Cardiac rehabilitation: need of a global program for full recovery

P5655

Diabetes mellitus in cardiac rehabilitation program - facing a challenge

P5657

The pre-discharge six-minute walking test and prediction of all cause mortality after cardiac surgery

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Purpose: The 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 have been shown to correlate with mortality. However, the value of a pre-discharge 6mWT on long-term prognosis after cardiac surgery is not clear and merits further research.

Methods: We analyzed data from 304 patients (mean age 66±11 years, 22% females, LVEF 52.6±11%, BMI 26.9±4.8, 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 predicted values calculated on the basis of individual age, height, weight and sex. Patients were grouped according to tertiles of their performance at 6mWT. The endpoint was represented by all cause mortality. The predictive value of 6mWT was tested in univariate and multivariate analysis (Cox analysis).

Results: At entry 6mWT, 83 patients were in the lower 33% of their predicted values, 179 patients were in the > 33% to 66% and 42 were in the > 66%. At pre-discharge 6mWT, 31 patients were in the lower, 76 patients were in the medium, while 197 were in the higher tertile of their predicted values. 27/304 (9%) patients died in a 2-year follow-up. Patients who died had a lower LVEF (44±13% vs 53±10%, p =0.0004), a lower albumin level (3.8±0.4 vs 3.9±0.4 mg/dl, p =0.05), received a lower rate of b-blockers (62% vs 84%, p=0.01) and a higher rate of diuretics (88% vs 59%, p=0.003) and had a lower % 6mWT (42 vs 71%, p <0.0001). The 2-year mortality was 36%, 9% and 4.6% according to %6mWT tertiles (p<0.0001). At multivariate analysis only reduced LVEF and reduced %6mWT at pre-discharge were significant predictors of mortality (p<0.0001 both).

Conclusions: The inability to increase physical functional capacity following cardiac rehabilitation after cardiac surgery identifies patients at increased risk of all cause mortality in the subsequent 2 years.

P5656

Low functional capacity is not a predictor of absence of systolic function recovery in patients with systolic dysfunction after an acute coronary syndrome


Introduction and Purpose: Systolic dysfunction (left ventricle ejection fraction [LVEF] <40%) is one of the most powerful prognostic indicators after an acute coronary syndrome (ACS). Predictors of systolic function improvement after an ACS are scarcely known. The aim of the study was to evaluate whether low functional capacity has an effect in the improvement of LVEF in patients with systolic dysfunction after an ACS undergoing a cardiac rehabilitation program (CRP). Methods and Results: We studied 99 patients with LVEF<40% with recent ACS, age 55±11 (median ± SD); M/F 86/9 (90.5% male). Patients were divided into two groups according to the presence of improvement of ejection fraction (n=82, 86.3%) or lack of improvement (n=13, 13.7%) after an 8-week exercise-based CRP. 95.6% of patients underwent PCI, with no differences between groups in the rate of PCI (95% vs 100%, p=NS). 99% of patients were under antiplatelet drugs, 96.3% under beta-blockers, 94.5% under statins, 82.6% under ACEi/ARBs and 70.6% under aldosterone inhibitors at the moment of referral to CRP, with no differences between groups. Improvement of ejection fraction was observed in the majority of patients (86.3%), with a mean gain in EF of 14.8±8.2 points. Functional capacity prior and after the program was assessed by a maximal exercise test. Patients with EF improvement had a higher but not significant exercise capacity at the beginning of the program (6,9±2.77 vs. 5.5±3±0.2 MET; p=0.09), and a trend toward higher improvement in functional capacity at the end of the
program (mean gain in METs 3.6±2.15 vs 2.39±2.43, p=0.06). In a multivariate logistic regression model, including age, gender, hypertension, diabetes, sedentarism, smoking, abdominal obesity, body mass index, basal ejection fraction, basal functional capacity and functional capacity gain in METs, none of those factors was found to be independent predictor of improvement in left ventricular function.

Conclusion: Neither basal functional status nor functional gain after CRP can predict an EF improvement in patients with left ventricular dysfunction after ACS. Nevertheless CRP should be offered to all patients with LV dysfunction after ACS, in order to improve their physical capacity, their quality of life and their adherence to life style recommendations.

P5659
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-Comrey 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: Comparing 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.

P5660
Prolonged QTc and systemic inflammation: a deadly interplay in patients with rheumatoid arthritis
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Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease that is associated with increased rate of unrecognised myocardial infarctions and sudden cardiac death (SCD). Prolonged QTc interval has been associated with arrhythmogenic and sudden death in patients with long QT syndrome, but it remains controversial whether the same applies in the general population. Despite the previously reported association of CRP with SCD, no studies have so far examined the association of QTc with mortality in RA, a condition characterised by high inflammatory burden.

Methods: Three hundred and fifty seven RA patients with detailed baseline cardiovascular and RA-specific characteristics and 12-lead electrocardiograms (ECCs) were followed up for a mean of 63.8±15.3 months. Linear and Cox regression analyses were used to (i) identify variables that associate with QTc and (ii) examine the independence of the association of QTc with all cause mortality after adjustment for cardiovascular and RA-specific risk factors.

Results: The mean age of the study population was 60.6±12.0 years, 267 (74.8%) were females, mean QTc was 425.0±22.5 ms and 44 (12.3%) patients died during follow-up period. CRP (beta 0.156, p=0.021) was the most significant independent predictor of QTc prolongation after age and female gender. Insulin resistance and amitriptyline use also associated independently with QTc in RA patients. Crude HR for all cause mortality per 50msec increase in QTc was 2.16 (95% CI: 1.9 to 4.31, p=0.013). This association remained significant after adjustment for cardiovascular (hypertension, history of cardiovascular disease, insulin resistance and pack-years of smoking) and RA-specific (disease activity score, health assessment questionnaire, prednisolone use) risk factors (OR 2.29, 95% CI: 1.07 to 4.89, p=0.033) but lost statistical significance when CRP was included in the model (OR=1.87, 95% CI: 0.83 to 4.22, p=0.134). ROC curve analysis determined a QTc cut off for increased mortality at 426.5ms (AUC 0.615, p=0.013). The crude HR for overall mortality for RA patients at the prolonged QTc group (≥426.5ms), was 2.65 (95%CI: 1.45 to 4.85, p=0.002).

Conclusions: Fifty ms increase in QTc interval associate with doubling of the odds for all-cause mortality in patients with RA. It is likely that the increased inflammatory burden in RA, may lead to QTc interval prolongation which could at least partially explain the increased burden of sudden death in this population.

P5661
Association of circulating vitamin D and calcium levels with risk of cerebrovascular disease: systematic review and meta-analysis
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Background: Vitamin D and calcium have been associated with a wide range of non-skeletal diseases. However, evidence supporting their individual associations with incident cerebrovascular disease is scarce.

Methods: We conducted a meta-analysis of prospective cohort studies, published before February 2012 and sought from MEDLINE, EMBASE and BIOSIS databases, and any reported cerebrovascular disease by circulating vitamin D (25-hydroxy vitamin D [25(OH)D] as active metabolite) and calcium levels. Two independent investigators abstracted information on 25(OH)D and calcium, outcomes and other characteristics from selected studies. Relative risks (RRs) were pooled by random-effects meta-analysis and were further examined under different study level characteristics.

Results: From 5,778 initial references, nine unique prospective cohort studies (involving 69,160 participants and 1,583 incident cerebrovascular events) met our inclusion criteria. Seven studies focused on circulating 25(OH)D levels and 3 reported calcium levels. For 25(OH)D, in a comparison of individuals in the top third vs. those in the bottom third at baseline, the combined RR for cerebrovascular disease, adjusted for several conventional risk factors, was 0.60 (95% CI 0.48, 0.72). The corresponding RR in the prospective studies that reported on baseline circulating calcium levels for cerebrovascular disease was 1.40 (95% CI 1.19, 1.64). There was no apparent evidence of heterogeneity or publication bias among included studies.

Conclusions: Available data indicate that higher circulating level of vitamin D is associated with a decreased risk of cerebrovascular disease. Conversely, higher circulating calcium concentration is associated with an increased risk of cerebrovascular disease.

P5662
Subclinical coronary atherosclerosis across the peri-menopausal age: association between flogistic activation and coronary calcium score
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Introduction: Menopause is associated with increased incidence in coronary artery disease in women. Coronary calcium score (CCS) is a marker of subclinical atherosclerosis (SA), with high negative predictive value for cardiovascular events, while hormonal replacement therapy has been demonstrated to reduce CCS. We aimed to describe determinants of CCS in peri-menopausal age, in an unselected Italian population.

Methods: We enrolled 780 women, mean age 61±8 years old (range 45-
Reclassification of cardiovascular risk in Europe: Persistent impairment of arterial stiffness is also a strong predictor of cardiovascular disease (CVD).

Methods: The European Study on Cardiovascular Risk Prevention and Management in Daily Practice (EURIKA) (NCT00882336) was a cross-sectional study conducted simultaneously in 12 European countries, recruiting 7641 patients (57%) were followed in the ANGELS of AF centres and 1060 Primary prevention: new markers and interventions in the field

Purpose: Cardiovascular disease (CVD) imposes a significant health burden throughout Europe. 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 algorithm has been updated to incorporate high-density lipoprotein cholesterol (HDL-C) levels (SCORE-HDL), thus providing a more accurate estimate of risk. 

Results: After 6 months, 105 patients had persistent impaired CAVI, whereas CAVI improved in the remaining 97 patients (Figure A). During the follow-up period (3.4±1.2 years), CVD events occurred in 16 (16%) patients with impaired CAVI and in 6 (6%) patients with improved CAVI (p<0.05). Age (p<0.05), multi-vessel disease (p<0.01) and persistent impaired CAVI (p<0.05) were independent predictors of CVD events. Patients with persistent impaired CAVI had worse CVD outcomes as compared to those with improved CAVI (p<0.05) (Figure B).

Conclusions: This study demonstrates that impaired arterial stiffness was associated with worse CVD outcome.

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.
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 study found that 50% of AF reports were not confirmed by echocardiogram for altering antithrombotic therapy in 24 patients. Specifically, appropriate OAC therapy was prescribed in 22/209 (10.5%) patients, anticoagulation therapy was started in 21 (1.0%) patients. In 158 patients (75.6%) anticoagulation therapy was prescribed 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 risk-stroke evaluation phase, 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 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.

P5666
Five years follow-up of blood pressure in parents and children
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Purpose: Because intramural lifestyle modification improved blood pressure not only in parents but in their children pairs over one year, the aim of this observational study was to assess BP in 3407 parents and their children participating in the PEP Family Heart Study over five years.

Subjects and Methods: We assessed systolic (SBP) and diastolic blood pressure (DBP) in 1738 adults and 1669 youths defining SBP and/or DBP ≥ 140/90 mmHg in adults and ≥ 95th percentile in youths as hypertension. PASW 17 was used for statistics, p<0.05 was considered significant.

Results: In 180 men (median age 39 years) mean DBP significantly decreased from 131.2±14.1 mmHg at baseline to 129.4±13.8 mmHg after five years and in 1058 women (median age 36 years) from 118.4±13.6 to 116.7±13.2 mmHg. DBP in men worsened 85.2±10.4/7.6±9.3 mmHg at baseline and after 5 years 85.8±10.0/7.6±9.3 mmHg. However, in 863 boys (median age 6.0 years) age-and gender-specific SBP significantly increased from 103.9±2.1 to 107.1±2.10.2 mmHg as well as in 806 girls (median age 6.0 years) from 102.9±2.9 to 106.1±9.7 mmHg. At baseline, 311 adults had hypertension including 70 individuals taking antihypertensive drugs. Over 5 years, in both genders SBP decreased by 9% and DBP by 6% in the drug treated group and SBP/DBP by 6% in 241 hypertensive adults by 6% in 241 hypertensive adults.

Conclusion: BP significantly decreased in adults whereas in youths BP significantly decreased maximal EST capacity compared to ED patients without hypertension and 42 hypertensive men without ED. Abnormal HR responses were defined as follows: CI as an inability to achieve at least 80% of the predicted HR reserve and HR recovery as a HR decline less than 12 bpm; 1 min after EST.

Results: Post hoc analysis, men with both hypertension and ED had significantly decreased maximal EST capacity compared to ED patients without hypertension (by 1.10 METS, P<0.01) and hypertensive patients without ED (by 1.35 METS, P<0.01) (left figure). ED patients without hypertension had similar maximal capacity with hypertensive men without ED. Interestingly, men with both hypertension and ED more frequently had abnormal HR recovery and CI compared to ED patients without hypertension and hypertensive non ED patients (all P<0.05, ANCOVA, middle and right figure).

Conclusions: Our study showed a lower FMD in IBP patients. Inflammation and immune response play a key role in promoting endothelial dysfunction, considered the first stage of atherosclerotic process. IBP patients in active phase are at higher risk for atherosclerosis progression.

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P5667
Endothelial function and cardiovascular risk in inflammatory bowel diseases
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Purpose: Inflammatory bowel diseases (IBD) are chronic relapsing-remitting disorders of the gastrointestinal tract comprising two major entities, Ulcerative Colitis (UC) and Crohn’s Disease (CD). The present study was designed to evaluate flow-mediated dilatation (FMD) at the brachial artery in CD/UC patients in comparison to healthy control subjects in order to determine whether endothelial dysfunction is independent of both traditional cardiovascular disease risk factors. Intima-media thickness at the common carotid artery (another early marker of atherosclerosis) was also calculated.

Methods: Forty-nine patients (25 males, aged 41±16 years; 23 UC pts) and forty healthy subjects (controls, 16 males, mean age 45±15) were enrolled in the study. The diagnosis of UC/CD was based on the standard clinical, endoscopic and histological criteria. Disease activity was assessed for CD by means of Crohn’s Disease Activity Index (CDAI) (15) and for UC with Disease Activity Index (DAI). IBD patients were under medical treatment with traditional drugs (Salicylates or Steroids) or with biologics anti-TNFα antibodies (Infliximab or Adalimumab). All underwent physical examination, laboratory investigations, electrocardiography, ambulatory blood pressure monitoring, ultrasound examination of the carotid arteries and FMD.

Results: FMD values were lower in IBD patients than controls (6.1±3.3 vs 8.2±3.4, p=0.003). IBD group had significantly (p<0.05) higher serum C-Reactive Protein levels (8.8±6.7 mg/dl) compared with controls (1.5±2.1 mg/dl) and higher values of erythrocyte sedimentation rate (25.5±11.6 mm/h vs 4.3±4.7 mm/h; p<0.05). No significant difference in FMD were between UC/CD groups (5.9±3.5 vs 4.6±2.6; p=0.67), although both groups showed statistically significant lower FMD values compared with controls (CD: 6.3±2.6 and UC: 5.9±3.5 vs controls 8.2±3.4, p=0.017 and p=0.012 respectively).

The groups were perfectly matched for all cardiovascular risk factors and characteristics. We did not find differences between IMT values in IBD and controls group. Regarding the impact of disease evaluation on endothelial function, we found no significant difference in UC duration compared with CD one (71±65 vs 59±62 months).

Conclusions: Our study showed a lower FMD in IBP patients. Inflammation and immune response play a key role in promoting endothelial dysfunction, considered the first stage of atherosclerotic process. IBP patients in active phase are at higher risk for atherosclerosis progression.

P5666
Erectile dysfunction is associated with an increased number of abnormal non-ST parameters recorded during exercise stress testing in middle-aged hypertensive patients
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Purpose: Erectile dysfunction (ED) is a powerful predictor of cardiovascular risk, especially in men with hypertension. Exercise capacity (measured in metabolic equivalents, METS), heart rate (HR) recovery following exercise stress test (EST) and chronotropic index (CI) have emerged as variables holding significant prognostic value. We examined whether presence of ED confers an incremental effect on EST non-ST parameters in hypertensive patients.

Methods: EST parameters of three groups of non-diabetic, middle-aged, men, matched for age, lipid profile and smoking were analyzed: 68 treated hypertensive (Grade I/II) ED patients, 57 ED patients without hypertension and 42 hypertensive men without ED. Abnormal HR responses were defined as follows: CI as an inability to achieve at least 80% of the predicted HR reserve and HR recovery as a HR decline less than 12 bpm; 1 min after EST.

Results: Post hoc analysis, men with both hypertension and ED had significantly decreased maximal EST capacity compared to ED patients without hypertension (by 1.10 METS, P<0.01) and hypertensive patients without ED (by 1.35 METS, P<0.01) (left figure). ED patients without hypertension had similar maximal capacity with hypertensive men without ED. Interestingly, men with both hypertension and ED more frequently had abnormal HR recovery and CI compared to ED patients without hypertension and hypertensive non ED patients (all P<0.05, ANCOVA, middle and right figure).

Conclusions: Our study confirms an incremental unfavourable impact on the non-ST EST parameters when combined with hypertension. This study has important implications for the identification of hypertensive patients at high risk for future CV morbidity and suggests that close follow-up should be considered for patients with ED.

P5669
Diabetic nitrate supplementation reverses age-related diastolic and vascular dysfunction
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Purpose: Impaired nitric oxide (NO) bioavailability is a hallmark in cardiovascular dysfunction during aging. Dietary nitrate can be bioactivated in vivo to form nitrite and NO as an alternative NO generation pathway as compared to enzymatic NO formation. We hypothesized that impaired cardiovascular functions in senescent mice relate to a diminished NO-bioavailability and that chronic dietary nitrate supplementation reverses this age-related dysfunction.

Methods: Young (YN 6 months) and old (ON 22 months) C57Bl/6 mice were held for 8 weeks on a 0.1% sodium nitrate supplementation regimen administered in the tap water. Age-matched mice served as controls (YC and OC). Nitrite and Nitrate were measured by chemiluminescence and HPLC (ENO-20) tech-
We studied 320 non-diabetic patients with ultrasonographically diagnosed NAFLD and 313 non-diabetic patients without NAFLD who were comparable for age, sex and drinking less than 40 g alcohol/week. Carotid atherosclerotic burden in low-risk patients with metabolic syndrome (IMT) and plaque. All subjects were divided to the metabolic syndrome (MetS) according to International Diabetes Federation criteria.

Results: NAFLD patients had a significantly increased carotid IMT (0.99±0.38 vs. 0.86±0.22 mm; P<0.001) than those without the condition. The prevalence of increased IMT, defined as IMT ≥1 mm, and carotid plaque were 52.5% and 34.1% in the patients with NAFLD vs. 35.8% and 18.8% in the patients without 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 for increased IMT was 1.236 (95% CI, 1.023-1.467, P=0.016) without MetS and 1.178 (95% CI, 1.059-1.311, P<0.003) with MetS. 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.

**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 gestational age, birth weight, length and head circumference, fasting glucose, total, LDL-, and HDL-cholesterol, triglycerides, fibrinogen, D-dimers and APAo within 24 hours after birth. Cardiovascular risk profiles of mothers (assessed: 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 pregnancy showed increased IMT and increased IIMT. The prevalence of increased IMT, defined as IMT ≥1 mm, and carotid plaque were significantly higher in the patients with NAFLD vs. those without this condition (all P<0.05). NAFLD-associated adjusted odds ratio for increased IMT was 1.236 (95% CI, 1.023-1.467, P=0.016) without MetS and 1.178 (95% CI, 1.059-1.311, P<0.003) with MetS. 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.

**P5673**

**Low framingham risk patients with a family history of cardiovascular disease have a significant incidence of increased carotid intima-media thickness: the impress study**

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**Background:** Measurement of carotid intima-media thickness (IMT) has been shown to be beneficial in pts with increased CV risk. Pts with low CV risk however have few events and further risk stratification has little benefit. We therefore sought whether low risk patients with a family history of premature CVD would benefit from measurement of IMT.

**Methods:** We studied 552 pts (210 men; age 52±6) with a first degree relative with premature atherosclerosis. Framingham 10 year risk was ≥7.5% for all risk data. Patients with diabetes mellitus were excluded from this study. IMT was acquired by a trained study nurse and measured offline by an experienced sonographer in the far wall in three planes of the common carotid artery within 2cm of the bifurcation. Age-corrected values for the 75% CI from normal were used as a cut-off for analysis.

**Results:** 516 pts had low risk, 32 intermediate risk and 2 were high risk. BMI was increased (26±5) and there was a mod incidence of smoking (38%) and HTN (33%). Total cholesterol (TC) was 5.3±1.2 mmol/L and HDL was 1.4±0.04 mmol/L; 61% of patients had regular exercise. IMT in the pt cohort was 0.69±0.13 mm and there were significant differences in IMT between the low and intermediate risk groups but not between the intermediate and high groups. In the pts with low CV risk, 269 (52%) had increased age-corrected IMT. There were significant differences in HTN, BMI, SBP, TC and risk (all p<0.05) between those at low risk with normal and those with increased IMT. In a multiple linear regression model the independent predictors of increased IMT in the low risk group were BMI (p=0.0003) and HDL (p=0.0001). Model Chi-Sq=30.6, p<0.001.

**Conclusions:** Pts with a family history of CVD and low Framingham cardiovascular risk have a significant incidence of increased age-corrected IMT and should benefit from early intervention to reduce further risk reduction. Further longitudinal studies are needed to confirm this.
trimester of pregnancy had newborns with significantly lower HDL cholesterol values than newborns of mothers who never smoked (24.9 mg/dl vs 34.2 mg/dl; p = 0.005). Babies of smoker mothers showed a greater APAO than non-smoker ones (5.2 ± 1.05 mm vs 4.6 ± 0.96 mm; p = 0.007). APAO was negatively correlated with D-dimers levels (r = -0.376, p = 0.001), total-to-HDL cholesterol ratio (r = -0.221, p = 0.029) and negatively associated with HDL-cholesterol (r = -0.249, p = 0.013).

Conclusions: Our study shows that APAO is positively associated with newborn's D-dimer levels, total-to-HDL cholesterol ratio and maternal smoking, whereas is inversely correlate with HDL-cholesterol. Thus, neonatal APAO is affected by prenatal and maternal factors.

Primary prevention: new markers and interventions in the field

Objective: To evaluate the effect of 5-years cardiovascular prevention 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 (n = 3168) who had the similar age, education and cardiovascular morbidity. The cardio-vascular prevention program included preventive counseling for participants with CVD risk factors. All cardiovascular endpoints were registered during 10 years (5 years of active prevention and 5 years of monitoring). In this study we calculated the number of gained life years saved (LYS) in intervention group compared with control groups number 1, 2 and 3 was 101,6, -7,3 and 7,3 on 1000 participants in 5 years and 257,1, -50,2 and 39,4 in 10 years, accordingly.

Conclusion: In men with high education effect of cardiovascular prevention program was most prominent, especially after stopping the active intervention. Cardiovascular prevention program for men aged 40-59 based mainly on the preventive counseling was highly effective on men with normal blood pressure. In men with baseline hypertension, even mild, risk factors correction without effective medication treatment did not improved the prognosis significantly.

Conclusions: In patients with CVD, rosuvastatin improves endothelial function and decreases aortic stiffness. The degree LDL-cholesterol reduction is a determinant of the improvement of aortic stiffness.

Arterial function in familial combined hyperlipidemia: effect of rosuvastatin

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Purpose: Familial combined hyperlipidemia (FCH) is a common genetic dyslipidemia with increased early cardiovascular risk. Arterial function is an important predictor of outcomes. The purpose of our study was to explore the effect of rosuvastatin on arterial function in FCH patients.

Methods: We studied 33 never treated, normotensive, non-diabetic FCH subjects (mean age 42 years, 27 men) without cardiovascular disease. Arterial studies were performed before and at a mean of 5 months after treatment with rosuvastatin 10 mg daily. Endothelium-dependent flow-mediated dilation (FMD) and endothelium-independent nitrate-mediated dilation (NMD) of the brachial artery, carotid-femoral pulse wave velocity (PWV, an index of aortic stiffness) and carotid augmentation index (Ax, a marker of arterial wall reflections) were measured non-invasively.

Results: Treatment with rosuvastatin significantly reduced the levels of total cholesterol (300 vs. 184 mg/dl), LDL-cholesterol (204 vs. 108 mg dl), triglycerides (262 vs. 142 mg/dl) and apo-B (153 vs. 87 mg/dl) and significantly increased HDL-cholesterol levels (43 vs. 47 mg/dl), (all P<0.05). Rosuvastatin increased P5677 Preliminary results of the impress study: reducing cardiovascular risk factors in a nurse-led primary intervention program for high risk participants

M.J. Carrington1, F. Schulte1, B. Haluska1, T.H. Marwick2, J. Holliday1, S. Stewart1 on behalf of IMPRESS Investigators. 1Baker IDI Heart and Diabetes Institute, Melbourne, Australia; 2University of Queensland, Princess Alexandra Hospital, Brisbane, Australia

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 (Impress Study (IMPRESS)) is a 3 year nurse-led, multicentre, randomised controlled 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 healthcare 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). 43% (32±4 mmHg) and 23% (0.6±0.9 mmol/L) blood pressure were significantly lower in the red arm compared to the grey arm (29±5 mmHg and 46% (1.1±0.9 mmol/L) respectively). Of these, 142 were randomised, 61 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 5.3±1.04 to 4.73±1.12 mmol/L (Δ - 0.57±0.55 mmol/L), ii) LDL cholesterol from 3.6±0.99 to 2.84±0.95 mmol/L (Δ - 0.75±0.41 mmol/L), iii) triglycerides from 2.84±1.93±0.30 mmol/L (Δ - 0.53±0.33 mmol/L). 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; Optical 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 those supplemental therapy could affect plaque stabilization. The cap thickness of fibroatheroma is a major determinant of vulnerable plaques and optical coherence tomography (OCT) has been an imaging modality for assessing such micro-structural changes due to high resolution (10–20 μm). The primary objective of this study is to evaluate the effect of ezetimibe addition to flavusation on progression of coronary atherosclerotic plaque evaluated by OCT.

Methods: A total of 90 angina pectoris patients with intermediate non-culprit lesions were enrolled and divided into two groups: flavusation group (statin group; n=45) or ezetimibe-flavusation group (ezetimibe group; n=45). Serial OCT analyses were 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 in both groups. Although the lumen 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 of the fibrous-cap thickness was significantly greater in the ezetimibe group than in the statin group, although the change of the lumen area and lipid laden area were similar.

OCT comparison analysis

<table>
<thead>
<tr>
<th>Statin-group (n=26)</th>
<th>Ezetimibe-group (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen area (μm)</td>
<td>4.1±1.1 4.3±1.1</td>
</tr>
<tr>
<td>Fibrus-cap thickness (μm)</td>
<td>0.03±0.03 0.13±0.05</td>
</tr>
<tr>
<td>Angle of lipd (°)</td>
<td>254±87.0 209±83.4</td>
</tr>
<tr>
<td>Change of lumen</td>
<td>0.00±1.06 0.08±1.08</td>
</tr>
<tr>
<td>Change of thickness</td>
<td>-45.0±52.6 -40.9±45.9</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001 0.05 &lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: The lipid lowering therapy by statin and ezetimibe could increase the fibrous-cap thickness of lipid-rich plaque than statin monotherapy.

The centralized pan-levant survey on the under-treatment of hypercholesterolemia CEPHEUS-levant,- 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 1002 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: 989 patients were included 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 (MS). The significant predictors of LDL-C goal attainment were (a) absence of metabolic syndrome (b) statin mono-therapy (c) age <55 years (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.

MIND AND HEART: ENTANGLED AND EQUALLY IMPORTANT

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 studied. 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 53% 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 if valid contact details were available. Patients were excluded if they had cognitive and/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-legged 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<0.01; cognitive problems p<0.01) at time 2. Conversely, school problems (p<0.05), symptoms (p<0.05) and cognitive problems (p<0.05) at time 1 negatively predicted SOC at time 2.

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 intervention and prevention efforts. As such, improv-
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 Steenke 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 patients.

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 (< 0.30) and was removed. Two items on ED, either the male patient or partner, were combined as one variable for ED; therefore analyses were computed on 11 items. Chronbach’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 education nurses: 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 surveys and methods of teaching, assessment of clinical and theoretical competencies and course evaluations.

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 care, whereas 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 multidisciplinary 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 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 practical clinical practice.

Conclusions: The challenges of implementing the curriculum for HF nursing in Europe were met. Entry requirements for the nurses, the organisation 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 healthcare 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 yet which psychosocial factors contributes to aggravate prognosis 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 impact on long-term 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 measured by questionnaire of PHQ-9 (the Patient Health Questionnaire), anxiety disorder was by GAD-7 (Generalised Anxiety Disorder) and anger was by TAI (Trait anger scale). We defined depression as high PHQ-9 score (>10), anxiety disorder as high GAD-7 score (>10) and anger as high TAI 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 lower survival rate from cardiovascular death (p = 0.05) or composite endpoint (cardiovascular death and hospitalization), as well as those with anxiety or anger symptoms. Mass data analysis revealed that 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 (3TCMR) a cohort of 98 consecutive cocaine addicts and observed cardiovascular pathology in a high percentage of them, mainly decreased biventricular systolic function (LVEF, RVEF) and increased left ventricular mass (LVM). Our aim now was to follow up with 3TCMR the first 30 subjects of this cohort found to have cardiovascular pathology, after 1 year of a rehabilitation program.

Method: 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 3TCMR scan after their rehabilitation program. 3TCMR protocol included TrueFISP cine sequences in the usual planes, STIR sequences, myocardial late gadolinium enhancement (LGE) study after gadolinium-DTPA (0.1mmol/kg), and T2W TSE study of the aorta. Images were analyzed by 2 blinded, independent observers.

Results: Mean follow-up was 13.3±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 quited cocaine (group A). A showed a significant decrease in both end-diastolic and end-systolic volumes (LVEDV, LVESV, RVEDV, RVESV) and in-
crease in LVEF and RVEF with a mild, non-significant decrease in LVM (ΔLVM = -1.4g). Patients that had not quited cocaine (group B) showed no 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>Group</th>
<th>LVEDV (mL)</th>
<th>LVEF (%)</th>
<th>LVESV (mL)</th>
<th>RVEDV (mL)</th>
<th>RVESV (mL)</th>
<th>RVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>160 ± 30</td>
<td>72 ± 7</td>
<td>160 ± 46</td>
<td>72 ± 7</td>
<td>32 ± 4</td>
<td>52 ±7</td>
</tr>
<tr>
<td>B</td>
<td>155 ± 28</td>
<td>75 ± 12</td>
<td>155 ± 39</td>
<td>74 ± 13</td>
<td>32 ± 5</td>
<td>53 ±7</td>
</tr>
</tbody>
</table>

Δ group A 10 ± 3 5 ± 2 10 ± 3 10 ± 2 10 ± 3
p 0.03 0.01 0.02 0.01 0.003

Δ group B 5 ± 2 4 ± 2 10 ± 3 1 ± 1 1 ± 1
p 0.79 0.45 0.25 0.73 0.89 0.59

Conclusion: These preliminary results show that 1 year of cocaine abstience 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**


Department of Internal Medicine, University of Pisa, Pisa, Italy; 1University of Pisa, Department of Psychiatry, Pharmacology & Neurobiology & Biotechnology; Pisa, Italy

**Purpose:** Both insomnia and short sleep duration have been associated with increased risk 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 255 patients (males 51%, mean age 49±10 years) from 4 Kentucky State prisons. All participants underwent a physical assessment for CHD risk factors, including blood pressure (BP), waist circumference, body mass index (BMI), and lipid profile (cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL)). Pittsburgh Sleep Quality Index (PSQI) was assessed using a single item from the Medical Outcomes Survey Short-Form 36, asking participants to rate their overall health as excellent, very good, good, fair, or poor. Due to low frequencies, inmates with excellent health perceptions were combined with very good and inmates with fair health perceptions were combined with poor.

**Results:** A total of 69 (29.3%) of inmates perceived their health as excellent or very good. 144 (47.4%) inmates perceived their health as good, and 70 (22%) perceived their health as fair or poor. After adjusting for age in logistic regressions, inmates who reported fair or poor health had a significantly greater likelihood of triglyc-

**P5688**

**Improving adherence to antihypertensive agents in chronic kidney disease**

Z. X. Zeng, A. Y. Tu, Y. Y. Li, Z. H. Liu, X. J. Zeng on behalf of a name. 1Department of nephrology, second people’s hospital, chengdu, china; 2People’s Republic of China

**Purpose:** Hypertension is a modifiable and very important risk factor in chronic renal disease (CKD), and medication adherence (MA) is critical in reaching the 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 hypertensive 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 ≥ 9.9 vs. < 9.9) 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±7/6±9 mmHg and in control was 146±8/119±12 mmHg. Cr clearance increased from 51.2±0.2 to 64±3.0 ml/min (p<0.001) in the group of good MA. By contrast, Cr clearance decreased significantly from 52.1±2.9 to 40±3.6 ml/min (P<0.001) in the controls. During this time, urine protein excretion decreased from 1.4±0.5 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, P=0.05) in the controls. 20 patients had G2, 28 patients stroke, 38 patients had got pneumonia, 11 patients renal dialysis and 11 patients renal death in the observation groups (2% in control). In the treatment group, but incidence of hyperkaelaemia was similar between two groups.

**Conclusions:** Good MA is associated with a greater controlled hypertension, better protection of heart and kidney and may decrease mortality than the poor MA.

**P5687**

**Self-rated health perception predicts coronary heart disease risk factors in prison inmates**

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**Introduction:** Coronary heart disease (CHD) is the primary cause of death in prison inmates. Screening for CHD risk factors is not routinely done in prisons. There is evidence that self-rated health perception is a predictor of health status in the general population and may serve as an inexpensive screening tool for identifying prisoners at risk for CHD. For this purpose of the study was to determine the potential of self-rated health perception as a screening tool for identifying prisoners with CHD risk factors.

**Methods:** The study included 304 male inmates (aged 19 to 77 years; mean age = 36±4.9±7 years) from 4 Kentucky State prisons. All participants underwent a physical assessment for CHD risk factors, including blood pressure (BP), waist circumference, body mass index (BMI), and lipid profile (cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL)). Health perception was assessed using a single item from the Medical Outcomes Survey Short-Form 36, asking participants to rate their overall health as excellent, very good, good, fair, or poor. Due to low frequencies, inmates with excellent health perceptions were combined with very good and inmates with fair health perceptions were combined with poor.

**Results:** A total of 69 (29.3%) of inmates perceived their health as excellent or very good. 144 (47.4%) inmates perceived their health as good, and 70 (22%) perceived their health as fair or poor. After adjusting for age in logistic regressions, inmates who reported fair or poor health had a significantly greater likelihood of triglyc-

**P5689**

**Resistant hypertension, a true burden or do we miss secondary causes?**

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**Purpose:** Resistant hypertension, defined as a blood pressure (BP) not reaching treatment targets despite the use of 3 antihypertensive agents is a major health concern. Our center initiated a program using renal denervation (pRDN) as a treatment modality for resistant hypertension. Before undergoing pRDN, patients are screened to confirm the diagnosis of resistant hypertension and exclude (secondary) causes. The purpose of the study is to describe the results of our screening program.

**Methods:** Patients referred to our center for renal denervation underwent a step-wise screening program, commencing with an ambulatory BP measurement to exclude white coat hypertension. Subsequently, all antihypertensives are phased out in order to perform reliable laboratory testing, imaging by MRI and repeat BP measurements. Based on these results, the decision is made in a multidisciplinary team whether a patient is eligible for pRDN.

**Results:** In total, 126 patients (56 men; 70 women, mean age 62±12 years), diagnosed by their own physician as having resistant hypertension or intolerance for...
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
during previous stages (see table).

Reasons for excluding patients:

<table>
<thead>
<tr>
<th>White coat hypertension</th>
<th>18 (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperaldosteronism</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Significant renal artery stenosis</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Glycemic acidosis</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>11 (15%)</td>
</tr>
<tr>
<td>Multiple main arteries</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Prior renal artery stenting</td>
<td>4.3 (4%)</td>
</tr>
<tr>
<td>Other (i.e. single kidney, patient refusal, non-compliance)</td>
<td>21 (29.5%)</td>
</tr>
</tbody>
</table>

Conclusion: Extensive screening for secondary causes of hypertension can eluci-
date 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.

**Results:**

- **Genotype distribution** for non-HT and HT was: GG: 50.9%, GA: 41.8%, AA: 9.7%; 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 (443.8±344.6 vs 430.8±59.9, p=NS). Importantly, 455A genotype presented with significantly more levels of fibrinogen compared to the GG-GA in HT patients (535.4±253.6 vs 414.2±80.0, p<0.001). Moreover, HT 455A homozygotes had significantly increased D-
dimers levels (µg/l) compared to 455G allele carriers (640.3±83.6 vs 485.5±27.6, p<0.05). No difference was observed for non-HT regarding D-dimers between the 455AA genotype and GG-GA (477.6±74.7 vs 450.8±40.7, p=NS). Interest-
ingly, 455AA genotype presented with higher IV(%) 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 (109.1±4.6 vs 92.2±2.4, p=0.05, for IX(%). However, no difference was observed in IV(%) and IX(%) levels between 455AA 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.
erance 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 (56.9%, p<0.01). There was no difference in 24h blood pressure and stipping 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<0.001). Patients with newly recognized DM and patients with increased fasting glucose were charac-
terized by higher VFV as compared with patients without these abnormalities. In a multivariate model including age, sex, MS components, 24h BP levels, SVF and VFV, AHI was independently related with male gender (beta=-0.31; p<0.001) and VFV (beta=0.27; p<0.01).

Conclusions: In our studied group of patients with resistant hypertension abdom-
inal 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.

Elevation of reactive oxygen metabolites could be associated with the acute hypertensive stress in members of a disaster responder on the great east Japan earthquake


Background: On March 11, 2011, a major earthquake, which registered 9.0 on the Richter scale, struck large areas of the northeastern Japan. The Japan Self-Defense Forces (JSDF) was asked to send members to afflicted area as disaster responders. They suffered from physical and emotional stress, and some resulted in acute hypertension. In disaster medicine, acute hypertension may cause acute coronary syndrome, heart failure and aortic dissections several days after disaster. They may be such as dyslipidemia and hypertension are known to be associated with the augmentations of oxidative stress (OS), how-
ever the association between OS and acute hypertension in subjects of disaster responders of the earthquake is not clear.

Purpose: The study aim is to investigate if serum derivative of reactive oxygen metabolites (d-ROMs), which reflects OS as a biomarker related to acute hypertension after a disaster relief operation.

Methods: We collected blood samples and measured height, body weight and blood pressures (BP), from 77 JSDF members (75 for male, age 20-47, mean age 33.5±6.1 years) after completing the mission relief operation. They were allocated to two groups (with or without hypertension (either systolic BP ≥ 140 or diastolic BP ≥90 at the time of completing the mission)) and serum parameters including blood chemistry, sulfate containing amino acids and arginine metabo-
ilites with HPLC analysis, d-ROMs with FREE (Free Radical Elective Evaluator) and cytokine array with Bio-plex analysis (Bio-Rad) were compared between two groups.

Results: Blood pressure was 143.2±17.9/97.9±10.2 mmHg in subjects with acute hypertension (n=14), and 122.6±10.7/77.1±7.3 mmHg without hypertension (n=63). Age, height and body weight were higher in hypertensive sub-
jects. Diastolic BP in those with hypertension was increased in those with acute hypertension compared with those without hypertension (307.8±51.9 vs 274.2±48.8 CARR U, respec-
tively, p<0.05). Plasma homocysteine, cysteine, glutathione, arginine, citrulline, ornithine levels were unchanged. The blood chemistry testing including AST/ALT, BUN/Cr, CK/My, C/TG, Na/K/CI were not different. Plasma HDL-C and glu-
cose levels tended to be lower in the group of acute hypertension. 26 inflam-
matory cytokines, such as interleukin-1, tumor necrosis factor-α and monocyte chemoattractant protein-1 were not different between two groups.

Conclusions: Serum d-ROMs level is associated with acute hypertension of dis-
aster responders on the Great East Japan Earthquake. The OS marker may be a useful biomarker related to acute hypertension in the disasters.

P5694

Natriuretic peptide deficiency and abnormal regulation of the Renin Angiotensin Aldosterone System in obese hypertensive subjects

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Objectives: To test the hypothesis that relative natriuretic peptide (NP) deficiency together with inadequate suppression of the renin-angiotensin-aldosterone system (RAAS) on a high salt intake is a characteristic feature in obese hypertensive men (ObeseHT).

Background: More information is needed on the interplay between a high salt intake, the NPs, and the RAAS on blood pressure (BP) in obese men.

Methods: We studied 103 obese men (body mass index (BMI) ≥30 kg/m²); 63 had 24-hours ambulatory BP (AMPB) ≥130/80 mmHg (ObeseHT) and 40 had 24-

Results: The obese men had higher mean (±SD) urinary sodium excretion in a 24-hours urinary collection, a surrogate marker for sodium intake, serum levels of mid-regional-pro-atrial natriuretic peptide (MR-proANP), plasma renin activity, and plasma angiotensin II levels.

Discussion: The urinary concentrations of 8-hydroxy-2'-deoxyguanosine (8-OHdG) were higher in the first group it was significantly (P<0.001) higher in the second group that shows destruction of endothelium. In HD combined with HVS patients there was a trend with NEC index in the group with isolated HD (P=0.1). However, in the first group reliability of differences with the healthy persons (P=0.0001) was higher than in the second (P<0.001) that indicates more marked destruction of endothelium in HD combined with HVS. Patients. Von Wille-
brand factor appeared to be statistically significantly higher compared to the control both in the first (P<0.001) and in the second (P<0.006) groups. However, in the first group it was significantly (P=0.019) higher in the second group that demonstrates greater dysfunction of endothelium in the group of HD combined with HVS patients.

Conclusions: Thus, in both groups of HD patients increase in DEC number was associated with the acute hypertensive stress in HD patients. In the group of HD combined with HVS patients DEC number and von Willebrand factor function were higher than in the group of HD without HVS patients that shows more marked dysfunction of endothelium in this group.

P5695

Impact of cardiovascular risk factors and inflammatory status on urinary 8-OHdG in essential hypertension

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1Hospital La Fe, Valencia, Spain; 2Hospital de San Juan de Alicante, Alicante, Spain; 3Hospital de Gandia, Gandia, Spain; 4University Clinical Hospital of Valencia, Comunidad valenciana, Spain; 5Hospital de la Zarza, Logroño, Spain

Purpose: The urinary concentrations of 8-hydroxy-2'-deoxyguanosine (8-OHdG) reflect the oxidation status of hypertensive subjects and it can be used for monitor-
ing oxidative stress changes. However, the influence of cardiovascular risk factors

Havudoc method (1978) as well as quantitative determination of von Willebrand factor (vWF) functional activity with immunofluorimmetrical analysis method using monoclonal antibodies. Statistical processing of results was fulfilled with the help of an application program package “Statistica for Windows, Release 6.0.”

Results: Both in the first and in the second groups the symptoms of endothelial lesion were revealed. DEC number in the first (7.30±1.27 χ 107 per 1 l of blood) and in the second (5.96±1.12 χ 107 per 1 l of blood) groups were significantly higher than in the group of healthy persons (4.6±1.49 χ 107 per 1 l of blood) that shows destruction of endothelium. In HD combined with HVS patients there was a trend with NEC index in the group with isolated HD (P=0.1). However, in the first group reliability of differences with the healthy persons (P=0.0001) was higher than in the second (P<0.001) that indicates more marked destruction of endothelium in HD combined with HVS. Patients.

Conclusions: Thus, in both groups of HD patients increase in DEC number was associated with acute hypertension in subjects of disaster medicine. The cardiovascular risk factors, such as dyslipidemia and hypertntion are known to be associated with the augmentations of oxidative stress (OS), however the association between OS and acute hypertension in subjects of disaster responders of the earthquake is not clear.

P5696

BIOMARKERS IN HYPERTENSION

P5697

V. Shchekotov, P. Barlamov, P. Urban. Medical Academy, Perm, Russian Federation

Purpose: To estimate the state of endothelial dysfunction in patients with hypertension (HD) combined with hypertenstion syndrome (HT). Methods: Preliminary testing of 137 patients aged 23-63 suffering from stages I- II HD by means of Nijmegen questionnaire detected HVS in 38 persons (27.8%). Detailed examination of two groups of patients was carried out. The first group included 18 patients with HD combined with HVS, the second - 30 patients with HD without HVS, the control - 30 practically healthy subjects. All groups were comparable by the sex and age. The lesion of endothelium was studied by means of calculation of blood plasma desquamated endothelocytes (DEC) with
and inflammation on the urinary levels of this marker in hypertension has never evaluated. The purpose of this study was to analyze the impact of cardiovascular risk factors, and established inflammatory markers on 8-OHdG in essential hypertension.

**Methods:** We studied 149 asymptomatic hypertensive patients (61±14 years). A routine physical examination, laboratory analyses and echo-Doppler study were performed. Urinary 8-OHdG and plasma TNF-alpha, sTNF-R1, sTNF-R2 and IL-6 were determined.

**Results:** 8-OHdG/creatinine levels were higher in hypertropic patients (p=0.02), and correlated with left ventricular mass index (r=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=0.02) and women (p=0.006). Furthermore, 8-OHdG/creatinine correlated with TNF-alpha, sTNF-R1, sTNF-R2 (p<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 hypertension 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 increasing 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>78±6</td>
<td>73±8</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±42.3</td>
</tr>
</tbody>
</table>

significantly higher levels of blood pressure and lower plasma apelin and relaxin levels compared to the healthy offspring of healthy parents. This group of individuals needs a closer follow-up and further examination.

**P5700**

**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. This activation is expected to 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-lymphocyte 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 (BMI >30, 7M,1F) 11 years), 9 hypertensives with BMI<29 (7M,2F,11 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 as well, 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 two-year follow-up study**

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**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 vs stage II r=0.86, p<0.0001; stage II vs stage III r=0.96, p<0.0001 and r=0.96, 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 variability.

**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.
with hyper trophy. Measured variations in peptide levels, exceeding 35% in a 12-month follow-up and 41% in a 24-month follow-up, may indicate an increase in cardiovascular risk, and therefore may imply adjustment in the medical treatment.

In addition, this study shows a link between neurohormonal and inflammatory activation in these 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 CAD. 115 patients with stable CAD who underwent percutaneous coronary intervention were treated with alpidemide 5mg or azelnidipine 5mg for 6 months. Non-culprit coronary lesions were analyzed by intravascular ultrasound (IVUS) in hypertensive patients with CAD. 115 patients with stable CAD who underwent percutaneous coronary intervention were treated with alpidemide 5mg or azelnidipine 5mg. Total plaque area and volume were measured.

**Results:** Decreased blood pressure significantly decreased from 138±74 mmHg at baseline to 128±95mmHg at 10 months follow-up (p<0.003). Aldosterone was decreased during follow up period (69 pg/ml to 65 pg/ml) whereas renin 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 other biomarker and change of plaque volume.

**Conclusions:** Decreased aldosterone is likely to contribute to plaque regression in hypertensive patients with stable CAD.

**Experimental Hypertension**

**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) were fed a regular Chow (normal-salt diet) and high-salt diet (8% salt) for 4 weeks from 8 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 WKYs and SHRs. At 12 weeks of age, PRA was higher in SHR than in WKYs. High-salt diet for 4 weeks decreased PRA and plasma angiotensin II concentration both in SHR and WKYs. On the other hand, high-salt diet did not decrease cardiac tissue expression of renin and (pro)renin receptors in myocardium both in SHR and WKYs. Prorenin decaying peptide did not affect blood pressure, PRA, plasma levels of angiotensin II expression of renin and (pro)renin receptors, but decreased the development of cardiac damage such as perivascular fibrosis and cardiomyocyte hypertrophy. In addition, this study shows a link between neurohormonal and inflammatory activation in these patients.
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 separately 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 activity (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 relationship, 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 mmHg, P < 0.01) and by ω-conotoxin (0.88 ± 0.14 to 0.11 ± 0.05% 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 for the baroreflex, which was significantly decreased by cilnidipine (113 ± 10 vs. 19.4 ± 1.3 mmHg, P < 0.01) and by ω-conotoxin GVIA (50 μg/kg bolus, n = 5) examined.

Conclusion: Both cilnidipine and ω-conotoxin GVIA decreased the slope of the peripheral arc, which reduced the operating-point AP. While the neural arc characteristics were not altered, the neural arc gain at the operating point was decreased significantly by 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 cilnidipine, suggesting 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 hypertension. 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 inhibitor ibandronate on ROS production, possible beneficial influence on endothelial dysfunction 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 fluorescence and chemiluminescence, respectively, in vivo or in vitro. Angiotension 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 p47(phox) in aortic tissue and VSMCs, and improved the impaired endothelium-dependent vasodilation in SHR. Addition of geranylgeranyl, but not farnesyl or mevalonate reversed the inhibitory effects of ibandronate. Moreover, inhibition of geranylgeranyl-transferase mimicked the effect of ibandronate on this excessive oxidative response. FPP synthase inhibitor ibandronate exerts potent antioxidant effects in cultured VSMCs and in the vasculature of SHR mediated by Rac1/NADPH oxidase pathway. These ibandronate effects may contribute to the vasoprotective effects for impaired endothium in SHR.

Nanoparticle delivery of natural polyphenols improves resistance to oxidative stress in endothelial progenitor cells

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Purpose: Recent studies have provided increasing evidence that cardiovascular disease, such as atherosclerosis, restenosis after PCI and myocardial regeneration after infarction, not only depend by cells formerly residing in the location of the vascular or myocardial insult, but are also influenced by bone-marrow-derived endothelial progenitor cells (EPC). EPC circulate into peripheral blood and significantly contribute to neovascularization and endothelialization as part of the process of vascular repair. Several studies have reported decreased EPC numbers and dysregulated EPC proliferation and adhesion in presence of oxidative stress. Strategies that can prevent or ameliorate EPC number and function are currently of special clinical interest. Aim of this study is to prepare innovative therapeutic systems to increase EPC viability reduced by oxidative stress by natural products.

Methods: Human EPC were cultured from peripheral blood and characterized by the presence for Dil-Ac-LDL uptake and EPC markers. Total polyphenols and antioxidant capacity of grape seeds extract (GSE) were measured by Folin-Ciocalteu’s phenol reagent and FRAP reagents, respectively. Cilnidipine significantly decreased the production of ROS, translocation of NADPH oxidase (ROS) production were assayed using the tetrazolium salt reduction (WST-1) assay and a fluorescent probe CM-H2DCFDA, respectively. Nanoparticles (NP) were prepared by ionotropic crosslinking of a novel thiolated quaternary ammonium-chitosan conjugate (N-Ch-SH). A hyaluronic acid solution (0.0125 mg/ml, 600 ml) in phosphate buffer pH 7.4, 0.13 M (PB), containing p-GSE and r-GSE (0.33 mg/ml), was added to a stirred N-Ch-SH solution (2 mg/ml, 5 ml) in HEPES buffer pH 7.4, 0.13 M (HEPES). GSE demonstrate strong antioxidant capacity. In particular, p-GSE showed the highest value (12.9%) compared to r-GSE (vs 3.7%). GSE showed also a higher content of total polyphenols (2.35 GAE g/l) compared to r-GSE (1.09 GAE g/l). NP size was 318±37 nm, with 24 h stability; the encapsulation efficiency of both GSE was nearly 100%. Free NP showed low cytotoxicity on EPC; encapsulated p-GSE (p-GSE NP) were more active than free p-GSE for inhibiting H2O2 cytotoxicity (p<0.013 vs p-GSE NP). Moreover, p-GSE NP significantly inhibits intracellular ROS production induced by H2O2 compared to free p-GSE (p<0.0015 vs p-GSE NP).

Conclusion: Nanotechnology has great potential for delivering nutraceuticals. These results suggest that the p-GSE NP are a highly promising polyphenols carrier systems particularly useful to protect endothelial cell from oxidative stress and improve EPC survival.

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 useduring pregnancy has been reported in recent years. Only a limited evidence on safety profiles is available and very little is known about mechanisms of adverse effect on the fetus. We hypothesized that drug-induced bradycardia is the leading mechanism. We focused our investigation on agents with negative chronotropic effect.

Methods: ED4 and ED8 chick embryos were studied by video microscopy and ultrasonic biomicroscopy ex vivo after intraartificial injection of 200 μl of metoprolol, ibavudine, 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 ED4 embryos and prolate ellipsoid formula in video recordings (ED4). Cardiac output was calculated from equation CO=μ(m/min)×[V(μl)/HR(BPM)]. Embryotoxicity was tested in vivo after administration of various doses of studied drugs between ED3-ED8. We describe an increase of heart rate in ED4 embryos and a significant decrease in cardiac output in ED4 embryos after administration of metoprolol (33%), carvedilol (27%) and ibavudine (55%) compared to controls (6%). In more mature ED 8 embryos this effect was more pronounced (metoprolol 51%, carvedilol 54%, ibavudine 53%, controls 6%). 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%) mediated by significant decrease in cardiac output, likely leading to embryonic death. Metoprolol in usual doses appears to be relatively safe in pregnancy whereas carvedilol and ibavudine might have a potential adverse effect on fetus.
Anti-hypertensive effects of heat shock protein inducer geranylgeranylationcetone via suppression of aortic smooth muscle cell migration and contraction

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Purpose: In hypertension, the chronic activation of the renin-angiotensin system (RAS) leads to dysfunction 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, hypercontractility 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 inducer geranylgeranylationcetone (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 vasoco面容ation in rat thoracic aorta. The thoracic aorta was isolated from SD rat (male, 6 week old). We assessed effects of acetylcysteine (Ach) on 1 μM PE-induced contraction in 3 mm aorta rings, and it compared with 10 μM GGA pretreatment.

Results: As a result of wound healing assay, 1 μM Ang II significantly induced migration when compared with vehicle. Whereas, GGA 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 against remodeling of vascular smooth muscle cells and contraction of rat thoracic aorta.

Coronary blood flow is slow in prediabetic and diabetic patients

BioRedenerv: Neutrophil Gelatinase-Associated Lipocla (NGAL) and Kidney Injury Molecule-1 (KIM-1) as markers for acute kidney damage after renal denervation

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Background: Renedeval (RD) is one possible treatment option of therapy resistant arterial hypertension. Besides therapeutical success, procedural complications such functional and structural kidney injury are of major clinical interest. Urinary neutrophil gelatinase-associated lipocla (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 RD.

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 RD. 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. Blood and urine specimens were sent to the laboratory for centrifugation and frozen storage at – 80°Celsius until assayed.

Results: The conventional biomarker creatinine showed no increase in the early post RD period. Urinary creatininebaseline 0.9 mg/dl [IQR: 0.8-1.1]; p<0.001 vs. creatinine 2nd day: 0.9 mg/dl [IQR:0.6-1.1]; p<0.01. No increase of KIM-1 levels could be observed (KIM-1: Baseline: 0.89 IQR [0.52-1.88] vs. KIM-1: 2nd day: 0.83 IQR [0.52-1.77]; p<ns) after RD. Neither a decline of the estimated GFR (eGFRbaseline: 75.6 [64.5-87.4]ml/min/1.73 m2 vs. eGFR 2nd day: 74.5 [56.3-91.4] ml/min/1.73 m2, p<0.30) could be shown. Four weeks after RD creatinine levels slightly decreased (creatinine, 4weeks: 0.81 mg/dl IQR [0.76-1.0] vs. creatinine Baseline: 0.9 mg/dl IQR [0.8-1.0]; p<0.07) and eGFR significantly improved (eGFRbaseline: 75.6 [64.5-87.4]ml/min/1.73 m2 vs. eGFR4 weeks: 87.4 [60.9-105.2] ml/min/1.73 m2, p<0.04). Correspondingly, no differences of KIM-1 levels (KIM-1: 4weeks: 0.91 [QR 0.63-1.35] vs. KIM-1: Baseline: 0.86 IQR [0.52-1.88]; p<0.29) and NGAL levels (urinary NGAL4 weeks:12.4ng/ml [8.0 – 29.2] vs. NGAL: Baseline: 14.0 ng/ml IQR [9.7-45.8]; p<0.59).

Conclusion: There were no differences of NGAL and KIM-1 levels prior to and after RD, proving the safety of the invasive procedure. Additionally, a slight improvement of the kidney function could be documented in the follow up.

Coronary blood flow is slow in prediabetic and diabetic patients 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. We compared each patient 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 prediabetics 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 related to a composite endpoint of mortality, stroke and reinfarction and to mortality. 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 trends in short- and long-term mortality after myocardial infarction in patients with and without diabetes mellitus

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Purpose: To study temporal trends in short- and long-term outcome after myocardial infarction (MI) according to diabetes status.

Methods: All consecutive patients admitted for ST-segment elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) at our center between 1985 and 2008 were included. Baseline characteristics, pharmacological and invasive treatment modalities, and survival status were collected. The study patients were compared according to prevalent diabetes.

Results: We identified 14,434 patients hospitalized for MI, of whom 2,015 (14%) had prevalent diabetes. The risk of presenting with diabetes increased from 8% to 17% from 1985 to 2008. Diabetic patients presented with a higher prevalence of cardiovascular risk factors. With time, the use of evidence-based therapies subdivided regarding heart rate at admission at CCU (A1 (n=800)/B1 (n=305); HR≈70bpm; A2 (n=1648)/B2 (n=891); HR>70bpm). We analyzed the population in terms of demographic variables, type of ACS, comorbidities, cardiovascular (CV) risk factors and clinical, analytical and imaging parameters. Primary endpoint was defined as cardiovascular death (CVD). Median follow-up was 2.5 years.

Conclusions: Temporal mortality reductions after myocardial infarction between 1985 and 2008 were at least as high in patients with diabetes compared to those without. However, long-term mortality remained higher in diabetic patients. Awareness of the high risk profile of diabetic patients is warranted and might stimulate optimal medical care and their outcome.

In-hospital and follow-up mortality associated with hypoglycemia and hyperglycemia in patients with acute coronary syndrome


Introduction: Abnormal glucose metabolism is associated with increased mortality after acute myocardial infarction. In patients with acute coronary syndrome (ACS), hyperglycemia predicts death, but the prognostic significance of hypoglycemia is controversial. This study aimed to evaluate the impact of abnormal glucose metabolism (hyper- and hypoglycemia) on in-hospital and follow-up mortality of patients with ACS.

Methods: We evaluated the prognostic significance of hypoglycemia (< or =70 mg/dL) and hyperglycemia (> or =140 mg/dL) in 4,497 consecutive patients with ACS (32.1% STEMI, 19.2% unstable angina) from our hospital (2003-2010), basing on glucose levels on admission. We analyzed their incidence and associated both with in-hospital and follow-up (median: 3.1 years, ROC: 1.6-5.0 years) mortality. In multivariable Cox models, we compared the prognostic value of hyper- and hypoglycemia with normoglycemia (<70 and >140 mg/dL) regardless of the GRACE risk score and presence of diabetes mellitus (DM).

Results: 265 patient died during in-hospital phase (5.9%) and 760 during the follow up (18.0%). Hyperglycemia predicted both in-hospital (OR 4.609, 95%CI: 3.475-6.13; p<0.001) and follow-up death (HR 1.844, 95% CI 1.598-2.137; p<0.001) compared with normoglycemia. In contrast, hypoglycemia only predicted in-hospital death (OR 4.397, 95%CI 1.163-16.627, p=0.011). After multivariate analysis, both hypoglycemia (OR 4.928, 95%CI 1.445-16.858, p<0.009) and hyperglycemia (OR 2.328, 95%CI 1.113-3.785, p<0.001) remained as strong predictors of in-hospital death, independently of GRACE risk score and the presence of DM. However, hyperglycemia loss its predictor value in follow-up mortality after adjusting by DM and GRACE risk score (p=0.776).

Conclusions: Both admission hypo- and hyperglycemia predicted in-hospital death in ACS patients, independently of the GRACE risk score and the presence of DM, but not follow-up mortality.

In-hospital follow-up mortality associated with tight glycemic control in diabetic patients with acute coronary syndrome

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Objective: The continuous insulin infusion and tight glycemic control in diabetic patients undergoing coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) improved perioperative outcomes.

Methods: One hundred fifty six patients with coronary artery disease (CAD) undergoing CABG or PCI were studied: 52 nondiabetic patients served as the control group; diabetic patients were randomized to tight glycemic control (TGC) (n=52) or standard glycemic control (SGC) groups (n=52) for almost 2 days after surgery, with insulin infusion followed by continuous intravenous insulin treatment. In the groups were studied fasting plasma glucose, impaired fasting glucose and continuous glycemic monitoring system (CGMS).

Results: Tight glycemic control (target serum glucose concentration 7.0-9.9 mmo/l, accompanied with a continuous intravenous insulin infusion) after CABG and PCI reduced incidence of cardiovascular events (p<0.005), pneumonia (p<0.05), stroke (p<0.001). TGC after PCI also reduced incidence of cardiovascular events (p<0.009), stroke (p<0.001), early stent thrombosis (p<0.001). The plasma glucose reduction was more pronounced in the TGC than in the SGC group (p<0.01) after the treatment period. The outcomes after surgery in control nondiabetic group and TGC group hadn’t significant difference.

Conclusion: Continuous insulin infusion to achieve tight glycemic control for at least 2 days after surgery is associated with improved in-hospital perioperative outcomes.
The prognostic significance of HbA1c in patients with newly detected glucose abnormalities and acute myocardial infarction treated invasively

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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 patients 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 etiology (hazard ratios, 1.37; 95%CI 1.10-1.71, P=0.016) 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 analyses. 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<0.005). Analyses revealed that increase of HbA1c was 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 1.42-1.62; 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 pts with IGT and new DM was one of the strongest independent risk factors of death in these study populations.

Statins pre-treatment modulates the relation between plasma fluorescent AGE and high sensitivity C-reactive protein in diabetic patients with acute coronary syndrome

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Purpose: High sensitivity C-reactive protein (hs-CRP) could have a role as a mediator in inflammation and atherosclerosis. Also, it has been proposed that advanced glycation end-products (AGE), by the interaction with its receptor (RAGE), can increase inflammatory response. Therefore, the aim of our study was to analyze the possible relation between advanced glycation end-products (AGE) and hs-CRP in patients with acute coronary syndrome (ACS).

Methods: AGE and hs-CRP were analyzed by fluorescence spectroscopy and turbidimetric assay, respectively, in plasma of 156 consecutive ACS patients admitted to coronary care unit (62.7±13.5 years, 24.2% female). 46.2% had a diagnosis of ST segment elevation myocardial infarction. 27.6% were diagnosed as type 2 diabetes, and 36.7% were treated with statins before ACS. Invasive coronary procedures were performed in 91.3% of the patients. The study population was divided into two groups: a) patients with diabetes and b) non diabetic ACS patients. hs-CRP was expressed in mg/L.

Results: In comparison with non-diabetic patients, diabetics were older (68.6±10.6 vs. 60.4±13.9 years; p<0.05), presented more incidence of hypertension (62.8% vs. 36.3%; p<0.05) and were in higher Killip class (p<0.05). However, no significant differences were observed in gender, body mass index, dyslipemia or kidney diseases, non ST-segment elevation myocardial infarction and procedural interventions. Glucose, fructosamine and glycated haemoglobin levels were higher, as expected, in diabetics than in non-diabetic patients, but there was no difference in fluorescent AGE levels. A direct association was observed in diabetics, but not in non-diabetics, between AGE and hs-CRP levels (r=0.368; p=0.018). Importantly, this association disappeared in diabetic patients under statins treatment before ACS (r<0.055; p=0.845), but it was maintained in diabetic patients with no statins pre-treatment (r=0.634; p<0.001) independently of other pharmacological treatments, other co-morbilities and possible confounding parameters.

Conclusions: It was observed a positive relation between AGE and hs-CRP in diabetic patients with type 2 diabetes according to the criteria of the American Diabetes Association. Therefore, the therapeutic utility of this finding in ACS patients should be further investigated.

Plasma renin strongly predicts all-cause and cardiovascular mortality in patients with type 2 diabetes: a 10-year cohort study

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Purpose: Diabetes mellitus is a major risk factor for mortality worldwide and is strongly linked to the activation of the renin-angiotensin system. This study sought to evaluate the association between plasma renin concentration (PRC) and mortality risk in patients with type 2 diabetes (T2DM).

Methods: PRC (median: 12.6 (6.0-27.0) ng/mL) was measured in 1319 patients with T2DM (mean age: 64.0±9.8 years; 29.7% females) referred to coronary angiography. After a median follow-up of 9.9 years, a total of 557 participants (42.1%) with PRC measurement at baseline had died (372 CVD deaths). Multivariable adjusted Cox analysis revealed that compared to patients in the lowest PRC quartile (Q1), those in the highest quartile were at increased risk of all-cause and CVD mortality: HR 2.48, 95%CI 1.91-3.24 and HR 3.5, 95%CI 2.6-4.6, respectively. Analyses of specific causes of CVD death showed that for each SD increase in log-PRC there was a 47% (p<0.001) increase in risk of death due to heart failure. The relationship between PRC and CVD mortality remained stable after adjustment for established CVD risk factors, ongoing medication and angiotensin II levels.

Conclusions: These findings suggest a role for PRC as a promising prognostic marker in a broad range of high CVD risk patients with T2DM.
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 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. The examined EPCs were 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±0.28% vs. 0.39±0.27%, P=0.042 and 1.03±0.25% vs. 0.67±0.23%, P=0.028, respectively). Brachial artery FMD was not 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 relationship between circulating CD133/KDR(+)% and CD34/KDR(+)% and brachial artery FMD in T2DM patients. T2DM-CAD patients and healthy subjects. Circulating CD34/KDR(+)% vs. CD34/KDR(+)% and HbA1c were strong predictors of artery endothelial dysfunction.

Conclusions: Hyperglycemia 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 1,137 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=0.018] and non-diabetic patients [HR IC 95%: 1.30 (1.04-1.64), p=0.018].

Figure 1

Conclusions: The GG was a strong, independent predictor of long-term all-cause mortality in hospitalized patients with ACS, regardless of diabetes status.

Treatment with DPP4-inhibitors is associated with a lower rate of in-hospital complications among diabetic patients with acute myocardial infarction

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Background: We studied the association between treatment with oral hypoglycemic medications and the clinical presentation of diabetes patients with acute myocardial infarction (AMI).

Methods: Multivariable logistic regression analysis was used to evaluate the risk of in-hospital complications among 445 diabetic patients with acute coronary syndromes enrolled in the Acute Coronary Syndrome Israeli Survey (ACSISS) 2010. Patients were categorized into 3 groups according to hypoglycemic medications at time of admission: 1) DPP 4 inhibitors (as monotherapy or in combination DPP4i), 2) Metformin (monotherapy or in combination, excluding DPP-4) and 3) other oral hypoglycemics.

In hospital complications

<table>
<thead>
<tr>
<th>Medication</th>
<th>DPP4i</th>
<th>Metformin</th>
<th>Other oral</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip</td>
<td>2±0.7</td>
<td>16.4</td>
<td>35.8</td>
<td>0.0008</td>
</tr>
<tr>
<td>Post M angina</td>
<td>0</td>
<td>2.6</td>
<td>7.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>6.3</td>
<td>12.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Infections</td>
<td>0</td>
<td>6.6</td>
<td>21.2</td>
<td>0.0009</td>
</tr>
<tr>
<td>Length of stay</td>
<td>5±3.8</td>
<td>5±6.5</td>
<td>7±6.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Results: Patients in the DPP4i group displayed similar baseline clinical characteristics to the other 2 groups, with the exception of a younger age and a lower frequency of prior CHD and CRI. Medical therapy with DPP4i was associated with a significantly lower rate of in-hospital complications and a shorter duration of in-hospital stay as compared with treatment with metformin or other oral antiglycemic drugs. Consistently, multivariate logistic regression modeling showed that treatment with DPP-4i was associated with a lower risk (OR=0.31; p<0.01) of in-hospital complications compared with other oral hypoglycemic therapy.

Impact of depressive syndrome and subclinical inflammation on one-year outcome in myocardial infarction patients depending on type 2 diabetes mellitus presence

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Purpose: Evaluate the impact of subclinical inflammation markers and depressive syndrome severity on one-year outcome in myocardial infarction (MI) patients depending on the co-morbid diabetes mellitus presence.

Material and methods: 195 patients (101 males and 94 females) admitted to hospital with STEMI and discharged to continue outpatient treatment were enrolled in the study with an age median (Me) of 58 (54; 65) years. 99 patients had no diabetes, age Me 58 (54; 65) years. 99 patients (101 males and 94 females) admitted to hospital with STEMI and discharged to continue outpatient treatment were enrolled in the study with an age median (Me) of 58 (54; 65) years. 99 patients had no diabetes, age Me 58 (54; 62) years. The age differences in the groups were not significant. The severity of depressive syndromes was assessed by the Beck Depression Inventory. According to the depression level all the patients were divided into two subgroups: subgroup I included those with the signs of depression and subgroup II, patients without depression. Interleukin (IL-6, IL-8, IL-10) and high-sensitive C-reactive protein (CRP) concentrations were measured by ELISA at days 3-5 after the MI onset. All-cause mortality, the number of readmissions for unstable angina and myocardial infarction were assessed a year after the index event. The absence of above-mentioned endpoints was regarded as a favorable outcome. Statistics 6.0 software was used for statistical data processing.

Results: Diabetic patients with the signs of depression more often had an adverse one-year outcome than those without depression: 25 (71%) and 13 (20%) cases, respectively, p=0.001. Additionally, diabetic patients with an adverse outcome and depression symptoms had higher levels of IL-6 (4.49 (2.9; 8.75) pg/ml and 1.62 (0.68; 4.9) pg/ml, respectively, p=0.02), IL-8 (3.01 (2.12;3.54) pg/ml and 1.61 (1.66;2.48) pg/ml, respectively, p=0.02), CRP (13.1 (6.6; 25.5) mg/ml and 6.8 (4.8; 10.5) mg/ml, respectively, p=0.001) compared with those without depression signs. Non-diabetic patients with the signs of depression also more often had an adverse outcome than those without depression: 10 (62%) and 5 (6%) cases, respectively, p=0.001. Non-diabetic patients with the signs of depression had higher levels of CRP (8.1 (4.6; 19.5) mg/ml and 3.8 (1.8; 6.5) mg/ml, respectively, p=0.01), IL-8 (11.8 (4.9; 18.8) pg/ml and 5.4 (2.9; 10.7) pg/ml, respectively, p=0.01) and lower levels of anti-inflammatory IL-10 (6.0 (3.3;3.89) pg/ml and 1.53 (1.06;3.16) pg/ml, respectively, p=0.04) levels compared with those without depression.

Conclusion: An adverse one-year outcome of MI patients with co-morbid type 2 diabetes mellitus was characterized by a high frequency of inflammatory and depressive symptoms.
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 levels 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 (39 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. 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 placebo patients; these were temporally 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 MIPO could be adequately controlled with MIPO.

**P5727**
Plasma triglyceride level may not predict the clinical outcomes in patients with controlled LDL-C 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 study included 7,170 consecutive patients who underwent PCI in our institution between 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 level 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 multivessel disease and the presence of coronary angiographic BCC lesion were associated with increased hazard ratios (HR). (HR=1.23, 95% Cl 1.010–1.456, p=0.039, HR=1.483, 95% Cl 1.162–1.962, p=0.001, respectively). However, follow-up TG level over 300 mg/dL was not statistically significantly interms of MACCs (HR=0.891, 95% CI 0.692–1.148, p=0.372).

Conclusions: Plasma TG level was not closely associated with MACCs 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 kringle 4 type 2 repeats in apolipoprotein(a), the characteristic protease component of lipoproteins, and specific in a haplotype of the SLC22A3-LPAL2-LPA region are associated with an increased risk of coronary disease. We examined the possibility that rs3798220 and rs10545872, polymorphisms located in LPA, the gene for apolipoprotein(a), and related to the number of kringle 4 type 2 repeats, may serve as specific markers for the association between haplotypes in the SLC22A3-LPAL2-LPA region and acute myocardial infarction.

Methods and Results: The study population comprised 2136 cases with acute myocardial infarction and 1211 controls. The rs3798220 C (frequency 2%) and rs10545872 G (frequency 7%) alleles of LPA were associated with increased risk of acute myocardial infarction (P=0.0024). None of these polymorphisms included in a haplotype analysis of the SLC22A3-LPAL2-LPA region were singly related to disease, whereas specific haplotypes were associated. Risk haplotypes CCCTTGATG (P=0.0022) and CCCTGGATC (P=0.0074) were correlated with the rs3798220 C (rs=0.77) and rs10545872 G (rs=0.28), alleles, respectively.

Conclusions: Considerable proportions of the effects of the CCCTTGATG and CCCTGGATC haplotypes could be explained by linkage disequilibrium with rs3798220 C and rs10545872 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

Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a Ca++-independent lysip, mostly produced by monocytes/macrophages, which circulates in plasma associated to LDL and to a much lesser extent to HDL. By hydrolysing oxidized phospholipids on LDLs surface it generates oxidized fatty acids and lysophosphatidylcholine, two triggers of the inflammation cascade that could elic proatherogenic 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 ELSIA 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 were included. CV event-free survival was compared between Lp-PLA2 groups by Kaplan-Meier and propensity score matching analysis.

Results: Full follow-up data were obtained in 544 (75%) patients after a median follow-up of 7.2 years (range 1–12.7 years) during which 62 (11.3%) CV deaths and 146 (26.8%) CV events were observed. At propensity score matching analysis, compared to the low Lp-PLA2 activity patients, those in the high Lp-PLA2 activity group showed more CV deaths (17.6% vs. 8.4%, respectively, p=0.01), more CV events (33.3% vs. 23.5%, respectively, p=0.02) and more acute coronary syndromes (24.6% vs. 14.4%, respectively, p=0.01). At variance, patients of the high compared to the low Lp-PLA2 mass group did not show differences on overall and any single cardiovascular events.

Conclusions: A high Lp-PLA2 activity, but not a high Lp-PLA2 mass, bears independent prognostic information in high-risk Caucasian patients referred for coronary angiography.

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**Lipoprotein-associated phospholipase A2 (LpPLA2), cardiovascular events and mortality in patients with type 2 diabetes mellitus on hemodialysis**

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Patients undergoing maintenance hemodialysis are at high cardiovascular risk. Whether cholesterol lowering with statins reduces cardiovascular (CV) events in these patients is still not clear. In an attempt to identify unknown factors relevant to adverse outcomes, we measured lipoprotein-associated phospholipase A2 activity (LpPLA2-A) and concentration (LpPLA2-C), also commonly referred to as “mass”), a lipoprotein-bound enzyme involved in inflammation and atherosclerosis, in patients of the 4D Study Group. LpPLA2-A and LpPLA2-C were measured with reagents from Diadexus Inc. (San Francisco, CA) at baseline in 1255 dialysis patients with diabetes mellitus who were subsequently randomized to receive either Rosuvastatin 20 mg daily or placebo. After 12 months, we evaluated a CV event (cardiovascular death, hospitalization for MI or stroke). We used Cox models adjusting for multiple factors including LpPLA2-A and LpPLA2-C quartiles at baseline as well as treatment group and all significant predictor variables at baseline. The hazard ratios and 95% confidence intervals (CI) for the lowest LpPLA2-A tertile vs. the highest were 1.38 (1.03-1.83) for the composite primary CV endpoint, 1.38 (0.73-2.62) for cardiac death, 1.60 (0.78-3.38) for sudden cardiac death, 1.13 (0.69-1.83) for non-fatal myocardial infarction, 1.34 (1.00-1.79) for all cardiac events combined, and 1.67 (1.26-2.21) for death from all causes, respectively. The hazard ratios and 95% confidence intervals comparing the highest quartile of LpPLA2-C with the first quartile were 1.31 (1.01-1.71) for the composite primary CV endpoint, 1.14 (0.78-1.70) for cardiac death, 1.01 (0.61-1.68) for non-fatal myocardial infarction, 1.28 (1.00-1.65) for death from all causes, respectively. In conclusion, in patients with type 2 diabetes mellitus undergoing maintenance hemodialysis, the activity and concentration of LpPLA2 are independent prognostic factors for cardiovascular events and mortality.

**Awareness of arterial hypertension, hyperlipidaemia and diabetes among patients admitted with acute coronary syndrome**

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Purpose: Early intervention of cardiovascular risk factors (hyperlipidaemia, arterial hypertension and diabetes mellitus) can reduce an individual risk of cardiovascular events and mortality. Unfortunately, in part of population these factors are not detected and thus not treated. The aim of our work is to describe awareness of these risk factors in population of patients admitted for acute coronary syndromes (ACS; myocardial infarction and unstable angina).

Methods: The data originated from a registry of ACS in non-PCI hospitals in the Czech Republic from 2008–2011. In total, 6266 cases of ACS were included in the analysis. This registry collected data on consecutive patients with ACS who were treated during a given period in the 32 participating hospitals. Results: Out of 6266 patients discharged from hospital after ACS event 82.0% patients had arterial hypertension, 79.6% hyperlipidaemia, and 36.0% diabetes mellitus. However, out of 5076 patients with arterial hypertension 467 (9.2%, 95% CI 8.4–10.0) did not know about the hypertension before hospitalization. Concerning diabetes the proportion of newly diagnosed risk factor was seen in hyperlipidaemia – 4857 patients had hyperlipidaemia, but 1676 patients (34.3%, 95% CI 33.0–35.7%) was not aware of this risk factor before admission. Concerning diabetes the proportion of newly diagnosed diabetes in the time of ACS event was minimal – only 93 (4.2%, 95% CI 3.4–5.1%) cases of 2229 patients with diabetes mellitus.

Conclusions: Hyperlipidaemia, arterial hypertension, and diabetes mellitus are important risk factors of coronary artery disease. Nevertheless a significant proportion of patients admitted for ACS are not aware of the presence of these risk factors before the ACS event – particularly in the case of hyperlipidaemia. More than one third (34.3%) of patients with hyperlipidaemia in our ACS population did not know about the diagnosis before their ACS event.

**Long-term intensive therapy with standard rosuvastatin dosing regresses atherosclerosis in a Japanese population. Does plaque stabilization contribute to this regression? The JART Extension study**

R. Nohara on behalf of the JART study group. Cardiovascular Center, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan.

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 multicenter 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; targeted 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 baseline of LDL-C was 7.78±2.85 (SD) mg. LDL-C was 86.0±19.7 mg/dL. Followed-up with no difference in the JART study (83.7±23.9 mg/dL). The 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). Additionally, we conducted the analysis of plaque characterization using the gray-scale median (GSM) at baseline and 24 months in some typical high risk patients.
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.

**Methods:** A total of 9,292 consecutive patients who underwent PCI with DES in COMET (CathOlic medical center persuAneous Coronary InTervention) 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, their 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 B2C 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.

**Polyunsaturated omega-3 fatty acids reduce lipoprotein associated phospholipase A2 (Lp-PLA2) levels in patients with stable angina undergoing percutaneous coronary intervention**

**Methods:** In a prospective, double-blind, placebo-controlled, randomized study, Lp-PLA2, oxidized LDL, myeloperoxidase and interleukin-6 were determined at baseline, 3-5 days and 30 days of administration of omega-3 PUFA 1 g/day (n = 30) or placebo (n = 24) in CAD patients until PCI.

**Results:** At baseline both treatment groups did not differ significantly. The treatment with omega-3 PUFA resulted in reduction in Lp-PLA2 levels by 10.7% (p=0.02) and oxidized LDL by 10.9% (p=0.014) at 30 days, with no change in myeloperoxidase and interleukin-6. Compared with placebo patients who received omega-3 PUFA had lower levels of Lp-PLA2 by 9.42% (p=0.041) and oxidized LDL by 12.3% (p=0.10). The effect of omega-3 PUFA on Lp-PLA2 occurred between day 3-5 and 1-month measurements. There were no correlations between Lp-PLA2 and oxidized LDL both at baseline and after treatment. The multivariate model showed that only assignment treatment and myeloperoxidase levels at baseline were the independent predictors of Lp-PLA2 changes after 1-month treatment (R2=0.37, P=0.005).

**Conclusions:** Administration of omega-3 PUFA can decrease Lp-PLA2 levels in patients with stable angina undergoing PCI. This novel effect may contribute to the benefits derived from omega-3 PUFA in patients with cardiovascular diseases.
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=4.40, 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 in the inclusion, in the model, of the time 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=0.587, 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 pleotrophic effects of the statins is more evident in the early phase post-ACS.

Table 1. Adjusted hazard ratio by aspirin and venous thromboembolism/pulmonary embolism

<table>
<thead>
<tr>
<th>No aspirin therapy (95% CI)</th>
<th>Aspirin therapy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per 10 year increase</td>
<td>0.94 (0.92-0.95)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.00 (0.91-1.0)</td>
</tr>
<tr>
<td>Charlson co-morbidity index</td>
<td>0.94 (0.90-0.98)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.84 (0.76-0.92)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.16 (1.12-1.21)</td>
</tr>
<tr>
<td>Ulcer medication</td>
<td>1.04 (0.96-1.12)</td>
</tr>
<tr>
<td>Hormon treatment</td>
<td>0.99 (0.97-1.02)</td>
</tr>
<tr>
<td>ACE-inhibitor/Angiotensin II blockers</td>
<td>1.02 (0.94-1.11)</td>
</tr>
</tbody>
</table>

*p-value for interaction between aspirin and variables.

49% males and 3982 (10%) used statin. The crude incidence rate of recurrent VTE/PE was 35 or 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.

Conclusion: 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.

Purpose: Clopidogrel can reduce thromboembolic events in acute coronary syndrome (ACS) patients. But poor clopidogrel metabolism regarding the gene polymorphisms may have impact on ACS patients. Our study is to explore the gene polymorphisms such as CYP 2C19, ABCB1 and PON1 in large Chinese ACS patients.

Methods: Patients admitted to Fuwai Hospital from 2005 to 2008 with ACS within 4 weeks were enrolled. All patients had signed informed consents for blood gene samples and genetic analysis. The detection of gene polymorphisms was performed by TaqMan real-time PCR method. The alleles genotyped were CYP2C19 *2 -*8, *17, ABCB1 and PON1. Patients were classified as one of the 5 categories by clopidogrel metabolizer phenotypes as Extensive [without any "loss-of-function" (LOF) allele *2-*8 or "gain-of-function" (GOF) allele *17], Intermediate (with only one LOF allele), Poor (with two or more LOF alleles), Ultra (with one or two GOF alleles) or Unknown (with one LOF allele and one GOF allele).

Results: A total of 2800 Chinese ACS patients were enrolled with mean age of 59.0±12.3 y and 79.8% males. Seventy four percent of the patients were diagnosed as STEMI, 22.0% as NSTEMI and 4.0% as unstable angina. The success rate of PCI was 90.7%. 47.8% patients had diabetes mellitus and 17.6% prior cerebrovascular disease. The frequency of CYP2C19, ABCB1 and PON1 genotypes in Chinese ACS patients. Comparing to the previous reports in Caucasians, LOF genotypes of CYP2C19 are more common in Chinese. Further exploration is needed to clarify the relation between genotypes characteristics and clinical outcomes in Chinese patients.

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 secondary 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 up for new VTE or PE death, or until December 31, 2009. The risk of recurrent VTE or PE associated with statin-use was studied by multivariable Cox proportional-hazards models.

Results: A total of 38,839 individuals were included, mean age 63(±17) years,
Impact of lipoprotein (a) on the incidence of subsequent cardiovascular events in patients with acute coronary syndrome

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Objectives: Lipoprotein (a) [Lp(a)] has been demonstrated as an independent risk factor for cardiovascular heart disease (CHD), but its role in predicting long-term outcome in patients with acute coronary syndrome (ACS) has not been examined. This study was undertaken to verify the predictive value of Lp(a) in patients with ACS.

Methods: A consecutive series of 713 hospitalized patients (539 males, 64±10 years old) diagnosed as ACS from January 2008 to May 2009 were enrolled. A retrospective chart review and analysis from the inpatient medical record system were undertaken. The subsequent major adverse cardiovascular events (MACE) (macar dead, non-fatal myocardial infarction, coronary revascularization, and stroke) were obtained by telephone call or clinic visit. The Cox proportional hazard models were used to evaluate the relationship between Lp(a) and MACE before and after adjustment of the potential confounders.

Results: During the 1.6±0.7 years follow-up, 14 cardiac deaths, 9 non-fatal myocardial infarctions (MI), 69 revascularizations, and 8 strokes occurred. Patients developing subsequent MACE had higher Lp(a) levels at baseline than those without such events [23.4 (11.95-37.7) ng/mL vs. 14.4 (8.3-26.5) ng/mL, p<0.001]. Before adjustment of the lipid and non-lipid variables, the risk of subsequent MACE in ACS patients steadily increased in proportion to the elevation of serum Lp(a) levels with the hazard ratio (HR) 1.93, 95% confidence interval (CI) 1.07-3.49 when Lp(a)>152 mg/dL (p<0.05); HR 3.29, 95% CI 1.89-5.72 when Lp(a)>313 mg/dL (p<0.001). The trend was slightly weakened but still there after adjustments. The Hazard ratio for the incidence of subsequent MACE associated with one unit increase of ln Lp(a) was 1.51 (95% CI 1.19-1.90, p<0.01). This result risked from Lp(a) showed a decreasing trend with the elevation of age, and the HR of <60 years old group, 60-70 years group and >70 years group was 1.95 (95% CI 1.31-2.50, p<0.001), 1.65 (95% CI 1.12-2.44, p<0.005) and 1.36 (95% CI 0.99-1.87, p<0.05), respectively.

Conclusions: Lp(a) is an independent risk factor for subsequent cardiovascular events in patients with ACS. The risk brought by Lp(a) seems would be attenuated by elevated age.

Cholesterol ester transfer protein role during acute phase of myocardial infarction

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Introduction and aim: The HDL phenotype induced by enhanced cholesteryl 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 activity 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-isoprostane levels, CETP % 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 ΔCETP on HDL. CRP, IL-2, TNF-α, 8-isoprostane levels.

Results: We observed a decrease in CETP activity between D1 and D3/D5, followed by a recovery by the D30 (14.6±0.9; 11.0±5.0; 10.4±4.8; 14.9±5.5, respectively; p<0.001). Consistently, HDL size increased between D1 and D5, but reduced to baseline by D30 (7.73±0.4; 7.65±0.9; 7.68±0.4; 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; 4.3-1.0] vs 5.0; 5.1-2.6 mg/dL, above and below median.

Conclusions: Based on the gold standard method more 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.
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often used cardioprotective medication on admission (aspirin, beta blockers, IEC and statins). In hospital complications were also more frequent in group I: bleeding (13% vs 8%, p=0.023) and heart failure (43% vs 14%, p=0.001). Patients in group I were also less likely to receive treatment and strategies advocated by current guidelines. Using multivariate logistic regression, GFR was an independent predictor of mortality (OR=0.98, IC [0.96-0.99], p=0.007). Indeed, according to GFR classification, 60% of patients with MDRD <30, 30% MDRD 30-60, 15% MDRD-30, 10% MDRD<15 mL/min/1.73 m², OR for total mortality was 1.76 (IC [1.26-2.68], p=0.007). Creatinine level was not an independent predictor of mortality in multivariate analysis.

Conclusions: Decreased glomerular filtration rate is an independent predictor of in-hospital mortality in patients with STEMI undergoing primary percutaneous coronary intervention or thrombolysis. Not only creatinine level but also GFR by MDRD is necessary for all patients with STEMI. Short-term prognosis is quite poor in these patients. This poor outcome is in part related to non adherence to guidelines.

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 larger 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: Prior to pulmonary vein isolation we performed 64-slice computed tomodography on 314 patients with paroxysmal or persistent AF. Diagnostic findings were categorized as normal, nonobstructive CAD and obstructive CAD (luminal stenosis ≥ 50%). 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 shown.

Conclusions: We observed 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.

Critical Role of Comorbidities in Coronary Disease

Critical Role of Comorbidities in Coronary Disease

P5748

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 the 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 >1000 randomly selected sites in 50 countries. Patient eligibility included age ≥18 years, newly diagnosed non-valvular AF, and 1 additional 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 10,511 AF patients enrolled in the current report, 1048 had a history of ACS. Mean age 71.2±9.5 years, 72.0% 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 ischemic attack, and 30.8% congestive heart failure. OAC alone was used in 31.4% of all ACS patients; OAC plus one or more antplatelet (AP) agent was more frequently used among patients with stenting (Table).

Presence of atrial fibrillation in patients with acute myocardial infarction undergoing percutaneous coronary intervention predicts contrast-induced nephropathy

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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 with or without combined use of ASP therapy that OAC alone in ACS patients a stent, whilst in patients without a stent rates of OAC monotherapy and combined use of OAC AP were similar. As such, the data indicate that ESC guidelines for patients with AF and ACS history – which recommend combined use of OACs and APs regardless of PCI in the 3-6 months post ACS and in the long term – are more frequently adopted in ACS patients with a stent than those without a stent.
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=80) and those without AF (n=2952) 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 years), higher rate of DM (47.5% vs 35.6%) and diabetes (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), Tn-I (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. 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 beta-blockers (63.4 vs 80.2%; p<0.001), clopidogrel (52.8 vs 37.4%; p=0.002). COPD was associated with a trend (p=0.056) to be constituted as an independent predictor of 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).

**Conclusions:** In our ACS patient population, AF was associated with greater 5-year mortality, regardless of AF or ACS type.

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**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 (STE) and without (NSTE) segment elevation.

Methods: 676 patients were studied (mean age 61.6±11.4 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 analyzed 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).

**Conclusions:** The presence of AF predicts CIN in patients with AMI undergoing PCI, regardless of pre-existing AF or new-onset AF.
Obstructive sleep apnoea (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 optimal medical therapy and whom coronary revascularization procedures are no longer feasible or helpful. We evaluated 31 patients (16 males; age: 62±10y, body mass index: 29.8±4.5kg/m²). Co-morbidities were common (diabetes 100%, hypertension 93% and diabetes 61%) and all patients presented persistent angina despite optimal anti-ischemic medical therapy and preserved systolic function (ejection fraction on eckocardiography: 53±11%). Patience reported poor 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 with OSA or without OSA, age, gender, BMI, baseline age, gender, BMI were the best at 30.4±5.4kg/m² (p=0.26) similar ESS (10.6 vs. 11.6), non-significant trend to higher frequency of diurnal (66 vs. 91%, p=0.13) and nocturnal angina (45 vs. 77%, p=0.07).

Conclusions: This preliminary study showed a high frequency of OSA in consecutive 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 (CPAP)
B. Shivalkar, J. Verbraecken, K. Kluppels, H. Vrints, H. Heuten, R. Salgado, P. Parizel, C. Vrints. Antwerp University Hospital, Antwerp, Belgium

Purpose: The mechanisms underlying the increased risk of cardiovascular disease (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±9.8 years; BMI: 29.8±4.5) and age and BMI matched non-OSA controls (n = 18; age: 46±9.8 years; BMI: 27.9±3.9). We excluded patients with diabetes, heart disease, cancer, chronic kidney disease, liver disease and chronic lung disease. The patients received a 2D Doppler and Doppler-echo stress echocardiography, pulse oximetry, 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: 29.8±4.5kg/m²). Co-morbidities were common (diabetes 100%, hypertension 93% and diabetes 61%) and all patients presented persistent angina despite optimal anti-ischemic medical therapy and preserved systolic function (ejection fraction on eckocardiography: 53±11%). Patience reported poor 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 with OSA or without OSA, age, gender, BMI, baseline age, gender, BMI were the best at 30.4±5.4kg/m² (p=0.26) similar ESS (10.6 vs. 11.6), non-significant trend to higher frequency of diurnal (66 vs. 91%, p=0.13) and nocturnal angina (45 vs. 77%, p=0.07).

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Critical role of comorbidities in coronary disease

Obstructive sleep apnoea is highly frequent in patients with refractory angina
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Purpose: Obstructive sleep apnoea (OSA) is common among patients with stable coronary artery disease and may contribute to poor cardiovascular outcome.

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: 29.8±4.5kg/m²). Co-morbidities were common (diabetes 100%, hypertension 93% and diabetes 61%) and all patients presented persistent angina despite optimal anti-ischemic medical therapy and preserved systolic function (ejection fraction on eckocardiography: 53±11%). Patience reported poor 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 with OSA or without OSA, age, gender, BMI, baseline age, gender, BMI were the best at 30.4±5.4kg/m² (p=0.26) similar ESS (10.6 vs. 11.6), non-significant trend to higher frequency of diurnal (66 vs. 91%, p=0.13) and nocturnal angina (45 vs. 77%, p=0.07).

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creased death.  

**Aim:** To evaluate preventive effect if blocker ibudidine on autonomic heart rate regulation after inhalation of j2 – agonist salbutamol in patients with COPD and CHD.  

**Methods:** 23 clinically stable patients with COPD II-III were randomized to inhale single dose of 400 mcg salbutamol via a metered-dose inhaler or spacer or to intake drug combination of 5 mg ibudidine po followed for 2 hours by inhalation dose of 400 mcg salbutamol on two separated consecutive days. Autonomic regulation of heart rate was assessed via heart rate variability (HRV) estimation, HRV was evaluated via time and frequency domain analysis of 10 min. ECG record as the standard deviation of interbeat intervals SDNN, the power in the low-frequency (LF) band (0.04 to 0.15 Hz) and the high-frequency (HF) band (<0.15 to 0.4 Hz).  

**Results:** Salbutamol alone significantly decreased autonomic cardiac modulation. Salbutamol in combination with ibudidine did not cause any changes of SDNN, LF, HF, heart rate and LF/HF ratio and increased normalized value of HF spectral power. It reflects positive tendency of normalization of autonomic cardiac regulation.

**Conclusion:** Ibudidine protects autonomic regulation of heart rate in patients with COPD after salbutamol inhalation.

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**P5759**  
**In-hospital and follow-up mortality associated to impact of in-hospital timi bleeding and chronic kidney disease**  

**Introduction:** In-hospital and follow-up mortality independently of GRACE risk score. This observed association deserves further studies with a higher number of patients.

**Patients 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 transcoronary 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 mmHg) or not calculated but with no evidence of indirect signs of PHT). Primary endpoint was major adverse cardiac events (MACE) in the follow-up at 6 months.  

**Results:** 154 (17.1%) of the 902 patients had PHT. These patients were older (p < 0.001), had higher prevalence of smoking (p = 0.001) 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 < 0.001) and coronary artery bypass grafting (p = 0.002) more often. At admission, they had 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.

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**P5761**  
**Isolated coronary surgery - associated acute kidney injury - a comparison of two 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 thresholds given for serum creatinine (Cr) increase and glomerular filtration rate (GFR) 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-Dec08, excluding 31 on preoperative dialysis. AKI was defined by using either largest Cr increase or greater eGFR decrease, postoperative compared to baseline. In all patients, aperoperative baseline Cr 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 with AKI. The RIFLE classes by creatinine and estimate glomerular filtration rate (eGFR) were used to evaluate the impact of AKI on outcomes.

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**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 (IB) 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 unclear.

**Methods:** In a Taiwan national-wide 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 primary end point was the composite CVE of death, non-fatal myocardial infarction and non-fatal stroke at one year.

**Results:** Both IB 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 IB and CKD have 10.5 fold risk to suffer from the primary end point compared with those without IB 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 IB and CKD both in the ST elevation and non-ST elevation ACS populations (both p < 0.01).

**Conclusions:** IB or CKD is independently associated with poor outcome and patients with both IB and CKD have the worst outcome in the ACS.
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 in-hospital mortality estimated by sCr and eGFR criteria were 0.86 (95% confidence interval: 0.78 to 0.95) and 0.85 (95% confidence interval: 0.77 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 initiative for quality improvement.

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 nicornadil 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 (nicornadil n=81, control n=85) with estimated glomerular filtration rate (eGFR) <1.5 mg/dl. In 0.9% saline 100 ml was administered intravenously for 30 minute just prior to coronary angiography in the nicornadil group, whereas same volume of saline was given to the control group. Increase in serum creatinine (Scr) >0.5 mg/dl or an absolute increase of >0.5 mg/dl was defined as CIN.

Results: Baseline characteristics were similar between the nicornadil and the control group. Baseline Scr (1.67±0.67 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 nicornadil 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/dl, respectively, P = 0.621). The incidence of CIN was also similar between the two groups (7.8% vs. 8.6%, p=0.810).

Conclusion: Prophylactic intravenous infusion of nicornadil did not decrease the incidence of CIN in renal failure patients undergoing coronary angiography.

P5765 Influence of chronic kidney disease on the acute therapy, in-hospital events and mortality in patients with acute myocardial infarction

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Background: The presence of chronic kidney disease (CKD), although prevalent in patients (pts) with acute myocardial infarction (AMI) continues to be underestimated in large international studies.

Purpose: The purpose of this study was to evaluate the impact of CKD on the clinical management of pts AMI, in-hospital complications and mortality.

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 [CHR] 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=0.07) after adjustment for confounding variables.

Conclusions: In patients with AMI with normal creatinine levels, occult renal failure should not be underestimated in clinical practice.
Methods: We studied 2726 pts with AMI included in a national multicenter registry. We considered two groups: pts with CKD and pts without CKD. The presence of CKD was defined by creatinine ≥2mg/dl (n=101) or on dialysis (n=14). We compared age, gender, cardiovascular risk factors, electrocardiographic presentation of AMI, acute therapy and invasive strategy adopted. Defined as the primary end-point in hospital mortality and secondary end-point as the presence 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: Presence 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 48.3%, 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), lopinoglycifib/llb 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), coronary angiography (65.2% vs 90.3%, p<0.001) and more in-hospital complications and mortality. How-

Conclusions: Our results suggest that pts with CKD and AMI have less cardio-

vascular complications and have more in-hospital complications and mortality. How-

ever, CKD in these patients was not an independent factor of mortality.

P5767

Cockcroft-gault, modification of diet in renal disease or chronic kidney disease epidemiology collaboration in renal disease and acute coronary syndromes?


Introduction: Approximately 30-40% of patients with Acute Coronary Syndromes (ACS) have chronic kidney disease (CKD) and it is associated with poor prognosis and high risk of bleeding events. The more common equations used to determine the glomerular filtration rate (GFR) are the Cockcroft-Gault (C-G) and the MDRD (Modification of Diet in Renal Disease). A new equation is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), that seems to be more accurate than the MDRD and it is suggested that it could replace the MDRD. However, little is known about the utility of the new equation in ACS.

Aims: To determine the prevalence of CKD with the C-G, MDRD and CKD-EPI equations and the incremental prognostic value of the new equation compared to the classical equations (occurrence of bleeding complications during the hospitaliza-

tion in patients with ACS).

Methods: Between 1/2004 and 12/2010 3270 inpatients with ACS were included. TIMI (Thrombolysis in Myocardial Infarction) bleeding definition was used. We de-

termined the prevalence of CKD with the three equations. Univariate analysis was performed by cross-tabulating the bleeding risk of the new equation compared to the two others. To compare the incremental prognostic value, we used the concept of net reclassification improvement (NRI).

Results: The prevalence of CKD was 30.4% with the C-G and 26.8% with the MDRD and 36.1% with the C-G. 140 (4.3%) patients had a TIMI bleeding event; the higher risk was observed in subgroups with the lower GFR for all equations. Compared to the MDRD, the new equation reclassified 5.2% of patients and the total NRI was 3.58%. The CKD-EPI equation reclassified 10.7% of patients com-

pared to C-G; however the total NRI was -7.5%.

Conclusion: The CKD-EPI detected more prevalence of CKD and reclassified patients at high risk of bleeding better than the MDRD equation but detected lower prevalence than the C-G and reclassified patients at high risk of TIMI bleeding worse than C-G.

P5768

Anemia impairs improvement of myocardial ischemia by percutaneous coronary intervention on stress myocardial perfusion imaging

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Background and Aim: Presence of anemia affects the major adverse cardiac events (MACE) and mortality of patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI). However, relationship between pres-

ence of anemia and improvement of myocardial ischemia after PCI is uncertain. The aim of this study is to clarify the effect of anemia on improvement of myocar-

dial ischemia by PCI on stress myocardial perfusion imaging (MPI).

Methods: We performed stress MPI (drug stress: n=47, exercise: n=36) be-

fore and after successful PCI and evaluated clinical parameters in 83 patients (62.5±9.5 years old, 63 men) without major complication during PCI and residual significant organic stenosis with myocardial ischemia by stress MPI. We exclude the patients who failed to attain target heart rate during exercise and terminate the study or do not achieve stress drug stress MPI. We allocate SPECT images in 17 segments on a 5-point scale (0: normal to 4: de-

fect) and assessed the summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS). SDS was calculated as follows: SDDS=SRS-SSS. We defined %SDS as indicator of improved myocardial perfusion ischemia. PCI. %ΔSDS was calculated by the following formula; %ΔSDS = SDDS before PCI - SDDS after PCI. Anemia was defined according to the WHO definition (hemoglobin <13g/dl in men, hemoglobin <12g/dl in women). We evaluated improvement of anemia on %ΔSDS.

Results: %ΔSDS showed significant relationship with hemoglobin level (r=-0.35, p=0.015), use of calcium channel blocker (r=0.22, p=0.04), estimated GFR (r=0.33, p=0.002), left atrium diameter (r=-0.30, p=0.007) and left ventricular mass index (r=0.23, p=0.041). Although hemoglobin level was significantly de-

creased after PCI (before: 12.9±0.33 g/dl vs. after: 11.9±0.33 g/dl, p=0.004), there were no correlation between %ΔSDS and decrease in hemoglobin level. In patients with anemia, %ΔSDS was significantly lower than those in without anemia (0.50 vs. 0.84 respectively). Anemia was an independent predictor for %ΔSDS. We found %ΔSDS was dependent on initial hemoglobin level and an independent predictor for %ΔSDS (p=0.009).

Conclusion: This study suggests that improvement of ischemia provided by PCI was impaired in patients with anemia. It may relate to MACE or mortality of pa-

tients with anemia after PCI. We should pay attention to anemia as a therapeutic target in PCI patients.
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 ischemic 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±9 years with 77% (47/61) were more than 60 years of age. Seven patients was checked in only 50% (31/61) of these patients and 71% (22/31) patients had low levels. Coeliac serology was performed in only 5% (3/61) patients, which was normal. Among these, 92% (56/61) patients were on aspirin, 50% (30/61) on clopidogrel while only 11% (7) on warfarin. Oesophago-gastro-duodenoscopy (OGD) was performed in 75.5% (45/61) of the referred patients with 13.04% (6/46) had non-erosive gastritis, 8.69% had peptic ulcer disease while angiodyplasia, gastric erosions, gastric polyps 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 4.3% each. OGD was normal in the rest; none had cancer or active bleeding. Coeliac serology was performed in 49.09% (33/61) patients and CT colonogram in 5%. Colorectal cancer was found 8.33% (3/36) patients, benign polyps in 5.55% (3/55) and diverticulosis in 22%. Less than 1% patient had proctitis, haemorrhoids and pseudomembraneous colitis.

Conclusion: A large number (73%, 169/230) of the anaemic patients with ACS/HID 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.
clinical, laboratory findings, medication and interventions, PAD remained an independent predictor of 5-year mortality (HR 1.609, 95% confidence interval 1.330-1.946, p<0.001).

Conclusion: A history of PAD is a powerful, independent predictor of adverse long-term outcomes among unselected patients with ACS.

Association of family history of premature cardiovascular disease with traditional cardiovascular risk factors and coronary heart disease in an Indian industrial population

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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 and 10 and PFH and CHD in an Indian industrial population.

Methods: Data on CHD risk factors and prevalent CHD were captured from 19,973 individuals in the SSIP study conducted in ten industrial centres spread across India. Information on PFH status on CHD and stroke (before the age of 60 years) in parents and siblings was obtained. Individuals with PFH were compared with age, sex and centre matched control subject without PFH. Additionally individuals with PFH and CHD 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 1.80-3.75), even after adjustment for all traditional risk factors of CHD.

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 (12.0)</td>
<td>39.92 (10.20)</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m2), Mean (SD)</td>
<td>24.79 (3.87)</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>124.78 (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)</td>
<td>184.76 (38.55)</td>
<td>173.95 (40.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl), Mean (SD)</td>
<td>138.92 (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>&lt;0.001</td>
</tr>
</tbody>
</table>

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 treated 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.

Obesity paradox: the impact of body mass index on short- and long-term mortality in patients with acute coronary syndrome


Introduction: Although obesity seems to be an independent risk factor of cardiovascular diseases, recently data suggests lower risk of short-term mortality in obese patients with acute coronary syndrome.

Objective: To investigate the obesity paradox in obese patients with acute coronary syndrome, receiving percutaneous intervention treatment in a high volume interventional heart center.

Method: Between 01.01.2009 and 31.12.2010 all together 2305 patients were consecutively enrolled to the study. Obesity paradox was investigated according to the short- and mid-term survival data and BMI of the patients. Statistical analyses were performed using a test and logistic regression.

Results: Patients were divided into 4 groups based on BMI: <20 (underweight, n=78); 20-24.9 (normal, n=651); 25-29.9 (overweight, n=897); >30 (obese, n=677). We considered normal weight group as a basis for comparison. There was no difference in the number of STEMI patients among the different groups (44/56, 2%; 346/531, 1%; 343/484, 8%; 325/428, 0%). Proportion of female patients was significantly higher in the overweight group and significantly lower in the obese group (54/69, 2%, 280/43, 0%; 290/32, 3%, 252/37, 2% p<0.001). Age in obese group was significantly lower (72.6±14.5, 69.1±13.9, 67.8±12.5, 64.7±14.5 p<0.001) with higher incidence of diabetes (0/2%, 10/0.02%, 26/6%, 65/9%, 60% p<0.002). At 30 days and at 6 months mortality of overweight group was significantly lower. compared to the normal weight group (58/897, 6.6%, 60/651, 9.2% p<0.036; 6 month: 75/671, 19.6%, 137/697, 19.6% p<0.001). In case of obese patients, there was no difference in the 30 days survival (mortality: 43/677, 6.4%; 65/651, 9.2% p=NS) but life expectancy at 6 months was significantly better (mortality: 76/897, 11.2%; 67/651, 19.6%; p<0.002).

Conclusion: We assume that “Obesity Paradox” 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 leaft 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, gender, hypertension (≥140/90 mmHg or medical therapy), hypercholesterolemia (total cholesterol >200 mg/dl or statin), diabetes, family history of CAD and smoking habit.

Results: 538 patients (mean age: 64±11, 62%, male) formed the study population. Any degree of CAD was present in 117 patients (20%) 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 14.9; 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 35.8; 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.
P5777 The value of 2D longitudinal strain for detection of significant coronary artery disease in patients without visual segmental wall motion abnormalities

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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 were calculated as the mean LS of the 6 segments in apical, middle and basal level respectively. LSa-m 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.

P5778 The use of beta-blockers is associated with a well-developed coronary 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 invasively. Multivariate analysis was performed to assess clinical parameters associated with CFI.

The median CFI (0.37± 0.15) was used as cut-off point between patients with a well- and a poorly developed collateral circulation. The multivariate analysis showed that beta-blockers were positively associated with a well-developed collateral circulation (B=0.072, p=0.019). Serum leukocytes were negatively associated with a well-developed collateral circulation (B=0.012, p=0.013). As expected the presence of angina pectoris (AP) was negatively associated with a well-developed collateral circulation (B=-0.139, p=0.09).

In a unique cohort of CTO patients we show that high serum leukocytes are associated with a poorly developed collateral circulation. Interestingly the use of beta-blockers is positively associated with a well-developed collateral circulation shedding new light on the potential mode of action of this drug in patients with AP.

P5779 Prediction of hyperemic flow on coronary lumen volume depends on minimum vessel diameter included

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Purpose: An allometric scaling law between the coronary vascular volume (V) and hyperemic blood flow (Q) is currently used to noninvasively estimate the functional impact of coronary artery disease: Q=K.V^B, where K and B are scaling factors. Previous validation in vivo yielded B=0.7, but was limited by a spatial resolution of 500 μm. We hypothesized that B and therefore the prediction of Q depends on the smallest vessel diameter included in the assessment of V.

Methods: Fluorescent microspheres were injected into the coronary vessels of canine hearts at maximal vasodilation. The diastolically arrested hearts were excised and the coronary arteries filled with fluorescent cast material. The vascular bed was reconstructed in 3D, using an imaging cryomicrotome and the volume of the vessels was determined. Microsphere locations were used to derive the relative Q per subtree. The volume of each subtree depends on the diameter of the smallest vessels, Dm, included. Dm was varied between 40 and 800 μm.

Results: Figure A and B demonstrate typical reconstructed trees for Dm=40 μm and 500 μm. Log-log fits of V versus Q resulted in B of 0.88 (r²=0.95) for Dm=40 μm, decreasing nonlinearly to 0.76 (r²=0.76) for Dm=800 μm. The earlier reported B=0.7 was found with Dm=500 μm. Using B=0.7 as reference, the deviation in predicted hyperemic flow was calculated for Dm=40 μm and 400 μm as a function of V as shown in figure C. For the clinically realistic value of V=0.8 ml, Q is overestimated by 17.7 percent for Dm=400 μm and 66.7 percent for Dm=40 μm.

P5780 Non-invasively measured coronary flow reserve of the infarct related artery is predictor of mid-term outcome in STEMI patients treated with prim 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 trans thoracic echo and...
Influence of age on the clinical characteristics, impact of acute myocardial infarction redefinition. Prognostic significance of long-period heart rate.

Results: Median FUP was 13 months. From patients 14 reached endpoint (9 pts needed new IRA PCI. 5 pts got heart failure). Among analyzed parameters significant univariate predictors of combined endpoint were: IRA CFR, LV EF, HDL cholesterol, glucose blood level (all measured on the 7th day). ROC analysis for IRA-CFR (area under the curve 0.801, p>0.001, 95% CI 0.656-0.946) revealed that IRA-CFR of 1.89 had sensitivity of 75% and specificity 83% to predict combined endpoint. In regression logistic analysis in model that included all univariate predictors IRA CFR (beta= -3.081, p= 0.03, Exp (B) =0.0366, 95% CI 0.0018-0.7265) and glucose blood level (p= 0.02) were significant independent predictors.

Conclusion: Non-invasively assessed coronary flow reserve of the infarct related artery 7 days after primary PCI is STEMI patients is independent predictor of clinical events during mid-term follow-up.

P5781

Influence of age on the clinical characteristics, impact of acute myocardial infarction redefinition: a prospective analysis of 30 978 patients

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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 yrs, 65-74 yrs, ≥ 75 yrs), 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 outliers 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.

P5782

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 disease and the type (1M1) and (2M2) are considered the most relevant ischemic events. The differences about clinical expression and prognosis are not fully understood, since MI2 had a generally weak representation in the majority of the clinical trials. We aimed to determine any potential differences between MI1 and MI2. 744 patients admitted with MI (68.8±13.4y, mean±SD) were analyzed. 45.3% of MI1 were primary outcomes were in-hospital (IH) and 24-months mortality (2M). Between the MI type [N=50 (8.6%)] vs. 26 (16.1%), p=0.422]. The 2M was higher in the MI2 group [N=79 (13.6%) vs. 45 (28%), p<0.001, OR 2.639, IC95% 1.4-10.8], as was the MIH readmissions ((N=51 (8%) vs. 26 (16.1%), p=0.001, OR 1.797, IC95% 1.07-2.99) and re-infections (N=57 (9.8%) vs. 24 (14.9%), p=0.069) than MI1.

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 discuss if long-term medical management should be the same as in MI1, or should consider MI2 particularities.

P5783

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 dependence (Barthel test) and comorbidities (simple comorbidity index).

Results: Mean age was 77.5±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 test) 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 13.4), cognitive impairment (RR=4.2, 95% CI=1.6-10.8), physical dependence (RR=2.3, 95% CI=1.1 to 5.6) and comorbidity (RR=2.1, 95% CI=1 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 highest: 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.

NUTRITIONAL UPDATES

P5784

Prognostic significance of long-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 myocadiac function in spontaneously hypertensive rats.


Purpose: Clinical and experimental studies have demonstrated that aldosterone blockers increase survival in patients with advanced heart failure (HF). The beneficial role of this blockade before clinical evidence of HF is uncertain. The purpose of this study was to evaluate the effects of early spironolactone (SPR) administration on cardiac remodeling in spontaneously hypertensive rats (SHR).

Methods: Thirty-six 13 month old SHR were divided into two groups: control (CTL, n=15) and SPR (n=21, 20mg/kg/day for six months). Arterial pressure was measured by indirect tail-cuff method at the beginning (13 month old) and end (19 month old) of the experiment. Echocardiogram (ECHO) was performed to evaluate cardiac structures and left ventricular (LV) function. Myocardial function was measured in LV papillary muscle preparations (control, n=12; SPR, n=19).

Ventricular hypertrophy was evaluated by cardiomyocyte cross-sectional area (CSA) and ventricular weight measurements. Myocardial hydroxyproline concentration was analyzed by spectrophotometry. Concentrations of Na+, K+, and Mg2+ were measured in serum. Statistics: Student’s t and Fisher exact tests. Significance level: p<0.05.

Results: Arterial pressure was not different between groups at the beginning (CTL: 199±13; SPR: 190±21mm Hg; p>0.05) and end (CTL: 184±24; SPR: 197±72mmHg; p<0.05) of the experiment. ECHO performed at the end of the experimental period did not show differences in cardiac structures or LV systolic and diastolic function between groups. In vitro myocardial function was improved in SPR vs. CTL (developed tension: 7.0±1.6 vs. 5.2±1.4 g/mm²; maximum rate of developed tension: 61.0±17.4 vs. 46.8±5.0 g/mm²/s; rate of tension decline: 29.8±7.96 vs. 21.6±5.40 g/mm²/s; p>0.05). Right ventricular and atrial weights were lower in SPR vs. CTRL (Na+: Ctl: 533±95; SPR: 393±58 μm²/p; p<0.01). Myocardial hydroxyproline concentration was lower in SPR but with no statistical difference (p=0.086). Serum Na+, K+, and Mg²⁺ levels were not different between groups. Mortality rate, although lower in SPR (12.5% vs. 25.0%), was not significantly different between groups (p=0.05).

Conclusion: Aldosterone blockade initiated before clinical evidence of heart failure shows beneficial effects on cardiac remodeling and myocardial function in spontaneously hypertensive rats.

Neurohormonal updates 1091

CT-proendothelin-1 in heart failure: associations with clinical characteristics and comorbidities.

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Background and aim: Levels of endothelin-1 (ET-1), a powerful vasoconstrictor, were shown to be increased in heart failure (HF). Whereas intact ET-1 is rather fragile, its C-terminal fragment (CT-proET-1, released in equimolar amounts) is very stable and has a favourable pre-analytical profile. Recently, elevated levels of CT-proET-1 were found to be associated with adverse prognosis in patients with HF. We therefore analyzed CT-proET-1 levels in a large cohort of patients with systolic HF and investigated its associations with clinical characteristics and comorbidities.

Methods: 923 participants of the Interdisciplinary Network Heart Failure Study were included prior to discharge after hospitalisation for cardiac decompensation. All subjects had systolic HF with a left ventricular ejection fraction (LVEF) ≤40%. Besides a thorough clinical assessment, blood chemistry including electrolytes, markers of renal function and inflammation, and natriuretic peptides were measured. Serum samples were obtained at baseline and stored at -80° C for later analysis of CT-proET-1.

Results: Mean age was 68±13 years, 71% were male, 44% were in NYHA class III or IV, and mean LVEF was 30±14%. The median CT-proET-1 level was 96 pmol/L (quartiles 72; 138 pmol/L). Significant correlations (p<0.01) were found regarding age (r=0.40), endystolic left atrial diameter (r=0.27), LVEF (r=0.21), glomerular filtration rate (r=-0.56), creatinin (r=-0.19), haemoglobin (r=-0.35), erythropoetin (r=0.39), NT-proBNP (r=0.62), LDL cholesterol (r=0.16), triglycerides (r=0.20), interleukin-6 (r=0.38), high sensitivity C-reactive protein (r=0.30). Furthermore, CT-proET-1 levels were higher in NYHA class III/IV vs IV (116 pmol/L (89-160) vs 85 pmol/L (65; 119)) and with the presence of diabetes mellitus (116 (84; 156) pmol/L vs 87 (67; 122) pmol/L). No association was found for potassium- or aldosterone-levevs, systolic or diastolic blood pressure, and enddiastolic left ventricular diameters (all r<0.05).

Conclusion: In this large well-characterized cohort of HF patients important correlates of the stable endothelin-1 fragment CT-proET-1 were identified. These include markers of the severity of HF as NYHA functional class, NT-proBNP and left atrial size, as well as typical comorbid conditions of HF like anaemia, diabetes mellitus, inflammation, and kidney dysfunction. Since these comorbidities adversely impact on prognosis, CT-proET-1 may have a role as surrogate marker of impaired prognosis and/or tool to monitor the course of HF.
LVEF and CO. Hemodynamic parameters, unlike CRP and NT-proBNP are independently associated with sST2. Our results imply that in dilated cardiomyopathy, sST2 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 22.9-60.4].  

**Results:** Both NT-proBNP (r = -0.46, p < 0.001) and sST2 (r = -0.18, p < 0.001) inversely correlated with eGFR. Although statistically significant, the degree of correlation between ST2 and sST2 was weaker. Patients were divided according to eGFR in 3 subgroups: ≥ 60 ml/min/1.73 m²; 30-60 ml/min/1.73 m², and < 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 = 0.75). The combination of the two biomarkers according to cut-off points significantly increased their prognostic discriminator capacity 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.

**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.

**P5789**  
Effect of adaptive servo-ventilation on muscle sympathetic nerve activity and cardiac function in patients with heart failure and central sleep apnoea  
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**Backgrounds:** Daytime sympathetic nerve activity is enhanced in patients with heart failure (HF) and central sleep apnoea (CSA). Such patients often benefit from improved cardiac function when adaptive servo-ventilation (ASV) resolves CSA. However, whether greater suppression of CSA contributes to more improved ejection fraction and a greater decrease in muscle sympathetic nerve activity (MSNA) remains unknown. To determine the effect of reducing CSA by ASV on MSNA during the daytime and cardiac function in patients with HF.  

**Methods:** Thirty patients with HF (NYHA II and III; ejection fraction, < 45%) and CSA (apnoea-hypopnoea index (AHI) ≥ 10/h) were studied. We determined MSNA and performed echocardiography at baseline and at 3.3±0.6 months of follow-up. Compliance with ASV and change in AHI were determined from data collected by integral countercurrents in devices and from cardiorespiratory polygraphic findings.  

**Results:** Ejection fraction and MSNA significantly changed in the ASV group (ejection fraction, 31.9±7.1% to 37.1±12.0%, p < 0.001; burst rate, 54±17 to 41±17/min, p < 0.001; burst incidence, 75.1±18 to 62±21/100 beats, p < 0.01) but not in the control group. The average use of ASV and changes in AHI both correlated with changes in MSNA and ejection fraction. Bivariate analysis showed that a change in AHI was a common independent predictor of changes in MSNA and in ejection fraction (table).  

**Conclusion:** Suppression of CSA by ASV is closely associated with both sympathoexcitation and increased ejection fraction in patients with HF and CSA.

**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 (FU).  

**Methods:** In the DIAST-CHF observational study n=1937 patients (±50years) with risk factors for heart failure or previously confirmed diagnosis of heart failure (diastolic dysfunction: EF ≤ 45%) were included (FU: 1-FU) at 1-FU compared to baseline. Improvement or worsening PHF was defined as a change greater than one standard deviation (baseline values) compared to baseline. All patients underwent standardized blood sampling, detailed echocardiography and 6-minute-walking-testing (6-MWT). Data are shown as Mean (± SD).  

**Results:** At 1-FU n=718 (84%) had PHF+, n=137 (16%) had PHF-. Age 65±6/7±3.6, height 176±8/173±7 cm, female gender 51.5/54.7%, LVEF 61.6/6.1±26.1/5.9±8% (all p<0.05 PHF+ vs. PHF-). 6-MWT 524. 4±109.5/496.8±22.6 (p<0.001) NT-proBNP 129.8±147.8/220.3±45.0 pg/ml (p<0.03), MR-proADM 0.58±0.17/0.69±0.34 mmol/l (p<0.001) and MR-ProANP 95.1±49.3/121±50.9 pmol/l (p<0.001) PHF+ vs. PHF- all p<0.001. E/e 9.8±2.4/10.1±3.5 (p=0.003), LAVI 23.8±7.2/26.3±6.9 m²/m² (p=0.007) and LVMI 111.5±25.4/120.2±22.8 g/m² (p=0.045) all PHF+ vs. PHF-. LVEF (61.6 vs. 61.9%), LVEF (61.6 vs. 61.9%) and LVEF (61.6 vs. 61.9%) were 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<0.003), 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 great cardiac vein than in the orifice of left coronary artery (7.7±4.4 vs. 6.7±3.6 pmol/L, 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 pmol/L, p=0.019). In addition, subcutaneous infusion of Ang II (250 ng/kg/min) in 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 1 hour compared to controls; whereas it was blunted by the pretreatment of ARB, RNH-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 cheyne-stokes respiration

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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 Cheyne-Stokes respiratory (CSR), 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 their neurohumoral abnormalities.

Methods and Results: Forty two patients with CHF and CSR (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>
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<th>Baseline</th>
<th>O2</th>
<th>ASV</th>
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<tbody>
<tr>
<td>AHI (times/h)</td>
<td>16 ± 7.4</td>
<td>14 ± 6.8</td>
<td>&lt; 0.01</td>
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<tr>
<td>ANP (pg/ml)</td>
<td>165.5 ± 205.7</td>
<td>152.4 ± 233.1</td>
<td>0.22</td>
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<tr>
<td>BNP (pg/ml)</td>
<td>245.8 ± 517.5</td>
<td>214.8 ± 477.8</td>
<td>&lt; 0.01</td>
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<tr>
<td>Plasma norepinephrine (pg/ml)</td>
<td>848.8 ± 471.1</td>
<td>765.4 ± 450.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>vs. Baseline</td>
<td>-54 (-90)%</td>
<td>-88 (-121)%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Urinary catecholamines (mg/day)</td>
<td>0.450 ± 0.161</td>
<td>0.382 ± 0.131</td>
<td>&lt; 0.01</td>
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<tr>
<td>vs. Baseline</td>
<td>-20 (-42)%</td>
<td>-14 (-34)%</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>High-sensitive troponin T (ng/ml)</td>
<td>0.042 ± 0.064</td>
<td>0.028 ± 0.019</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>vs. Baseline</td>
<td>-51 (-65)%</td>
<td>-36 (-50)%</td>
<td>&lt; 0.01</td>
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Data are presented as median (inter quartile range).

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 ASV, O2 to some extent is effective for CSR.

Overnightbeneficialimpacts of adaptive servoventilation on cardiac overload, sympathetic nervous activity, and myocardial damage in chronic heart failure patients with cheyne-stokes respiration

P5792

Copeptin in hyponatremia and its relation to steroid hormone levels 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 interaction of renal function and other effects of volume regulation and Copeptin, the analytically accessible C-terminal fragment of AVP, was reported to indicate a worse prognosis in heart failure, but its interaction with hyponatremia and sodium disorders remains uncertain. Therefore, we aimed to investigate the neurohumoral abnormalities and their relationship to aldosterone and cortisol levels, renal function parameters and systolic blood pressure.

Methods: We analyzed data from n=926 patients from the Interdisciplinary Network Heart Failure Study (ISRCTN23325295) and the clinical follow-up of the Patients and methods: Plasma Nt-proBNP (Elecys, Roche) was measured on admission in patients admitted < 24h for acute MI. Patients with chronic atrial fibrillation or pace maker were excluded. The mean of standard deviation of RR intervals (SDNN), percentage of RR intervals with > 50ms variation (pNN50), square root of mean squared differences of successive RR intervals (rMSSD), and frequency domain parameters (total power (TP), high frequency and low frequency power ratio (LF/HPF)) were assessed by 24-h heart ECG monitoring at 5±2 days after MI onset.

Results: Among the 1018 patients included, median (IQR) Nt-proBNP value was 681 (159-2432) pg/ml. Patients with highest quartile of Nt-proBNP were older, more likely to be women, hypertensive, had higher admission heart rate, lower LVEF, but were less likely to be smokers. Highest Nt-proBNP quartile group had lower SDNN, LF/HPF and total power but similar pNN50 and rMSSD levels. Nt-proBNP levels was negatively associated with TP (r=-0.17, p<0.001), SDNN (r=-0.19, p<0.001), LF/HPF (r=-0.37, p<0.001), and LF (r=-0.29, p<0.001) but not HF (r=-0.43, p=0.172). Multiple regression analysis showed that plasma copeptin level remains predictive of LF/HPF (β<0.05; p=0.015), after adjustment for confounding (Beta-blockers, female, and age).

Conclusions: Our population-based study suggests the importance of NT-proBNP in predicting decreased HFV after acute MI. Moreover, our results highlight that high Nt-proBNP levels are associated with a decrease in the effects of the sympathetic system.
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 after adjustment 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 remodelling 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.

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 pmol/L) are referred for specialist cardiology assessment within a two week wait (2WW).

Method: 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 a BNP/2WW referral pathway in Oxford 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 67/86 (78%) of GP surgeries in the region. Of these 11 (5.2%) were high (BNP > 116 pmol/L) and referred for specialist cardiology assessment within a two week wait in the 2WW HF clinic. The final diagnoses after specialist assessment and echocardiography were recorded.

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 not referred.

The prognostic role of brain natriuretic and N-terminal pro-B-type natriuretic peptide 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.
come in acute coronary syndromes. Our aim was to evaluate the incremental prognostic value of the combination of these biomarkers in patients with myocardial infarction (MI).

Methods: We studied 522 patients admitted at our Coronary Care Unit with the diagnosis of acute MI (either ST or non ST segment elevation) within 12 hours of symptoms’ onset and included in our internal MI registry. From blood sample obtained on admission BNP, hemoglobin, white blood count, CRP, troponin I, plasma glucose and creatinine were determined. All patients underwent coronary arteriography and the left anterior descending artery (LAD) involvement along with the reocclusion status (complete or not) were recorded. Ejection fraction was estimated on admission with echocardiography. The primary endpoint was the composite of MI, stroke and death during a one-year follow-up period.

Results: The mortality rate at one-year follow-up was 11.3% (59 deaths) and the incidence of the composite end-point was 21.9%. Optimal values of BNP (356.5 pg/ml) and CRP (8.06 mg/L) for predicting the composite end-point were determined by maximum likelihood analysis.

Discussion: Our results suggest that combination of CRP and BNP plasma levels has an incremental prognostic value in the long term risk stratification of patients with acute MI.

First evidence of increased serotonin activity in Takotsubo cardiomyopathy

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Background: Takotsubo 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 norepinephrine 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 serotonergic activity during the acute phase of TTC.

Objective: To investigate evidence of serotonin release from patients with TTC in comparison with patients with blood aldosterone excess (AHO) and their associations with blood aldosterone (ALDO) and renin (REN) levels.

Methods and results: Plasma serotonin levels in 14 consecutive patients with TTC according to the “MayoClinic” 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 modifi-
cations. Troponin levels were higher in patients with MI than in patients with TTC (median Troponin level, 92.8 ng/ml [interquartile range, 11.2 to 21.6] vs. 2.4 ng/ml [interquartile range, 1.2 to 3.8] 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. 45% [interquartile range, 36 to 45] respectively; P=0.06). Troponin levels 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. 0.9 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.

Prognostic significance of plasma concentrations of C-terminal ET-1 precursor fragment in patients with suspected Chronic Heart Failure

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Background: Heart failure (HF) is characterised by endothelial dysfunction and impaired release of endothelin, a powerful vasoconstrictor that may contribute to cardiovascular function. We sought to describe the relationship of CTProET1, a stable fragment of pro-endothelin, to patient characteristics and prognosis in patients with suspected chronic HF.

Methods: Patients with suspected HF referred from the local community (population ~550,000) to a specialist clinic were invited to participate. Consenting patients underwent a systematic evaluation including prior medical history, medical conditions, signs, electro- and echocardiograms, standard haematology and biochemistry profiles and measurement of CTProET1 and amino-terminal pro-brain natriuretic peptide (NTproBNP).

Results: Of 2,689 patients referred, the median age was 72 years (IQR: 65 to 78), 79% were women, 1045 had left ventricular systolic dysfunction (LVSD), 420 had a major echo abnormality other than LVSD, 269 had no major echo abnormality but an NTproBNP >400 ng/L, (of whom 85 had atrial fibrillation and 29 had eGFR <30 min/ml and 555 had none of the above. Median (IQR) CTProET1 overall was 79 (61-108) pg/ml and for each of the four sub-groups was 86 (66-120), 84 (63-115), 97 (65-94), and 69 (58-92) pg/ml, respectively. The mortality rate at one-year follow up was 11.3% (59 deaths) and the incidence of the composite end-point was 21.9% (59 deaths) and the incidence of the composite end-point was 21.9% (59 deaths).

Discussion: By applying multivariate Cox regression analysis, elevated levels of CTProET1 turned out to be the only predictors of the composite end-point (HR=4.95, 95% CI 2.89-8.47, p=0.001). By applying multivariate Cox regression analysis, elevated levels of both CRP and BNP (adjHR=2.204, 95% CI 1.125-4.318, p=0.021), ejection fraction (adjHR=0.941-0.986, p<0.001), incidence of AF (adjHR=1.773, 95% CI 1.129-2.785, p=0.013), creatinine (adjHR=1.182, 95% CI 1.028-1.360, p=0.019) and glucose levels (adjHR=1.002, 95% CI 1.000-1.005, p<0.002) turned out to be the only predictors of the composite end-point.

Conclusions: Our results suggest that combination of CRP and BNP plasma levels has an incremental prognostic value in the long term risk stratification of patients with suspected chronic HF.

Magnetic resonance imagining, echocardiography and biomarker characterisation and neuro-hormonal correlates of early cardiac and arterial remodelling in abdominal obesity subjects

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Purpose: We investigated early changes in cardiac vascular structure and function involved in the progression to heart failure (HF) in healthy subjects with abdominal obesity and their association with blood aldosterone (ALDO) and renin (REN) levels. The contribution of obesity to the incidence of HF is increasing. This condition is associated with an activation of the renin angiotensin aldosterone system (RAAS) that may contribute to early changes in cardiovascular structure and function.

Methods: Asymptomatic subjects with AO and age and sex matched controls (healthy volunteers) underwent trans-thoracic echocardiography, magnetic reso-
nance imaging (MRI) (cardiac remodeling index (CRI) = LV mass/LV end diastolic volume); arterial compliance indexes (aortic pulse wave velocity and total arterial compliance (TAC)); and total peripheral vascular resistances (TPVR), carotid intima-media thickness (CIMT), pulse wave velocity (PWV) and ALDO, REN, and blood fibrosis biomarkers measurements.

Results: We enrolled 116 AO (body mass index: 37.1±3.4 kg/m²) and 53 con-
trols (24.3±2.0 kg/m²). Subjects with AO had higher ALDO (mean [range] 59 (33 – 106) vs. 34 (18 - 65) pg/ml, p<0.0001), LV mass (mean [standard deviation]: 97.25±24.64g, p<0.003), and CRI (mean ± standard deviation): 0.69±0.16 (p=0.004), but CIMT and PWV were unchanged. When adjusted for gender, i) there was a step-by-step decline in TAC between controls (mean±SEM: 2.10±0.06 mmHg/ml); subjects without CR (CR): (1.82±0.06 mmHg/ml) and subjects with CR (CR+) (1.42±0.09 mmHg/ml, p=0.005 for inter-group comparisons) and ii) TPVR were lower than in controls for CR- (14.7±1.05 mmHg/ml vs. 16.8±1.05 mmHg/ml, p=0.005) but not for CR+ subjects (17.5±0.7 mmHg/ml). In multivariate analyses, REN was significantly associated with LV mass (p=0.022) and CRI (p=0.006). Procollagen-III-N-terminal peptide was independently associated with diastolic dysfunction (p=0.038).

Conclusion: Decline in peripheral vascular resistance is the earliest detectable hemodynamic change in AO. When early CR is detectable in such subjects change in TPVR gives way to a decline in proximal arterial compliance. Early extracellular matrix remodeling is also detectable in AO and is related to diastolic dysfunction. Furthermore, CR was associated with REN, suggesting that renin
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 an out 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 value.

**Results:** 121 CHF patients at NYHA III/IV (60/55/16) were followed for 16±11 months in an outpatient clinic. Gr1 (60 patients) and Gr2 (61 patients) were well matched (age 69±4 vs. 68±1 years, respectively, p=NS). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]). During study period there was no significant difference between groups in overall mortality (respectively [p=NS]).

**Conclusions:** NT-proBNP-guided preemptive treatment of patients with CHF did not result in reduced overall and cardiovascular mortality, and did not decrease hospitalizations but significantly prevented admissions for ADHF. In our study, NT-proBNP-guided treatment was significantly more effective in Gr1 (NT-proBNP-guided therapy) by 55% (p=0.047). However, hospitalizations for acute decompensated heart failure (ADHF) were significantly reduced in Gr1 (NT-proBNP-guided therapy) by 55% (p=0.047).

**P5804 Apelin potentiates B-type natriuretic peptide-mediated vasodilation in health but not in heart failure**

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**Purpose:** The novel peptide apelin has vasodilator and inotropic actions and antinatriuretic effects. There is interest therefore in the therapeutic potential of apelin in heart failure (HF), especially as plasma apelin levels are reduced in HF. We investigated the effects of apelin on the vasodilator response to B-type natriuretic peptide (BNP), another cardioprotective neurohumoral of pathophysiological significance in HF. We did this in normal rabbits and rabbits with a well validated model of HF.

**Methods:** Mesenteric arteries (MAS) were obtained from normal (42 vessels/12 rabbits) and HF (37 vessels/12 rabbits) male New Zealand White rabbits. HF was induced by coronary artery ligation under general anaesthetic with sacrifice 8 weeks later. Segments of MA were mounted on a 4-channel myograph under physiological conditions. Vessels without intact endothelium were discarded. All vessels were pre-constricted with norepinephrine and cumulative concentration-response curves were constructed. BNP (1x10-9M - 3x10-6M) of the presence and absence of 30 minutes of preincubation with 1μM of apelin.

**Results:** The mean LVEF of the HF rabbits was 42.5±(SD 5.7)% by echocardiography (normal-70%). In normal vessels BNP produced modest concentration-dependent relaxation in the control MAS (max relaxation 14.3±SEM 6%) which was potentiated in the MAS pre-treated with apelin (max relaxation 35.0±SEM 7%, p<0.01). This potentiating effect was lost in HF vessels (max relaxation of 14.0±SEM 8% in control MAS vs 9.3±SEM 4% in MAS pre-treated with apelin, p=0.8).

**Conclusion:** Apelin enhances the arterial vasodilator action of BNP in normal rabbits but not in rabbits with HF. These data provide a new insight into the interactions of apelin and suggest that some cardioprotective properties of apelin are lost in HF.

**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 currently 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 work up. Easily available biomarkers for cardiac toxicity are desirable to support the treatment continuation decision.

**Methods:** Prospective pts with mRCC assigned for first-line treatment with sunitinib were analyzed for cardiac history. Monitoring included assessment of symptoms, ECGs 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:** 45 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 1594 pg/ml, IQR 996-4474) 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 therapy all but 1 pt could continue sunitinib without dose reduction, the pt with heart failure recovered on discontinued.

**Conclusion:** NT-proBNP is an easily assessed marker of cardiac toxicity. Low NT-proBNP may rule out cardiotoxicity in unspecific symptoms. 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:** Graft denervation in heart transplant recipients causes sinus tachycardia, occasionally requiring pharmacologic heart rate reduction. Currently, no long term data regarding effects of the novel II 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 after 36 months in 30 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. Median patient age was 53.3±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±8.8 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 peri-operative mortality.

Materials and Methods: We studied a sample of 632 patients referred for OHT from POLCARD-HF register (2003-2007). Firstly, we identified 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 values. (1) both markers not elevated, (2) elevated hsCRP, (3) elevated NT-proBNP, elevation, (4) elevation of both markers and calculated 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, SBP/DBP 103/67±15/11 mmHg, LVEF 22±8, serum Na 136±4 mmol/l, NT-proBNP 3942±5637 pg/ml, hsCRP 6.5±5.2 pg/ml. HFS by Aaronson 8±1. Using univariate regression analysis we confirmed that classical risk factors were independent predictors of EP in the whole group: HR (p<0.0001), SR (p<0.011), EF (p<0.0001), hsCRP (p<0.0001), NT-proBNP (p<0.0001) and serum Na (p=0.0001). Cut-off values for NT-proBNP and hsCRP established by ROC analysis were 2435 pg/ml and 2.45mg/l respectively. Analysis of Kaplan-Meier survival curves and frequency of events revealed that subgroup (1) had better prognosis compared to subgroup (2) - 13% vs 24% of patients reached EP (Chi2=8.5319; p=0.0035) and pendent predictors of EP in the whole group: NYHA (p<0.0006) and serum Na (p=0.0128) in subgroup (1) and Na (p=0.0128) in subgroup (2).

Conclusions: NT-proBNP and hsCRP elevation in combination could potentially be utilized as a prognostic tool for identification of highest-risk patients who require heart transplantation first and differentiation from those who can safely wait for the procedure. This new approach to risk stratification before OHT seems promising, although still needs to be further investigated.

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 (MVRsas) associated with a still high operatory 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 aorta 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 MVRsas 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. Pulse wave velocity (PWW) was determined in the descending thoracic aorta.

Results: Patients were divided into 2 groups:
- Group A, Follow up more than 10 years (mean age 56.6, SD 5.9)
- Group B, Follow up less than 10 years (mean age 56.7, SD 10.2)

Patients with follow up inferior to 10 years showed a wide range of PWW. 60% of patients had a stiff thoracic aorta (PWW>7m/s) versus 21% of patients with a follow up more than 10 years (10 to 30 years) (p=0.05). Only 7% of survivors more than 10 years had a stiffer aorta versus 36% of patients with a follow up less than 10 years. None of survivors more than 10 years had a PWW>9 m/s versus 33% of patients with a follow up less than 10 years.

Conclusions: Patients with a high aortic compliance have survived more than 10 years from the mitral valve replacement. MVRsas patient can be viewed as a special artificial population. In this population aortic compliance may be a decisive factor for long term survival.
Assessment of left ventricular volume, shape and function after surgical restoration of dyskinetic anterolateral 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 postinfarction left ventricular aneurysms. In this study we evaluated the potential of dual-source multi-slice computed tomography (MSCT) in the measurement of essential parameters: 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; age 67 ± 13 years, 29 male) with anterolateral left ventricular aneurysm underwent left ventricular restoration and were assessed by two-dimensional strain echocardiography and MSCT (Somatom Definition, Siemens) before and a short time after surgery (3 to 7 days). Sphericity index (SI) as short to long axis ratio, apical concavity 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 also 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 ± 140.2 ml to 200.9 ± 83.0 ml, LVEVS from 228.4 ± 117.0 ml to 135.3 ± 79.0 ml) and indexed LV volumes (LV-EDVI from 159.5 ± 70.7 ml/sqm to 103.2 ± 63.8 ml/sqm, mean change: -33.7 ± 17.0%; LV-ESVI from 116.5 ± 56.0 ml/sqm to 68.9 ± 37.0 ml/sqm, mean change: -39.0 ± 20.0%). Absolute mean diastolic aneurysm volume was 68.6 ± 67.0 ml with slight systolic increase to 72.1 ± 60.0 ml, demonstrating adverse volume shift. Indexed aneurysm volume showed the same tendency, with A-EDVI 34.4 ± 27.0% ml/sqm > 10.4 ± 14.0% ml/sqm (+ mean change: + 28.88%). Significant changes of diastolic ACI from 0.74 ± 0.15 to 0.63 ± 0.18 and systolic ACI from 0.92 ± 0.36 to 0.72 ± 0.20 showed a tendency towards more ellipsoidal LV shape after repair. Significant changes of diastolic SI from 0.62 ± 0.07 to 0.72 ± 0.11 may beexplained through shortening of the LV long axis after repair. No significant changes in the systolic SI were found.

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.

Heart failure syndrome in cardiovascular surgery; an old but still unresolved problem

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Objectives: Despite recent advances in surgical techniques and perioperative management, lung 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-hepatic syndrome in cardiac surgery patients.

Methods: Postoperative LD was defined as serum total bilirubin (Tbili) concentration of > 1.6 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 years) who underwent open heart surgery since 2007. (2) Next, to determine factors affecting recovery from LD, 97 postcardiac surgery patients who underwent ventilator 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. 2.1%, p < 0.001), postoperative renal failure (25.9% vs. 4.0%, p < 0.001), and respiratory complications (40.0% vs. 8.9%, p < 0.01). Multivariate analyses revealed preoperative 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 who developed LD went left ventricular restoration and recovered from liver dysfunction. Univariate analysis showed that postoperative Bilb, body weight, creatinine, hemodialysis, preoperative mechanical support, and right VAD, as well as post-operative ventricular assist index (CPB) on day 1 (r=0.53±3.7; 12.4±4.5 mmHg, p < 0.05), and Bilb on day 3 (r=26.4±6.4 vs. 15.1±9.7 ml/dl, p < 0.05) were higher in patients with reuniting LD. Multivariate analysis demonstrated that CPB on postoperative day 3 (odds ratio=1.32; p < 0.05) and Bilb 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 preoperative 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 CPV 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-oxidant) and BAX (pro-oxidant) 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 interrelations. Significant increases were detected in plasma levels of S100P (P = 0.027) and RAGE (P = 0.026) post- versus pre-surgery. A significant decrease was seen in plasma levels of S100A6 post-surgery (P = 0.0036) 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 = 0.606).

In CABG surgery with CPB, plasma levels of S100B and RAGE increase post surgery with a concomitant decrease in S100A6. There is a positive correlation between S100B and a negative correlation between S100A6 levels 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.
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 demonstrated a marked reduction of myocardial uptake of LCFA, while myocardial glycogen uptake is compensatorially increased, and are often accompanied by cardiomyopathy. However, the molecular mechanisms of CD36 in the myocardium remain unclear. Aim: To explore the pathophysiologic role of CD36 in pressure overload cardiomyopathy, we analyzed CD36 knockout (KO) mice at the baseline and under the pressure overload.

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% vs 85.7%, P<0.001). At 4 wks after TAC, KO showed significantly higher heart weight (HW) to tibia length (TL) ratio than that of WT (HW/TL mg/mm; 10.4±1.6 vs 8.6±0.8, P<0.001). 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/mm;13.9±5.7 vs 9.2±2.0, P<0.009, FS%;24.1±1.1 vs 34.9±3.0, P=0.0007), 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 1 wk after TAC, myocardial glucose uptake was enhanced in both KO and WT mice. The phosphorylation of AMPK was not different between KO mice with and corresponding WT mice, suggesting that even in the pathological condition, myocardial glucose uptake is compensatorially increased in KO mice and AMP to ATP ratio might not be different between KO and WT mice. KO with TAC showed enhanced phosphorylation of p70 ribosomal protein compared to WT with TAC. These data suggest the possibility that the loss of CD36 results in cardiac hypertrophy with systolic dysfunction in the pathological condition.

Conclusion: The LFCA transporter CD36 plays important roles regulating cardiac hypertrophy and function.

Direct renin inhibitor prevents ventricular remodelling and sudden arrhythmic death in mice with dilated cardiomyopathy

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Purpose: Progression of left ventricular (LV) remodelling 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 neuron-restrictive silencer factor 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/d 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). 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, ß-myosin heavy chain, transforming growth factor (TGF)-ß1, TGF-ß3, the inhibitor of metalloproteinase-1, and angiotensin converting enzyme (vs. vehicle; all 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 end diastolic pressure, and furthermore repressed incidence of ventricular arrhythmias during electrophysiological study in dnNRSF-Tg. Conclusion: Inhibition of RAS by aliskiren significantly repressed 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.

Circularizing dendritic cells decrease in patients with chronic heart failure but exhibit increased expression of Toll-like receptors

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Purpose: Immune activation and inflammation play an important role in pathophysiology and progression of chronic heart failure (CHF). While proinflammatory cytokines have extensively been studied, little is known about the pathophysiologic role of the cellular immunity in CHF. We aimed to assess the number of dendritic cells (DCs), the most potent antigen presenting cells, in patients with CHF and to evaluate their associations with markers of disease severity. To further elucidate the function of DCs we focused on their expression of Toll-like receptors (TLR) which are crucial for their activation.

Methods: The study population included 98 patients with CHF (age: 66±10 years, 77% male, N-terminal pro-B-type natriuretic peptide (NT-proBNP); 2748±995 pg/ml, 52% ischemic etiology) and 97 controls (NT-proBNP; 234±179 pg/ml). Flow cytometry was used to characterize circulating DCs defined by low expression of lineage cocktail and high expression of HLA DR. CD123 and CD11c were used for further identification of the myeloid (mDC) and plasmacytoid (pDC) DC subset. Cells are expressed as percentage of leukocytes. TLR 2 and 4 and intracellular TLR 9 were measured as mean fluorescence intensity (MFI). Mann-Whitney-U-test was used for the comparison between patients and controls. Associations between DC subsets and continuous variables were assessed using Spearman-Rho correlation coefficient.

Results: DCs (0.2±0.1% vs. 0.3±0.10% to 1.1 vs 34.9, p<0.004) as well as the mDC subset (0.1±0.01% vs. 0.18±0.09% to 1.1 vs 34.9, p<0.004) and the pDC subset (0.06±0.03% vs. 0.07±0.03%, p<0.03) were significantly lower in CHF patients than in controls. Expression of TLR 2 (3576±1566 MFI vs. 1895±818 MFI, p<0.001) and TLR 4 (270±176 MFI vs. 57±49 MFI, p<0.001) on mDCs were increased in the CHF group compared with controls while there was no significant difference for the expression of intracellular TLR9 on pDCs (p=0.86). Significant differences between patients with ischemic and non-ischemic etiology of CHF were neither found in pDCs (p=0.49) and their subsets (mDC:p=0.53, pDC:p=0.79) nor in the expression of TLR 2 (p=0.76) and 4 (p=0.61) on mDCs and TLR 9 (p=0.72) on pDCs.

Conclusion: CHF is associated with decreased circulating levels of both DC subsets irrespective of CHF etiology. Interestingly, both DC subsets showed an increased expression of TLR in CHF patients. These alterations of the cellular immune system might reflect an increased activation of the immune system which guides activated antigen-presenting cells into damaged tissue in CHF patients.

TGFBeta1-dependent apoptosis requires concomitant NO-release

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Background: The pro-apoptotic effect of TGF-ß1 requires an activation of eNOS. Activation TGFß1-receptors and/or increases of nitric oxide acutely increase the expression of the TGFß1-inducible early gene (TIEG1), TIEG1 controls bax mRNA expression. Based on these findings we hypothesized that a loss of eNOS-derived nitric oxide formation, as it is seen at early stages of heart failure, is not simply detrimental but also attenuates mitochondria-related cardiac apoptosis.

Method: We screened for eNOS-related NO-dependency of 32 well known heart failure-associated genes related to apoptosis, hyper trophy, stem cell mobilization, calcium handling, and fibrosis. To exclude species-specificity of our results we
Mitochondrial transhydrogenase: yin and yang of heart failure

Conclusion: In conditions of heart failure, eNOS expression is reduced. The data of this study support a species-independent regulatory mechanism, by which this loss of eNOS-derived NO attenuates the TGF-β1-mediated apoptotic program of cardiomyocytes.

Method and Results: To analyze the role of the NNT in cardiomyocytes under physiological, but also pathological conditions, we took advantage of a loss-of-function mutation in the Nnt gene in C57BL/6J (J-), but not C57BL/6N (N-). Moreover, we successfully knocked-out NNT in C57BL/6J mice, which were confirmed by PCR, Western blot and enzymatic assays. In isolated cardiomyocytes that were exposed to a physiological increase in workload (by β-adrenergic stimulation), mitochondrial Ca\(^{2+}\) uptake stimulated Krebs-cycle induced regeneration of NADP\(^{+}\), keeping its redox state constant. Under these conditions, loss of eNOS (J-J) led to an increased mitochondrial H2O2 formation (vs. J-N), supporting the relevance of the forward reaction of the NNT and its role in cardiomyocyte regeneration during physiological workload. In contrast, under conditions in which ADP-induced acceleration of NADH-coupled respiration over-whelmed Krebs cycle-induced regeneration of NADH (in isolated mitochondria or cardiomyocytes), the reversal of the NNT reaction was observed at the expense of NADPH, resulting in increased H2O2 formation. In isolated working hearts that were exposed to an acute increase of afterload from 80 to 120 mmHg for 15 min, reverse NNT-mediated NADPH oxidation resulted in oxidation of glutathione and peroxisorinexin by 25% and 45%, respectively, which was blunted 2.5- and 3-fold in J-mice lacking the NNT. Accordingly, 6 weeks after aortic banding (TAC), NNT-deficient J-mice were substantially protected from oxidative stress, cardiac fibrosis, LV dysfunction and decompensation in vivo.

Conclusions: While under physiological conditions, the forward NNT reaction regenerates NADPH, the reversal of the NNT reaction in response to pathological cardiac workload consumes NADPH to support NADH-coupled respiration at the cost of decreased antioxidative capacity. This represents a novel mechanism how increased cardiac afterload triggers mitochondrial ROS production that results in maladaptive remodelling.

Role of microRNA-133a in the regulation of angiotensinogen in experimental diabetic cardiomyopathy

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Objective: To study the potential role of microRNA (miR-133a) in diabetic cardiomyopathy.

Background: Increased fibrosis is present in the myocardium in diabetes mellitus (DM). At early stages, there is also an increased expression of Angiotensino-
Results: We compared Ca2+ handling proteins according to HF aetiology, ICM showed higher levels of calmodulin (27%, p<0.05), calcium (22%, p<0.05) and Ca2+-Calmodulin-dependent kinase II (CaMkIIb) nuclear isoform 96%, p<0.01) than control group. However, these proteins in ICM did not significantly increase. Furthermore, ICM showed a significant elevation in MEF2C (23%, p<0.05), and GATA4 (51%, p<0.05); also NFT1 (53%, p=0.01) was increased, producing the resultant translocation of this transcriptional factor into the nucleus. These results were supported by fluorescence and electron microscopy analysis. In addition, DCM only had a significant increase in GATA4 (52%, p<0.05). Correlations between NFT1 and MEF2C in both groups (ICM r=0.36 and DCM r=0.51, p<0.05) were found; only ICM showed a correlation between GATA4 and NFT1 (r=0.42, p<0.05).

Conclusions: This study shows an activation of Ca2+ handling machinery synthesis and their cardiac transcription pathways in HF, being more markedly increased in ICM. Furthermore, there is a significant association between MEF2, NFT1 and GATA4. These proteins could be therapeutic targets to improve myocardial function.

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 transformation of 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. We tested the role of cell-specific TGFβ signaling in these models, contrasting antibody-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 ( Corm) Tgfbr2 foxed mice) or with systemic injection of TGFβ-neutralizing antibody (NAB) were subjected to proximal LAD-ligation (MI) together with tachycardia in coronary ligated (TAC) patients. Outcome was assessed by echocardiography, staining for myocardial fibrosis, gene- and protein expression (qRT-PCR, immunoblot) and immunohistochemistry (SMA3D). 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 SMA3D activation was not suppressed with dominant non-CM SMA3D phosphorylation. TGFβ-activating kinase (TAK1), which is critical in pressure-overload, was not activated by ISO. Myocyte-derived Coll was not increased, while the fibroblast-specific marker periostin was significantly up-regulated with ISO.

While myocardial function and dilation was worse in the MI model compared to TAC and ISO, the Iso-bron area was virtually absent, as was SMAβ3 or TAK1 activation. Likewise, Coll or periostin expression was not changed. CM-Tgfbr2 knockdown did not alter function or fibrosis in this model.

Conclusion: ISO-induced myocardial fibrosis and mild hypertrophy. Hence, 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 TGFβ.

Conclusions: The chronic inflammatory remodeling of viable myocardium upon MI involves substantially less fibrosis and CM-related TGFβ signalizing seems to play a minor role.
Myocardial: M-EPO, M-EPOR, iron storage protein - ferritin (M-FR), iron acquisition protein - transferrin receptor (M-TIR), Iron Regulatory Protein 1 (M-IRP1) - by ELISA – ng/mg protein - expression; myocardial iron load - by Instrumental Neutron Activation Analysis, µg/g - were assessed in the explanted FH, compared to non-failing hearts (NHF n=11).

With regard to presence of anemia (by WHO), patients were divided into two subgroups: A+: n=11 and A−: n=22. Both subgroups: A+ vs A− vary with regard to Hct, Hb, but also to EPO (47.2±3.8 vs 28±3.0 mIU/L, p=0.0473 respectively), mPAP (39±9 vs 30±13, p=0.0530 mmHg), mPWP (30±8 vs 20±9, p=0.007 mmHg), Na+ (134±7 vs 139±4, p=0.0485 mmol/l). M-TIR was lower in A+ than in A− (LV =136±6 vs 218±13, p=0.0446) and (RV−130±9 vs 195±13), p<0.0688), without differences in M-EPO/M-EPOR/M-IRP1 and iron load. In LV, A+ subgroup by Pearson analysis we found correlation between M-IRP1 and M-EPO (r=0.7, p=0.0107) and M-EPOR (r=0.79, p=0.010) respectively). In the failing LV M-EPO/EPOR expression seems to be connected with regulatory protein M-IRP1.

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Background: Myocardial lipid content (MYLC) and yellowish ventricular ejection fraction (EF) are inversely correlated in heart failure patients with type 2 diabetes (HF-T2D). 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.

Purpose: To investigate the correlation between changes in MYLC and SMLC in HF-T2D patients.

Methods: Fifteen HF-T2D patients (EF<45%) underwent 8 hours of high (intralipid+heparin) and low (hyperinsulinaemic euglycemic 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(mean±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=0.63 (high FFA)). SMLC and the level of insulin resistance (HOMA-IR) correlated positively in both study arms (correlation coefficient r=0.02, p=0.02, (low FFA); 0.30, p=0.017, (high FFA)) whereas no association was found between MYLC and HOMA-IR.

Conclusion: In HF-T2D 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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Myocardiac 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 statistically significant.

Results: There was a reduction in the in the ejection fraction (EF) in echocardiograms performed at 2 weeks, in WT-diabetic (WT-D) 51.3±2.7 vs. p=0.003 and OPN KO mice 48.2±2.0, p=0.003 compared to control mice. Similarly, left ventricular systolic volume (LVESV) and left ventricular diastolic diameter (LVEDV) An improvement in EF was observed in the KO-D group at 4 weeks when compared to WT-D (59.2±6.7 vs 51.4±6.8 respectively). At 8 weeks, the WT-D group had a greater posterior wall thickness (1.11±0.06 vs 1.01±0.04), larger LVEDV as well as a larger LVEDV compared to KO-D (P<0.05) there was no difference in EF at 8 weeks (WT-D=51.4±4.6 versus KO-D=53.3±4.6). ECG readings indicated smaller mean SR and R amplitude in the WT-D group when compared to KO-D at 8 weeks (P<0.05). ECG intervals were prolonged in the WT-D group but not in the KO-D. TUNEL-staining assay revealed an increased cardiac myocyte apoptosis in WT-D compared to KO-D (0.51±0.07 vs. 0.02±0.09; respectively P<0.017) as well as fibrosis (KO-D 0.08±0.01 vs. WT-D 0.10±0.06 with P value of 0.023).

Conclusion: Lack of osteopontin expression is associated with an earlier recovery of systolic dysfunction in a diabetic cardiomyopathy model.
Background: A novel strategy combining the angiotensin receptor blocker (ARB) Valsartan (VAL) with a neprilysin inhibitor (NEPi) to augment beneficial endoge-
nous 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 NEPi 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 NEPi prodrug AHU-377 (AHU), and its active metabo-
lite, LBQ-657 (LBQ). Drugs were used separately and in combination. [3H]proline-
incorporation and [3H]uridine-incorporation were used to assess collagen produ-
tion and protein expression, respectively. Assays were run in triplicates and repeated 3-4 times.

Results: In triplicate, AHU had no effects in either cell type (not shown). Addition of 10 mM LBQ enhanced the inhibitory effects of VAL on car-
diac fibrosis and hypertrophy at each dose compared to VAL alone. In NCF, the highest dose of LBQ dose afforded complete inhibition of AngII-induced collagen accumulation.

Cardiac effects of combined ARB+NEPi

<table>
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<th>VAL dose (mM)</th>
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<td>144±17</td>
<td>124±15</td>
<td>112±14</td>
</tr>
</tbody>
</table>

Data displayed as % of unstimulated control (+100%). **p<0.001 vs unstimulated control.

Conclusions: Our data show that the combination of ARB and NEPi augments the anti-fibrotic and anti-hypertrophic effects mediated by ARB alone. These novel findings and recent promising clinical data support further study of combined ARB and NEPi inhibition (ARNi) in cardiovascular disease.

Influence of heart failure on nuclear organization and protein expression in human hearts

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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 is-
chemic 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 al-
terations remains unknown. Therefore we wanted to explore if changes in gene expression associated with NCT occur in human explanted cardiomyocytes.

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 human controls (CNT). Genome-wide gene expression was determined using Affymetrix Human Gene 1.0 ST arrays. Background correction, normalization, probe summarization was done with Partek Genomics Suite software using MA probeset algorithm.

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 CNT when compared with human CNT. XP01 (exportin-1 gene) was up regulated in both groups of patients in accordance with previously described 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. XPO1, related to nucleocytoplasmic transport, was up regulated in both 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 associated with NCT occur in human explanted cardiomyocytes.

Hepcidin: a key regulator of iron homeostasis in advanced heart failure

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Correction of iron deficiency with the use of iv iron supplementation in patients with heart failure (HF) with/without anemia seem to produce promising results. How-
ever, 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 Results: Study group 33 patients, left/right ventricle (LV/RV) (LVEDV 245±84 ml; LVEF 28±11%; RV 32±10 mm), NT-
proBNP (546±461 pg/ml), TNF-alpha (15±8.7 pg/ml), hsCRP (0.72±0.99 mg/dl). Serum iron homeostasis assessment: iron, FR, TR,TSAT, sTfr, sTfr/logTBTC, UIBC, EPO, Prohepcidine (HEP). Myocardial M-Iron (Intru-
mental Neutron Activation Analysis, μ/g), F-R, sTfr-M (ELISA – ng/mg protein) in the explanted failing hearts (FH), compared to non-failing hearts (NFI n=11).

In the whole group out of all serum and myocardial variables Pearson correlation found HEP to correlate with TBTC (r=0.40, p=0.0033), UIBC (r=0.40, p=0.0039), TNF-alpha (r=0.42, p=0.0044) and creatinine (r=0.42, r=0.0246). Bas-

Based on TSAT, patients were divided into two subgroups: IR deficiency for ery-
thropoietin therapy (TSAT<15%; n=11) and without IR deficiency (TSAT>15%; n=22).

In the whole group out of all serum and myocardial variables Pearson correlation found HEP to correlate with M-Iron (r=0.84, p=0.0190), LVEDV (r=0.64, p=0.0346), and creatinine (r=0.56, p=0.0703).

However the stepwise regression analysis, M-Iron (RV) (r=0.75, p=0.0538), was the only predictor for HEP levels.

Conclusions: In HF patients HEP levels are related to inflammation (TNF alpha) and renal function (creatinine). HEP is associated with serum IR transport (sTfr-M, UIBC). In reduced serum iron group, M-Iron was the only predictor for HEP levels.
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% O2 and 90% N2).

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 vasodilatation 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 vasodilatation in controls (P=0.96). 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 nucleocytoplasmic 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.