NOVEL ASPECTS ON PROGNOSIS IN HYPERTENSION

Relation between blood pressure lowering therapy and cardiovascular events and mortality in hypertensive patients with coronary artery disease and type 2 diabetes: the HIJ-CREATE sub-study

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Purpose: To explore the optimal systolic blood pressure target in hypertensive patients with coronary artery disease (CAD) and type 2 diabetes in the subsity of the HIJ-CREATE trial.

Methods: HIJ-CREATE was a multicenter, prospective, randomized, controlled study that compared the effects of candesartan-based therapy with those of non-ARB-based standard therapy on MACE in 2,049 hypertensive patients with angiographically documented CAD. Of the 2,049 participants, 780 (38.1%) were complicated with type 2 diabetes. In both groups, titration of antihypertensive agents was performed to reach the target blood pressure (BP) of <130/85 mmHg. The primary endpoint was the time to first major adverse cardiac events (MACE). In accordance with endpoint events in addition to biochemistry tests and office BP was determined during the scheduled 6, 12, 24, 36, and 60 month visits. Achieved BP were defined as the mean value of systolic BP in patients who did not meet with MACE and the mean value of systolic BP prior to MACE in those who met with MACE during follow-up.

Results: During a median follow-up of 4.2 years (follow-up rate of 99.6%), the primary outcome occurred in 259 (33.2%) diabetic patients and in 293 (23.1%) non-diabetic patients (p < 0.0001). The participants were divided into equal quartiles based on the mean systolic BP during follow-up. The relationships between achieved systolic BP and the incidence of MACE did not follow J-shaped curves in both groups (Figure).

Conclusions: The present study suggests that the excessive BP lowering regimen of the contemporary era causes no harm even in high risk population. Nonetheless, along with BP lowering therapy, the establishment of an optimal management strategy for hypertensive CAD patients with diabetes is essential.

The effect of visit-to-visit variability in blood pressure on stroke and coronary events in the TNT, IDEAL and CARDS trials

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Purpose: It has been proposed that visit-to-visit variability in systolic blood pressure (SBP) predicts CV risk independently of mean SBP. This study assessed the association between visit-to-visit variability in BP and the risk of CV events (CVE) among high-risk patients in the TNT, IDEAL and CARDS trials, and investigated whether BP and BP variability contributed to differences in clinical benefits observed with different statin treatment regimens.

Methods: One hundred and thirty-four patients (93 men, mean age 70±11 years) with hypertension underwent MDCT for evaluation of coronary artery disease. MDCT analysis focused on the presence of plaques, the degree of stenosis, and the plaque characteristics. Traditional parameters included Framingham risk score (FRS), carotid intima-media thickness (IMT), and left ventricular mass index (LVMi).

Results: During a mean follow-up of 3.3 years, ACS events occurred in 10 patients. In the multivariate analysis, the number of low attenuation plaque (LAP) was identified as an independent predictor of ACS events (p < 0.001). Case examples are presented in Figure. Curved planar reconstruction image of right coronary artery demonstrated the presence of LAP (arrows) (Figure A), which developed ACS event 3 years after MDCT examination (Figure B). Increased events rate was observed in patients with ≥2 LAP compared with those without LAP (p < 0.001) (Figure C). There were no significant differences between patients with and without ACS events in the FRS, carotid IMT, LVMi, and any of the laboratory parameters.

Conclusions: We demonstrated that LAP on MDCT predicted more accurately future ACS events in patients with hypertension than traditional parameters.

Pulse wave velocity as independent predictor of stroke in patients with essential hypertension: data from a Greek 6-year-follow-up study

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Purpose: Although arterial stiffening is related to atherosclerosis progression, its prognostic role in cerebrovascular events in hypertension is not fully elucidated. The aim of the present study was to assess the prognostic role of arterial stiffness for the incidence of stroke in a cohort of essential hypertensive patients.

Methods: We followed up 1128 essential hypertensives (mean age 56.1 years, 587 males, office blood pressure (BP) ≥144/91 mmHg) free of cardiovascular disease for a mean period of 6 years. All subjects had at least one annual visit and at baseline underwent blood sampling for assessment of metabolic profile and arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior BP). The distribution of visit-to-visit variability in BP and evaluate any impact of these BP parameters on the treatment effect in these trials.

Results: Vis-à-vis variability in SBP and diastolic blood pressure (DBP) were significant risk factors for stroke and coronary events after adjusting for treatment (Table) and/or other BP parameters (data not shown). The treatment effect (atorvastatin 80 mg [ATV 80] vs ATV 10 in TNT; ATV 80 vs simvastatin 20-40 mg in IDEAL; ATV 10 vs placebo in CARDS) for reducing risk of stroke (HR 0.81, 95% CI 0.69-0.945) and coronary events (HR 0.81, 95% CI 0.74-0.88) was not affected by adjustment for SBP or DBP variability or other BP parameters.

Conclusions: Higher visit-to-visit variability in BP is associated with significantly increased CV risk. The clinical benefit seen with intensive atorvastatin therapy in TNT and IDEAL, or atorvastatin therapy vs placebo in CARDS, in reducing CVE in high-risk patients is not mediated through reduction in BP or BP variability.

Low attenuation coronary plaque on multidetector computed tomography predicts three-year acute coronary syndrome events in patients with hypertension

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Purpose: Arterial hypertension is an established risk factor for acute coronary syndrome (ACS). Multidetector computed tomography (MDCT) is an accurate and less invasive technique for assessment of the degree of coronary artery lumen narrowing and characterization of coronary atherosclerosis. We therefore aimed to investigate the predictive power of MDCT for ACS events and compared with traditional parameters in patients with hypertension.

Methods: One hundred and thirty-four patients (93 men, mean age 70±11 years) with hypertension underwent MDCT for evaluation of coronary artery disease. MDCT analysis focused on the presence of plaques, the degree of stenosis, and the plaque characteristics. Traditional parameters included Framingham risk score (FRS), carotid intima-media thickness (IMT), and left ventricular mass index (LVMi).

Results: During a mean follow-up of 3.3 years, ACS events occurred in 10 patients. In the multivariate analysis, the number of low attenuation plaque (LAP) was identified as an independent predictor of ACS events (p < 0.001). Case examples are presented in Figure. Curved planar reconstruction image of right coronary artery demonstrated the presence of LAP (arrows) (Figure A), which developed ACS event 3 years after MDCT examination (Figure B). Increased events rate was observed in patients with ≥2 LAP compared with those without LAP (p < 0.001) (Figure C). There were no significant differences between patients with and without ACS events in the FRS, carotid IMT, LVMi, and any of the laboratory parameters.

Conclusions: The present study suggests that the excessive BP lowering regimen of the contemporary era causes no harm even in high risk population. Nonetheless, along with BP lowering therapy, the establishment of an optimal management strategy for hypertensive CAD patients with diabetes is essential.
PWV was split by the median (8.1 m/sec) and accordingly subjects were classified into those with high (n=566) and low values (n=562). Stroke was defined as rapid onset of a new neurological deficit persisting at least 24 hours unless death supervened confirmed by computed tomography and magnetic resonance angiography and/or cerebrovascular angiography findings.

**Results:** The incidence of stroke over the follow-up period was 2.03%. Hypertensives who had stroke (n=23) compared to those without stroke at follow-up (n=1105) were older at baseline (63±8 vs 55±10 years, p=0.015), had higher office BP levels (155±13 vs 143±17 mmHg, p=0.018) and prevalence of high PWV levels (67% vs 43%, p=0.021). No difference was observed between hypertensives with stroke and those without stroke with respect to baseline renal function and lipid levels (p=NS for all). By univariate Cox regression analysis it was revealed that high baseline PWV levels predicted stroke (hazard ratio=1.307, p=0.014). Moreover, in multivariate Cox regression model, baseline age (hazard ratio=1.098, p=0.03) and PWV (hazard ratio=1.125, p=0.017) but not baseline office BP levels turned out to be independent predictors of stroke.

**Conclusions:** In essential hypertensive patients, PWV predicts future development of stroke, independently of age and office BP. These findings support that PWV constitutes a potent prognosticator of cerebrovascular events and its estimation is essential in order to improve risk stratification in hypertension.

### Prediction of cardiovascular events and all-cause mortality with brachial-ankle pulse wave velocity: a systematic review and meta-analysis of cohort studies

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**Purpose:** Brachial-ankle pulse wave velocity (baPWV) is increasingly recognized as a surrogate end-point for cardiovascular (CV) disease. We performed a meta-analysis of all longitudinal cohort studies for determining the ability of baPWV to predict risk of CV events and all-cause mortality.

**Methods:** The MEDLINE, Cochrane and EMBASE databases, and reviewing reference lists from retrieved articles and abstracts from large international cardiovascular vascular conventions were searched until January 2012. Longitudinal cohort studies that reported relative risk (RR) estimates with 95% confidence intervals were included. Reviewers extracted data independently and summary estimates of association were obtained using a fixed- or random-effects model. Risk estimates between subgroups were compared with an interaction test.

**Results:** Of the 17 studies included (8,217 participants, mean follow-up 3.37 years), 14 reported results on total CV events (5,406 individuals), 6 on CV mortality with brachial-ankle pulse wave velocity: a systematic review and meta-analysis of cohort studies. PWA-derived central systolic BP was closer to measured pressure (2.70mmHg lower; SE=1.18) compared to conventional BP (8.03mmHg higher; SE=2.13). The use of surrogate measures for central artery blood pressure (BP) may significantly increase the accuracy of routine blood pressure measurements and potentially provide a better understanding of cardiovascular disease risk. The Seven Countries Study is one of the landmark epidemiological studies that encompassed 12 cohorts in 7 countries with a total of over 10.000 participants (992) had a 35 years' survival, while for those with hypertension, 26.5% of the 573 participants with hypertension at entry, 92.7% had a 23 years' survival (logrank=76.067, p<0.001). In those who had hypertension, but also carried a burden of family history of hypertension (118 participants), survival was 24 years for 93.2% of the deceased, while for those who were free of parental hypertension (124 participants), survival was 30 years for 74.2% of the deceased. When CAD mortality has been additionally looked into, 24.1% of the hypertension-free participants (992) had a 35 years survival, while for those with hypertension, 26.5% of the 573 participants had a 33 years survival.

**Conclusion:** In the Serbian cohorts of the Seven Countries Study, as a result of the 40 years follow up, we have shown that participants who were hypertension-free at entry, had a longer life expectancy, both for overall and CAD mortality – 4 and 2 years, respectively, while for those who had hypertension and whose family history was also remarkable for hypertension, survival was shorter for 6 years.

### Influence of family history of hypertension and hypertension per se on overall and cardiovascular mortality in the Seven Countries Studies: the 40 years follow up results

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**Purpose:** The Seven Countries Study is one of the landmark epidemiological studies that encompassed 12 cohorts in 7 countries with a total of over 10.000 men in a follow up going beyond 4 decades with a response rate nearing 95% worldwide. Its meticulously detailed design and systematic follow up, enables us to assess different aspects of the presence and impact of traditional risk factors on a myriad of outcomes. In this particular case, we sought to determine influence of family history of hypertension and hypertension per se on overall and coronary artery disease (CAD) mortality.

**Methods:** All subjects enrolled in the 3 Serbian cohorts of the Seven Countries’ Study, were men aged 40-59 years at entry (1962-1964) who were subsequently followed every 5 years.

**Results:** Of 1566 men, aged 48.53 years, 1298 deaths of known cause (82.9%) were available for further analysis, while data on presence of hypertension and family history of hypertension was available for all. Looking at overall mortality, 992 participants were hypertension free at entry, out of which 82% were deceased at the closure of the 40 years’ follow up, with 27 years’ survival; while of the 573 participants with hypertension at entry, 92.7% had a 23 years’ survival (logrank=76.067, p<0.001). In those who had hypertension, but also carried a burden of family history of hypertension (118 participants), survival was 24 years for 93.2% of the deceased, while for those who were free of parental hypertension (124 participants), survival was 30 years for 74.2% of the deceased. When CAD mortality has been additionally looked into, 24.1% of the hypertension-free participants (992) had a 35 years survival, while for those with hypertension, 26.5% of the 573 participants had a 33 years survival.

**Conclusion:** In the Serbian cohorts of the Seven Countries Study, as a result of the 40 years follow up, we have shown that participants who were hypertension-free at entry, had a longer life expectancy, both for overall and CAD mortality – 4 and 2 years, respectively, while for those who had hypertension and whose family history was also remarkable for hypertension, survival was shorter for 6 years.
Central blood pressure: a possible powerful predictor of the development of hypertension

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Aims: Vascular mechanisms are known to have vital roles in the development of hypertension. We examined whether the central aortic systolic blood pressure, a marker of the function in systemic arterial tree, might be a more powerful predictor of the development of hypertension as compared with the brachial-ankle pulse wave velocity (baPWV), a marker of stiffness in large to middle-sized arteries.

Methods and Results: In 1268 Japanese men without hypertension (43.6 ± 8.9 years old), the relationships of the baPWV and second peak of the radial pressure wave form (SP2) measured at the first examination with the presence of hypertension at the second examination (after 3 years’ follow-up) were examined. Hypertension was detected at the second examination in 154 men. Estimated areas under the curve to predict the presence of hypertension at the second examination were as follows: brachial-ankle PWV at the first examination = 0.716 and SP2 at the first examination = 0.843. The best cutoff point of the baPWV and SP2 for predicting the development of hypertension than a baPWV of >12.7 m/s, independent of other covariates including the first peak of the radial pressure waveform. The net reclassification index of this cutoff point of SP2 for predicting the development of hypertension was 0.211 (p = 0.001).

Conclusion: In middle-aged Japanese men without hypertension, SP2 may be a more powerful predictor of the development of hypertension than the baPWV, independent of the conventionally known risk factors for the development of hypertension.

N-terminal fragment of brain natriuretic peptide predicts vascular health and subclinical atherosclerosis: results from MEHLP study

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Background: Evaluation of subclinical atherosclerosis and vascular health have been used to predict cardiovascular events. Several indexes have been evaluated, i.e. coronary artery calcium score (CACS) by computed tomography scan (CT), intima-media thickness (IMT) of common carotid artery and ascending aorta dilatation (AAD) by echocardiography. Brain natriuretic peptide (BNP) and its metabolite, N-terminal fragment of BNP (NTproBNP), might reflect vascular pathophysiology, beyond heart involvement.

Methods: The MEHLP study is a screening study aimed to evaluate the amount of cardiovascular subclinical pathology in an asymptomatic general population. To aim the population were adults aged 45 years (1474 people, 61 ± 14 years, m±SD, males 48%, left ventricular ejection fraction 58 ± 9%, cardiac mass index 118 ± 42 mg/m²) from the community of Montignoso, Massa, Italy, was screened with biohumoral evaluation comprehensive of NT-proBNP, CACS assay by thoracic CT, IMT and AAD (the latter in 850subjects) by echography.

Results: Diabetes, hypertension and hypercholesterolemia were present in 11%, 41% and 38% of subjects, respectively; 13% were actual smokers, 31% past smokers. Median NT-proBNP was 59 ng/L (IQR range 33-101), CACS, IMT (biateral sum) and AAD were, respectively, 126 (± 212) U.A., 1.6 (± 0.3) mm and 32.4 (± 3.4) mm, with 11%, 15% and 4% of people showing CACS, IMT and AAD respectively higher than 400 U.A., 2 mm and 40 mm. CACS > 400 U.A., IMT > 2 mm and AAD 40 > mm were all predicted at ROC analysis by plasma NT-proBNP levels (AUCs 0.589, 0.591, 0.564 respetively. p < 0.05 for all). NT-proBNP was higher in patients with a) CACS > 400 U.A. (64, 42-128 vs. 57, 32-98, p < 0.01), b) IMT > 2 mm (72, 38-139 vs. 59, 32-95, p < 0.01), c) AAD 40 > mm (65, 36-171 vs. 59, 33-99, p < 0.05), despite no differences in left ventricular ejection fraction, nor in cardiac mass; this findings were confirmed in the subset of hypertensives, while not in subject with diabetes, hypercholesterolemia, or with past/present smoking habit.

Conclusions: NT-proBNP level, within the upper normal range, predicts subclinical coronary atherosclerosis and vascular health, namely in asymptomatic hypertensive subjects, with no relation with heart structural and functional involvement, possibly reflecting a vascular source of production and secretion.

Selective serotonin reuptake inhibitors exert a negative effect on peripheral wave reflections

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Purpose: In view of the high likelihood that hypertensives will have comorbid anxiety and depression, all hypertensives should be screened for concurrent psychiatric illnesses and treatment. We hypothesized that there is a relationship between the administration of selective serotonin reuptake inhibitors (SSRIs) and arterial stiffness, a hallmark of the cardiovascular aging process.

Methods: We studied 210 consecutive untreated stage I-II essential hypertensive subjects (aged 62±9 years, 110 female, office blood pressure (BP) = 163±91 mm Hg). The patients were divided into group A (n=83), those receiving SSRIs and group B (n=127), those without taking any antidepressant therapy. Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (c-f PWV) by means of a computerized method (Complior SP). Venous blood sampling was performed for the estimation of routine metabolic profile.

Results: The two groups did not differ regarding age, gender, office systolic/diastolic BP as well as serum glucose and triglycerides levels (93±9 vs 84±7 mg/dl and 128±8 vs 119±9 mg/dl, respectively. p=NS in all cases). Group A was characterized by increased levels of body mass index (32.4±3 vs 29.2±4 kg/m², p=0.015) and elevated cholesterol plasma levels compared to group B (231±32 vs 220±30 mg/dl p=0.05). Group A compared to group B exhibited significantly increased c-f PWV (8.4±0.3 vs 7.2±0.5 m/sec, p=0.02) and this difference remained significant after adjustment for confounders (p=0.03). In the SSRI treated hypertensives, c-f PWV was correlated with age (r=0.35, p=0.015) and office systolic BP (r=-0.33, p=0.02), while no significant correlation was demonstrated with cholesterol levels (p=NS).

Conclusions: The administration of SSRIs exerts an incremental effect on arterial stiffness, thus accelerating the vascular aging process.

Renin-angiotensin aldosterone system gene polymorphisms and their association with vascular impairment in patients with essential hypertension

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Purpose: The angiotensinogen (M235T) and aldosterone synthase (CYP11B2) gene polymorphisms have been positively associated with vascular properties. Therefore, in the present study we examined whether these variants affect carotid-femoral pulse wave velocity (cf-PWV), flow mediated dilation (FMD), ultrasound measurement of the C-IMT, augmentation index, ankle-brachial index and plasma aldosterone by means of mass spectrometry.

Methods: The study population consisted of 318 untreated essential hypertensives and a control group, consisted of 193 matched subjects. cf-PWV, FMD, ultrasound measurement of the C-IMT, augmentation index and ankle-brachial index were evaluated. The gene mutations frequencies were determined using polymerase chain reaction (PCR) technique. Serum cystatin-C levels and inflammatory biomarkers were measured by the ELISA method.

Results: TT homozygotes had significantly lower FMD compared with M allele carriers (p<0.05). c-IMT was correlated with age (r=0.35, p=0.015) and office systolic BP (r=-0.33, p=0.02), while no significant correlation was demonstrated with cholesterol levels (p=NS).

Conclusions: The administration of SSRIs exerts an incremental effect on arterial stiffness, thus accelerating the vascular aging process.

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similar results were obtained for hypertensives, though without reaching statistically significant (p=0.07). Moreover, after adjustment for co-variables, cystatin-C levels correlated significantly with PWV values both in total (r=0.27, p<0.03) and in hypertensive populations (r=0.23, p=0.0008). Interestingly, in unvariable analyses, increased levels of cystatin-C (above 75th percentile) correlated with higher PWV values (p=0.0018).

Conclusions: We have shown that TT homozygotes had significantly lower FMD in controls and c-IPWV was higher in TT homozygotes compared with MM+MT genotypes in hypertensive patients. In addition, we have observed higher values of IMT in -344TT homozygosity, in the group of hypertensives, while T allele carriage was significantly associated with higher prevalence of atherosclerotic plaques in the study population. Our results suggest that angiotensinogen genotypes are associated with arterial stiffness, whereas CYP11B2 promoter variant potentially constitutes a marker of subclinical atherosclerosis in untreated hypertension.

7397 Insulin resistance is associated with increased large artery stiffness in normotensive healthy adults

Aim: At present there is limited evidence on the relationship between insulin resistance (IR) and measures of large artery stiffness (AS) and wave reflections in normotensive healthy adults. Aim of the present study was to explore this issue in 90 normotensive (Systolic)<130 mmHg, DBP<80, diastolic (D) BP 69.6±7.7 mmHg), normoglycemic, non-obese, otherwise healthy adults (mean age 48.1±10 yrs, 50% female).

Methods: IR was assessed with HOMA-Index and subjects were classified into tertiles of this index. Hemodynamic indices by tertiles of HOMA index values of IMT in -344TT homozygosity, in the group of hypertensives, while T-allele carriage was significantly associated with higher prevalence of atherosclerotic plaques in the study population. Our results suggest that angiotensinogen genotypes are associated with arterial stiffness, whereas CYP11B2 promoter variant potentially constitutes a marker of subclinical atherosclerosis in untreated hypertension.

Conclusions: We have shown that TT homozygotes had significantly lower FMD in controls and c-IPWV was higher in TT homozygotes compared with MM+MT genotypes in hypertensive patients. In addition, we have observed higher values of IMT in -344TT homozygosity, in the group of hypertensives, while T allele carriage was significantly associated with higher prevalence of atherosclerotic plaques in the study population. Our results suggest that angiotensinogen genotypes are associated with arterial stiffness, whereas CYP11B2 promoter variant potentially constitutes a marker of subclinical atherosclerosis in untreated hypertension.

7398 Multidisciplinary cardiac rehabilitation and survival in The Netherlands
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Purpose: This study assessed the effects of multidisciplinary cardiac rehabilitation (CR) on survival in a large cohort of patients with coronary artery disease in The Netherlands.

Methods: The cohort consisted of persons insured with Achmea, a health insurance company in the Netherlands covering approx. 20% of the Dutch population (3.3 million insured persons). All patients with an acute coronary syndrome (ACS) with or without ST elevation and patients that underwent coronary revascularization in the period 2007-2010, based on insurance claims, were included. Patients were categorized as having received CR when an insurance claim for CR was made within the first 180 days after the cardiac event or revascularisation. Properly scored weighting was used to control for confounding by indication.

Results: A total of 35,919 patients were analyzed, of which 11,014 (30.7%) used CR. Median follow-up time after CR was 19.3 months (min. 0 months, max. 42 months). Crude mortality rates during the study period were 2.6% (287 patients) for CR users and 8.7% (2,160 patients) for nonusers (adj. HR 0.68, p<0.001). The table shows mortality rates among different patient categories. There was a non-significant difference (p=0.14) in survival between CR users receiving physical therapy (adj. HR 0.62) and CR users not receiving physical therapy (adj. HR 0.74).

Mortality rates in CR users and non-user

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<thead>
<tr>
<th>Mortality rates in CR users (%)</th>
<th>Mortality rates in non-users (%)</th>
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<tr>
<td>Crude mortality rates for CR users (%)</td>
<td>Crude mortality rates for non-users (%)</td>
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<td>Adj. HR</td>
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<tr>
<td>CABG valve surgery</td>
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<td>ACS without ST elevation</td>
<td>20.5</td>
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<td>Total</td>
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CR = cardiac rehabilitation, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, ACS = acute coronary syndrome.

Conclusions: Among patients with an acute coronary syndrome and/or coronary revascularization in The Netherlands, the use of multidisciplinary CR was associated with a survival benefit of 32%.

7399 Cardiovascular rehabilitation after a first acute coronary syndrome and the risk of recurrence and death in patients from the French MONICA registries
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Purpose: Cardiovascular rehabilitation following the occurrence of an acute coronary syndrome (ACS) has become more and more commonly used over the past years. However, differences still remain in prescription rates, depending on age, gender or the severity of the event. The aim of this work was to assess the prognostic influence of rehabilitation after ACS in the current medical practice.

Methods: Our study was based on 2008 data from the French MONICA population-based registry which collects all cases of ACS occurring in people aged 35-74 in 3 French areas located in North, North-Eastern and South-Western France. The population consisted of 1689 consecutive hospitalized ACS, after exclusion of those who died in the first 28 days of follow-up. The relationship between prescription of cardiovascular rehabilitation and composite outcome (ACS- recurrence or death) was analyzed using Cox models adjusted for living area, age, number of diseased vessels, diabetes, cardiovascular treatments and delays between symptoms and the first medical care.

Results: There were 171 ACS-recurrences or deaths during a median follow-up of 18.1 months. The population consisted of 23.6% of women. The rate of cardiac rehabilitation was significantly higher in men than in women (36% vs. 26%, p<0.0001) and decreased with age. Multiivariate adjustment the risk of composite outcome occurrence was identical in men and women for STEM1 but higher in women for UA/NSTEMI [adjusted HR 1.75, 95% confidence interval (1.10 to 2.77)]. Rehabilitation was associated with a decrease of ACS-recurrences and deaths whatever the definition of ACS (global adjusted HR 0.48, (0.32 to 0.73)). However a significant interaction between rehabilitation and gender has been found in UA/NSTEMI (p=0.04) but not in STEM1. A stratified analysis for gender in UANSTEMI showed a significant benefit of rehabilitation in women [adjusted HR 0.6, (0.01 to 0.44)] but not in men [adjusted HR 0.82, (0.39 to 1.72)].

Conclusions: Whatever the definition of ACS, cardiovascular rehabilitation was associated with a reduction of ACS-recurrence and death, and benefits both sexes. However rehabilitation seems to be more beneficial in women presenting UA/NSTEMI in whom rehabilitation is less prescribed and in whom the rate of recurrence and death is higher.
Phase II comprehensive cardiac rehabilitation prevents readmission for heart failure in patients with chronic heart failure and high brain natriuretic peptide levels

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Purpose: The purpose of this study was to investigate the effects of phase II comprehensive cardiac rehabilitation (CR) in patients with chronic heart failure (CHF) and high brain natriuretic peptide (BNP) levels.

Methods: We studied 312 patients with CHF (215 males; age, 71±10 years) who were hospitalized for acute decompensated heart failure. Patients were classified into four groups according to BNP levels at the time of discharge and participation in phase II CR. The CR with low BNP group (n = 67) included patients who participated in CR and had BNP levels less than 200 pg/mL, the CR with high BNP group (n = 74) included patients who participated in CR and had BNP of 200 pg/mL or more, the non-CR with low BNP group (n = 64) included patients who did not participate in CR and had BNP levels less than 200 pg/mL, and the non-CR with high BNP group (n = 104) included patients who did not participate in CR and had BNP levels of 200 pg/mL or more. Readmission for heart failure was analyzed using Cox proportional hazard model, Kaplan–Meier survival analysis based on cardiovascular risk factors including age, medication, left ventricular ejection fraction, BNP levels, and participation in phase II CR. Results: Multivariate Cox proportional analysis showed that participation in phase II CR was a significant predictor for readmission of heart failure (adjusted hazard ratio, 0.66; p < 0.05). Kaplan–Meier survival analysis revealed that the CR with low BNP group had the lowest readmission rate (p < 0.05), while the CR with high BNP group showed the same readmission rate as the non-CR with low BNP group (Figure).

Conclusion: Participation in phase II CR is a strong predictor for heart failure readmission and prevents readmission for heart failure even in patients with CHF and high BNP levels.

Compliance to a cardiac rehabilitation program: what benefits and prognosis impact?


Background: Cardiac rehabilitation programs (CRP) have consistently demonstrated the ability to improve cardiovascular risk factors and reduce morbi-mortality. Thus, compliance to CRP is an essential requirement to achieve the goals of secondary cardiovascular prevention.

Objective: To assess the clinical benefits and CRP compliance impact on prognosis in a coronary heart disease population.

Methods: We evaluated a total of 241 patients referred to a CRP after an acute coronary syndrome (ACS), recruited between September 2008 and November 2010. Information on socio-demographic, clinical and functional data was collected prior to post CRP. Functional capacity was assessed in metabolic equivalent (METS), determined by exercise stress testing. Telephonic interview to patients with at least 12 months of follow-up after index event was performed to assess the occurrence of composite endpoint of overall mortality and nonfatal cardiovascular events.

Results: Study population consisted of 241 patients, mostly male (89%), aged 54±10 years (range 28-80). Non-compliance was found in 24 (10%) patients and it was more common in women than men (23% vs 8%; p=0.030) and in obese patients (18% vs 8%; p=0.024). No significant differences were found in other baseline characteristics, including ACS type and severity indicators. At 6 to 12 months post index event, health status comparison between the 2 groups demonstrated that compliers achieved better control of cardiovascular risk profile: higher smoking cessation rate (70% vs 18%; p=0.001) and higher rates of adequate physical activity (≥600 METS/minute/week) [82% vs 25%, p=0.022]. A significant improvement was found, only in the compliant group (CG), regarding functional capacity (–0.8±1.6 METS, p=0.001) and lipid profile (LDL-cholesterol: –9.1±39.6, p=0.001; HDL-cholesterol: +3.2±8.7, p=0.001 and triglycerides: –38.7±102.7, p=0.001). There were no significant differences between the two groups regarding compliance to pharmacological therapy. Follow-up was available in 227 (94%) patients, with a mean follow-up of time of 25.7 months. Composite endpoints were found in 23 (10%) patients and tended to be more frequent in non-CG (17% vs 9%; p=0.182). With Cox regression analysis, non-compliance behavior was associated with a higher likelihood of cardiovascular endpoints occurrence, although no statistical significance was achieved (HR: 2.2, 95% CI:0.7-6.4).

Conclusion: CRP compliant patients have a significant higher improvement in cardiovascular risk profile, functional capacity and tend to suffer less cardiovascular events than non compliant patients.

The effects of respiratory muscle trainings on systemic inflammation and fibrosis process in patients with heart failure


Background: Number of studies showed the effectiveness of Respiratory Muscle trainings (RMT) as a part of comprehensive cardiac rehabilitation (CR). The mechanisms of their positive effects in cardiac patients are still not well known.

Objective: To study the relations of long-term effects of RMT started in patients with NYHA III-IV class heart failure (HF), with the intensity of systemic inflammation and fibrotic processes of heart.

Methods: 61 patients 64.1±5.2 years old with NYHA III-IV HF were randomized to either an exercise training group (EG) (30pts) or to a control group. The CG patients had standard CR according to the national guidelines. The EG participated additionally in a RMT with gradual increase of inspire and expire resistance. 12-15 RMT were held at the hospital with following continuation at home for 12 months by patients themselves. Trainings were held for 20-30 minutes 1-2 times every day. Plasmatic levels of C-reactive protein (CRP), aldosterone and the carboxyterminal propeptide of human type I procollagen (PIIIP) were studied at discharge point and in 12 months.

Results: In 12 months peak VO2 increased significantly in EG (11.5±8.2 vs 5.4±3.6 ml/kg/min in EG vs 9.1±7.2 vs 12.1 ml/kg/min in CG, p<0.05). EG patients showed significant decrease in CRP level (5.2±2.4 mg/dl in EG vs 8.1±2.1 mg/dl in CG, p<0.05), aldosterone level (80.5±9.1 pg/ml in EG vs 151±18.3 pg/ml in CG, p<0.05), PIIIP (67±5.7 pg/ml in EG vs 104±11.2 pg/ml in CG, p<0.05). RMT helped to stabilize mean pulmonary pressure (33.5±4.7 mm Hg in EG vs 44.2±7.6 mm Hg in CG, p<0.05). Health related quality of life measured by SF-36 increased in both groups, but results in physical functioning, bodily pain, vitality, role emotional scales were significantly higher in EG patients.

Conclusion: RMT in patients with HF are effective in decreasing the level of systemic inflammation, neurohumoral activation and collagen synthesis and thus regarding fibrosis, besides improving physical capacity, stabilizing pulmonary pressure and increasing health-related quality of life.

Beneficial effects of rehabilitation in comparison with resynchronization therapy in patients with NYHA III heart failure

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Background: Indications to cardiac resynchronization therapy (CRT) have been extended in 2010. However, there is large group of patients with ejection fraction<35%, severe heart failure (HF) and QRS>120ms who are not qualified to CRT. They are treated with optimal pharmacotherapy. We compared outcomes of rehabilitation of patients in NYHA III heart failure and patients with implanted CRTD device without rehabilitation.

Methods: The study included 47 patients with NYHA III HF and EF<35% on optimal pharmacotherapy. CR treatment started after 3 months of panel treatment. We analyzed 12 months outcomes with clinical and functional parameters. The patients were divided into two groups: CR treatment followed (CR group) and control group (CG) without rehabilitation. We performed a multivariate analysis to calculate statistical significance.
mal pharmacotherapy. The etiology of HF was comparable in both groups. 27 patients with QRS>120ms had CRT-D implanted and 20 patients with QRS<120ms had ICD implantation and went through the training program (aerobic exercises on ergometer, 3 times a week for 3 months). All patients were optimally treated pharmacologically. They had echocardiography and cardiopulmonary exercise test (CPX) performed at baseline and after 6 months.

Results: Conclusions are presented in Table 1.

Conclusions: Rehabilitated patients with NYHA III heart failure have better outcomes when compared with CRT group. Rehabilitation is a noteworthy therapeutic option for patients with severe heart failure and no indications to CRT.

### NOVEL APPROACHES TO EXERCISE TRAINING

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#### 3804 Biventricular filling impairment limits cardiac performance during exercise in healthy subjects

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Background: Constraints in current imaging techniques have resulted in considerable disagreement as to what constitutes normal changes in left and right ventricular (LV, RV) volumes during exercise. The aim of this study was to determine if biventricular end-diastolic and end-systolic volumes (EDV and ESV) using a novel CMR methodology during strenuous exercise.

Methods: Twenty-two healthy and physically active subjects (19 male, 3 female, age 32±7 years) underwent CMR at rest and during supine exercise on a programmable cycle ergometer. Biventricular volumes were obtained at rest (heart rate 63±11 bpm) and during exercise at moderate (115±14 bpm) and strenuous (155±11 bpm) workload intensities. Images were acquired during exercise and free-breathing (12-18 contiguous 8mm slices) using an ungated real-time CMR sequence. We developed software to enable retrospective synchronization of long and short-axis images with compensation for respiratory phase translation.

Results: There was excellent inter-observer agreement for all volume estimations (intra-class correlation coefficients r=0.97 and r=0.98 for EDV and ESV respectively, p<0.0001). Biventricular cardiac output (CO) increased by 11±15% from rest to moderate exercise (7.7±1.4 vs. 16.3±4.8 ml/min; p<0.0001) and by a further 30±16% to strenuous exercise (16.3±4.8 vs. 21.1±5.3 ml/min; p<0.0001). The total 174±60% increase in CO was due to a 146±23% increase in HR and a 9±13% increase in stroke volume (SV). Interestingly, SV increased during moderate exercise (124±27 vs. 141±34 ml; p=0.0001) but then decreased during strenuous exercise (141±34 vs. 135±30 ml; p=0.0002). The early increase in SV was due to augmentation of both systolic function (end-systolic volume (ESD) -15±11%, p<0.0001) and diastolic filling (end-diastolic volume (EDV) +2±7%, p=0.02). Although during strenuous exercise there was further augmentation of systolic function (ESD -20±16%, p<0.0001 and EDV -20±16%, p<0.0001), diastolic filling was reduced (-10±7%; p<0.0001). This reduction in EDV during strenuous exercise occurred in all subjects and was greater for the RV than for the LV (12±8 vs. -7.5%, p<0.03). All other changes in cardiac volumes were similar for LV and RV (p<0.05).

Conclusions: A novel CMR methodology of biventricular volume assessment was used to demonstrate augmentation of biventricular filling and ejection during moderate and strenuous exercise in healthy subjects. However, at higher exercise intensities, diastolic filling is compromised and attenuates further stroke volume increases.

#### 3806 Music as additional therapeutic option to exercise training for endothelial dysfunction in patients with stable coronary artery disease

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Purpose: To evaluate the effects of listening to favorite music added to regular exercise training on the endothelial function, assess through changes of circulating blood markers of endothelial function: the stable end products of nitric oxide (NOx) and related - nitrosothiols (RSNO) - responsible for bioavailable nitric oxide, in patients (pts) with stable coronary artery disease (CAD).

Methods: 65 pts with stable CAD were studied. At baseline and 3 weeks later, in all pts values of NOx and RSNO were evaluated and exercise test was performed. After the initial study, pts were randomized to trained (T=25, music and trained (MT=20) and non-trained (NT=20) group. Patients in T and MT groups underwent supervised 3 weeks aerobic exercise training at residential center, while non-trained group received usual community care. Additionally to exercise training, patients in MT group were listening their favorite music for half an hour every day. To elucidate the dynamic of nitric oxide metabolism in the circulation, NOx and RSNO concentration were determined according to the modified Sallie-Griess method.

Results: Baseline values of NOx and RSNO were similar in T, MT and NT group.

- After 3 weeks NOx increased significantly in T group from 3.5±0.5 to 4.0±0.5 μmol/l (P<0.05) and RSNO (from 9.5±1.3 to 12.5±1.2 μmol/l; P<0.05) and those values were significantly higher than in NT group (P<0.05 and P<0.001).
- After 3 weeks value of NOx was significantly higher in MT than in T group (P<0.05).
- In all groups, value of RSNO increased after 3 weeks: in T group from 3.5±0.5 to 4.0±0.5 μmol/l (P<0.05) in MT from 3.2±1.3 to 5.3±1.3 μmol/l (P<0.001) and in NT group (P=0.01) at 3.2±1.3 μmol/l.
- Different rate of increased RSNO in examined groups resulted in significantly higher RSNO in T group than in NT group (P<0.05). In T and NT group (P=0.05) and in NT in TG (P<0.001) at the end of the study. Level of exercise test at baseline were similar in T, MT and NT. After 3 weeks exercise capacity significantly increased in T and MT group (P<0.001 both), however increase in exercise capacity was higher in T than in T group (45% vs 27%).

Conclusion: In pts with stable CAD listening to favorite music in addition to regular exercise training and standard therapy, leads to more pronounced improvement in endothelial function, expressed through higher increased of NOx and RSNO, than exercise training alone. These improvement in endothelial function is associated with significant improvement in exercise capacity.

### 3805 Evaluation of a newly designed shirt-based ECG and breathing sensor for home based training as part of cardiac rehabilitation for coronary artery disease

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Background: The advantages of a structured cardiac rehabilitation (CR) program are well known. However, participation in phase III CR is low. This problem could be overcome by implementing a home-based supervised CR, but new technology is needed to allow that supervision and improve adherence to CR. The novel designed tool (HeartCyclone’s GE-Systm) is intended as a closed-loop cardiovascular disease management tool with support for both the professional and the patient, focused on CR based on physical exercise. The patient side system comprises a wireless sensor attached to a shirt that senses vital parameters such as heart rate, blood pressure and respiratory rate. The CR system and activity durummed according to current guidelines and exercise capacity assessed by estimated metabolic equivalents (METs) was achieved on exercise stress testing.

Results: Forty-five patients were evaluated, 38 (84%) male, mean age of 54 (±9 years).
years. Among these, 19 (42%) were dyslipidemic, 7 (16%) diabetic, 13 (29%) hypertensive, 20 (44%) were overweight, and 24 (53%) were current smokers. Regarding echocardiography baseline group analysis, left ventricle ejection fraction (LVEF) was 56±5%, left atrial volume was 51±15 cm³. E/E’ ratio was 9.3±3. and left ventricular TDI peak systolic velocity (medium between septum and lateral wall longitudinal movements) was 8.9±2.0 cm/sec. Exercise capacity at baseline was 9.5±2.2 METS and correlated inversely with E/E’ ratio (r = -0.440, p = 0.009) and left atrial volume (r = -0.385, p = 0.022). A positive correlation between exercise capacity and left ventricular peak systolic velocity (r = 0.359, p = 0.04) was found while no correlation was observed with LVEF. Correlation between exercise capacity and E/E’ or LV peak systolic velocity remained significant after adjustment to other possible confounding factors, as age, gender, weight and diabetes, which can also influence exercise capacity. E/E’ and left atrial volume at the admission were also inversely correlated with functional status at the end of the CRP (r = -0.517, p = 0.004; r = -0.489, p = 0.006 respectively). Conclusions: Higher LV filling pressures may influence negatively the exercise capacity as demonstrated by the inverse correlation found between peak METS level and diastolic parameters: E/E’ and left atrial volume, although regional LV systolic function also correlated with exercise capacity, global LV function did not. These results suggest that the evaluation of sensitive parameters of left ventricular function may help to better clarify the influence of cardiac function in exercise performance.

**3808**

**Passive whole-body exercise training with periodic acceleration improves endothelial function in sedentary subjects**

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**Introduction:** Periodic acceleration in the direction of the spinal axis through repetitive movements increases shear stress to the vascular endothelium. Thus, we assessed the hypothesis that whole-body periodic acceleration with a new "passive exercise" device would enhance release of nitric oxide (NO) into the circulation and endothelial function in sedentary adults.

**Methods:** We enrolled twenty sedentary subjects (42±4 years; 12 women, 8 men) not taking any medication. Each subject was randomly assigned to remain sedentary or perform exercise training for 4 weeks, followed by cross-over. Periodic acceleration was applied with a horizontal motion platform (AT101; Non-invasive Monitoring Systems) at a frequency of 2–3 Hz and approximately 0.25 g for 45 min. Venous blood was sampled before and immediately after the first and 20th sessions. The amount of plasma NO end-products (nitrate plus nitrite) was measured by the Griess reaction. Increases in right brachial artery diameter at baseline to 24±9 mmol/L after the completion of 20 sessions (p < 0.05) was found while no correlation was observed with NO concentration in plasma. After the 20th session, plasma NO concentrations remained significantly higher than baseline.

**Results:** Whole-body exercise training with periodic acceleration improves vascular endothelial function through an increase in NO release in sedentary adults. This device may offer an alternative exercise for patients whose medical conditions limit physical activity.

**3809**

**Exercise echocardiography - effects of endurance training and ageing**

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**Purpose:** To study the effects of endurance training and ageing on echocardiographic measures of myocardial function at rest and during exercise.

**Methods:** Four groups of healthy, normal weight males; master athletes (running ~60 km/wk for the last 20 years), young athletes with similar level of physical activity, and sedentary age-matched controls underwent endurance test determining VO2peak, and echocardiography at rest and during supine bicycle exercise test at 60% of maximum workload. Linear regressions were performed to simultaneously assess the effects of training (two groups) and age (continuous) on echocardiographic measures. Results: VO2peak differed considerably between young and old and between athletes and non-athletes. Dimensions of left atrium and ventricle as well as trans-mural flow pattern at rest were affected by both training and age. See table. Effects of training and ageing on echocardiographic measures of myocardial function at rest and during exercise.

**3814**

**Sustainable TNF receptor antibodies as an alternative strategy to STEMI reperfusion therapy**

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**Objectives:** The aim of the study was to investigate circulating markers of apoptosis in relation to infarct size, left ventricular dysfunction and remodeling in an STEMI-Surviving Myocardial Infarction (STAMI) population undergoing primary percutaneous coronary intervention (PCI).

**Background:** Immediate re-opening of the acutely occluded infarct-related artery via primary PCI is the treatment of choice in STEMI to limit ischemia injury. However, the sudden re-initiation of blood flow can lead to a local acute inflammatory response and further endothelial and myocardial damage.

**Methods:** We included 48 patients with STEMI undergoing primary PCI. Blood samples were collected prior to PCI and after 24 hours. Plasma was separated for later analysis of soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2, sFas and sFas ligand (sFasL) by ELISA. Infarct size, left ventricular (LV) dysfunction and remodeling were assessed by cardiac magnetic resonance imaging at imaging at 5 days and four month after STEMI.

**Results:** The levels of sTNFR1 at 24 h as well as the relative increase in sTNFR1 and sTNFR2 over 24 h showed consistent and significant correlations with infarct size and LV dysfunction. Moreover, both sTNFRs correlated with Troponin I and matrix metalloproteinase (MMP)-2 measurements. Soluble Fas and sFasL did not overall correlate with measures of infarct size or LV dysfunction.

**Conclusion:** In STEMI patients, circulating levels of sTNFR1 and sTNFR2 are associated with infarct size and LV dysfunction. This provides further evidence for the role of apoptosis in ischemia-reperfusion injury.

**3815**

**Hemostatic and fibronolytic profile in patients with ST-segment elevation myocardial infarction resistant to fibrinolysis**

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**Objective:** To analyze whether it exists some association between hemostatic and fibrinolytic factors determined in circulating plasma and if it correlates with the concomitant coronary angiographic and haemodynamic features in STEMI with resistant fibrinolysis.

**Methods:** We included 20 patients (age 57±13y; 10 female) who underwent PCI as the first treatment of choice in patients with STEMI. Fibrinolytic failure was defined as the treatment of STEMI by PCI. For susceptibility reasons, the fibrinolysis continues being the first line treatment about 30-70% of these patients, however in 40% of them is ineffective for unknown reasons.

**Aim:** To analyze whether it exists some association between hemostatic and fibrinolytic factors determined in circulating plasma and if it correlates with the concomitant coronary angiographic and haemodynamic features in patients resistant to fibrinolysis compared to those who were not resistant.

**Results and Methods:** 20 patients (age 57±13y; 10 female) who underwent PCI as the first treatment of choice in patients with STEMI. Fibrinolytic failure was defined as the treatment of STEMI by PCI. For susceptibility reasons, the fibrinolysis continues being the first line treatment about 30-70% of these patients, however in 40% of them is ineffective for unknown reasons.
for a first STEMI with initial TIMI 0 flow were included. Of these, 10 underwent primary PCI (group A) and the other 10 were subjected to rescue PCI (Group B) because of ineffective fibrinolysis (TKK). In all patients tissue factor activity (TFa), TF Ag and tissue factor pathway inhibitor (TFPI), von Willebrand factor (VWF), D-dimer, plasmin inhibitor activated (PAI-1) and tissue plasmin activator (t-PA) were determined. The coronary thrombus was obtained during PCI by aspiration catheter in all patients. Specimens were submitted to immunohistochemical analysis. In order to know if all patients underwent primary PCI a thrombus sensitive to lysis, thrombus formation by thrombin was induced "in vitro", and an effective thrombolysis by r-TPA was observed in 100% of patients. There were no differences between both groups in terms of age, sex, cardiovascular factors, time symptoms onset to balloon, infarct localization and number of affected vessels. Patients who underwent rescue PCI showed a higher D-dimer plasma level regarding patients who underwent primary PCI (2234.3±706.5 vs 774.5±1398.9 ng/ml, p<0.03). In plasma, D-dimer levels were associated to TFa (R=0.95, p=0.01) and TFVW levels (R=0.65, p=0.04). In the thrombus, TFVW plasma levels were correlated with PAI-1 (R=0.79, p=0.006), CD34 (R=0.85, p=0.004) and P-selectin (R=0.77, p=0.002). However, in patients who underwent primary PCI, D-dimer levels were associated with t-PA (R=0.85, p<0.001) and TFVW levels were inversely associated with TFPI (R=0.87, p<0.01) in plasma. In addition, in the thrombus the content of fibrin was associated with CD34 and TFVW (R=0.71, p=0.03; R=0.73, p=0.02, respectively).

Conclusion: There are clearly different correlations of thrombotic and fibrinolytic factors. Resistant patients to fibrinolysis show positive correlations between strongly thrombotic factors, while in no resistant patients to fibrinolysis there are a trend to haemostasis between prothrombotic and fibrinolytic factors.

Figure 1. Kaplan-Meier curves of mortality by PBT

Conclusions: PBT is strongly associated with mortality in STEMI pts even after 9 years. Efforts should be made to shorten PBT in all pts.

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**Primary percutaneous coronary intervention with and without thrombus aspiration**

**Background:** Manual thrombus aspiration in patients with Stein elevation myocardial infarction (STEMI) is at present routinely undertaking in most of the catheterization laboratories performing primary PCI. Successful retrieval of thrombus burden is considered reasonable. However, its benefit in low risk patients is not established. We wanted to know whether asymptomatic reinfarction would be the mainstay of primary percutaneous coronary intervention (PCI).

**Object:** To determine the safety and efficacy of selective thrombus aspiration during Primary Percutaneous Coronary Intervention (PCI).

**Material and Methods:** This observational prospective study was conducted in the catheterization laboratory of a tertiary care cardiovascular centre. A total of 150 consecutive patients who underwent primary PCI were enrolled. Aspiration was done only when thrombus burden was considered significant. After completion of procedure angiographic and electrocardiographic signs were recorded and clinical follow-up was documented up to 1 year. The primary end point was a resolution of ST elevation within 60 minutes and myocardial blush grade II and III. Secondary endpoint was death and MACCE up to 1 year.

**Results:** Mean age was 51±12 years and 95% were male. Hypertension was present in 46.7% patients, 24.7% were diabetic and 37% were current smokers. Left anterior descending artery was culprit in 65% of patients. More than 90% of culprit vessels were thrombus laden. Multivessel disease was present in 38% of patients and 22.7% had past history of myocardial infarction. Out of 150 patients 117 (78%) underwent thrombus aspiration. No significant difference in ST resolution within 60 minutes (72.6% vs 81.8%, p<0.005) and myocardial blush grade II & III (41.6% vs 78.9%, p<0.001), and the difference was even more pronounced in the age group >60 years. Frequency of MI and RT did not differ between our institution and the national data.

Conclusions: We found no correlation between LBBB chronicity and incidence of myocardial infarction. The frequency of RT is low, but somewhat higher in the group <80 years. In this age group, a new LBBB identified only half of the patients with a final diagnosis of MI, which means that strict adherence to reperfusion guidelines may leave half of the patients untreated.

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**Left bundle branch block and suspected myocardial infarction: an under-treated patient group?**

**Purpose:** According to ESC guidelines, a new or presumed new left bundle branch block (nLBBB) in patients with suspected myocardial infarction (MI) constitutes an indication for acute reperfusion treatment (RT). Our aim was to investigate if this group of patients was treated according to guidelines as well as comparing them with patients having a previously known LBBB (oLBBB).

**Methods:** Retrospective collection of data from the Swedeheart registry for patients with LBBB and suspected MI, admitted to the CCU at Örebro University Hospital during 2009 and 2010. All data was checked against medical records. The definition of LBBB, MI and RT follows the Swedeheart registry criteria. We divided the patients in two age groups: <80 or ≥80 years and analyzed LBBB chronicity (nLBBB or oLBBB), diagnosis of MI and prevalence of RT. Regarding frequency of MI and RT, we compared our data with the entire national Swedeheart database for 2009 (3001 patients with LBBB). For statistical calculation we used Fisher’s exact test and SigmaStat v3.5 software.

**Results:** A diagnosis of MI was significantly more common in the group ≥80 years compared to <80 years (53.8% vs 24.5%, p<0.006). The prevalence of MI was similar in the groups nLBBB and oLBBB (30% resp 36%, p=0.946). RT was significantly more often administered to patients with nLBBB compared to oLBBB (41.6% vs 7.8%, p<0.001), and the difference was even more pronounced in the age group ≥80 years. Frequency of MI and RT did not differ between our institution and the national data.

Conclusions: Whether aspiration thrombectomy should be the mainstay of primary percutaneous coronary intervention (PCI) in all patients or should it be reserved for high risk group of patients.

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**Long term effect of minimising pain-to-balloon time on mortality in ST-elevation myocardial infarction. The ANIN Myocardial Infarction Registry**

**Background:** Pain to balloon time (PBT) has been shown to affect in-hospital mortality in a continuous, non-linear fashion. Current ACC/AHA Guidelines suggest that PBT should be <90 min and as short as possible. It is unclear whether significant minimisation of PBT is maintained over the years.

**Objectives:** We sought to evaluate the influence of PBT on long term clinical results in patients (pts) with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) at a high volume centre.

**Methods:** In a prospective “all-comer” registry clinical and procedural characteristics, PBT and 9-year mortality were determined in consecutive STEMI pts treated with pPCI at our institution and the national data.

**Results:** In a prospective “all-comer” registry clinical and procedural characteristics, PBT and 9-year mortality were determined in consecutive STEMI pts treated with pPCI at our institution and the national data. Overall 9-year mortality was 28% (294 pts). Multivariable logistic regression models indicated that longer PBT were associated with a higher mortality in a continuous, non-linear fashion. Current ACC/AHA Guidelines suggested that PBT should be revised regarding the importance of LBBB chronicity.

Figure 1. Kaplan-Meier curves of mortality by PBT

Conclusions: PBT is strongly associated with mortality in STEMI pts even after 9 years. Efforts should be made to shorten PBT in all pts.

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**Optimisation of myocardial reperfusion in STEMI**

**Background:** Pain to balloon time (PBT) has been shown to affect in-hospital mortality in a continuous, non-linear fashion. Current ACC/AHA Guidelines suggest that PBT should be <90 min and as short as possible. It is unclear whether significant minimisation of PBT is maintained over the years. Efforts should be made to shorten PBT in all pts.
Drug eluting stents are associated with lower MACE rates compared to bare metal stents in small coronary arteries treated by primary PCI for STEMI

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Purpose: Drug eluting stent (DES) implantation has been shown to improve outcomes in primary PCI for STEMI, although there is limited data about their use in small coronary arteries. We aimed to compare medium-term outcomes of patients with small coronary arteries with DES versus BMS placement for primary PCI for STEMI.

Methods: 2170 consecutive patients underwent primary PCI for STEMI at a single high-volume centre between October 2003 and September 2010. Of these, 883 had culprit arteries with reference vessel diameter <3mm, which were defined as small coronary arteries. The primary end point was major adverse cardiac events (MACE), defined as death, myocardial infarction (MI), stroke and target vessel revascularization (TVR). Median follow-up was 2.0 years (IQR 0.7-3.6 years).

Results: 246 patients underwent PCI with DES and 637 with BMS. Patients undergoing DES implantation were older, more likely to be diabetic and more likely to have undergone previous PCI. Kaplan-Meier estimates (Figure 1) of medium-term MACE demonstrated a significant difference in favour of DES (21.1% vs. 14.6%, p=0.04). Age-adjusted Cox analysis demonstrated this benefit to be maintained with respect to the primary endpoint (hazard ratio 0.70 [95% CI 0.49-0.97]). In addition, this difference persisted after regression adjustment incorporating a propensity score model as a covariate (hazard ratio 0.82 [95% CI 0.47-0.96]).

MACE demonstrated a significant difference in favour of DES (21.1% vs. 14.6%, p=0.04). Age-adjusted Cox analysis demonstrated this benefit to be maintained with respect to the primary endpoint (hazard ratio 0.70 [95% CI 0.49-0.97]). In addition, this difference persisted after regression adjustment incorporating a propensity score model as a covariate (hazard ratio 0.82 [95% CI 0.47-0.96]).

Figure 1

Conclusions: In patients with small coronary arteries, DES implantation appears to be associated with lower MACE rates than BMS implantation in primary PCI for STEMI.
Are functional and absolute iron deficiencies equally detrimental in heart failure?


Introduction: Iron deficiency (ID) has shown to worsen prognosis in patients with heart failure (HF). ID can be absolute or functional.

Objective: To assess the prognostic significance of ID (both absolute [defined as ferritin <30 μg/L] and functional [defined as ferritin ≥30 μg/L and transferrin saturation <20%]) in a real-life HF outpatient population.

Patients: 678 patients (72% men, median age 70.3 years [IQR 60.5-77.2] were studied. Aetiology of HF was mainly ischemic heart disease (52.2%). Median LVEF was 34% [IQR 26-43%]. Most patients were in NYHA class II (65.6%) or III (26.3%). Median follow up was 3.4 years [IQR 1.84-5.04].

Results: ID was present in 452 patients (51.1%), being absolute in 81 (9.2%) and functional in 371 (42.3%). Only 238 patients with ID were anaemic (52.7%). During follow up 313 deaths were recorded. ID was associated with higher mortality (odds ratio, OR = 1.66 [IQR 1.18-2.34, p=0.004]. In the multivariable analysis (backward step), ID only remained an independent predictor in non-anemic patients. OR 1.48 [IQR 1.18-1.86], p=0.001, specifically in non-anemic population.

Methods: We enrolled 1007 consecutive patients with systolic CHF (age 65±12 years, mean±SD, males 72%, LV ejection fraction -EF- 33±10%, 274 (29%) with diagnosed diabetes, undergoing a comprehensive clinical, humoral (including gly- cated haemoglobin, HbA1c), echocardiographic and neurohormonal evaluation. For subgroup analysis, patients were divided into tertiles of LVEF (50-38%, 38-28%, < 28%). Endpoint was cardiac mortality.

Results: During a 5-year follow-up (median 36 months, range 0.3-60), 154 cardiac deaths occurred. In the whole population, no differences were evident in clinical, neurohormonal, echocardiographic parameters, nor in outcome between diabetics and nondiabetics. Conversely, patients with HbA1c(1c) >7 showed higher plasma renin activity (PRA, 3.66; 0.62-6.13 vs. 2.28; 0.41-4.1 ng/mL/h, p<0.01), NT-proBNP (1602; 826-3498 vs. 1076; 401-3112 ng/L, p<0.01), and worse clinical status (43% of patients with HbA1c(1c) >7 being NYHA III/IV vs. 35% of patients with HbA1c(1c) ≤7, p<0.05), with no difference in any other parameter. HbA1c(1c) >7 predicted cardiac mortality (events in 22% vs. 14% p = 0.04). In the sub- group with slightly reduced LVEF patients with HbA1c(1c) >7 showed higher PRA and cardiac natriuretic peptides. In this group, HbA1c(1c) along with NT-proBNP (but not the diagnosis of diabetes) resulted the only independent predictors of outcome, whereas this did not occur in patients with moderate-to-severe LV dys- function.

Conclusions: Glycemic metabolic imbalance enhances neurohormonal activation and worsen prognosis, in HF patients, beyond diagnosis of diabetes. This association appears prominent at early stage of CHF, characterized by slight LV systolic dysfunction, when chronic hyperglycemia might have a specific impact on cardiac remodeling process, by eliciting neuroendocrine activation.

The presence of restrictive (but not obstructive) pattern of impaired pulmonary function is related to impaired exercise tolerance. Further studies are needed to explain this finding.

Glycometabolic imbalance is a main determinant of neurohumoral activation and cardiac mortality in mild systolic heart failure.

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Purpose: To assess the impact of glycemic imbalance on neuroendocrine activation and outcome in chronic heart failure (CHF) patients with different degrees of left ventricular (LV) systolic dysfunction.

Methods: We enrolled 1007 consecutive patients with systolic CHF (age 65±12 years, mean±SD, males 72%, LV ejection fraction -EF- 33±10%, 274 (29%) with diagnosed diabetes, undergoing a comprehensive clinical, humoral (including gly- cated haemoglobin, HbA1c), echocardiographic and neurohormonal evaluation. For subgroup analysis, patients were divided into tertiles of LVEF (50-38%, 38-28%, < 28%). Endpoint was cardiac mortality.

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Figure 1: Survival according to iron deficiency.

Conclusion: ID, mainly functional deficiency, was very frequent in a HF outpatient population of different aetologies and carried a higher risk of death, specifically in the non-anemic population.

Do mitral valve replacement versus repair in patients with severe ischemic mitral regurgitation affect survival?

V. Shumaviec, Y. Ostrovski, A. Shket, A. Janushko, A. Lysjonok, O. Jdanovich, A. Beresneva. Belarus Cardiology Centre, Minsk, Belarus

Purpose: The long-term survival of patients with severe compromised ischemic left ventricle and concurrent functional mitral regurgitation is reduced. We performed this study to understand how mitral valve replacement versus repair affects survival and reveal the predictors of mortality in this high-risk popula- tion.

Surgery for Valvular Heart Disease: Predictors of Outcome

Methods: We enrolled 1007 consecutive patients with systolic CHF (age 65±12 years, mean±SD, males 72%, LV ejection fraction -EF- 33±10%, 274 (29%) with diagnosed diabetes, undergoing a comprehensive clinical, humoral (including gly- cated haemoglobin, HbA1c), echocardiographic and neurohormonal evaluation. For subgroup analysis, patients were divided into tertiles of LVEF (50-38%, 38-28%, < 28%). Endpoint was cardiac mortality.

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Conclusions: Glycemic metabolic imbalance enhances neurohormonal activation and worsen prognosis, in HF patients, beyond diagnosis of diabetes. This association appears prominent at early stage of CHF, characterized by slight LV systolic dysfunction, when chronic hyperglycemia might have a specific impact on cardiac remodeling process, by eliciting neuroendocrine activation.

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Purpose: The long-term survival of patients with severe compromised ischemic left ventricle and concurrent functional mitral regurgitation is reduced. We performed this study to understand how mitral valve replacement versus repair affects survival and reveal the predictors of mortality in this high-risk popula-
Methods: 850 patients (mean age, 57.9±8.3 years) from 2000 to 2020, with coro-
nary artery diseases and significant ischemic mitral regurgitation (≥2) were oper-
ated – in 767 pts CABG + MV repair were performed and in 63 pts MV replacement were combined with CABG. Groups were matched by propensity score using de-
mographic dates, co-morbidity, coronary status, LV remodeling, MV deformation and MR grade by quantitative echocardiography. Survival (with mean follow-up 4.5±3.8 years) and New York Heart Association functional class were compared. The impact of mitral valve replacement versus repair on survival by comparing these propensity matched subgroups was analyzed.

Results: Follow-up was 100%. Before matching 10-year survival was significantly worse in replacement group (long-rank p=0.003). After propensity matching we’ve received homogenous cohort of 69 pts with severe compromise significantly worse in replacement group (long-rank p=0.003). After propensity-matched analyses were found LV ESD (HR=1.085, 95% CI 1.018–1.12, ±0.003) and underestimation in EuroSCORE II (O/E ratio; 1.20). STS PROM is better than EuroSCORE II in terms of discrimination ability. These results have implications for risk judgment in AVR for AS.

Aortic valve replacement: relationship between aortic stenosis severity and perioperative mortality risk scores

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Purpose: We assumed that perioperative mortality risk scores (Euro I and II and STS) were related with aortic stenosis (AS) severity assessed by aortic valve area (AVA).

Methods and results: We compared pre and postoperative clinical and echocar-
diographic parameters with perioperative mortality risk scores for patients undergoing AV replacement according with AVA: group 1 (area<0.75 cm², n=78) with group 2 (area<0.75 cm², n=259). Mean age was 66.12±7.39 years, mean BMI 26.4±14.4%, LV end diastolic diameter (LVEDD) was 50.15 vs 60.18±16 mm Hg; mean AVA was 0.83±0.06 vs 0.61±0.09 cm² (p=0.001); indexed stroke volume was 41±11 vs 46.12±12 ml/m² (p<0.001). Mean Euro I, Euro II and STS mortality scores were 6.25±8.8%, 3.91±7.2% and 2.6±2.3%, respectively. Survival scores were significantly greater in group 2 than group 1: Euro I 3.4±3.4% vs 6.5±9.3%, Euro II 1.5±1.1% vs 3.4±7.7%, STS 1.8±1.3% vs 2.9±2.4% (p<0.001). Postoperative mortality rate was 2.9% in 0 group 1 and 3.4% in group 2 (p=0.092). All scores were significantly correlated (for Euro I vs Euro II, Euro I vs STS and Euro II vs STS, the coefficients were 0.754, 0.641 and 0.563, respectively; p<0.001) and were significantly greater in deaths vs survivors (Euro I 13% vs 3%, Euro II 11% vs 2% and STS 5% vs 2%; p<0.001). All scores were neg-
atively correlated with AVA: r = -0.242 (Euro II), r = -0.235 (Euro I) and r = -0.292 (STS); p<0.001. Pre and postoperative left ventricular ejection fraction and postoperative systolic pulmonary artery pressure were significantly different by comparing deaths vs survivors: 46±13% vs 62±13%, 46±15% vs 57±10% and 37±5 mm Hg vs 31±10 mg Hg (p<0.001, 0.039 and 0.033), respectively.

Conclusion: Perioperative mortality risk and death rate seem to be related to AS severity in patients undergoing isolated AV replacement.

Predictors of persistent severe diastolic dysfunction after aortic valve replacement in aortic stenosis compared with aortic regurgitation

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Purpose: 1. To evaluate the effect of aortic valve replacement (AVR) on left ven-
tricular (LV) diastolic function and LV remodeling, comparing patients with aortic stenosis (AS) to patients with aortic regurgitation (AR).

2. To identify the parameters appropriate for prediction of immediate and medium term evolution in these patients.

3. To assess the independent predictors for persistence of the restrictive LV diastolic filling pattern (LVDDF) after isolated AVR.

Methods: 5 years prospective study on 397 patients with restrictive LVDDF un-
dergoing AVR for AS (Group A - 226 pts) or AR (Group B - 171 pts). Patients were evaluated preoperatively and at 10 days, 1, 3, 6-months, 1 year and yearly 5 years postoperatively. Depending on the LV EF, each of the two groups were divided into 2 subgroups: pts with LV EF<50% (Group A1-137 pts and group B1-102pts) and pts with LV EF>50% (group A2-99 pts and group B2-69 pts). Statistical analysis used SYSTAT and SPSS programs for the simple and multiple regression analysis and relative risk calculations.

Results: 1. The evolution of the LV diastolic function was different in AS group (area after AVR diastolic filling improved compared with AR group). At 1 year post surgery the percent of the patients with persistent restrictive LVDDF was 23.01% in AS group and 60.23% in AR group.

2. At 5 years, cardiovascular event-free survival, including hospital visits caused by heart failure symptoms and sudden cardiac death was significantly higher in the patients with preoperative AS (87.17%) compared with AR group (64.91%).

3. The parameters appropriate for prediction of immediate and medium term evo-
lution were age, preoperative NYHA class, LVF, atrial fibrillation, coronary artery disease and smoking.

4. Simple and multivariable regression analysis identified as independent pre-
cursors for persistence of a restrictive LVDDF: AR (RR=19.2), E/E’ ratio>12 (RR=21.1), the LA dimension index >30mm/m² (RR=8.2, p=0.0017), LV endys-
tolic diameter (LVEDS) ≥55mm (RR=6.6), severe pulmonary hypertension (PHT) (RR=9.7) and 2 degree MR (RR=12.0).
Conclusions: 1. Restrictive flow pattern is reversible mostly after AVR for AS than for AR, both in the early and medium postoperative period.
2. The parameters predicting fatal outcome and hospitalisation for heart failure on medium postoperative NYHA class, LVEF, atrial fibrillation, coronary artery disease and smoking.
3. The echographic predictors for persistence of a restrictive LVDFP in patients with AR and LV systolic dysfunction were: AR, E/E' > 12, LVESD > 55mm, the LA dimension index > 30mm²/m², severe PHT and associated 2 degree MR.

Additional ablation of complex fractionated atrial electrograms in long-lasting persistent atrial fibrillation. Does it change the ablation success? Results from the German ablation registry

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Introduction: In therapy of paroxysmal and long-lasting persistent atrial fibrillation (AF) pulmonary vein isolation (PVI) is a well-established therapeutic option. In ablation of long lasting persistent AF substrate modification is usually required. Addition of ablation of complex fractionated atrial electrograms (CFAE) has been used as an additional option in ablation.

Purpose: The aim of our study was to evaluate the efficacy of ACFAE in patients with persistent AF and the procedural outcomes of PVI and ACFAE. We compared the results of PVI to a group of ACFAE and to a group of patients with persistent AF who did not undergo ACFAE.

Methods: From 2005 to 2010 in our institution a total of 354 consecutive patients with persistent AF underwent de novo catheter ablation of persistent AF. Ablation was performed in two different groups: Group A (n=118) received PVI only and Group B (n=236) received PVI and ACFAE. The baseline characteristics of both groups were similar, except more redo procedures in the CFAE group (38.3% vs. 20.9% p < 0.001).

Results: The acute success rate was similar in both groups (Group A 95%, Group B 96.2%). There was no difference in the percentage of symptomatic AF (PVI: 12.9%, 30.3%; CFAE: 11.9%, 30.3%). After 1 year of follow-up, the success rate was similar in both groups (Group A 92.1%, Group B 92.6%). The percentage of SA rhythm at 1 year was 73.6% in Group A and 71.3% in Group B (p=0.11).

Conclusion: Our results show that ablation of CFAE in addition to PVI lead to a change of ablation success in patients with persistent AF. The additional ablation of CFAE did not improve the acute and long-term outcome compared to PVI alone.

OUTCOMES AND COMPLICATIONS OF CATHETER ABLATION FOR ATRIAL FIBRILLATION

Five years follow up of patients undergoing persistent atrial fibrillation using the stepwise approach: BLOC-AF study


Introduction: Data on long-term rhythm outcome after persistent AF (PaAF) ablation are limited. The BLOC-AF study (Bordeaux Long term Outcome after Catheter ablation of persistent AF) evaluates long-term success rates and predictors of success after stepwise ablation of PaAF.

Methods: 165 consecutive pts with persistent AF undergoing de novo catheter ablation (stepwise approach: PVI, ablation of fractionated electrograms, and linear ablation) were included, with the desired procedural endpoint being AF termination. Repeat ablation was performed for pts with recurrent AF/At after a 1 month blanking period. A minimum follow up (FU) of 48 months with repeated Holter monitoring was performed. Arrhythmia recurrence was defined as AF (95.2%) or atrial tachyarrhythmia (4.8%) lasting > 3 months, in sinus rhythm ≥ 30 sec. Interim analysis of the first 75 pts (51.5 ± 9 years, LVEF 57.5% ± 14%, 56% long-standing PaAF) has completed FU is presented.

Results: AF was terminated during the index procedure in 60 of 75 pts (80%). During the follow up, 24 pts (32%) had recurrence of AF. After 5 years of follow up (FU) 75% of pts were in SR (p=0.006). AF was predicted of AF termination (At p=0.006). Arrhythmia-free survival rates were 46%, 31%, and 16% at 1, 2, and 5 years, respectively.

Conclusions: Despite the limitations of the study design, the BLOC-AF study provides important data on the long-term outcome after catheter ablation of persistent AF.

Rhythm control in elderly patients with persistent atrial fibrillation: a randomized comparison of catheter ablation versus antiarrhythmic drugs

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Purpose: We conducted a prospective randomized study to compare efficacy and safety of catheter ablation versus antiarrhythmic drugs (AADs), in a cohort of elderly patients with persistent atrial fibrillation (AF).

Methods: 354 consecutive patients, aged ≥ 70 years, were randomly assigned in a 1:2 fashion to catheter ablation (Group A, 118 patients) or AADs (Group B, 236 patients). Study endpoints were: treatment failure, defined as any atrial tachyarrhythmias lasting > 3 months, and treatment-related adverse events (acute when ≤ 1 month of procedure and long-term when > 1 month of procedure).

Results: At a mean follow-up of 42±17 months, 45% of Group B patients were in sinus rhythm (SR) vs. 53% in Group A after one procedure (p=0.39) and 75% after redo procedures (p=0.001) (see figure). Fifteen acute adverse events occurred (12 in Group A vs. 3 in Group B, p=0.001), mainly periprocedural cerebral thromboembolism (6 in Group A vs. 2 in Group B, p=0.02). The independent predictors of post-ablation cerebrovascular accidents were prior stroke (OR 1.195, 95% CI 1.057-1.350) and AF duration at the procedure (OR 1.011, 95% CI 1.001-1.021). At follow-up, 69 long-term adverse events occurred (12 in Group A vs. 57 in Group B, p=0.001): Group B patients resulted associated with a significant difference in the incidence of adverse events between the two groups.
Asymptomatic cerebral lesions in pulmonary vein isolation under therapeutic anticoagulation


Background: Left atrial radiofrequency ablation has been shown to carry a risk of asymptomatic cerebral lesions. No data exists in patients under full anticoagulation throughout the ablation procedure. The aim of this study was to quantify the amount of silent cerebral lesions assessed by preprocedural and postprocedural MRI in these patients and to identify clinical or procedural parameters that increase the risk.

Methods: A total of 111 consecutive patients undergoing catheter ablation for paroxysmal (n=69; 62.2%) or persistent (n=42; 37.8%) atrial fibrillation were included in the study. Pulmonary vein antrum isolation, roofline, mitral isthmus line, and CFAE ablation using 3.5mm open-irrigated tip catheters were performed, as needed. All patients underwent preprocedural and postprocedural cerebral MRI.

Results: Postprocedural MRI revealed new embolic lesions in 14 patients (12.6%), all of them asymptomatic. The only clinical parameter showing a significant correlation with cerebral embolism was smoke in transesophageal echocardiogram (p=0.012). Type of atrial fibrillation showed a trend with 6/63 paroxysmal (9.5%) vs. 8/34 persistent patients (23.5%; p=0.098). Additionally, the CHA2DS2-VASc-Score revealed a trend to significance (p=0.057). Procedural parameters contributing to an increased risk were electrical cardioversion (p=0.026) and CFAE lesions (p=0.016). The only two factors showing a trend to significance in multivariate analysis remained CFAE ablations and smoke in TEE.

Conclusions: Radiofrequency ablation in patients under therapeutic anticoagulation is associated with a substantial risk of silent embolism detected by cerebral MRI. Significant risk factors for cerebral lesions are CFAE ablations and smoke in TEE and electrical cardioversion during the ablation procedure.
mild or moderate aortic incompetence was defined as AI ≤ 2+.

Conclusions: Severe mitral regurgitation is a strong and independent predictor of adverse outcome after TAVI and plays a crucial role in the selection process.

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The impact of pulmonary hypertension on outcome in TAVI patients: a two-centre experience

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Background: The prognosis of patients with aortic stenosis (AS) and pulmonary hypertension (PH) is poor though not fully understood. Transcatheter aortic valve implantation (TAVI) facilitates treatment of patients in end-stage AS many of whom are suffering from severe PHT. The aim of our study was to elucidate the impact of PH on outcome after TAVI.

Methods and results: Pre and 90 days post TAVI, pulmonary artery systolic pressure (PASP) was determined non-invasively by echocardiography in 326 patients undergoing TAVI. PASP was classified as absent (<30mmHg), mild to moderate (30-60mmHg), and severe (>60mmHg).

Conclusions: Degree of MR improves post TAVI, regardless of etiology of MR and pathology of the mitral valve. Long term assessment of MR should be performed in order to confirm persistence of MR improvement.

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Perivalvular aortic regurgitation: a major predictor of 1-year mortality after a successful TAVI procedure - Insights from the FRANCE2 registry

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Background: A significant peri-valvular aortic regurgitation (AR) is observed in 15-20% of the cases after a successful transcatheter aortic valvular implantation...
Transcatheter aortic valve implantation (TAVI) in clinical practice / New insights in myocardial infarction by multimodality imaging

3879 The impact of transcatheter aortic valve implantation on resource use. Results from the German transcatheter aortic valve interventions registry

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Purpose: Transcatheter aortic valve implantation (TAVI) has been shown to improve survival compared with standard therapy in patients with severe aortic stenosis who are ineligible for surgery. Especially older patients with aortic stenosis cannot always be offered conventional surgical aortic valve replacement at an acceptable risk. Therefore TAVI is currently an alternative treatment option. The effects of TAVI on resource use regarding hospital stays have not been reported from a large scale cohort.

Methods: Patients with symptomatic, severe aortic stenosis are included in the prospective multicentre German transcatheter aortic valve interventions registry since 2009. This registry monitors current use, outcome of transcatheter aortic valve interventions in daily clinical practice, and assesses safety, effectiveness and health economic data. We performed an analysis regarding inpatient hospital stays for a subset of patients who underwent TAVI and completed the one-year follow-up. These results refer to hospital stays one year before and after TAVI.

Results: Resource use data were eligible for 415 patients who survived 12 months after TAVI (average age 81.9 ± 5.9 years; men 73.7%). In the year before TAVI 2.4 inpatient hospital stays were recorded on average (95% CI 2.1 - 2.7). Among the this average number due to cardiovascular causes was 2.0 ± 1.2, indicating the clinical relevance and severity of this heart disease. Of those patients who give information about hospital stays (n=354), 33.6% had one admission (2 admissions: 29.2%, 3: 18.1%, >4: 9.3%). >5.4% due to any cause. 12 months after the TAVI procedure 35.2% (142/403) of the patients had at least one hospital stay. The mean duration till rehospitalisation was 25.7 ± 17.5 weeks. The Kaplan-Meier estimation for the one-year rehospitalisation rate was 30.2%. Patients with rehospitalisation had on average 1.5 ± 0.9 admissions with a mean duration of 2.5 ± 2.9 weeks. Of those patients who give information about the number of hospital stays 70.4% reported one admission due to any cause (2: 20.0%, 3: 5.9%, ≥4: 37.3%, ≥5: 3.0%).

Conclusions: Among patients from the German transcatheter aortic valve interventions registry with severe aortic stenosis TAVI resulted in meaningful reductions in resource use regarding inpatient hospital stays one year after TAVI. The authors are grateful to the members of all clinics, which provided data to the German transcatheter aortic valve interventions registry.

NEW INSIGHTS IN MYOCARDIAL INFARCTION BY MULTIMODALITY IMAGING

3888 Effect of manual thrombus aspiration during primary ST-segment抬升 myocardial infarction on infant size: a delayed enhancement MDCT study

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Objectives: We sought to assess whether manual thrombus aspiration could reduce infant size in patients with acute ST-elevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention (PCI).

Background: The efficacy of manual thrombus aspiration during primary PCI for acute MI remains controversial.

Methods: We studied 86 consecutive patients presenting with first acute STEMI (Killip-II) within 12 hours after the symptom onset who underwent randomization to conventional PCI without thrombus aspiration (group I, N=42) or conven- tional PCI without thrombus aspiration (group II, N=44). The use of glycoprotein IIb/IIIa inhibitor (GPI) was left to the discretion of the operator. All patients received aspirin 300 mg and clopidogrel 600 mg before PCI and underwent delayed enhancement (DE) multi-detector computed tomography (MDCT) immediately after PCI without injection of an additional contrast media for assessment of infant size, defined as the total volume of myocardium showing DE. DE MDCT was repeated at 2 months after PCI. The primary endpoint was infant size reduction at 2 months. Baseline clinical characteristics and angiographic findings were similar between the 2 groups. There were no differences between group I and II in symptom-to-door-time (204±205 min vs. 217±168 min), door-to-balloon-time (70±42 min vs. 69±25 min), PCI-to-MDCT time (17±15 min vs. 13±6 min), Pre-PCI TIMI 0/1, post-PCI TIMI 3, or the use of GPI. Markers of myocardial repolarisation showed benefit in group I but not in group II (Table 1).

Results: Infant size was reduced (p<0.0001) by a mean difference of 0.38 ml in group I vs. 0.54 ml in group II (p=0.002). The difference in the size of myocardium showing DE between group I and II was 0.16 ml (p=0.045).

Conclusions: Manual thrombus aspiration during primary PCI for acute STEMI reduces infant size.
by 2-dimensional echocardiography were similar between group I and II (17±1.8 mL vs. 22±2.3 mL and 58±11% vs. 55±10%, respectively). At 2 months, there was no difference in infarct size and left ventricular ejection fraction between the groups: 15±1.0 mL vs. 17±1.2 mL and 62±12% vs. 60±12%, respectively. No adverse cardiac events occurred in either group during the 2-month clinical follow-up.

Conclusions: Manual thrombus aspiration was not associated with reduction in infarct size in patients with acute ST-elevation MI receiving timely reperfusion therapy.

In vivo non invasive quantitative assessment of passive diastolic stiffness of infarcted myocardium using shear wave imaging

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Background: Quantitative imaging of myocardial stiffness is important for the evaluation of systolic (active) and diastolic (passive) LV function. No tool is available to quantify non-invasively myocardial stiffness, which is determinant in case of diastolic heart failure. Shear Wave Imaging (SWI) is a new non invasive ultrasound technique that allows quantitative time-varying myocardial stiffness in vivo. In this study, we investigate the potential of this new technique to quantify the change of passive diastolic myocardial stiffness in ovine model of ischemic heart failure.

Methods: SWI was performed in vivo on five open-chest sheep. A linear conventional ultrasonic transducer (8 MHz) was positioned on the LV anterior wall. Shear waves were generated remotely in the myocardium using the acoustic radiation force induced by the ultrasonic probe. The shear wave propagation was imaged in real-time using an ultrafast scanner prototype (12 000 frames/s, Supersonic imagine, France). The local myocardial stiffness was derived from the shear wave speed. 12 shear wave propagation experiments were performed every 60ms to measure the stiffness variation within one cardiac cycle. Myocardial stiffness was also assessed invasively in the same region using the pressure-segment length relationship obtained by transvenous pressure sensors (Sonimetrics, Canada). The ligation of one diagonal of the left anterior descending coronary artery was achieved to induce ischemia during 2 hours, and reperfusion was performed during 30 minutes. Measurements were made at baseline, during ischemia and after reperfusion.

Results: Diastolic stiffness of the ischemic myocardium was found to increase after 45 minutes of ischemia. The shear wave speed increased from 0.81±0.16 m/s to 1.5±0.4 m/s (p<0.01). After reperfusion, diastolic stiffness increased even more strongly and diastolic shear wave speed reached 2.8±1.1 m/s (p<0.002). The slope of the end-diastolic pressure-segment relationship, which increased from 10.3±4.2 to 31±6.2 kPa, confirmed the stiffening. The peak diastolic strain rate decreased (from 2.4±0.35 s-1 to 0.8±0.13 s-1) demonstrating impaired relaxation of the ischemic segment. Finally, TTC staining performed on the explanted myocardium confirmed the presence of a large infarcted zone.

Conclusions: SWI was able to quantify non-invasively the increase of passive diastolic myocardial stiffness after myocardial infarction and reperfusion. We believe that this new non invasive real time ultrasound evaluation of passive myocardial stiffness may provide important information for prevention of sudden cardiac death and even with implantable cardioverter defibrillators which cannot be acquired on magnetic resonance imaging.

Myocardial fibrosis and fat may be substrates of critical ventricular arrhythmia. comparison of 320 slice CT images in subjects who had ventricular fibrillation with sustained ventricular tachycardia

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Purpose: If specific organized substrates of ventricular fibrillation (VF) are identified, they may provide important information for prevention of sudden cardiac death. 320 slice CT can acquire images in one heart beat and even if arrhythmia occurs during acquisition, clear heart images can be obtained. We compared 320 slice CT heart images in subjects who had VF with those who had sustained and non-sustained ventricular tachycardia (VT).

Methods: A total of 94 subjects who had VF (18 subjects; age, 57±16 yrs), sustained VT (18 subjects; 60±20 yrs) or non sustained VT (58 subjects; 59±15 yrs) underwent 320 slice CT (Aquilion). If there was a contrast defect in myocardium in early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis (MF). If the contrast defect continued in late phase with CT values < -9 HU, we diagnosed myocardial fatty change (MFC).

Results: There were no significant differences of several factors except ratio of complete right bundle branch block as represented in the table. On CT, there were no significant differences in percentage of coronary arteries with >50% stenosis among the 3 groups, but MF was significantly more common in VF group (67%, all MF was in left ventricle) than in non sustained VT group (28%, p<0.05), MFC was significantly more common in sustained VT group (56%, half of MFC was in right ventricle) than in VF group (22%, p<0.05) and in non sustained VT group (29%, p<0.05).

Conclusions: MF and MFC may be substrates of VF or sustained VT. 320 slice CT can evaluate coronary arteries and myocardium in subjects with arrhythmia and even with implantable cardioverter defibrillators which cannot be acquired on magnetic resonance imaging.

Association between left ventricular longitudinal function and neurohormonal activation after acute myocardial infarction. A two dimensional speckle tracking study

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Background: N-terminal pro-B type natriuretic peptide (NT-proBNP) is released in response to increased myocardial wall stress and is associated with adverse outcome in acute myocardial infarction. However, little is known about the relation between longitudinal deformation indices and NT-proBNP.

Methods and results: We consecutively included 611 patients with acute myocardial infarction admitted to a tertiary centre and performed echocardiography within 48 hours of admission. Global longitudinal myocardial function was assessed using 2-dimensional speckle tracking (DSTE) simultaneously with measurement of plasma NT-proBNP. A significant linear relation between NT-proBNP and global longitudinal strain (GLS) was found (r=-0.0001, r=-0.44). GLS emerged as the strongest predictor of log(NT-proBNP) (p<0.001). In patients with preserved systolic function (LVEF >45%), GLS remained strongly correlated with NT-proBNP (r=-0.0001, r=-0.50). The C statistic associated with prediction of upper versus lower quartiles of NT-proBNP was significantly higher for GLS compared to LVEF (0.76 vs. 0.56; p<0.0001).

Conclusion: Left ventricular longitudinal function assessed by GLS exhibits a stronger association with NT-proBNP levels in acute myocardial infarction compared to LVEF. In patients with apparently preserved systolic function GLS is superior to LVEF in identifying increased neurohormonal activation.

Two-dimensional longitudinal strain is more accurate than three-dimensional longitudinal strain to identify infarcted LV segments in STEMI patients


Purpose: To compare 2D vs 3D longitudinal strain (LS) in normal hearts and in patients with recent STEMI.

Importantly, this comparison was made directly using the same ultrasound devices.
Methods: In 123 healthy subjects (aged 44.1±14 years, range 18-75) and 46 patients (58.1±13 years) with recent STEMI, three apical LV views for measuring 2D-LS (70±9 fps) and 4-beat LV full-volume data sets (31±4 fps) for measuring 3D-LS were acquired 8.3 days after primary PCI using Vivid E9 scanner and analyzed with dedicated softwares (BT11, GE Healthcare, Horten, N). All subjects were selected for good image quality, sinus rhythm and adequate 2D/3D speckle-tracking in at least 14 of all 17 segments. In pts, 2D-LS and 3D-LS were compared against 3D wall motion score (WMS) and delayed-enhancement at magnetic resonance (DE-MRI) performed ≥24h apart from echo study, both at segmental and global levels.

Results: In healthy subjects, global 2D-LS values were significantly lower than 3D-LS (−2.1±1.9% vs. −19.1±2.1%, bias 1.3±1.2%, p<0.001), with whom were also weakly correlated (r=0.37, p<0.001). In pts, global 2D-LS had closer correlations with infarct size index at DE-MRI, 3D WMS index and EF (r=0.65, 0.70, -0.68) than global 3D-LS (r=0.36, 0.48, -0.56, respectively, p<0.01 for all). Segmental 2D-LS values showed a higher discriminative power (F ANOVA = 144 vs 50 for 2D-LS vs 3D-LS, p<0.001) to identify segments with (dys)kinesia (AUC 0.81 vs 0.70) or transmural necrosis (AUC 0.83 vs 0.73, p<0.0001 for all).

Conclusions: Significant differences were identified between 2D-LS and 3D-LS in both normals and STEMI patients. Between the two tested vendor-specific algorithms, 2D-LS was more accurate than 3D-LS to identify infarcted LV segments and to reflect global LV dysfunction in STEMI patients.

**Necrosis and ischemia for risk stratification in patients with known or suspected ischemic cardiomyopathy. Study with stress cardiac magnetic resonance**


Objectives: To determine the prognostic value of necrosis and ischemia analyzed with dyssynchronous stress cardiac magnetic resonance (CMR) for predicting major events in patients with systolic dysfunction and known or suspected ischemic myocardiopathy.

Methods: 274 patients with depressed ejection fraction (<50%, 38±9%) referred for study with stress CMR for known or suspected ischemic cardiomyopathy. We quantified (number of segments, s) the presence of severe ischemia (dyssynchronous-induced perfusion deficit and wall motion abnormalities) and the extent of necrosis (late gadolinium enhancement in >50% wall thickness). We considered abnormal if more than one segment was altered.

Results: Ischemia and necrosis were ruled out in 89 patients (32%), Necrosis in 184 (67%) and severe ischemia in 22 (8%). During a median of follow-up of 329 days, 28 first events were detected (10%, death or infarction). Patients were excluded when suffered a major event or revascularization. Major more events were detected in patients with necrosis (12% vs 7%, p<0.01) and especially in those with severe ischemia (45% vs 7%, p<0.001). After adjusting for baseline characteristics and CMR indexes, predictors of major events were (HR with 95% CI) end-systolic volume (1.01 [1.01-2.02 per m/m², p=0.001), extent of necrosis (1.1 [1.01-1.2] per s, p=0.02) and extent of severe ischemia (2.1 [1.7-2.7] per s, p<0.001).

Risk of major events was higher (p<0.01) in patients with severe ischemia (45%) compared with those with necrosis but without ischemia (8%) and those without necrosis or ischemia (6%).

Conclusions: In patients with known or suspected ischemic cardiomyopathy, the presence of severe ischemia is the most powerful prognostic index. A simultaneous study of viability and ischemia is recommendable for risk stratification.

**P3908 History of stroke in patients with coronary artery disease in the REACH Registry: impact on cardiovascular and bleeding event rates**

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Methods and results: From the REACH registry of 55,656 patients (of which 4460 (16.9%) had prior stroke/TIA) and 4-year follow-up were analyzed. Patients with prior stroke/TIA were older (70.5±9.7 years vs. 67.6±10.0 years, p<0.0001), more frequently female (34.1% vs. 28.2%, p<0.0001), and had higher baseline risks of bleeding and CV events.

Patients with a history of stroke/TIA had increased risks of all-cause death, MI and stroke relative to patients without history of stroke/TIA. While total bleeding was not increased, non-fatal hemorrhagic stroke (HS) rates were increased in...
these patients. In addition, among patients on dual antiplatelet therapy, there was a 7-fold (95% CI: 1.7-29.3) crude and a 4.9-fold (1.1-20.8) adjusted increase in the risk of non-fatal HS in patients with vs. without prior stroke/TIA. The excess risk of HS was greatest in the 1st year following a stroke/TIA (adjusted HR: 3.62, 95% CI: 1.67-7.85, p< 0.0003), whereas beyond 1 year, risk was not increased (adjusted HR = 1.11, 95% CI: 0.47-2.61).

Cruce and adjusted 4-year outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior history of stroke/TIA</th>
<th>Crude HR</th>
<th>p</th>
<th>Adjusted HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=5129)</td>
<td>(n=4460)</td>
<td>(95% CI)</td>
<td>(96% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>11.2 (2072)</td>
<td>1.67 (1.53-1.82)</td>
<td>&lt;0.0001</td>
<td>1.21 (1.10-1.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MI</td>
<td>6.0 (1097)</td>
<td>1.48 (1.31-1.68)</td>
<td>&lt;0.0001</td>
<td>1.22 (1.07-1.40)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.1 (739)</td>
<td>3.43 (3.06-3.85)</td>
<td>&lt;0.0001</td>
<td>2.72 (2.41-3.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total serious bleeds</td>
<td>2.5 (460)</td>
<td>1.39 (1.14-1.69)</td>
<td>0.001</td>
<td>1.06 (0.86-1.30)</td>
<td>0.61</td>
</tr>
<tr>
<td>Non-fatal haemorrhagic stroke</td>
<td>0.3 (49)</td>
<td>0.6 (19)</td>
<td>1.96 (1.63-3.4)</td>
<td>0.013</td>
<td>1.74 (0.99-3.03)</td>
</tr>
</tbody>
</table>

Adjusted included all baseline characteristics found to be independent correlates of prior stroke/TIA.

Conclusions: In CAD, a history of stroke/TIA is associated with an increased risk of death, MI, or stroke. However, it is also associated with a disproportionate increase in HS, particularly when patients receive dual antiplatelet therapy and in the first year following stroke/TIA. This suggests that while these patients are at high risk of cardiovascular events, increasing antiplatelet therapy carries a specific risk of HS.

P3910

Triple antiocoagulant therapy following an acute coronary syndrome: prevalence, bleeding rate and utility of the HAS-BLED score

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Purpose: The aim of this study was to evaluate the prevalence of triple antiocoagulant therapy (TT; warfarin, aspirin and clopidogrel) and associated bleeding risk, compared to double antiplatelet therapy (DAPT; aspirin and clopidogrel) in patients discharged from a Coronary Care Unit (CCU) following an acute coronary syndrome. Furthermore, we investigated the accuracy of the HAS-BLED risk score in predicting bleeding events in TT patients.

Methods: We retrospectively identified all patients from the Lund municipality on TT upon discharge from the CCU at Skane University Hospital in Lund between 2005 and 2010. TT patients were compared with age- and sex-matched controls discharged with DAPT. Major bleeding was defined in accordance with the HAS-BLED derivation study: Any bleeding requiring hospital care or occurring in a haemoglobin level of more than 20 mg/L or requiring blood transfusion.

Results: A total of 2423 patients were screened, of whom 159 (6.6%) were on TT. The mean age was 67.2 (±5.9) years. The most common indication for TT was atrial fibrillation (n=43.69%) followed by apical akinisia (n=60, 37.8%). The mean duration of TT was 37 (±3.3) months. Upon termination of TT, Warfarin was discontinued in 82 (52.2%) patients and clopidogrel in 57 (36.3%). The cumulative incidence of spontaneous bleeding events was significantly higher in the TT group at one year (10.2% vs 3.2%, p< 0.001). The HAS-BLED score significantly predicted spontaneous bleeding events in TT patients (area under the ROC curve 0.67, 95% CI = 0.54 – 0.79, p=0.048).

Conclusions: TT was relatively common following an acute coronary syndrome and associated with a threefold increase in major bleeding at one year compared to DAPT. The HAS-BLED risk score predicted bleeding events with moderate accuracy. Careful patient selection and clinical follow-up for TT appears warranted.

P3911

Prognosis of unrecognized myocardial infarction in elderly men and women: the Rotterdam Study

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Background: Unrecognized myocardial infarction (MI) is frequent in the general elderly population. Its prognosis is reportedly at least as unfavorable as that of recognized MI, particularly in men. However, contemporary data with long follow-up are lacking.

Objective: To investigate the long-term prognosis of unrecognized MI with respect to all-cause and cause-specific mortality, and to investigate any sex-differences in prognosis.

Methods: In the population-based Rotterdam Study (2672 men and 3862 women), we determined the presence of unrecognized MI and recognized MI at the baseline (1990-1993). The cohort was followed for nearly two decades for all-cause and cause-specific mortality.

Results: During 82,268 person-years of follow-up (median 15.6 years) 3,412 persons died (1300 due to a cardiovascular cause). Both men and women with unrecognized MI had an increased risk of all-cause mortality (Hazard ratio [95% confidence interval] = 1.72 [1.43 – 2.07] and 1.36 [1.14 – 1.61] respectively). Having an unrecognized MI increased the risk of cardiovascular mortality by two-fold among men (2.19 [1.86 – 2.91]) and by approximately 30% among women (1.36 [1.03 – 1.81]), and by approximately 40-45% the risk of noncardiovascular mortality (1.46 [1.14 – 1.89]; 1.39 [1.10 -1.75]) in men and women respectively. Recognized MI was associated with an increased risk of all-cause mortality in men and women (1.67 [1.45 – 1.94]; 1.87 [1.54 – 2.28]).

Conclusions: The long-term prognosis of persons with unrecognized MI is worse than that of persons without any type of MI. In men the prognosis is as unfavorable as that of persons with recognized MI. This adverse prognosis applies to both cardiovascular mortality and noncardiovascular mortality.

P3912

Impact of positive airway pressure therapy for cardiovascular outcomes in patients with coronary artery 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 coronary artery disease (CAD) and sleep-disordered breathing (SDB).

Methods: We studied 1693 consecutive patients who underwent polysomnography from November 2004 to July 2011, and enrolled 150 patients with SDB (apnea-hypopnea index [AHI] ≥ 15), who had been admitted to hospital because of CAD before polysomnography. They were divided into two groups; a PAP-treated group (AHI > 15 hour and treated with continuous positive airway pressure or adaptive servo ventilation) and an untreated SDB group (AHI ≤ 15 hour and untreated with PAP devices). The frequency of death and hospitalization due to cardiovascular events (acute coronary syndrome, coronary intervention, heart failure, stroke, and fatal arrhythmia) between the groups was analyzed using multivariate analysis.

Results: The mean follow-up period was 35.2±23.8 months and 26% of the patients died or were re-admitted to hospital due to CVD. Kaplan-Meier survival curve indicated that event-free survival was significantly higher in the PAP-treated group than in the untreated SDB group (Figure 1). Multivariate analysis showed that the risk for death and hospitalization was significantly higher in the untreated SDB group (hazard ratio [HR], 2.62; 95% confidence interval [CI], 1.09 to 6.64; p < 0.05) than the PAP-treated group.

Conclusion: In patients with CAD and SDB, the use of PAP therapy improves long-term cardiovascular outcomes.

P3913

Time course of depressive symptoms and first coronary heart disease and stroke in older adults. A prospective observational study cohort: the Three-City study

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Objective: To prospectively investigate the association between the course of depressive symptoms over time and the occurrence of coronary heart disease (CHD) and stroke events in older adults.

Setting: The Three-City Study is a French multisite (Bordeaux -(South-West), Dijon (East) and Montpellier (South East)) community-based prospective cohort.

Participants: 7308 men and women aged 65 years and over with no history of CHD, stroke or dementia were recruited through the electoral rolls of these cities.

Depressive symptoms assessed by the CESD questionnaire and other risk factors were quantified at baseline and after 2 and 4 years of follow-up. Incident CHD and stroke events were adjudicated by an independent expert committee. Depressive
In conclusion, the results of this study support the possible clinical usefulness of the left ventricular systolic function 2-D strain measures in detecting CHF patients prone to experience major arrhythmic events.

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- G.R. Hong, Y.J. Choi, J.S. Lee, S.M. Kim, W.J. Park, J.W. Son, J.H. Cho, H. Houle, J.W. Hal, N.S. Chung, Yong University College of Medicine, Cardiology Division, Seoul, Korea, Republic of; Yonsei University College of Medicine, Cardiology Division, Seoul, Korea, Republic of; 2 Yerunam University, Daegu, Korea, Republic of; 3 Busan National University Hospital, Busan, Korea, Republic of; 4 Siemens Medical Solution, Mountain View, United States of America

**Background:** Conventional echo-Doppler parameters could not predict exercise capacity and symptoms in patients with compensated chronic systolic heart failure (HF). We have previously shown that left ventricular (LV) vortex flow is closely correlated with hemodynamic changes in the LV. The aim of this study was to evaluate whether quantitative LV flow vortex analysis by contrast echocardiography (CE) was superior to conventional echo-Doppler parameters to predict exercise capacity in patients with systolic heart failure.

**Methods:** 35 patients who had chronic systolic dysfunction (EF < 40%) underwent 2-dimensional CE with intravenous infusion of Definity® and imaged at a mechanical index of 0.4-0.6 in the A4C and AP/LV views. The morphologic and pulsatility parameters of LV vortex flow were measured using Omega Flows® (Siemens Medical Solution, Mountain View, CA). After CE, 6 minute walk test and cardiopulmonary exercise test were performed in all patients.

**Results:** There were no significant correlation between conventional echo-Doppler parameters and exercise capacity. However, vortex pulsatility parameters RS and VRS showed significant correlation with 6 minute walking distance (r = 0.645, p = 0.01, r = 0.598, p = 0.05, respectively) and VO2 (r = 0.577, p = 0.01, r = 0.503, p = 0.03, respectively). Vortex morphology and location parameters did not show significant correlation with exercise capacity. Figure represents patients who have higher vortex pulsatility (A) show longer 6MWD than lower pulsatility (B) with comparable conventional echo-Doppler parameters.
Conclusion: The data from this study shows that quantitative LV flow vortex parameters are superior to conventional echo-Doppler measures to predict exercise capacity in patients with chronic compensated systolic heart failure.

**P3919**

The incremental prognostic value of inotropic contractile reserve combined with advanced mitral regurgitation in identifying responders to cardiac resynchronization therapy

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**Purpose:** Inotropic contractile reserve (ICR) during dobutamine stress echocardiography may play a pivotal role in identifying responders to cardiac resynchronization therapy (CRT) and to compare it with other echocardiographic indices used in predicting CRT response.

**Methods:** 42 pts referred for clinically indicated CRT were evaluated. All patients underwent low-dose dobutamine stress echocardiography to assess inotropic contractile reserve, defined as an improvement of ejection fraction (EF) ≥5%. Mitral regurgitation (MR) severity was divided in four grades and advanced MR was defined as the presence of grade III or IV regurgitation. The interventricular mechanical delay index (by PW Doppler) and Opposing Wall Delay Index (by TDI) were used to assess interventricular and intraventricular dyssynchrony respectively. Responders were defined by ≥15% reduction in left ventricular end systolic volume after CRT.

**Results:** 42 pts (mean age 68±7 years old, 28 men, NYHA III-IV) were included. The mean QRS duration was 154±9ms. During a 12-month follow-up, 29 pts (69%) had responded. The ejection fraction before CRT was 24±5% and increased to 31±4% after CRT (p<0.05). The presence of ICR was the strongest predictor of response to CRT (area under the curve, 0.84; p<0.01) combined with interventricular dyssynchrony index (area under the curve, 0.66; p<0.05) and intraventricular dyssynchrony index (area under the curve, 0.74; p<0.05). The combination of ICR with the presence of advanced MR offered even greater predictive value (area under the curve, 0.89; p<0.05).

**Conclusions:** Inotropic contractile reserve was a stronger predictor of CRT response than conventional and TDI indices, and its diagnostic value can be further enhanced when combined with the presence of advanced functional MR. Dobutamine stress echocardiography may facilitate differential diagnosis between LVNC and DCM. In DCM, and 63% (range: 55-74) in controls. Maximal systolic thickness of “non-compacta” was 1.6±0.01 cm in LVNC compared to 0.4±0.02 cm in DCM (p<0.0001), and 0.2±0.01 cm in controls (p<0.0001). Maximal systolic thickness of “compacta” was lower in LVNC (0.50±0.02 cm) compared to DCM (1.0±0.05 cm; p<0.0001) and controls (1.1±0.03 cm; p<0.0001). Maximal systolic thickness of “compacta” was ≤8.2 mm (range 3.5-8.2) in LVNC versus ≥8.5 mm (range 8.5-14.0; p<0.0001) in DCM and ≥8.6-15.0; p<0.0001 in controls. The ratio of maximal systolic thickness of the indexed basal septum to that of the “compacta” was ≥0.64/m² (range 0.64-1.90) in LVNC versus ≤0.61/m² (range 0.29-0.61) in DCM and ≥0.57/m² (range 0.28-0.57) in controls.

**Conclusion:** Maximal systolic “compacta” thickness ≥8.2 mm and a ratio of indexed septal wall thickness to “compacta” thickness ≥0.64/m² is specific for LVNC. This observation may be particularly useful in patients with dilated ventricles and facilitate the differential diagnosis between LVNC and DCM.

**P3921**

Visual assessment of apical rocking predicts response and long-term survival following cardiac resynchronization therapy


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**Background:** Motion of the left ventricular (LV) apical myocardium perpendicular to the LV long axis (apical rocking), is an often observed phenomenon in synchronously contracting ventricles. In this study, we tested if visual assessment of apical rocking can predict reverse remodeling and survival in cardiac resynchronization therapy (CRT) candidates.

**Methods:** A total of 201 patients eligible for CRT (63±11 years, ejection fraction 26±6%) underwent standard echocardiographic examination before and 12±2 months after device implantation. Three blinded physicians were asked to predict response to CRT (yes/no) by visually assessing the presence of apical rocking and extend and localization of infarct scar. Response was defined as LV end-systolic volume decrease ≥15%. Patients were followed for an average period of 37±19 months for the occurrence of cardiac death.

**Results:** Visually assessed apical rocking predicted reverse remodeling with a sensitivity, specificity and accuracy of 90, 86, and 91%, respectively. Physicians’ prediction of CRT response integrating apical rocking and scar burden resulted in a sensitivity, specificity and accuracy of 95, 85, and 90%, respectively. When corrected by CRT, visually detected apical rocking was the only parameter associated with favorable outcome, whereas worse functional class, a high scar burden (≥6 segments) and atrial fibrillation were associated with poorer survival (Figure). Baseline LV ejection fraction and QRS duration did not predict outcome.

**Conclusions:** Simple visual assessment of apical rocking is a robust predictor of response and long-term survival after CRT. In patients with heart failure of ischemic origin, visual assessment of scar burden further enhances predictive power of visible LV dyssynchrony.

**P3922**

Diagnostic and prognostic role of global longitudinal strain in patients with heart failure and normal ejection fraction


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**Introduction:** Many patients have clinical and bio-marker evidence of heart failure but normal left ventricular (LV) ejection fraction (EF) (<50%). More subtle abnormalities of systolic function may explain the syndrome. We measured global longitudinal strain (GLS) to identify LV systolic dysfunction in patients with HfEF. Methods: 313 patients referred to our clinic with symptoms and signs suggesting heart failure (median age 74 years, 42% women, 40% in atrial fibrillation (AF)) with an LVEF >50% were recruited. Three different subgroups were identified: 113 patients with no substantial cardiac disease, left atrium (LA) <40cm; and NT-proBNP ≥400ng/l; 99 “gray cases” (LA ≥40 cm or NTproBNP <400ng/l); and 138 with definite HfEF (LA ≥40 cm and NTproBNP >400ng/l). All underwent detailed echocardiography. Peak systolic strain was defined as the peak negative

**Results:**

**P3920**

Improved differential diagnosis between left ventricular non-compaction and dilated cardiomyopathy


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**Introduction:** Left ventricular non-compaction (LVNC) is characterized by a two-layered myocardium consisting of a non-compacted inner and a compacted outer layer. Since left ventricles of many LVNC patients are dilated and exhibit poor systolic function, LVNC can be misinterpreted as dilated cardiomyopathy (DCM). This study assesses whether novel echocardiographic criteria may facilitate differential diagnosis between DCM and LVNC.

**Methods:** Transthoracic echocardiography was performed in 30 LVNC patients (mean age 36.3±17 years), 40 age-matched patients with DCM, and 42 age-matched controls. Maximal systolic thickness of "non-compacta" and "compacta" was measured in standard short axis views (2-D) at the apical or midventricular level in the segments with most prominent recesses (LVNC) or most prominent trabeculations (DCM and controls). The thickness of the basal septum was measured in parasternal long axis view (M-mode).

**Results:** LV ejection fraction was 37% (range: 10-59) in LVNC, 29% (16-51) in DCM, and 63% (range: 55-74) in controls. Maximal systolic thickness of “non-compacta” was 1.8±0.01 cm in LVNC compared to 0.4±0.02 cm in DCM (p<0.0001), and 0.2±0.01 cm in controls (p<0.0001). Maximal systolic thickness of “compacta” was less in LVNC (0.50±0.02 cm) compared to DCM (1.0±0.05 cm; p<0.0001) and controls (1.1±0.03 cm; p<0.0001). Maximal systolic thickness of “compacta” was ≤8.2 mm (range 3.5-8.2) in LVNC versus ≥8.5 mm (range 8.5-14.0; p<0.0001) in DCM and ≥8.6-15.0; p<0.0001 in controls. The ratio of maximal systolic thickness of the indexed basal septum to that of the “compacta” was ≥0.64/m² (range 0.64-1.90) in LVNC versus ≤0.61/m² (range 0.29-0.61) in DCM and ≥0.57/m² (range 0.28-0.57) in controls.

**Conclusion:** Maximal systolic “compacta” thickness ≥8.2 mm and a ratio of indexed septal wall thickness to “compacta” thickness ≥0.64/m² is specific for LVNC. This observation may be particularly useful in patients with dilated ventricles and facilitate the differential diagnosis between LVNC and DCM.
After symptom onset for acute MI were taken on admission. Serum levels of ADMA, SDMA (its biologically inactive symmetrical stereoisomer and L-arginine) were determined using high-performance liquid chromatography. LTL was assessed by extraction of leukocyte DNA from venous blood samples and performing real-time PCR. The L-arginine/ADMA ratio was used as a biomarker of vascular oxidative stress and endothelial dysfunction. Patients from the lowest L-arginine/ADMA tertile were compared with patients from the higher L-arginine/ADMA tertiles. Results: Demographical data, chronic treatments, cardiovascular risk factors and history were similar for the 2 groups. Strikingly, in patients with the lower L-arginine/ADMA tertile, LTL was markedly reduced when compared with the highest L-arginine/ADMA tertiles (1.15 vs 1.27 ratio T5-T1, p=0.005). LTL was negatively correlated with age (r=-0.356, p=0.0042). Moreover, a trend for a positive correlation between LTL and L-arginine/ADMA ratio was noted (r=0.339, p=0.053) but not with SDMA (r=-0.069, p=0.686).

Conclusion: Our study showed that, in MI patients, reduced LTL was associated with increased levels of vascular oxidative stress, as assessed by serum L-arginine/ADMA ratio levels. Further experimental studies are now needed to explore the relationship between L-arginine metabolism pathways, endothelial dysfunction and mechanisms of leukocyte telomere shortening.

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**Comparison of left ventricular discoordination and dysynchrony assessment by radial strain imaging in cardiac resynchronization therapy**

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Background: Patients with nonischemic etiology, left bundle-branch block (LBBB) and QRS duration ≥150 ms are more likely to derive benefit from cardiac resynchronization therapy (CRT) than those without. This study aimed to compare mechanical discoordination and dysynchrony in CRT candidates.

Methods: Speckle-tracking strain imaging was performed in 120 CRT candidates and 60 patients with LVEF ≤35% and QRS duration <120 ms. CRT candidates were divided into subgroups according to the etiology of heart failure (ischemic vs nonischemic). QRS morphology (LBBB vs non-LBBB) and QRS duration (<150 ms vs <150 ms), respectively. Dysynchrony indices based on time-to-peak radial strain of anteroapical and posterior walls (AS-P delay) and standard deviation of time-to-peak radial strain (RS-SD) were measured. Discoordination was indexed using the mid-ventricular radial discoordination index (RDI-M).

Results: RDI-M could distinguish between patients in the narrow and wide QRS groups and between subgroups with and without favorable characteristics. Compared to ischemic candidates, nonischemic candidates had greater myocardial thinning (P=0.003), smaller myocardial thickening (P=0.009) and a greater RDI-M (%P=0.001). In contrast, AS-P delay and RS-SD failed to demonstrate significant differences between ischemic and nonischemic subgroups. CRT candidates with ischemic etiology were more likely to show dysynchrony without significant discoordination than nonischemic candidates.

Conclusions: Mechanical discoordination performed better than dysynchrony in differentiating CRT candidates with and without favorable characteristics.

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**Reduced leukocyte telomere length are associated with increased levels of vascular oxidative stress in patients with acute myocardial infarction**

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Purpose: Asymmetric dimethylarginine (ADMA), competes with L-arginine to inhibit NO synthase (NOS), leading to a decreased NO bioavailability, increasing vascular oxidative stress and endothelial dysfunction. Recent data suggest that reduced leukocyte telomere length (LTL) could be associated with increased risk for acute myocardial infarction (MI). The aim of our study was to analyse the relationship between LTL and ADMA, as a biomarker of oxidative stress, in patients with acute MI.

Methods: Blood samples from 33 consecutive patients hospitalized ≥24 hours after symptom onset for acute MI were taken on admission. Serum levels of ADMA, SDMA (its biologically inactive symmetrical stereoisomer and L-arginine) were determined using high-performance liquid chromatography. LTL was assessed by extraction of leukocyte DNA from venous blood samples and performing real-time PCR. The L-arginine/ADMA ratio was used as a biomarker of vascular oxidative stress and endothelial dysfunction. Patients from the lowest L-arginine/ADMA tertile were compared with patients from the higher L-arginine/ADMA tertiles.

Results: Demographical data, chronic treatments, cardiovascular risk factors and history were similar for the 2 groups. Strikingly, in patients with the lower L-arginine/ADMA tertile, LTL was markedly reduced when compared with the highest L-arginine/ADMA tertiles (1.15 vs 1.27 ratio T5-T1, p=0.005). LTL was negatively correlated with age (r=-0.356, p=0.0042). Moreover, a trend for a positive correlation between LTL and L-arginine/ADMA ratio was noted (r=0.339, p=0.053) but not with SDMA (r=-0.069, p=0.686).

Conclusion: Our study showed that, in MI patients, reduced LTL was associated with increased levels of vascular oxidative stress, as assessed by serum L-arginine/ADMA ratio levels. Further experimental studies are now needed to explore the relationship between L-arginine metabolism pathways, endothelial dysfunction and mechanisms of leukocyte telomere shortening.

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**Heart failure: what can we do for you today?**

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Purpose: Spontaneous hemolysis is associated with plasma free hemoglobin release in that it could increase oxidative stress phenomenon and enhance vascular cell damage, leading to endothelial dysfunction and ultimately atherosclerosis. We investigated if free hemoglobin release could be related to endothelial injury and atherosclerotic lesion extent in patients with cardiovascular risk factors (CRF).

Methods: Patients with cardiovascular risk factors who underwent coronary angiography for suspected stable coronary artery disease were eligible for inclusion. Levels of endothelial (CD144+ EMPs), erythrocytes (CD235a+ RBCMPs), platelets (CD41+ PMPs) and leukocytes-derived microparticles (CD11+ LMPs) were measured by flow cytometry methods on free platelets plasma samples. Levels of circulating free hemoglobin (CFH) were analyzed by absorption spectro-photometry methods. Significant CAD was angiographically defined as presence of at least 1 stenosis ≥50% luminal diameter narrowing. The atherosclerotic lesions extent was evaluated by the Gensini score calculation.

Results: A total of n= 97 subjects (63.6±1.1 years, 78% male gender/32% diabetes) fulfilled the inclusion criteria. These patients had significantly higher levels of CFH compared to healthy subjects without CRF. We observed higher levels of CFH in diabetic patients compared to non-diabetic subjects (10.21±0.9 vs 8.2±0.5 AU, p<0.03), whereas no significant influence of other risk factor (hypertension, dyslipidaemia, active smoking) was noted. Moreover, CFH levels were correlated with CD144+ EMPs (r=0.26, p=0.01), suggesting a potential link between hemolysis and endothelial dysfunction. Significant CAD was diagnosed in n=71 patients in whom the Gensini score was significantly correlated with CFH levels (r=0.44, p=0.001), as well as LMPs (r=0.31, p=0.01) and fasting glycerol (r=0.49, p=0.001). Multivariate regression analysis revealed that CFH levels were independently related to atherosclerotic lesions extent (p=0.017) after adjustment for other confounding factors.

Conclusions: In circulating free hemoglobin levels are associated with endothelial injury in patients with cardiovascular risk factors and atherosclerotic lesions severity in stable CAD subjects. These results suggest that CFH might influence coronary artery disease development.
Epigenetic regulation of cell adhesion and blood flow would impact the vascular response to reactive hyperemia and that these responses always reflect, in part, the degree of baseline endothelial activation.

**Methods and results:** Endothelial function was assessed in 647 patients (age 67±11, 468 males) with (n=464) or without coronary artery disease. Radial artery diameter and blood flow were measured at rest, 4.5 minutes after occlusion of a pneumatic cuff placed distal to the measurement site (low-flow-mediated constriction, L-FMC), and during the 4.5 minutes following cuff deflation (FMD). There was a strong inverse correlation between resting radial artery diameter and FMD (r=−0.34, P<0.0001). Of note, there was a strong positive correlation between resting radial artery blood flow and radial artery diameter (r=0.68, P<0.0001). The occlusion of the wrist cuff caused a 74±22% decrease in blood flow and a 2.5±2.5% vasoconstriction in radial artery diameter (L-FMC). Providing support to the concept that L-FMC (like FMD) is systematically related to changes in blood flow, there was a strong correlation between L-FMC and the reduction in blood flow caused by the inflation of the pneumatic cuff (r=0.26, P<0.0001). After 4.5 minutes of distal ischemia, the release of the pneumatic cuff caused a reactive hyperemia (302±43%). 2.5 minutes of ischemia caused a 24±7% reduction in L-FMC and a subsequent FMD (r=0.19, P<0.0001) for the correlation between increase in arterial diameter and the increase in arterial blood flow.

**Conclusions:** Arterial biomechanics and shear stress are important determinants of endothelial tone in resting conditions as well as during reactive hyperemia. By measuring the change in arterial diameter in the setting of reduced shear stress, L-FMC quantifies ‘resting’ endothelial function. In contrast, FMD reflects the (endothelial) reactivity to supranormal increases in shear stress (endothelial reactivity, or reactivity). From this perspective, a lower FMD in subjects with larger conduit arteries may not be representative of abnormal endothelial function but rather of an increased basal endothelial activity.

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**Epigenetic regulation of cell adhesion and communication by enhancer of zeste homolog 2 in human endothelial cells**

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**Objective:** Epigenetic modifications such as DNA and histone methylation have long-term effects on gene expression. The histone methyltransferase Enhancer of zeste homolog 2 (Ezh2) mediates trimethylation of lysine 27 in histone 3 (H3K27me3). This marks as a repressive epigenetic mark. Previous studies demonstrated an essential role for Ezh2 in the differentiation of human embryonic stem cells. In differentiated endothelial cells, however, information about the function of Ezh2 is missing. Therefore, the aim of our present study was to identify Ezh2 target genes in endothelial cells.

**Methods and Results:** Whole genome mRNA expression arrays identified 964 genes that were regulated by more than twofold 72 hours after siRNA-mediated knockdown of Ezh2 in human umbilical vein endothelial cells (HUVEC). Among them, genes associated with the gene ontology terms “cell communication” and “cell adhesion” were significantly overrepresented suggesting a functional role for Ezh2 in the regulation of angiogenesis. Indeed, matrigel angiogenesis assays revealed significantly impaired tube formation of HUVEC after silencing of Ezh2. To identify direct target genes of Ezh2, we performed chromatin immunoprecipitation experiments using a H3K27me3 antibody followed by whole genome promoter arrays (ChIP-on-chip) and identified 5,585 genes whose promoters were associated with H3K27me3. Comparative analysis with our mRNA expression data identified 276 genes that met our pre-defined criteria for putative Ezh2 target genes: i) up-regulation by more than twofold after knock down of Ezh2 and ii) association with H3K27me3. Notably, we observed a striking overrepresentation of genes involved in canonical and non-canonical Wnt signaling pathways. Epigenetic regulation of several Wnt-signaling genes by Ezh2 (namely catherin 13, integrin α1, VE-cadherin, Claudin-1, transforming growth factor α, frizzled homolog 7, lymphoid enhancer-binding factor 1, and wingless-type MMTV integration site family member 5B) was specifically confirmed by PCR analysis of DNA enrichment after chromatin immunoprecipitation using the H3K27me3 antibody.

**Conclusion:** Combining mRNA expression arrays and ChIP-on-chip analysis after siRNA-mediated silencing of Ezh2, we identified 276 Ezh2 target genes in endothelial cells. Ezh2-dependent repression of genes involved in cell adhesion and communication contributes to epigenetic regulation of angiogenesis.

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**The effects of AdVEGF-B and AdVEGF-D on angiogenesis and arteriogenesis in a novel porcine model of percutaneous bottleneck stent induced chronic myocardial ischemia and test adenosine (Ad) VEGF-D and VEGF-B gene therapy in this model.**

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**Purpose:** Purpose of this study was to develop a novel porcine model of chronic myocardial ischemia and test adenosine (Ad) VEGF-D and VEGF-B gene therapy in this model.

**Methods:** Ischemia was induced by restricting coronary blood flow in either proximal left circumflex artery (LCX) or left anterior descending artery (LAD) by installing a bare metal stent covered by a bottleneck shaped tube in domestic pigs. One week after the stent placement, gene transfer was conducted. Collateral vessels were assessed by the modified Miles assay, myocardial contrast echocardiography (MCE) and index of myocardial resistance (IMR) measurements, respectively.

**Results:** Notable collateral vessel formation to LCX and LAD area in the respective models was observed. Ejection fraction during stress decreased from 80% to 40% and 66% in the LAD and LCX models, respectively. The mean IMR was significantly increased at baseline, one week and five weeks, respectively. Infarct scar covered 12% and 20% of the left ventricle and cardiovascular mortality was 20% and 50% in the LCX and LAD models, respectively. ANGPTL4 was an insufficient capillary vessel enlargement, increased myocardial perfusion, and caused myocardial edema six days after gene transfer, but the effects were disappeared four weeks after gene transfer. These data provided evidence that adenoviral VEGF-B and VEGF-D gene transfers on blood vessel growth in the ischemic heart will be presented in detail in the congress.

**Conclusions:** We have established a novel porcine model of chronic myocardial ischemia, which is minimally invasive, repeatable, and which offers multiple clinically relevant endpoints. The LCX model, which is not as severe as the LAD model, can be applied to studies concerning collateral vessel formation while the more severe LAD model can be applied to study treatments for ischemic cardiomyopathy.

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**Protection against stroke through preservation of vascular integrity by angiopoietin-like 4 (ANGPTL4)**

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**Aims:** Timely recanalization of the occluded artery is the treatment for ischemic stroke, but has limited application. We demonstrated that ANGPTL4 has vasculoprotective effects in myocardial infarction by counteracting VEGF-induced permeability. Given the impact of vascular leakage and edema formation in tissue damage during stroke, preserving vascular integrity represents a pertinent strategy for brain protection. Therefore we hypothesized that ANGPTL4 might exert cerebral protection in stroke.

**Methods and Results:** In a mouse model of ischemic stroke, with 1 hour ischemia followed by 24 hr reperfusion, injection of ANGPTL4 at ischemia led to a decreased infarct size, as assessed by TTC staining (p<0.0008) and cerebral MRI (p<0.003). Brain edema was decreased in the ANGPTL4 treated group (p<0.002). Using PECAM1 stained vessels we showed that vascular network was preserved in ANGPTL4-treated mice (vascular density p<0.0017 and branching points p<0.002). We then assessed integrity of tight and adherens junctions using VE-cadherin and Claudin-5 immunostainings. We showed a significant increase in VE-cadherin and Claudin 5 areas (normalized to endothelial cell surface) in ANGPTL4-treated mice. Thus ANGPTL4 protects from global vascular damage, but also specifically protects from ischemia-induced junctions disruption. ANGPTL4 protective effect on junctions was further assessed in vitro using microvascular endothelial cells (HDMEC) treated with VEGF-A,ANGPTL4 and stained with VE-Cadherin antibody. The straight and tight VE-Cadherin junctions were disrupted (p<0.001). ANGPTL4 restored a normal morphology of cadherin junctions in infarcted hemispheres of ANGPTL4-treated mice. Thus ANGPTL4 counteracts VEGF2-induced Src signaling and protects VE-Cadherin junctions from Src dependent disassembly. Moreover, ANGPTL4 protected neuronal loss after stroke, as assessed by the increased number of NeuN-positive cells (neurons) in treated mice (p<0.001). Finally, mouse behaviour was also significantly improved in treated mice (p<0.01).

**Conclusion:** ANGPTL4 treatment counteracts the loss of vascular integrity in a mouse model of ischemic stroke, by restricting Src kinase recruitment downstream VEGFR2. Consequently, ANGPTL4 reduces edema, infarct size, neuronal loss and finally improves mouse behavior. These results show that ANGPTL4 is a relevant target for vasculoprotection, thus conferring cerebral protection during stroke.
A national, multicentre, randomized controlled trial of the efficacy of structured care algorithm in achieving individual blood pressure targets at 26 weeks in primary care.

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Purpose: To determine the effectiveness of a structured care algorithm to optimise risk profiling and blood pressure (BP) control in a primary care cohort with persistently elevated blood pressures (BP), we undertook the Valsartan Intensified Primary care Reduction of Blood Pressure (VIPER-BP Study).

Methods: Prospective, multi-centre randomized controlled trial involving 119 primary care clinics and 2185 patients. Overall, 1562 patients (aged 59±12 years, 62% men, 67% prior hypertension and BP 150±7/88±11 mmHg) who remained above their individualized BP target (national guidelines) despite standardized “run-in” treatment were randomized (1:2 ratio) to enhanced usual care (UC, n = 504) or the VIPER-BP intervention (n = 1068). The latter comprised automated risk profiling plus standardized guideline-based, stepwise pharmacological treatment (initial angiotensin receptor blocker (ARB) monotherapy or combination regimens). We compared systolic and diastolic BP, general health and quality of life, and adverse events.

Results: After 26 weeks, a greater proportion of patients in VIPER-BP reached their BP target (n.s.) and were taking fewer prescribed drugs (p<0.0001). VIPER-BP was also associated with a greater proportion of patients reporting their health status was “good” compared to UC (p<0.0001). A greater proportion of patients in VIPER-BP reporting an improvement in their quality of life (p<0.0001) and had better self-rated health (p<0.0001). The rate of adverse events was not significantly different between the two groups (8.2% in VIPER-BP compared to 7.6% in UC).

Conclusion: Despite hypertension treatment, the proportion of uncontrolled hypertensive patients remains high and the non-adherence to treatment is a major issue. One of the aims of this study was to determine the predictive factors of anti-hypertensive medication adherence in uncontrolled hypertensive patients treated by general practitioners in France.

Methods: HBP-ADHERENCE observational study was conducted in France from March to September 2011. A population of 25460 hypertensive patients was included by 1049 French general practitioners. Hypertensive patients whose blood pressure was not controlled with at least two antihypertensive drugs were included. Adherence was determined according to a validated questionnaire. Comparative analyses were performed on two subgroups of patients: “adherent or minor non-adherent” versus “major non-adherent”.

Results: Mean systolic and diastolic blood pressure (SBP/DBP) were 157±11/91±8 mmHg. The majority of patients (60%) were over 60 years old and nearly 40% were women. Patients were classified as “major non-adherent” in 44% of cases and were more predictive factors of adherence. Major non-adherent patients had a significantly higher number of drugs prescribed (5.4±2.6 versus 4.6±2.4 p<0.0001), larger number of daily medication intakes (3.6±2.9 versus 3.0±2.3 p<0.0001) and less knowledge about their treatments (73.7% versus 88% p<0.0001) than adherent or minor non-adherent patients. A multivariate analysis, independent factors strongly associated with risk of major non-adherence were: (OR, 95% CI): “fear of adverse effects (2.7, 1.2-6.3), presence of at least one symptom (1.93, 1.8-2.45), sedentariness (1.55, 1.21-1.97), excessive alcohol intake (1.65, 1.24-2.20). The regular practice of home blood pressure measurement was the only factor inversely correlated to the risk of major non-adherence (0.64, 0.48-0.86).

Conclusion: In this real life study, we identified several modifiable factors to predict risk of non-adherence in uncontrolled hypertensive patients. Therapeutic education focusing on the expected benefits of antihypertensive drugs, their mechanisms of action and their adverse effects, as well as a wider use of long acting fixed-dose combinations would improve long-term effective care of hypertensive patients.

Valsartan suppresses cardiovascular events in hypertensive subjects with diabetes mellitus (DM) comparable to those with impaired glucose tolerance (IGT)

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Purpose: The randomized Nagoya Heart Study has demonstrated that comparable cardiovascular outcomes were comparable between the valsartan- and amloidipine-based treatments in Japanese hypertensive patients with diabetes mellitus in terms of glucose intolerance. The present subanalysis aimed to clarify whether or not the effects of these two drugs differ depending on the pattern of glucose intolerance (diabetes mellitus: DM vs. impaired glucose tolerance: IGT).

Methods: Treatment effects were evaluated among 942 hypertensive subjects with DM (valsartan; N=471; amloidpine, N=472) and 208 hypertensive subjects with IGT (valsartan, N=471; amloidpine, N=472; and 208 hypertensive subjects with IGT (valsartan, N=105; amloidpine, N=105). The primary outcome was a composite of acute myocardial infarction, stroke, coronary revascularization, admission attributed to heart failure, or sudden cardiac death. The median follow-up period for all subjects was 3.2 years.

Results: Among hypertensive subjects with DM, 101 events occurred, against only 9 among those with IGT (hazard ratio: 2.48 [95% CI: 1.27-4.82]; P=0.007). Results in the subset who remained IG during the follow-up period (hazard ratio: 2.07 [95% CI: 1.05-4.10]; P=0.041) was consistent with the overall results. A higher number of cardiovascular events occurred in DM subjects compared to IGT (hazard ratio: 2.8 [95% CI: 1.22-12.10]; P=0.020). Similar trend was observed in the valsartan-based treatment, but it was not statistically significant (hazard ratio: 1.79 [95% CI: 0.79-4.07]; P=0.166). The cumulative number of new DM from IGT was lower in the valsartan-based treatment (N=33) than in the amloidipine-based treatment (N=43), although it was not statistically significant (hazard ratio: 0.77 [95% CI: 0.52-1.08]; P=0.125).

Conclusions: Comparative cardiovascular events increased in the order of IGT, new onset DM from IGT, new onset DM from senescence DM in Japanese hypertensive subjects. In the amloidipine-based treatment, more cardiovascular events occurred in DM compared to IGT, but not in the valsartan-based treatment. Moreover, the number of new onset DM from IGT was less in the valsartan-based treatment than in the
Impact of intensive blood pressure lowering therapy on left atrial volume and function and the incidence of first atrial fibrillation in elderly hypertensive patients with preserved systolic function

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Purpose: The risk of atrial fibrillation (AF) associated with left atrial (LA) remodeling is increasing in elderly hypertensive (HTN). Intensive BP lowering therapy would have a beneficial effect on LA structure and function and decreases the incidence of first AF in elderly HTN.

Methods: We studied 240 subjects ≥65 years, who were divided into 4 groups by mean office BP for past 2 years; normal (n=73, 75±5 yrs, 37 men), intensive controlled HTN (systolic BP-130 and diastolic BP-<80mmHg, n=74, 74±4 yrs, 42 men), poor controlled HTN (systolic BP-140 or diastolic BP-≥90, n=147, 77±4 yrs, 51 men) and good controlled HTN (130/80±BP-<140/90, n=52, 74±5 yrs, 21 men). LA volume, emptying function (EF), strain rate (SR) and strain were measured by speckle tracking echocardiography at baseline and after 2 years.

Results: There was no difference in LV ejection fraction among 4 groups. LA volume, EF, SR and strain in intensive controlled HTN were more preserved and comparable to normal including diastolic function at baseline and after 2 years. The incidence of first AF was significantly lower in intensive controlled HTN for 2 years.

Conclusion: LA structure and function were preserved in intensive controlled HTN associated with preserved diastolic function and comparable to normal. Intensive BP lowering therapy had a beneficial effect on LA structure and function and would be recommended to prevent LA remodeling and first AF even in elderly HTN.

Table 1. Parameters at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Intensive HTN</th>
<th>Good HTN</th>
<th>Poor HTN</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mmHg</td>
<td>126±875</td>
<td>126±857±5</td>
<td>136±285±5</td>
<td>144±290±1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic fraction (E/WD)</td>
<td>0.4±0.1</td>
<td>1.4±0.1</td>
<td>1.8±0.8</td>
<td>10.4±1.8*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA dimension, mm</td>
<td>39±5</td>
<td>40±5</td>
<td>41±5</td>
<td>45±5*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Max. LA velocity, ml/min</td>
<td>41±11</td>
<td>44±11</td>
<td>53±14*</td>
<td>66±14*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Min. LA volume, ml²</td>
<td>23±8</td>
<td>25±8</td>
<td>31±10*</td>
<td>44±14*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA total EF%</td>
<td>45±7</td>
<td>46±7</td>
<td>41±9*</td>
<td>33±5*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA passive EF%</td>
<td>22±8</td>
<td>20±7</td>
<td>17±6*</td>
<td>14±5*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA active EF%</td>
<td>30±8</td>
<td>30±7</td>
<td>28±7*</td>
<td>22±6*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LA peak strain</td>
<td>24±8±6.3</td>
<td>24±5.8</td>
<td>22±4.6*</td>
<td>18±5.0*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SR-systole, s⁻¹</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
<td>1.1±0.3*</td>
<td>1.0±0.4*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SR-early diastole, s⁻¹</td>
<td>-1.0±0.3</td>
<td>-1.0±0.3</td>
<td>-0.8±0.3*</td>
<td>-0.8±0.3*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SR-late diastole, s⁻¹</td>
<td>-1.4±0.4</td>
<td>-1.4±0.4</td>
<td>-1.4±0.5*</td>
<td>-1.0±0.4*</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*p<0.05 vs normal; #p<0.05 vs intensive HTN.

Conclusions: DAPA is associated with modest mean reductions in sBP and dBP in patients with TZDM, with no increased risk of orthostatic hypotension and without any clinically relevant changes in heart rate. These post-hoc observations are intriguing and further studies will be needed to evaluate potential clinical benefit in hypertensive patients.

SPORT CARDIOLOGY – PRE-PARTICIPATION SCREENING: CONSEQUENCES AND PITFALLS

Exercise related out-of-hospital cardiac arrest: incidence, prognosis, and prevention of sudden death

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Purpose: Although regular physical activity has beneficial cardiovascular effects, exercise can trigger an acute cardiac event. We aimed to determine the incidence of exercise related out-of-hospital cardiac arrest (OHCA) and whether exercise-related OHCA is associated with higher survival rates than non-exercise-related OHCA in persons aged ≥35 years.

Methods: We analyzed all OHCA cases prospectively collected from January 2006 to January 2009. The relation between exercise during or within 1 hour before OHCA and outcome was analyzed using multivariable logistic regression, adjusting for age, gender, public location, bystander witness, bystander cardiopulmonary resuscitation (CPR), automated external defibrillator (AED) use and shockable initial rhythm. Incidence is shown per 100,000 person-years.

Results: Of 2517 OHCA, 145 (5.8%) were exercise-related, of whom 7 were ≤35 years. Most patients were men (93.1% and 85.7%, respectively). The incidence of exercise-related OHCA was 2.0 in all ages and 0.2 in those ≥35 years. Survival after exercise-related OHCA was distinctly better than after non-exercise-related OHCA (44.8% vs. 15.4%) (unadjusted odds ratio 4.13; 95%CI 2.93-5.82;P<0.001), even after adjustment for other prognostic factors (odds ratio 1.57; 95%CI 0.4-3.73;P=0.03). Patients ≤35 years did not benefit from exercise: survival was 33.3% versus 34.5%, respectively (adjusted odds ratio 0.47; 95%CI 0.04-5.37;P=0.54). In-hospital treatment did not differ between groups.

Conclusions: Exercise-related OHCA has a low incidence, particularly in the young and predominantly affects men. Cardiac arrests occurring during or shortly after exercise carry a markedly better prognosis than cardiac arrests that are not exercise-related in persons older than 35 years.

Costs of cardiovascular screening with ECG in young athletes in Switzerland

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Purpose: Adding ECG to cardiovascular screening in young athletes remains controversial. One of the reasons refers to costs of the screening program and the subsequent cardiac examinations generated mainly by the false positive ECG. The aim of this study was to assess the total costs of a program of cardiovascular screening with ECG in young athletes in Switzerland using basically the 2010 recommendations of the European Society of Cardiology (ESC) for interpretation of ECG in athletes.

Methods: In this observational prospective study, competitive athletes from 14 to 35 years were examined following the 2005 ESC proposal. ECG was interpreted based on the ESC 2010 recommendations (adapted). Further examinations were proposed in cases of positive findings. The costs of the screening and of all subsequent examinations was calculated for each athlete according to the Swiss medical tariffs. We present the interim results of this study.

Results: From 02/2011 to 02/2012, 920 athletes were examined. Mean age was 19.9±6.5 years, 75% were men. Football (35%) and ice hockey (12%) were the sports most often represented. Mean weekly training’s hours was 7.9±4.8 for a
mean period of 9.0±5.6 years. A total of 55 athletes (5.9%) required further examinations:
in 4.0% the ECG was abnormal, in 1.4% because of history and in 0.9% because of physical examination. Following cardiac examinations were made: 50 echocardiograms, 46 exercise stress tests, 18 Holter monitoring, 6 ambulatory blood pressure monitoring, 5 cardiac magnetic resonances, 4 ECG with pharmacological exposure, 4 family screening with ECG, 1 signal averaged ECG and 1 genetic test for long QT syndrome. A new cardiac diagnosis was found in 17 (1.8%) athletes: 5 idiopathic ventricular arrhythmia, 5 idiopathic atrial arrhythmia, 3 Wolf-Parkinson-White ECG-pattern, 1 long QT syndrome type 1, 1 mitral valve prolapse, 1 bricapic atrial valve and 1 systemic hypertension. Total mean cost per athlete was 138 Swiss Francs (102-3815 Swiss Francs).

Conclusion: Preliminary data of this study indicate that cardiovascular screening in young athletes using strict criteria for interpreting ECG is feasible in Switzerland at low cost. These data should aid the implementation of this policy in our country.

3979 Concentric remodelling of the right ventricle in African football players
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Purpose: We have previously shown that male Caucasian athletes have a larger increase of both LV and RV size than Africans athletes. African athletes, however, had similar LV mass but markedly more concentric remodelling LV than the Caucasian athletes. Thus, the aim of this study was to investigate if a similar remodelling between black and white athletes is present in the RV.

Method: As a part of the mandatory heart screening, 555 male elite football players (509 Caucasians and 46 Africans) and 46 Caucasian controls were examined. RV and diastolic diameter (RVD) were measured from a RV focused apical 4 chamber view. Measurements of RV free wall thickness (RWT) in end diastole were performed by a subcostal view. Relative wall thickness on the right side (RVRWT) was calculated by dividing RWT with RVD2 multiplied with two. Body mass index (BMI) and body surface area (BSA) were calculated, and all echo measurements were performed blinded.

Results: Body mass index (BMI) and body surface area (BSA) were calculated, and all echo measurements were performed blinded. No athlete with Brugada ECG-pattern had a history of syncope of undetermined origin. In standard ECG tracing there was 3 Brugada type 2/3 pattern (0.5%). In ECG changes requiring further investigation is low, possibly due to “self selection” in elite cohort. While ECG abnormalities are more common in endurance athletes they rarely reflect structural disease. Further evaluation in a sub-elite cohort is warranted.

Conclusion: In elite Australian athletes, Type 1 or training related ECG changes are common and more prevalent in endurance athletes. The prevalence of Type 2 ECG changes requiring further investigation is low, possibly due to ‘self selection’ in elite cohort. While ECG abnormalities are more common in endurance athletes they rarely reflect structural disease. Further evaluation in a sub-elite cohort is warranted.

3980 Prevalence of significant ECG abnormalities in elite Australian athletes
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Purpose: The effectiveness and cost-effectiveness of an athlete screening program is dependent on the prevalence of abnormalities on screening tests such as electrocardiography (ECG). As the prevalence of ECG abnormalities in athletes is unknown, the aim of this study was to evaluate the frequency of ECG abnormalities in a cohort of elite Australian athletes.

Methods: A total of 450 elite Australian athletes (age 16-35) competing at national and international level underwent 12-lead ECG examination. They were followed up for a mean period of 9.0±5.6 years. A total of 55 athletes (5.9%) required further examinations: in 4.0% the ECG was abnormal, in 1.4% because of history and in 0.9% because of physical examination. Following cardiac examinations were made: 50 echocardiograms, 46 exercise stress tests, 18 Holter monitoring, 6 ambulatory blood pressure monitoring, 5 cardiac magnetic resonances, 4 ECG with pharmacological exposure, 4 family screening with ECG, 1 signal averaged ECG and 1 genetic test for long QT syndrome. A new cardiac diagnosis was found in 17 (1.8%) athletes: 5 idiopathic ventricular arrhythmia, 5 idiopathic atrial arrhythmia, 3 Wolf-Parkinson-White ECG-pattern, 1 long QT syndrome type 1, 1 mitral valve prolapse, 1 bricapic atrial valve and 1 systemic hypertension. Total mean cost per athlete was 138 Swiss Francs (102-3815 Swiss Francs).

Conclusion: Preliminary data of this study indicate that cardiovascular screening in young athletes using strict criteria for interpreting ECG is feasible in Switzerland at low cost. These data should aid the implementation of this policy in our country.

3981 Bradycardia ECG-pattern recorded with V1 and V2 in the third intercostal space in young athletes
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Purpose: The prevalence of Brugada ECG-pattern is about 1/2000, mostly of type 2 and 3. In some circumstances, type 2 and 3 can convert in type 1 pattern, the only diagnostic. Registering ECG with V1 and V2 in the third intercostal space (3IC) can raise the sensibility of recording a Brugada ECG-pattern and the prognostic value of this tracing seems to be similar as the standard ECG. The aim of this study was to analyse the prevalence of Braduga ECG-pattern in a cohort of young athletes registering ECG also in the 3IC.

Methods: ECG was analysed as part of a prospective ongoing study about the impact of cardiovascular screening with ECG in young (14-35 years) competitive athletes. Besides a standard tracing, ECG was recorded with V1 and V2 in the 3IC. The prevalence of Braduga ECG-pattern type 1, 2 and 3 was analysed. Particular care was taken to distinguish an incomplete right bundle branch block pattern from a Brugada pattern.

Conclusion: ECG of 556 athletes (72% males, age 19.9±6.3 years) was analysed. In standard ECG tracing there was 3 Brugada type 2/3 pattern (0.5%). In ECG recorded in the 3IC there were 21 (3.8%) Brugada type 2/3, no type 1 was recorded. Of these 21 athletes, 20 were males (prevalence in males 4.9%), 1 female. There was no difference in females (0.6%). Of 20 males, 15 had a Brugada type 3 pattern (3.7% of males), 5 had a type 2 pattern (1.2%). The female had a type 3 pattern. No athlete took medications known to elicit a Brugada ECG-pattern.

3982 Sudden cardiac death risk assessment, combining cardiorespiratory fitness with cardiovascular risk factors
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Purpose: To investigate if the combination of cardiorespiratory fitness (CRF)
HEART FAILURE: FEAST OR FAMINE?

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Background & Purpose: Association between hearts and other organs such as cardio- or vaso-active substances such as interleukin-33, which may promote novel therapeutic targets in patients with heart failure. This is the first to evaluate the global gene expression of intestines in heart failure patients with poor outcome in HF. Pre-albumin as emerged as the best marker for protein malnutrition. Malnutrition has been increasingly recognized as associated with poor outcome in HF. Pre-albumin as emerged as the best marker for protein malnutrition.

Methods: A total of 3328 randomly selected men aged 42-60 from eastern Finland was selected. In this population based follow-up study (mean follow-up time was 19 years). Exercise stress test was performed and information on risk factors was collected. SCD was defined as cardiac deaths that occurred 24 hours after onset of symptoms. The population was divided into low and high CRF (MET 8 as cut-offpoint) and analyzed with dichotomously divided risk factors. The risk factors in table, age, C-reactive protein, alcohol consumption and exercise-induced myocardial ischemia (1mm ST depression in electrocardiogram) were included in cox multivariable models.

Results: Low CRF combined with all measured risk factors was associated with a higher risk of SCD (table). The highest risk factor ratio for progress of heart failure. This may be given by several factors: presence of metabolic syndrome, increased diastolic blood pressure, or higher insulin resistance. In contrast to stated risk factors, recent studies reported overweight and obesity to be associated with a lower risk of death, even after multivariate ad- justment. Obesity paradox is called “Curistin paradox” (Curtis et al., J. Intern Med). Aim of this study is comparison of mortality of acute heart failure (AHF) patients with overweight (BMI <25) and normal weight (BMI >25) by means of the modern “propensity score” statistical method. Differences between patients, who are comparable in their selected characteristics and parameters (difference <10%) and differ in BMI only – so called data set balancing. Based on a Hosmer-Lemeshow test, a model with 6 variables was chosen (sex, age, hypertension, diabetes mellitus, atrial fibrillation, and selective coronaryography).

Method: From the 5.343 patients from the AHEAD database (4,153 AHEAD Main and 1,190 AHEAD Network), 4,523 patients hospitalised with AHF and with available BMI data were assessed. The propensity score method is based on selection of patients, who are comparable in their selected characteristics and parameters (difference <10%) and differ in BMI only – so called data set balancing. Based on a Hosmer-Lemeshow test, a model with 6 variables was chosen (sex, age, hypertension, diabetes mellitus, atrial fibrillation, and selective coronaryography). Differences between patients, who are comparable in their selected characteristics and parameters (difference <10%) and differ in BMI only – so called data set balancing. Based on a Hosmer-Lemeshow test, a model with 6 variables was chosen (sex, age, hypertension, diabetes mellitus, atrial fibrillation, and selective coronaryography).

Results: Normal weight was recorded in 27% of patients, 39.5% of patients had overweight, and 28% of patients were obese. In hospital mortality was 10.3% and according to BMI 12.8%, 10.3%, and 8.3% (p = n.s. for normal vs. overweight, p = 0.005 for normal vs. obesity). In the balanced cohort, the overall mortality was 12.0% and not different between patients with overweight 12.2%, with obesity 7.6% (p = 0.051 for normal weight vs. obesity).

Conclusion: The propensity score method decreased the in-hospital mortality difference between patients with overweight and normal weight, nevertheless the obesity paradox was confirmed, since the patients with obesity had lower in-hospital mortality in comparison to patients with normal weight.

Preceding starvation prevents acute doxorubicin cardiotoxicity via autophagy activation

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Doxorubicin is a highly effective anti-neoplastic drug, but its clinical use is limited by the adverse effects on the heart. Active autophagy has recently been reported in doxorubicin cardiotoxicity but its pathophysiological role remains unclear. In the present study, we examined effects of preceding starvation on autophagy, a potential inducer of autophagy, on doxorubicin cardiotoxicity. Autophagy was induced in green fluorescent protein-microtubule-associated protein 1 light chain 3 (GFP-LC3) transgenic mice by injection of 10 mg/kg doxorubicin twice per week. The experimental group was deprived of food for 48 h before each injection of doxorubicin to induce autophagy. Doxorubicin treatment caused left ventricular dilatation and dysfunction at 1 week after the initial injection (the left ventricular dimension) (LVDD) = 3.94 ± 0.25 mm and ejection fraction (EF) = 46.7 ± 4.4%, which were significantly mitigated by the preceding starvation (LVDD = 3.41 ± 0.31 mm and EF = 63.9 ± 6.4%, both p < 0.05 compared with the control). Cardiomyocyte autophagy appeared markedly activated in the doxorubicin-treated group according to assessment of LC3 by immunohistochemistry and Western blotting. According to LC3 expression, autophagy appeared to be rather attenuated by the preceding starvation. Unexpectedly, however, myocardial ATP content was decreased in the doxorubicin-treated group and this reduction was restored by the preceding starvation. Electron microscopy suggested that autophagic process is indeed initiated but not completed in the doxorubicin-treated group, i.e., autophagosome digestion is insufficient, and that this incompleteness was partially improved by starvation. Finally autophagy flux assay using chloroquine confirmed that doxorubicin impairs final digestion step of autophagy in cardiomyocytes. In conclusion, preceding starvation ameliorates doxorubicin cardiotoxicity, of which underlying mechanism may be, at least in part, restoration of autophagy flux which is impaired by doxorubicin. Our findings imply that fasting could be a possible strategy for preventing doxorubicin cardiotoxicity.
Heart failure: feast or famine? / Restenosis: still the achilles heel of percutaneous coronary interventions? 683

Thirty-two of the patients (4.8%) died in hospital. Patients dying in hospital were older, had lower admission systolic blood pressure, worse admission renal function and higher BNP. Patients with in-hospital death also had significantly lower total cholesterol levels (12.91±1.45 mg/dL vs. 15.00±1.26 mg/dL) in those discharged alive; lower albumin: 32.0 (4.0) vs 35.4 (4.8) mg/dL; and lower pre-albumin: 13.2 (5.2) vs 18.2 (7.1) mg/dL. Higher pre-albumin predicted in hospital survival with a HR of 0.59 (95% CI: 0.32-0.95, p=0.001). Association with outcome was independent of other variables also associated with outcome in an univariate approach (systolic blood pressure, age, blood urea, BNP, total cholesterol and albumin). An admission pre-albumin <18 mg/dL predicted in hospital death with a HR of 5.64 (95% CI: 1.20-26.51, p=0.03).

Conclusions: Malnutrition as assessed by lower pre-albumin predicted in-hospital death in patients admitted with acute HF. HF patients with admission pre-albumin <18 mg/dL have more than five-fold higher risk of in-hospital death than those with higher admission pre-albumin.

Are total cholesterol levels important for hospital and long time prognosis of patients with acute heart failure?


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The purpose of this study was to evaluate if there is an association of total cholesterol levels with hospital and long time mortality of patients admitted for acute heart failure. The AHEAD MAIN registry is a database conducted in 7 university hospitals, all with 24 hour cath lab service, in 4 cities in the Czech Republic. The database included 4 153 patients hospitalised for acute heart failure in the period 2006 – 2009. Median age was 73.8 years, 42% females, more than 70 years 60%, ejection fraction below 30% 37.9%. The data were collected prospectively using a database accessible via the Internet website and were evaluated continuously (intra- and interhospital mortality). The long-term mortality was followed by a centralised database of the Ministry of Health of the Czech Republic and recent data from the year 2010. The log rank test was used for the analysis of long term survival. The independent influence of total cholesterol level on mortality and survival was assessed using multivariate logistic regression and Cox proportional hazards model respectively. Of 4 153 patients, 526 (12.7%) patients died during hospitalisation. The median length of hospitalisation was 7.1 days (5.5 days for those patients who died and 9.7 days for those who were discharged home). 2 384 patients had complete records for total cholesterol levels – 946 females and 1437 males were included in this analysis. The median total cholesterol level was 4.40 mmol/L. For the calculation of long term mortality, the cohort was divided into three groups: total cholesterol levels below 4.50 mmol/L, 4.50-5.49 mmol/L and above 5.50 mmol/L. Total cholesterol levels were important for hospital mortality for both genders (p<0.001). In the long-term follow up (78 months) patients with total cholesterol level below 4.50 mmol/L had the worst prognosis (p<0.001). The independent influence of total cholesterol on hospital and long time mortality was confirmed in the multivariate analysis when total cholesterol level <4.5 mmol/L was combined with other predictors revealed in the univariate analysis. Total cholesterol levels are important for in-hospital mortality and long term survival of patients admitted for acute heart failure.

The prognostic importance of evaluating nutritional status in patients with chronic heart failure


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Background: Low nutritional status is one of the unfavorable prognostic factors in some clinical setting. However, the association between nutritional indexes and outcomes in patients with chronic heart failure (CHF) is unclear. The purpose of this study was to clarify the impact of nutritional status on cardiac prognosis in patients with CHF.

Methods and Results: We evaluated controlling nutritional status score (CONUT), prognostic nutritional index (PIN), and geriatric nutritional risk index (GNRI) in consecutive 388 patients with CHF (mean 69.6±12.3 years) admitted to our hospital. CONUT consists of 2 biochemical parameters (serum albumin and total cholesterol level) and 1 immune indicator (total lymphocyte count). PIN consists of 1 biochemical parameter (serum albumin) and 1 immune indicator (total lymphocyte count). GNRI consists of 1 biochemical parameter (serum albumin) and ratio of body weight to ideal body weight. Patients were prospectively followed with the endpoints being cardiovascular death or rehospitalization. There were 108 events (including 33 deaths and 75 rehospitalizations) during follow-up of 37.7 months. Patients with cardiac events showed higher age, more severe New York Heart Association (NYHA) functional class, lower prevalence of valvular heart disease, lower body mass index, lower serum triglyceride level, lower serum high-density lipoprotein cholesterol level and higher serum brain natriuretic peptide (BNP) compared with those without cardiac events. Furthermore, patients with cardiac events showed higher CONUT score (6.3-8 vs. 2.1-3, P<0.001), lower PIN score (151.2, 26.3-15.7 vs. 88.6, 35.2-40.0, P<0.001), lower GNRI score (84.9, 76.8-92.3 vs. 95.3, 89.8-101.3, P<0.001) compared with those without cardiac events. In Cox proportional hazards analysis, CONUT (hazard ratio 40.9, 95% CI 16.4-105.8, P<0.001), PIN (hazard ratio 6.4, 95% CI 5.4-25.1, P<0.001), and GNRI (hazard ratio 11.6, 95% CI 3.7-10.0) were independently associated with cardiac events after adjustment of age, gender, NYHA functional class and serum levels of BNP. Among these nutritional indexes, CONUT had the highest hazard ratio. Kaplan-Meier analysis revealed a significantly higher cardiac event rate in patients with low nutritional indexes than in those without it.

Conclusion: Low nutritional status was associated with unfavorable outcomes in patients with CHF. It was suggested that evaluating nutritional status may provide a pivotal prognostic information in patients with CHF.

Impact of stent fracture on long-term clinical outcomes after sirolimus-eluting stent (SES) implantation


Purpose: Stent fracture (SF) is associated with adverse events after drug-eluting stent implantation. However, few data exist on its long-term clinical impact in real world practice. Therefore, we evaluated the impact of SF on long-term clinical outcomes after sirolimus-eluting stent (SES) implantation.

Methods: Consecutive 2404 patients who had undergone the first SES implantation from November 2002 to December 2007 and received follow-up angiography within 12 months were analyzed. Angiographic stent fracture was defined as apparent separation of stent segments. Some tips, including focus image, inverse image, and image without catheter or contrast media were used to obtain the exact prevalence of SF. The incidence of clinical outcomes, including all-cause death, myocardial infarction (MI), stent thrombosis (ST), target lesion revascularization (TLR), and major adverse cardiac events (MACE, defined as all-cause death, MI, and TLR) was compared between SF and non-SF groups.

Results: Because 446 of the 2404 patients were excluded because of no angiographic follow-up within 12 months, the entire study population consisted of 2048 patients (3218 lesions) and was classified into two groups: 243 patients with SF and 1805 without SF. The median duration of follow-up was 4.9 years. At 4-year follow-up, the rates of TLR, MI, and MACE were significantly higher in the SF group than in the non-SF group (38.3% vs. 17.2%, P<0.001; 2.1% vs. 0.6%, P=0.03; 42.4% vs. 25.0%, P<0.001, respectively), whereas the rate of all-cause death was similar between groups (6.5% vs. 10.5%, P=0.20). The figure shows the cumulative incidence of definite or probable very late ST.

Figure 1. Cumulative incidence of very late stent thrombosis.

Conclusions: Our study suggests that SF is associated with higher rates of late adverse events except all-cause death after SES implantation.

Stent fracture and restenosis at stent fracture site after sirolimus-eluting stent and everolimus-eluting stent implantations: impact of stented vessel


Background: Stent fracture (SF) and its related restenosis are concerns of sirolimus-eluting stent (SES) implantation. However, everolimus-eluting stent (EES) may have a potential for the reduced prevalence of SF. We assessed SF and restenosis at SF site in terms of stented vessel after SES and EES implantations.

Methods: A total of 8817 stent-implanted lesions (SES 6000, EES 2217) from
**4023** Decreased interleukin-33 serum levels after coronary stent implantation are protective against in-stent restenosis

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**Background:** Restenosis after stent deployment is an overreaction of the wound healing response after vascular injury and is characterized by the sequence of inflammation, granulation, and extracellular matrix remodeling. Interleukin-33 (IL-33) is a recently described member of the IL-1 family of cytokines and is a ligand for the ST2 receptor. Circulating IL-33 was increased in patients with inflammatory disorders such as rheumatoid arthritis, systemic sclerosis, inflammatory bowel disease and liver failure. However, the predictive value of IL-33 for the development of in-stent restenosis (ISR) is not known.

**Methods:** We included 387 consecutive patients undergoing percutaneous coronary intervention (PCI) of whom 193 had stable angina, 93 non-ST-elevation myocardial infarction (NSTEMI), and 101 ST-elevation MI (STEMI), respectively. Blood was taken directly before and 24 hours after stent implantation. Plasma levels of IL-33 were measured by a specific ELISA. The presence of ISR was initially evaluated by clinical means. When presence of myocardial ischemia was suspected, coronary angiography was performed to confirm the suspected diagnosis of ISR.

**Results:** Bare metal stents (BMS) were used in 283 and drug-eluting stents (DES) were used in 104 patients. Clinical ISR was present in total in 34 patients (8.8%). IL-33 was detectable in 185 patients and was below detection limit in 202 patients. In patients with decreased IL-33 (n=95), unchanged or non-detectable levels (n=210) or increased levels of IL-33 after PCI (n=82), ISR-rate was 2.1%, 9.5% and 14.6%, respectively (p <0.05). This association was independent from clinical presentation and risk factors as well as numbers and type of PCI.

**Conclusion:** In patients with both stable and unstable coronary artery disease, a decrease of IL-33 serum levels after stent implantation is associated with a lower rate of in-stent restenosis. **Figure 1. SF rate and restenosis rate at SF site**

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**4024** Efficiency of statin treatment on EPC recruitment depends on baseline EPC titer, and does not improve angiographic outcome in coronary artery disease patients treated with the Genous stent

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**Objective:** To assess the effect of high dose Atorvastatin treatment on endothelial progenitor cell (EPC) recruitment and angiographic and clinical outcome in coronary artery disease (CAD) patients treated with the GenousTM EPC capturing stent.

**Methods:** The HEALING IIB study was a multi-center, open-label, prospective trial that enrolled 100 patients. Patients were started on 80mg Atorvastatin qd, at least two weeks before index procedure and continued for at least 4 weeks after the index procedure.

**Results:** 87 Patients were included in this analysis. EPC levels significantly increased as early as 2 weeks after start of statin. Remarkably, among this group, 31 patients proved to be non-responder to Atorvastatin treatment (i.e. no increase in EPC levels) while 56 patients were responders (i.e. rise in EPC count between week -2 and 0). Compared to responders, non-responders had a significantly higher baseline EPC count (70±10 vs. 41±5, p<0.01) with a lower LLL at 6 and 18 month FU (0.81±0.07 vs. 0.88±0.08, p=0.05 and 0.50±0.08 vs. 0.62±0.08 p<0.01 respectively, see figure). Furthermore, baseline EPC count inversely correlated with LLL at 6 month follow-up (FU) (R=-0.42, p<0.001).

**Conclusion:** Patients with higher EPC count at baseline showed no increase in EPC recruitment in response to statin treatment but had favorable LLL at 6 and 18 month FU, whereas patients with lower EPC count were responsive to statin therapy but EPCs might be less functional as they had higher LLL at 6 and 18 month FU. These data imply that, although statin treatment can enhance EPC titer in these patients with low baseline levels, there is no indication for a possible beneficial clinical effect with EPC capture stents.

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**4025** Drug-eluting stents for the treatment of chronic total occlusion: a comparison with sirolimus, paclitaxel, zotarolimus, biolimusA9, EPC capture and everolimus-eluting stent: multicenter registry

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**Aim:** The aim of this study is to compare the safety and efficacy of Sirolimus (SES), Paclitaxel (PES), Zotarolimus (ZES-Ri Endeavor Resolute), BiolimusA9 (BES), EPC capture (ECS) and Everolimus-eluting stent (EES) on the outcome of patients with chronic total occlusion (CTO).

**Methods:** A prospective analysis of 1576 patients with 1738 CTOs (396 SES, 526 PES, 219 ZES-R, 209 BES, 148 ECS, 240 EES) in six high volume Asian centers after successful recanalization of CTO was performed. The study endpoints were 30 days and 12 months major adverse cardiac events (MACE), 12 months angiographic restenosis and target lesion revascularization (TLR). **Table 1. See table for clinical results.**

**Conclusion:** The use of drug-eluting stents in patients with CTO was safe with low acute complication. Patients treated with 2nd generation DES such as ZES-R, BES and EES showed lesser rate of restenosis compared with 1st generation drug-eluting stents.
Results: Data are shown in the table.

### Table 1. Antithrombotic use in AF patients according to CHADS2 score and continent in cohort 1

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>European</th>
<th>Asia</th>
<th>Australia</th>
<th>North America</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42.2%</td>
<td>37.7%</td>
<td>34.7%</td>
<td>46.5%</td>
<td>40.4%</td>
</tr>
<tr>
<td>1</td>
<td>25.4%</td>
<td>22.8%</td>
<td>20.3%</td>
<td>28.4%</td>
<td>26.1%</td>
</tr>
<tr>
<td>2</td>
<td>11.7%</td>
<td>12.7%</td>
<td>15.3%</td>
<td>13.2%</td>
<td>16.2%</td>
</tr>
<tr>
<td>3</td>
<td>10.3%</td>
<td>10.1%</td>
<td>10.8%</td>
<td>8.8%</td>
<td>11.8%</td>
</tr>
<tr>
<td>4</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Conclusions: The progression pattern of late restenosis differs among various DESs. Although the mechanism of this phenomenon is unclear, different clinical follow-up may be necessary depending on DES types.

### Table 1. Comparison of areas under the curve (AUC, or c statistic) and Net Reclassification Improvement (NRI) for HEMORR2HAGES, ATRIA and HAS-BLED

<table>
<thead>
<tr>
<th>Bleeding Risk Score</th>
<th>AUC</th>
<th>95% CI</th>
<th>p</th>
<th>ATRIA</th>
<th>95% CI</th>
<th>p</th>
<th>HAS-BLED</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEMORR2HAGES</td>
<td>0.65</td>
<td>(0.57, 0.73)</td>
<td>0.13</td>
<td>0.55</td>
<td>(0.47, 0.63)</td>
<td>0.02</td>
<td>0.51</td>
<td>(0.42, 0.60)</td>
<td>0.01</td>
</tr>
<tr>
<td>ATRIA</td>
<td>0.61</td>
<td>(0.51-0.72)</td>
<td>0.22</td>
<td>0.50</td>
<td>(0.41-0.59)</td>
<td>0.03</td>
<td>0.47</td>
<td>(0.38-0.56)</td>
<td>0.87</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>0.65</td>
<td>(0.56-0.73)</td>
<td>0.02</td>
<td>0.60</td>
<td>(0.50-0.69)</td>
<td>0.01</td>
<td>0.56</td>
<td>(0.45-0.66)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: The HAS-BLED score performed significantly better in predicting “any clinically relevant bleeding”. Given its simplicity and superior performance to other scores, the HAS-BLED score would be more attractive for the estimation of OAC-related bleeding risk in clinical practice.

### Table 1. Antithrombotic use in AF patients according to CHADS2 score and continent in cohort 1

<table>
<thead>
<tr>
<th>CHADS2 Score</th>
<th>Europe (n=437)</th>
<th>Asia (n=357)</th>
<th>Australia (n=1122)</th>
<th>North America (n=3107)</th>
<th>Other (n=1114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant</td>
<td>50.6%</td>
<td>25.2%</td>
<td>57.6%</td>
<td>26.8%</td>
<td>59.3%</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>22.7%</td>
<td>42.3%</td>
<td>19.2%</td>
<td>41.6%</td>
<td>17.6%</td>
</tr>
<tr>
<td>Both</td>
<td>9.4%</td>
<td>6.7%</td>
<td>10.3%</td>
<td>11.7%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Neither</td>
<td>17.4%</td>
<td>25.8%</td>
<td>12.9%</td>
<td>19.9%</td>
<td>17.7%</td>
</tr>
</tbody>
</table>

Conclusions: These international observational data indicate regional differences in OAC use for stroke prevention in AF in Asia and Europe, reflecting a potential overuse of OAC in Europe for patients at low risk for stroke according to existing risk scores and an underuse in Asian patients at higher risk.
and 5 strokes (0.99%/year) and 10 major bleeding events (1.97%/year) in the warfarin group (continuing on VKA), in the 30 days after stopping study drug with the mean CHADS2 Score of 1.8±1.1 would have been 5.75%. Fifteen patient groups following study drug discontinuation before the end of the trial.

Conclusions: The excess in thrombotic and bleeding events in the apixaban arm after study drug discontinuation at the end of ARISTOTLE seems to be related to an increased risk associated with the new initiation of a VKA that extends over several weeks rather than a direct effect of apixaban.

4046CHA2DS2VASc score and thromboembolic and bleeding complications after successful cardioversion of acute atrial fibrillation
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Purpose: It has been common practice to perform cardioversion of acute (<48 hours) atrial fibrillation without anticoagulation. The objective was to determine the incidence of thromboembolic and bleeding complications related to cardioversion of acute atrial fibrillation in patients with and without periprocedural anticoagulation.

Subjects and methods: A total of 5652 cardioversions were performed in 2569 consecutive patients with atrial fibrillation lasting <48 hours in three hospitals. For this analysis, embolic and bleeding complications were evaluated in 1632 cardioversions and with 4020 cardioversions with no periprocedural anticoagulation.

Results: Cardioversions were successful in 5326 (94%) cases. Thirty-eight thromboembolic events (in 35 patients) occurred within 30 days after cardioversions. All were after successful procedures and 29 (76.3%) were strokes. One patient had simultaneous stroke and peripheral embolisation after one cardioversion. Incidence of embolic events was higher in cardioversions with no periprocedural anticoagulation (0.92% vs. 0.20%, p=0.003), but there was no significant difference in bleeding events (0.10% vs. 0.20%) between the groups. The embolic events were significantly related to CHA2DS2VASc score (p>0.0001) in patients with no periprocedural anticoagulation (Table).

Table 1. Incidence of thromboembolic events

<table>
<thead>
<tr>
<th>CHA2DS2VASc score</th>
<th>No anticoagulation</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>8 (0.3%)</td>
<td>1 (0.24%)</td>
</tr>
<tr>
<td>2-3</td>
<td>13 (0.7%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>≥4</td>
<td>14 (0.8%)</td>
<td>2 (0.53%)</td>
</tr>
</tbody>
</table>

Conclusions: The incidence of postcardioversion thromboembolic complications is high in patients with high CHA2DS2VASc score after cardioversion of acute atrial fibrillation when no anticoagulation is used. The present data supports the view that effective anticoagulation should be used in these patients also during cardioversions of short attacks of atrial fibrillation.

4047 Stroke prevention in non-valvular atrial fibrillation: long-term results after 6 years of the watchman left atrial appendage occlusion pilot study
P.B. Sick, Z. Turi, E. Grube, S. Moebius-Winkler, G. Schulier, M. Kaiser-Church, J. Bobrek, H. Williams, R. Mohan, C. Granger, D. Holmes, J. Airaksinen. 1Hospital Barmherzige Bruder, Department of Cardiology, Regensburg, Germany; 2Cooper Hospital, Camden, United States of America; 3Academic Hospital, University of Bonn, Bonn, Germany; 4University of Leipzig, Heart Center, Leipzig, Germany; 5Prairie Heart Institute, Springfield, United States of America; 6Midwest Cardiology Research Foundation, Columbus, United States of America; 7Beaumont Hospital, Michigan, United States of America; 8Mayo Clinic, Rochester, United States of America

Purpose: The WATCHMAN LAA Closure device (Boston Scientific, Plymouth, MN) is made of nitinol, incorporates fixation barbs around its perimeter and has like signs in 45 (0.4%) segments. During the follow-up period (2.3±0.8 years), attack (TIA), Warfarin was restarted in these patients for 3 months without further evidence of thrombus. Two patients had an embolic stroke; one at 2 months and one at 39 months in the setting of severe concurrent carotid disease. These data reflect in 5 patients assigned to apixaban and 6 patients assigned to warfarin.

Conclusions: The longterm data suggest that WATCHMAN LAA Closure is safe and feasible, with two embolic strokes through more than 6 years of active follow up. This reflects a 90% lower stroke rate as compared with the expected stroke rate according to the CHADS2-score.

4048 Apixaban and warfarin are associated with a low risk of stroke following cardioversion for atrial fibrillation: results from the ARISTOTLE Trial
G. Flaker, R. Lopez, S. Al-Khatib, A. Hermosillo, L. Thomas, J. Zhu, W. Ruzyllo, P. Mohan, C. Granger, L. Wallentin on behalf of Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation. 1University of Missouri, Columbia, Missouri, United States of America; 2Duke University, Durham, North Carolina, United States of America; 3Instituto Nacional de Cardiología de Mexico, Mexico, Mexico; 4Fujiwara Hospital, Beijing, China, China; People’s Republic of; 5National Institute of Cardiology, Warsaw, Poland; 6Bristol Meyers Squibb, New York, NY, United States of America; 7Uppsala Clinical Research Center, Uppsala, Sweden, Sweden

Purpose: In patients with atrial fibrillation for longer than 48 hours, there is an increased rate of thromboembolic events which is lowered with vitamin K antagonists and anticoagulants. The risk of thromboembolic events after cardioversion in patients treated with apixaban, a factor Xa inhibitor, is unknown.

Methods: In the Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, apixaban 5 mg bid reduced stroke, death, and caused less bleeding as compared to warfarin (INR 2.0-3.0) in patients with atrial fibrillation and risk factors for stroke. During the trial if cardioversion was performed, it was recommended that investigators continue randomization to treatment before and after the procedure. Thromboembolic events including stroke, systemic embol, and myocardial infarction were compared between patients receiving apixaban or warfarin.

Results: 18,201 patients were included in the ARISTOTLE trial. A total of 577 (3.2%) patients underwent cardioversion during the trial including 286 (49.6%) assigned to apixaban and 291 (50.4%) assigned to warfarin. The median time to cardioversion was 5 months and approximately 75% of the procedures occurred by follow-up year one. Key baseline characteristics including gender, CHADS2 score, LVEF, and estimated duration of AF were similar in patients receiving apixaban and warfarin. In the first 90 days, no patient in either group suffered a stroke or systemic embolism. After cardioversion for a median follow-up of 233 days (range 1-489) in the apixaban group and 393 days (range 213-607) in the warfarin group, the composite of stroke, systemic embolism, and myocardial infarction occurred in 5 patients assigned to apixaban and 6 patients assigned to warfarin.

Conclusions: In patients with atrial fibrillation and risk factors, the risk of thromboembolic events after cardioversion is low in patients treated with either apixaban or warfarin. Apixaban appears to be a safe alternative to warfarin for stroke prevention after cardioversion.
Combined CT angiography and CT myocardial perfusion imaging to detect functionally significant stenoses in patients with suspected coronary artery disease - comparison with fractional flow reserve

Methods: 40 patients with chest pain and suspected CAD underwent CTA and CTP assessment including CTA, CTP which were acquired using 320-row detector. CTA was performed in all major vessels and assumed 0.5 in vessels with 50% stenosis and 0.95 in smooth arteries. FFR < 0.8 indicated significant stenosis. CTA and CTP images were assessed by consensus between two blinded observers.

Results: Functionally significant stenoses were present in 53% of patients and 33% of vessels. The presence of 50% stenosis on CTA had a vs. 18.9% on CTP. FFR was lower (0.93 ± 0.05) and NPV of 0.95 ± 0.05 were independently associated with slow-flow. The cut-off values for CT density and plaque volume for slow-flow were 39.0 HU (sensitivity 69.2%, specificity 75.0%, AUC 0.75), 103.4 mm3 p=0.03) in lesions with slow-flow than without. Multiple logistic regression analysis showed that CT density (odds ratio (OR): 0.97, 95% CI: 0.99-1.02) and plaque volume (OR: 1.01, 95% CI: 1.00-1.02) were independently associated with slow-flow. The cut-off values for CT density and plaque volume for slow-flow were 39.0 HU (sensitivity 69.2%, specificity 83.4%, area under the receiver-operating characteristic curve (AUC) 0.80) and 78.7 mm3 (sensitivity 69.2%, specificity 75.0%, AUC 0.75), respectively. For predicting slow-flow during PCI, the diagnostic power of combination of lower CT density <39.0 HU and greater plaque volume >78.7 mm3 showed 40% of sensitivity, 96.6% of specificity, 75.0% of positive predictive value, 89.0% of negative predictive value, and 87.6% of diagnostic accuracy.

Conclusion: Lower CT density and greater plaque volume were significantly related to slow-flow phenomenon during PCI. MDCT may help to predict poor outcome after PCI in patients with CAD.
were defined as cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization. Cardiac event-free survival was estimated using the Kaplan-Meier survival methods with log-rank statistics. The proportions of selected variables with outcome were assessed in the multivariate Cox proportional hazard models.

**Results:** A very low, low, intermediate or high pre-test probabilities was observed in, respectively, 11.2%, 41.4%, 41.4% and 5.4% of study patients. During follow-up (736±337 days), a total of 12 (4.0%) cardiac events occurred including nonfatal myocardial infarction in 1 (0.3%), unstable angina requiring hospitalization in 2 (0.6%), cardiac revascularization in 9 (0.0%). In this study, of 12 patients with cardiac events, 5 patients (41.7%) with a high pre-test probability of CAD, 3 (25%) with an intermediate, and 4 (33.3%) with a low were observed. Kaplan-Meier event-free survival rate in patients with very low, low, intermediate and high risk pre-test probability of CAD was 0%, 3.3%, 2.4% and 29.4%, respectively. Patients with high pre-test probability had significantly more cardiac events as compared with very low, low and intermediate pre-test probabilities (p < 0.001). The event rate was 0% among patients with very low pre-test probability. Multivariant model revealed that high pre-test probability was the only significant predictor of cardiac events (risk ratio 11.3; 95% confidence interval 3.5-36.8).

**Conclusion:** CAGS zero by MDCT did not predict future cardiac events completely. The prognostic value of pre-test probability of CAD for patients with very low risk, low, and intermediate was excellent. The cardiac event rate was 0% among patients with very low pre-test probability. Coronary CTA could be avoided for these patients, especially those with very low pre-test probability.

**Impact of lipid lowering on prevention of plaque progression detected by coronary computed tomography angiography.**

H. Ito, S. Motoyama, M. Sarai, H. Kawai, H. Harigaya, H. Naruse, S. KAN, S. Kato, J. Ishii, Y. Ozaki, Fujita Health University, Department of Cardiology, Toyoake, Japan

**Purpose:** There are some reports that the severity of coronary artery stenosis by coronary computed tomography angiography (CTA) was associated with cardiac event rate. So, it would be important to find out the optimal treatment for prevention of plaque progression. Our previous study showed that serial CTA was useful to evaluate the plaque volume change of coronary arteries noninvasively. The aim of this study was to investigate the factors associated with the plaque progression of coronary arteries detected by CTA.

**Methods:** We studied 199 patients (84% male, mean age 66±10 years) undergoing CTA twice for any purpose. The median period from 1st to 2nd CTA was 9 months. Coronary artery plaques were compared between 1st and 2nd CTA, and patients were classified into two groups; progression group (n=27) and non-progression group (n=172). The patients background and laboratory findings contributed to plaque progression were investigated.

**Results:** Coronary risk factors were similar in two groups. There were no significant differences in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride, glucose level, and Hemoglobin A1c between two groups at baseline. In progression group, total cholesterol at baseline (209±39 vs 193±37 mg/dl p=0.0039) was significantly higher, however, there was no significant different at 2nd CTA. Patients on statin was not significant different both at 1st (44.4 vs 45.4%, p=0.901) and 2nd CTA (59.3 vs 75.6%, p=0.0745) between progression and non-progression group. At 2nd CTA, LDL-C (110±34 vs 96±31 mg/dl p=0.0274) was significantly higher in progression group than non-progression group. Furthermore, patients with LDL-C <100mg/dl at 2nd CTA were significantly more frequent in progression group (74.1 vs 37.8%, p<0.0004). Cut-off value of plaque progression by CTA was determined as 103 mg/dl in 100mg/dl Receiver Operating Characteristic curve, and sensitivity and specificity were 74% and 61.4%, respectively.

**Conclusions:** Plaque progression of coronary arteries by CTA was associated with poor control of LDL-C level at 2nd CTA. The present study confirmed that LDL-C <100mg/dl was reasonable for secondary prevention of coronary artery disease. CTA might have potential to provide the optimal strategies for improve of prognosis.

**The Australian national genetic heart disease registry**

J. Ingles1, T. Sarinara2, A. Evans3, J. Kawa3, R. Weintraub4,
J. Voeha5, I. Winship6, J. McGaughran7, J. Altherton8,
C. Semsarian9, 1. University of Sydney, Sydney Medical School, Sydney, 2. Centenary Institute, Sydney, 3. University of Tasmania, Medical School, Launceston, 4. Royal Children's Hospital, Melbourne, 5. Royal Melbourne Hospital, Department of Cardiology, Melbourne, 6. Royal Melbourne Hospital, Department of Clinical Biochemistry, Melbourne, 7. Royal Brisbane & Women's Hospital, Brisbane, Australia

**Purpose:** There are now over 40 cardiovascular diseases known to have a genetic cause. Current studies are limited by a lack of detailed clinical information and large patient cohorts, leaving many key clinical and genetic questions unresolved. The Registry aims to recruit every Australian family with a genetic heart disease, and will provide a valuable resource to better understand these conditions.

**Methods:** Patients are recruited from specialised cardiac genetics clinics and through self-referral. Written informed consent is required and clinical data are collected and entered into a central Registry database. Diseases included are the inherited cardiomyopathies (hypertrophic cardiomyopathy [HCM], familial dilated cardiomyopathy [FDC], arrhythmogenic right ventricular cardiomyopathy [ARVC], isolated left ventricular noncompaction [LVNC], primary arrhythmogenic disorders [long QT syndrome [LQTS], catecholaminergic polymorphic VT [CPVT], Brugada syndrome [BrS]) and familial valve diseases (bicuspid aortic valve disease [BAV]).

**Results:** To date 1032 individuals from 611 families have enrolled. The mean age of registrants is 46±20 years, 520 (50%) are males and 711 (69%) have clinical disease (remainder are at-risk relatives). There are 428 (41%) individuals with a clinical diagnosis of HCM, with a mean age of 52±18 years. Among these, 354 (58%) are HCM families, 117 (33%) have had gene testing with a gene mutation identified in 70 (60%) families, which includes 6 (5%) families with multiple gene mutations. There are 93 (9%) individuals with LQTS, 39 (4%) with FDC, 25 (2%) with BAV, 23 (2%) with ARVC, 15 (1%) with CPVT, and 11 (1%) with BrS. Importantly, 813 (79%) registrants have consented to be approached for future research studies.

**Conclusions:** The Australian National Genetic Heart Disease Registry is a unique resource for the study of these diseases. The Registry will provide an accurate and up-to-date source of information for health professionals and families, and will emerge as an important resource for future research in genetic heart diseases.

**Poster Session 5**

**GENETIC ASPECTS/VENTRICULAR ARRHYTHMIAS**

**Outcome of screening of relatives to patients with long QT syndrome; a nationwide Danish study.**

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**Aims:** According to international recommendations relatives to patients with long QT syndrome (LQTS) are offered cascade screening. In this Danish study we assessed the outcome of clinical and genetic cascade screening of LQTS families nationwide.

**Methods and results:** Patients with LQTS were identified from Danish national registers and patient files were reviewed. A total of 288 patients with LQTS were identified in 79 families and included 209 relatives. The majority of diagnosed relatives identified by cascade screening were asymptomatic. Symptomatic probands and family members most often presented with syncope, followed by aborted cardiac arrest (abSCD), unspecific symptoms and sudden cardiac death (SCD). Syncope, abSCD and SCD most often occurred at rest. The most pronounced QTc prolongation was seen in probands and patients with serious cardiac events. A disease-causing mutation was found in 59 probands (81% of 73 probands tested). The majority of mutations were localized to the KCNH2 gene (63%). A total of 180 (63%) patients were on beta-adrenergic blocking agents (BB) and 67 (23%) patients had an implantable cardiac defibrillator (ICD). Appropriate ICD therapy was given to 12 (29%) probands and three (12%) family members. Fourteen (33%) probands and two (8%) family members experienced ICD complications.

**Conclusions:** By cascade screening we identified almost 3 affected relatives for each proband. Probands were noteworthy more clinically affected compared to the relatives, but a considerable fraction of the diagnosed relatives were symptomatic and 14 family members (7%) fulfilled guideline criteria for ICD implantation.

**A new MOG1 transcript variant implicated in arrhythmias**

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A missense mutation in the MOg1 gene has been recently identified in one Brugada syndrome (BrS) patient. This gene has been shown to interact with the cytoplasmic loop II (between transmembrane domains III and IIII) of Nav 1.5. This interaction plays a critical role in the regulation of sodium current density, increasing the whole-cell INa current. In our study we screened a cohort of 181 BrS and 79 IVF (idiopathic ventricular fibrillation) patients by direct sequencing on all the three alternative transcript variants of the Mog1 gene. All patients were screened for mutations on the SCN5A, CACNA1c and GFP1L, associated with BrS.
A novel mutation affecting the transmembrane domain of the KCNJ2 protein is associated with high prevalence of life-threatening ventricular arrhythmias in a family with Andersen-tawil syndrome

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Purpose: The clinical phenotype in Andersen-Tawil syndrome (ATS) is characterized by a prevalence of life-threatening ventricular arrhythmias. Although several ATP2B1 gene variants have been described, the specific genetic cause is still elusive.

Methods: A cascade family screening was performed in a 5-generation family identified with the KCNJ2 mutation in the proband. Subsequently, 10 of 21 screened individuals appeared to be mutation carriers (median age 38 [range 10-75] years, 3 female). Mutation carriers underwent clinical examination including biochemical panel, cardiac ultrasound, Holter ECG and exercise stress test. Genotype-positive family members were followed-up for a median of 36 months (range 26-48 months).

Results: 1): At baseline, 2 patients survived ACA, 3 had syncope or pre-syncope attacks and 2 reported palpitations. Exercise-induced non-sustained bidirectional tachycardia (Br) was documented in 4 patients, 2 of whom received implantable cardioverter-defibrillators for primary prevention and 2 for secondary prevention. 2): During follow-up, 1 primary prevention and 1 secondary prevention patient received in total 4 adequate ICD shocks. In total, life-threatening ventricular arrhythmias were documented during childhood between 7 and 17 years of age in 5 of 10 mutation carriers. 3): All mutation carriers presented with characteristic mild dysmorphic features. Only 1 patient suffered from periodic paralysis, and 1 had renal dysplasia requiring extirpation at the age of 3.

Methods: The diagnostic yield coming from ICVD clinic is satisfactory in most of the cases. The experience of a family with a SD case motivates relatives to accept better the usefulness and the economic burden of genetic screening. The importance of genetic testing as a prophylactic health approach should be further highlighted.

Abstract P4089 - Table. ICVDs diagnostic yield and genetic family screening

| ICVDs | HCM | LQTS | ARVC | BrS | DCM | LVP
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<tbody>
<tr>
<td>Positive probes (%)</td>
<td>13/19/22.3%</td>
<td>14/23/60.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of relative/positive probes (Range per family)</td>
<td>52 (0-10)</td>
<td>48 (0-14)</td>
<td>79 (0-12)</td>
<td>6</td>
<td>6 (3)</td>
<td></td>
</tr>
<tr>
<td>Mut(+)/Phen(+)/% of total tested relatives</td>
<td>33.1%</td>
<td>47%</td>
<td>52%</td>
<td>67%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Conclusions: These results provide strong evidence that AF mortality clusters in families. The results also provide strong evidence that the excess relatedness among AF deaths has a strong heritable contribution, as it is observed in both close and distant relationships.

P4090 Long QT3 mice have disrupted sympathovagal balance and in vivo ventricular stimulation does not determine risk of sudden cardiac death, suggesting that a second perturbation may be required

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Purpose: Long QT 3 (LQT 3) is a cause of sudden cardiac death (SCD) by T or -dysfunction. It is characterized by the loss of four amino acids in the first transmembrane domain of the KCNJ2 protein. Our screening discovered two novel, unreported amino acid variants on Mog1. LQT3 mice have disrupted sympathovagal balance and SCD often occurs during sleep, rest and bradycardia, suggesting that heightened parasympathetic tone provokes TdP in LQT 3. It is challenging to ascertain the risk of SCD in these patients. We performed in vivo electrophysiological studies (EPS), ventricular tachycardia (VT) stimulation and telemetry in LQT 3 (LKPQ) and wild type (WT) mice, without and with pacing with the muscarinic agonist, carbacol.

Methods: EPS were performed in young (8-week) and old (>6 months of age) anesthetised mice with a 1.1F catheter inserted into the right ventricle via the right atrium in a propofol anesthesia. Ventricular arrhythmias were induced by a 1 Hz pacing protocol (1:1 to 3:2 coupling) which was applied for 60 sec. The number of induced VT/VT/VT episodes was counted. The number of induced VT/VT episodes was counted and corrected for the absolute number of induced VT episodes. Ectopyinduced VT episodes were considered only if they were preceded by an extrastimulus. VT episodes were categorised in term of stability, with VT/VT/VT episodes being unstable and VT/VT being stable. The number of induced VT/VT/VT episodes was calculated for each group. The number of induced VT/VT/VT episodes was compared between the groups using the Mann-Whitney U test. P-values < 0.05 were considered as significant.

Results: The overall average relatedness of the 4,335 AF deaths was significantly lower than expected (empirical p < 0.001). We also observed significant excess relatedness when close relationships (genetic distance closer than first cousins) were ignored (empirical p < 0.001). Significantly elevated risks (p < 0.0001) were estimated for first- to fifth-degree relatives (1st: 1.70; 2nd: 1.23; 3rd: 1.28; 4th: 1.23; 5th: 1.25).

Conclusions: Inherited cardiovascular diseases (ICVDs) in the every day clinical practice: diagnostic yield and genetic family screening

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Purpose: Inherited cardiovascular diseases (ICVDs) have variable clinical expression and incomplete penetrance. The aim of this study is to identify the diagnostic yield of genetic testing on each disease in every day clinical practice and the response of family members to family screening.

Methods: 109 probands were clinically diagnosed with Hypertrophic Cardiomyopathy (HCM), Long QT syndrome (LQTS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), Dilated Cardiomyopathy (DCM-LMNA), Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Brugada syndrome (BrS) and Marfan syndrome (MFS) according to the latest diagnostic criteria for each disease. Molecular and genetic analysis was performed. Family members (n=210 out of 352 that were invited) of mutation positive probands (n=58) were clinically assessed and genetically evaluated. Available data were used to evaluate the impact of sudden death (SD) on the number of relatives that accepted to be tested.

Results: A pathogenic mutation was identified in 58 out of 109 (52.3%) index cases suffering from the above mentioned ICVDs. In most common ICVDs (HCM, LQTS, ARVC, BrS), the Mut(+)-Phen(-) relatives reached an average of 30.2% (Table). We categorized the families on SD-families and non-SD-families regarding the presence or not of SD on their pedigrees. On SD-families, we suggested on 198 relatives to be tested while 130 of them proceeded on genetic screening. Similarly, 80 out of 154 relatives were tested on non-SD-families. Relatives response on genetic screening is strongly stimulated by the presence of a SD case in the family [OR: 1.91 (CI: 1.24-2.96, p: 0.003)].

Conclusion: The diagnostic yield coming from ICVD clinic is satisfactory in most of the cases. The experience of a family with a SD case motivates relatives to accept better the usefulness and the economic burden of genetic family screening. The importance of genetic testing as a prophylactic health approach should be further highlighted.
The effect of corticosteroid, antiarrhythmic agents, and radiofrequency catheter ablation on ventricular tachycardia associated with cardiac sarcoidosis

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Purpose: Ventricular tachycardia (VT) and sudden death are commonly observed in cardiac sarcoidosis; however, the clinical impact of a multimodality therapy is still uncertain.

Methods: We enrolled 35 patients (55±12 years; 11 male) who had a diagnosis of sustained VT associated with cardiac sarcoidosis. All patients were initially treated with corticosteroids and antiarrhythmic agents unless they refused to take them. Steroid therapies were started with an initial dose of 30 mg/day, and the doses were gradually decreased over a period of 6 to 12 months to 5–10 mg/day as a maintenance dose. If the VTs recur even on the antiarrhythmic and steroid therapies, radiofrequency catheter ablation (RF-CA) was performed. Patients who underwent RF-CA before being medicated, including with corticosteroids and antiarrhythmic agents, were excluded from this study. The clinical impact of both a steroid and antiarrhythmic therapy associated with RF-CA was evaluated.

Results: All patients received antiarrhythmic drugs and 32 patients received steroid therapy. During a 51.37-month follow-up (22.65% patients were free from any VT episodes. The ejection fraction and prevalence of a Gallium-67 uptake were still uncertain.

Conclusion: To our knowledge, this is the first report of in vivo EPS in the JKQ mouse. Our results concur with human studies where VT stimulation is unhelpful in predicting risk of SCD. HRV assessment shows disrupted sympathovagal balance in LQT3 patients.

Changes in NT-proBNP level after successful PVC ablation in patients without structural heart disease: evidence for PVC-induced chronic wall stress

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Purpose: NT-proBNP is synthesized in ventricular myocardium in response to increased wall stress. A high, chronic PVC burden has been associated with a reversible cardiomyopathy. However, the majority of patients with symptomatic PVCs presents with only slightly impaired or normal LV function. We evaluated NT-proBNP levels before and after ablation to determine the potential wall stress caused by PVCs in symptomatic patients with slightly impaired or normal LV function.

Methods: Eighty patients (42 male, 48±16y) with a LVEF >50% referred for ablation due to non-sustained PVCs were included. All patients underwent clinical evaluation including standardized echocardiography, 24hr Holter monitoring and assessment of NT-proBNP before and 3 months after ablation. Symptoms increased 1-year mortality risk [HR=1.9 (95% CI 0.85-4.35).

Conclusion: In this study early VT/VF was associated with increased risk of in-hospital death but not with increased post discharge, whereas late VT/VF was associated with increased risk of 30 day death and a trend for increased 1-year mortality risk.

Outcome of patients with acute coronary syndromes complicated by ventricular tachycardia or fibrillation in the acute coronary syndrome israeli survey (ACIS)

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Background: Most of the data regarding the occurrence of VT/VF among patients hospitalized due to acute myocardial infarction (AMI) and its associated prognosis were obtained before the reperfusion era, whereas data on VT/VF in the era of primary percutaneous coronary intervention (PCI) are limited and conflicting regarding early and late prognosis. Aim: To evaluate the incidence and outcome of patients with AMI presenting with early and late VT/VF.

Methods and results: We studied 7699 patients from the Acute Coronary Syndrome Israeli Survey (ACIS) between the years 2002-2010 which included ST elevation (n=3573) and non ST elevation MI: ACS (n=4096). We divided them into 3 groups: patients with no VT/VF, early (<48h) VT/VF and late (>48h) VT/VF. Of the 7699 patients with ACS, 7369 (96%) had no VT/VF, 166 (2.1%) had early VT/VF and 194 (1.7%) had late VT/VF. Baseline characteristics were significantly different among the 3 groups; with higher number of coronary risk factors and comorbid conditions in the VT/VF groups and notably younger age (mean 60±12 years) in the early VT/VF group.

Patients with late VT/VF had a more complex hospital course with higher frequency of mechanical and arrhythmical complications other than VT/VF, and longer hospital stay.

Mortality

<table>
<thead>
<tr>
<th>No VT/VF</th>
<th>Early VT/VF</th>
<th>Late VT/VF</th>
<th>P value</th>
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<tr>
<td>In hospital Mortality</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>271 (3.7)</td>
<td>25 (15.1)</td>
<td>38 (26.4)</td>
<td>-0.001</td>
</tr>
<tr>
<td>Mortality 1 year</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>531 (9.5)</td>
<td>24 (20.3)</td>
<td>41 (40.2)</td>
<td>-0.001</td>
</tr>
<tr>
<td>MACE (30d mortality/MI/APEP)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>618 (8.3)</td>
<td>31 (18.7)</td>
<td>45 (33.6)</td>
<td>-0.001</td>
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</table>

After adjustment for multiple confounders early VT/VF was shown to be associated with increased risk of in-hospital death (OR=2.8; CI 95% 1.3-5.9), but not with increased post discharge 30-day death (HR=0.94; CI 95% 0.12-7.1) or 1-year mortality risk (HR=1.3; CI 95% 0.5-3.2). In contrast, late VT/VF was associated with increased 30-day mortality risk (HR=6.7; CI 95% 1.7-19.15) and a trend for increased 1-year mortality risk (HR=1.9 (95% CI 0.85-4.35).
Premature extrasystoles (PES) originating from right ventricular outflow tract (RVOT) are often observed in patients without structural heart diseases and are generally considered as benign ventricular arrhythmias. However, ventricular fibration (VF), and/or polymorphic ventricular tachycardia (PVT) are occasionally initiated by the PES. The aim of this study was to clarify how to differentiate malignant (M) PES from benign (B).

Methods: Consecutive 30 patients, in whom radiographic catheter ablation was conducted for PES originating from RVOT, were enrolled. Spontaneous VF and/or PVT initiated by the PES were showed in 9 patients (M-gr). Coupling interval, QRS duration, QRS morphology and optimal ablation site of the PES in M-gr were compared with them in the other 21 patients group (B-gr).

Results: There were no differences between M-gr and B-gr in coupling interval (419±30msec vs. 438±31mssec, ns) and QRS duration (166±1.1mssec vs. 153±15mssec, ns). The prevalence of notch on QRS in inferior leads of PES was significantly higher in M-gr than in B-gr (9/9 vs. 3/21, p<0.01). Broad R wave (>150mssec) in I was significantly more frequently observed in M-gr than in B-gr (7/9 vs. 1/21, p<0.01). The prevalence of aVR/aVL (the ratio of negative amplitude of aVR to aVL) >1 was not significantly higher in M-gr than in B-gr (7/9 vs. 4/21). PVCs originated from posterior side of free wall, in free wall in 7 out of 9 patients in M-gr, and 1 out of 21 patients in B-gr (p<0.01).

Conclusion: In conclusion, PES originating from posterior side of free wall in RVOT, with notch in inferior leads and broad R wave in I, frequently initiate VF and/or PVT. Malignant form of PES in RVOT could partially depend on the localization of its origin.

Effect of vagal nerve on the monophasic action potential of ventricular outflow tract

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Objective: Vagal nerve may be related with idiopathic ventricular tachycardia (IVT). The present study was aimed to investigate the effect of vagal nerve on the monophasic action potential (MAP) of ventricular outflow tract.

Methods: Eight adult mongrel dogs were involved. Bilateral vagosympathetic nerves were decentralized for stimulation. Metoprolol was given to block sympathetic effects. Three MAP recording electrode were placed at the left ventricular outflow tract (LVOT), right ventricular outflow tract (RVOT) and right ventricular apex (RVA) respectively through right femoral artery and vein. MAP was recorded at the LVOT, RVOT, RVA with or without vagal stimulation (VS) respectively.

Results: MAP duration (419±30ms/sec vs. 438±31ms/sec, ns) and QRS duration (166±1.1ms/sec vs. 153±15ms/sec, ns) were not significantly different between two groups. The prevalence of notch on QRS in inferior leads of PES was significantly higher in M-gr than in B-gr (9/9 vs. 3/21, p<0.01). Broad R wave (>150ms/sec) in I was significantly more frequently observed in M-gr than in B-gr (7/9 vs. 1/21, p<0.01). The prevalence of aVR/aVL (the ratio of negative amplitude of aVR to aVL) >1 was not significantly higher in M-gr than in B-gr (7/9 vs. 4/21). PVCs originated from posterior side of free wall in free wall in 7 out of 9 patients in M-gr, and 1 out of 21 patients in B-gr (p<0.01).

Conclusion: In conclusion, PES originating from posterior side of free wall in RVOT, with notch in inferior leads and broad R wave in I, frequently initiate VF and/or PVT. Malignant form of PES in RVOT could partially depend on the localization of its origin.

Electromechanical coupling interval: a new marker of PVC in LV dysfunction

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Introduction: Mechanisms responsible of PVC-induced left ventricular (LV) dysfunction are not fully understood. We studied whether the electromechanical coupling interval to the preceding cardiac cycle and other characteristics of the PVC were associated with LV dysfunction.

Methods: We prospectively included 29 patients (pts) (55±16 years, LV ejection fraction (LVEF) 41±17% and 62% male) with frequent PVC (>10% in 24 hours Holter) referred for ablation from 2009 to 2011. Electromechanical coupling interval was estimated as the interval between diastolic notch in the pulse wave and onset of PVC. Site of origin of PVC, percentage of PVC, percentage of pts with interpolated PVC, electrical coupling and electromechanical coupling interval were measured. Results: 11 pts (38%) had reversible cardiomyopathy (basal LVEF 30% [24-35%] and 6 month LVEF 47% [40-51%], p<0.01. 18 pts (61%) had normal heart. There were no statistical differences on site of origin of PVC (right ventricular outflow tract 33% vs 66%, left ventricular outflow tract 62% vs 37%, others 33% vs 66%, p=0.48), percentage of PVC (15% [11-49%] vs 12% [10-43%] per 24 hours, p=0.30), percentage of pts with interpolated PVC (27% vs 16%, p=0.77) and electrical coupling (504 ms [455-565 ms] vs 465 ms [412-696 ms], p=0.77). Electromechanical coupling interval of the PVC was significantly shorter in pts with PVC and LV dysfunction (24 ms [6-06 ms] vs 89 ms [55-216 ms], p<0.01) and show a better correlation than electrical coupling interval with basal LVEF (r=0.46, p=0.045).

Conclusions: In pts referred for frequent PVC ablation, electromechanical coupling interval is a marker of reversible cardiomyopathy. This suggest an association between early irruption of PVC in the preceding mechanical cardiac cycle and the development of LV dysfunction.

Digitalis use and multivessel disease independently predict ventricular fibrillation at reperfusion in PCI-treated patients with STElevation myocardial infarction

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Purpose: Ventricular fibrillation (VF) during reperfusion in STElevation myocardial infarction (STEMI) is an infrequent event, but confers increased in-hospital mortality. We assessed clinical characteristics associated with VF during reperfusion in an unselected population of STEMI patients treated with percutaneous coronary intervention (PCI).

Methods: It total, 1744 consecutive STEMI patients were admitted to a Swedish tertiary care hospital for primary PCI during 2007-2009. Clinical characteristics and information about presence of VF were obtained from the Register of Information and Knowledge about Swedish Heart Intensive care Admissions. Medical records were reviewed to determine VF timing in relation to the infarct-related artery (IRA) opening. Clinical and angiographic characteristics were tested for association with VF during reperfusion with logistic regression analysis.

Results: Acute IRA occlusion was present in 1127 patients (age 66±12 years, 72% male) at admission, of whom 26 (2.3%) developed VF at IRA opening. Increased risk of VF during reperfusion was observed for aspirin, beta-blockers or digoxin at admission. VF before reperfusion, inferior location of infarct and multivessel disease. In multivariate analyses, only multivessel disease and the use of digoxin remained independently associated with reperfusion VF (Table). Reperfusion VF was not associated with either age, gender, body mass index, history of hypertension, heart failure, diabetes, stroke, PCI, CABG, myocardial infarction, IRA or the presence of left main artery stenosis.

Clinical factors associated with VF during reperfusion in PCI-treated acute STEMI

P4097

<table>
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<tr>
<th>Characteristic at admission</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Medications:</td>
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<tr>
<td>Aspirin</td>
<td>2.75</td>
<td>1.22-6.21</td>
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<tr>
<td>Beta-Blockers</td>
<td>3.49</td>
<td>1.52-7.74</td>
</tr>
<tr>
<td>Digitals</td>
<td>8.80</td>
<td>1.85-42.05</td>
</tr>
<tr>
<td>VF before reperfusion</td>
<td>5.04</td>
<td>1.92-13.97</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>3.05</td>
<td>1.14-8.12</td>
</tr>
<tr>
<td>Inferior localization</td>
<td>2.82</td>
<td>1.11-7.14</td>
</tr>
</tbody>
</table>

Conclusion: Multivessel disease and digitalis use at admission independently predict VF at IRA opening in patients with acute STEMI. Our data further support a proarrhythmic effect of digitalis in the setting of acute coronary syndrome.

Electroanatomical substrate mapping guidance for left ventricular aneurysmectomy in patients after myocardial infarction

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Introduction: Left ventricle aneurysmectomy (LVAR) with peri-infarction...
is an effective approach for the treatment of post-MI patients who present with VT. The purpose of this prospective study was to evaluate the efficacy of catheter-based electroanatomical mapping (EAM) prior to aneurysmectomy to identify the arrhythmogenic areas as a guide for surgical resection and cryoablation.

**Method:** We included 35 pts (MF: 28/7), average age 64 years (38 – 79). Mean LVEF prior the surgery was 23.5% (20-50%) and post MI aneurysms were documented by echocardiography or LV angiography. VT inducibility was confirmed prior to surgery and EAM was performed (CARTO, Biosense-Webster) to identify border zones and late/fractionated potentials. The surgeon used the EAM image during surgery, and VT arrhythmogenic zones were eliminated by aneurysmectomy, endocardial resection and cryotherapy. An EP study and EA mapping were repeated at -3 mo after surgery.

**Results:** In 27 pts we performed LVAR + CABG, in 5 pts LVAR + mitral valvuloplasty and in 3 pts LVAR + cryotherapy. The EF improved significantly to 48%. The end-systolic volume decreased from 142ml to 93ml. Pre-surgery, VT was inducible in 24 pts (68.5%), but after LVAR only in 4 pts (11%). Post-surgical EAM revealed reduction of late and fractionated potentials. When present, MRI revealed significant scar tissue reduction in all pts.

**Conclusion:** EA mapping prior to LVAR can facilitate arrhythmogenic substrate elimination with significant reduction of VT induction – this minimizes the risk of life threatening arrhythmias.

**P4099 Intraoperative Echocardiography for the Evaluation of Ventricular Arrhythmia in Patients With Idiopathic Ventricular Fibrillation**

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**Background:** Diagnosis of idiopathic ventricular fibrillation (IVF) before its occurrence is very challenging, because cardiac arrest could represent the first or the only sign of the disease. Heterogeneity of ventricular repolarization has been previously reported to be linked to ventricular tachycardia in patients with ischaemic and idioventricular cardiomyopathy. The purpose of this study was to test the hypothesis that IVF might also be associated with ventricular repolarization abnormalities.

**Methods and Results:** Spatial dispersion of recovery time as an index of heterogeneity of ventricular repolarization was assessed by means of a 10 electrode signal-averaged vector- and high-resolution electrocardiograph (187-ch SAVP-ECG) in a group of 14 consecutive patients (13 male, 48±17 year-old) who were diagnosed with IVF and who received ICDs for secondary prevention after an episode of resuscitated sudden cardiac death. A control group consisting of 22 healthy persons (22 male, 35±7 year-old) was set for comparison. Recordings took a maximum of 10 minutes and were obtained without any complication. The patients with IVF did not present with characteristic ECG abnormalities. Spatial dispersion of corrected recovery time (defined as the time between the R wave peak and the first positive maximum derivative of T wave corrected by Bazett’s formula) was significantly higher in the IVF group compared with the control group (94±17 milliseconds versus 63±19 milliseconds P < 0.001).

**Conclusions:** 187-ch SAVP-ECG is a simple and reliable method for the evaluation of ventricular repolarization. It may be useful to reveal patients with latent IVF.

**P4100 Predictors and prognostic value of ventricular fibrillation during acute coronary syndromes**


**Introduction:** Different types of arrhythmias are originated in the setting of acute coronary syndromes (ACS) due to electrical instability and ischemia. The most important is ventricular tachycardia which degrades to ventricular fibrillation (VF). VF during hospital stay is associated with a poor prognosis.

**Objective:** Assess the predictors and prognosis of VF during ACS.

**Methods and results:** We performed a prospective study including 902 consecutive patients (P; aged 64.0±13.2 years, 77.5% male) admitted in a Coronary Unit for the period of 2 years, with a 6 month follow-up. The VF rhythm was identified in 51 P (5.7%) during hospital stay. This arrhythmia was not associated with any cardiovascular risk factor, relevant past medical history (including ischemic cardiomyopathy or valvular heart disease) or previous medical therapy. At admission, the P with VF presented with higher heart rate (HR; p=0.0014) and lower systolic blood pressure (SBP; p=0.001). ACS with ST segment elevation was the most common type of ACS in those P (p=0.001). During hospital stay, VF was more frequent in P with multivessel disease (2 or 3 vessels, p=0.008), higher maximum Killip class (p=0.008), intraventricular conduction delay (p=0.001), intra-aortic balloon pump (p=0.009) and mechanical ventilation (p=0.001). In multivariate analysis, HR at admission (OR 1.003; 95% CI 1.001-1.005), SBP at admission (OR 0.98; 95% CI 0.96-0.99), KMax=1 (OR 4.15; 95% CI 1.60-10.73) and AV block > 2 (OR 6.82; 95% CI 2.37-19.57) remained independently associated with VF. VF was predictor of death during hospital stay in univariate (p<0.001) and multivariate analysis (OR 6.64; 95% CI 1.87-23.64), and adjusted for other recognized prognostic factors (age, diabetes, LVEF<40%, KMax=1, NT-proBNP and peakcreat). Throughout follow-up, VF was not associated with death or other major adverse cardiovascular events (MACE).

**Conclusion:** VF is a serious arrhythmia associated with ACS. It carries worse clinical manifestations and prognosis during hospital stay, but seems to not imply continuing risk over time.

**P4101 Circulating biomarkers of extracellular matrix remodeling are associated with ventricular arrhythmia in heart failure patients**

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**Background:** Ventricular arrhythmia is a major contributor to cardiovascular mortality in heart failure (HF) patients. This study evaluated biomarkers with extracellular matrix (ECM) remodeling. The aim of this study was to assess the correlation between circulating biomarkers of ECM and ventricular tachycardia/fibrillation in ischemic and non-ischemic heart failure patients carrying an implantable cardioverter defibrillator (ICD).

**Methods and results:** Blood samples were obtained from 90 HF patients (left ventricular ejection fraction (LVEF) <25%) with an ICD and it was analyzed for ECM proteins and CRP as control. Healthy volunteers (LVEF >60%; n=10) served as control group. C-reactive protein (CRP) did not differ between groups, excluding acute inflammatory response being a potential proarrhythmic trigger. Ventricular tachycardia/fibrillation were assessed using stored ICD electrograms. Increased levels of osteopontin, matrix metalloproteinase (MMP)-2, MMP-7, MMP-9, and N-terminal brain natriuretic peptide (NT-proBNP) were detected in all heart failure patients, whereas circulating tenascin-C was reduced compared to healthy controls. With respect to the biomarker levels, ventricular tachycardia (VT) or fibrillation (VF) among heart failure patients was associated with elevated MMP-7 and NT-proBNP levels compared to the heart failure patients without ventricular tachycardia. Considering the best performance of biomarker predicting VT/VF in heart failure patients, logistic regression analysis identified osteopontin and MMP-9 as strongest predictors of HF-associated ventricular arrhythmia after adjustment for gender and β-blocker treatment.

**Conclusions:** Heart failure correlates with elevated circulating biomarkers of extracellular matrix remodeling. Monitoring of plasma osteopontin and MMP-9 may contribute to ventricular arrhythmia risk stratification in HF patients.

**P4102 Efficacy of ICD therapy in high-risk children with Long QT syndrome**

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Long QT syndrome (LQTS) is an inherited disorder caused by mutations in the genes encoding cardiac ion channels. Affected patients are characterized by increased risk for polymorphic ventricular arrhythmias (PVA), aborted cardiac arrest, and sudden cardiac death (SCD). Beta-blocker therapy is considered the most efficient therapy for patients, however it does not protect all patients. An ICD implantation is recommended for patients at high risk for cardiac events, including those who have recurrent syncope despite beta-blocker therapy. The study aimed to describe a single-centre experience in management of patients with severe forms of LQTS treated with ICDs.

**Methods and results:** The study population consisted of 30 LQTS pts from 29 unrelated families aged from 7 to 32 (mean age 16±5 years; 15 boys) from a broader group of 340 LQTS pts. Genotype was known in 16 pts (53%): 2 had compound mutations, 1 boy had compound mutation in KCNQ1 and Lange-Nielsen syndrome -JLN), 6 patients had single mutation in KCNH2 and 2 pts patients had single mutations in KCNQ1 and KCNE1. 7 pts had LQT1, 10 pts LQT2, 5 pts LQT3, 7 pts JLN syndrome -JLN, 6 patients had single mutations in KCNH2 and 7 pts patients had single mutations in KCNQ1. Mean QTc on resting ECG was 509±36 ms. All pts except one had multiple syncpe before ICD implantation. Mean age at implantation was 12±4 years (from 4 to 18 years). Mean ICD follow-up length after the implantation was 50±18 months. Inefficient beta-blocker therapy was the major or the only indication for ICD in 24 cases (80%). Among the other indications were: high concentration of SCD cases in patients’ families (2 cases), severe bradycardia with transient AV block during 24-hours Holter monitoring (3 cases) and aborted cardiac arrest (1 case). During the follow-up, 16 pts (53%) experienced PVA during ICD follow-up:15 pts experienced sustained VT treated with ICD shocks; episodes of spontaneously terminated asymptomatic VF were registered in 7 pts, and unsustained ventricular tachycardia - in 4 pts. Inappropriate shock (T oversensing) was registered in 1 patient. Among genotyped pts the greater part of VF was found in pts with combined mutations in patient with JLN. Furthermore multiple episodes of VF were registered in 3 pts with LQT1 and in 1 with LQT2.

**Conclusions:** ICD implantation was needed in about 9% of children with LQTS,
who were exposed to a high risk of SCD. ICD appears to be an effective therapy option for primary (14 pts) or secondary (1 patient) prevention of SCD in 50% of pts. ICD monitoring allowed to reveal unsatisfactory efficiency of beta blockers in 53% of pts with severe course of disease. Nearly all children with LQTS were not exposed to inappropriate ICD shocks over a 4.2±1.5 years of follow up.

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**P4103 Takotsubo cardiomyopathy and arrhythmic risk**

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**Purpose:** "Takotsubo" cardiomyopathy (TTC) is a recently described cardiac syndrome, usually triggered by intense emotional and/or physical stress, characterized by transient severe localized left ventricular dyskinesia and changes of ST segment that can mimic acute myocardial infarction, without significant coronary artery stenoses. Although the prognosis is considered good, TTC is associated with significant alterations of the QT interval that could trigger life-threatening cardiac arrhythmias. The aim of our study was to assess the extent of the alterations of the QT interval and the arrhythmic risk associated with this disease.

**Methods:** From August 2008 to December 2011 we prospectively enrolled all pts (n=318) admitted to our Department with TTC (P=0.08). Myocardial fibrosis was also significantly observed in VT/VF group more than non-VT/VF group (P=0.03). The grade of MVO and amyloid deposition of peri-coronary neurons tended to be higher in VT/VF group.

**Conclusion:** VT/VF in amyloidosis may depend on the degree of amyloid deposition and myocardial fibrosis. Ischemic change by MVO and coronary spasm by amyloid deposition of peri-coronary neurons might lead to VT/ VF.

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**P4104 J waves in the early recovery phase of acute myocardial infarction and its clinical implication**

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**Purpose:** J waves can be arrhythmogenic and to be studied in ischemic heart disease. We studied the prevalence and clinical significance of J waves in the early recovery phase of myocardial infarction (MI).

**Methods:** In 152 consecutive patients with acute MI, electrocardiogram (ECG) was monitored for one week after coronary intervention for revascularization. The mean age was 68.6±13.9 years, and 78.3% were males. J waves were diagnosed when the amplitude was ≥1.0 mm as either notch or slur at the terminal part of the QRS complex in contiguous 2 or more leads on 12-lead ECG recorded at the end of monitoring for one week. The relationship between the location of J waves and the location of MI and the culprit lesion were determined. Then the ECG parameters and the incidence of arrhythmias were compared between groups with and without J waves. Finally, the rate dependency of J waves was evaluated in the conducted beats of atrial premature beats.

**Results:** J waves were present in 60.5% (92/152) of patients which was higher than 16.4% that observed in the age and sex comparable subjects. The mean amplitude was 1.4 mm. J waves were more frequent in inferior MI (67.7% versus 55.2%, respectively, P=0.0142). The vectorial tachyarrhythmias (VTA), premature beats, non-sustained ventricular tachycardia (VT), ventricular fibrillation (VF), occurred more frequently in the group with J waves including sustained VT or VF (P=0.012). Furthermore, the patients with the amplitude of the J wave ≥2 mm or greater was associated with higher incidence of VTA. As the RR interval became shorter by the conduction of atrial premature beats, the amplitude of the J wave was augmented suggesting tachycardia dependency or phase 3 block.

**Conclusions:** J waves of the patients in the early recovery phase of MI had a higher prevalence of J waves and they were associated with ventricular arrhythmias. The augmentation of J waves at higher rate suggested a role of conduction delay for the pathogenesis. The significance and mechanism of J waves are to be determined in post-MI patients.

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**P4105 Amyloid deposition of intramural coronary arteries and peri-coronary neurons in epicardium may be the cause of ventricular arrhythmia in cardiac amyloidosis**

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**Background:** Patients with amyloidosis have poor prognosis and it is difficult to treat because of ventricular arrhythmia, especially ventricular tachycardia (VT) and ventricular fibrillation (VF). However, cause of VT/VF is unclear. In this study, we investigated pathological factors to cause VT/VF.

**Methods:** We studied 27 patients with amyloidosis of AL or AA type diagnosed at autopsy. Patients were divided into 2 groups: VT/VF group and non-VT/VF group. We histopathologically investigated about cardiac weight, micro vessel obstruction (MVO) in myocardium, amyloid deposition of peri-coronary neurons in epicardium, and myocardial fibrosis. Percentage of MVO numbers due to amyloid deposition was counted microscopically, and scored 3 (over 50%), 2 (25-50%), 1 (under 25%), 0 (0%). Myocardial fibrosis was assessed in one-to-four grading by Masson staining.

**Result:** Cardiac weight was 579±94g in VT/VF group and 406±81g in non-VT/VF group. Cardiac weight of VT/VF group was significantly larger than non-VT/VF group (P<0.001). Myocardial fibrosis was also significantly observed in VT/VF group more than non-VT/VF group (P=0.03). The grade of MVO and amyloid deposition of peri-coronary neurons tended to be higher in VT/VF group.

**Conclusion:** VT/VF in amyloidosis may depend on the degree of amyloid deposition and myocardial fibrosis. Ischemic change by MVO and coronary spasm by amyloid deposition of peri-coronary neurons might lead to VT/VF.

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**P4106 Prevalence of J wave and early repolarization pattern in a large population of aircrew members**

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**Purpose:** The association between early repolarization pattern (ER) and cardiac mortality remains discussed. However, in aviation medicine the risk of sudden death related to ventricular arrhythmias in Aircrew Members (AM) with ER remains a matter of concerns. Particularly, fitness assessment in this situation is not easy to take for the fighter pilots who are involved in military operations, flying above hostile countries (Afghanistan, Libya ...) alone in their fast jets. Moreover, the specific conditions of combat flights (accelerations more than +9Gz and a speed of application up to 6 Gz/s) induce some important cardiac-physiological constraints in these pilots, leading to variations in electrophysiological conditions, vaso-vagal balance, refractory periods ... Consequently, a severe arrhythmia can be favoured in a pilot with a non-structurally or a non-electrophysiologically normal heart.

**Methods:** AM (military and civilian jet and transport crew) are periodically examined for fitness assessment at the same health care center (CHU) with a standard 12-leads ECG at each visit. All ECGs were independently evaluated in random order by two physicians using the definition of ER without using computerized analysis.

**Results:** From 01/09/2009 to 31/08/2010, we analysed 8862 standard resting 12-leads ECG of AM (77.2% male, mean age male: 36.8±10.2 yo, mean age female: 30.5±8.7 yo), including deployed fighter pilots. Prevalence of ER was 2.84% [N= 251 (231 male = 92.2%, 20 female = 7.8%)], 165 in inferior leads (65.7%), 89 in lateral leads (39.4%), 13 in both (5.1%), 21 slurring pattern (83.6%), 92 notching pattern (36.6%), 51 both pattern on same ECG. J wave was ≥2.5 mm in 12 ECG (4.78%), 2.2-5.5 mm in 40 (13.94%), 1.5-2.5 mm in 72 (28.6%), 1.1-1.5 mm in 123 (49%).

**Conclusion:** Our results are closed to the results of the most recent studies. Moreover among our AM, no cardiovascular event occurred. All AM were very closely evaluated for a familial or a personal history of sudden cardiac death or cardiac symptoms. When this history was noted, we had decided to perform non-invasive test (echo, Holter ECG, stress test); no significant abnormality was noticed. We think that such an evaluation may be performed in a subgroup at increased risk. As in the Brugada’s syndrome (BS), a risk stratification of ER should be discussed). We must keep in mind the first times of the history of BS before the risk stratification and the more recently statements with the importance of clinical history!
**ELECTROPHYSIOLOGIC STUDIES/SUDDEN CARDIAC DEATH**

**P4107 How do female electrophysiologists deal with radiation exposure during pregnancy: Results from the EPIC global survey**

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**Background:** Awareness of radiation exposure is variable among different settings of practice in invasive electrophysiology (EP) laboratories around the world.

**Methods:** As part of a web-based questionnaire on individual practices focusing on radiation exposure during invasive EP procedures, a total of 8 questions were aimed specifically at female cardiologists.

**Results:** A total of 165 physician (50 female) responses were received with the majority of them located in the US (38%), Canada (8%), Italy (7%) and Germany (6%). The majority of responders (60%) were located in Asia and South America. Nearly 80% of participants were qualified cardiologists for more than 3 years (45% for more than 10 years). Of the 50 female participants, 18 were pregnant at some time during their time in the catheterization laboratory or interventional cardiology (total of 28 pregnancies). Only 2 colleagues received structured advice on specific radiation protection, while others obtained advice from senior female colleagues or from the web-based information. During their 1st pregnancy, 10 of 14 colleagues continued to work in the cath lab in the first trimester, while 9 continued during the 2nd and 2 of them during their 3rd pregnancy. Two thirds of colleagues continued to work as first-hand operator, or supervised junior colleagues without being directly exposed. Personal protection was worn in 6, 9 did wear double layers of lead aprons and 2 used a protection cabin. Of note is that fetal badges were issued in all cases, but only in 2 cases showed higher readings. Female colleagues continue to work up to 6 (4, 3±2) times less in pregnancy compared to and 30 minutes after valve implantation. The changes observed were compared to the last 70 consecutive cases who had intracardiac electrograms prior to and 30 minutes post implantation. Also, 12 colleagues showed an increase in PR interval (33±9 milliseconds; p<0.001). Similarly the prolongation of HV interval was higher in p<0.05). In patients with pregnancy was scarce, all but one pregnancy were successful with the majority of them located in the US.

**Conclusions:** The baseline presence of RBBB and LAHB was a determining factor influencing the prolongation of HV electrograms immediately after CoreValve implantation. In addition, annulus size, the sinus of Valsalva diameter and annulus/prosthesis size ratio may all influence the increments in intracardiac electrograms and PR intervals. These changes do not seem to influence the need for pacemaker implantation.

**P4109 Remote navigation and electroanatomical mapping with an electromagnetic vectorial catheter miniaturized for human use**

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**Purpose:** Remote catheter navigation is a promising area of development. A novel system based on rapidly changing magnetic forces generated by electromagnetic magnets may overcome the slow movement of a previous system based on permanent magnets. The aim of this study was to prove the accuracy and safety of the system in the human being.

**Methods:** This device is composed of 8-magnets located at the tip of the cathode to be remotely controlled from a console. The magnets are controlled using a computer-based interface and a custom-made catheter mounted with magnets. The catheter was successfully navigated to the predefined sites in all cases. The catheter was successfully navigated to the currently manually acquired sites in 95.8% of the 653 tagged sites in 23±1.4±1.8 sec. The initial and final distances to the target sites in the automatic mode were 39±8±21 and 1.9±0.9 mm. There were 2 adverse events: ischemic stroke treated with thrombolysis and a cardiac tamponade which required pericardiocentesis at the end of the procedure. Both patients with complete resolution of the complication. There were also 4 pericardial effusions and 1 AV femoral fistula which resolved spontaneously.

**Conclusions:** Remote catheter navigation by electromagnetic forces is fast and accurate both by the operator and automatic modes. This novel system appears safe although there are some concerns about the safety of leaving a stiff sheath bended/rotated alone in the LA for LV mapping.

**P4108 Determinants of immediate intracardiac intervals prolongation after percutaneous aortic valve implantation**

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Percutaneous aortic valve implantation (PAVI) in patients (pts) with aortic stenosis may induce changes in atrioventricular conduction, as assessed by intracardiac electrograms. However, there is little information on factors influencing changes in intracardiac electrograms in pts immediately after CoreValve implantation. The aim of this study was to analyze determinants of immediate increases in surface and intracardiac intervals after PAVI.

**Methods:** From a total of 160 pts with aortic stenosis undergoing PAVI, we analyzed the last 70 consecutive cases who had intracardiac electrograms prior to and 30 minutes after valve implantation. The changes observed were compared with intervals obtained from the surface electrocardiogram (ECG) before and after the procedure. The mean age was 78±6 years; 43 (61%) were female. The increases in PR, ORS, AH and HV intervals were defined as the differences between measurements taken 30 minutes post implantation and at baseline. Also, the increments of AH and HV were corrected according to cycle length.

**Results:** There was a significant inverse correlation between the increase in PR interval and the annulus/prosthesis size ratio (r=0.34; p<0.002). There were also significant correlations between the increment in corrected-HV with the annulus size, as assessed by angiography (r=0.35; p<0.01). The increment of corrected-HV correlated significantly with sinus of Valsalva diameter assessed by echocardiography (r=0.38; p<0.001). The increment of corrected-AH correlated with the depth of valve implantation (r=0.51; p<0.0001). The patients with dissection showed a higher increase in PR interval (33±55 vs 6±32 milliseconds; p<0.04). The increment in QRS duration was significantly higher in patients with ejection fraction >40% at baseline study (36±8 vs 17±5 milliseconds; p=0.01). In pts with right bundle branch block (RBBB) the increment of corrected-HV was significantly higher (p<0.001). Similarly the prolongation of HV was higher in pts with baseline RBBB and left anterior hemiblock (LAHB).

**Conclusions:** The baseline presence of RBBB and LAHB was a determining factor influencing the prolongation of HV electrograms immediately after CoreValve implantation. In addition, annulus size, the sinus of Valsalva diameter and annulus/prosthesis size ratio may all influence the increments in intracardiac electrograms and PR intervals. These changes do not seem to influence the need for pacemaker implantation.

**P4110 Management of challenging transseptal access in patients with hypermobile septum/interradial aneurysm or stilt septum/septal scarring**

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**Purpose:** Transseptal access to the left atrium (LA) and ventricle is indispensable for the ablative treatment of atrial and ventricular tachyrhythmias. Successful ablation of atrial fibrillation may necessitate repeated left atrial ablations. However, repeat transseptal procedures may lead to increased local stiffness of the interatrial septum, rendering the transseptal puncture more difficult at index procedure. Moreover, transseptal puncture in patients with hypermobile/aneurysmal interatrial septum may be challenging with the classical Brock-enbrough needle approach. We sought to assess safety and efficiency of a novel transseptal needle system for transseptal puncture in patients with difficult/risky transseptal access.

**Methods:** From January 2011, we performed 485 transseptal ablation procedures for atrial arrhythmias. The classical ‘Brockenbrough’-needle approach (71 cm BRK-1, SJM) for transseptal access was applied in all patients under TEE guidance. When the transseptal puncture was met with difficulties, the novel RF-navigation needle (NRG, Baylis, Canada) was used. RF-needle travelled to the previously manually acquired sites in 95.8% of the 653 tagged sites in 23±1.4±1.8 sec. The initial and final distances to the target site in the automatic mode were 39±8±21 and 1.9±0.9 mm. There were 2 adverse events: ischemic stroke treated with thrombolysis and a cardiac tamponade which required pericardiocentesis at the end of the procedure. Both patients with complete resolution of the complication. There were also 4 pericardial effusions and 1 AV femoral fistula which resolved spontaneously.

**Conclusions:** Remote catheter navigation by electromagnetic forces is fast and accurate both by the operator and automatic modes. This novel system appears safe although there are some concerns about the safety of leaving a stiff sheath bended/rotated alone in the LA for LV mapping.
Epicardial electrophysiological mapping of ganglioneuronal plexi for concomitant atrial fibrillation

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Purpose: Ganglioneuronal plexi (GP) are hopeful optional targets for MAZE procedure. This study was aimed to reveal and identify activity of GP by epicardial location.

Methods: Fifteen patients with concomitant atrial fibrillation underwent intraoperative epicardial electrophysiologic mapping in our institution. Autonomic GP were identified by rapid atrial pacing via a temporary pacemaker after removal of fatty epicardial tissues on the surface. A 24-point high-frequency stimulation (1000/min, 18V) was achieved by placing tessews directly on the left atrial epicardium. Diagram of epicardial mapping locations is shown below. (Picture) Locations where the stimulation resulted in ventricular slowing with doubling of the electrocardiographic R-R interval were identified as active GP.

Results: Active GP were found in 13 out of 15 patients. The incidence of activity by epicardial location is shown below. (Table)

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<tr>
<th>Location by location</th>
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<tr>
<td>1</td>
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<td>2/15 (13%)</td>
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<td>2</td>
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<td>7</td>
<td>3/15 (20%)</td>
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Figure 1. Diagram of epicardial mapping locations

Conclusion: Active GP could be identified dominantly in the inferior right area in left atrium.

Distribution of delayed potentials on the right ventricular endocardium in patients with late potentials on signal-averaged electrocardiograms due to arrhythmogenic right ventricular cardiomypathy


Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a progressive inherited disease characterized by life-threatening ventricular arrhythmias, which are related to desmosomal protein abnormality. The purpose of this study is to clarify the distribution of delayed potentials (DPs) on the right ventricular endocardium in ARVC patients with ventricular tachycardias (VT) and late potentials (LPs) after QRS segment on the signal-averaged electrocardiograms (SAECG).

Results: A total of 46 ARVC patients (80%) had DPs, although they were not identifiable in the remaining 12 patients (20%). DPs were located in the RV basal area (100%), particularly in inferobasal wall in 30 patients (81%), RV posterobasal wall in 17 patients (46%), RV lateralbasal wall in 20 patients (54%), anterobasal wall and/or RV outflow tract (RVOT) in 7 patients (19%) and RV basalseptum in 8 patients (22%). They were distributed in the RV mid to apical area in only 2 patients (5%). VT was eliminated by endocardial catheter ablation in 24 (63%) of 39 patients with inducible VT by programmed electrical stimulation. DPs were mainly located in the inferobasal area in 20 (63%) of 32 successful patients. Distribution of fractionated electrograms or double-potentials was not predictable for successful ablation site.

Conclusions: In ARVC patients, DPs were mainly located in the basal RV wall especially in the inferior region around tricuspid valvular annulus. We conclude that catheter ablation following endocardial mapping should be applied first in the RV inferobasal wall in patients with LPs on SAECG.
Cavotricuspid isthmus radiofrequency catheter ablation for atrial flutter: outcomes from a controlled nonrandomized long-term study

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Cavotricuspid isthmus radiofrequency catheter ablation (CTA RFA) is recommended for typical atrial flutter since it is safe and effective to maintain sinus rhythm, but the long-term outcomes have not been compared with those in patients with other types of atrial arrhythmia and/or other management. This study investigated the outcomes after CTA RFA for atrial flutter, expected to maintain sinus rhythm and possibly to reduce mortality and morbidity.

Methods: We examined the clinical course of 8,962 consecutive patients with atrial fibrillation and/or atrial flutter. The outcomes in 675 patients with CTA RFA for typical atrial flutter (in whom 32% had a pre-ablation history of atrial fibrillation) were compared with those in other patients.

Results: Complete cavotricuspid isthmus block was successfully obtained in 97% of the patients. Median follow-up was 934 ± 1134 days. Death (n = 1,125) stroke/thromboembolic events (n = 715) or bleeding events (n = 791) were recorded in 2,035 ± 962 patients. Kaplan-Meier analysis showed that patients who underwent CTA RFA had longer survival than other patients (p < 0.0001) and higher net clinical benefit (freedom from combined death, stroke, thromboembolic and bleeding events, p < 0.0001). Using cox proportional-hazards model, results remained significant after adjustment for age, CHADS2 and HAS BLED scores, use of cardiovascular medications and other confounders. Patients in the ablation group revealed lower risk of all-cause mortality (hazard ratios [HR] = 0.56, 95% confidence interval [CI], 0.40-0.78; p = 0.0007) and of bleeding events (HR = 0.71, 95% CI, 0.52-0.96; p = 0.03), resulting in a significant net clinical benefit (HR = 0.67, 95% CI, 0.54-0.83; p = 0.0002).

Conclusions: Atrial flutter with CTA RFA is independently associated with a lower mortality and morbidity as compared with other sustained atrial arrhythmias such as atrial fibrillation.

Use of Wearable Cardioverter Defibrillator after implantable cardioverter defibrillator explantation: clinical experience from 151 German patients

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Purpose: Several studies and case reports have described successful use of the wearable cardioverter defibrillator (WCD) for protection from sudden cardiac death (SCD) among European patients. We sought to evaluate the experience with the WCD in German patients whose implantable cardioverter defibrillators (ICDs) had been explanted or deactivated.

Methods: Patients who were prescribed a WCD due to ICD explantation or deactivation between 2009 and 2011 in Germany were retrospectively analyzed in our study. We reviewed medical charts to collect demographic information, primary reason for ICD implantation, and primary reason for ICD explantation or deactivation. Patients’ duration of WCD use and electrocardiogram (ECG) from device recording were gathered from the manufacturer’s post-market database.

Results: 151 German patients (male = 86.7%, mean age = 61 ± 11 years) underwent ICD explantation (n = 150) or deactivation (n = 1). 45.0% of patients received an ICD for primary prevention, 19.2% for secondary prevention, and 35.8% not available during chart review. Infection was the major reason for ICD explantation (80.1%), followed by lead defect (1.9%), radiotherapy (0.6%), and reasons unknown (16.6%). Patients were on average 52.38 days (mean = 44, ranging from 1 to 225 days); the average daily use was 20.6 ± 4.2 hours. One patient experienced a sinus arrest and recovered spontaneously. Two others underwent ventricular tachyarrhythmia arrest and were successfully treated by the WCD with single 150 joule shocks. Both patients were unconscious during the episodes, survived acutely, and had ICD re-implanted afterwards.

Conclusions: Of German patients who underwent ICD explantation or deactivation were at high risk of SCD (1.0% per patient-month). WCD was an effective bridge for protection from SCD when the ICD therapy was discontinued. Compliance among the patients was high.

Predictive value of programmed ventricular stimulus in ischemic cardiomyopathy and dilated cardiomyopathy patients with preserved systolic function

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Purpose: Up to date, programmed ventricular stimulation (PVS) is not considered as a reliable risk stratifier for primary prevention of sudden cardiac death in patients with structural heart disease and preserved systolic function. The objective of the present study is to investigate the prognostic value of PVS in ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) patients with left ventricular ejection fraction (LVEF) > 40%.

Methods: We followed up for a mean period of 52.4 months 76 patients with ICM and 39 with DCM (65.9 years old, mean LVEF = 45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia and 39 with DCM (65.9 years old, mean LVEF = 45.5%). All patients underwent PVS based on the presence of syncope or non sustained ventricular tachycardia (VT) and/or polymorphic ventricular tachycardia (VT) or polymorphic VT leading eventually to VF (ventricular fibrillation).

Results: Sustained monomorphic VT or VF was triggered in 40 cases (30/76 patients and 10/39 of DCM patients) and subsequently implantable cardioverter defibrillators (ICD) was implanted in 36/40 of these patients. During the follow-up period, 7 patients died; 2 experienced sudden cardiac death and 5 non cardiac death. Although no difference was observed between patients with VT/VF induction and those without in the incidence of total mortality (10% vs. 4%, log rank p = 0.20), the incidence of sudden cardiac death was higher in the former group than in the latter group (log rank p = 0.05), indicating an absolute negative prognostic value of PVS for patients without VT/VF induction. Appropriate ICD activation was observed in 24 patients (66.7%) with VT/VF induction was (21 cases with antiarrhythmic pacing, 16 with shocks, 13 with both) and the time for the first appropriate activation was 23 months after ICD implantation.

Conclusion: During long-term follow-up, DCM and ICM patients with preserved systolic function and VT/VF inducibility experienced a significant incidence of appropriate ICD therapy. Additionally, SCD was absent in non inducible patients with structural heart disease. PVS may be considered as a reliable risk stratifier for primary prevention of sudden cardiac death in high risk patients with structural heart disease and preserved systolic function.

Return of spontaneous circulation after unwitnessed out-of-hospital cardiac arrest with asystole on initial rhythm

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Purpose: In unwitnessed out-of-hospital cardiac arrest (OHCA) patients with asystole on initial rhythm, it is extremely hard to achieve return of spontaneous circulation (ROSC) or obtain a good neurological outcome. The crucial pre-hospital variables for ROSC after unwitnessed OHCA have not been fully understood. Our objective was to determine the pre-hospital variables which have significant impact on ROSC after unwitnessed OHCA in patients with asystole on initial rhythm.

Methods: Of 522,801 resuscitation-attempted adult patients with OHCA's, 151,379 bystander-unwitnessed arrests of presumed cardiac origin with asystole on initial rhythm were analyzed in a prospectively recorded nationwide Utstein-style database in Japan over 5 years (2005–2009). The primary endpoint was ROSC before arrival to hospital that represents the earliest endpoint reflecting the “unbiased” initial resuscitation success. The secondary endpoint was 1-month survival with favorable neurological outcome (cerebral performance category scale = 1 or 2).

Results: Overall ratio of 1-month survival and that with favorable neurological outcome were 0.64% (n = 901) and 0.15% (n = 211), respectively. ROSCs were achieved in 101 patients before arrival to hospitals. The incidence of ROSC was higher in men than in women (men: 0.78%, women: 0.64%; p = 0.002). The age was younger in ROSC group than in non-ROSC group (ROSC group: 74.3 ± 15.8 years, non-ROSC group: 76.4 ± 13.8 years; p < 0.0001). The percentage of administration of automated external defibrillator (AED) before arrival to hospital was higher in ROSC group than in non-ROSC group (ROSC group: 12.5%, non-ROSC group: 3.0%; p < 0.0001). The ROSC group had a shorter call-response time interval than non-ROSC group (ROSC group: 6.3 ± 3.5 minutes, non-ROSC group: 7.3 ± 3.7 minutes; p < 0.0001). Multivariate logistic regression analysis revealed that the following independent factors were found to have a significant impact on the probability of ROSC: 1) Pre-hospital ROSC (OR = 14.6, 95% confidence interval [CI] = 1.09 to 1.00), 2) call-response time interval (unit OR, 0.97; 95% CI, 0.95 to 1.03), and 3) pre-hospital administration of AED (OR, 4.49; 95% CI, 3.69 to 5.41).

Conclusions: Three pre-hospital variables (age, call-response time interval, and administration of AED) were crucial variables for predicting ROSC after OHCA with asystole on initial rhythm. Thereby, even in patients with asystole on initial rhythm after unwitnessed OHCA, ROSC will be achieved if patient is younger, call-response time interval is shorter, and AED is administered before arrival to hospital.
Long-term follow-up and predictors of arrhythmic events in the brugada registry of the piedmont region of Italy

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Introduction: Brugada syndrome is an arrhythmogenic disease characterized by increased risk of sudden death (SD) and so far the only proven therapy is the implantable cardioverter defibrillator (ICD), although there are some evidence in favor of hydroquinidine. The question of risk stratification in patients with Brugada ECG pattern, especially if asymptomatic, remains still very controversial. The aim of our study is to analyze the long-term prognosis and the role of clinical and electrophysiological risk factors in the Brugada Registry of Piedmont Region in Italy.

Methods and results: Four hundred and eighteen patients with spontaneous or drug-induced type 1 Brugada ECG were enrolled consecutively. A well-defined area of Northern Italy. Mean age was 45±14 years; 42% had spontaneous diagnostic ECG; 72% were asymptomatic, 26% had syncope, 1% aborted SD. Pwave electromechanical systolic ventricular potential (PES) was performed in 251 patients (60%) and ventricular fibrillation (VF) was induced in 99 (39%). In 158 subjects (63%) PES was performed with up to 2 extrastimuli (protocol A), in 93 (37%) up to 3 extrastimuli (protocol B), and the rate of VF induction was 41% and 37% respectively (p=NS). Ventricular refractory period (VRP) was available in 135 patients and it ≥200 ms in 89, <200 ms in 46. During a mean follow-up of 48 months the incidence of SD/VF was 3% (0.75% per year) in the whole population, 50% (0.25% per year) in patients with VRP <200 ms, 7% (1.8% per year) in those with VRP ≥200 ms, 1% (0.25% per year) in the asymptomatic. Predictors of arrhythmic events in the whole population were asD0 (p=0.0001), RR=7; C95%-7.50%, syncope (p=0.0001, RR=7; C95%-2.27) and induction of VF at PES (p=0.0005, RR=17; C95%-2.129). When induction at PES with 2 and 3 extrastimuli was considered independently, only induction with protocol A was predictive of events at follow-up (p=0.007). No spontaneous type 1 ECG, or a VRP <200 ms were predictive of events. In the asymptomatic no independent risk factors were identified.

Conclusions: In the whole population of Brugada patients of the Piedmont region, syncope and positive PES with up to 2 extrastimuli were the only predictors of arrhythmic events. No predictors of SD were identified in the asymptomatic, mainly due to the low number of events at follow-up.

Electriccardiogram fails to identify high-risk individuals: analysis of a series of 50 sudden death cases

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Purpose: Electrocadioogram (ECG) is an essential and easily available diagnostic test in the management of cardiomopathies and channelopathes. We aim to explore the value of ECG for the diagnosis of SD.

Methods: ECGs from 50 consecutive cases (age 36±20 years, 36 men) were reviewed, and SD were identified and follow up to the final diagnosis. The ECG findings were compared with final diagnosis.

Results: Final diagnoses were hypertrophic cardiomopathy in 13 patients, Brugada syndrome in 6, dilated cardiomyopathy in 6, and ventricular fibrillation in 158 subjects (63%) and the rate of VF in SD was 41% and 37% respectively (p=NS).

Conclusions: Despite the clear usefulness of ECG in the diagnosis of SD cases, it can be normal or unspecific in an important percentage of patients. In this sense, SD screening programs that include only a baseline ECG, could lead to a loss of sensitivity. A comprehensive study including cardiac imaging, clinical and genetic information, are also important besides ECG findings to achieve a definitive diagnosis.
Cardiac conduction system involvement in patients with steinert’s myotonic dystrophy

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Introduction: Steinert’s myotonic dystrophy (DM1) is an autosomal dominant genetic disease: male/female ratio is 1:1 and an affected parent has a 50% risk of transmitting the disease in each pregnancy. In Europe and North America it is the most common muscular dystrophy (1:8000 population). Affected patients have a lower life expectancy with an average age of death of 53 years and there is a correlation between the age of onset of dystrophy and age of death: respiratory failure and cardiovascular arrest are the main causes. The cardiac involvement is quite common, especially in the conduction system, which can sometimes cause sudden death.

Patients and methods: From January 2010 to September 2011 at our Centre 39 patients were evaluated with Steinert muscular dystrophy. The inclusion criteria was the confirmation of Steinert’s dystrophy by genetic analysis and clinical examination. Muscle strength with MRS (muscular impairment rating scale).

Results: 39 patients were evaluated: 21 males and 18 females aged between 22 and 73 years. 23.1% (n = 9) presented family history of sudden death, while 17.9% (n = 7) reported idiopathy or syncope. PR > 0.24s, was shown to be influenced by patients’ age (p = 0.02), disease duration longer than two years (p = 0.02) and five years (p = 0.027), by severe neuromuscular involvement (p = 0.027), assisted walking (p = 0.028, evidence of obstructive lung disease (p = 0.043), presence of Supraventricular Premature Contractions, single (0.040) and couples (0.06) at Holter monitoring. Complete Left Bundle Branch Block was observed in 2 patients, and left anterior fascicular block in 4 (10.3%). The retrospective analysis of ECGs, disclosed an increase of PR in 20.5% of cases, and widening of QRS in 5.1%. The progression of AV conduction delay was showed to be influenced by sex (p = 0.032) and neuromuscular involvement (0.046). The development of Atrial Fibrillation was recorded in three patients. No significant abnormalities were found at Echocardiography.

Conclusions: We observed that an important involvement of the conduction system in the observed patients trends up to deteriorate quickly. Therefore it is essential that they continue to be assessed periodically. In addition to the ECG abnormalities also others parameters seems to be associated with an increased risk of sudden death: positive family history, pulmonary involvement and degree of neuromuscular involvement.

Significant incidence of sudden cardiac arrest under 55 with no better survival than older age groups

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Purpose: Sudden cardiac arrest (SCA) incidence rises with advancing age but the burden among younger individuals has greater societal consequences. Temporaneous data on the burden of SCA is lacking. Therefore, we compared SCA incidence and survival in the community between residents ≤55 years of age and older subjects.

Methods: Complete population-based SCA incidence was prospectively identified using multiple sources in a large community in the Northwestern US (population ≥65,000) between 2002 to 2005. By a detailed review of medical records and medical examiner documentation for SCA circumstances and clinical profile, only adult subjects with primary cardiac etiologies were included.

Results: Between 2002 and 2005, a total of 1,142 adult SCA cases were identified (700 men [61%], mean age 67.15 yrs; 442 women [39%], 73.15 yrs). Nearly one quarter (256 cases, 22%) were 55 years or younger and 42% were 65 or older with a male predominance in the younger groups and a greater proportion of females among those ≥75 yrs. Cumulative rates (%) per gender and age-group are shown in Figure. Survival rates to hospital discharge were not significantly different between subjects ≤55 and ≥55 years (7.5 vs 7.0%, P = 0.77; Fisher’s exact test). The race/ethnicity distribution of the population was Caucasian (63%), African American (9%), Asian (3%), Hispanic (2%), and Other (3%).

Conclusions: The proportion of subjects under age 55 among cardiac arrest victims in the community is substantial and is likely to have a great societal consequences. Especially since younger age does not provide a survival advantage, a continued focus on improved and early risk prediction of SCA is warranted.

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Circulating microRNAs after cardiac arrest

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Purpose: Prediction of clinical outcome after cardiac arrest is clinically important. While the potential of circulating microRNAs (miRNAs) as biomarkers of acute coronary syndromes is an active field of investigation, it is unknown whether miRNAs are associated with outcome in cardiac arrest patients.

Methods: Twenty-eight patients with cardiac arrest treated by therapeutic hypothermia after cardiac resuscitation were enrolled in this prospective, single centre, proof-of-concept study. Blood samples were obtained at 48 hours after cardiac arrest.
Impacts of rewarming speed differences on outcomes of therapeutic hypothermia in out-of-hospital cardiac arrest: is rapid rewarming efficient?

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Background: Although therapeutic hypothermia (TH) has been reported to improve neurological outcomes of patients with out-of-hospital cardiac arrest (OHCA), procedures of TH remain to be established. Particularly, rewarming speed that maximizes protection afforded by TH has not been identified.

Methods: We analyzed data from 408 patients submitted to the multicenter registry of OHCA patients treated with TH from 2005 to 2009 in Japan. The patients were retrospectively divided into three groups according to rewarming speed: 53 patients with rewarming speed 1.0-1.9°C/12 hours (Slow group), 54 patients with rewarming speed ≥2.0°C/12 hours (Rapid group), 301 patients with rewarming speed <1.0°C/12 hours (Slow group). We defined favorable neurological outcomes as cerebral performance category 1 or 2.

Results: There was no significant inter-group difference in gender, age, and percentages of presence of bystanders, bystander cardiopulmonary resuscitation and ventricular fibrillation in initial ECG. Incidence of return of spontaneous circulation before admission and target temperature were also comparable between the three groups, but the duration of hypothermia at target temperature in the Rapid group was shorter than that in the other groups (26.1±11 hours for Rapid group, 33.1±13 hours for Slow group, p=0.01). Both the mortality and the rate of favorable neurological outcomes in 30 days were not statistically different in all three groups (Figure 1A, 1B).

Conclusion: As compared to neuron-specific enolase, circulating miRNAs are modest but significant predictors of neurological outcome and mortality in this small group of patients with cardiac arrest. This motivates assessing the prognostic value of miRNAs in larger cohorts of cardiac arrest patients.

Circadian variation in shockable heart rhythm and survival in out-of-hospital cardiac arrests

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Purpose: Out-of-hospital cardiac arrest (OHCA) frequency is known to have circadian variation, but little is known about whether shockable heart rhythm (VF/pulseless VT) and survival among OHCA patients also show circadian variation.

Methods: Data from all OHCA in Copenhagen were collected from 1994-2010 including age, sex, initial heart rhythm and emergency medical system (EMS) response time. Occurrence of shockable heart rhythm and 30-day survival according to time of day were analyzed by logistic regression models, adjusted for sex, age and EMS response time.

Results: Of 6,766 patients included, 70.2% suffered OHCA at home. Median age among patients with and without initial shockable heart rhythm was 66 (IQR 55-76) and 73 (IQR 60-82) years, respectively. The median EMS response time was 5.0 minutes (IQR 4.7, Figure). Daytime OHCA (7 am to 3 pm) accounted for 43.5% (n=2945), evening OHCA (3 pm to 11 pm) for 37.8% (n=2556) and nighttime OHCA (11 pm to 7 am) for 18.7% (n=1265). Compared with nighttime, daytime and evening OHCA were positively associated with shockable heart rhythm (OR 1.90, CI 1.57-2.29; OR 1.76, CI 1.45-2.13) and increased 30-day survival (OR 1.62, CI 1.18-2.22; OR 2.06, CI 1.50-2.81), despite a constant EMS response time.

Conclusion: OHCA during daytime and evening are associated with higher occurrence of shockable heart rhythm and higher 30-day survival compared with OHCA during nighttime, indicating circadian variation of these parameters, despite constant EMS response time.

Cardiac screening of first-degree relatives after sudden cardiac death in young population

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Purpose: In several cardiac diseases, sudden cardiac death (SCD) could be the first and last manifestation. SCD in the young is a strong risk factor for the presence of inherited cardiac disease in surviving first-degree relatives. Therefore, screening and identification of high-risk subjects could reduce the incidence of SCD. We sought to evaluate the prevalence of disease and diagnostic effectiveness of a cardiac screening of first-degree relatives of patients of premature SCD or aborted cardiac arrest (ACA).

Methods: One hundred first-degree relatives of 11 referred families after SCD (n=9) or ACA (n=2) of a family member were analysed. A detailed family history of SCD, electrocardiogram (ECG), echocardiogram, treadmill test and 24 hours ECG-monitoring were performed in all cases. Additional test were performed depending on the underlying disease, cardiac magnetic resonance imaging (CMR)-MRI and electrophysiological mapping (EAM-M). After confirmatory or established the diagnosis in 15 relatives and EAM identified myocardial scar on 4 of 6 patients with ARVC.

Conclusion: In our population, a cardiac screening of first-degree familial of patients with SCD was found to have a high effectiveness identifying high-risk subjects. Systematic familial study of victims of SCD or ACA with inherited cardiac disease could identify a number of asymptomatic patients who could benefit from early treatment to prevent complications.
Risk factors for sudden cardiac death: Results from the Nordic arrhythmogenic right ventricular cardiomyopathy registry

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Purpose: Risk factors for sudden cardiac death (SCD) in arrhythmogenic right ventricular cardiomyopathy (ARVC) are not clear. We aimed to study this in a registry study of ARVC patients.

Methods: The study was based on a newly started Nordic ARVC registry including patients from centers in Denmark, Sweden and Norway. It was performed as a retrospective cross sectional case control study. The outcome was defined as death from sudden cardiac death in ARVC which is a sudden unexpected death from cardiac arrhythmias, myocardial degeneration or structural abnormalities, including death from cardiac arrest in patients with a history of the disease. New criteria were defined in 2010 in order to include patients in the registry.

Results: A total of 325 patients were included with a median age of 50 years (IQR 40-59) from centers in Denmark (257), Norway (50), and Sweden (18). The male/female ratio was 2.3/1. The cohort was divided into two groups according to sex, age, and presence of symptoms at the time of diagnosis. The male patients were older (50 years, IQR 40-60) than the female patients (45 years, IQR 35-55) and had a higher percentage of patients with symptoms at presentation (80% vs 50%). The median age of the patients was 50 years (IQR 40-60) and the median follow-up time was 12 years (IQR 9-18). The median duration of symptoms was 5 years (IQR 3-10) and the median duration of symptoms at presentation was 3 years (IQR 1-6).

Conclusions: Overall survival from in-hospital cardiac arrest to discharge in our referral hospital was 45.7%. Factors such as telemetry monitoring, defibrillator presence on all inpatient floors, and the prompt arrival of a properly trained cardiac arrest team to the patient’s bedside contributed to successful resuscitation attempts.

Does adding up ventilation to chest compression modify memory retention when training general population to cardiopulmonary resuscitation?

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Background: Chest compression only cardiopulmonary resuscitation (CC-CPR) without ventilation has been proposed as an alternative to standard cardiopulmonary resuscitation (C-PHR) for bystanders since the ILCOR Guidelines 2005. However, there has been controversy regarding the relative effectiveness of both techniques. We used by Cox regression the mean age of participants was 56±18 years. At T0, both groups had usual levels of initial knowledge of CPR without statistically significant difference. At T1, both groups remained perfectly similar. At T2, again both groups were similar for most criteria except for “start CPR at the request of the Automatic External Defibrillator (AED)” (p=0.031). Conversely, significant differences were found when comparing assessments at T0 and T2 in CC-CPR group, best intervention remembered in T2 (p=0.010) to deliver first shock with CPR was found. At T0 and T2 mean intervention time was respectively 173±64 and 156±49 sec in CC-CPR group and 163±60 and 164±57 sec in S-CPR group. General knowledge score was significantly higher in CC-CPR group (p=0.049).

Conclusion: Retention after CC-CPR training appears to be more effective at six months when compared to S-CPR in general population. It allows a faster delivery of first external electric shock and improves technical quality of the main elements of CPR.

Survival from inpatient cardiac arrest in a referral hospital for cardiology and cardiosurgery

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Purpose: We sought to estimate survival from inpatient cardiac arrest at the Cardiac Surgery Center, a tertiary referral hospital for Cardiology and Cardiovascular Surgery.

Methods: We recorded cardiac arrests over a 48-month period, using the Utstein style of recording data for cardiac and surgical patients, who are distributed on 3 inpatient floors. The arrival time of the cardiac arrest team (CAT) was calculated from the first “code blue” call to the bedside. All our patients are on telemetry, so the initial arrest rhythm can be accurately recorded. Our institution has a dedicated CAT which includes the on call cardiology and cardiac surgery Registrars and SHOs, anaesthesiologist, and nursing supervisor, all of whom have been trained in Advanced or Immediate Life Support (ALS and ILS). Biphasic defibrillator shocks are delivered every 3 min according to current heart attack guidelines. A general knowledge score was calculated.

Results: The population was comprised of 129 patients of which 57% were male and 71% probands. The median age was 49 (IQR 38-59) years and 73% had an APBR. Median redressive follow up was 7 (IQR 4-12) years and during follow up there were 2 patients suffering SCD, 12 suffering aborted SCD, 6 patients suffering an electric storm and 25 patients experiencing appropriate ICD shocks.

Conclusions: Survival from inpatient cardiac arrest to discharge in our referral hospital was 45.7%. Factors such as telemetry monitoring, defibrillator presence on all inpatient floors, and the prompt arrival of a properly trained cardiac arrest team to the patient’s bedside contributed to successful resuscitation attempts.

ECG changes during hypothermia as potential markers of mortality of successfully resuscitated patients

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Introduction: Therapeutic hypothermia (TH) is the therapy of choice to improve neurologic outcome and survival of patients remaining comatose after successfully resuscitated. The reversible electrophysiologic changes induced by TH, e.g. bradycardia and prolongation of QT intervals, may increase the risk of malignant arrhythmias.

Methods: Our goal was to analyse the data of 32 patients treated with TH in the University from 01/01/2009 to 30/11/2010. We compared the heart rate, PQ, QRS, QT and corrected QT (QTc) intervals measured during TH (on 32-34°C) to those of during normothermia(NT), and relationship among survival and these intervals were evaluated three times: immediately before (T0), immediately after (T1) and 6 months after (T2) training. Fifteen criteria of CPR performance and intervention time measurements were assessed. A general knowledge score was calculated. The main results of the two groups were compared using the Mann-Whitney test and the chi-square test when appropriate. The ability to perform CPR correctly in both groups over time (6 months) was evaluated using the McNemar test and the Wilcoxon test when appropriate.

Results: Mean age of patients was 56±18 years. At T0, both groups had usual levels of initial knowledge of CPR without statistically significant difference. At T1, both groups remained perfectly similar. At T2, again both groups were similar for most criteria except for “start CPR at the request of the Automatic External Defibrillator (AED)” (p=0.031). Conversely, significant differences were found when comparing assessments at T0 and T2 in CC-CPR group, best intervention remembered in T2 (p=0.010) to deliver first shock with CPR was found. At T0 and T2 mean intervention time was respectively 173±64 and 156±49 sec in CC-CPR group and 163±60 and 164±57 sec in S-CPR group. General knowledge score was significantly higher in CC-CPR group (p=0.049).

Conclusion: Retention after CC-CPR training appears to be more effective at six months when compared to S-CPR in general population. It allows a faster delivery of first external electric shock and improves technical quality of the main elements of CPR.

ECG changes during hypothermia as potential markers of mortality of successfully resuscitated patients

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Introduction: Therapeutic hypothermia (TH) is the therapy of choice to improve neurologic outcome and survival of patients remaining comatose after successfully resuscitated. The reversible electrophysiologic changes induced by TH, e.g. bradycardia and prolongation of QT intervals, may increase the risk of malignant arrhythmias.

Methods: Our goal was to analyse the data of 32 patients treated with TH in the University from 01/01/2009 to 30/11/2010. We compared the heart rate, PQ, QRS, QT and corrected QT (QTc) intervals measured during TH (on 32-34°C) to those of during normothermia(NT), and relationship among survival and these intervals were evaluated three times: immediately before (T0), immediately after (T1) and 6 months after (T2) training. Fifteen criteria of CPR performance and intervention time measurements were assessed. A general knowledge score was calculated. The main results of the two groups were compared using the Mann-Whitney test and the chi-square test when appropriate. The ability to perform CPR correctly in both groups over time (6 months) was evaluated using the McNemar test and the Wilcoxon test when appropriate.

Results: Mean age of patients was 56±18 years. At T0, both groups had usual levels of initial knowledge of CPR without statistically significant difference. At T1, both groups remained perfectly similar. At T2, again both groups were similar for most criteria except for “start CPR at the request of the Automatic External Defibrillator (AED)” (p=0.031). Conversely, significant differences were found when comparing assessments at T0 and T2 in CC-CPR group, best intervention remembered in T2 (p=0.010) to deliver first shock with CPR was found. At T0 and T2 mean intervention time was respectively 173±64 and 156±49 sec in CC-CPR group and 163±60 and 164±57 sec in S-CPR group. General knowledge score was significantly higher in CC-CPR group (p=0.049).

Conclusion: Retention after CC-CPR training appears to be more effective at six months when compared to S-CPR in general population. It allows a faster delivery of first external electric shock and improves technical quality of the main elements of CPR.
The same irrespective of depression history. Kaplan–Meier estimates for freedom from all-cause mortality and rLTVA is shown in Fig 1. History of depression (hazard ratio 0.96, 95% CI 0.82–1.15, P = 0.7) and antidepressant use (hazard ratio 1.49, 95% CI 0.88–3.2, P = 0.10) did not predict the rLTVA hazard ratio 0.96, 95% CI 0.62–1.54, P = 0.3) did not predict the rLTVA hazard ratio 1.49, 95% CI 0.88–3.2, P = 0.10). This relationship remained non-significant after a multivariate analysis to control for cardiovascular risk factors for SCD. Conclusions: SCD with history of depression are not at significantly greater risk of recurrent arrhythmias and death as compared to other survivors of rLTVA.

**P4136** Detection of pulseless electrical activity by a public access defibrillator using ECG and ICG

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Purpose: Emergency pulse checks are challenging in the out of hospital resuscitation setting even when carried out by trained rescuers. As a consequence, current European Resuscitation Council (ERC) guidelines have eliminated pulse checks for ALS responders or minimally trained operators. A hemodynamic and automated by sensing technique, capable of automatically diagnosing cardiac arrest, together with current electrocardiogram (ECG) algorithms embedded in a Public Access Defibrillator (PAD), would aid in the management of collapsed patients. An impedance cardiogram (ICG) recorded via defibrillator pads could be used and may provide opportunities for improvement over ECG alone: an ICG+ECG algorithm could be more accurate for the detection of Pulseless Electrical Activity (PEA) and provide advice about cardiodiopulmonary resuscitation (CPR). Algorithms reported in the literature offer impressive results by coupling the ECG and ICG. However, the required analysis may not be feasible in an emergency setting, when limited by the low processing power in any compact and low cost PAD.

Methods: A retrospective analysis of ECG+ICG recorded in cardiac arrest patients and controls was used to train an algorithm to detect PEA. Data were collected following ethical approval and were marked and documented by trained physicians. Segments where CPR was administered were excluded. ECG+ICG were recorded in 132 cardiac arrest patients (53 training, 79 validation) and 97 controls (47 training, 50 validation).

The detection of QRS complexes in the ECG, using a modified Pan-Tompkins approach, triggers the analysis of the ICG signal in order to detect the changes in impedance which could be masked by other electrical activities during chest compressions and ventilation. A threshold for the changes in the high pass filtered ICG (fc=1.5Hz) was used as a discriminator.

Results: The diagnostic algorithm indicated PEA with sensitivities and specificities (95% confidence intervals) of 89.4% (88.4–90.5) and 94.5% (94.2–94.8) for the validation set.

Conclusions: An algorithm to detect PEA, embedded in a compact PAD which simultaneously assesses ECG+ICG in real time offers encouraging results.

**P4137** Analysis of the relation between T-waves alternans and myocardial ischaemia diagnosed by gated-SPECT: results of the SPECTACLE study

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Sudden cardiac death (SCD) concerns every 50000 patients in France. Coronary artery disease should be responsible for 80% of SCD. There is need to find new predictive markers of the occurrence ventricular arrhythmia, and microvolt T wave alternans (mTWA) seems to be a promising one. The objective of our study was to analyze the relation between ischemia assessed by gated-SPECT and mTWA. Between February 2009 and January 2011, we have analyzed mTWA by Modified Moving Average method in 2235 patients, who had a myocardial gated-SPECT. Maximal mTWA was measured during pre-test, exercise and recovery phases.

Thirty nine percent (861 patients) had an ischemia and a maximal mTWA significantly higher than patients with normal myocardial perfusion: 54 [38–69] vs 36 [34–49] μV; p < 0.05. Six hundred and thirty patients have had a stress induced by diprydamole and 1605 an exercise test associated or not with diprydamole. The mTWA distribution was the same whatever the type of stress used and whether there was a myocardial ischemia or not. Patients undergoing a gated-SPECT with diprydamole sole have had a maximal microvolt mTWA statistically lower than the exercise group: 32 [22–47] vs 69 [52 – 90] μV; p < 0.0001. The presence of ischemia under diprydamole solely didn’t affect the level of mTWA. The analysis of the exercise population had shown that there is no difference for maximal and for exercise mTWA between the groups independently of the presence of ischemia. However there is a significant difference in recovery phase: 39 [27– 53] vs 36 [25 – 49] μV; p< 0.0014 for ischemia vs no ischemia groups. The same irrespective of depression history. Kaplan–Meier estimates for freedom from all-cause mortality and rLTVA is shown in Fig 1. History of depression (hazard ratio 0.96, 95% CI 0.82–1.15, P = 0.7) and antidepressant use (hazard ratio 1.49, 95% CI 0.88–3.2, P = 0.10) did not predict the rLTVA hazard ratio 0.96, 95% CI 0.62–1.54, P = 0.3) did not predict the rLTVA hazard ratio 1.49, 95% CI 0.88–3.2, P = 0.10). This relationship remained non-significant after a multivariate analysis to control for cardiovascular risk factors for SCD. Conclusions: SCD with history of depression are not at significantly greater risk of recurrent arrhythmias and death as compared to other survivors of rLTVA.
Heart rate increasing during the exercise was correlated with mTWA in recovery phase (Rho = -0.22; p = 0.0001). The presence of necrosis zones has influenced mTWA in recovery phase.

To conclude, patients with ischemia in gated-SPECT seem to have a higher mTWA during recovery phase. However myocardial ischemia solely is not sufficient to induce an important mTWA.

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Improved prognosis after implementation of chest compression device in out-of-hospital cardiac arrest

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Out-of-hospital cardiac arrest (OHCA) is associated with a poor prognosis. Following European Resuscitation Council Guidelines for Resuscitation 2010, application of several cardio-pulmonary resuscitation (CPR) devices may improve prognosis when used by well-trained providers. The load-distributing band (LDB) device (AutoPulse) was used for chest compressions during CPR. The aim of this study was to assess if there changes improved the outcomes after OHCA before and after implementation of the LDB.

Methods: The study was carried out in the Emergency Medical Services from 2009 to 2011 based on analyzing 188 emergency call-out reports. Patients were divided into two groups: 83 patients, when LDB device was used during CPR, were included in the first group (CPR-A); 95 patients were included in the second manual CPR group (CPR-M). The primary endpoint was Return of Spontaneous Circulation (ROSC) as determined at scene, but we also recorded survival to hospital admission. Groups were compared using IBM SPSS Statistics 19 software for odds ratio (OR) and relative risk (RR).

Results: We found that ROSC significantly increased after implementation of LDB device: 44 (52.6%) out of 83 patients of CPR-A group and 24 (25.2%) out of 95 patients of CPR-M group (OR 2.32). On the other hand the probability of an adverse outcome in the group CPR-M was higher than in patients with CPR-A (RR 1.55). CPR duration in LDB group was 19.6 min for CPR-A group and 28 min for CPR-M group. Among patients who survived to hospital admission, 26 (33.7%) belonged to CPR-A group, and 17 (17.9%) to CPR-M group. No significant difference was found in age, gender and cause out-of-hospital cardiac arrest.

Conclusion: The implementation of LDB device is associated with improved ROSC and survival to hospital admission after OHCA, therefore it is expedient to apply it in pre-hospital environment.

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Normal limits of the adult electrocardiogram for ages 16-90 years

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Purpose: Normal limits for the adult electrocardiogram (ECG) have been determined in many previous studies, but they all carry their imperfections: study populations are often small, they do not cover the full range of ages or give data only for one sex, or they focus on only a limited set of parameters. In this study, we established an up-to-date and comprehensive set of clinically relevant normal limits for the adult ECG, covering all ages for both sexes.

Methods: The study population included 13,364 by all evidence healthy individuals between 16-90 years.

Results: We determined age- and sex-dependent normal limits of the adult ECG, covering all ages for both sexes.

Conclusion: The implementation of LDB device is associated with improved ROSC and survival to hospital admission after OHCA, therefore it is expedient to apply it in pre-hospital environment.

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First validation of esophageal long-term electrocardiography as an alternative technique for long-term heart rhythm monitoring

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Introduction: Diagnosing arrhythmias by conventional Holter-ECG can be cumbersome because of small p-waves, which impair visual ECG interpretation. Moreover, computer-based arrhythmia detection in continuous ECG recordings only relies on R-R-interval detection as a surrogate marker for true atrial activity. Prolonged periods of rhythm monitoring have been suggested, in particular for the detection of paroxysmal atrial fibrillation. However, longer monitoring intervals without reliable detection of true atrial activity are a limitation of techniques such as implantable loop recorders. Esophageal long-term electrocardiography (eECG) offers a way out due to the anatomic vicinity of the esophagus to the atria and its favorable bioelectric properties.

Methods: We recorded long-term eECGs from 30 subjects with a novel miniaturized ECG recorder optimized for esophageal use. The device can be worn comfortably behind the ear and connected to the recording device (interelectrode spacings 60 and 15 mm) during 3 days with 500Hz sampling frequency and high 24-bit resolution. A bag made of soft waterproof tissue protects the device, removal of the device during showering is unnecessary. Simultaneously, a conventional surface Holter-ECG was registered. We evaluated feasibility, signal quality and tolerance of this new method.

Results: Data was recorded for 21 subjects 28 (33,7%) belonged to CPR-A group, and 17 (17,9%) to CPR-M group. No significant difference was found in age, gender and cause out-of-hospital cardiac arrest. CPR-A group included 83 patients, when LDB device was used during CPR, and CPR-M group included 98 patients.

Conclusion: Esophageal long-term electrocardiography has the potential to overcome current limitations of conventional Holter-ECGs. In particular, excellent atrial signal quality will improve automatic wave detection and therefore will facilitate accurate analysis of true atrial activity.

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Relationship of fragmented QRS and delayed contrast enhanced cardiovascular magnetic resonance (DE-CMR) imaging in patients with myocardial infarction

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Background and objective: Q waves on a 12-lead electrocardiogram (ECG) are considered a classic hallmark of myocardial infarction. However, Q waves may regress and disappear with time especially in patients treated with reperfusion therapy despite there being continued evidence of myocardial scarring. A prior study has suggested that the fragmented QRS complex on an ECG is a highly sensitive and specific marker of myocardial scar on a nuclear stress test. We investigated the association of the fragmented QRS complex versus the Q wave with myocardial scar detected by delayed contrast enhanced cardiovascular magnetic resonance (DE-CMR) imaging in patients with myocardial infarction.

Methods: ECGs of 130 subjects with myocardial infarction who underwent a DE-CMR were analyzed. Myocardial infarctions were labeled transmural if hyperenhancement extended throughout the entire LV wall at any point. Q and QW MI were defined according to the current AHA criteria. Q waves were defined as a notching of the QRS complex with R peaks between Q and R waves, and its favorable bioelectric properties. Prolonged periods of rhythm monitoring have been suggested, in particular for the detection of paroxysmal atrial fibrillation. However, longer monitoring intervals without reliable detection of true atrial activity are a limitation of techniques such as implantable loop recorders. Esophageal long-term electrocardiography (eECG) offers a way out due to the anatomic vicinity of the esophagus to the atria and its favorable bioelectric properties.

Methods: We recorded long-term eECGs from 30 subjects with a novel miniaturized ECG recorder optimized for esophageal use. The device can be worn comfortably behind the ear and connected to the recording device (interelectrode spacings 60 and 15 mm) during 3 days with 500Hz sampling frequency and high 24-bit resolution. A bag made of soft waterproof tissue protects the device, removal of the device during showering is unnecessary. Simultaneously, a conventional surface Holter-ECG was registered. We evaluated feasibility, signal quality and tolerance of this new method.

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Conclusion: Esophageal long-term electrocardiography has the potential to overcome current limitations of conventional Holter-ECGs. In particular, excellent atrial signal quality will improve automatic wave detection and therefore will facilitate accurate analysis of true atrial activity.

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Conclusion: Esophageal long-term electrocardiography has the potential to overcome current limitations of conventional Holter-ECGs. In particular, excellent atrial signal quality will improve automatic wave detection and therefore will facilitate accurate analysis of true atrial activity.
Frontal plane ST-segment and QRS complex abnormalities as predictors of extent of necrosis and left ventricular dysfunction assessed by 3 Tesla cardiac MR

Purpose: Some ECG changes are related to left ventricular dysfunction (LVD). Few studies have correlated the ECG findings with cardiac magnetic resonance (CMR). Our purpose was to explore the ability of the ST-segment patterns in the frontal plane compared to established data of the QRS complex to identify LVD and extent of necrosis assessed by 3 Tesla CMR.

Methods: Consecutive patients (pts) referred for 3 Tesla CMR evaluation constituted the study population. A 12-lead ECG was obtained in the same day of the CMR scan. QRS complex duration, abnormal Q waves, and ST-segment morphology (normal=upslope ST-segment; or abnormal=ST-despersion or downslope ST-segment) on leads DI or DII (the one with the largest R wave) and aVF leads were studied. These leads were selected due to the usual projection of the QRS complex and ST-segment, and to evaluate the usefulness of this simplified methodology. For detection of the presence and extent of infarcted myocardium, a breath-hold, T1-weighted, contrast-enhanced inversion-recovery segmented gradient echo sequence was used. Late gadolinium enhancement images were acquired 10 min after manual intravenous administration of 0.2 mmol/kg of gadolinium. LV end-diastolic volume (EDV) and LV end-systolic volume (ESV) were calculated using the Simpson method. LV dysfunction was defined as LV ejection fraction less than 50%.

Results: Seventy consecutive patients, 48 male, mean age 64±15 years, were included. The most common indication for CMR was coronary artery disease and chronic valvular disease. Thirty four pts had LVD and 44 pts had LGE. QRS duration was longer in pts with LV dysfunction as compared to patients with preserved LV function (114±27 ms vs. 97±19 ms, p< 0.001). Overall, abnormal Q waves and segment abnormalities were more frequent in pts with LVD and/or necrosis (p<0.05 for all cases). Indeed, pts with chronic DI-DII ST-segment abnormalities had lower LV ejection fraction (43±16% vs. 56±12%, p<0.001) and larger segments of necrosis (5±2.5 vs. 1.5±1.2; p< 0.001) than pts with normal DI-II ST-segment. For LVD detection, QRS >110 ms odds ratio was 7.14 (95% CI 2.09-28.6), abnormal Q wave was 5.89 (95% CI 1.81-20.1) and abnormal ST-segment on DI-II was 6.82 (95% CI 2.08-23.3).

Conclusions: The current hypothesis generating study demonstrates for the first time that chronic ST-segment abnormalities on DI-II are strongly related to LVD and to the extent of myocardial necrosis as assessed by CMR.

Epicardial cooling increases opportunity of spiral wave termination: a simulation study
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Purpose: Ventricular fibrillation (VF) is the major cause of cardiac death. There are many studies to investigate the mechanism to generate and maintain VF. However, the mechanism has not been clear yet. During VF, scroll wave rotate around a line of phase singularly called filament. Recently, increased opportunity for self-termination of VF under moderate hypothermia was demonstrated. In this study, we investigated the possibility of VF termination in a cooling heart using computer simulation.

Methods: We performed computer simulations to observe the behavior of scroll wave propagation. The left and right ventricular slab models were designed to reflect part of the ventricular wall with a thickness of 10 mm and 5 mm, respectively. The ventricular walls were composed of discrete myocardial units: 10 million units for left ventricle and 5 million units for right ventricle. The membrane kinetics in the simulated myocardium was represented by modified Luo-Rudy equations, which can simulate the effects of myocardial cooling. Electrical heterogeneity and rotational anisotropy through the ventricular wall were also incorporated into the model. Scroll waves were generated using an S1-S2 cross-field stimulation. Then, we simulated scroll wave reentry using northermohria (37°C), moderate hypothermia (32°C), and severe hypothermia (27°C) heart model.

Results: The spiral wave filaments, expressed as a continuum of phase singularities, within the ventricular wall were stable, and therefore the scroll wave reentry sustained. In the case of global myocardial cooling, prolongation of action potential duration (APD) and reduction of conduction velocity were simulated and observed. In addition, fluctuations in the filament were increased with time, and finally the scroll wave reentries were terminated. This might be due to heterogeneous increase in the APD through ventricular wall by cooling. To improve the possibility of terminating VF, we additionally simulated the effects of epicardial cooling on scroll wave behavior. When we set the linear gradient of myocardial temperature from epicardium (32°C) to endocardium (37°C), scroll wave reentries were terminated earlier.

Conclusions: Our simulation results suggest that heterogeneous myocardial cooling from the epicardial surface can increase the opportunity of self-termination of VF.

A left-to-right intertrial frequency gradient during atrial fibrillation can be detected using standard 12-lead ECG
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Introduction: The presence of an intertrial frequency gradient may be used to guide catheter ablation of atrial fibrillation (AF). In the 12-lead ECG, Lead V1 has been shown to reflect right atrial (RA) activity, but a reliable tool for non-invasive estimation of the RA fibrillatory frequency is lacking. We hypothesized that a left-to-right frequency gradient (i.e., faster fibrillating left atrium) with a frequency difference of at least 1 Hz could be detected using spatiotemporal QRS cancelation and time frequency analysis of standard 12-lead ECG.

Methods: Nineteen recordings from 13 patients (mean age 61±10 years, 11 male) undergoing catheter ablation of persistent AF were studied. Standard 12-lead ECG was recorded simultaneously with electrogmographs from the right and left atrial appendages. AF frequency spectra were calculated from all 12 leads using spatiotemporal QRS cancelation and Welch periodogram.

Results: Mean left and right atrial appendage fibrillatory frequency was 5.6±1.2 and 7.2±1.3 Hz respectively (p<0.01). In 11 patients, a left-to-right frequency gradient was identified (range 1.0 to 1.5 Hz), whereas the remaining cases either had no gradient preceding 1 Hz (n=10) or a significant right-to-left gradient (n=4). The LA frequency was identified as a second peak in the frequency spectrum of Lead V6 in five of the 19 recordings. A high correlation was seen between invasively and non-invasively measured RAA frequency (r=0.94, P<0.001) and LA frequency (r=0.91, P<0.03). Four of five cases with an invasively measured interatrial left-to-right gradient were correctly identified (positive predictive value 80%), as was 13 of 14 cases without such gradient (negative predictive value 93%). The single false positive case had a left-to-right gradient of 0.7 Hz and the one false negative had a left-to-right gradient of exactly 1.0 Hz.

Conclusions: Patients in AF with a clinically significant left-to-right atrial frequency gradient can be identified using spatiotemporal QRS cancelation and time frequency analysis of standard 12-lead ECG. This enables improved non invasive patient characterization that, in future studies, may prove useful in selecting patients for catheter ablation of AF.

Role of new task force ECG criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy

Introduction: Former ECG signs included in the Task Force Criteria 1994 (TF94) for diagnosis of arrhythmogenic right ventricular dysplasia/cardiacmyopathy (ARVD) have been replaced by new ones in 2010 (TF10) that include the age of the probands (12 or 14 years), the extension and distribution of repolarization abnormalities in the preordial leads and the presence of intraventricular conduction abnormalities. For example, R-waves in V1 are now considered as a major sign but the presence of an S-wave in V3-Ts without complete right bundle branch block (RBBB) is now considered a minor sign.

Methods: We have analyzed the ECG TF10 in 47 patients with ARVD (66% male, 55±15 years) and compared them with the previous TF94. All of them had a complete 12-lead ECG at diagnosis, without previous antiarrhythmic drugs or ion disturbances. None of them were under pacemaker therapy. ECG findings were divided into major and minor repolarization and depolarization signs according to TF criteria.

Results: The ECG was abnormal in 86% of the patients. All of them were on mean PR interval (mean PR interval 177±25 ms). Mean duration of the QRS complex was 107±27 ms (48% had a QRS width >110 ms, 7% an incomplete RBBB and 47% a complete RBBB). Epsilon waves were present in 23% and a terminal S-wave >55 ms in 13% of the patients. Distribution of negative T waves in the preordial leads in the absence of RBBB was: V1-V3 (32%), V1-V3 and beyond (6%), V1-V2 (4%), and 47% had negative T waves in V1-V4 with RBBB. In 11% of the patients there were no repolarization abnormalities. TF94 major depolarization signs (epsilon waves or QRS >110 ms) were fulfilled by 51% of the patients, whereas TF10 major depolarization signs (epsilon waves) were present in 23% of them (p=0.05), and 6% of the patients had a left-to-right gradient of 0.7 Hz. TF94 did not include major repolarization signs, and with the TF10, 38% of the patients had a major criteria. Minor repolarization criteria were present in 38% of the patients with the TF94 and in 51% with the TF10.

Conclusions: There are significant differences in ECG signs between former and new Task Force Criteria appeared in 2010. Repolarization ECG signs were present in 38% of the patients with the TF94 and in 89% with the TF10, and depolarization signs was present in 51% of the patients with the TF84 and in 36%
Higher stroke rate in patients undergoing elective PCI

Methods: Between 2005 and 2008, 47,407 consecutive patients undergoing PCI were randomized to standard outpatient management (HM-) group and remotely monitored group (HM+). We evaluated regular outpatient visits, emergency visits, delivered shock therapy, and their adequacy and hospitalization associated with the ICD. Geographical data and availability of the access to the cardiology department were also analyzed.

Results: Both groups of patients were comparable with respect to the demographic data, clinical data and parameters of the ICD with significant difference only in the representation of single and dual chamber devices between the groups. Almost two-thirds of the total 621 outpatient controls were carried out in the HM+ group. The number of planned inspections decreased by more than 40% in the HM+ group, but the number of extra controls with the physician assistance called upon the inspection of HM messages significantly increased. Mortality did not differ significantly in both groups as well as the number of hospitalized patients and patients with delivered shock therapy. The proportion of inadequate shocks, however, was significantly reduced in the HM+ group.

Conclusion: Home Monitoring system proved to be effective in reducing the number of planned visits and the proportion of inadequate shock therapy with no impact on the overall mortality in our patient group. Patients with poorer accessibility of the adequate medical management tend to prefer to be monitored remotely.

IN-STENT-RESTENOSIS AND INVASIVE CORONARY IMAGING

Higher stroke rate in patients undergoing elective PCI for in-stent-lesion in clinical practice in Europe: PERSPECTIVES results of the EHS PCI registry

Methods: A total of 22,917 patients underwent elective PCI, in 1,835 (8.0%) had ISR in elective PCI in clinical practice in Europe: PERSPECTIVES. Between 2005 and 2007, 47,407 consecutive patients undergoing PCI were enrolled in the PCI-Registry of the Euro Heart Survey to document patient characteristics, PCI details and hospital complications. We examined the difference in treatment of ISR versus de novo-lesions in elective PCI.

Results: A total of 22,917 patients underwent elective PCI, in 1,835 (8.0%) had ISR. Patients with ISR were younger, more often male, more often had prior MI or CABG and diabetes. They were more likely to receive unfractionated heparin rather than LMWH. No differences were found for the use of GP IIb/IIIa blockers, while bivalirudin was more frequently administered in patients with ISR. Patients with ISR got stents in 75%, of which 3/4 were DES. In patients with de-novo-lesions, 95.4% received stents, with 48.3% DES. There were no differences in hospital mortality between both groups, however death/MI/Stroke was significantly higher in patients undergoing PCI for ISR (1.4% vs 0.9%)

Conclusions: Patients undergoing elective PCI for ISR were younger and had more comorbidities. They more often received DES. In hospital complications were low, however the rate of death/MI/Stroke was higher in ISR mainly due to a higher rate of stroke.
Virtual histology intravascular ultrasound comparison of neointimal morphology of in-stent restenosis with drug eluting stents versus bare metal stents

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Background: The process of in-stent neointimal hyperplasia (NIH) between drug-eluting stents (DES) and bare metal stents (BMS) might be different. We compared the composition of in-stent NIH between BMS and DES using Virtual Histology Intravascular Ultrasound (VH-IVUS).

Methods and Result: VH-IVUS was performed in 63 patients (BMS 40 and DES 23) who underwent coronary revascularization because of in-stent restenosis. The regions of interest was placed between the luminal border and the inner border of the struts. NIH tissue composition was reported as percentages of NIH area: percent fibrous (%FI), percent fibrofatty (%FF), percent necrotic core (%NC), percent dense calcium (%DC). Mean follow-up times between stent implantation and VH-IVUS was 874±462 days for DES treated lesions and 694±622 days for BMS treated lesions (n.s.). At the sites of stent dital edge, stent proximal edge and in-stent minimum lumen area, %NC volume was higher in DES than in BMS (p<0.001). All NIH %DC volume was lower in DES than in BMS (64±12% vs. 70±13%; p=0.016), whereas NIH %NC volume was higher in DES than in BMS (11±5% vs. 8±6%; p=0.02).

Conclusions: VH-IVUS analysis demonstrated that the composition of NIH was different between DES and BMS, suggesting that the process of in-stent NIH in DES and BMS is diverse.

Purpose: Bare metal stent (BMS) implantation triggers a foreign body reaction resulting in neointima formation and restenosis. Silicone carbide coating (SiC) shields the metal from both circulating blood and the vessel wall. We investigated whether this coating decreases clinical target revascularization (TLR).

Methods: Two commercially available L-605 Co Cr BMS (stent A: amorphous SiC coating and stent B: uncoated) were implanted in 2731 patients over two consecutive 18 month periods (2006-2008). Diabetics and patients presenting with restenosis (25%) were excluded as in those patients drug eluting stents were used. TLR rates were evaluated at 1 year post PCI.

Results: Procedural and outcome data are presented in the table. Logistic stepwise backward regression analysis identified post-PCI minimal luminal diameter (adjusted odds ratio 0.56; 95% CI[0.42-0.73]; P<0.001), total implanted stent length (1,01 (1.00-1.02); P<0.003), NSTEMI/unstable angina (1.89 [1.41-2.54]; P<0.001), stent A (1.62 [1.20-1.98]; P<0.002) and triple vessel PCI (2.68 [1.02-7.05]; P=0.045) as significant independent predictors for clinical TLR. Although non-significant, non-compliant balloon post-dilatation (0.66 [0.35-1.24]; P=0.20) was kept in the model to accuracy for an increase in data over the study period. Hosmer & Lemeshow goodness of fit P-value was 0.35. Because 2.0-3.0 mm stents A had lower strut thickness (60 μm versus 80 μm), subgroup analysis (n=2382 lesions) was performed. Higher clinical TLR rates for stent A persisted in this small stent subgroup (1.62 [1.17-2.23]; P=0.003).

Conclusion: Compared with BMS, SiC-coated BMS implantation resulted in significantly higher TLR rates.
**P4154**

**No harmful effect of stem cell mobilization by granulocyte-colony stimulating factor on restenosis or late luminal loss after sirolimus-eluting stent (SES) implantation**

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**Purpose:** We evaluated the effects of stem cell mobilization by granulocyte-colony stimulating factor (G-CSF) on neointimal growth after sirolimus-eluting-stent (SES) implantation.

**Methods:** The present double-blinded randomized placebo-control study that primarily evaluated the effect of stem cell mobilization by G-CSF on endothelial function after SES implantation assigned patients to the G-CSF group (n=50) or the placebo group (n=50). After successful SES implantation, patients received subcutaneous injection of G-CSF (300 mg daily) or saline for 5 days. Follow-up angiography was performed 9 months after SES implantation.

**Results:** Plasma CD34+ cell level did not differ between the 2 groups at baseline (0.94±0.55 vs. 0.93±0.68/mL, p = 0.96). It significantly increased after G-CSF injection (0.94±0.55 vs. 18.39±13.55/mL, p < 0.001) but did not in the placebo group (0.93±0.68/L vs. 1.35±2.36/L, p = 0.22). Follow-up angiography was performed in 41 patients (82%) at 250.0±22.6 days in the G-CSF group and 46 patients (92%) at 287.0±10.3 days in the placebo group (p = 0.14 and p = 0.18, respectively). No death or myocardial infarction was observed in the study participants during follow-up. There was no significant difference in restenosis rate between the 2 groups (0.0% vs. 6.5%, p = 0.10). Late luminal loss was not significantly different (0.17±0.25 mm vs. 0.30±0.36 mm, p = 0.06). Regression analysis showed no significant correlation between plasma CD34+ cell level after study drug injection and late luminal loss at follow-up (r = -0.14, p = 0.21).

**Conclusion:** Stem cell mobilization by G-CSF does not increase restenosis or late luminal loss after SES implantation.

**P4155**

**Comparison of mid-term angiographical outcomes of drug-eluting stents in hemodialysis patients**


**Purpose:** Even in the drug-eluting stent era, the high restenosis rate in hemodialysis patients remains unresolved. We compared the mid-term angiographic outcomes of four different coronary artery lesions treated with sirolimus-eluting stents (SES), paclitaxel-eluting stents (PES), zotarolimus-eluting stents (ZES), and everolimus-eluting stents (EES) in hemodialysis patients.

**Methods:** From December 2003 to April 2011, 551 lesions in 337 hemodialysis patients were treated with drug-eluting stents exclusively and successfully. Of these lesions, 338 lesions in 225 (66.8%) hemodialysis patients who had undergone 8-month angiographic follow-up were analyzed.

**Results:** Binary restenosis rates were 26.0% in SES, 25.3% in PES, 30.0% in ZES, and 20.3% in EES patients (p=ns). Quantitative coronary analysis data are shown in the table. The late loss of EES was significantly smaller than that of SES, PES, and ZES (0.0% vs. 6.5%, p = 0.10). Late luminal loss was not significantly different (0.17±0.25 mm vs. 0.30±0.36 mm, p = 0.06). Regression analysis showed no significant correlation between plasma CD34+ cell level after study drug injection and late luminal loss at follow-up (r = -0.14, p = 0.21). 

Table 1

<table>
<thead>
<tr>
<th></th>
<th>SES</th>
<th>PES</th>
<th>ZES</th>
<th>EES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions</td>
<td>169</td>
<td>75</td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>3.01±0.58</td>
<td>3.03±0.63</td>
<td>3.14±0.47</td>
<td>3.00±0.51</td>
</tr>
<tr>
<td>MLD pre (mm)</td>
<td>0.91±0.58</td>
<td>0.85±0.60</td>
<td>0.72±0.72</td>
<td>0.76±0.61</td>
</tr>
<tr>
<td>MLD post (mm)</td>
<td>2.67±0.56</td>
<td>2.71±0.59</td>
<td>2.79±0.47</td>
<td>2.62±0.46</td>
</tr>
<tr>
<td>MLD follow-up (mm)</td>
<td>1.98±0.87</td>
<td>1.98±0.77</td>
<td>1.92±0.60</td>
<td>2.15±0.81</td>
</tr>
<tr>
<td>% Stenosis pre</td>
<td>69.9±17.7</td>
<td>72.1±18.7</td>
<td>77.1±22.3</td>
<td>75.1±18.5</td>
</tr>
<tr>
<td>% Stenosis post</td>
<td>14.5±7.9</td>
<td>14.4±8.2</td>
<td>15.1±11.0</td>
<td>15.6±7.7</td>
</tr>
<tr>
<td>% Stenosis follow-up</td>
<td>36.7±24.7</td>
<td>36.8±22.9</td>
<td>41.1±22.0</td>
<td>30.9±22.9</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.76±0.61</td>
<td>1.86±0.69</td>
<td>2.06±0.46</td>
<td>1.86±0.58</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>0.70±0.87</td>
<td>0.81±0.81</td>
<td>0.98±0.54</td>
<td>0.47±0.69</td>
</tr>
</tbody>
</table>

RVD: reference vessel diameter; MLD: minimal lumen diameter. *p<0.05 vs. SES, PES, ZES.

**Conclusion:** EES might be superior to other drug-eluting stents in angiographic results of hemodialysis patients.

**P4156**

**Severe insulin resistance is a predictor of restenosis after drug-eluting stent implantation**

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**Introduction & Hypothesis:** Percutaneous coronary intervention (PCI) is an effective treatment for patients with ischemic heart disease; especially, restenosis is suppressed after drug-eluting stent (DES) implantation. The aim of this study was to clarify the factors associated with coronary restenosis after DES implantation and evaluate the homeostasis model assessment of insulin resistance (HOMA-IR) index as a predictor of restenosis. We researched the clinical records of 258 patients who had been subjected to elective PCI and DES implantation between May 2007 and December 2010. We evaluated these patients by the value of HOMA-IR, and examined the relationship between restenosis and HOMA-IR.

**Results:** The overall restenosis rate was 14% (37/258). HbA1c levels were no difference between positive and negative of restenosis. But positive of restenosis was significantly greater than negative of restenosis (7.17±6.32 vs 5.47±7.94, p=0.038) in HOMA-IR index. We distributed three groups by value of HOMA-IR (less 2.5; n=115, 2.5 to 5.0; n=56, over 5.0; n=87), the rate of restenosis was significantly higher in HOMA-IR over 5.0 group (23.0%) than in the other groups (11.3% and 7.1%, p=0.014). Logistic analysis showed that the only independent predictor of restenosis was HOMA-IR over 5.0 (OR 2.87, p=0.004).

**Conclusion:** The results suggested that severe insulin resistance was a predictor of restenosis after drug-eluting stent implantation; furthermore, that improvement of insulin resistance may contribute to prevent coronary restenosis after drug-eluting stent implantation.
Impaired production of anti-inflammatory cytokines in diabetic patients after primary PCI: a pericoronary stent model

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Objectives: We investigated IPH, macrophage phenotype, and IL-10 production in diabetic ACS patients after PCI.

Methods: In 23 ACS patients with diabetes (HbA1c(NGSP) > 6.5% or HOMA-IR > 2.5), atherothrombosis debris was retrieved using filter-based distal protection device (Filter), during primary PCI with BMS implantation. The debris was stained with antibodies to CD163 (Hb scavenging macrophage), CD14 (proinflammatory macrophage), glycoporphin A (GPA, intraplaque hemorrhage) and IL-10. We investigated IPH, macrophage phenotype, and IL-10 production in coronary plaques from ACS patients with diabetes, in association with bare metal stent (BMS) restenosis after primary PCI.

Results: Restenosis rate were 17.4%. Conventional risk factors, such as diabetes, dyslipidemia and hypertension were not different between the 2 groups, at the time of index PCI and after 9-month medical treatment. GPA, CD14, CD163, and IL-10 were not different between the two groups. However, IL10/CD163 ratio was higher in diabetic ACS patients compared to non-diabetic patients. Further, diabetic ACS patients showed significant higher IL-10 production than non-diabetic patients (P=0.053). Furthermore, certain known atherosclerosis risk factors showed considerable OR: diabetes mellitus, 4.0; hypertension, 4.5; hypercholesterolemia, 1.4 and hypertriglyceridemia, 7.

Conclusions: Our primary results showed that Hs-CRP and genetic factors are clinical predictors of restenosis, among them, eNOS polymorphism was more powerful. Interestingly, these results demonstrated that traditional risk factors are more powerful than the novel one for predicting ISR. The final result is pending with larger population.

Figure 1

Tissue characteristics in in-stent restenosis lesions after various drug-eluting stents and bare-metal stent assessing with optical coherence tomography

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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 assessments of in-stent restenotic tissue using optical coherence tomography (OCT) were performed and the differences of morphological characteristics among various DESs were reported. In this study, we clarify the difference among the restenotic tissue characteristics after various DESs and bare-metal stent (BMS) implantation.

Methods: Between May 2008 and February 2012, we assessed in-stent restenosis lesions in 281 patients after various stents implantation including sirolimus-eluting stent in 125 patients, paclitaxel-eluting stent in 56 patients, zotarolimus-eluting stent in 21 patients, everolimus-eluting stent in 34 patients, biolimus-eluting stent in 9 patients, and BMS in 36 patients using OCT. The morphological qualitative assessment of neointimal tissue at the minimum lumen area site by OCT, including restenotic tissue structure (homogeneous, heterogeneous, and layered type), restenotic tissue backscatter, visible microvessels, lumen shape, and the presence of intraluminal materials, was performed.

Results: The patients were 230 men and 51 women, and the mean age was 68.9±9.8 years. There was significant difference among the distributions of restenotic tissue structure type in various stents (p<0.05) as shown in figure 1. This trended to be different among the rates of presence of intraluminal materials in various stents (p<0.064) as shown in figure 1. There were no difference
in other parameters including restenotic tissue backscatter, visible microvessels, and lumen shape.

Conclusions: The pathophysiology of si-stent restenosis might be different among various stents.

Comparison of neointimal tissue characteristics among bare-metal stent, paclitaxel-eluting stents and zotarolimus-eluting stents using integrated-backscatter intravascular ultrasound


Purpose: Drug-eluting stent (DES) had dramatically reduced angiographic restenosis and target lesion revascularization (TLR) by decreasing neointimal hyperplasia. However, ISR in DES still occurs to limited extent. Although neointimal tissue characteristics are essential to understand the pathophysiology of ISR, they have not been fully investigated. The aim of this study is to compare the differences of neointimal tissue characteristics among BMS, paclitaxel-eluting stents (PES) and zotarolimus-eluting stents (ZES), using intravascular ultrasound (IVUS) and integrated-backscatter IVUS (IB-IVUS).

Methods: We investigated 95 de novo lesions to be treated with BMS (N=18), PES (N=20), and ZES (N=17). We performed longitudinal IVUS analyses within stented segments to confirm minimum lumen area (MLA) at follow-up. Neointimal tissue characteristics judged by grayscale-IVUS were categorized as homogeneous or heterogeneous. Neointimal tissue characteristics were also analyzed using IB-IVUS, which characterized as following four characteristics: calcific, dense-fibrous, fibrous, or lipidic. We compared them among BMS, PES, and ZES.

Results: TLR rate showed no significant difference in three groups (22% in BMS, 30% in PES, 18% in ZES, p=0.67). Neointimal area at MLA site was significantly larger in BMS than PES and ZES (6.1 mm² in BMS, 3.7 mm² in PES, 2.6 mm² in ZES, p<0.001). Most neointimal tissue categorized homogeneous by grayscale-IVUS (100% in BMS, 95% in PES, 88% in ZES, p=0.3). IB-IVUS analysis revealed that there were no significant differences in lipidic tissue components of neointima among three groups (0.76 mm² in BMS, 0.59 mm² in PES, 0.53 mm² in ZES, p=0.53). Calcific tissue and dense fibrous tissue components of neointima also showed no significant differences in lipidic tissue components of neointima among three groups (calcific tissue: 0.16 mm² in BMS, 0.17 mm² in PES, 0.21 mm² in ZES, p=0.63), dense-fibrous tissue: 0.40 mm² in BMS, 0.31 mm² in PES, 0.30 mm² in ZES, p=0.52). However, fibrous tissue components of neointima were significantly higher in BMS compared with PES and ZES (3.50 mm² in BMS, 2.31 mm² in PES, 2.32 mm² in ZES, p<0.001). In comparison between PES and ZES, neointimal tissue characteristics by IB-IVUS showed no significant differences (calcific: p=0.42, dense-fibrous: p=0.84, fibrous: p=0.94, lipidic: p=0.73).

Conclusions: IB-IVUS analyses revealed that neointimal tissue in BMS contained more fibrous tissue than PES and ZES, which suggested more stable neointima in BMS compared with PES and ZES. In addition, PES had similar neointima to ZES by IB-IVUS analyses.
value of ≤0.8 was considered as significant in determining ischemia. The minimal lumen area (MLA) was measured by OCT and IVUS.

Results: Although both MLA obtained by IVUS and OCT showed a significant positive correlation to the FFR values, MLA obtained by OCT appeared to have a better correlation to FFR values than MLA by IVUS. (OCT: R=0.679, P<0.001, IVUS: R=0.573, P<0.001). The best cutoff value of the MLA to predict FFR <0.80 was 2.49 mm² by IVUS (sensitivity, 94.7%; specificity, 76.9%; AUC, 0.877) and <2.24 mm² by OCT (sensitivity, 94.7%; specificity, 76.9%; AUC, 0.947).

Conclusion: OCT-based MLA measurement may provide better estimation of physiological coronary epicardial stenosis than IVUS.

P4168

VH-IVUS predictors for lesion specific myocardial ischemia in intermediate coronary artery stenosis

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Purpose: Aim of this study was to investigate characteristics and predictors of virtual-histology intravascular ultrasound (VH-IVUS) derived plaque geometry and composition associated with lesion specific myocardial ischemia upon FFR criteria in the angiographically intermediate coronary stenosis.

Methods: 104 coronary segments of the 73 patients with intermediate stenosis were prospectively enrolled from 2 centers. VH-IVUS and FFR examination were performed simultaneously for all segments. Functionally significant stenosis was defined as FFR less than 0.80. All angiographic, VH-IVUS data were analyzed in core laboratory.

Results: Lesions with FFR ≤0.8 showed significantly smaller minimal lumen area (2.68 ± 0.77 mm² vs. 4.02 ± 1.69 mm², mean ± SD, P<0.001) and larger plaque burden (77.58 ± 7.8% vs. 68.9 ± 10.2%, P < 0.001). Non-calcified VH-IVUS derived (≥10%) plaques were significantly associated lower FFR than calcified plaques (27.4% in FFR ≤ 0.80 vs. 6.5% in FFR > 0.80, P = 0.017, Odds ratio=5.47, CI: 1.19-25.08). Lesions with calcium (DC), fibrotic (FI) and fibrofatty (FF) (NC: 20.2 ± 7.0% vs. 6.0 ± 4.8%, P<0.001) had significantly worse correlation to FFR values than MLA by IVUS. (OCT: R=0.679, P<0.001). VH-IVUS derived MLA (P=0.048, P=0.015), respectively.

Conclusions: In the intermediate coronary artery stenosis, lesions with non-calcified, ≤70% plaque burden with smaller minimal lumen area could be used as VH-IVUS predictors for lesion specific myocardial ischemia.

P4169

Percutaneous occlusion of left atrial appendage with the amplatzer cardiac plug: results from clinical, echocardiographic and CT follow-up in 100 implanted patients

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Background: Percutaneous left atrial appendage (LAA) occlusion has proved to be safe and not inferior in the prevention of cardioembolic events in non-valvar atrial fibrillation (AF) when compared to treatment with vitamin K antagonists (VKA). Data from large studies are lacking information on the use of Amplatzer Cardiac Plug (ACP). The aim of our study is to demonstrate that the ACP is safe and effective in the short and medium term.

Methods: Data from 106 consecutive LAA occlusion patients (pts) submitted to two Centers for performing percutaneous LAA occlusion were collected from December 2008 to January 2012. All pts had an high thromboembolic risk (CHA2DS2-VASc ≥ 2) and at least one contra-indication to oral anticoagulant therapy. After the procedure all pts were treated with dual antplatelet or anticoagulation therapy for 4 weeks. Pts were re-evaluated with clinical or instrumental follow up (FUP) with computer tomography (CT) or transthoracic echocardiography (TEE).

Results: Mean age was 75±11 yrs. 57.1% M. The ACP was successfully implanted in 100 of 106 pts (94%). Permanent AF was present in 71% of pts, while persistent and paroxysmal AF were present in 11% and 18%, respectively. After the procedure five pericardial effusions were observed, three of which needed pericardectomy. Two pts experienced a transient ischemic attack, one the day after the procedure and the other 16 months later. One patient, treated with ASA, clopi-dogrel and fondaparinux for one month, was affected by intracranial haemorrhage two weeks after the procedure. At a mean FUP of 13±7,3 months (0 pts lost to FUP) 6 patients were dead for non procedural related causes (2 cases of pulmonary embolism, 2 cancer, one of worsening heart failure, one necrotic core (DC), dense collagen (DC), fibrotic (FI) and fibrofatty (FF) (NC): 20.2 ± 7.5% vs. 21.0 ± 9.3%, P<0.001). Lesions with ≥70% plaque burden were associated with lower FFR values (36.8% in FFR ≤ 0.80 vs. 8.6% in FFR > 0.80, P = 0.004, Odds ratio=2.22, CI: 1.60-24.11) even though plaque composition by VIH-IVUS were not different in necrotic core (NC), dense collagen (DC), fibrotic (FI) and fibrofatty (FF) (NC): 20.2 ± 7.5% vs. 21.0 ± 9.3%, P<0.001. Multiple procedures were performed in 7 pts, 1 of them was a failed implantation, 1 without embolization. No ischemic stroke was observed in any implanted patient. TEE was performed in 46 patients at 6±7 months after the procedure and CT in 33 pts at 11±8 months, failing to demonstrate any malposition or embolization of the device. In 2 cases there was a residual intragranic atrial septal defect. In one patient TEE demonstrated a small thrombus on the device that was successfully treated with fondaparinux for one month. Mital valve motion, transmittal flow and left superior pulmonary vein were not affected by the presence of the device.

Conclusions: Data from our experience suggest that percutaneous LAA occlusion with ACP is safe and an effective alternative to VKAs in selected high risk patients with non valvu lar AF and is associated with a high procedural success rate. Our mid-term follow up in 100 implanted pts with no ischemic stroke after a mean of 13 months confirms the acute results.

P4166

Pericardial effusions: incidence, diagnosis, and management strategies

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Background: Patients with atrial fibrillation (AF) who undergo percutaneous left atrial appendage closure (LAA closure) are at risk of pericardial effusions (PE). PE are a potential diagnostic challenge, often difficult to diagnose and to manage. The aim of this study was to report on the incidence of PE in patients after LAA occlusion and describe diagnostic and management strategies.

Methods: We retrospectively selected 60 consecutive non-high risk patients with at least one percutaneous LAA closure (LAA closure was performed with Watchman™ device). The incidence of PE was evaluated through transesophageal echo (TEE) and chest radiograph. In case of TEE suspicion of PE, a CT scan was performed. Management strategies were evaluated.

Results: A total of 54/60 patients developed PE at a median follow-up of 123 days (range: 30-365). PE were more frequent after the LAA occlusion with Watchman™ device (45/54 vs. 9/54). A PE was diagnosed in 39 patients (66%) by TEE, 11 patients (18%) by radiography and 5 patients (8%) by both methods. CT scan was performed 22/39 (56%) TEE-positive cases. An additional 1 patient was observed during the CT follow-up. There were no differences in the incidence of PE between male and female patients. A total of 12 patients (22%) required medical treatment or surgical intervention to manage PE. A total of 11 patients (20%) developed PE after the first month, 12 patients (22%) after the second month and 3 patients (5%) after the third month. In 10 patients (18%) PE were managed by treatment with aspirin or clopidogrel and in 1 patient (2%) by pericardiocentesis. No patients required surgery or died of PE.

Conclusion: The incidence of PE after percutaneous LAA closure is high and may present a diagnostic and management challenge. The management strategies are effective. A total of 22 patients (40%) required medical treatment or surgery to manage PE.

P4167

In-stent-restenosis and invasive coronary imaging / Non coronary and TAVI interventions

In-stent-restenosis and invasive coronary imaging / Non coronary and TAVI interventions
Refining transcatheter left atrial appendage closure: eliminating the anaesthetist and reducing the cost
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Introduction: The validity and benefit of transcatheter LAA closure for protection from thromboembolic stroke in non-valvular AF has been well established. However, to date, all studies have performed this procedure under general anaesthesia. Given that most candidates for LAA occlusion are often aged greater than 75 years, with multiple co-morbidities, general anaesthesia confers significant risk to this patient cohort, as well as additional costs to the procedure. We therefore sought to determine the safety of performing this procedure under conscious sedation, and to determine any cost implications of this strategy.

Methods: Fifty four (44 men, 10 women; mean age 75.7 ±6.2 years) with non-valvular AF and a high risk for cardioembolic stroke (mean CHA2DS2-VASc score 3.8 ±1.5), and high risk for oral anticoagulation, underwent percutaneous LAA closure using the WATCHMAN device. All procedures were performed under conscious sedation and transoesophageal echocardiographic (TOE) guidance. IV Midazolam was titrated to observed patient needs, with monitoring of O2 saturations. The follow-up program included clinical and echocardiographic review within 10 days.

Results: The LAA was successfully occluded 50 patients (92.5%) under conscious sedation. In four cases the device was not implanted due to unsuitable appendage anatomy. The mean procedural and fluoroscopy times were 67.3 ±16.1 and 16.1 ±6 min respectively. The mean device size was 24.6 ±1.3 mm. There were no significant procedure or device related adverse events. There were no anaesthesia related complications. All were performed as day-case procedures. Follow-up TOE showed closure of all LAA orifices. None of the patients experienced major adverse events during a follow-up (5-22 months).

Conclusion: Our study demonstrates that conscious sedation is a safe and well tolerated alternative to general anaesthesia for transcatheter LAA occlusion. The use of conscious sedation removes the requirement for general anaesthesia and thus, reduces anaesthesia-related morbidity as well as anaesthesia related costs. Additionally, this approach facilitates the performance of LAA closure as a day-case procedure, with a consequent further reduction in procedure-related costs.

P4172
Left atrial appendage occlusion: the link between imaging techniques and clinical events
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Purpose: Left atrial appendage (LAA) transcatheter occlusion is a recent alternative for the prevention of thromboembolism in patients with non valvular atrial fibrillation (AF). Different imaging techniques have been used for establishing the complete occlusion of LAA and the transesophageal echocardiography (TEE) is still the most common tool used. Nevertheless very limited data is available about mid to long term outcome in patients who have undergone this procedures. Our aim was to verify if advanced cardiac imaging including cardiac computed tomography angiography (CCTA) and transesophageal echocardiography (TEE) are related to clinical events over a three years follow-up.

Methods: We evaluated 50 patients with concomitant to anticoagulant (mean age 77.6 ± 8; male 60%; mean CHA2DS2-VASc score 4.1 ±1.2; HAS-BLED score 3.1 ±1.0) who had undergone LAA transcatheter occlusion procedure performed using the AmplatzerCardiac Plug (ACP, Agra Medical, Plymouth, MN) in our center between January 2009 and January 2012. After a short period of dual antiplatelet drugs all patients were chronically treated with a single antiplatelet agent.

Results: At a mean 24 ±12 months follow-up period we controlled 31 cases using CCTA, 16 of these (52%) had an incomplete stentorifice flow after LAA occlusion is not associated to a higher incidence of clinical cerebrovascular events. CTA has a high sensitivity to identify peri-device leaks and thrombi. TEE is still the most used technique in the evaluation and can represent the unique tool in a subgroup of patients who develop absolute contraindications to intravenous administrations of iodinated contrast agents during F-P period.

Conclusion: Our data, according to previous findings, suggest that residual flow after LAA occlusion is not associated to a higher incidence of clinical cerebrovascular events. CTA has a high sensitivity to identify peri-device leaks and thrombi. TEE is still the most used technique in the evaluation and can represent the unique tool in a subgroup of patients who develop absolute contraindications to intravenous administrations of iodinated contrast agents during F-P period.
"Migraine side effect" after PFO closure as secondary

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Migraine side effect after PFO closure as secondary impact of mitral annulus dimensions assessed by 3D transthoracic echocardiography guidance during simultaneous measurement of left ventricular volume and pressure during percutaneous mitral valve repair with the evole mitrACLIP system

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The purpose of this study was to determine the frequency of occurrence of the migraine after transcatheter closure of PFO in patients younger than 55 yrs old with cryptogenic stroke or TIA.

Methods: All 224 consecutive patients (mean age 40±9.9 yrs; 103 men, 108 pts -40 yrs old, 116 pts 40-55yrs old) with cryptogenic thromboembolism who underwent PFO closure between 1999 and 2011 as secondary prevention were included. Mean follow-up period was 37.8±32.5, median 27 months (range, 3-151 months). There were 33 (14.7%) pts lost to follow up. Every patient was treated at least 6 moths with aspirin (yrs 1999-2003) or aspirin and ticlopidin (2004-2006) or aspirin and clopidogrel (3-6 months, 2007-2011) after procedure. All pts were sent the questionnaire concerning the presence of migraine before and after PFO closure.

Results: The migraine occurred in the study group before PFO closure in 68 (30.4%) pts, that is three times more frequently than in general population (30% vs 10%). Noticeable improvement (expressed in lower frequency rate or severity of migraine attacks, in patients' subjective opinion) or disappearance of migraine symptoms after procedure was reported by 55 pts (80.9%) vs 13 pts (19.1%) without improvement (p<0.0001). There were no new cases of migraine after the PFO closure.

Conclusions: 1/ Migraines are seen more frequently in patients with PFO than in general population. 2/ Percutaneous PFO closure with Amplatzer septal occluder leads to recovery of migraine or noticeable amelioration of symptoms in significant percentage of patients.

Transcatheter echocardiography guidance during percutaneous closure of patent foramen ovale

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Background: Percutaneous closure of PFO has been increasingly performed for several indications; mostly due to cryptogenic stroke. We aimed to evaluate the safety and efficacy of transcatheter echocardiographic (TTE) guidance during percutaneous closure of PFO.

Methods: Between 2005-2012, 188 patients (91 males; age 40±10.3 y) underwent transcatheter PFO closure. In all patients transoesophageal echocardiography performed subsequently to diagnose, assess the size and evaluate for suitability of the defect for percutaneous closure. During the procedure fluoroscopy and TTE were used for guidance.

Results: Overall, 74 (43.3%) Amplatzer, 76 (44.4%) Occlutech Figulla and 21 (12.3%) BioSTAR PFO occluder devices were used. The indications for PFO closure were ischemic stroke in 123 (65.4%), recurrent transient ischemic attacks in 65 (34.6%) patients. In all patients, percutaneous intervention was performed successfully under TTE guidance. There have been no neurologic/cardiovascular complications during the immediate and long term follow-up (median 28 months).

There was significant difference between the mean fluoroscopic time from the beginning which is 8.6±3.4 min in former versus 3.2±0.8 in latter (p<0.001).

Figure 1

Conclusion: Our study confirms the efficacy and safety of TTE guidance during percutaneous closure of PFO which shortens the procedural time and obviates the need for general anesthesia or endotracheal intubation.

Simultaneous measurement of left ventricular volume and pressure during percutaneous mitral valve repair with the evole mitrACLIP system

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Objectives: To investigate acute changes in left ventricular (LV) pressure-volume (PV) relationships during percutaneous edge-to-edge mitral valve repair (MVR) (Evolve MitraClipTM) using a conductance catheter.

Background: Percutaneous MVR with the Evolve MitraClipTM has emerged as an alternative to surgery for treating severe mitral regurgitation. However, its effects on left ventricular performance (including left ventricular contractility, preload and afterload) are yet unknown.

Methods: Simultaneous pressure-volume (PV) loops were recorded during the MitralClip procedure at baseline and after clip implantation using a 7-French central-lumen pigtail conductance catheter (CD Leycom, Zoetermeer, The Netherlands). PV loops were analysed using a dedicated software package (Conduct NT, Version 3.18.1.1, CD Leycom) to yield parameters of LV contractility, and end systolic (WSES) and enddiastolic wall stress (WSED). Pulmonary pressures were measured from standard right heart catheterization and cardiac index (CI) calculated by the Fick principle.

Results: PV loops were successfully obtained in 23 patients (median age 80 yrs, 10 (43%) patients with functional MR, LV ejection fraction 49±18%, of which 22 (96%) had a reduction in MR to grade 2+ or less. Mitral clipping slightly reduced end systolic pressure-volume relationship (from 1.31 ± 1.10 mmHg/ml; p<0.035), while Starling contractile index was not affected. WSES increased after MitralClipping (from 185 ± 197 mmHg), whereas WSED was markedly reduced (from 52 to 28 mmHg) (both p<0.05). Finally, MitralClipping increased CI (from 2.6 ± 3.0 L/min/m²; p<0.001) and reduced pulmonary capillary wedge pressure (from 15 to 12 mmHg, p<0.001).

Conclusions: MitralClip implantation results in a slight increase in LV afterload and marked decrease in preload, while LV contractility is preserved. This partly explains the favourable hemodynamic effects of percutaneous MVR.

Impact of mitral annulus dimensions assessed by 3D echocardiography on procedural results of percuturated edge-to-edge mitral valve repair and left atrial and left ventricular reversed remodeling


Background: Percutaneous mitral valve repair (PMVR) using the edge-to-edge technique has become a treatment option for selected patients with severe mitral regurgitation. This study evaluated the impact of mitral annulus dimensions on reduction of mitral regurgitation after PMVR and prediction of left atrial (LA) and left ventricular (LV) remodeling.

Methods: In 30 high-surgical risk patients with severe functional mitral valve regurgitation (age 74±9 years) 3D transesophageal echocardiography (TEE) was performed before PMVR to assess mitral annulus area, circumference, anterior-to-posterior diameter and postero medial-anterolateral diameter. 3D color Doppler TEE was used for direct planimetry of the vena contracta area (VCA) to define mitral regurgitation severity before and after PMVR. At 6 months follow-up, changes of LA volume and LV enddiastolic and endsystolic volumes were assessed by 2D transthoracic echocardiography.

Results: VCA by 3D color Doppler TEE was reduced from 0.45±0.17 cm² to 0.19±0.11 cm² after PMVR. Patients with a reduction of VCA >50% (n=22) had a significantly smaller pre-procedural mitral annulus area compared to patients (n=8) with a reduction ≤50% (11.9±3.2 vs. 17.2±10.1 cm², p=0.034). Mitral annulus circumference (13.0±1.9 vs. 15.5±4.9 cm, p=0.002), mitral annulus anterior-to-posterior diameter (3.6±0.6 vs. 4.1±1.0 cm, p=0.098) as well as annulus postero medial-anterolateral diameter (4.0±0.7 vs. 4.5±1.3 cm, p=0.197) tended to be smaller in patients with a reduction of VCA >50%. The reduction in LA volume as well as LV enddiastolic volume at 6 months follow-up was significantly greater in patients with a reduction of VCA >50% after PMVR (10.6±5.5 and 10.5±7.9% compared to those of patients with a reduction of regurgitant VCA ≤50% (3.1±9.1 and -1.9±7.7%; p=0.013 and p=0.024, respectively) while there was no difference in reduction of LV end systolic volume between both groups (5.4±7.3 vs. 5.3±5.7%, p=0.905).

Conclusions: In patients with very large mitral annulus dimensions, effectiveness of PMVR is reduced. Less effective PMVR is associated with less LA and LV remodeling.

Mitril Valvuloplasty long-term follow-up of single balloon (Balt) versus Inoue balloon techniques

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This study aimed to demonstrate that mitral balloon valvuloplasty (MBV) with the Balt single balloon (BSB) has similar outcome and long-term follow-up (FU) than MBV performed with the Inoue worldwide accepted technique.
From 1987 to 2010 a total of 526 procedures were performed, being 312 with a FU, 56 (17.9%) with Inoue balloon (IB) and 256 (82.1%) with BSB. The mean FU in IB group was 33±27 (2 to 118) and 55±33 (1 to 198) months, p=0.0001. Univariate Analysis (UA) and multivariate Cox analysis (MVA) were utilized to determine independent predict variables of survival and event free survival (EFS) in both techniques groups. The major events (ME) were death, cardiac surgery and new MVV. In IB and BSB groups there were, respectively: female 42 (75.0%) and 222 (86.7%); mean age 37±10.0 (19 to 63) and 38±12.6 (13 to 83) years, p=0.7138; sinus rhythm 51 (91.1%) and 215 (84.0%), p=0.1754; echo score: ≤ 3 (53.9%) and ≤ 3 (to 10) and 7.2±1.5 (4 to 14) points, p=0.0526; echo mitral valve area (MVA) pre-MBV 0.96±0.18 and 0.93±0.21 cm², p=0.2265; post-MBV mean MVA (Gorlin) were 2.00±0.52 and 2.02±0.37 cm², p=0.9594. At the end of the FU there were in IB and BSB groups, respectively: echo MVA 1.71±0.61 and 1.54±0.51 cm², p=0.0552; new severe mitral regurgitation in 5 (8.9%) and 17 (6.6%) patients, p=0.5633; new MVV in 1 (1.8%) and 3 (5.1%), p=0.4779; mitral valve surgery in 3 (5.4%) and 27 (10.4%), p=0.3456; deaths 2 (3.6%) and 11 (4.3%), p=1.000; cardiac deaths 1 (1.8%) and 9 (3.5%), p=1.000; ME 5 (9.8%) and 46 (19.0%), p=0.1449. In UA and MCA the BSB or IB technique do not predict survival or EFS. The independent risk factors to survival (MVA with 2 models with 5 and 6 variables) were: age >50 years (p=0.016, HR=0.233, 95% CI 0.071-0.764), EF >8 (p=0.011, HR=0.405, 95% CI 0.23-0.702, 95% CI 0.043-0.327), MVV dilation area ≤ 1.5 cm² and mitral valve surgery in the FU, p=0.0525. The mean FU was 4.2±1.15 years. Survival curves showed that for the whole group the survival and EFS in the FU. Independent predictors of survival were: age >50 years, EF >8 points, MVV dilation area and mitral valve surgery in the FU. Independent risk factors as EFS were prior commissurotomy and post-MBV MVA ≥1.50 cm².

Methods: We retrospectively reviewed those patients with severe prosthetic para-valvular regurgitation (MR) who underwent an attempt of percutaneous closure in our hospital. Data were collected regarding demographic characteristics, comorbidities, location and size of the leak, mortality and medium-term and echocardiographic outcomes.

Results: The study comprises 11 procedures in 10 patients, which took place between October 2010 and July 2011. The mean age was 75.4±6.6 years and 54.5% were female. The medium Euroscore was 42.84%±21.24. Mean LVEF was 53.7%±14.38 and 7 patients also had an aortic prosthesis (5 of them mechani-

Given the above, the conclusion is that there is no significant difference in survival or event-free survival between the two techniques. The methods used involved univariate and multivariate analysis, and the results were statistically significant. The authors conclude that paravalvular leaks can be effectively treated using percutaneous techniques, and that these methods are safe and efficacious for patients with symptomatic paravalvular leaks. The limitations of the study include the small sample size and the use of retrospective data.
Three dimensional rotational angiography fused with multimodal imaging modalities offers a novel, accurate, fast and safe way to guide endomyocardial injections

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Purpose: Development of protein- and cell-based therapy for advanced ischemic cardiomyopathy requires efficient and widely applicable intramyocardial (IM) delivery strategies. We tested whether a novel mapping technique, based on imaging modalities readily available in most cardiac centers, is a safe and equally effective substitute for existing electrophysiological mapping systems (NOGA) to guide IM injections.

Methods: AMI was induced in 25 kg pigs (n=10) using a 45 min balloon inflation in the proximal LAD. After 6 w, head to head comparison between NOGA and ExaGuide (Magnetic Resonance Imaging) guided IM injections was performed in a subset of 8 pigs. 200μL injections of 2 different colored 15 μm fluorospheres were sequentially performed using a Myostar catheter: the first series of injections (18±3 pigs) were delivered using NOGA, the second series of injections (18±3 pigs) was performed using the house developed technique (LARCA). The latter fuses the injection spot, identified from delayed enhancement (DE)-MRI, with a 3D rotational angiography. Subsequent integration with live biplane fluoroscopy enables guided IM injection. In an additional subset of 4 pigs, we tested whether LARCA could be fused with DE-CAT and 18F-FDG PET/CT, as an alternative for MRI incompatible patients. Ex vivo 3D stacks of 5 mm slices were reconstructed to quantify injection accuracy towards the infarct border, defined by 2,3,5-triphenyltetrazolium chloride. Fluorescent injection spots were identified by UV illumination.

Results: MRI after 6 w revealed significant functional impairment and LV remodeling (LVEF 37±12%, LVEDV 188±49 mL, infarct size 17±5% of LV mass). During NOGA-procedures, 4/6 animals required DC-shock for major ventricular arrhythmias vs 1/6 during LARCA-procedures. Total online procedure time was significantly shorter for LARCA (8±2 vs 15±3 h, p=0.06). The second series of injections (18±3 pigs) was significantly faster vs the first series using NOGA, the mean time from injection to the injection spot was 4.8±0.5 s for LARCA-MRI (n=42) vs 5.4±0.5 s for NOGA (n=49), p>0.40. LARCA-MRI and NOGA enabled spatial confinement of respectively 69% vs 63% of all injections to a distance less than 5 mm from the infarct border. LARCA fused with DE-CAT and PET/CT, resulted in a mean injection distance of 6.0±0.7 mm (n=44) to the targeted infarct border. LARCA resulted in a mean injection depth of 3.4±0.3 vs 2.5±0.3 mm for NOGA, p>0.06.

Conclusion: 3D Rotational angiography fused with multimodal imaging offers a new and promising strategy to guide IM injections towards the infarct border zone.

Endovascular stenting for palliation in malignant superior vena cava syndrome

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Superior vena cava obstruction can occur in late or progressive stages of various tumor diseases involving the mediastinum. To assess feasibility, short and long term efficacy and complication rate of interventional therapy, i.e. recanalization, PT A and stenting of such lesions we analysed 16 consecutive patients with cancer related superior vena cava syndrome. Clinical follow up was performed every 3 months up to 52 months. Cancer driven mean survival time after PT A-stenting was 10.2 months (8 days – 52 months). Immediate technical success rate and acute clinical success rate was 100%; NYHA class improved from 3.31 (±0.60) to 1.8 (±0.75). Especially those in class 4 benefited most and improved to class 2. Symptom relief was reached within 24hms. All patients remained free from restenoses or recurrent superior vena cava syndrome for the entire follow up or for their remaining life span. We did not have any acute or chronic complication (stent migration, perforation, bleeding). Patients were discharged the day after an uneventful and unidiopodlogoph, in some cases on low molecular heparin or vitamin K antagonists.

Thus, for palliation of superior vena cava syndrome in progressive cancer disease interventional treatment is recommended. PT A and stenting is technically safe and clinically efficient for both rapid and long term symptom relief. It should be considered as first choice treatment.
**P4187**

**Arrhythmia device lead extraction using evolution mechanical dilator sheath**

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**Background:** Transvenous lead extraction (TLE) has undergone an explosive evolution by increasing technology due to incremental problem of lead infections and lead malfunctions. We aimed to present our experience in TLE with Evolution Mechanical Dilator Sheath.

**Methods:** Between June 2009-January 2012, Evolution sheath was used for extraction of 158 leads in 75 patients. Indications for extraction, procedural success and complications were defined according to HRS guidelines.

**Results:** Indications for TLE were infection (58.6%), lead malfunction (40%) and lead displacement (1.4%). Extracted devices were PM in 34 cases (45.3%), ICD in 29 cases (38.7%) and CRT-D in 12 cases (16%). Among 158 leads, 38 (24%) were RV, 54 (34.2%) were defibrillator coil, 53 (33.6%) were atrial and 13 (8.2%) were CS electrodes. Median time from preceding procedure was 88 months (21-240 months). Clinical success was 98.6% and complete procedural success with Evolution system alone was 88% (66 patients). Partial success was achieved in 3 leads with remaining small ventricular tip. Major complications were observed in 1 (1.3%) patient without any mortality.

**Conclusions:** Our experience has confirmed that the hand powered Evolution system is an effective extraction tool for chronically implanted pacemaker/ICD leads.

**P4188**

**Comparison of knowledge-based weaning (KBW) and physician-driven weaning of mechanically ventilated patients in the coronary care unit**


**Introduction:** Knowledge-based weaning (KBW) of mechanical ventilation is a form of closed loop ventilation successfully used to decrease duration of ventilator assistance in general intensive care units (ICU). However, its use in specialty ICUs has not been validated.

**Objectives:** To find out if KBW reduced weaning times in coronary care units (CCU).

**Methods:** Patients: Single center tertiary hospital CCU. Inclusion: age 21-85; assisted-mode mechanical ventilation < 24 h, stable neurology. Exclusion: Poor short-term prognosis; pregnancy; hemodynamic instability. Randomization: 1:1 to KBW or usual care. Ventilator: Evita XL (Drager Medical, Lubeck, Germany) with SmartCare. Primary outcome: Total weaning time (time from inclusion to extubation without reintubation for 72 h). APACHE-II score used to stratify illness severity.

**Results:** Of 1/12/2009 to 31/12/2011, 251 patients were screened. 61 did not give consent. Of the 244 remaining, 136 did not meet entry requirements (75 poor short-term prognosis, 27 mechanical ventilation > 24 h, 3.84 and 2.98 days for KBW (p=NS). Mean age 68.0, (range 33-84) and mean APACHE-II score 18.2. 28 patients treated with KBW or usual care. Ventilator: Evita XL (Drager Medical, Lubeck, Germany) with SmartCare. Primary outcome: T otal weaning time (time from inclusion to extu- bation without reintubation for 72 h); APACHE-II score used to stratify illness severity.

**Results:** Indications for TLE were infection (58.6%), lead malfunction (40%) and lead displacement (1.4%). Extracted devices were PM in 34 cases (45.3%), ICD in 29 cases (38.7%) and CRT-D in 12 cases (16%). Among 158 leads, 38 (24%) were RV, 54 (34.2%) were defibrillator coil, 53 (33.6%) were atrial and 13 (8.2%) were CS electrodes. Median time from preceding procedure was 88 months (21-240 months). Clinical success was 98.6% and complete procedural success with Evolution system alone was 88% (66 patients). Partial success was achieved in 3 leads with remaining small ventricular tip. Major complications were observed in 1 (1.3%) patient without any mortality.

**Conclusions:** Our experience has confirmed that the hand powered Evolution system is an effective extraction tool for chronically implanted pacemaker/ICD leads.

**P4189**

**Predictors and clinical outcome of significant paravalvular aortic regurgitation following transcatheter aortic valve implantation**

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**Purpose:** Although transcatheter aortic valve implantation (TAVI) has emerged as a good alternative treatment for high surgical risk patients with severe aortic valve stenosis, significant paravalvular aortic regurgitation (PAR) remains a frequent complication. Therefore our aim was to investigate the determinants and short- and mid-term clinical consequences of PAR.

**Methods:** We studied 130 patients (mean age 81±8 years, 39 male) who underwent a TAVI with the Medtronic-CoreValve bioprosthesis. Clinical parameters were obtained from the medical history, laboratory analysis, echocardiography, cardiac computed tomography and angiography. Clinical outcome was assessed up to 12 months after TAVI.

**Results:** Following TAVI, PAR grade ≥2 occurred in 37 patients (28%). Multivariate analysis identified sinus width (per mm, OR: 1.32, 95%CI: 1.11-1.57, p=0.002) as the only independent predictor for PAR≥2. Thirty-day mortality and 1 year cumulative mortality were not significantly different between the PAR≤2 and PAR>2 groups. Cardiac mortality was significantly higher in the PAR>2 group versus the PAR≤2 group at 1 month (19% vs. 1%, p=0.016) and 1 year (28% vs. 2%, p=0.008).

**Conclusions:** Significant paravalvular aortic regurgitation occurs in 30% of patients treated with transcatheter aortic valve implantation using the Medtronic-CoreValve device. The risk for significant PAR is related to anatomical and morphological characteristics of the aortic valve and root and is higher in male patients. Significant PAR is associated with cardiac mortality but not with all-cause mortality and functional class.
Conclusion: In TAVI immediately after prosthesis deployment significant AR is frequent and can be corrected by balloon dilatation of the prosthesis or pullback maneuvers. In self-expanding prostheses without massive AR further expansion of the prosthesis can be waited for before initiation of further interventions.

Purpose: Transcatheter aortic valve implantation (TAVI) is an alternative for patients with aortic stenosis with high surgical risk. These valves are sutured to a stent which is expanded in a heavily calcified region. Our objective was to describe stent under-deployment (UD) and asymmetrical expansion which may impair valve hemodynamics.

Methods: From June 2008 to January 2012, 63 consecutive patients underwent TAVI. We selected 56 patients with available transesophageal echocardiography (TEE) imaging. Variables (inner stent area (SA), anterior-posterior diameter (APD) and lateral orthogonal diameter (LD)) were measured in 2D and 3D TEE. Mean values of 2D and 3D was used. We assessed stent circularity, defined as 1-APD/LD). Values >10% were considered non-circular. UD was defined as nominal area (of each valve size) minus SA. Indexed UD was obtained dividing UD by nominal area.

Results: Mean age was 82.8. Procedure approach was transfemoral in 80.4%. Valve sizes: 58.9%(23mm), 37.5%(26), and 3.6%(29). In 80.4% the valve used was XT model, the remaining the old TFX. Mean SA were 3.27±0.8 cm²(23); 3.93±0.1 (26) and 3.96±0.2 (29). The final SA fitted progressively in the native aortic annulus, showing a linear trend between SA and valve annulus (p<0.001).

In our series, mean UD was 0.88±0.8 cm²(23); 1.37±1.0 (26) and 2.63±0.2 (29). Mean indexed UD was 24%, thus, the valve expands only to 75% of its nominal area. Comparing TAVI approaches and prosthesis models, we found no differences in indexed UD. However, indexed UD increases keeping a linear relationship (p<0.001) with the valve sizes (21.2%(23), 25.9%(26), 39.8%(29)). This suggests that larger stents loose part of the radial force in spite of the higher stent height. Post-procedural gradients of under-deployed valves (20% UD cut-off) were numerically but not statistically higher than the non-UD valves. Regarding the circularity analysis, we found that 37.5% of the valves were non circular. The formation was mild (maximum 30%). No differences were found between TAVI approach, valve size or model. No correlation was found between non-circularity and severe aortic regurgitation.

Conclusions: Under-deployment in the balloon-expandable valve was substantial (mean 24% of nominal area) and related to the valve size (higher UD in larger prostheses), suggesting that larger stents loose radial force. Symmetrical expansion of the stents was fair (62.5%). New XT valve shows no improvement compared to old TFX. Correlation of these results with clinical events was not evident in our small series, but further investigation in this field is warranted.

Purpose: To investigate the clinical and hemodynamic outcomes in patients with prosthesis-patient mismatch after TAVI with both core valve and Edwards Sapien XT valves.

Methods: Clinical assessment and echocardiographic parameters were recorded at baseline and prior to discharge in 137 patients undergoing TAVI. PPM was defined as indexed effective orifice area (EOAi) <0.85 cm²/m².

Results: From the 137 patients, 57 (41.6%) had prosthesis-patient mismatch. Among patients with CoreValve 36 (45%) had PPM, whereas 21 (36.8%) patients with the Sapien XT had PPM (p=0.21). Severe PPM was present in 7.5% in CV patients and in 5.3% in XT patients (p=0.62). The procedural success rate was 100% and device success rate was 96%. There was a significant reduction in mean (50.03±14.13 to 9.4±4.15 mmHg, p<0.001) and peak gradients (84.3±20.29 to 18.03±7.8 mmHg, p<0.001) as measured by echocardiography.

The EOAI was significantly increased (0.66±0.28 cm²/m², p<0.001) as measured by echocardiography.

Conclusions: PPM after TAVI with both CoreValve and Edwards Sapien XT valves have not been investigated.

Methods: Clinical and hemodynamic parameters (aortic valve annulus diameter, left ventricular ejection fraction (LVEF), pulmonary artery systolic pressure (PASP)) defined as moderate if pulmonary artery systolic pressure (PASP) was between 45 and 55 mmHg, severe if PASP was >55 mmHg and 2 patients (6.9%) had severe PPM.

Results: Of the 21 patients (63%) with PPM, 13 had PASP ≥55 mmHg and 8 had PASP >55 mmHg. In TAVI immediately after prosthesis deployment significant AR is frequent and can be corrected by balloon dilatation of the prosthesis or pullback maneuvers. In self-expanding prostheses without massive AR further expansion of the prosthesis can be waited for before initiation of further interventions.

Conclusions: 3D TEE planimetry of aortic annulus improves the assessment of prosthesis/annulus discongruence and predicts the appearance of significant AR after TAVI.
Results: There was a significant reduction in mean (50.03±14.13 to 9.4±4.15 mmHg, p<0.001) and peak gradients (84.34±20.29 to 18.03±7.8 mmHg, p<0.001). From the 137 patients, 57 (41.6%) had post-TAVI complications. Among patients with CoreValve implantation 36 (45%) had PPM, whereas 21 (38.6%) patients with Sapien XT implantation had PPM (p=0.21). Severe PPM was present in 7.5% in CV patients and in 5.3% in XT patients (p=0.62). In the CoreValve group, predictors of PPM included only preprocedural EOA (OR: 0.002; CI: 0.001-0.688, p<0.05) and female gender (OR: 0.611, 95% CI: 0.387-0.975, p=0.04). In the Sapien XT group, baseline LVEF (OR: 0.951; 95% CI: 0.904-0.999, p<0.05) and baseline PASP (OR: 0.954, 95% CI: 0.913-0.996, p<0.05) were unadjusted predictors statistically significant. Prognostic factors for PPM were analyzed after adjustment for age, baseline LVEF (OR: 0.948, 95% CI: 0.899-0.999, p<0.05) and baseline PASP (OR: 0.953, 95% CI: 0.912-0.997, p<0.05) remained predictors of PPM. Procedural factors were not associated with PPM in either valve.

Conclusions: PPM is a frequent finding in the TAVI era. Predictors of PPM differ between the CoreValve and the Sapien XT valve, and are mainly associated with the severity of stenosis at baseline in CoreValve and with the functional capacity of the left ventricle in Sapien XT.

Impact of valve type and annular size on post TAVI aortic valve regurgitation

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Purpose: Transcatheter Aortic Valve Implantation (TAVI) is becoming the mainstay of treatment for high-risk inoperable patients with aortic valve stenosis. Aortic valve regurgitation (AR) is a common finding following TAVI. We studied the association of post-TAVI AR with the valve type, size and annular size.

Methods: Between April 2009 and January 2012 TAVI was performed in 137 (80 CV and 57 ES) high-risk patients with severe aortic stenosis (age: 79.9±6.9 years; logistic Euroscore 23.15±12.28%; 58.4% female; NYHA III 78.1%; aortic valve mean gradient 50.01±14.13mmHg). ARV was evaluated based on the American Society of Echocardiography classification (mild, moderate, severe).

Results: Annular size was greater in patients with CV compared to patients with ES (20.04±1.44mm vs 22.22±1.79mm in 26mm ES p<0.01). Mean annular size in 23mm ES was 20.79±0.84mm in 26mm CV vs 24.37±1.11 in 28mm CV (p<0.01). Patients with CV had greater rates of moderate-to-severe AR compared to ES (37.5% vs 14%, p<0.01, Figure). Patients with severe AR had a median annular size of 25.33±0.57mm compared to those with moderate AR who had 22.19±1.93mm, p<0.009.

Conclusions: Post TAVI ARV is more common in patients with greater aortic valve annular size. Furthermore, patients receiving the CoreValve have greater degree of ARV after implantation.
Methods: We measured Baseline BNP, peak BNP within 48 hours after TF-AVI and predischarge BNP in 104 patients with complete 1-year follow-up.

Results: BNP was elevated at baseline (298.2, IQR 145.8, 661.6 pg/ml) and showed an acute increase after TF-AVI (508.9, IQR 253.3, 866.8 pg/ml) followed by regression towards baseline levels prior to discharge (327.2, IQR 159.2, 634.6 pg/ml), p= 0.001. Acute BNP increase (ΔBNP/peak-baseline) is significantly higher in 30 days non-survivors (277.1 IQR 252.1, 810 pg/ml) than in survivors (132.8 IQR -10.1, 301 pg/ml), p= 0.028, and is found to be an independent predictor of 30 days survival. Kaplan-Meier (KM) survival analysis showed a reduced 30 days survival in patients with a ΔBNPpeak-baseline ≥ 248.9 pg/ml, p= 0.002. For 1-year survival, predischarge BNP level (250.8, IQR 152.9, 621.8 pg/ml) and ΔBNPdischarge-baseline (211.8 IQR -521.5, -91.1 pg/ml in survivors vs. 108.4 IQR 12.2, 272.6 pg/ml in non-survivors, p=0.002) are independent predictors. KM analysis showed that 1-year survival is significantly lower in patients with a predischarge BNP ≥ 327.2 and a ΔBNPdischarge-baseline ≥ 38.3 than in those not fulfilling both criteria, p= 0.001.

Conclusion: BNP values are elevated in patients undergoing TF-AVI. They further increase acutely after procedure and regress to baseline levels prior to hospital discharge. Acute BNP increase is an independent predictor of reduced 30 days survival, while reduced 1-year survival is predicted by higher predischarge BNP levels and failure of BNP to decline at discharge below baseline BNP level.

P4200 Decrease in sheath size for transfemoral Aortic Valve Implantation: what are the consequences?


Background: Vascular complications are frequent and remain a recognized limitation of transcatheter aortic valve implantation (TAVI), associated with increased morbidity and mortality. Whether the recent reduction in sheath size has led to a decrease in vascular complications is unknown.

Methods: Since May 2006, 250 consecutive patients underwent TAVI with the Edwards SAPIEN prosthesis in our institution using either the transfemoral (TF, n=190), or the transapical (TA, n=60) approach. Suitability for TF was based on ilio-femoral angiography and computed tomography of the iliofemoral access. Up to October 2009, TF Edwards SAPIEN (ES) implantation required 22 or 24F sheath, inserted surgically in 100% of cases, whereas the SAPIEN XT (SXT) prosthesis was compatible with reduced sheath size of 18 or 19F inserted percutaneously with pre-closure (Prostar XL, 10F) in 98% of cases. The consequences on vascular complication are reported according to the VARC classification.

Results: TF TAVI was performed using ES prosthesis in 78 pts and SXT in 112 pts. All baseline characteristics were similar in the two populations, except the Log EuroSCORE was higher in the ES (1.8 ± 1.7) than in the SXT (1.1 ± 1.1) group (p<0.001). The periprocedural complications (ES: 7.7% vs. SXT: 8.1%) whereas incidence of minor vascular complications was higher in the SXT cohort (18.9 vs 9%, p= 0.05). Vascular complications required urgent vascular surgery in 7 cases (3.7% ES: n=4, SXT: n=3), and covered stent in 12 (6.3%, all in the SXT group). Importantly, the rate of TA TAVI significantly decreased from 37% in the ES era to 6.9% after onset of the SXT prosthesis (p<0.05).

Conclusions: The reduced sheath size used for Sapien XT implantation did not decrease the risk of major vascular complications after TF TAVI but increased the rate of minor vascular complications. However, smaller sheath size allowed for implantation of more valves with the Sapien XT prosthesis has turned TF TAVI into a true percutaneous procedure feasible in smaller iliofemoral vessels, thus reducing markedly the indication for TA TAVI.

P4201 Lower pacing rate with CoreValve TAVI: high implantation or Accutrak catheter, or both?

M. Drury-Smith, S. Lakshmanan, R. Giri, M. Fayaz, J. Cotton, M. Bhabra, S. Khogali. Heart and Lung Centre, Wolverhampton, United Kingdom

Introduction: Permanent pacemaker implantation (PPI) post transcatheter aortic valve implantation (TAVI) is a well recognised complication and the greater requirement after CoreValve TAVI compared with surgery (33% vs 8%) has caused concerns. Pre-existing bundle branch block (BBB), larger valve size, post dilatation and low implantation have been shown to independently increase the risk of PPI requirement. Implantation below the aortic annulus can result in compression of conduction tissue and heart block. A modified delivery catheter (ACCU-TRAK) may allow a more controlled release expansion of the prosthesis, preventing low implantation and reducing PPM need. We evaluated the PPM requirement in all our TAVI patients (pts) treated before and after the introduction of the Accutrak catheter.

Methods: TAVI was performed in 101 pts: trans-femoral (80 pts), left subclavian (16 pts) and direct aortic approach (5 pts). A high valve deployment strategy of ≥ 1.1 mm below the aortic annulus was routinely employed. 12 of these had a PPM and were excluded from analysis. Of the remaining 89 patients, 20 patients post TAVI using the Accutrak catheter. Procedural outcomes were analysed (table) Results: Recognised predictors of PPM requirement post TAVI, were similar in both groups and were not significant (table). A total of 9 patients required a new
Hybrid endovascular repair for aortic arch pathology: intermediate outcomes and complications

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Objectives: To evaluate the outcomes of hybrid endovascular repair for aortic arch pathology.

Methods: This study was a retrospective analysis involving patients who under went hybrid endovascular repair for aortic arch pathologies.

Results: Twenty-one patients (16 men; mean age, 64.7±16.2 years) with aortic arch pathologies were treated by hybrid endovascular repair. The indications for treatment included increased aneurysm size in 16 cases (71.4%), rupture or impending aneurysmal rupture in 5 cases (23.8%), and rapid growth of aortic dissection (≥10 mm/mo) in 1 case (4.8%). Supra-aortic vessel transposition and stent-graft implantation were achieved in all cases. Two types of stent-graft were used, as follows: the Solar thoracic stent-graft in 14 patients (66.7%); and the Valiant stent grafts in 7 patients (33.3%). Peri-operative complications affected 5 patients (23.8%), as follows: bleeding (n=4, 19.0%); stroke (n=3, 14.3%); re- nal failure (n=2, 9.5%); vascular injury (n=1, 4.8%); and respiratory failure (n=1, 4.8%). Two patients died within 30 days (9.5%). Technical success was achieved in 15 patients (71.5%). Early endoleaks were noted in 4 patients (19.0%). One patient died during follow-up (mean, 21.3±11.6 months) due to a de novo aortic dissection. Persistent early endoleaks were noted in 4 patients (19.0%); 2 of the 4 patients were successfully managed with implantation of additional stent-grafts. No late onset endoleaks were noted. The death-free survival and re-intervention-free survival rates during follow-up were 85.7% and 90.5%, respectively.

Conclusion: Hybrid treatment with supra-aortic vessel transposition and endovascular repair may be an option in frail patients in whom open procedures are too risky.

Early changes of left ventricle deformation indices after transcatheter aortic valve implantation. A speckle tracking echocardiographic study

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Purpose: Transcatheter aortic valve implantation (TAVI) has been established as a reliable alternative treatment in high risk patients, resulting in symptoms and left ventricle function improvement. The aim of this study was to evaluate the impact of TAVI on early recovery of left ventricle function using echocardiographic left ventricular deformation parameters and to define their possible correlation with myocardial function.

Methods: In 16 patients (6 females, 81±5 years; EuroScore: 24±4%) with severe aortic stenosis but free of significant coronary artery disease who underwent TAVI with the CoreValve® System (Medtronic CoreValve, Minneapolis, Minnesota) by transfemoral (71%) or subclavian (5%) approach. Demographic, procedural and baseline biological data obtained in all patients were analyzed. Blood samples including inflammatory parameters were taken during 7 days after TAVI. Statistical study analyzed correlation between inflammatory parameters including SIRS (defined as recommended guidelines) with demographic and periprocedural data. Influence of inflammatory variables on in-hospital and late outcome was analyzed.

Results: The mean age was 83±6.1 years, mean logistic EuroSCORE was 21±14. Twenty eight patients (36%) developed SIRS during the first 72 h after TAVI. SIRS patients were characterized by hyperventilation (78.8%, P<0.001), tachycardia (>76%, P<0.001), leukocytes >12.9×109/L (78%, P<0.005) and fever (89.3%; P<0.001) compared with patients without SIRS. Occurrence of SIRS was associated with significant increase of CRP (p<0.06), CPK-MB (p<0.03), decrease of hematocrit (p=0.005) and mean arterial pressure (p=0.08). In multivariate analyses, increase in leukocyte count at 48h (OR=1.7, p=0.15), tachycardia (OR=4.4, p=0.005) and anemia (OR=1.4, p=0.03) were predictive of SIRS. Fifty seven percent of patients had a significant elevation of CRP after TAVI (p<0.04). Increasing CRP was correlated with Glomerular Filtration Rate (GFR) decrease (p=0.11), fibrinogen (p=0.001) and leukocyte count increase (p=0.06). Temperature ≤36.0°C or ≥38.0°C was the only independent predictive factor of CRP elevation (p=0.01). SIRS and CRP values weren’t related to 30-day and 6-months mortality.

Conclusion: SIRS and CRP elevation are frequently observed after TAVI. Increase in leukocyte count, tachycardia and anemia are predictive of SIRS. Increasing CRP is correlated with GFR decrease. Temperature ≤36.0°C or ≥38.0°C was the only independent predictive factor of CRP elevation. This study doesn’t confirm that the inflammatory syndrome is associated with poor outcome at 30 days and 6 months.

Incidence, predictive factors and prognostic value of inflammatory reaction following transcatheter aortic valve implantation (TAVI)

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Purpose: Systemic inflammatory response syndrome (SIRS) which occurs following cardiovascular surgery is implicated in undesirable physiological alterations and may be associated with adverse clinical events. The incidence and consequences of inflammatory reactions that occur after TAVI are largely unknown. Therefore, we aim to assess predictive factors and impact of inflammatory reaction on outcome after TAVI.

Methods: Between July 2008 and January 2012, we included 76 consecutive patients who underwent TAVI for symptomatic aortic stenosis with the CoreValve® System (Medtronic CoreValve, Minneapolis, Minnesota) by transfemoral (71%) or subclavian (5%) approach. Demographic, procedural and baseline biological data obtained in all patients were analyzed. Blood samples including inflammatory parameters were taken during 7 days after TAVI. Statistical study analyzed correlation between inflammatory parameters including SIRS (defined as recommended guidelines) with demographic and periprocedural data. Influence of inflammatory variables on in-hospital and late outcome was analyzed.

Results: The mean age was 83±6.1 years, mean logistic EuroSCORE was 21±14. Twenty eight patients (36%) developed SIRS during the first 72 h after TAVI. SIRS patients were characterized by hyperventilation (78.8%, P<0.001), tachycardia (>76%, P<0.001), leukocytes >12.9×109/L (78%, P<0.005) and fever (89.3%; P<0.001) compared with patients without SIRS. Occurrence of SIRS was associated with significant increase of CRP (p<0.06), CPK-MB (p<0.03), decrease of hematocrit (p=0.005) and mean arterial pressure (p=0.08). In multivariate analyses, increase in leukocyte count at 48h (OR=1.7, p=0.15), tachycardia (OR=4.4, p=0.005) and anemia (OR=1.4, p=0.03) were predictive of SIRS. Fifty seven percent of patients had a significant elevation of CRP after TAVI (p<0.04). Increasing CRP was correlated with Glomerular Filtration Rate (GFR) decrease (p=0.11), fibrinogen (p=0.001) and leukocyte count increase (p=0.06). Temperature ≤36.0°C or ≥38.0°C was the only independent predictive factor of CRP elevation (p=0.01). SIRS and CRP values weren’t related to 30-day and 6-months mortality.

Conclusion: SIRS and CRP elevation are frequently observed after TAVI. Increase in leukocyte count, tachycardia and anemia are predictive of SIRS. Increasing CRP is correlated with GFR decrease. Temperature ≤36.0°C or ≥38.0°C was the only independent predictive factor of CRP elevation. This study doesn’t confirm that the inflammatory syndrome is associated with poor outcome at 30 days and 6 months.

Abstract P4201 – Table 1

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Pre-Accurate (46)</th>
<th>Post-Accurate (43)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Mean age (years)</td>
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<td>22.4</td>
<td>12.4</td>
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<tr>
<td>Mean logistic EuroSCORE</td>
<td>99</td>
<td>Core/Valve size (mm)</td>
<td>29±24.0±22</td>
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<td>Mortality (%)</td>
<td>2.0</td>
<td>Post-dilation balloon valvuloplasty performed (n)</td>
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<tr>
<td>Vacular complications (%)</td>
<td>5.9</td>
<td>PPM post TAVI (n)</td>
<td>6</td>
</tr>
<tr>
<td>Stroke rate (%)</td>
<td>2.0</td>
<td>PPM post TAVI (n)</td>
<td>1</td>
</tr>
<tr>
<td>PPM post TAVI (%)</td>
<td>10.1</td>
<td>New ppm post TAVI (%)</td>
<td>5</td>
</tr>
</tbody>
</table>

*New pacemaker post TAVI within 30 days of procedure.

PPM (10.1%) post TAVI. There was no significant difference in PPM requirement between the pre and post-Accurath groups (10.9 vs 9.3, p=1.0).

Conclusion: In our cohort, the need for PPM (10%) is lower than previous reports and is independent of the Accurath catheter. We would advocate a high deployment strategy. Further evaluation of the effect of Accurath catheter on PPM requirement in “middle to low” implantation centres is required.

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Mitral regurgitation after transcatheter aortic valve implantation with the Medtronic-CoreValve prostheses: incidence, predictors and impact of bleeding after TAVI

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Background: Mitral regurgitation (MR) is a risk factor on long-term survival in elderly patients who undergo an aortic valve replacement (AVR). The impact of mitral regurgitation in patients who undergo transcatheter aortic valve implantation (TAVI) is unknown. The aim of the study was to assess the influence of MR on survival in TAVI patients treated with a Medtronic CoreValve prostheses.

Methods: In this single center prospective observational study we included 100 patients (age 81±6 years; 40 male) with severe symptomatic aortic valve stenosis who underwent TAVI with the Medtronic-CoreValve bioprosthesis and underwent a post procedural echocardiographic evaluation. Other clinical parameters were obtained from the medical history.

Results: From the patients with an MR grade <3 (n=94) pre-procedural, 14% increased to MR grade ≥3 after TAVI (p=0.002) and from 6 patients with moderate to severe MR pre-procedural only one patient had a MR grade <3 after TAVI. Forty percent of the patients with significant grade (≥3) MR died within 1 year versus 20% of the patients with MR grade <3 (p=0.051); 30-day mortality and 30-day cardiovascular mortality were not influenced by MR grade ≥3 following TAVI.

Conclusion: After TAVI with a CoreValve prosthesis there is a significant increase in MR grade in patients with MR grade <3. One year survival shows a tendency to be impaired in patients with a significant MR post TAVI.

Renal outcome after transcatheter aortic valve implantation

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Background: Renal function impairment is a frequent complication after cardiac valve procedures. Data on risk factors for renal impairment after transcatheter aortic valve implantation (TAVI) are limited.

Methods and Results: In 299 consecutive TAVI patients (mean age 80.4±7.12 years; 54.8% women) we assessed renal function through plasma creatinine measurement and estimated glomerular filtration rate at baseline, peak during 72 h post procedure and at discharge and monitored individuals for incident renal failure (none, 213 (71.2%); stage 1 renal impairment, 62 (20.7%); stage 2, 15 (5.0%); and stage 3, 9 (3.0%). Mean creatinine concentrations in the sample were 1.10 (0.90-1.50) mg/dl at baseline and MDRD estimated glomerular filtration rate resulted in 56.63±23.30 ml/min/1.73 m². As expected, logarithmically transformed baseline creatinine was related to incident renal failure (Odds ratio [OR] 1.91, 95% confidence interval [CI] 1.19-3.10, P=0.007). Correlates of renal failure besides age and sex in age and sex-adjusted logistic regression analyses were body mass index (OR 1.09 95% CI 1.03-1.15, P<0.001) and logarithmically transformed procedure time (OR 2.24, 95% CI 1.08-4.70, P=0.03). In linear regression analyses procedure time was strongly related to peak change in glomerular filtration rate.

Conclusions: Besides age and sex, body constitution and procedure time are correlates of acute kidney injury after TAVI. When assessing periprocedural risk these factors should be considered in particular in elderly patients with pre-existent renal impairment.

Predictors of mortality post balloon aortic valvuloplasty, results from the BRAVO registry

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Purpose: There have been notable advances in balloon aortic valvuloplasty (BAV) technique including RV pacing and improved management of the large sheath access site. However, a subgroup of patients continues to have poor outcomes despite intervention, and prognostic variables have not been identified in a contemporary context. We sought to examine the correlates of 1-year mortality from a recent BAV registry.

Methods: We conducted a retrospective review of patients who underwent non-emergent, retrograde BAV at two high volume centers from 1/1/2005 - 31/5/2010. Baseline demographic, laboratory, hemodynamic, and procedural characteristics were compared according to 1-year survival post-index BAV procedure. From
Off-label indications for trans-catheter aortic valve implantation

Three patients were included: 1) pure severe aortic insufficiency, bicuspid aortic valve stenosis, and prosthetic valve severe mitral regurgitation.

In all patients implantation of valve was successful: 6 patients received Edwards-Sapien valve (3 trans-axillary and 3 transfemoral) and 5 patients received Edwards-Sapien (4 trans-axial and 1 trans-femoral). In-hospital mortality was 0%. Valve hemodynamic end function were excellent except patient 1 who received Edwardsinside a Mitroflow prosthetic aortic valve in whom trans-aortic gradients remained high. In AR and MR cases, no significant residual regurgitation was observed.

Conclusions: TAVI is good alternative to surgical AVR in high-risk patients with severe AS. TAVI for off-label indications such as pure aortic insufficiency, bicuspid aortic valve stenosis, and failed prosthetic valve (both aortic and mitral), is feasible and safe may be considered in selected patients.

Incidence and predictors of combined safety endpoints occurrence after transcatheter SAPIEN XT and CoreValve implantation. A single Centre experience

Methods and Results: We enrolled consecutive patients undergoing TAVI with Edwards SAPIEN XT – SXT (Edwards Lifesciences, Irvine, California; n = 50) or Medtronic CoreValve – CoV (Medtronic Inc, Minneapolis, Minnesota; n = 50). A good device success was achieved with both SXT and CoV (98% versus 90%, p = 0.20). After TAVI, transthoracic echocardiography and aortography showed higher paravalvular regurgitation incidence with CoV (p < 0.0001) without differences in terms of moderate/severe regurgitation among groups (p = 0.03, SXT versus CoV). In-hospital, major vascular complications (p = 1.00), life-threatening bleedings (p = 1.00), stroke (p = 1.00) and death (p = 1.00) occurrence were similar throughout SXT and CoV. A statistical trend toward worse renal function after CoV implantation was observed (p = 0.056). Permanent PM need was more frequent after CoV implantation (p < 0.0001). At 1-month follow-up, cumulative VARC-combined safety endpoints incidence was 17% versus 34.6% (p = 0.01, SXT versus CoV), mainly driven from a numerically higher stroke (10%) and Acute Kidney Injury Stage 3 incidence (6%) associated with CoV. At multivariate analysis, TAVI with SXT (odds ratio - OR 0.20, 95% confidence intervals - CI [0.05- 0.86]; p = 0.03) and a previous percutaneous coronary revascularization history (OR 0.08, [0.008-0.94]; p = 0.04) were found protective against safety endpoints occurrence.

Conclusions: Together with a previous history of percutaneous coronary revascularization, TAVI with Edwards SAPIEN XT was found independent predictor of lower VARC-combined safety endpoints occurrence, as compared with Medtronic CoreValve. Larger cohorts are needed to confirm these results.

Impact of acute normobaric hypoxia on regional myocardial function: a speckle tracking echocardiography study

Aim of this study was to evaluate the influence of hypoxia on myocardial function.

Methods: Fourteen subjects underwent two-dimensional speckle tracking echocardiography (2D-STE) examination during normoxia and in a normobaric hypoxia chamber. Examinations were performed at rest and during bicycle exercise test. The following parameters were quantified in both atria and ventricles: Strain (S), systolic strain rate (SRS), early (SRE) and late (SRA) diastolic strain rate. In addition, left ventricular (LV) overall twist, systolic twist- and diastolic untwist rate were quantified.

Results: During hypoxia SRS and SRE increased significantly in both ventricles compared to baseline. The increase of LV SRS and SRE during normoxic exercise was significantly higher when compared to baseline under hypoxia (for SRS: 0.55±0.22 vs. -0.34±0.24 1/s, p = 0.024; for SRE: 0.56±0.29 vs. 0.23±0.29 1/s, p = 0.005). For the right ventricle (RV) no significant difference of exercise induced increase of systolic-strain (SRS) (-3.07±0.52 under normoxia vs. -1.28±0.24 1/s under hypoxic conditions, p = 0.47) was observed. LV overall twist, systolic twist- and diastolic untwist rate were enhanced during hypoxia. A shift from passive conduit (S) to active contraction (SRE) phase during hypoxia was noted for the right atrium (SRE/SRA 0.72±0.13 under hypoxia vs. 1.71±0.17 under normoxia). SRE/SRA of RA correlated to systolic pulmonary pressure (r = -0.78, p = 0.01) (Figure 1).

Conclusions: Exposure to normobaric hypoxia leads to an increase of LV overall twist and regional myocardial deformation in both ventricles. The contractile reserve during hypoxic exercise is reduced in LV. In addition, hypoxia had an impact on the ratio of passive conduit to active contraction phase in right atrium.

Inhibition of Interleukin-1 activity by anakinra improves left ventricular myocardial deformation and torsion in patients with CAD and coexistent rheumatoid arthritis: a randomized trial

Background: Inhibition of Interleukin-1 activity by anakinra is used for the treatment of rheumatoid arthritis (RA) and shows favourable effects on left ventricular function in these patients. We investigated the effects of anakinra on LV function in patients with CAD and coexistent RA.

Methods: 40 patients with CAD and coexistent RA were randomized to receive a single injection of anakinra (100mg s.c.). At baseline and 3 hours after the injection we assessed: a) WMSI and EF by 2D echocardiography b) the LV Global systolic deformation (GSD) c) systolic (Sm) and early diastolic (Em) myocardial velocities of the mitral annulus by using tissue Doppler (TDI) d) the ratio of E wave of the mitral inflow measured by pulsed wave Doppler to the Em e) Fas, Fas ligand, nitrotyrosine (NT) and TNF-α. To evaluate LV twist and torsion we selected the LORECA method.

Results: At 3 hours of anakinra injection, there were an increase in Sm (7.2±1.7, vs. 9.1±1.2 cm/s) and Em (7.7±2.7 vs. 9.1±3.1 cm/s) velocity along with a decrease in the E/Em ratio (12.1±10.2, vs. 9.5±7.9) (p < 0.001). Furthermore, there were an improvement in torsion (14.2±5.6, vs. 18.2±5.5 degrees) and GSD (-16.2±4.7, vs. -19.0±4.9), as well as WMSI (1.33±0.43 vs. 1.21±0.31) and EF (51.8±10.0% vs. 57.6±10.9%), compared to baseline (p < 0.001). Additionally, there were a decrease in NT (median 6.66 vs. 6.15), PC
Prognostic significance of speckle tracking-derived multivessel coronary disease

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Purpose: We aimed to identify prognostic factors in unsellected cohort of patients with multivessel coronary disease (MCD) among parameters derived from: state of the art echocardiographic assessment including speckle tracking echocardiography (STE), functional tests including diastolic exercise testing and 6-min walk test (6MWMT) and full biochemistry panel including besides traditional risk factors NT-proBNP, CRP, HbA1c, thrombomodulin, von Willebrand Factor, and carotid disease.

Materials & Methods: 83 patients with recent diagnosis of stable MCD (at least two vessels with stenosis > 70% in coronary angiography), age 63.4±9.2 years, were followed up for approximately 20 months (21.3±31) to assess the occurrence of primary end-point: End1 (all cause death or myocardial infarction) and secondary end-point: End2 (mortality, myocardial infarction, cardiac hospitalization or need for unplanned revascularization). Mean LVEF was 49.5±10.2% and predominant angina class was CCS III (69%). The management was individualized based on heart team decision in 55% angioplasty and 22% bypass grafting rate.

Results: There were 3 deaths (3.6%), 12 MI (14%), 4 ischemic strokes (5%), 36 hospitalizations (43%) and 11 unplanned revascularizations (13%) during the follow-up period. In univariate analysis the following prognostic factors of End1 were identified: age > 60 years (p = 0.003), HbA1c < 7% (p = 0.003), leukocytosis (WBC) > 9.5 x 10^3/μl (p = 0.001), 6MWMT > 270 [m] (p = 0.007), global systolic longitudinal strain rate (GLSR) < 0.8 [1/μs] (p = 0.002), left ventricle torsion < 11.8 [°/s] (p = 0.03), diabetes (p = 0.02). End2 was predicted by HbA1c > 6.65% (p = 0.0003), WBC > 7.2 x 10^3/μl (p = 0.0001) and left ventricular rotation at papillary muscle level > 1.5 [°] (p = 0.02) in univariate analysis. In multivariate analysis WBC > 9.5 x 10^3/μl, HbA1c > 7.3% and GLSR < 0.8 [1/μs] were independent predictive factors for End1. Only HbA1c level > 6.6% and WBC > 7.2 x 10^3/μl I remained as multivariate predictors of End2.

Conclusions: The results of our study confirm the importance of established systematic risk factors: hypergycemia defined by HbA1c and inflammatory conditions (leukocytosis). However, novel echocardigraphic parameters derived by STE, especially GLSR and left ventricle torsion, emerge as predictors of adverse outcome superior to traditional echocardiographic indices. Novel biomarkers and functional tests did not prove functional usefulness in this group of patients.

Left ventricular torsion and its relation to functional capacity in hypertensive patients

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Purpose: In patients (pts) with hypertension (HA) left ventricular (LV) apical rotation at rest and torsion can be predictors of LV functional reserve. The aim of our study was to asess the relationship between apical rotation and torsion of LV at rest and functional capacity in pts with HA.

Methods: A total of 100 hypertensive patients (pts aged 50±11 years, 16 women and 24 men, with slightly elevated body mass index (28±3 kg/m²) and first/second degree hypertension. We performed standard two-dimensional and Doppler echocardiography (2DE) and carotid Doppler examination (CPET) using “breath by breath” method, measuring oxygen uptake (VO2) at anaerobic threshold (AT).

Analysis of echocardiographic data was done offline, using EchoPAC workstation.

Results: In 45 out of 50 pts with preserved LV systolic function, we measured normal diastolic function and 32 had diastolic dysfunction of first/second degree, 22 pts (55%) had concentric remodeling. We found following average values of 2DE and 4DE parameters: left ventricular mass 27±7.4 mm², relative wall thickness 0.44±0.07, end-systolic volume 51.5±13.5 mm³, diastolic end-systolic volume 109.39±22.6, LV ejection fraction 56±3.5%, apical rotation 5.87±3.23deg, apical rotation rate S-wave 48.46±19.95deg/s, apical rotation rate E-wave -46.88±22.16deg/s, apical rotation ratio A-wave -31.51±16.29deg/s, apical circumferential strain -12.51±3.62% LV torsion 10.05±4.2deg. Average VO2 at AT was 18.92±4.17ml/kg/min. We established significant negative correlation between VO2 at AT and apical rotation (r=-0.361, p=0.028), rotation ratio S-wave (r=-0.342, p=0.039) and LV torsion (r=-0.433, p=0.008). According to Regression Model apical rotation was selected to be the strongest independent negative predictor of VO2 at AT (β=-0.36, p=0.034). In respect to demographic and 2DE parameters of LV function and risk of progression to arterial hypertension the following parameters showed significant positive correlation between apical rotation and torsion and age (rotation)=0.32, p=0.043; torsion)=0.37, p=0.016 and left atrial mitral annular velocity (rotation)=0.32, p=0.042; torsion)=0.38, p=0.013.

Conclusions: Our data showed that older age and diminished LV compliance resulted in increased apical rotation at rest and torsion of LV and also, that namely pts with higher values of apical rotation at rest had lower functional capacity expressed through AT.
**Conclusion:** Delayed LV diastolic relaxation is seen in healthy chronic smokers, even after abstinence from smoking for several hours. Acute smoking inhalation induces a further delay in diastolic relaxation while systolic function is preserved.

**Methods:** In 25 patients with first-time acute ST elevation myocardial infarction, myocardial viability was assessed using 2DSTE and ceMRI to predict recovery of function at 6 months follow-up. For each left ventricular segment in a 16-segment model, peak radial, circumferential and longitudinal strain was determined using 2DSTE (EchoPAC, GE Ultrasound, Horton, Norway), and the relative extent of hyperenhancement using ceMRI.

**Results:** Of 192 segments with impaired function early after AMI, 65 showed regional recovery. Compared with segments showing functional improvement, those that failed to recover had lower peak radial (18.1% ± 34.2%; p < 0.001), circumferential (18.7% ± 19.0%; p < 0.001) and longitudinal (-19.5% vs. -13.8%; p < 0.001) strain and a greater extent of hyperenhancement (71.2% ± 25.0% vs. p < 0.001). Among strain parameters, circumferential strain yielded greater area under the curve (0.914) than radial and longitudinal strain (0.717 and 0.743, respectively). The predictive value of circumferential strain (sensitivity 80.3%, specificity 81.2%, at a cutoff value of 12.5%) could be compared to that of hyperenhancement by ceMRI (sensitivity 87.8%, specificity 88.1%, area under the curve 0.939, at a cutoff of 46% hyperenhancement).

**Conclusions:** Myocardial deformation imaging based on 2DSTE is a powerful novel modality to identify reversible myocardial dysfunction after AMI.

**Evaluation of left ventricular segmental strain by three-dimensional echocardiography**


**Background:** Three-dimensional speckle tracking imaging (3DS) allows assessment of regional strain with high accuracy.

**Aims:** To validate the feasibility of 3DS in comparison to two-dimensional speckle tracking imaging (2DS).

**Methods:** Forty-nine subjects (all women, age 63 ± 12 years) contributed to the present analysis. The feasibility of regional data collection and estimates of regional strains differ between 3DS and 2DS. It is still unclear whether feasibility of regional data collection and estimates of regional strains differ between 3DS and two-dimensional speckle tracking imaging (2DS). We examined this issue in the present study.

**Methods:** Standard 2D echocardiography and 3D data set collection by using Vivid E9 with 4V probe (GE Healthcare) were performed in 212 subjects, who participated in an annual health examination. Apical long axis, four chamber and two chamber views were recorded to assess longitudinal strain by 2DS. 3DS and 2DS were analyzed off line by EchoPAC(GE Healthcare). We excluded subjects in whom 4 or more of 18 LV segments were unsuitable for strain determination, and 49 subjects (all women, age 63 ± 12 years) contributed to the present analysis.

**Results:** The feasibility of 3DS was lower at LV base level (Figure). There were significant differences between strain by 3DS and longitudinal strain by 2DS in the mid-anterosertal (-25.3% vs. 21.4%, p < 0.0001), mid-lateral (-18.1% vs. -24.3%, p = 0.0001), mid-posterior (-23.7% vs. -18.9%, p < 0.0001) and mid anterior strain (-25.9% vs. -19.0%, p = 0.0001). Strain in the other segments and global strain were similar in 3DS and 2DS.

**Conclusions:** There are regional differences in feasibility of 3DS and data agreement between 3DS and 2DS. 3DS provides significantly lower estimates of strains in mid-level of the ventricle compared with 2DS.
Assessment of left ventricular myocardial deformation and mechanical dysynchrony in patients with heart failure: insights from three-dimensional wall motion analysis

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Purpose: Impaired myocardial contractility is detected with two-dimensional speckle tracking echocardiography (2DSTE) in heart failure patients with normal ejection fraction (HFNEF); however, 2DSTE is limited by ignorance of actual three-dimensional myocardial motion. Therefore, this study is aimed to further explore the myocardial function including the global dysynchrony in HFNEF with three-dimensional speckle-tracking echocardiography (3DSTE) which circumvent the limitations of 2DSTE.

Method: We enrolled thirty-three healthy subjects (48±12 years; 48.5% male), 53 patients with HFNEF (70±10 years; 56.6% male) and 41 with reduced ejection fraction (HFREF) (65±10 years; 87.5% male) in our study. 3D-STE was performed (Toshiba Medical Systems, Japan) to obtain global area strain (AS), longitudinal (LS), circumferential (CS) and radial strain (RS). For LV dysynchrony, AS-systolic dys synchrony index (AS-SDI) was calculated from the standard devi ation of time to peak segmental AS of 16 segments.

Results: Global AS, CS, LS and RS in patients with HFNEF were significantly higher than their counterparts with HFREF (all p < 0.001) but lower than in the normal group (all p < 0.05) (Table 1). Intriguingly, AS-SDI was significantly pro longed in patients with HFREF when compared with the control group (16.3 ms vs. 74.9±18.9 ms vs. 35.7±16.3 ms; both p < 0.001 vs. control), and was more severe in the HFREF group (p < 0.001). Based on normal cutoff value of ≥ 68ms, the prevalence of LV systolic dys synchrony was significantly higher in HFREF than that in patients with HFNEF (61.0% vs. 20.8%, chi-square = 15.83, p < 0.001).

Conclusions: As a combination of both LS and CS, not only can 3D-derived global AS accurately detect subtle myocardial dysfunction in HFNEF, it can also assess LV dysynchrony more comprehensively in a 16-segmental mode during one cardiac cycle, which might be promising for further exploring the pathophysiology of HFNEF.

Area strain for the assessment of regional left ventricular wall thickening using 3D Speckle Tracking

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Background: 3D speckle tracking is a promising new technology. It allows reconstructing LV motion in time and space. Shortening in the longitudinal and circumferential directions can be combined in an area strain (aS) measurement which in contrast to wall thickening (radial strain) does not require endo- and epicardial border detection. We investigated the relation between aS and wall thickening by two geometrically independent measurements.

Methods: In 12 patients, 3D full volume echocardiographic clips of the LV were acquired. 3D endo- and epicardial border detection was performed to calculate wall thickening, whereas 3D speckle tracking was used to assess aS. All geometric measurements were performed frame-by-frame at 336 sites on refined endocardial boundaries.

Results: S27±22 wall thickness – aS datapairs were retrieved. In ROC analysis, an aS >−15.3% was able to detect a systolic wall thickening >−20% with a sensitivity of 83.2% and a specificity of 80.2%. The area under the ROC curve was 0.88. As expected from deformation theory, there was a nonlinear relation between wall thickening and aS (Poisson effect). The estimated Poisson’s ratio of myocardium was 0.39, showing even the compressible nature of myocardial tissue should be considered by applying a Poisson’s ratio below 0.50.

Conclusion: aS derived from 3D speckle tracking reflects local wall thickening during the cardiac cycle and has the potential to detect regional contraction abnormalities. In principle, aS can be converted directly into radial strain using basic elastic deformation formulas (Poisson effect), but the compressible nature of myocardial tissue should be considered by applying a Poisson’s ratio below 0.50.

Myocardial function left ventricular deformation


Purpose: To assess the prevalence of LV systolic dyssynchrony was significantly higher in HFREF patients than in HFNEF patients.

Method: We selected for this analysis all those exams that were coincident with no transplantation within 5 hours of the routine surveillance endomyocardial biopsy procedure and with histologically proven absence of rejection at the moment of the procedure.

Results: We enrolled thirty-three healthy subjects (48±10 years; 56.6% male) and 41 with reduced ejection fraction (HFREF) (65±10 years; 87.5% male) in our study. 3D-STE was performed (Toshiba Medical Systems, Japan) to obtain global area strain (AS), longitudinal (LS), circumferential (CS) and radial strain (RS). For LV dysynchrony, AS-systolic dys synchrony index (AS-SDI) was calculated from the standard devi ation of time to peak segmental AS of 16 segments.

Conclusions: Our results demonstrated that DR was detected in 19% of type 2 diabetes patients without DR (14 vs. 8 patients, P < 0.01). Conventional echocardiography showed no differences in LV ejection fraction (63.6±6.4% vs. 64.8±5.9%) and LV mass index (200±47 vs. 203±62 g/m²) between the 2 groups (P = 0.05). However, pts with DR had a longer disease duration than patients without DR (14±8 vs. 9±7 years, P = 0.01). Conventional echocardiography showed no differences in LV ejection fraction (63.6±6.4% vs. 64.8±5.9%) and LV mass index (200±47 vs. 203±62 g/m²) between the 2 groups (P = 0.05). However, pts with DR had a significantly lower LV global longitudinal strain (-18.3±1.21 vs. -18.13±1.22%, P = 0.05) and strain rate (-0.84±1.55 vs. -0.95±1.33, P = 0.05) compared with pts without DR. After adjustment with age, gender, Hba1c, duration of disease and conventional cardiovascular risk factors, multivariate linear re-gression revealed that DR was independently associated with impaired LV global longitudinal strain rate (β =−0.28, confidence interval [CI]=0.17 to 0.00, P < 0.01), but not LV global strain (β =−0.18, CI=0.22 to 0.00, P=0.09).

Conclusion: To our knowledge, this is the first study describing normal values of area strain by 3DSTE in heart transplants recipient in the first year after the procedure and with histologically proven absence of rejection at the moment of the evaluation.

Diabetic retinopathy is associated with the occurrence of subclinical diabetic cardiomyopathy in patients with type II diabetes

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Purpose: To assess whether diabetic retinopathy (DR) is an independent predictor of subclinical diabetic cardiomyopathy in patients with type 2 diabetes (DM).

Method: We performed a prospective, observational, longitudinal study of 40 type 2 DM patients (52.9±12.4 years; 53% female) without overt CVD. Full-dose fundus photography with standard fields in 114 type 2 DM pts (62.9±12.4 years; 53% female) without overt CVD. Detailed transthoracic echocardiography was performed to measure global left ventricular (LV) function, including longitudinal strain and strain rate.

Results: DR including both non-proliferative and proliferative retinopathy was detected in 22 pts (55%). There were no significant differences in age (63.6±6.2 vs. 62.1±10), female gender (50 vs. 56%), fasting glucose (7.5±2.5 vs. 7.4±1.9 mmol/L) and HbA1c (8.0±1.3 vs. 7.6±1.2%) between pts with or without DR (all P > 0.05). However, pts with DR had a longer disease duration than patients without DR (14.9±8 vs. 9.7±7 years, P < 0.05). The area under the ROC curve was 0.88. As expected from deformation theory, there was a nonlinear relation between wall thickening and aS (Poisson effect). The estimated Poisson’s ratio of myocardium was 0.39, showing the compressible nature of myocardial tissue should be considered by applying a Poisson’s ratio below 0.50.

Conclusion: Our results demonstrated that DR was detected in 19% of type 2 DM pts without overt CVD. The occurrence of DR was independently associated with subclinical LV myocardial dysfunction as detected by two-dimensional speckle tracking imaging. The findings of the study suggested that microvascular
Ejection fraction and deformation in response to effects of radiotherapy on right and left heart function

Purpose: Evaluation of cardiac function is mandatory for cancer patients who receive potentially cardiotoxic (CTX) regimens, in whom analyses of ejection fraction (EF) and myocardial mechanics have shown subclinical myocardial damage. We sought to define the demographic, clinical and chemotherapy regimens associated with CTX.

Methods: We enrolled 166 patients (50±14, 77 women) receiving anthracycline 214±112 mg/m² (group A, n=65), trastuzumab (group T, n=53) or with A dose 213±89 mg/m² (group AT, n=48). Conventional echo indices (EF, mitral annular s’ and e’ velocity) and myocardial deformation indices (global longitudinal peak systolic strain [GLS], strain rate [SR-s] and early diastolic strain rate [SR-e] from speckle tracking) were measured at baseline and follow-up (10±8 months). The association of regimen with ΔEF was sought in a multiple linear regression (p<0.05).

Results: Age (p=0.03), gender (p=0.001), dyslipidemia (p=0.03), and radiation therapy (p=0.001) were significantly different among three groups. Reduction of EF was in group AT (Fig. 1: ΔEF reduction in EF ≤ 10% occurred in 6 group A, 0 group T and 4 group AT patients. SRs significantly decreased in groups T and AT. There were no significant differences in s’, e’, GLS and e’ among the groups. Combination regimen (group AT) was correspondently associated with ΔEF after adjusting for age, gender, dyslipidemia and radiation therapy (p=0.011, 0.522, 95% CI [-1.342 to -0.564]).

Figure 1. The change in EF and SRs.

Conclusion: Combined A+T is most conducive to reduced EF and SR-s is reduced in T and A+T. Some patients are sensitive to anthracycline and/or radiation therapy. Careful assessment of LV dysfunction is warranted in all patients receiving CTX agents.

Ejection fraction and deformation in response to three different chemotherapeutic regimens

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Purpose: Evaluation of cardiac function is mandatory for cancer patients who receive potentially cardiotoxic (CTX) regimens, in whom analyses of ejection fraction (EF) and myocardial mechanics have shown subclinical myocardial damage. We sought to define the demographic, clinical and chemotherapy regimens associated with CTX.

Methods: We enrolled 166 patients (50±14, 77 women) receiving anthracycline 214±112 mg/m² (group A, n=65), trastuzumab (group T, n=53) or with A dose 213±89 mg/m² (group AT, n=48). Conventional echo indices (EF, mitral annular s’ and e’ velocity) and myocardial deformation indices (global longitudinal peak systolic strain [GLS], strain rate [SR-s] and early diastolic strain rate [SR-e] from speckle tracking) were measured at baseline and follow-up (10±8 months). The association of regimen with ΔEF was sought in a multiple linear regression (p<0.05).

Results: Age (p=0.03), gender (p=0.001), dyslipidemia (p=0.03), and radiation therapy (p=0.001) were significantly different among three groups. Reduction of EF was in group AT (Fig. 1: ΔEF reduction in EF ≤ 10% occurred in 6 group A, 0 group T and 4 group AT patients. SRs significantly decreased in groups T and AT. There were no significant differences in s’, e’, GLS and e’ among the groups. Combination regimen (group AT) was correspondently associated with ΔEF after adjusting for age, gender, dyslipidemia and radiation therapy (p=0.011, 0.522, 95% CI [-1.342 to -0.564]).

Figure 1. The change in EF and SRs.

Conclusion: Combined A+T is most conducive to reduced EF and SR-s is reduced in T and A+T. Some patients are sensitive to anthracycline and/or radiation therapy. Careful assessment of LV dysfunction is warranted in all patients receiving CTX agents.
by speckle tracking derived right ventricular (RV) and left ventricular (LV) global longitudinal peak systolic S and SR, obtained before, early after and at 1 month follow-up after RT.

Results: Total radiation dose delivered was 51.7±4.9 Gy in LSBC group, 54.7±9.1 Gy in LSLC group. The mean dose to the heart was 6.3±4.5 Gy and the mean heart volume receiving 30 Gy (V30) was 7.3±6.5% in LSBC group. In pts with LSLC, the mean dose to the heart was 21.5±7.2 Gy and V30 was 30.1±10%. Compared to baseline, RV-S was significantly decreased early after RT and at first month follow-up in both groups (-23.3±4.3 vs. -19.9±3.4 vs. -19.6±3.8, respectively, p<0.001, in LSBC group). RV-SR changed significantly in pts with LS (1.57±0.3 vs. -1.36±0.28 vs. -1.24±0.29 respectively, p<0.001) although we did not note any significant change in pts with LSLC (<1.9±0.26 vs. -1.26±0.26 vs. -1.09±0.66, respectively, p>0.192). Interestingly, LV-S differed significantly in LSBC group (-20.7±4.4 vs. -19.2±3.6 vs. -19.0±3.7, respectively, p<0.03). No decline in LV deformations was observed in pts with LSBC (<20.03±0.3 vs. -19.6±0.31 vs. -19.5±0.26, respectively, p=0.95).

Conclusion: Pts receiving RT for LSBC and LSLC have decreased RV-S whereas LV-S was only reduced in LSLC group following RT. RV-SR was also decreased in pts with LSLC. Reduction in RV-S and SR is likely due to higher radiation exposure of the right ventricle due to its anterior location. Moreover, high dose radiation exposure to heart reduced LV-S in LSLC group. This study demonstrated RT has a depri effect on both RV and LV S-SR, is first to be reported.

**P4229**

Reduced left ventricular contractility with electrical dyssynchrony increases the dyssynchronization by speckle tracking strain rate analysis

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Background: Left ventricular (LV) dyssynchrony was reported as a useful index for predicting the response to cardiac resynchronization therapy. However, it has not been clear which factors influence on the dyssynchrony in patients with electrical dyssynchrony. Thus, we evaluated the degree of LV dyssynchrony in patients with right ventricular (RV) pacing by speckle tracking strain rate analysis. Methods: Echocardiography was performed in 81 consecutive patients with RV pacing. As a dyssynchrony index, the time difference between 1st peak of LV septum and that of posterior wall (IVS-PW delay) was measured by M-mode at mid-LV level. We used off-line software EchoPAC (GE Ultrasound) for SR analysis and measured radial SR at mid-LV short axis view. The dyssynchrony index (DI) was defined as the ratio of average myocardial thinning (negative SR) to thickening (positive SR) of 6 segments during the ejection period (Figure). Results: Twenty-seven patients were LV ejection fraction (LVEF) <50% (lowEF) and 54 patients were >50% (highEF). Mean value of IVS-PW delay was 30.1±7.3ms, and there was no significant difference between IVS-PW delay of lowEF group and that of highEF group (30.4±5.0ms vs. 29.9±9.3ms, N.S.). DI of lowEF was significantly higher than that of highEF (28±23ms vs. 8±10ms, p<0.001). DI correlated with the LV end-systolic volume (r=0.536, p<0.001), QRS duration (r=0.26, p=0.001). In multivariate analysis, the independent predictor of DI was LVEF (p<0.001).

Figure 1. DI of high EF and low EF

Conclusions: Dysynchrony in patients with RV pacing was constantly high regardless of LVEF, while dysynchrony was enhanced by reduced LVEF. Reduced LV contractility with electrical dyssynchrony increased the dyssynchrony and might cause a vicious circle of LV pump failure.

**P4230**

Effect of left ventricular twisting for the accuracy of two-dimensional longitudinal strain analysis

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Purpose: 2D longitudinal strain (LS) calculation could be influenced by loss of speckles due to left ventricular (LV) twisting motion. 3D speckle tracking echocardiography (STE) is theoretically more accurate for LS measurements. If LV twisting motion affects 2D LS calculation, we hypothesized worst correlation of LS between 2DSTE and 3DSTE was observed at apical level, and best correlation was noted in the middle level due to helical nature of myocardial fibers.

Methods: We acquired 2D apical 4-, 2-chamber and long-axis views and 3D full volume datasets (GE, Vivid E9) in 54 patients with various cardiovascular disease (mean age 64±18 years, 29 male, LVEF 54±12%). Using 2D/3D speckle tracking software, global LS and averaged LS at 3 LV levels (basal, middle and apical) were calculated. In 44 of 54 patients who could be also analyzed LV twist on the 2D short axis views, patients were divided into two groups according to the median value of LV twist (13.4 degree) for investigating the effect of LV twisting.

Results: A good correlation of global LS was noted between the two methods (2DSTE: -15.8±5.3, 3DSTE: -15.4±4.6, r=0.89, p<0.01) with no significant bias (0.4±0.3, N.S.). Correlation of averaged LS and their mean bias were 0.52±0.59 at basal level, 0.89±1.17 at middle level and 0.73±1.46 at apical level, respectively. Correlation of global LS between the two methods was higher in group of patients who had LV twist value less than 13.4 degree (r=0.93) compared to group of patients with LV twist values >13.4degree (r=0.68).

**P4231**

Assessment of left ventricular dysynchrony with real-time 4D ultrasound system: comparison with Doppler Myocardial Imaging

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Background: Different current echocardiographic methods have been proposed to evaluate left ventricular mechanical dyssynchrony (LVMD). The very latest generation of real-time 4D ultrasound systems (RT4DE) have the ability to acquire a full volume dataset in one cardiac cycle. Aim of the study was to compare the assessment of LVMD by Pulsed Wave- Doppler Myocardial Imaging (PW-DMI) and RT4DE.

Methods: 10 healthy volunteers (NL) and 27 pts with left bundle branch block (QRS wide 147±7ms, EF 38±7±12.8%, 66±11ys) and different etiology dilated cardiomyopathy (DCM-LBBB) were studied. RT4DE full volume acquisitions were divided into 16 subvolumes corresponding to the standard myocardial segments to derive timevolume curves for each (TMV). Time to peak contraction (minimum volume) in each segment is normalized for the R-R duration, and 16-SDI-4D is defined as the standard deviation of these timings, expressed as a percentage of cardiac cycle duration. The identification of the latest contracting segment of the LV was studied with TMV Map imaging demonstrating areas of delayed contraction (orange color). Dyssynchrony index by PW-DMI was measured as standard deviation of the time from beginning of QRS to the end systolic velocity in 6 basal segments (6-SDI-PW-DMI).

Results: Data acquisition and analysis with RT4DE was feasible in 35/37 pts (93.9%). The technique provided quick qualitative and quantitative assessment of LVMD in one single heart cycle, during high volumes per second (vps) acquisition (38±14 vps); latest segmental TMV was of apical basal distribution in 3/25 pts, mild basal distribution in 7/25 pts, and basal distribution in 15/25 pts respectively; 16-SDI-4D was significantly higher in the DCM-LBBB group compared with NL (9.7±7.4% vs. 4.1±1.7%, p=0.05).
Brain natriuretic peptide is independently associated with indices of left ventricular filling pressure but not with left ventricular mass in asymptomatic individuals.

Methods: Plasma NT-pro BNP concentrations were measured in 1,593 healthy subjects free of manifest cardiovascular disease, recruited from the London Life Sciences Prospective Population (LOLipop) study. All subjects underwent comprehensive transthoracic echocardiography, including tissue Doppler imaging, for measurement of LV mass, LV ejection fraction and LV filling pressure indices with NT-pro BNP were explored. Increasing age, male gender and European white ethnicity were independently associated with higher NT-pro BNP. There was an independent association of reduced LVEF (β=0.4, p<0.001), increased E/E' (β=0.12, p<0.001) and increased LAVI (β=0.24, p<0.001) with higher NT-pro BNP. An initial significant association observed between increasing LVMi (β=0.13, p<0.001) and higher NT-pro BNP was subsequently abolished after adjustment for LAVI (β=0.06, p=0.41). Type-2 diabetes, hypertension and the presence of LHV were not associated with NT-pro BNP.

Conclusions: NT-pro BNP is unlikely to be a useful biomarker for the detection of hypertrophic LV remodeling, being more closely associated with the morphological parameters of increased LV filling pressure and with LVH.

Decreased velocity propagation of the left ventricle is associated with increased arterial stiffness.

Methods: We studied 113 consecutively newly diagnosed EH patients stage I-III (age 51±12.41% females) without prevalent cardiovascular disease. All patients underwent: a) complete conventional and Tissue Doppler Imaging (TDI) echocardiographic study, b) assessment of heart rate-corrected augmentation index (AIx75) using Sphygmocor, and c) a 24-hour ambulatory blood pressure monitoring (ABPM). The study population was divided into two groups according to the median value of velocity propagation (VP): group A (n=57, VP<95cm/sec) and group B (n=56, VP≥95cm/sec).

Results: The two groups did not differ regarding age, gender, 24hr systolic and diastolic BP. Group B compared to A had significantly higher values of AIx75 (71.2±31.4 vs 50.3±19.5; p<0.045) and minimum volumes (44.4±28.4 ml vs 22.3±10.3; p<0.039) and lower LA ejection fraction (39.9±14.9 ml vs 55.7±19.0 ml; p<0.047). Also, TDI in group B had significantly lower values of Sm, Em and Em/Am ratio (7.1±5.2 vs 3.7±2.5; p=0.03) and LA ejection fraction presented a significant negative correlation with LAV/A’ ratio (r=-0.43, p=0.042). Area under the receiver operating characteristic curve to diagnose elevated left ventricle filling pressures by LA ejection fraction was 0.814 (66.3; 95.7%).

Conclusions: LA ejection fraction by 3D echocardiography recognizes patients with elevated left ventricle filling pressures, therefore it might be valuable alternative at time of diastolic function evaluation.
Diagnostic value of exercise E/E' ratio for the early detection of diastolic heart failure in non-obstructive HCM patients

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Background: Heart failure in patients with diastolic dysfunction has a 25% five year mortality. It is likely that early detecting patients with diastolic abnormalities will lead to favorable prognosis and survival. Recently, studies on tissue Doppler imaging (TDI) have found that the ratio of the peak early diastolic velocity of mitral annulus (E/E') has good correlations with diastolic function. It is still unclear how the indices of diastolic function will change for those non-obstructive hypertrophic cardiomyopathy (HCM) patients. The objective of this study was to test the diagnostic value of exercise E/E' ratio for the early detection of diastolic heart failure (DHF) in non-obstructive HCM patients.

Methods: Echocardiography was performed in 54 non-obstructive HCM patients with normal LVEF and 61 controls before and immediately after cardiopulmonary exercise testing (CPET). According to the level of E/E' ratio, the patients were divided into three subgroups: group a: E/E' ratio < 10 both before and after exercise; group b: early DHF, E/E' ratio < 10 before exercise but ≥ 10 after exercise; group c: early DHF, E/E' ratio ≥ 10 both before and after exercise.

Results: (1) The E/E' ratio of patients elevated after exercise (P < 0.01), but that of the controls didn’t. (2) The VE/VCO2 slope of the patients (28.8 ± 5.2) was higher than that of the controls (26.9 ± 5.7) (P < 0.01), but the VO2max of the patients (50.2 ± 12.5) was lower (24.3 ± 5.2) than that of the controls (27.6 ± 3.9) (P < 0.01). (3) In the patients, exercising E/E' ratio had good correlations with exercising S' lateral, exercising E' lateral, and VE/VCO2 slope (P < 0.05 → 0.01). (4) About 1/5 of the patients were found to be early DHF.

Conclusions: Exercising E/E' lateral ratio can detect early DHF in non-obstructive HCM patients. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Diastolic tissue doppler velocities predicts adverse outcome after st-elevation myocardial infarction treated with primary percutaneous coronary intervention

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Purpose: To investigate which diastolic echocardiographic parameters that best predict prognosis after an ST-elevation myocardial infarction (STEMI).

Method: From September 2006 to December 2008, 391 patients were admitted with a STEMI, treated with primary Percutaneous Coronary Intervention (pPCI). All patients were examined by echocardiography 1-5 days after the STEMI (median 2 days, IQR 1-3). In total 26 patients were excluded, 14 due to atrial fibrillation and 12 due to inadequate quality of the echocardiographic examination. Treatment effect was assessed in relation to death (n = 29), hospitalization with clinical signs of heart failure (CHF, n = 48) and re-MI (n = 25). Follow-up time was from 25 to 139 months (IQR 19-92 months).

Results: The diastolic color tissue Doppler velocities, global e' and a', were the only diastolic parameters that remained as independent predictors of the combined outcome (Death, CHF, and re-MI) in a multivariable Cox regression analysis using forward selection including all diastolic parameters and age, previous myocardial infarction (pre-MI) and peak troponins (Tnl). Even after adjusting for Tnl, e' 2.32 (1.20–4.49, P = 0.013) and a' 1.00 (0.56–2.30, P = 0.72) were independent predictors of the combined endpoint with a hazard ratio of 1.18 (1.01–1.39) per 1 cm/s decrease (p = 0.045). Patients who had values of both e' and a' below the median, had more than double the risk of an adverse outcome than patients with both e' and a' above the median (See Table). Cox regression model depicting the risk of reaching the combined endpoint for patients stratified according to e' and a' higher or below the median (cut-off points 5.4 cm/s for e' and 6.4 cm/s for a' respectively).

Conclusions: The diastolic tissue Doppler velocities seem superior to the conventional echocardiographic diastolic parameters in terms of predicting prognosis after pPCI for patients with STEMI. The early and late diastolic tissue velocities should be evaluated together as they interact on prognosis.

Presence of preoperative diastolic dysfunction predicts postoperative pulmonary edema in patients undergoing major noncardiac surgery


Purpose: Patients with left ventricular (LV) diastolic dysfunction are vulnerable to develop pulmonary edema. But the clinical implications of diastolic dysfunction has not been clearly elucidated in patients who underwent noncardiac surgery.

The aim of this study was to evaluate the impact of LV diastolic dysfunction for predicting post-operative (pOP) pulmonary edema. Those patients with early DHF have no obvious symptoms and this part of patients should be paid more attention to so as to improve their prognosis.

Methods: To investigate which diastolic echocardiographic parameters that best predict prognosis after an ST-elevation myocardial infarction (STEMI).

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Results: The diastolic color tissue Doppler velocities, global e' and a', were the only diastolic parameters that remained as independent predictors of the combined outcome (Death, CHF, and re-MI) in a multivariable Cox regression analysis using forward selection including all diastolic parameters and age, previous myocardial infarction (pre-MI) and peak troponins (Tnl). Even after adjusting for Tnl, e' 2.32 (1.20–4.49, P = 0.013) and a' 1.00 (0.56–2.30, P = 0.72) were independent predictors of the combined endpoint with a hazard ratio of 1.18 (1.01–1.39) per 1 cm/s decrease (p = 0.045). Patients who had values of both e' and a' below the median, had more than double the risk of an adverse outcome than patients with both e' and a' above the median (See Table). Cox regression model depicting the risk of reaching the combined endpoint for patients stratified according to e' and a' higher or below the median (cut-off points 5.4 cm/s for e' and 6.4 cm/s for a' respectively).

Conclusions: The diastolic tissue Doppler velocities seem superior to the conventional echocardiographic diastolic parameters in terms of predicting prognosis after pPCI for patients with STEMI. The early and late diastolic tissue velocities should be evaluated together as they interact on prognosis.
Results: The population was stratified according to tertiles of the MPI. The risk of a re-MI, being admitted with CHF or dying, increased with increasing tertile of MPI (See Figure), being approximately three times as high for the third tertile compared to the first tertile (hazard ratio 2.7, 95% CI 1.6 to 4.6, p = 0.001). MPI provided independent prognostic information in a multivariable Cox proportional hazard model adjusted for baseline variables (age, gender, previous MI, peak troponins, known CHF) and the systolic and diastolic echocardiographic parameters (LVEF, diastolic function grade, left ventricular mass index and left ventricular dimension in diastole), with a hazard ratio of 1.18 (p=0.018) for the combined endpoint per each 0.1 increase in MPI.

Conclusion: MPI assessed by TDI M-mode is a quick, simple and reproducible measure, which provides independent prognostic information incremental to conventional echocardiographic parameters of systolic and diastolic function in patients with STEMI treated with pPCI.

Exercise left ventricular filling pressure: prognostic implications in patients after acute myocardial infarction

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Purpose: To evaluate the prognostic value of exercise left ventricular filling pressure to outcomes in patients (pts) after acute myocardial infarction.

Methods: 83 pts (68 men; mean age 57 years), 13±3 days after acute myocardial infarction were studied. In all pts left ventricular filling pressure was estimated from the ratio of transmitial and annular velocities (E/E') at rest and after bicycle exercise (25W, 3-min increments). Patients were classified according to E/E' ratio at rest: 48 had E/E' ≤ 10 (Group I) and 35 had E/E' > 10 (Group II). Patients were followed for cardiovascular hospitalization and death for 24 months.

Results: Of 83 pts exercise E/E' rise in 23 (27.7%) pts: for Group I in 11 pts (from 0.9 to 9.4±1.1, P=0.006; difference 21.9%), and for Group II in 12 pts (from 11.5±0.9 to 14.0±1.3, P<0.001; difference 27.1%). Exercise duration was significantly shorter in pts with than in pts without raised exercise E/E' (P<0.025). During follow-up period, there were 19 cardiovascular hospitalizations (8 in pts with and 11 in pts with exercise increased E/E'; 13.3% vs 47.8%) and one cardiovascular death (in Group II in patient with exercise increased E/E').

Conclusion: Exercise left ventricular filling pressure in patients after acute myocardial infarction is associated with higher rate of subsequent cardiovascular hospitalization and death.

Diastolic but not systolic function is associated with coronary flow reserve in chronic heart failure patients

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Purpose: Coronary flow reserve (CFR) is a measure of microvascular function in the absence of coronary artery stenosis and reduced CFR has been shown to be associated with poor outcome in ischemic diaphagitic cardiomyopathy. Studies on other populations have shown an association between diastolic function and CFR, but this relationship is poorly examined in heart failure. The purpose of the study is to assess the association between CFR systolic and diastolic function in chronic heart failure patients.

Methods: 38 heart failure patients with left ventricular ejection fraction (LVEF < 35%) underwent transthoracic echocardiography. CFR was calculated using the biplane Simpson model. Pulsed wave Doppler was used to measure transmitial inflow velocities. Tissue Doppler velocities were measured 4 places in the mitral ring and were averaged. Peak coronary flow velocity (CFV) was measured in the mid-distal part of LAD at rest and during 2 minutes of stress using color guided pulse wave Doppler. CFR was calculated as the ratio between CFV at rest and during stress.

Results: Median LVEF was 31 (interquartile range [IQ] 26.33.5) and CFR was 1.77 (IQ 1.26-2.42). CFR was correlated with E/A (r=0.51 p=0.006), E/E' (r=0.48 p=0.003), IVRT (r=0.51 p=0.002), deceleration time of E (r=0.34 p=0.04), LVEF (R=0.34 p=0.04), S' (r=0.37 p=0.02) but not to LVEF or wall motion score index (all p>0.05).

Conclusion: In heart failure patients CFR was associated with all 5 measures of diastolic function but with systolic function only S' was associated. The patients with low CFR showed a more restrictive filling pattern. High filling pressure and increased wall-stress might be involved in the reduction of CFR.

Association between Eas index by tissue Doppler imaging and ventricular stiffness index or ventriculoarterial interaction in patients with preserved left ventricular ejection fraction

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Purpose: Left ventricular (LV) stiffness contributes to cardiac afterload, LV hypertrophy and substrate of cardiac function. We previously reported that Eas index by tissue Doppler imaging (TDI) was associated with aortic stiffness by transesophageal echocardiography. Therefore, the purpose of this study was to evaluate the association between Eas index and LV elastance or ventriculoarterial interaction.

Methods: We calculated TDI velocities from two mitral annular sites in consecutive 500 patients with preserved LV ejection fraction (PLVEF). TDI velocities were quantified by Eas index of diastolic and systolic pressure: e'/a' x s'. We also examined LV diastolic elastance index (Ed), arterial elastance index (Ea), LV end-systolic elastance index (Ees), ventricular-vascular coupling index (10 Ed/Ees) and total stiffness index (10 Ed+Ea+Ees). Furthermore, we investigated the relation between plasma natural logarithm (ln) - brain natriuretic peptide (BNP) levels and LV stiffness parameters.

Results: The Eas index was significantly and negatively correlated with Ed (r=-0.466, p=0.0001), Ea (r=-0.180, p=0.0002), ventricular-vascular coupling index (r=-0.117, p=0.016), total stiffness index (r=-0.289, p=0.001) and plasma ln-BNP levels (r=-0.333, p=0.0001). However, Eas was not associated with index. Finally, multivariate logistic regression analysis showed that plasma ln-BNP levels were most closely correlated with Ed (p=0.0001).

Conclusion: The Eas index by TDI in patients with PLVEF may be a helpful tool for evaluating aortic stiffness, cardiac afterload and diastolic LV function.

The prognostic role of dobutamine stress contrast echo in patients with known or suspected coronary artery disease in different age groups

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Purpose: Dobutamine stress contrast echo (DSCE) is a valuable adjunct in clinical practice for the assessment of the presence and extent of coronary disease (CAD). The aim of the current study was to evaluate the prognostic role of DSCE in patients with known or suspected CAD in different age groups.

Methods: We retrospectively studied 3148 (63.2% male) consecutive patients with known or suspected CAD in different age groups.

Results: Of 3148 patients, ischemic response to DSCE was illustrated, whereas the remaining patients had no abnormal finding during DSCE. During follow-up end-points were noted in 545 (17.3%) patients. Logistic regression analysis revealed that DSCE response was the strongest predictor for adverse outcomes (OR 6.258, 2.1310 to 18.3816, 95% CI), especially for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI). Especially for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI). Particularly for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI). Especially for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI). Particularly for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI). Especially for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI). Particularly for middle-aged patients. 5-year event-free proportion was 0.660 (95% CI).

Conclusion: Dobutamine stress contrast echo is a strong predictor of end points in patients with known or suspected CAD, especially for middle-aged patients.

Systolic and diastolic function

<table>
<thead>
<tr>
<th>Total</th>
<th>n=38</th>
<th>CFR = 1.77</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF %</td>
<td>31 (26.33.5)</td>
<td>29.5 (22.34)</td>
<td>31.5 (27.33)</td>
</tr>
<tr>
<td>E/A</td>
<td>0.9 (0.71.5)</td>
<td>1.0 (0.61.5)</td>
<td>0.7 (0.61.0)</td>
</tr>
<tr>
<td>E/E'</td>
<td>12.5 (8.918.0)</td>
<td>16.4 (11.618.0)</td>
<td>9.3 (5.817.0)</td>
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<tr>
<td>Deceleration time (ms)</td>
<td>200 (160-240)</td>
<td>180 (140-200)</td>
<td>218 (170-270)</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>100 (80-115)</td>
<td>100 (80-115)</td>
<td>110 (100-120)</td>
</tr>
<tr>
<td>Atrial volume index (mm3/cm2)</td>
<td>40.4 (25.54.9)</td>
<td>47.1 (40.58.8)</td>
<td>27.9 (19.41.9)</td>
</tr>
</tbody>
</table>

End-systolic pressure-volume relation and gender difference of diagnostic utility of dobutamine coronary flow velocity reserve in 3 major coronary subsets (Figure, Panel A, B, C).

Methods: We enrolled 929 patients (618 males; mean age 63 ± 12; ejection fraction 48 ± 17%; Wall Motion Score Index = 1.48 ± 0.63; ischemic dilated cardiomyopathy, n = 109; dilated cardiomyopathy, n = 222; valvular, n = 90, known or suspected coronary artery disease, n = 508), with negative exercise (238 patients), atypical angina (190) stress echocardiography result. Cardiovascular hemodynamics were assessed during stress: end-systolic pressure/volume ratio (ESPVR); ventricular arterial coupling (VAC) indexed by the ratio of the ESPVR to cardiac output (CO), stroke volume (Vs) and heart rate (HR) calculated at baseline and at peak stress. Changes form rest to peak stress (∆values) were tested as predictors of main cardiovascular events. Combined death and heart failure hospitalization.

Results: During a median follow-up of 16 months (interquartile range 6-32), 52 deaths and 94 hospitalization occurred. Receiver-operating-characteristic curves, and the corresponding areas under the curve, show the predictor performance of hemodynamic changes during stress (∆ESPVR, ∆VAC, ∆Ea and ∆CO) in the EX, DP and DOB subsets (Figure, Panel A, B, C).

Conclusion: Patients with negative stress echocardiography may experience an adverse outcome, which can be identified by ∆ESPVR and ∆VAC.

Feasibility, symptoms, adverse effects and complications associated with non invasive assessment of coronary flow velocity in women with suspected or known coronary artery disease. Experience in 1455

Methods: We calculated CFVR in the left anterior descending coronary artery (LAD) with TTE during adenosine infusion. The pulse wave Doppler of blood flow velocity was recorded in the LAD at rest and after maximum vasodilation by adenosine infusion (140 mg/kg/min in 5 minutes). We analyzed 1455 consecutive CFVR TTE studies starting from January 2000 to december 2010. The patients (age: 66.4±11.9 years old and 14.69 years old) were referred for CFVR studies for different reasons: 933 (64.1%) for programed follow up after elective and 430 (25.4%) for angina, 11 (0.8%) for hypertrophic cardiomyopathy, 38 (2.6%) for hypercholesterolemia, 77 (5.3%) for systemic scle-rosis, 25 (1.7%) for others reasons.

Results: A complete CFVR study was achieved in 1429 pts (feasibility: 98.9%), the test being performed almost in the early phase of acute coronary syn-drome and in obese women. In the remaining 26 patients (1.8%) the study was interrupted because of hyperpnea (8), general malaise (8), failure to visualize LAD (2), chest pain without EKG changes (2), nausea and headache (2), chest pain with ischemic EKG (1), hypertensive status (ystolic blood pressure 200 mmHg, 1), hypotension (70/50 mmHg, 1), caffeine assumption (1). Minor symptoms or adverse effects occurred in 548 pts (38.3%) not requiring test termination: hyperpnea (239,167%), flushing (134,9,4%), chest pain without EKGchanges (7%), headache (95,6,5%), minor arrhythmias (3.5%), chest pain with EKG changes (1.5%). No major complications were observed during all studies.

Conclusion: Non invasive assessment of CFVR in LAD by TTE is a feasible method with very low incidence of adverse events and complications in women with suspected or known CAD. It can be used and safely performed in the evaluation of women with atherosclerotic LAD disease and in a broad spectrum of cardiac disease with microvascular impairment.

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Coronary flow velocity reserve in 3 major coronary arteries can be a promising alternative for fractional flow reserve in determining hemodynamic significance of coronary artery disease

Methods: We calculated CFVR in the left anterior descending coronary artery (LAD) with TTE during adenosine infusion. The pulse wave Doppler of blood flow velocity was recorded in the LAD at rest and after maximum vasodilation by adenosine infusion (140 mg/kg/min in 5 minutes). We analyzed 1455 consecutive CFVR TTE studies starting from January 2000 to december 2010. The patients (age: 66.4±11.9 years old and 14.69 years old) were referred for CFVR studies for different reasons: 933 (64.1%) for programed follow up after elective and 430 (25.4%) for angina, 11 (0.8%) for hypertrophic cardiomyopathy, 38 (2.6%) for hypercholesterolemia, 77 (5.3%) for systemic scle-rosis, 25 (1.7%) for others reasons.

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fractional flow reserve (FFR) in assessing hemodynamic significance of coronary artery disease (CAD).

**Methods:** A prospective study in 157 vessels of 142 patients with suspected coronary artery disease. The primary endpoint was a composite of all-cause mortality and acute MI. According to SE results, the patients were stratified into three groups: group I: normal SE and normal stress electrocardiography (sECG) (n = 2,107), group II: normal SE and abnormal sECG (n = 868), and group III: abnormal SE (n = 347). Results: Patients in group III were older than patients in groups I and II (67.10 ± 12 years and 57.12 ± 12, respectively) and was comprised of a higher rate of male patients (71% in group III, 59% in groups I and II). Group III patients had a significantly higher prevalence of diabetes (12% vs. 6%), dyslipidemia (34% vs. 22%), and hypertension (28% vs. 17%) than patients in groups I and II. In multivariate Cox proportional regression analysis with adjustment for baseline demographics and comorbidities, no difference was found in the outcome of patients in groups I (reference group) and II (hazard ratio 0.18, 95% CI 0.62-2.94). An abnormal sECG was a significant factor impacting survival, and increased the risk of MI and/or death by 2.11 (95% CI 1.16-8.31, p = 0.014).

**Conclusion:** The negative predictive value for MI and/or death of a patient with normal SE is extremely high. Our study proves that there is no difference in the cardiac outcome of patients with ischemic changes in the ECG during SE and those with normal ECG during a stress echocardiography study.

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**P4252**

Ranolazine improves coronary flow reserve in patients with angina but no obstructive coronary artery disease

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**Background:** Ranolazine reduces the Na-dependent cardiac overload via inhibition of the late sodium current, improving diastolic tone and oxygen handling during myocardial ischemia. In patients with angina, evidence of myocardial ischemia, but no obstructive coronary artery disease (CAD), microvascular coronary dysfunction plays a key role. Transthoracic Doppler-derived coronary flow reserve (CFR) is known as an index of coronary arterial reactivity and decreases under the condition with microvascular dysfunction as well as coronary artery stenosis. The aim of this study was to assess the effect of ranolazine on CFR in this patient group.

**Methods:** 52 patients (36 M, 16 F; mean age 63 ± 10 years) with angina and evidence of myocardial ischemia, but no obstructive CAD was enrolled in a double-blind, placebo-controlled trial. All of them underwent coronary angiography, to exclude obstructive CAD, and catheterization was performed by the femoral approach after local anesthesia induced with 0.5% lidocaine. The patients were assigned to Ranolazine (26 patients) or placebo (26 patients) for 8 weeks (350 mg twice a day for 4 days, then 500 mg twice a day for other 4 weeks). Transthoracic two-dimensional echocardiography was performed with an ultra-

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**References:**

sound imaging system (Vivid7, GE Healthcare, Wauwatosa, WI, U.S.A.). Coronary flow was assessed in the left anterior descending coronary artery (LAD), and was identified as the color signal directed from the base to the apex of the left ventricle, containing the characteristic variastic biphasic flow pattern. CFR were determined as the ratio of hyperemic, induced by intravenous dipyridamole administration, to baseline diastolic coronary flow velocity. CFR was assessed before and after 8-weeks therapy.

**Results:** There were no significant differences in baseline characteristics between Ranolazine and placebo group. CFR was successfully performed in all patients. Baseline CFR was not significantly different in Ranolazine and placebo group (1.85 ± 0.27 vs. 1.87 ± 0.29 – p = ns). After 8 weeks CFR significantly increased in Ranolazine group (2.02 ± 0.18 vs. 1.85 ± 0.27 – p = 0.007) but not in placebo-group (1.90 ± 0.24 vs. 1.87 ± 0.29 – p = ns). No patient dropped out during 8 weeks therapy. Side effects were similar in both groups.

**Conclusions:** In patients with evidence of myocardial ischemia, but no obstructive CAD, Ranolazine is able to improve CFR. This is probably due to improvement in microvascular coronary dysfunction. Larger studies will be able to confirm these data.

**Dipyridamole coronary flow reserve stratifies left ventricular torsion at rest, peak and during exercise**

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1UCD Cardiology – V. Monaldi Hospital, Naples, Italy; 2Second University of Naples, Department of Cardiology, Naples, Italy

**Background:** Coronary flow reserve (CFR) assessment by transthoracic ultrasound of the left anterior descending (LAD) artery during dipyridamole echocardiography has been shown to predict prognosis in large unselected populations, and to be correlated with significant stenosis of the LAD. Aim of the present study was to assess the prognostic impact of CFR in subjects with acute coronary syndrome and proven absence of LAD disease.

**Methods:** 325 patients with ACS underwent high-dose dipyridamole stress with combined assessment of CFR in the LAD and wall motion analysis, followed by coronary angiography. 152 patients without LAD disease (stenosis ≤ 50%) and with interpretable CFR recordings were monitored for major adverse cardiac events (MACE) for a mean of 30 months.

**Results:** 22 patients developed events during follow-up. Patients who experienced MACE differed from stable patients in terms of age, prevalence of diabetes, number of deceased vessels and CFR values. Multiple logistic regression analysis for the prediction of MACE demonstrated independent value only for CFR (∼0.001), smoke (p<0.01) and age (p<0.05). ROC curve analysis showed that a CFR < 0.25 is able to predict MACE with a sensitivity of 86.4% and a specificity of 80% (AUC = 0.86).

**Table 1**

| Age (years) | 65±11 | 58±10 | p < 0.005 |
| Sex (M/F) | 156 | 90/34 | NS |
| Diabetes (n) | 8 (37%) | 13 (17%) | 0.016 |
| Hypertension (n) | 4 (19%) | 23 (18%) | NS |
| Hypercholesterolemia (n) | 14 (64%) | 9 (65%) | NS |
| Triglycerides (n) | 3 (19%) | 6 (48%) | NS |
| WMSI | 1.27 ± 0.18 | 1.17 ± 0.28 | p < 0.001 |
| 0/1/2 vessel CAD (n) | 1/4/7 | 47/71 | p < 0.001 |
| CFR | 2.1 ± 0.33 | 2.5 ± 0.44 | p = 0.001 |

**Conclusions:** In a population of patients with ACS, CFR significantly improves prediction of MACE when added to standard clinical variables, even in the absence of LAD disease. This finding promotes the role of ultrasound-assessed CFR in the risk stratification after ACS, supporting the concept that CFR reflects global atherosclerotic burden, endothelial dysfunction and microvascular damage, more than just mirroring focal LAD disease.
P4257
Prediction of left ventricular function recovery with the use of 2D speckle tracking echocardiography in patients 12 months after acute ST-elevation myocardial infarction

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Introduction: Prediction of left ventricular function recovery is of clinical importance for the management and prognosis of patients after myocardial infarction. The aim of this study was to assess if the use of 2D speckle tracking in resting echocardiography may be helpful in the prediction of left ventricular function recovery in patients 12 months after ST-elevation myocardial infarction (STEMI).

Material and methods: The study group consisted of 96 patients (69 male, mean age 58±10 years) with first STEMI treated with successful primary percutaneous coronary intervention. 7-12 days after STEMI, all patients underwent resting echocardiography. All acquired images were analyzed off-line using 2D speckle tracking technique. Measurements included peak systolic longitudinal and transverse strain (SLS and STS), peak longitudinal and transverse strain (PLS and PTS) including possible postisometric shortening, systolic longitudinal and transverse strain rate (SLSR and STSR) at baseline (rest). After 12 months each patient underwent control resting echocardiography with visual assessment of functional recovery in akinesic/dyskinetic segments defined as improvement from dyskinesia and akinesia to hypokinesia or normokinesia.

Results: At baseline there were 265 segments with akinesis or dyskinesis. 112 (42%) of those segments showed functional recovery after 12 months. Longitudinal strain parameters SLS (AUC=0.710, p<0.001) and PLS (AUC=0.773, p<0.001) had good, while SLSR only satisfactory (AUC=0.648, p=0.001) diagnostic value for predicting function recovery. The highest prognostic value of 72.9% was for PLS < -10.4% and for 67.5% for SLS <-10.1%, while diagnostic accuracy for low-dose dobutamine stress echocardiography in the study group was 75.8%, with sensitivity of 61.8%, and specificity of 85.2%. Transverse parameters of strain had non-satisfactory diagnostic value for predicting functional recovery 12 months after STEMI.

Conclusions: Longitudinal strain parameters assessed by 2D speckle tracking had comparable prognostic value to requiring experience and administration of pharmacoagent low-dose dobutamine stress echocardiography for the prediction of left ventricular functional recovery in patients 12 months after STEMI. The presented method may be less dependent on subjectivity factor and it is more convenient in usual viability interpretation based on dobutamine stress echocardiography and offer a methodological background for fully computerized algorithms.

P4258
The additive diagnostic role of coronary flow reserve determined by transthoracic Doppler echocardiography in assessment of real significance of stenosis on right coronary artery

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Purpose: Multi-slice computed coronary angiography (MSCT) provides a morphological information about coronary artery disease, but precise quantification of coronary stenosis remains difficult. Coronary flow reserve (CFR) determined by Transthoracic Doppler Echocardiography (TDE) gives a new insight into the functional significance of coronary luminal narrowing. We have tried to assess the additive value of CFR determined by TDE over MSCT in prediction of a significant stenosis on right coronary artery (RCA) using the Invasive coronary angiography (ICA) as reference method.

Methods: This prospective study included 70 patients. Patients were referred for ICA because of previously detected non-invasive lesions on RCA by MSCT. Additional measurements of CFR by TDE were performed on totally 61 vessels. Feasibility for RCA was (9/70) 71.4%. All patients underwent ICA 24-48 hours after CFR. Significant coronary artery stenosis was defined as more than 70% diameter reduction. CFR was determined as ratio between the peak diastolic flow velocity during adenosine infusion and at basal condition, a cutoff value for significant stenosis was -2.

Results: There was a good correlation (r=0.56, p<0.001) between morphological changes detected with ICA and functional parameters of stenosis determined by CFR and a considerable correlation between invasive and noninvasive coronary angiography (r=0.57, p<0.001). A much weaker correlation was between MSCT angiography and CFR (r=0.22, p=0.086).

MSCT had sensitivity 86.2%, specificity 69.1%, positive predictive value 59.5%, negative predictive value 90.5% and accuracy of 75.9% in detection of significant RCA stenosis. CFR had sensitivity 76.9%, specificity 85.3%, positive 80.0% and negative predictive value 82.9% and accuracy 81.7%. When the results of both methods were agreed accuracy was improved to 90.0%, sensitivity 76.9%, specificity 100.0%, positive 100.0% and negative predictive value 85.0%.

ROC curve estimation of MSCT angiography in detection of significant RCA stenosis (Area 0.81, p<0.001) for diameter of stenosis of 67.5% had a sensitivity 86.0% and specificity 63.6%, ROC curve of CFR (Area 0.84, p<0.001) for CFR >2.02 had a sensitivity 76.9% and specificity 68.6%. Comparing ROC curves there was no statistical difference (p=0.747).

Conclusion: CFR determined by TDE had an additive diagnostic value in evaluation of real significance of atherosclerotic lesions on RCA detected with MSCT angiography, what emphasize importance of comprehensive non invasive imaging approach integrating morphologic and functional information.

P4259
QRS fragmentation in patients with arrhythmogenic right ventricular dysplasia/cardiomypathy and complete right bundle branch block

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Patients with arrhythmogenic right ventricular dysplasia/cardiomypathy (ARVD/C) and complete right bundle branch block (RBBB) very often have recurrent ventricular tachycardia and develop biventricular heart failure in the follow-up requiring heart transplantation and/or diuretics. In other patients with ARVD/C excluding right bundle block QRS fragmentation in the S wave of right precardial leads identifies patients with recurrent VT, primary VF and recurrent ICD discharges; QRS fragmentation ≥ 3 leads characterised patients who died from sudden cardiac death.

Method: In a cohort of 374 patients with ARVD/C (208 males; mean age 46.5±14.8 years) there were 22 patients with complete RBBB. 17 patients with ARVD/C developed complete right bundle branch block and had biventricular heart failure in the follow-up of up to 6 years. In 5 patients with complete right bundle branch block both were initially evident. In all patients with ARVD/C and RBBB QRS fragmentation ≥ 3 of all 12 ECG leads and QRS fragmentation in the S wave of right precordial leads were analyzed.

Results: QRS fragmentation ≥ 3 of all 12 ECG leads and in the S wave of right precordial leads were present in 16/17 patients who developed RBBB and none of the 5 patients with initial RBBB. In one patient with initial RBBB QRS fragmentation ≥ 3 leads was present (r=12.5 p<0.001).

Conclusion: In patients with recurrent ventricular tachycardia who develop biventricular heart failure requiring heart transplantation and/or diuretics are characterised by QRS fragmentation in the S wave of right precardial leads ≥ 3 of all 12 ECG leads. These results are statistically significant. Patients with initial RBBB have an overall benign prognosis.

P4260
The impact of sleep apnea on the occurrence of heart failure in the patients with hypertrophic cardiomyopathy

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Purpose: This case-control study was conducted to evaluate the interrelation between the occurrence of heart failure (HF) and the sleep apnea in the patients with hypertrophic cardiomyopathy (HCM) excluding obstructive left-ventricular outflow tract obstruction in HCM.

Methods: 48 patients with apical HCM, mid-ventricular HCM, and non-obstructive left-ventricular outflow tract HCM were conducted polysomnography to assess the apnea-hypopnea index (AHI). The biomarkers and cytokines including brain-natriuretic peptide (BNP), plasma rennin activity, aldosterone, adrenaline, nor-
adrenalin, dopamine, soluble tumor necrosis factor receptor 1 (sTNFR1), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor beta (TGF-beta), urine 8-hydroxydeoxyguanosine (8-OHdG) were measured at the period of HF-recurrence. We divided those patients into two groups with (n=14) or without (n=34) a history of HF requiring hospitalization and compared above-mentioned parameters between two groups.

Results: HCM patients with a history of HF has significantly higher AHI (32.4±5.0 vs. 11.1±2.2, p<0.0001) and higher TGF-beta value (2.72±0.49 vs. 1.53±0.07, p=0.0016) comparing with those without a history of HF. The other indices of HF, inflammation, and oxidative stress, such as BNP, PRA, aldosterone, adrenalin, nor-adrenalin, dopamine, sTNFR1, TNF-alpha, IL-6, 8-OHdG have not shown any significant difference between two groups.

Conclusions: Sleep apnea may play an important role in the occurrence of HF in the patients with relatively benign HCMs. The elevation of TGF-beta may suggest the involvement of fibrosis in the pathogenesis of HF in the patients who have both HCM and sleep apnea.

Predictors of survival in patients with restrictive cardiomyopathy

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Backgrounds: Restrictive cardiomyopathy (RCMP) is a rare heterogeneous disease and the survival according to types of RCMP is unclear. We evaluated clinical outcomes of RCMP to identify predictors of survival.

Methods: From 1999 to 2010, we prospectively studied 98 consecutive patients (64 men, age;58±11 years) diagnosed as RCMP. All patients had the symptoms of heart failure and diastolic dysfunction with preserved left ventricular systolic function on echocardiography. Diagnosis of RCMP was initially made by typical echocardiographic findings and confirmed by endomyocardial biopsies. The endpoint was defined as death from any cause.

Results: Idiopathic RCMP was diagnosed in 11 (11%) patients, and infiltrative CMP in 87 (89%). The underlying cause of infiltrative CMP was amyloidosis in 77, light-chain deposition disease in 5, myocarditis in 2, hyperesinophilic syndrome in 2 and Fabry disease in 1. During a median follow-up of 6 months (IQR, 2-17), 75 (77%) patients died and 3 underwent cardiac transplantation (1 amyloidosis, 2 idiopathic RCMP). The actuarial 2 year survival rates were significantly different between infiltrative CMP and idiopathic RCMP (22±5% versus 91±9%, P<0.001) (Figure). Age (hazard ratio [HR] =1.036, P<0.001) and infiltrative CMP (HR=4.458, P=0.005) were independently related to survival on multivariate Cox analysis. On subgroup analysis of 82 patients with amyloidosis or light-chain deposition disease, only 39 (48%) patients underwent chemotherapy and tolerance to chemotherapy was significantly related to survival (HR=2.189, P=0.002).

![Figure 1. Survival by type of RCMP](https://example.com/figure1.png)

Conclusions: Idiopathic CMP was the predominant type of RCMP and related with much worsen survival. Early diagnosis of RCMP by echocardiography and timely institution of chemotherapy may improve the prognosis of cardiac amyloidosis.

Characterization of predictors of in-hospital cardiac complications of takotsubo cardiomyopathy: multi-center registry from Tokyo CCU network

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Background: Takotsubo cardiomyopathy (TC) is an acute cardiac syndrome characterized by transient left ventricular dysfunction and relatively good prognosis after discharge. However, cardiac complications during hospitalization remain to be fully determined.

Methods: We investigated 107 patients of TC (82 women, median age 73.9±11.1 years old) from Tokyo CCU Network database, comprising of 67 cardiovascular centers in the metropolitan area during January 1 to December 31 2010. Cardiac complications were defined as all-cause death, pump failure (Killip II/III/IV), sustained ventricular tachycardia (SVT), ventricular fibrillation (VF), and advanced atrioventricular block (AVB). We attempted to characterize cardiac complication groups (CC) by comparing patients with and without cardiac complication (NC) during hospitalization.

Results: CC was observed in 41 patients (all-cause death, n=9; pump failure, n=27; SVT, n=1; AVB, n=2; VF, n=2), and there was no complication in the remaining 66 patients. There was no difference in age (75.2±10.4 vs. 72.9±11.6; P=0.289), female gender (70.7% vs. 80.3%; P=0.144), peak creatinine kinase level (IU/L) (553±270 IU/L vs. 486±1024 IU/L, P=0.780), C-reactive protein level (mg/dL) (2.63±3.75 mg/dL vs. 1.90±4.25 mg/dL, P=0.579), and 75 elevation on electrocardiogram (68.3% vs. 75.8%, P=0.398), respectively. White blood cell count (WBC) (11189±4516/μL vs. 9020±3352/μL, P=0.005) and brain natriuretic peptide (BNP) (1125±1245 pg/ml vs. 376±764 pg/ml, P=0.004) were higher in CC than NC. Left ventricular ejection fraction was lower in CC than NC (42.3±11.6% vs. 53.1±11.0%, P<0.001).

Conclusion: Cardiac complications are not rare in patients with TC during hospitalization. Higher WBC and BNP levels and the presence of LV dysfunction seem to be possible predictors of TC with cardiac complications.

Prognostic role of clinical presentation in patients with hypertrophic cardiomyopathy. A single center experience

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Background and Aims: Hypertrophic cardiomyopathy (HCM) is a complex primary and genetically transmitted heart muscle disease characterized by highly variable natural history, from stable clinical course over many years to progressive congestive heart failure (HF) or sudden death (SD). The aim of the study is to evaluate the long-term prognostic impact of baseline symptoms in a cohort of HCM patients.

Methods and Results: We considered 212 HCM patients enrolled in the Trieste Heart Muscle Disease Registry. Implantable cardioverter-defibrillator (ICD) has been implanted in 23 (11%) patients during follow-up. The end-points of the study were death/heart transplant and SD/appropriate ICD shock. 106 (50%) were asymptomatic at diagnosis. Considering symptomatic patients at diagnosis, heart failure (HF), chest pain, syncope and palpitations were the main symptoms in 29, 33, 15 and 23% of the cases respectively. During a mean follow-up of 118±87 months, 44 (21%) patients died/underwent heart transplant (D/HTx) (15 pump failure deaths, 14 SD, 5 non cardiac vascular deaths and 10 HTx). Six patients had at least one appropriate ICD shock. D/HTx was observed in 11 (10%) symptomatic patients and in 33 (31%) symptomatic patients at diagnosis (p=0.016). At multivariate analysis a diagnosis in asymptomatic stage (HR 0.33, CI 95% 0.15-0.74, p=0.007), chest pain at diagnosis (HR 0.21, CI 95% 0.05-0.89, p=0.034) and lower left atrium area (for every 1 cm2 decrease HR 0.95, CI 95% 0.92-0.98, p=0.002) emerged as independent predictors of survival-free from D/HTx. Conclusions: Clinical presentation has a relevant prognostic role in HCM, since diagnosis in an asymptomatic stage and chest pain as main onset symptom were associated with a more favourable long-term outcome. Moreover, left atrium enlargement emerged as an independent predictor of D/HTx, whereas left ventricular ejection fraction and restrictive filling pattern were found to be independent predictors of SD or appropriate ICD shocks.
Left ventricular reverse remodeling in idiopathic dilated cardiomyopathy: a subgroup analysis of the population enrolled at the Florence referral center for cardiomyopathies

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Purpose: Idiopathic dilated cardiomyopathy (IDCM) is a myocardial disorder characterized by left ventricular dilation and systolic dysfunction. Recent data show that there is a positive correlation between the effect of optimal medical therapy on left ventricular reverse remodeling (LVRM) and on mortality in heart failure (HF) and/or IDCM pts. Aims of our study were to determine survival rates in IDCM patients experiencing LVRM and the potential role of cardiac resynchronization therapy (CRT).

Methods: Among 603 consecutive IDCM pts we studied a subgroup of 425 pts. 309 M (72.7%), mean age 53.5±12 yrs, with complete repeated echocardiographic evaluations. Mean indexed left ventricular (LV) end-diastolic diameter (IEDD) was 35.1±5.0 mm/m²; LV ejection fraction (EF) was 32.3±3.9%, NYHA class was 2.3±0.8. Pts were divided in three groups, based on enrolment periods: 1) 1977-1990 (n=71); 2) 1991-2000 (n=144); 3) 2001-2010 (n=210). The mean follow-up was 16.9±7.8, 10.9±5.0 and 6.3±3.9 yrs, respectively. No statistical difference was observed in gender, LVRR class (mean follow up was 1.6 years, 1.4 years and 1.9 years, respectively), LV function (IIEF ≤ 33 mm/m²) measured serum cTnT and cTnI in the aortic root (Ao) and coronary sinus (CS). Endomyocardial biopsy specimens were obtained for gene expression assays.

Results: During follow-up 72 pts (18.9%) died due to refractory HF, 38 (8.9%) due to heart transplantation. Survival rates for the entire population at 5, 10 e 15 years was 86%, 72% and 62%, respectively. Pts with emotional triggering survival was significantly higher (p=0.02) whereas pts with physical stress had more deaths (8.1% vs 14%, p=0.001). Only pts with emotional triggering had survival benefit from CRT (HR 0.59, 95% CI 0.41-0.87). Pts with physical stress had a trend towards a favorable effect of CRT with respect to LVRR (p=0.2). Conclusions: Emotional stress is associated with a decrease in LV iEDD of at least 10% or LV iEDD ≤ 33 mm/m². The importance of CRT in LVRR needs further confirmation.

Impact of serum cardiac troponin T and I on cardiac molecular changes and dysfunction in patients with hypertrophic cardiomyopathy

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Purpose: Serum cardiac troponin T (cTnT) could be a reliable indicator of myocardial necrosis. Recently, the assessment of troponin T and I could be a prognostic indicator in patients with chronic heart failure. However, the relationship between cardiac function, cTnT and cTnI has not been well characterized.

Methods: We checked serum cTnT and cTnI in 73 consecutive HCAM patients in stable condition. All patients underwent catheterization and we calculated the maximum systolic pressure (LV-HPdiff) and LV pressure half-time (T1/2) as indexes of contractility and the LV pressure half-time (T1/2) as an index of isovolumic relaxation. In addition, we examined transcardiac utilization of troponin T and I, we measured serum cTnT and cTnI in the aortic root (Ao) and coronary sinus (CS).

Results: We divided the patients into two groups [group A: cTnT ≤ 0.009ng/ml (n = 35), group B: cTnT group ≥ 0.009ng/ml (n = 38)], on the basis of median value of cTnT in the peripheral vein. Brain natriuretic peptide, serum cTnI, left ventricular mass index, and T1/2 were significantly higher in the lower group than those in the group A. Moreover, mRNA level of cTnT was significantly correlated with mRNA levels of sarco-endoplasmic reticulum Ca²⁺-ATPase and cytochrome c oxidase subunit 5B (r = 0.486, p < 0.04, respectively). Meanwhile, there was a significantly positive correlation between the transcardiac gradient of serum cTnT calculated by the difference of CS and Ao and mRNA levels of Troponin I (r = 0.515, P < 0.009).

Conclusions: In conclusion, these findings indicate that elevated peripheral blood cTnT might be associated with cardiac dysfunction, resulting from the impairment of Ca²⁺-handling protein and mitochondrial dysfunction. Meanwhile, transcardiac gradient of cTnT levels may reflect ongoing myocardial damage in stable patients with HCAM.
Fragmented QRS complexes on 12-lead ECG predict myocardial fibrosis in hypertrophic cardiomyopathy

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Purpose: It is well-established that fragmented QRS complexes (fQRS) on the 12-lead electrocardiogram (ECG) are a predictor of delayed gadolinium enhancement (DGE) on Cardiac MRI (CMR) and indicate myocardial scarring in patients with coronary artery disease and dilated cardiomyopathy. Moreover, fQRS appear to correlate well with arrhythmic events and mortality in these cohorts. However, the significance of fQRS in hypertrophic cardiomyopathy (HCM) is yet to be established. We sought to determine whether fragmentation on ECG is a predictor of delayed gadolinium enhancement (DGE) on CMR in patients with HCM.

Methods: The 12-lead ECGs of 82 consecutive patients with HCM who underwent CMR with gadolinium were analysed for the presence of fQRS by 2 independent readers blinded to the CMR findings. Patients with documented myocardial infarction (n=3) were excluded from further analysis. The ECGs were correlated to CMR findings, and patients separated into DGE positive (DGE+ve; n=44) and negative (DGE-ve; n=35) groups. ECG territories of fQRS were correlated with myocardial segments of DGE on CMR, in order to determine whether areas of fQRS predicted areas of DGE.

Results: Patients from the DGE+ve and DGE-ve groups were of similar gender (75% vs. 77% male respectively), age (54±19 vs. 57±11 years respectively, p=0.41). Fragmented QRS complexes were significantly more prevalent in the DGE+ve group than in the DGE-ve group (68.2% vs. 14.3%, p<0.001). The positive predictive value (PPV) of fQRS for DGE on CMR was 85.7%, with a specificity of 85.7%, sensitivity of 68.2% and negative predictive value of 68.2%. In the DGE-ve group with fQRS (n=30), fQRS ECG lead territory was predictive of regions of DGE on CMR in 73.3% (n=22) of patients.

Conclusions: The presence of fQRS on 12-lead ECG correlates with DGE on CMR in patients with HCM with good specificity and PPV. Electrocardiographic territories containing fragmentation also correlate with myocardial segments of DGE on CMR. This simple, inexpensive method may therefore be valuable for predicting scar or fibrosis in patients with HCM. Future work should focus on correlating fQRS with risk factors and events to determine its use in risk stratification.

Tissue Doppler imaging and prognosis in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy

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Aims: Assessment of left ventricular (LV) systolic and diastolic functions by tissue Doppler imaging (TDI) has been reported to be useful for predicting the prognosis in patients with hypertrophic cardiomyopathy (HCM). The purpose of this study was to evaluate the clinical significance of TDI parameters for prediction of cardiovascular events in asymptomatic or mildly symptomatic patients with HCM.

Methods and results: Eighty-five HCM patients (52 males, 55.6±14.8 yrs.) belonging to New York Heart Association (NYHA) functional class I or II were enrolled in this study. Patients with LV systolic dysfunction or a clinically documented history of atrial fibrillation were excluded. During a follow-up period of 4.5±1.7 yrs., 11 patients achieved the combined end-points. Patients who experienced cardiovascular events had larger LV size and left atrial volume compared with those who did not. Peak systolic, early diastolic (e'), and late diastolic TDI velocities were lower in patients who experienced cardiovascular events; moreover, e'/E' was higher in these patients. The event-free curve in patients with a high E'/E' value was significantly worse than that in patients with a low E'/E' value (Figure). Multivariate analysis revealed the deceleration times of E and e'/E' to be independent predictors of cardiovascular events.

Conclusion: Assessment of diastolic function by TDI is useful for risk stratification in HCM patients with no or mild symptoms. TDI measurements should be incorporated into the clinical management of HCM.

Importance of hypertrophy pattern in sudden death risk stratification among patients suffering from hypertrophic cardiomyopathy

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Purpose: To investigate differences in sudden death (SD) and associated arrhythmic events (ventricular tachycardia/fibrillation, resuscitated cardiac arrest and appropriate defibrillator discharge) rates among four discrete hypertrophic cardiomyopathy (HCM) phenotypes (asymmetric basal septal hypertrophy (ASH), mid-ventricular obstruction (MVO), apical hypertrophy (APH) and mid-ventricular hypertrophy/obstruction (MVO)) and to challenge the importance of hypertrophy type in SD prediction.

Methods: Hypertrophy phenotypes were recognized by means of echocardiography and MRI in 423 HCM patients (49.3±17.2 years, 66.2% male) followed up for a median of 84 months (7 years, range 6 to 480 months). Cumulative SD event rates through follow up were estimated by Kaplan-Meier method and differences were assessed by log rank test. To identify independent predictors of the study outcome, univariate and multiple Cox proportional hazard models were adopted. p-values <0.05 were considered significant.

Results: ASH was discovered in 259 patients (61.2%), LVOTO in 88 (20.8%), MVO in 65 (15.1%), and APH in 6 (1.4%). Incidence of SD was 6.2% for ASH, 5.7% for LVOTO, 5.0% for MVO, 4.3% for APH, with the latter being significantly lower (p=0.03) compared with the former three phenotypes. The positive predictive value (PPV) of fQRS for DGE on CMR was 85.7%, with a specificity of 85.7%, sensitivity of 68.2% and negative predictive value of 68.2%. In the DGE-ve group with fQRS (n=30), fQRS ECG lead territory was predictive of regions of DGE on CMR in 73.3% (n=22) of patients.

Conclusions: The presence of fQRS on 12-lead ECG correlates with DGE on CMR. This simple, inexpensive method may therefore be valuable for predicting scar or fibrosis in patients with HCM. Future work should focus on correlating fQRS with risk factors and events to determine its use in risk stratification.

Prognostic role of a high-sensitivity cardiac troponin T marker in patients with dilated cardiomyopathy

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Purpose: Although serum high-sensitivity cardiac troponin T (hs-cTnT) has become a well-established diagnostic and prognostic marker in acute coronary syndrome, its role as a risk marker in dilated cardiomyopathy (DCM) is unclear. The aim of this study was to determine whether hs-cTnT can be a reliable prognostic marker of cardiac events in DCM.

Methods: We performed clinical evaluation including measurement of hs-cTnT in 55 patients with DCM. The normal range of hs-cTnT is less than or equal to 0.014 ng/mL (97.5 percentile).

Results: Serum concentration of hs-cTnT was 0.017±0.023 ng/mL. During a mean follow-up period of 5.0±1.7 years, there were 17 cardiac events: heart failure death in seven, sudden cardiac death in two and hospitalization for heart failure in eight. Patients with abnormal hs-cTnT values (>0.014ng/ml) had significantly more frequent cardiac events than those with low hs-cTnT values (hazard ratio: 8.3, 95% confidence interval: 2.9 to 23.8, p<0.001). We divided the patients into four groups by their hs-cTnT levels: nonmeasurable levels (<0.003 ng/ml) and normal range levels (0.003-0.014 ng/ml) with low-hs-cTnT group, high-concentrations (0.015-0.028 ng/ml) and very high concentrations (0.028 ng/ml) in abnormal hs-cTnT group. Event-free rate was shown in Figure: hs-cTnT indicated a tendency of concentrations-depend increase in cardiac events.
Number of morphological kinds of ventricular premature beats with fragmented QRS waves on 12-lead Holter ECG predicted left ventricular fibrosis and fatty change on CT in hypertrophic cardiomyopathy

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Purpose: To determine the number of morphological kinds of ventricular premature beats (VPB) with fragmented QRS waves (FQRSW) on 12-lead Holter ECG in presence of the left ventricular (LV) fibrosis or fat on CT in hypertrophic cardiomyopathy (HCM) subjects.

Methods: This was a retrospective analysis of 49 consecutive HCM subjects who underwent CT (Aquilion one) and 12-lead Holter ECG (RAC-2103) within 3 months. If there was a contrast defect in myocardium in early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis. If contrast defect continued in late phase with CT values < 0 HU, we diagnosed myocardial fatty change.

Results: Fibrosis and fat were observed on CT in 28 and 12 subjects, respectively. The numbers of morphological kinds of both all VPB and VPB with FQRSW between the subjects with fat and those without. According to a receiver operating characteristic curve, best cutoff value for number of morphological kinds of both all VPB and VPB was greater in subjects with fibrosis than in those without (both P < 0.01), but there was no significant differences in the numbers of morphological kinds of both all VPB and VPB with FQRSW between the subjects with fat and those without. According to a receiver operating characteristic curve, best cutoff value for number of morphological kinds of all VPB, respectively.

Conclusions: Serum concentrations of hs-cTnT level was a useful prognostic marker for sudden cardiac death (SCD).

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in type non-A. (2) Intraventricular obstruction (15%), ventricular thrombi formation (4%), cardiac rupture (1%) and recurrence in acute phase (2%) were observed only in type A TCM, though the prevalences of pulmonary edema, pump failure and ventricular arrhythmias were similar in the two types of TCM. (3) During long-term follow-up (24±25 months), recurrence (type A=1% vs. type non-A=4%) and cardiac death (type A=2% vs. type non-A=0%) were rare in both types of TCM.

Conclusions: Patient characteristics and long-term prognosis were similar in type A and type non-A TCMs. However, there were differences in frequent triggers and incidences of acute complications between the two types of TCM. Attention should be paid to occult pheochromocytoma in type non-A TCM, and acute complications such as intracardiac thrombi and acute recurrence of TCM need to be closely monitored in type A TCM, especially in cases with intraventricular obstruction.

**P4276**

Prognostic value of the admission ECG for predicting complications in patients with tako-tsubo cardiomyopathy

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**Purpose:** Tako-tsubo cardiomyopathy (TTC) mimics acute myocardial infarction. A substantial number of patients develop adverse events during the acute course of TTC. This study assessed the prognostic value of the admission ECG for predicting complications in patients with TTC.

Methods: The study included 198 patients who fulfilled the current criteria for the diagnosis of TTC. Of these 198 patients, we observed 76 TTC patients (69f, 7m; 70±12 years). A total of 37 patients (49%) developed one (n=17) or more (n=20) adverse events such as pulmonary oedema (n=14), cardiogenic shock (n=4), ventricular tachycardia (n=7), atrial fibrillation (n=14), right ventricular involvement (n=15), intraventricular pressure gradient (n=6), thrombus and/or stroke (n=6), or death (n=2). Clinical parameters and the admission ECG were compared in patients with and without adverse events.

**Results:** Patients with adverse events were older (73±12 vs. 67±12 years, p=0.05) and more frequently female (52% vs. 14%, p=0.05). There was a higher rise in troponin (T=4.6±9.0 vs. 6.1±5.7 times the upper limit of normal, p=0.05) and a lower left ventricular ejection fraction (47±19 vs. 55±13%, p=0.007) in patients with adverse events. Angiographic ballooning pattern and left ventricular end-diastolic pressure were not different.

Time from symptom onset to first ECG (7.5±2.7 vs. 9.3±9.8 hours, p=ns) was similar in both groups. Patients with adverse events had a higher heart rate on admission (97±23 vs. 82±18/min, p=0.003), and there was a trend towards a higher number of leads with ST-segment elevation (4.4±2.3 vs. 5.3±2.3 leads, p=0.09) and a greater magnitude of ST-segment elevation (0.64±0.51 vs. 0.48±0.36 mV).

The number of patients with ST-elevation in V3 (89% vs. 74%) and V4 (60% vs. 30%, p=0.02) was higher in patients with adverse events. Regarding ST-elevation in the other leads, occurrence of an abnormal Q wave (32% vs. 30%), reciprocal ST-segment depression (27% vs. 28%) or T-wave inversion on the admission ECG was rare. According to the multivariable analysis, the presence of ST-segment depression in V1 and V2 provided the greatest discrimination between patients with and without adverse events.

**Conclusion:** Almost half of the patients with TTC develop adverse events. Especially elderly females with a high heart rate and a prolonged QTc interval on admission ECG are at increased risk for developing complications during the acute course of TTC.

**CARDIOMYOPATHIES: TREATMENT**

**P4277**

Long-term follow-up of 99 patients after transcoronary ablation of septal hypertrophy (TASH) for HOCM: No evidence for the induction of an arrhythmogenic substrate

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**Background and Aim of the study:** Prognosis after surgical myectomy for HOCM is beneficial even in long-term follow-up. However, after TASH only midterm follow-up data is available so far. In the present study we systematically analyzed the mortality in a 7-year follow-up after TASH.

**Methods:** All patients who underwent TASH-treatment at our institution within the year 2004 were included in the study (n=103, age 57.6±15 years). Follow-up was performed by telephone contact with either the patients or their general practitioners. Only 4 patients who lived abroad (Syria, Australia, Turkey, Italy) were lost in follow-up and were excluded from the study.

**Results:** Left ventricular outflow tract (LVOT) obstruction decreased significantly after the injection of 0.9±0.3 ml of ethanol (LVOT gradient at rest pre vs. post TASH: 76.0±17.5 mmHg, after provocation pre vs. post TASH: 163.6±60.4 mmHg, p<0.0001 for all). No patient died during the TASH procedure or during the follow-up time of 6.5±1.4 years. 10 patients died. 7 patients died from non-cardiac reasons (5.3±0.8 years after TASH) and 3 patients died suddenly (2, 9 and 79 months after TASH at the age of 57, 47 and 79 years). In this study population the yearly total mortality was 1.6%, the yearly sudden death rate 0.4% and the in-hospital mortality 0.0%.

**Conclusion:** Prognosis after TASH is excellent even in long-term follow-up. The sudden death rate in this study population is lower compared to untreated HOCM patients. There is no evidence for the induction of an arrhythmogenic substrate after alcohol ablation.

**P4278**

Identification of patients with idiopathic dilated cardiomyopathy and SCAD-HeFT inclusion criteria who could be considered for early ICD implantation

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**Purpose:** To identify patients with recently diagnosed idiopathic dilated cardiomyopathy (IDC) and symptomatic heart failure unlikely to improve despite medical treatment introduction/optimization and who could be considered for early ICD implantation.

**Methods and Results:** 189 consecutive patients with IDC and SCAD-HeFT criteria (LV ejection fraction ≤0.35 and NYHA classes II-III) evaluated for the study. Baseline characteristics were similar in the two groups (n=12, 6%, 4 died suddenly). According to the multivariable analysis, the presence of arrhythmias or death was an independent predictor of the need for an ICD (OR=1.18; 95% C.I. 1.04-1.33), while the presence of atrial fibrillation (OR=1.95; 95% C.I. 1.33-2.85) predicted the need for an ICD in 6 months later. Considering these parameters a model for the probability of non improvement estimation was developed.

**Conclusions:** In IDC, only a minority of patients still have SCAD-HeFT criteria after optimization of medical treatment or die in the meanwhile; applying simple clinical parameters it is possible to identify this patients, who could be considered for earlier ICD implantation.

**P4279**

Surgical correction of HOCM in patients with severe hypertrophy and septal myocardial fibrosis

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**Purpose:** The mechanism of sudden death in HOCM is ventricular tachycardia/fibrillation emanating from areas of fibrosis. The classic Morrow technique for HOCM in patients with severe left ventricular hypertrophy, right ventricular obstruction and myocardial fibrosis is not effective. A new technique of HOCM surgical correction in patients with severe hypertrophy and septal myocardial fibrosis was proposed.

**Methods:** The excision of the asymmetrical hypertrophied area of the interven- tricular septum (IVS) causing LVOT and RVOT obstruction simultaneously was performed from the coronal part of the zone of elevated RVOT obstruction of the LV. This excision was carried out on the right side of the IVS and not the whole IVS thickness. The areas of septal myocardial fibrosis were removed corresponding to the zone of delayed enhancement (DE) imaging. Septal myocardial fibrosis was detected by cardiovascular magnetic resonance with DE imaging after gadolinium infusion. 11 patients with biventricular obstruction, severe hypertrophy (NYHA Class 3) and episodes of ventricular tachycardia (VT) underwent this procedure. Ages ranged from 18 to 38 years. The follow-up period was 41±7 months.

**Results:** 9 patients were free of symptoms (NYHA class 1) and 2 patients had mild limitations. The mean echocardiographic LVOT gradient decreased from 87.9±12.8 to 96.6±3.4 mmHg, the mean value of gradient in RVOT was reduced from 44.6±5.7 to 4.0±1.4 mmHg. Echocardiographically determined septal thickness was reduced from 35.8±3.2 to 20.0±3.2 mm. Sinus rhythm returned in 38.3±7.3% of patients. The classic Morrow technique for HOCM in patients with severe left ventricular hypertrophy, right ventricular obstruction and myocardial fibrosis was not effective. A new technique of HOCM surgical correction in patients with severe hypertrophy and septal myocardial fibrosis was proposed.

**Conclusions:** This novel technique of HOCM surgical correction proves the precise removal of the areas of septal fibrosis and effective elimination of simultaneous LVOT and RVOT obstruction in patients with severe hypertrophy. A major advantage is that injuries, in particular to the conduction system, are easily avoided.
Long-term recovery of atrioventricular conduction after percutaneous transluminal septal myocardial ablation in patients with hypertrophic obstructive cardiomyopathy

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Objectives: Lesion of the atrioventricular (AV) conduction system is a well-known adverse effect of percutaneous transluminal septal myocardial ablation (PTSMA) in patients with hypertrophic obstructive cardiomyopathy (HOCM). Implantation of permanent pacemakers (PM) following PTSMA has been reported in 3 to 38% of patients, but data determining potential long-term AV recovery is sparse.

Methods: The AV-conduction was evaluated by ECG and 48 hours Holter recording at long-term follow-up 4.8±3.6 years after PTSMA. In patients with a PM or implantable cardioverter defibrillator (ICD) the device was adjusted to back-up VVI mode frequency 40. Documented high grade AV block defined as 2nd or 3rd degree was registered.

Results: Eighty six of 101 consecutive patients undergoing first time PTSMA from 1999-2011 (age 61±12 years) had no implantable device at baseline. Left bundle branch block was present in 7% and right bundle branch block in 13% of the patients at baseline. Twenty eight percent (24/86) of the patients without a device at baseline had a PM implanted for high grade AV block 6.4±2.9 days after PTSMA in 26 patients with normal AV conduction showed spontaneous recovery in 43% of these patients. This post-discharge recovery of the AV-conduction after PTSMA might suggest the potential for a more conservative pacemaker strategy.

Conclusions: After first time PTSMA a PM was implanted due to AV block in 26% of patients with no previously implanted device. The long-term evaluation of AV conduction showed spontaneous recovery in 43% of these patients. This post-discharge recovery of the AV-conduction after PTSMA might suggest the potential for a more conservative pacemaker strategy.

Long-term outcomes after heart transplantation for Emery-Dreifuss muscular dystrophy


Background: Emery-Dreifuss muscular dystrophy (EDMD) is an hereditary syndrome related to mutations in lamin A/C gene (LMNA) and is characterised by severe dilated cardiomyopathy, mostly slight peripheral muscular dys trophy, supra-ventricular arrhythmia and atrio-ventricular (AV) block. Transplantation for EDMD is rarely reported in the ISHLT registry. We aim to study outcomes after heart transplantation (HTx) for end-stage heart failure in twelve EDMD patients.

Methods: 12 cases of HTx performed for EDMD confirmed by genetic analysis in a single institution between 1997 and 2011 were compared to 12 patients age, sex and year of transplantation matched. Survival curves were analyzed by Kaplan-Meier method.

Results: Before transplantation, EDMD patients had similar age (56 vs 57 yo, p=0.81), sex ratio (42% male), pre-transplantation NYHA functional class III (p=0.207), left ventricular ejection fraction (LVEF=33% vs 32%, p=0.89), higher rate of supra-ventricular arrhythmia (100% vs 45%, p=0.002) and AV block (58% vs 12.5%, p=0.042) compared to non-EDMD. After HTx, NYHA functional class improved (19±1 vs 1±0, LVEF [72±5.91% vs 69±11.3%, p=0.49), rejection rate (19±3.8% vs 40±8.2% by year, p=0.45), infection rate (14% vs 6% by year, p=0.087), renal function (eGFR=89±13 ml/min, p=0.02) and they had higher incidence of RA block during the procedure (67% vs. 33%, p<0.01) than those who did not.

Eighty patients with PTSMA-related PMs were diseased at the time of follow-up and two patients declined participation in the long-term evaluation of AV conduction. In 43%(61/14 of patients 48 hour Holter recordings did not reveal high grade AV block which suggests post-discharge recovery of the AV conduction. No significant differences in baseline characteristics were found between patients with documented high grade AV block (n=8) and patients with documented normal AV conduction (n=67) at follow-up. Patients with high grade AV block at follow-up had higher incidence of AV block during the PTSMA procedure (63% vs. 42%, p=0.04).

Conclusions: After first time PTSMA a PM was implanted due to AV block in 26% of patients with no previously implanted device. The long-term evaluation of AV conduction showed spontaneous recovery in 43% of these patients. This post-discharge recovery of the AV-conduction after PTSMA might suggest the potential for a more conservative pacemaker strategy.

Distinguishing 320-slice CT-detected focal fibrotic lesions and non-fibrotic lesions in hypertrophic cardiomyopathy by assessment of regional myocardial-strain using two-dimensional Speckle-tracking

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Purpose: To distinguish focal fibrotic and non-fibrotic-lesions in LVM in HCM subjects, we compared myocardial-regional-peak-strain-values using two-dimensional Speckle-tracking transthoracic-echocardiography (TTE) in 320-slice-CT-detected fibrotic, non-fibrotic and normal-control-lesions.

Methods: Forty-subjects (20-consecutive-HCM-subjects [mean 59.1 years], 20-healthy-controls [mean 61.4years]) underwent speckle-tracking TTE, and analysis of regional-peak-longitudinal (LS) and transverse-strain (TS) in each of 17-LVM-segments (American-Heart-Association classification). In HCM-subjects, fibrotic-lesions were identified by early-phase defective-entainment and late-phase abnormal-enhancement by 320-slice-CT. Regional-peak-LS and TS were measured in MOC-detected fibrotic and non-fibrotic LVM lesions.

Results: In 20-HCM-subjects, 318-lesions (93.0%) yielded good-tracking on TTE. RV-lesions showed fibrotic-change in 10-subjects. Region-of-pale absolute-values were significantly lower in fibrotic-lesions than in non-fibrotic-lesions in HCM-subjects and controls (5.6±2.9%, 11.1±5.7%, 14.6±6.2%, respectively), furthermore these were significantly lower in non-fibrotic-lesions in HCM-subjects than controls (P<0.001). However there were no significant-differences of regional-peak-TS among fibrotic and non-fibrotic-lesions in HCM-subjects and controls (10.6±12.7%, 13.2±9.4%, 14.6±11.1%, respectively).

Hidden right ventricular dysfunction in asymptomatic first-degree relatives of arrhythmogenic right ventricular cardiomyopathy assessed by speckle tracking, compared with strain Doppler

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Purpose: According to modifications of criteria of ARVC, proposed to facilitate clinical diagnosis in first-degree relatives, who often have incomplete expression of the disease, the diagnosis of familial ARVC is based on one of the following findings: either mild global dilatation or reduction in RV ejection fraction (EF) with normal LV or mild segmental dilatation of the RV or regional RV hypokinesis. The potential utility of Strain-Strain rate (S-SR) Doppler and two-dimensional (2D) to quantitatively assess: (1) regional strain and strain rate (sR/sRr) function in asymptomatic family members of ARVC, with apparently normal RV, was evaluated.

Methods: 80 subjects were studied:40 first degree ARVC relatives with normal RV at standard echocardiography and 40 healthy controls. By E9-GE LV EF, LV diameters and volumes, RV dimension, fractional area change (FAC%) and RVOT fractional shortening (RVOTs%), RA volume were measured. By DTI velocity of (both P-0.001): longitudinal systolic RV-SR Doppler and 2D-SR in apical 4 and 2-chambers views were measured at level of RV free wall segments, all LV segments and RA wall. Circumferential and radial systolic LV 2D-SR were measured in middle short axis view. By 3D echocardiography with volumetric probe we measured RA and RV volumes.

Results: No significant differences were found between relatives and controls for RV dimensions (1.9±0.3 vs 2.0±0.3 cm), RVFAC (50.1±2 vs 51.1±11%) and RVOTs (64.8±13 vs 65.3±14%), RA max volumes by 2D (39±8.5 vs 37±7.5 ml; index: 20.3±4.5 vs 8.7±6 ml/m²) and by 3D (52±9.6 vs ±51±13 ml; index: 27.4±5.9 vs 28±10 ml/m²), 3D RV end-diastolic (31±10.5 vs 33±11 ml/m²)
Cardiac sarcoidosis has characteristic distribution of late gadolinium enhancement in magnetic resonance imaging in comparison with idiopathic dilated cardiomyopathy

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Purpose: Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) imaging is useful for the early diagnosis of cardiac sarcoidosis (CS). However, since some patients with dilated cardiomyopathy (DCM) also exhibit LGE, the differential diagnosis is sometimes difficult. This study aimed to identify the characteristic distribution of myocardial LGE in CS and to compare LGE patterns in CS with DCM.

Methods: Eighty one patients with suspect of CS and 52 patients with DCM underwent CMR imaging. The intra-left ventricular (LV) and intra-mural distribution of LGE was compared.

Results: LGE was present at 22 patients (27%) with suspect of CS and 30 patients with DCM (58%). In patients with CS, LGE was distributed into all LV segments, whereas LGE localized mainly in basal inter-ventricular septum in patients with DCM. The intra-mural analysis demonstrated that LGE was distributed into subepicardial to subendocardial layers in patients with CS, whereas LGE localized mainly in the mid-ventricular layer in patients with DCM. Especially, subepicardial and subendocardial LGE (with spared mid-ventricular layer), circumferential subepicardial LGE, and nodular (transmural) LGE were characteristic patterns in CS. The sensitivity and specificity were 23% and 97% in subepicardial and subendocardial LGE, 18% and 97% in circumferential subepicardial LGE, and 36% and 97% in nodular LGE, respectively.

Conclusions: In a group of patients referred for cardiac CMR evaluation, TAPSE, tricuspid Sm and global LVS correlated with RVEF obtained by CMR. Free wall RVLS and RVFAC correlated well with RVEF, providing a better estimation of RV systolic performance.
Methods: 55 HCM patients (37 males; mean age 43.1±18 years) underwent two CMR examinations (CMR-1 and CMR-2) separated by an interval of 7/19±410 days. Extent of LGE was measured and the rate of progression of LGE (LGE rate) was calculated as the ratio between the increase of LGE (in grams) and the time (months) between the CMR examinations.

Results: At CMR-1 LGE was detected in 45 subjects, with an extent of 13.3±15.2 grams. At CMR-2, 53 (96.4%) patients had LGE, with an extent of 24.6±27.5 grams. Patients with apical HCM had higher increment of LGE (p =0.004) and LGE-rate (p =0.001) than those with other patterns of hypertrophy (figure). The extent of LGE at CMR-1 and the apical pattern of hypertrophy were independent predictors of the increment of LGE. Subjects with worsened NYHA class presented higher LGE at CMR-1 and the apical pattern of hypertrophy were independent predictors of the increment of LGE. Patients with apical HCM had higher increment of LGE (p 0.004) and LGE-rate) was calculated as the ratio between the increment of LGE (in grams) and the time (months) between the CMR examinations.

Conclusions: DM increases the risk for cardiac complications, HF, hyperkinetic arrhythmias and myocardial fibrosis.

Figure 1. Increment of LGE in different HCM patterns.

P4288 Diabetes mellitus and cardiac complications in thalassemia major patients

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Purpose: The relationship between diabetes mellitus (DM) and cardiac complications has never been systematically studied in thalassemia major (TM). Our aim was to evaluate in a large retrospective historical cohort of TM if DM was associated with an higher risk of heart complications.

Methods: We compared 86 TM patients affected by DM with 709 TM patients without DM consecutively included in the Myocardial Iron Overload in Thalassemia (MIOT) database where the clinical history is recorded from the birth to the first T1 cardiovascular magnetic resonance (CMR) years 2006-2010. Myocardial iron overload (MOI) was evaluated by T2* multislice technique. Biventricular function was quantitatively evaluated by cine images. Myocardial fibrosis was evaluated by late gadolinium enhancement. All considered cardiac events were defined as clinical events developed after the DM diagnosis.

Results: In DM patients versus no-DM patients we found a significantly higher frequency of cardiac complications (46.5% vs 16.9%, P <0.0001), hyperkinetic arrhythmias (18.6% vs 5.5%, P <0.0001), hyperkinetic arrhythmias and myocardial fibrosis, also adjusting for the absence of MOI (all T2* cardiac segments with T2*>20 ms) and for the covariates significantly different between groups and significantly associated to the dependent variable (Table 1).

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>No-MOI</th>
<th>MOI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>3.14 (1.57-6.26)</td>
<td>3.31 (1.57-6.26)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperkinetic arrhythmias</td>
<td>4.09 (2.16-7.74)</td>
<td>4.23 (2.16-7.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial fibrosis</td>
<td>2.12 (1.24-3.83)</td>
<td>2.12 (1.24-3.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart dysfunction (LV and/or RV)</td>
<td>1.45 (0.37-2.33)</td>
<td>1.45 (0.37-2.33)</td>
<td>0.001</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>0.77 (0.37-1.60)</td>
<td>0.77 (0.37-1.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>0.96 (0.10-3.00)</td>
<td>0.96 (0.10-3.00)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions: DM increases the risk for cardiac complications, HF, hyperkinetic arrhythmias and myocardial fibrosis.

P4290 Left ventricular hypertrophy in individuals with sickle cell anaemia: physiology or pathology?

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Introduction: Left ventricular noncompaction (LVNC) cardiomyopathy is rare amongst Caucasians but studies in African/African-Caribbean origin (black) heart failure patients demonstrate that a high proportion fulfill criteria for LVNC (30%). Recent observations in elite athletes, have also demonstrated a 3-fold greater prevalence of increased LV trabeculations (LVHT) amongst black athletes compared with Caucasian athletes, with almost 15% fulfilling echocardiographic criteria for LVNC. We postulate that the LVHT observed in black individuals represents an ethnically determined cardiac response to increase preload. Sickle cell anemia is associated with an increased preload and a high cardiac output. The aim of this study was to evaluate the prevalence of LVHT amongst homozygous sickle cell disease patients.

Methods: Between 2005 and 2012, 99 consecutive normotensive sickle cell patients (53% male) underwent echocardiography.Echocardiograms were analysed for trabeculations defined as localised protrusions of the ventricular wall-strm in thickness associated with intertrabecular recesses and previously published criteria for LVNC. The results were compared with 132 healthy black controls (55% male).

Results: Sickle cell patients were older with compared to controls (33±11 years vs 21±6 years; p<0.0001) with no difference in systolic BP (118±11mmHg vs 120±15mmHg; p<0.165) in either group. Sickle cell patients had a mean Hb level of 8.6±1.2g/dl (range 5.5g/dl-11.6g/dl). Sickle cell patients displayed a higher prevalence of LVHT compared with controls (28.3% vs 12.1%; p=0.0002). Of the sickle cell patients, 20.8% fulfilled conventional Chin et al and 10% Jennis et al criteria for LVNC. None of the controls fulfilled the published LVNC criteria. Sickle cell patients with LVHT exhibited a larger LV cavity size compared to controls with LVHT (51.7±6.0mm; range 44-66mm vs 47.1±6.0mm; range 38-54mm; p<0.0001) but showed no difference in LVVd in Sickle cell patients without LVHT (mean LVVd was 51.1±6.0mm vs 51.9±6.1mm; p=0.604). There were no differences in LV systolic or diastolic function in sickle cell patients with or without LVHT (EF by Simpsons was 61±8.1% vs 61±8.4%;p=0.985; E/A ratio was 2±0.8 vs 1±0.7; p=0.511 and MV deceleration 191±36ms vs 194±51ms; p=0.792).

Conclusion: The high prevalence of LVHT in sickle cell patients compared with black controls further reinforces the likelihood of this morphological anomaly representing a physiological response to increased cardiac preload and endorses the need for robust criteria for diagnosing LVNC in black individuals.

P4291 T1 mapping in differentiation of diffuse myocardial disease in hypertrophic and dilatative cardiomyopathy


Background: T1 mapping was proposed as potentially valuable in quantitative assessment of diffuse myocardial fibrosis. We aimed to determine its role in differentiation of healthy myocardium from diffuse fibrosis clinical setting.

Methods and results: Thirty-nine subjects with known hypertrophic (HCM) or dilatative cardiomyopathy (DCM) were enrolled (age 47±7.4 years). Twenty-five age- and gender-matched subjects with low pre-test likelihood of cardiomyopathy served as controls. Single equatorial short-axis slice T1 mapping was performed on a 3 Tesla scanner prior and at 10, 20 and 30 minutes after administration of 0.2 mmol/l of gadobutrol. We quantified T1 values within the septal myocardium (T1s) and lateral myocardium (T1l) for each subject with R1 (T1s/T1l) and the R1 differences between the native and post-contrast myocardium (ΔRR). R1 native was significantly shorter in cardiomyopathies compared to control subjects (p<0.01). Conversely, post-contrast R1 were significantly longer in cardiomyopathies at all time-points (p<0.01). ΔRRs were significantly higher in cardiomyopathies in comparison to controls.
Effect of physical exercise on cardiac remodeling and oxidative stress in diabetic rats


Purpose: Oxidative stress is one of the main mechanisms involved in the pathogenesis of diabetic cardiomyopathy. Studies suggest that physical exercise (PE) improves myocardial glucose homeostasis and reduces myocardial damage from diabetes mellitus (DM). The aim of this study was to evaluate the effect of PE on myocardial oxidative stress and in vivo and in vitro cardiac structure and function in diabetic rats.

Methods: Male Wistar rats were divided into three groups: control sedentary (CS, n=15), diabetic sedentary (DS, n=15), and diabetic trained (DT, n=15). Diabetes mellitus was induced by intraperitoneal injection of streptozotocin (50mg/kg, single dose). Physical training was performed 5 times a week for 8 weeks in a treadmill. All at the end of the experimental period, rats underwent echocardiography. Myocardial functional was evaluated in left ventricular (LV) papillary muscle preparations during isometric contractions. Oxidative stress was measured in LV myocardial tissue sample with dichlorofluorescein and oxidative stress parameters, and ANCOVA for papillary muscle parameters using laboratory (BNP) and immunohistological parameters tested (CyPA, EMMPRIN, CD68, CD3, MCH II, virus genome), CyPA was identified as the only independent predictor for the primary endpoint yielding a relative risk of 2.5 (95% CI 1.2-5.2; p=0.018, figure) as well as a relative risk of 4.7 for all-cause mortality and heart transplantation alone (95% CI 1.1-19.8; p=0.036). Subgroup analysis also revealed CyPA as a predictor of outcome in the patients with non-inflammatory cardiomyopathy suggesting that CyPA is a prognostically relevant marker of myocardial damage beyond inflammation.

Conclusions: CyPA is an independent predictor of clinical outcome in patients with congestive heart failure.
serum caeruloplasmin (Table 1). Serum zinc trended higher in healthy volunteers compared with HCM patients. There were no significant differences in urinary zinc or copper between the two groups.

| Table 1. Differences in copper and zinc in patients with HCM compared with healthy volunteers |
|---------------------------------|---------------------------------|-----------------|
|                                | HCM Patients                     | Healthy Volunteers |
| Serum Copper umol/L            | 19.4±5.36SD                     | 18.27±5.36SD     | 0.04  |
| Serum Zn umol/L                | 18.28±5.43SD                    | 23.71±10.73SD    | 0.06  |
| Serum Caeruloplasmin g/L       | 0.24±0.05SD                     | 0.20±0.04SD      | 0.02  |
| Urinary Copper umol/24 hours   | 0.35±0.09SD                     | 0.33±0.11SD      | 0.51  |
| Urinary Zn umol/24 hours       | 8.23±5.42SD                     | 6.99±3.90SD      | 0.37  |

Conclusion: HCM patients exhibited overtly altered copper homeostasis. Coupled with the previous observation of LVH and fibrosis regression induced by copper chelation therapy these findings provide a mechanistic basis for copper chelation therapy to be tested in HCM.

P4295 Tyrosyl-tRNA synthetase: peculiarities of myocardial expression and autoimmune reactions at dilated cardiomyopathy

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Background: Aminoacyl-tRNA synthetases (ARS) are enzymes that play not only a leading role at the first prebiosomal step of protein biosynthesis, but may participate in binding of immune and autoimmune reactions. Antibodies (Abs) directed against ARSs are associated with different disease (myositis, arthritis, heart failure etc.). Moreover, the catalytic N-terminal module of tyrosyl-tRNA synthetase (TyrRS) may functions as immunemodulating factor (similar interleukin-8) and C-terminal module of TyrRS also shows the ability to stimulate the cell proliferation via cytokine-like EMAP II. The aim of investigation was to study the expression of TyrRS in myocardium and to examine the peculiarities of autoimmune reactions against full-size TyrRS and its N- and C-terminal modules at dilated cardiomyopathy (DCM).

Materials and methods: Recombinant proteins full-size TyrRS and its N- and C-terminal modules were isolated from the bacterial strains based on Echerichia coli BL21(DE3)pLysE. TyrRS expression in myocardium was identified by Western-blot analysis in paraffinopathologic specimens of three DCM-affected human myocardia and samples of myocardium of three practically healthy men who died from cardiac trauma as a control. The level of specific circulating Abs against full-size TyrRS and its N- and C-terminal modules were measured by ELISA method in sera of 30 DCM patients with CHF. III functional NYHA classes, chronically treated with beta-blocker, inhibitor ACE, diuretic. Sera of 20 healthy donors were examined as a control. To study the effect of auto-Abs, purified from DCM pts' sera with immunofluorescence chromatography, on TyrRS enzymatic activity we analyzed parameters changes of aminoacylation reaction of cognated tRNA catalyzed by TyrRS.

Results: The increased expression (on 43%) of TyrRS was revealed in total lysate and especially in nuclear subfraction of DCM-affected cardiomyocytes in compared to control.

The increased level (for 29.3%) of IgG class auto-Abs against full-size TyrRS, against its N- (for 18.5%) and C-terminal modules (for 65.5%) were found in blood serum of DCM patients, compared with healthy donors.

The degrees of DCM sera IgM Abs elevation against full-size TyrRS purified from DCM pts' sera in vitro provided a dose-dependent stimulating effect (practically twice enhancement) on TyrRS enzymatic activity.

Conclusion: These results demonstrated a novel antigen-target at DCM - tyrosyl-tRNA synthetase and revealed its potential role at disease development.

P4296 Cardiotoxic anticancer agents induce an increase in myocardial weight: a pathophysiologic study of models of cardiac mechanics

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Purpose: Administration of cardiotoxic anticancer agents results in a dose-dependent and significant increase in left ventricular mass (LVM). This study investigated the precise cardiac mechanisms that occur with this phenomenon in an effort to predict safe doses of anticancer agents.

Methods: A total of 229 consecutive patients with breast cancer (all females; mean age: 51±7 years) who completed adjuvant chemotherapy with three drugs (epirubicin, cyclophosphamide, and fluorouracil [CEF]) over a 60-month period were studied. Echocardiography was performed before and after several cycles of CEF.

The left atrial diameter (LAD), LV diameter in diastole/systole (LVDd/s), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), interventricular septal thickness (IVST), posterior wall thickness (PWT), LV ejection fraction (LVEF), stroke volume (SV), ratio of early to late ventricular filling velocity (E/A), mitral annulus velocity (e'), Tei index (TI), LVMI, LVM index (LVMx), diameter of inferior vena cava (IVC), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated. The calculations were based on the following formula: LVEF = (EDV - ESV)/EDV, where (EDV = LVEDV + LVESV), IVST = (IVS + PWT)/2, SV = stroke volume (EDV - ESV), E = early diastolic flow, A = late diastolic flow, SBP = systolic blood pressure, DBP = diastolic blood pressure, LVM = LVM index (LVMx = 1.05 × LVMI). The increased expression of ARSs is correlated with different disease (myositis, arthritis, heart failure etc.). Moreover, the catalytic N-terminal module of tyrosyl-tRNA synthetase (TyrRS) may functions as immunemodulating factor (similar interleukin-8) and C-terminal module of TyrRS also shows the ability to stimulate the cell proliferation via cytokine-like EMAP II. The aim of investigation was to study the expression of TyrRS in myocardium and to examine the peculiarities of autoimmune reactions against full-size TyrRS and its N- and C-terminal modules at dilated cardiomyopathy (DCM).

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The degrees of DCM sera IgM Abs elevation against full-size TyrRS purified from DCM pts' sera in vitro provided a dose-dependent stimulating effect (practically twice enhancement) on TyrRS enzymatic activity.

Conclusion: These results demonstrated a novel antigen-target at DCM - tyrosyl-tRNA synthetase and revealed its potential role at disease development.

P4297 A French registry of takotsubo syndrome in non-academic hospitals (OFSETT)

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Purpose: Takotsubo syndrome remains the subject of investigation. We reported on the management and processes of care in consecutive patients with Takotsubo syndrome using data from a French registry (OFSETT).

Methods: Between November 2010 and December 2011, 15 non-academic hospitals with a high volume of percutaneous coronary procedures (>1000) included consecutive patients diagnosed with Takotsubo syndrome according to the Mayo clinic diagnostic criteria.

Results: A total of 121 patients were enrolled: 89% were women and the mean age was 72±12 years. Most of the women (89%) were >50 years old. 8% of patients had diabetes, 30% were current smokers and 52% had hypertension. Symptoms of Takotsubo syndrome were chest pain (81%), dyspnoea (27%) and syncope (5%). The median maximum troponin level was 7.8 ng/mL and the mean maximum B-type natriuretic peptide level was 1013 pg/mL. ECG showed a negative T wave in 73% and 42% of patients had chest pain and 42% had a new Q wave in 29% of patients. One patient was treated with fibrinolysis. Coronary angiography was performed in all patients. Coronary arteries were angiographically normal in 78% of patients and showed >50% stenosis in 22%. Left ventricle (LV) angiography showed typical ballooning in 22% of patients. The mean LV ejection fraction was 42±13% on echocardiography and 46±10% on angiography. The target event was identified in 55% of the patients: mental stress in 61% and physical stress in 25%.

Conclusion: These observational data from 15 non-academic French hospitals provide insights into the characteristics of patients with Takotsubo syndrome and current processes of care for this population. Furthermore, they offer an opportunity for comparison with data from patients with acute myocardial infarction.

P4298 Syncope in hypertrophic cardiomyopathy: the diagnostic role of flow mediated dilation

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Introduction: Hypertrophic Cardiomyopathy (HCM) is an inherited myocardial disease characterized by unexplained increased left ventricular wall thickness associated with nondilated ventricular chambers in the absence of other cardiac or systemic disease. Syncope occurs in approximately 15–25% of patients with HCM. The principal causes can be arrhythmia and a primary haemodynamic mechanism. Abnormal blood pressure response during exercise and left ventricular outflow tract obstruction are the most important haemodynamic mech-
The extent and consequences of diagnostic uncertainty in individuals assessed for arrhythmogenic right ventricular cardiomyopathy

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Purpose: The diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC) depends on clinical tests. The findings of these tests can be non-specific in the early stages of the disease therefore long term follow up and serial testing are often necessary to make a definite diagnosis. The diagnostic criteria were revised in 2010 with the intention of increasing their sensitivity and specificity. Despite this there are individuals who can be given neither a definite diagnosis or reassurance because the manifestations of the disease are slow to develop. Relatives of affected individuals assessed as part of familial screening are particularly likely to fall into this category. Less than 50% of probands with ARVC have a identifiable pathogenic mutation, therefore genetic screening cannot resolve this problem. We constructed a registry of individuals who have been seen in the north of England for ARVC to determine how many individuals live with long term diagnostic uncertainty and the resources required for their ongoing follow up.

Method: Individuals seen by clinical services in connection with ARVC from 2005 to the present were identified retrospectively from clinical records. Major and minor diagnostic criteria for ARVC were identified from the results of clinical tests using the 2010 criteria.

Results: 92 individuals have been assessed for ARVC and found to have some clinical or genetic abnormality. 69 individuals (74%) lack a definite diagnosis. 21 are known to have a pathogenic mutation and were followed up to identify the expected phenotypic features over time. Genetic screening was not an option for the remaining 48 individuals. The mean duration of follow up for this group was 5.4 years, SD 4.5, range 1.1 to 21.1. For every 5 years of follow up individuals without a definite diagnosis had a mean of 3 echocardiographic examinations, 2 cardiac MRIs and 1 ambulatory ECG assessment.

Conclusions: The majority of individuals seen in clinical practice for suspected ARVC lack a definite diagnosis. These individuals live with diagnostic uncertainty of a potentially life threatening disease for many years and require regular follow up and repeated clinical testing to reassess their phenotype. Our findings underline the importance of research to identify the clinical significance of mutations and the need for a novel diagnostic test for presumptivcymal.

In dilated cardiomyopathy the stimulating potential of anti-beta1-receptor autoantibodies is positively correlated with the depression of left ventricular function

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Dilated cardiomyopathy (DCM) characterized by progressive cardiac dilation and dysfunction is one of the main causes of severe heart failure in younger adults. Previously we introduced a live cell assay for the detection of functional anti-beta1 receptor autoantibodies (beta1-aabs) using fluorescence resonance energy transfer (FRET) microscopy. Here we used this method to investigate the relationship between the receptor-activating potential of beta1-aabs and cardiac dysfunction in DCM.

Methods: The analyzed DCM population (n=97) had significant CAD excluded and was stable on medication according to current therapy guidelines for at least 3 months. In our outpatient-unit blood was drawn and immediately processed for lab testing. All patients tested underwent echocardiography to assess left ventricular (LV) function and age 40±5 agreement to AEC-recommendations. Serpa from n=43 healthy volunteers from whom echocardiographic data were available served as a reference (control). HEX-293 cells expressing human beta1-adrenoceptors and an Epac1-based cyclic Adenosine Mono-Phosphate (cAMP) sensor were used in the FRET assay. Upon beta1-aab-mediated receptor stimulation, intracellular cAMP levels increase, and cAMP-binding to the sensor results in conformational changes decreasing FRET between its chromophores cyan (CFP) and yellow fluorescent protein (YFP).

Results: Immunoglobulin G (IgG) prepared from healthy controls with normal cardiac function (n=49/97) and DCM patients was judged beta1-aab positive (9.6±4%). Beta1-aab positivity was subsequently defined as -mean ±2 SD of controls (=18.6% FRET activity). IgG prepared from n=49/97 DCM patients were judged beta1-aab positive (26.6±1% FRET activity, LVEF 32.8±1%). Allower, in DCM patients but not in control subjects there was a highly significant (p<0.0001) inverse correlation between FRET activity (+receptor stimulating potential of beta1-aabs) and LVEF (r=-0.4; R2=0.17).

Conclusion: In this study on 97 DCM patients we demonstrate for the first time that the decrease in cardiac function is significantly associated with the receptor-stimulating potential of activating beta1-aabs. Based on this promising result a large prospective follow up study is planned to correlate the beta1-aab levels, their time course, and the incidence of (a) peak & time-course of beta1-aab titers, (b) time to disease progression, and (c) beta-blocker treatment on the incidence, prevalence, and receptor stimulating potential of beta1-aabs in human cardiac disease.
The impact of dynamic intraventricular obstruction on left ventricular mechanics in hypertrophic cardiomyopathy

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Purpose: To assess LV mechanics in patients (pts) with obstructive (HOCM) and non-obstructive (NHCM) HCM versus normal subjects.

Methods: We prospectively enrolled 35 pts (52±15 years, 16 men) with HCM (19 with HOCM and 16 with NHCM, according to the presence/absence of a dynamic LVOT gradient > 30 mmHg) and 6 age- and gender-matched normal subjects (47±12 years, 12 men). Pts with aortic HCM have been excluded. A comprehensive echocardiogram was performed in all. LV filling pressures were assessed using the E/e' average ratio. Global longitudinal LV strain (GLS) and LV torsion parameters have been assessed by speckle tracking echocardiography. Peak basal and apical rotation and backrotation rates, apical and basal LV rotation and peak LV untwisting rate were determined. Time intervals from peak R wave (EKG) to each of them were measured and normalized to the RR interval. Mitral regurgitation (MR) severity was assessed in the second cluster.

Results: Pts with HOCM were older (p=0.009) and had more severe MR (p=0.001) than pts with NHCM. There were no significant differences between HOCM and NHCM pts regarding LV mass, E/e', systolic and diastolic myocardial velocities, ILS, and GLS (p=0.05 for all). Compared to normal subjects, pts with HOCM, unlike pts with NHCM, had higher values for apical LV rotation (21.7±8.5 vs 16.4±6.3°, p=0.001) and backrotation rate (p=0.00) at baseline (0.04°) and LV torsion (3.7±1.3 vs 2.8±1.8°/cm, p=0.002). Time to peak LV untwisting rate was significantly longer than in normal subjects in both HOCM and NHCM pts (p=0.001 and p=0.01, respectively). In pts, LV torsion was related to age (r=0.49, p=0.003), GLS (r=-0.67, p=0.0001) and the 2nd cluster (1.3 vs 2.8, p<0.001). Also, in NHCM pts, LV torsion was related to MR (GLS 0.25/s vs. 1.62, p=0.009) and death (MR 2.0 ng/ml vs 1.3, p=0.01), and the presence of dynamic obstruction (r=0.38, p=0.02). In multivariate analysis LV torsion was independently correlated with GLS (p=0.05, p=0.03) and the presence of dynamic obstruction (p=0.35, p=0.04).

Conclusions: In pts with HCM, LVOT obstruction is related to changes in LV mechanics: increased apical and basal rotation, increased LV torsion, and delayed LV untwisting. Increased LV torsion is independently related to the presence of dynamic LVOT obstruction. These findings could provide new insights into the pathophysiology of HCM.

Prevalence of psychiatric disorders in Tako-Tsubo cardiomyopathy

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Purpose: Tako-Tsubo cardiomyopathy (TTC) involves transitory left ventricular dysfunction, generally subsequent to stress. Most often, it affects post-menopausal women. Unusual prevalence of psychiatric disorders has been forwarded as an explanation of the deleterious and disproportionate catecholergic response to stress. However, this prevalence has never been clearly established.

The aim of our study was to determine the prevalence of psychiatric disorders in TTC.

Methods: A history of psychiatric problems and psychotropic treatment were examined prospectively in a population of 70 TTC patients recruited over 36 months in 3 hospital centers. These were compared with those of 53 anterior ST-segment elevation myocardial infarction (STEMI) and 51 anterior non-ST-segment elevation myocardial infarction (NSTEMI). These groups were matched for age and gender.

Results: Close on 61.4% of TTC presented a history of psychiatric problems versus 28.4% for ACS (p<0.001), i.e. 2.16-fold more. The most frequently encountered psychiatric disorders in TTC were anxiety (30%), depression (28%) and schizophrenia (3.2%). Long-term psychiatric treatment had been delivered to 47.8% of TTC patients versus 20.1% for ACS (p<0.001). The most commonly treated psychotropic treatments in TTC were.

Conclusion: The prevalence of psychiatric disorders in TTC is strong, as witnessed by the high intake of psychotropic treatments. Anxiety-related and depression-related disorders are most often at issue. The observed elevated prevalence of cancer and chronic respiratory insufficiency could be partly responsible for these disorders.

Clinical characteristics and short-term outcome of patients with Takotsubo syndrome and critical coronary stenosis: comparison with patients with Tako-tsubo with normal coronary arteries

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Purpose: Takotsubo syndrome (TTS) may be associated with significant coronary artery disease (CAD), but the prevalence, clinical characteristics and outcome of TTS with CAD and the pathogenetic role of CAD are not well defined.

The aim of the study was to compare the clinical characteristics and short-term outcome of pts with TTS and critical CAD with those with TTS with no CAD and no critical CAD.

Methods and Results: 184 consecutive pts (aged 71±12 yrs, 90% women) admitted with acute symptoms and ST-T changes who showed a reversible pattern of LV dysfunction, shock, major arrhythmias and LV thrombosis. Death occurred in 5/16 pts with CAD. TTC were characterized by dyslipidemia (40 vs 42%), presence of a trigger (56% vs 68%) and peak troponin I (3.3±1 vs 4.2). Presence of a trigger (56% vs 68%) and peak troponin I (3.3±1 vs 4.2) was observed between the 2 groups. Of the 16 pts with CAD, 11 had 1-vessel CAD, 3 multivessel CAD, 1 a previous inferior infarction treated with PCI and 1 previous PCI with no residual stenosis. In 11/15 pts there was no relation between the site of critical CAD and that of LV asynergy. During the acute phase there were 7 (3.8%) deaths and 36 (19%) major complications including LV failure, shock, major arrhythmias and LV thrombosis. Death occurred in 5/16 pts with TTS+CAD vs 4/172 pts with TTS + no CAD (19% vs 2.3%, p=0.009) and death + major complications in 5/16 pts with CAD vs 38/168 pts with TTS+CAD (32 vs 22%, ns). Age (p<0.001), female TTS (p=0.048) and troponin I peak (p=0.007) but not critical CAD were univariate predictors of death + major complications; at multivariate analysis, only age remained a significant predictor (odds ratio 1.05, CI 1.03-1.08, p<0.001).

Conclusion: 1) In a large population of TTS, 9% of pts show critical CAD; 2) Compared to pts with TTS and no CAD, pts with TTS + critical CAD are characterized by older age, male sex and lower LV ejection fraction and have a significantly higher in-hospital mortality and a higher incidence of major complications.

3) The lack of correlation between the site of critical CAD and that of LV asynergy suggests that in most pts critical CAD is an innocent bystander and not the culprit of the acute event.
Completely autologous biotube vascular grafts: eosin Y significantly promoted in vivo formation of functional biotubes in a short term

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Objectives: In our previous study, in vivo tissue-engineered autologous tubular tissues ‘BIOTUBES’ could reconstruct to vascular tissues within several months after implantation. BIOTUBES spontaneously turned into traditional silicone mold in dorsal subcutaneous pouches of animals for 1 month had homogeneous thin (less than 0.1 mm) connective tissue walls even though with high burst strength (ca. 10 kg) and equivalent compliance to that of native arteries. We challenged the possibility of extremely short term preparation of BIOTUBES by controlled release of eosin Y.

Methods and Results: Micropored acrylate tubes (diameter: 4 mm, length: 4 cm, pore size: 0.5 mm) filled with a PBS solution of agar (0.3%) including eosin Y (1%), as molds for BIOTUBES, were placed into dorsal subcutaneous pouches of Beagle dogs (ca. 10 kg) for 1 week. Eosin Y was continuously released through the micropores of the agar on the biotubes during this period. BIOTUBES were easily auto-implanted to the main artery of rabbits in vivo with the accompanying vein distal to the ligature. Local MAC-subpopulations are involved in arteriogenesis and growth. However, a detailed analysis which MAC-subpopulations...
in RA. GPF-positive cells in PVAT were more abundant after two weeks of HFD than after chow diet.

**Conclusions:** Two weeks HFD blunted insulin-induced microvascular recruitment. The ex-vivo data suggest that this can be attributed both to a loss of vasodilator capacity of RA in response to insulin, as well as altered PVAT properties. Furthermore, the phenotype of PVAT changes due to influx of inflammatory cells after a short HFD.

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**Saphenous vein aorto-coronary bypass graft arteriosclerosis in patients with chronic kidney disease:** more calcification, but less vasoconstrictor potential.

**Methods:** In patients with and without CKD (n=20), SVF calcification was determined. Using a bioassay of rat mesenteric arteries with intact (+E) and denuded (-E) endothelium, the vasoconstrictor response to coronary aspirate plasma was quantified and normalized to that by potassium chloride (KClmax = 100%).

**Results:** There was more dense calcium in patients with than without CKD (15.3±3.3% vs. 3.1±1% of plaque volume). Patients with CKD had more calcified coronary artery lesions than patients without CKD. In contrast, the release of serotonin was less in patients with than without CKD (0.4±0.1 μmol/L vs. 1.2±0.3 μmol/L), whereas that of catecholamines, endothelin, tissue factor, thromboxane, an inflammation factor (TNF) in coronary aspirate plasma was determined.

**Conclusion:** Calcification is more severe in patients with CKD, but the aspirate has surprisingly less serotonin and vasoconstrictor potential.

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**The effect of treatment with drospirenone/ethinyl estradiol alone or in combination with metformin on elastic properties of aorta in women with polycystic ovary syndrome**

**Methods:** Thirty-seven women with PCOS patients (mean age 23.1±5.0) randomized to oral treatment of alone OCP (n = 19) or OCP combination with metformin (n = 18) for 6 months. The elastic parameters of aorta; “aortic strain”, “aortic distensibility”, “aortic diameter alteration”, and “aortic stiffness index” have been calculated by appropriate formulae. The hormonal profile, HOMA-IR score, basal insulin and glucose levels were studied in both groups. Before and after 6 months treatment, echocardiographic measurements and laboratory tests were also obtained.

**Results:** After 6 months treatment, significant weight loss and decrease in BMI was observed in the metformin group (75.3±13.3 kg to 72.9±13.5 kg and 31.7±7.3 kg/m² to 30.4±7.3 kg/m², p < 0.001 and p = 0.001, respectively). Conversely in the yasmin group, increases in BMI and weight were observed (68.8±18.3 kg to 71.6±21.2 kg, and 26.4±6.2 kg/m² to 27.4±6.9 kg/m², p = 0.159 and p = 0.149, respectively). There were increases in aortic strain and distensibility (7.7±4.2 to 7.8±3.6 and 7.2±4.1 to 7.7±3.6, p = 0.926 and p = 0.593, respectively) and decreases in the stiffness index in the yasmin group but these were not significant (8.8±7.4 to 8.2±6.7, p = 0.772). In the metformin group, adjusted values of aortic stiffness index decreased significantly at 6 months follow-up (10.0±1.5 to 7.6±3.0, p = 0.021) and aortic distensibility and strain increased but not significantly (7.0±4.3 to 9.3±5.9 and 6.8±3.9 to 9.4±3.5, p = 0.163 and p = 0.071, respectively) at 6 months follow-up.

**Conclusion:** We demonstrated an improvement in the elastic parameters of aorta by adding metformin to OCP treatment. Additionally, a reducing in testosterone levels correlated with a reduction in aortic stiffness hence may be beneficial for cardiovascular disease. These results indicate that metformin plus OCP treatment may decrease cardiovascular disease risk in women with PCOS.
Molecular mechanism of tissue factor regulation through RAGE-MT1-MMP axis in HMGB-1 stimulated-endothelial cells

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Background: The atherosclerosis is understood as a blood vessel inflammation. HMGB-1 is one of the mediators released from necrotic cells or macrophages that receives inflammatory stimulus. It plays a key role in the systemic inflammation. Tissue factor (TF), a physiological initiator of coagulation cascade, is known to lead to inflammation which promotes the thrombus formation in the onset of acute coronary syndrome. We recently have shown that silencing of membrane type 1 MMP (MT1-MMP) suppressed the advanced glycation endproducts (AGE)-triggered TF protein expression and phosphorylation of NF-κB in smooth muscle cells. These results suggest that MT1-MMP also relates to inflammatory conditions in vascular wall. However, it is still unclear about the association of HMGB-1 and MT1-MMP mediated - TF expression. In this study, we investigated the molecular mechanism of TF expression in response to HMGB-1 stimulation and the involvement of MT1-MMP in endothelial cells.

Methods: Human aortic endothelial cells were stimulated with 50pg/ml HMGB-1. The protein levels of TF and phosphorylated NF-κB were determined by Western blotting. The MT1-MMP activity was measured by ELISA. MT1-MMP expression was silenced by small interfering RNA (siRNA). GTP-loading of RoA and Rac1 was assessed by pull-down assays.

Results: HMGB-1 increased MT1-MMP activity and activated small GTP binding protein RoA and Rac1 within 5minutes in endothelial cells, which was inhibited by silencing of receptor for AGE (RAGE) or MT1-MMP. TF protein expression was regulated by RoA activation as well as Rac1 dependent NF-κB or phosphorylation in HMGB-1 stimulated endothelial cells. siRNA to RAGE or MT1-MMP suppressed NF-κB phosphorylation and TF protein expression mediated via RoA and Rac1 activation induced by HMGB-1.

Conclusions: We clarified that RAGE/MT1-MMP axis modified the HMGB-1 mediated TF expression throught the RoA and Rac1 activation and NF-κB phosphorylation in endothelial cells. These results suggested that MT1-MMP was involved in vascular inflammation and might be a good target for treating acute coronary syndrome.

Pharmacokinetic interactions between clopidogrel and rosuvastatin: effects on vascular protection in subjects with coronary heart disease


Background/Objectives: Genetic polymorphisms in the hepatic cytochrome P450 (CYP2C19) affect the antiplatelet effects of clopidogrel. Rosuvastatin is partially metabolized by the same cytochrome. We hypothesized that pharmacokinetic interactions between these drugs might affect their individual responses on vascular protection.

Methods: Patients with stable coronary heart disease (N=20) were submitted to four consecutive 1-wk therapeutic regimens: aspirin, rosvastatin 40mg, rosuvastatin 10mg plus clopidogrel 75mg, clopidogrel 75mg and placebo. The loading dose of 300mg clopidogrel was given in the first day. Biochemistry, platelet function (multiplatelet analyzer), flow-mediated dilation (ultrasound of the brachial artery), endothelial progenitor cells, and microparticles (flow-citometry) were assessed at baseline and during the end of treatment. Viability was assessed by 7AAD and Annexin-V-staining.

Results: Patients with ET-1 levels above the median value had higher levels of C-reactive protein (0.03±0.01 vs. 0.35±0.008 in subjects without history of ischaemia, p<0.001) and the maximal concentration of sCD34+CD133+ and sCD34+KDR+ EPC was 5.3±2.3 and 0.9±0.7 respectively; p=0.04), and displayed longer clot formation time (573±15 and 522±7 sec respectively, p=0.01). Clot formation time predicted previous ischemic events in men and women [OR 1.22 (1.07, 1.38) and 1.33 (1.15, 1.50), respectively], after controlling for traditional risk factors. Body mass index and waist circumference predicted clot structure parameters, particularly in women, whereas insulin treatment was associated with thrombogenic clots in men. Aspirin, a known fibrinolytic agent, demonstrated little effect on clot structure/function.

Conclusions: Women with diabetes have a thrombogenic clot structure compared with men and gender-specific associations are detected between clotting parameters and cardiovascular risk factors/treatment. Improved clotting parameters with metformin therapy and the relatively minimal effect of aspirin may partly explain cardioprotection by the former and reduced clinical efficacy of the latter in diabetes.


Aims: Endothelial progenitor cells (EPC) represent an endogenous repair mechanism involving reendothelialization and reangiogenesis. Patients with both diabetes and vascular disease associated with endothelial dysfunction have low numbers of circulating EPC. The endothelin-derived peptide, endothelin-1 (ET-1), is increased in patients with diabetes and vascular disease. ET-1 has been suggested to contribute to endothelial dysfunction in this condition. Therefore, we investigated the relation between EPC and plasma ET-1 and the effects of dual ET-1 receptor antagonists on the number of EPCs.

Methods: In this double blind study patients with type 2 diabetes mellitus and microalbuminuria were randomized to treatment with the dual ETA/ETB receptor antagonist bosentan (125 mg bid; n=17) or placebo (n=19) for four weeks. Different EPC subpopulations were enumerated by flow cytometry using triple staining (CD34, CD133, Kinase domain receptor, KDR) at baseline and at the end of treatment. Viability was assessed by 7AAD and Annexin-V-staining.

Results: Baseline ET-1 levels correlated significantly with C-reactive protein levels. Patients with ET-1 levels above the median value had higher levels of CD34+CD133+ and CD34+KDR+ EPC (Table 1). There was no difference in markers of EPC apoptosis or circulating markers of endothelial damage between patients with ET-1 levels below or above the median. Four weeks treatment with bosentan did not change EPC levels.

Conclusions: Among patients with type 2 diabetes and vascular disease, high plasma levels of ET-1 is associated with higher number of EPC, possibly reflecting activation of an endothelial cell repair mechanism triggered by vascular damage. The recruitment of EPC does not seem to be regulated by ETA or ETB receptor stimulation since treatment with a dual ET-1 receptor blocker did not affect circulating EPC numbers.

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Apoptosis of vascular smooth muscle cells (VSMC) in advanced atherosclerotic plaques is an important cause of plaque instability and may result in plaque rupture followed by thrombosis and sudden death. Within several pro-apoptotic factors, enhanced reactive oxygen species generation has been suggested as a cause for VSMC death and plaque instability. However, the precise mechanism of oxidative stress-induced VSMC apoptosis is still poorly understood.

Results: We investigated the role of oxidative stress-induced apoptosis of VSMC using the ubiquitously expressed soluble adenylyl cyclase (sAC). Therefore, to investigate the role of sAC in apoptosis of VSMC was the aim of the present study. For this purpose, oxidative stress was induced in VSMC derived from rat aorta by treatment with 

Conclusion: Apoptosis of VSMC induced by 

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Results: We investigated the role of oxidative stress-induced apoptosis of VSMC using the ubiquitously expressed soluble adenylyl cyclase (sAC). Therefore, to investigate the role of sAC in apoptosis of VSMC was the aim of the present study. For this purpose, oxidative stress was induced in VSMC derived from rat aorta by treatment with H2O2 (200 μM) or DMG (inducer of mitochondrial superoxide production, 30 μM) for 6 hours. Both treatments led to pronounced release of mitochondrial cytochrome c, caspase-9-3-decrease of NF-κB phosphorylation and increase of apoptotic cell number (TUNEL).

Conclusion: Apoptosis of VSMC by treatment with 30 μM KHT (a specific inhibitor of sAC) or sAC-knockdown (shRNA-transfection) prevented the pro-apoptotic effects of H2O2 and DMG. Similarly, inhibition of protein kinase A prevented the pro-apoptotic effect induced by oxidative stress. Analysis of the underlying cellular mechanisms revealed that sAC-inhibition or knockdown led to a pronounced rise in phosphorylation of p38 mitogen-activated protein kinase under oxidative stress accompanied by p38-dependent phosphorylation/inactivation of the pro-
The p110alpha subunit of PI 3-kinase is crucially involved in neointima formation by mediating smooth muscle cell proliferation, migration and survival.

**Neutrophils contribute to DVT formation by forming procoagulant and prothrombotic neutrophil extracellular traps**

**Background:** Recent data suggest that circulating microparticles (MPs) contribute to inflammation, coagulation and vascular repair. The dynamics of MPs counts following STEMI (s-T elevation myocardial infarction, STEMI) and their relation to levels/activity of fibrinolytic factors are unknown. We studied trends on MP levels following STEMI and their relation to parameters of fibrinolytic system in consecutive patients.

**Methods:** Citrated platelet poor plasma was obtained from 48 STEMI patients and 40 “control” patients with stable CAD. In STEMI, study parameters were measured within 24h of primary percutaneous coronary intervention (PCI) (day 1) and days 3, 7 and 30 after admission. Small- (0.1-0.5 μm) apoptotic annexin V-binding MPs (AnV-MPs), CD42b+ platelet MPs (pMPs), CD144+ endothelial MPs (eMPs) and CD144+ monocyte MPs (mMPs) were quantified using a high resolution Apogee A50 flow cytometer. Fibrinolytic parameters (tissue-type [tPA]) were analysed by V-binding MPs (AnV-MPs), CD42b+ platelet MPs (pMPs), CD144+ endothelial MPs (eMPs) and CD144+ monocyte MPs (mMPs) were quantified using a high resolution Apogee A50 flow cytometer. Fibrinolytic parameters (tissue-type [tPA]) were analysed by V-binding MPs (AnV-MPs), CD42b+ platelet MPs (pMPs), CD144+ endothelial MPs (eMPs) and CD144+ monocyte MPs (mMPs) were quantified using a high resolution Apogee A50 flow cytometer. 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Leptin is expressed in human carotid atherosclerotic plaques and plays an active role in plaque stability via its effects on human vascular smooth muscle cells.

**P4323**

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**Methods**: Leptin and its receptor were co-localized with plaque VSMCs by immunofluorescence. Intraplaque leukocytes were investigated in cell culture.

**Results**: Leptin and its receptor were co-localized with plaque VSMCs by immunofluorescence. Intraplaque leukocytes were investigated in cell culture.

**Conclusion**: Leptin plays a role in plaque development and could be a potential therapeutic target.

Endothelial Microparticles (EMP) are taken up in an Annexin I/PSR dependent pathway by target cells and promote endothelial regeneration.

**P4324**

Endothelial Microparticles (EMP) are taken up in an Annexin I/PSR dependent pathway by target cells and promote endothelial regeneration.

**Methods**: The role of EMP in the progression of atherosclerosis is still unclear. Here, we present evidence that EMP influence endothelial-regenerating cells and promote regeneration signals important for endothelial regeneration.

**Results**: EMP are generated after starvation of human coronary endothelial cells (HCAEC) anodized by ultrafractuation. Flow cytometry analysis and electron microscopy were used to characterize size (<1 μm) and cellular origin of EMP.To test the effects of EMP in vivo and in vitro experiments were performed. Invivo, reendothelialization in mice after carotid injury was improved after peripertive EMP injection (29.8% vs. 50.7% remained denuded area, p<0.05). EPC level in blood, bone marrow and spleen were significantly increased in EMP-treated mice. In vitro, EMP promoted differentiation of mononuclear cells into early outgrowth EPC (58.3% vs. 39%, p<0.05), protected target cells against apoptosis, and accelerated migration of HCAEC (59% vs. 43%, p<0.05). We next demonstrated EMP uptake by target cells (HCAEC, early EPC, late EPC). Following experiments were performed to investigate a possible uptake mechanism.

**Conclusion**: EMP induce signals of endothelial replenishment in vivo and in vitro. The Annexin I/PSR dependent pathway was identified as a critical mechanism for EMP uptake by target cells.

Impaired perivascular adipocyte differentiation in angiotensin II receptor A(1) deficient mice: Possible role in pro-inflammatory phenotypic modulation of perivascular adipose tissue

**P4326**

Impaired perivascular adipocyte differentiation in angiotensin II receptor A(1) deficient mice: Possible role in pro-inflammatory phenotypic modulation of perivascular adipose tissue

**Methods**: The angiotensin II receptor A(1) (AT1) receptor in visceral white adipose tissue (WAT) is closely implicated in lipid metabolism and energy homeostasis.

**Results**: ATP32 increases perivascular adipocyte differentiation and expression of pro-inflammatory markers, while ATP32 decreases perivascular adipocyte differentiation and expression of anti-inflammatory markers.

**Conclusion**: The angiotensin II receptor A(1) (AT1) receptor in visceral white adipose tissue (WAT) is closely implicated in lipid metabolism and energy homeostasis.
Recently, perivascular adipose tissue (PVAT) has been shown to play a crucial role in the development of atherosclerosis; however, the effects of AT1 on PVAT properties and their functional relevance in atherogenesis remain undefined.

Methods and Results: We examined the functional specific difference of adipose tissue among epidymal WAT, PVAT surrounding thoracic aorta, and intercapsular brown adipose tissue (BAT) in 8-week-old apoE deficient (apoE/-) mice. The expression of brown adipocyte marker genes (UCP-1, PGHC-1, FABP4, PPARγ, and Cidea) were significantly higher in BAT and PVAT compared with WAT (p<0.01). White adipocyte marker genes (Igf1p, Dpt, Tcf21, and Hoxc9), which were highly expressed in BAT, showed a moderate expression level in PVAT, suggesting that PVAT has a distinctly different phenotype from the classical WAT and BAT. We next examined the properties of PVAT in 8-week-old apoE/-/AT1 receptor deficient (Agrp1/+) mice. After 4 weeks of western diet, the expression level of adipocyte differentiation marker genes (PPARγ, FABP4, c/EBPα) were markedly increased in apoE/-/ PVAT (P<0.05), which was completely diminished in apoE/-/AT1 receptor deficient (Agrp1/-) mice. After 4 weeks of western diet, the expression level of adipocyte differentiation marker genes (PPARγ, FABP4, c/EBPα) were time-dependently increased in Agrp1/-/ adipose tissue. In contrast, FABP4 and c/EBPα mRNA expressions were markedly inhibited in Agrp1/-/ adipose tissue, whereas PPARγ did not differ between the two groups during the differentiation process of adipocytes. AT1 is essentially implicated in the terminal differentiation of periaortic adipocyte.

Conclusion: Our findings demonstrate that AT1 regulates the expression levels of late stage of adipocyte-differentiation marker genes in PVAT, suggesting that AT1-mediated modulation of periaortic adipocyte differentiation could be a novel therapeutic target for the prevention of atherosclerosis.

Is NGAL assessment in patients referred to renal artery stenting for atherosclerotic renal artery disease conclusive of clinical value?


The zinc finger transcription factor Krueppel-like factor 4 (KLF4) is involved in the regulation of important cell functions, including proliferation, differentiation or activation. Monocytes (Mo) are essential mediators of cardiovascular repair processes, and human mo can be divided in CD14+CD16- mo and CD16+ mo (consisting of CD14+CD16+ and CD14-CD16+ mo). For the CD16+CD16- mo mouse analogues, i.e. Ly-6C(high)- and Ly-6C(low)-mo, it was shown that Ly-6C(high)-mo are crucial for phagocytosis and proteolysis of necrotic tissue in the early inflammatory phase after acute myocardial infarction (MI), whereas the reparative and proangiogenic properties of Ly-6C(low)-mo can promote healing of damaged myocardial tissue in the subsequent proliferative phase. So far, little is known about the expression and function of KLF4 in human mo subsets. In the present study, KLF4 expression was quantified in circulating mo subsets of healthy subjects (n=18; 78% male; median age, 58 years) and patients with coronary artery disease (CAD; n=52; 77% male; 70 years) using flow cytometry. In the present study, KLF4 expression was quantified in circulating mo subsets of healthy subjects (n=18; 78% male; median age, 58 years) and patients with coronary artery disease (CAD; n=52; 77% male; 70 years) using flow cytometry. In the present study, KLF4 expressing cells were significantly lower in CD14+CD16- mo (51.0%) compared to CD14+CD16+ mo (73.0%; p<0.01) and CD14+CD16+ mo (72.5%; p<0.01). Although the same distribution pattern was observed, the number of KLF4-expressing mo was significantly reduced in all 3 mo subsets of CAD patients (CD14+CD16- mo: 19.9%, p<0.01 vs. HS; CD14+CD16+ mo: 35.9%, p<0.01; CD14+CD16+ mo: 30.8%, p<0.001).

In summary, our findings demonstrate that the transcription factor KLF4 is highly expressed in CD16+ mo, i.e. an immune cell subtype with presumed reparative functions, whereas KLF4 was downregulated in all 3 mo subsets of CAD patients. The observed accumulation of KLF4-positive cells in the acute phase of MI might suggest that KLF4 may play an important role in regulating immune cell functions during cardiovascular repair processes.
was to determine new compositional and structural features of coronary plaques based on automated, objective analysis of VH-IVUS images.

Methods: A biometric computational analysis based on backtracking program was applied, with emphasis given on the low computational cost and processing time. Single and sequences of VH-IVUS images were analyzed. For each image analysis 29 parameters were computed.

Results: By the basic plaque characteristics (lumen, vessel areas, percent of stenosis, area and percent of each plaque component), the following parameters related with the spatial distribution and the homogeneity of plaque components were computed: a) the percent of lumen border that is surrounded by each component, b) the number of different segments and the area of the largest solid segment of each component. a) the number of different segments and the area of the largest single segment of each component within the plaque area. A sequence of VH-IVUS images that is recorded during catheter pullback along the coronary vessel is then analyzed in order to automatically classify the examined plaques as thin cap fibroatheroma, the most common type of vulnerable plaque. The classification is made according to standard criteria: a) The percent of the necrotic core area is >10%, b) the necrotic core covers more than 1/3 of the lumen border and c) the two previous conditions are met for at least three serial frames of the images sequence. The total number of sequential and non-sequential frames that meet the criteria (a) and (b) are also determined.

Conclusions: The quantifiable features of plaque components’ distribution and heterogeneity provided by the proposed system could provide further insight in the assessment of vulnerable plaques. Especially features of necrotic core and calcification in relation to lumen border may be significant determinants of plaque vulnerability and plaque-stein interaction. In this respect these new computed data might be useful for the detection of the vulnerable plaque as well as for the evaluation of stent deployment and selection.

Hypoxia reoxygenation-induced endothelial barrier failure: Role of RhoA, Rac1, and MLCK

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Background: Loss of endothelial barrier function leading to oedema formation during hypoxia-reoxygenation presents major impediment for the recovery of the organ. This loss of barrier function is mainly due to loss of cell-cell adhesions and endothelial contractile activity. Several signaling pathways including RhoA/Rock or Ca+2/PKC are activated during reoxygenation which could mediate barrier failure, but the precise role of these pathways is still elusive. The aim of the present study was to analyse the role of these signaling pathways in reoxygenation-induced barrier failure.

Methods: In cultured porcine aortic endothelial cells, the effect of hypoxia (30 min, PO2 = 5 mm Hg; pH 7.4) and reoxygenation (45 min, PO2 = 140 mm Hg; pH 7.4) was analyzed on endothelial permeability (albumin flux), contractile activity (MLC phosphorylation), Ca2+, PKC, RhoA, Rac1 (pull down assay), and cell-cell adhesions (contactin microscopy). BAPTA (10 μM), BIM (100 μM), C3Transferase (1 μg/ml), and Y27632 (10 μM) were used to inhibit Ca2+, PKC, RhoA, and Rock signalling, respectively.

Results: Reoxygenation lead to 150±7% increase in permeability, 2.5-fold MLC phosphorylation, and 2.5-fold Rock activation but had no effect on Rac1 activity (for all further parameters). Moreover, reperfusion caused a robust rise in cytosolic Ca2+-concentration, PKC activation, loss of cortical actin and VE-cadherin from cell-cell adhesions. Pharmacological inhibition of RhoA, Rock, Ca2+ or PKC with specific inhibitors exacerbated reoxygenation-induced barrier failure and abrogated the resealing of adhesion junctions. On the other hand activation of cAMP/Epac signalling by a cAMP analogue (100 μM), blocked reoxygenation-induced actin cytoskeleton derangement and hyperpermeability and enhanced endothelial cell resealing. However, it had no effect on RhoA or MLC. Inhibition of MLC kinase (ML-7 10 μM) along with Epac activation had an additive effect. The results were confirmed using isolated perfused rat hearts.

Conclusions: The present data suggest that Rho/Rock and Ca+2/PKC pathways are required for resealing of junctions and inhibition of these pathways can exacerbate the reoxygenation injury. Activation of cAMP/Epac pathway along with inhibition of contractile activation presents a new therapeutic intervention to prevent reoxygenation-induced vascular leakage.

Uric acid levels are associated with asymmetric dimethylarginine, L-arginine and arterial stiffness in hypertensive patients

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Purpose: Elevated uric acid (UA) levels are associated with increased cardiovascular risk, while arterial stiffening, L-arginine and asymmetric dimethylarginine (ADMA) contribute to diffuse vascular dysfunction. In this study, we investigated the relationships between UA levels, L-arginine, ADMA and arterial stiffness in essential hypertensives.

Methods: In our population of 160 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension (116 men, aged 49 years, office blood pressure (BP)=153±97 mmHg), the distribution of UA was split by the median (5.2 mg/dl) and accordingly subjects were classified into those with high and low UA. Among all participants, arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP).

Results: Patients with high UA (n=91) compared to those with low UA (n=69) exhibited higher 24-h systolic BP (138±8 vs 131±11 mmHg, p<0.0001) while arterial stiffening, L-arginine and asymmetric dimethylarginine (ADMA) contribute to diffuse vascular dysfunction. In this study, we investigated the present data suggest that UA is interrelated with diverse pathological mechanisms, especially pronounces endothelial dysfunction, underscoring its mainstay role in the progression of the hypertensive atherosclerotic disease.

The paraoxonase 55 L/M polymorphism influences the onset of acute coronary syndrome but not stable angina

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The paraoxonase1 (PON1) is an antioxidant enzyme synthesized by liver. It has two known polymorphisms: 192 Q/R and 5.5 L/M. Multiple studies, including ours, have associated these polymorphisms with coronary artery disease (CAD) risk. In CAD coexisting changes in the vessel wall in emphasis on atherosclerosis, clinically expressed by stable angina (SA), and acute thrombotic changes, expressed by acute coronary syndrome (ACS). However, the mechanism by which these variants influence the CAD susceptibility is still unknown.

Objective: The aim of this study was to evaluate whether PON1 polymorphisms influence the onset of ACS or SA.

Methods: Two case-control studies were performed. The first one included 1665 individuals, 728 with CAD and hospitalized with ACS (mean age 53.3±7.9 years, 73.9% male) and 937 controls without CAD (mean age 52.6±7.5 years, 79.3% male). The second one included a total of 1009 individuals: 209 consecutive patients with SA and significant CAD confirmed by coronary angiography (mean age 56±0.6±7 years, 71.3% male) and 800 controls without CAD (mean age 55±0.6±8 years, 72.9% male). In both studies, cases and controls were matched by gender and age. PON1 variants were analyzed using specific primers. The equilibrium of Hardy-Weinberg was investigated and a biivariate analysis (tables 3x2), with the odds ratio (OR) and 95% confidence intervals (CI), was performed in order to determine the CAD risk. A p-value <0.05 was considered statistically significant.

Results: PON 55 MM genotype showed an increased risk for ACS, with an OR of 1.38 (p=0.012) but not for SA (OR=1.00; p=0.994). PON 192 Q/R was not significantly associated either with the ACS or with SA.

Conclusions: This study supports the concept that PON 55 MM is an initiator factor for ACS. Not leading to stable angina but to ACS, this polymorphism may be particularly deleterious and may be involved in thrombogenic and not atherogenic mechanism. The patients carrying this genotype should be approached with particular care in terms of primary prevention, possibly through antplatelet or anticoagulant drugs.

Angiotensin II induces early mechanical heterogeneity along the abdominal aorta, preceding murine aeurysm formation

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Background: Abdominal aortic aneurysm (AAA) pathogenesis involves a broad spectrum of inflammation, cellular proliferation and extracellular matrix alterations. However, little is known about the initiation of aeurysm formation. In animal models, localized chemical damage to the aortic wall is used to trigger a focal vascular demarcation, eventually resulting in AAA. In contrast, suprarenal aneurysms can readily be induced in apoE-/- mice by systemic Angiotensin II (AngII) administration. In this study, we investigated the hypothesis that systemic AngII infusion induces focal mechanical alterations (i.e. heterogeneous strain along the abdominal aorta) that may initiate AAA formation.

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Materials and methods: AngII (1000ng/kg/min) or saline (control) was infused via osmotic pump in 10-week-old apoE−/− male mice (C57Bl6/J background). At baseline and after 2 days of treatment, systolic (SD) and diastolic (DD) diameters of suprarenal (SR) and infrarenal (IR) aortic segments were measured using M-mode ultrasonography, and strain was calculated as (SD-DD)/DD. Strain ratio along the aortal wall was calculated as SR-strain/IR-strain. Gene expression of the AngII type 1b receptor (Agtr1b), known to mediate the mechan-ical/vasocontractile response to AngII, was measured in SR and IR regions via qRT-PCR.

Results: AngII infusion for 2 days induced both a significant increase in SR-strain as well as a decrease in IR-strain, resulting in a significant strain heterogeneity (SR/IR strain-ratio: 2.5 ± 0.8 vs. 1.2 ± 0.3 at day 0; p=0.001). Saline infusion altered none of these parameters. While elevated SR-strain per se failed to demonstrate a correlation to SR diameter changes after 2 days, we found that SR/IR-strain ratio was positively correlated to early SR aortic diameter increase (R2=0.53; p<0.05). Overt atherosclerosis formation was only detectable after 4 days of AngII infusion, at the earliest. As a possible mechanism for these strain differences, Agtr1b expression was found to be 40-fold higher in IR aorta than in the SR aorta at baseline.

Conclusion: AngII infusion rapidly induces heterogeneous strain (SR–IR) along the aortal wall, preceding aneurysm formation. These strain differences may be due to initial heterogeneous AngII receptor density, and they correlated statistically with the initial dilatation of the aneurysm-prone SR region. These data suggest a mechanism for the early translation from systemic AngII infusion into a focal vascular response (AAA induction), and highlight vascular mechanical heterogeneity as a possible prerequisite of AAA formation.

Conclusions: The high discriminative ability of apoptotic CECs and apoptotic endothelial microparticles is a solid foundation for the development of clinical prediction models of CAV.

The experimental study of a new kind absorbable magnesium alloy stent

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Background and Objective: At present, the subacute thrombosis and restenosis after stenting can still not be resolved using stainless steel and self-expandable alloy-based drug-eluting stents fundamentally. Thus, the bioabsorbable stent becomes the focus of attention; and now, it is considered that the absorbable magnesium alloy stent is very promising in future. So, we try to study the mechanical property, effectiveness and safety of a new kind stent through animal experiments, which we designed and made by ourselves.

Methods: The 35 randomized hybrid dogs were randomly divided into 7 experimental groups, included: control, 24 h, 3, 7, 14, 21, 28 days’ groups, and five dogs in each group. An absorbable magnesium alloy stent was implanted in coronary artery and femoral artery in each experiment dog respectively. Each dog was reviewed the coronary and femoral angiography, and then the stent arteries were isolated for histopathological analysis at experimental end. Also, we measured the elastic lamina area, lumen area, and the percentage of intimal hyperplasia area with the computer image analysis software.

Results: 51 Stents were implanted in 35 dog’s coronary and femoral artery successfully. After stenting 24 h, 3, 7, 14, 21, 28 days, the reviewed coronary and femoral artery angiography showed that stent was completely degraded in 7 days, and the lumen of stenting vessels were patency without remarkable stenosis. Histopathological study showed that there was no intimal hyperplasia of 24 h, 3, 5, 7 days later in stenting vessels; there was only a slight intimal hyperplasia after 2 days, but no significant inflammatory response and thrombus formation during 4 weeks. The intimal hyperplasia area in each 2, 3, to 4 weeks group was (0.04±0.03)mm2, (0.10±0.03)mm2, (0.15±0.04)mm2, and the percentage of intimal hyperplasia area were 1.84±1.18, 3.72±1.12, 6.29±3.36 respectively, all these increased significantly compared each other (P<0.05).

Conclusions: In the canine model the absorbable magnesium alloy stent, which was absorbed in one week, has good biocompatibility and safety, and no significant inflammatory response and thrombus formation during 4 weeks. The intimal hyperplasia and restenosis was very slight after 4 weeks stenting. So, this may be a promising coronary stent in future.

Circulating apoptotic endothelial cells and apoptotic endothelial microparticles independently predict the presence of cardiac allograft vasculopathy

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Background: ST-elevation acute coronary syndrome (STE-ACS) is the leading cause of death. Mechanisms of coronary artery plaque rupture are poorly understood. In contrast to common knowledge implying monocytes and T-cells in the pathogenesis of acute coronary vascular syndromes, we hypothesize that circulating inflammatory cells mediate plaque rupture and thrombotic occlusion. The goal of this study was to phenotype inflammatory cells at the site of plaque rupture and to determine their effector functions.

Methods: STE-ACS patients who underwent primary percutaneous coronary intervention at the General Hospital were consented (n=70). Culprit site blood was aspirated with a thrombectomy catheter and particulate thrombus material was separated. In parallel, blood was sampled from the femoral arterial sheath. Flow cytometry was employed to determine cell types accumulating at the plaque rupture site. These results were complemented by ELISA, cell culture and immunofluorescence assays.

Results: The vast majority of inflammatory cells at the culprit lesion site are neutrophils. Coronary neutrophils produce neutrophil extracellular traps, release large amounts of MPO and are apoptosis-resistant. CD4CD28null T cells are increased with low content of Perforin and Granzyme B. Plaque-site monocytes display a CD14lowCD16high phenotype that is found in aggregation with platelets.

Conclusion: The selective enrichment of innate inflammatory cell subsets at the culprit lesion site suggests a disease-specific inflammatory process, supporting an outside-in mechanism of acute atherosclerotic vascular obstruction.

Conclusions: The present study is the first to examine the direct effect of Ang-(1-7) on CEs. Total mononuclear cells (MNCs) were isolated from peripheral blood by Ficoll density gradient centrifugation. Using staining by laser scanning confocal microscopy, CEs were identified as adherent cells that were isolated for histopathological analysis at experimental end. Also, we measured the elastic lamina area, lumen area, and the percentage of intimal hyperplasia area with the computer image analysis software.

Circulating apoptotic endothelial cells and apoptotic endothelial microparticles independently predict the presence of cardiac allograft vasculopathy

N. Singh1, E. Van Craeyveld1, M. Myers2, A. Ciarka2, W. Drogene2, R. Gondo3, F. Jacobs4, J. Vanhaecke5, J. Van Cleemput6, De Geest7 on behalf of Neha Singh. 1Center for Molecular and Vascular Biology, Catholic University of Leuven, Leuven, Belgium; 2Catholic University of Leuven, Leuven, Belgium; 3Department of Internal Medicine II, Division of Cardiology, Vienna, Austria; 4Justus-Liebig University Giessen, Institute for Biochemistry, Giessen, Germany

Objectives: Maintenance of endothelial homeostasis may prevent the development of cardiac allograft vasculopathy (CAV). We investigated whether biomarkers related to endothelial injury and endothelial repair discriminate between CAV negative and CAV positive heart transplant recipients.

Background: CAV is the most important determinant of cardiac allograft survival and a major cause of death after heart transplantation.

Methods: Two patients undergoing coronary angiography between 5 and 15 years after heart transplantation were recruited in this study. Flow cytometry was applied to quantify endothelial progenitor cells (EPCs), circulating endothelial cells (CECs), and endothelial microparticles. Cell culture was used for quantification of circulating EPC number and hematopoietic progenitor cell (HPC) number, and for analysis of EPC function.

Results: EPC number and EPC function did not differ between CAV negative and CAV positive patients. In univariable models, age, creatinine, steroid dose, granulocyte colony-forming units, apoptotic CECs, and apoptotic endothelial microparticles discriminated between CAV positive and CAV negative patients. The logistic regression model containing apoptotic CECs and apoptotic endothelial microparticles provided high discrimination between CAV positive and CAV negative patients (C statistic 0.812; 95% CI 0.689-0.932).

Conclusions: The high discriminative ability of apoptotic CECs and apoptotic endothelial microparticles is a solid foundation for the development of clinical prediction models of CAV.
Wnt4 contributes to intimal thickening by promoting VSMC proliferation via up-regulation of RCAN1

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Purpose: We investigated whether Wnt4-induced VSMC proliferation utilizes nuclear translocation of factor activated T-cells (NFAT) as a downstream effector as well as β-catenin. Vascular smooth muscle cell (VSMC) proliferation causes intimal thickening observed in early atherosclerosis and restenosis. We previously demonstrated that Wnt4/β-catenin signaling stimulates VSMC proliferation in vitro via cyclin D1 up-regulation and promotes intimal thickening. Although the “canonical” Wnt/β-catenin pathway plays a vital role in the promotion of Wnt4-driven VSMC proliferation, Wnts can also signal independently of β-catenin, amongst others via a calcium-related pathway involving NFAT. Here we assessed the role of NFATc1 (the predominant isoform in VSMCs) and the induction of known NFAT-responsive genes in Wnt4-induced VSMC proliferation and intimal thickening.

Methods: VSMCs were cultured and in some cases subjected to siRNA; extracted mRNA was analysed by Q-PCR while protein was assessed by Western blotting and/or immunocytochemistry. Mouse cardiac arterioles were cultured to induce intimal thickening and lesions were analysed by immunohistochemistry.

Results: Addition of recombinant Wnt4 protein in vitro induced a significant increase in the percentage of VSMCs with nuclear NFATc1 within 4h (by 2.3±0.83 fold; p<0.05, n=3), directly demonstrating the activation of Wnt4/Ca²⁺ pathway by Wnt4. Recombinant Wnt4 protein treatment for 6h in vitro significantly upregulated the mRNA levels of two previously identified NFAT-responsive genes, regulator of calcineurin 1 (RCAN1) and cyclooxygenase 2 (COX2) as well as Cyclin D1 by 1.54±0.28, 1.39±0.24 and 1.35±0.15 fold respectively (p<0.05, n=3). Treatment with NFAT inhibitor (11R-VWIT) for 24h in vitro significantly retarded Wnt4-induced VSMC proliferation from 46.3% to 30.0% (p<0.01, n=4), but knockdown (by 89±11% of NFATC1 in vitro resulted in a significant reduction of both Cyclin D1 and RCAN1 mRNA by 21±77 and 21±17% respectively (p<0.05, n=3). Finally, we observed elevated NFATc1 protein levels while RCAN1 protein was significantly increased in ligated mouse cardiac arterioles when compared to unligated control arterioles (161±16.1 vs 26±7.3 fluorescent pixels per area unit respectively, n=4).

Conclusions: Wnt4 is an important contributor to intimal thickening by playing a key role in the stimulation of VSMC proliferation via activation of both “canonical” β-catenin and “non-canonical” NFAT downstream pathways. We show here for the first time that RCAN1, a downstream target of NFAT, is up-regulated by Wnt4 signalling and may be a key modulator of intimal thickening.

A non-polymeric cilia-to-gelatinase-eluting stent inhibits neointimal proliferation stronger than sirolimus-eluting stents: an experimental study using optical coherence tomography in rabbit iliacal arteries

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Background: Drug-eluting stents (DES) are currently the best choice to reduce restenosis after coronary stenting. Optical coherence tomography (OCT) is a high-resolution intravascular imaging technique that precisely quantify neointimal proliferation and endothelial strut coverage.

Objectives: We tested, in a preclinical setting using an OCT imaging system, if the novel polymer-free cilia-to-gelatinase-eluting stent proved significant anti-restenotic efficacy without delaying endothelialization in this rabbit model and therefore merits attention as a promising stent development.

Methods: Bare metal stents Yukan Choice 2.5/12 mm with microporous surface (BMS) were polymer-free coated with either sirolimus (SES) or ciliatozine (CES) at 225 mcg/cm. Sixteen New Zealand White rabbits fed with western diet underwent implantation of different stents in both iliacal arteries via the carotid artery. The animals were equally divided into 2 groups: BMS vs. SES and BMS vs. CES. Stents were imaged in vivo using OCT at 28 days in 4 animals and after 90 days in the remaining 12 animals. OCT assessment of stent coverage was performed by classifying all visible struts and computing % of well- and malapposed struts, with and without endothelialization. Additionally, an algorithm of quantification of neointimal growth implemented (Figure) and applied to different stent segments and adjacent vessel areas.

Results: All struts were well apposed without significant differences in endothelialization between BMS, SES and CES. Relative proliferation area (S. Pk), calculated as neointimal area within a stent segment in relation to the stent area was significantly smaller in CES, but not in SES as compared to BMS (Figure).

Conclusions: The novel polymer-free cilia-to-gelatinase-coated stent proved significant anti-restenotic efficacy without delaying endothelialization in this rabbit model and therefore merits attention as a promising stent development.
vascular remodelling in the hypoxia induced mouse model of pulmonary hypertension.

Methods: We generated a smooth muscle specific p110 alpha deficient mouse and studied its effect on chronic hypoxia to induce pulmonary hypertension. Right ventricle (RV) systolic pressure was determined via invasive measurement using a millar pressure catheter. RV hypertrophy was assessed as ratio RV weight to LV + septum weight. Vascular remodelling was quantified and demonstrated as medial wall thickness and degree of vascular muscularization.

Results: RV systolic pressure in consequence to hypoxia was decreased in the p110 alpha deficient mice compared to wild-type littermates. Consistently, hypoxia induced RV hypertrophy was significantly reduced in hearts of p110 alpha deficient mice in comparison to wild-type hearts. Medial wall thickness of vessel with a diameter less than 50μm was significantly narrowed in lungs of Sm-specific p110 alpha KO mice. Morphometric analysis of the small pulmonary vessels (diameter < 70μm) revealed that a smaller fraction of fully and partially muscularized vessels in hypoxia treated p110 alpha deficient mice in comparison to hypoxia treated wild-type mice.

Conclusion: These results indicate that the PI3K isoform p110 alpha is crucial for vascular remodelling in hypoxia induced pulmonary hypertension. A Sm-specific loss of p110 alpha prevented vascular remodelling and would therefore represent a promising therapeutic approach.

### P4345 Valsartan inhibits aortic remodeling by blocking transforming growth factor-β1-Smads pathway in diabetic rats

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Objective: Angiotensin II (Ang II) and transforming growth factor β1 (TGFβ1) are closely involved in the pathogenesis of diabetic complications. We aimed to determine whether an aberrant thrombospondin 1 (TSP1)–mediated TGFβ1/Smads signaling pathway is involved in the re-endothelialization process of diabetic lesions.

Methods: Age-matched male Wistar rats (200-240 g) were randomly divided into 3 groups: control (n=8), diabetes (n=16) and valsartan (30 mg/kg/day) (n=16). Type 2 diabetes mellitus (T2DM) was induced by a high-calorie diet and streptozotocin injection. Morphological and biomechanical properties of the thoracic aorta were assessed by echocardiography and cardiac catheterization. Masson staining was used for histological evaluation of collagen. The expression of components in the TSP1–mediated TGFβ1/Smads signaling pathway was analyzed by immunohistochemistry and real-time quantitative RT-PCR.

Results: Ang II was upregulated in control rats, diabetic aortas showed increased dexamethasone sensitibility to achieved the gestational age and collagen deposition. Components in the TSP1–mediated TGFβ1/Smads signaling pathway was analyzed by immunohistochemistry and real-time quantitative RT-PCR.

Conclusions: TSP1–mediated TGFβ1/Smads signaling pathway activation plays an important role in macrovascular remodeling in T2DM in rats. Valsartan can block the pathway and ameliorate vascular fibrosis.
A novel adipocytokine, CTRP9 attenuates vascular smooth muscle cell proliferation and neointimal formation after vascular injury

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Background: C1q/TNF-related protein (CTRP) 9 is a novel adipocytokine that has beneficial effects on glucose metabolism and endothelial function. However, the role of CTRP9 in vascular remodeling is unknown. Here, we investigated the effect of CTRP9 on vascular smooth muscle cell (VSMC) proliferation and neointimal hyperplasia in a restenosis model.

Methods and Results: An adenovirus expressing CTRP9 (Ad-CTRP9) or β-galactosidase as a control was injected into the jugular vein of wild-type (WT) mice 3 d prior to vascular injury. Left femoral arteries of mice were injured by a 0.015 inch stainless-steel wire inserted from the lumen. Administration of Ad-CTRP9 increased CTRP9 levels by a factor of 5.1 ± 0.9 at day 5 after injection compared with control. At 21 days after vascular injury, delivery of Ad-CTRP9 significantly attenuated intimal hyperplasia compared with that of control (p < 0.01, n=8). Ad-CTRP9 also decreased the number of bromodeoxyuridine (BrdU) positive proliferating cells in the neointima at day 7 after vascular injury versus control. In cultured VSMCs, recombinant CTRP9 protein attenuated DNA synthesis increased by growth factors, including growth factor derived endothelial cell (GFP)-induced PDGF and heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) as assessed by BrdU incorporation. Furthermore, treatment of VSMCs with CTRP9 significantly attenuated PDGF βreceptor phosphorylation and ERK.

Conclusion: CTRP9 reduces VSMC growth and prevents neointimal thickening after vascular injury in vivo, suggesting that the therapeutic approaches to endothelial cells during Furin-dependent maturation of proNGF induces outside-in signaling by using RGD-peptides did not affect phosphorylation of Akt and LY294002 reduced by phosphorylation of Akt and paxillin, which was prevented by both the TrkA- and NGF-induced migration. Blockade of integrin-mediated migration and functional relevance is poorly understood. NGF is synthesized as a precursor (proNGF) that is cleaved into mature β-NGF by the protease convertin furin and subsequently secreted from cells acting as an autocrine signaling molecule. Here, we studied the effect of platelet-derived growth factor (PDGF-BB) and transforming growth factor beta-1 (TGF-β1), both highly expressed in restenotic lesions, on furin-dependent proNGF maturation and examined the impact of mature β-NGF on VSMC migration.

Methods and results: First, qRT-PCR and western blot analysis showed that PDGF-BB and TGF-β1 synergistically enhance NGF gene expression and proNGF secretion by vascular cells of the human vasculature like endothelial cells may offer an interesting approach for the prevention or treatment of vascular proliferative diseases. MicroRNAs (miRNAs) are a new class of small noncoding RNA molecules, comprising key regulators for major cellular events including proliferation, differentiation and apoptosis in human diseases. Up to now, the role of miRNAs for vascular smooth muscle cell function is still unclear. In the present study, we examined the regulation and impact of miR-146a following 146a inhibition.

Methods and results: First, qRT-PCR and western blot analysis showed that PDGF-BB and TGF-β1 synergistically enhance NGF gene expression and proNGF secretion by vascular cells. To examine miR-146a regulation and impact on NGF secretion, we performed miR-146a inhibition using antisense oligonucleotides (ASO) in VSMCs. miR-146a overexpression significantly downregulated and hence represents a molecular target for 146a resulting in a significantly decreased total cell count and migration of smooth muscle cells. In complementing in vivo experiments, the inhibition of miR-146a in injured murine femoral arteries significantly reduced the proliferation of neointimal smooth muscle cells as assessed by Ki67 staining. Data of the morphometric analysis showed a significantly decreased neointima formation following 146a inhibition.

Conclusion: These findings reveal a pivotal role of miR-146a for function in vascular smooth muscle cells, especially under conditions of pathological vascular remodeling processes. Thus, modulating miR-146a expression may represent a novel approach for the prevention and treatment of vascular proliferative diseases.

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MicroRNA-146a and its role in vascular smooth muscle cells during vascular remodeling processes

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Background: MicroRNAs (miRNAs) are a new class of small non-coding RNA molecules, comprising key regulators for major cellular events including proliferation, differentiation and apoptosis in human diseases. Up to now, the role of miRNAs for vascular smooth muscle cell function remains elusive. Here, the aim of this study was to examine the regulation and impact of miR-146a following 146a inhibition.

Methods and results: Using microarray-based expression analysis, we screened for regulated miRNAs during neointima formation. Restenosis was induced in C57BL/6N by dillation of the femoral artery, and miRNA was isolated 10 and 21 days after injury. About 59% of all known miRNAs was found to be abnormally regulated after 10 days what was even enhanced to 88% after 21 days. Noticeably, miR-146a appeared to be one of the most regulated miRNAs during restenosis. Analysis on isolated cells of the human vascular lineage like monocytes/macrophages, smooth muscle cells and endothelial cells showed a strong expression of miR-146a, especially in endothelial cells. In vitro, the upregulation of miR-146a could be attributed to the inflammatory stimulus Il-1β. To further assess the functional role of miR-146a, recombinant VSMCs were transduced with the precursor form of miR-146a that led to an attenuated migration, sprout formation and vessel network formation. On the other hand, using 2–O methylated RNA as inhibitor, reporter formation, vessel network formation and cell migration were significantly enhanced. In the following, computational miRNA target prediction, the TargetScan database, was used to find potential target genes for miR-146a. Quantitative Real-Time-PCR tests were performed after overexpression of miR-146a. The transcripts for TRAF6 and IRAK1, two key adapters in TRLR- and IL-1 receptor signaling cascades, were significantly downregulated and hence represent molecular targets for miR-146a. Further in vivo analysis showed that miR-146a induction seems to be mediated by NFκB. In complementing in vivo experiments, inhibition of miR-146a following dilatation of the femoral artery was performed. The data of Evans-Blue and WF staining showed significantly enhanced restenocardialization after 10 and 21 days. Conclusion: Determining the expression profile of differentially regulated miRNAs in restenosis development, we identified miR-146a likely involved in the disease development and progression and could further assess its functional role in the human vasculature.

Methods: Using microarray based expression analysis, we screened for regulated miRNAs during the development of restenosis. Neointima formation was induced in C57BL/6N by dilatation of the femoral artery and miRNA was isolated 10 and 21 days after injury. About 59% of all known miRNAs was found to be abnormally regulated after 10 days what was even enhanced to 88% after 21 days. Noticeably, miR-146a appeared to be one of the most regulated miRNAs during restenosis. Further expression analysis in isolated primary vascular smooth muscle cells revealed that miR-146a, besides in monocytes/macrophages and in endothelial cells, was highly expressed in vascular smooth muscle cells. In vitro, the upregulation of miR-146a could be attributed to the inflammatory stimulus Il-1β. In the following, computational miRNA target prediction, the TargetScan database, was used to find potential target genes for miR-146a. Quantitative Real-Time-PCR tests were performed after overexpression using precursor forms of miR-146a. The transcripts for TRAF6 and IRAK1, two key adapters in TRLR- and IL-1 receptor signaling cascades, was significantly downregulated and hence represents a molecular target for 146a. To further assess the functional role of miR-146a, smooth muscle cells were transfected with miR-146a inhibitors using 2-O methylated RNA targeting 146a resulting in a significantly decreased total cell count and migration of smooth muscle cells. In complementing in vivo experiments, the inhibition of miR-146a in injured murine femoral arteries significantly reduced the proliferation of neointimal smooth muscle cells as assessed by Ki67 staining. Data of the morphometric analysis showed a significantly decreased neointima formation following 146a inhibition.

Conclusion: These findings reveal a pivotal role of miR-146a for function in vascular smooth muscle cells, especially under conditions of pathological vascular remodeling processes. Thus, modulating miR-146a expression may represent a novel approach for the prevention and treatment of vascular proliferative diseases.
Ablation of PDGF receptor signaling reduces neoimtma formation after balloon angioplasty and does not affect the proliferation and migration of endothelial cells.

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Despite the introduction of new techniques such as drug-eluting stents, restenosis and stent thrombosis following angioplasty remain serious clinical problems. To prevent neoimtma formation and the development of stent thrombosis after balloon angioplasty and stent implantation, it is essential to reduce the accumulation of vascular smooth muscle cells (SMC) on the one hand and to ensure the re-endothelialization as far as possible on the other hand. The proliferation and migration of SMCs and endothelial cells (ECs) are mainly induced by receptor tyrosine kinases which are activated by growth factors. Previously, we could demonstrate that the mutation of central binding domains of the platelet-derived growth factor receptor (PDGFR) in a mouse model causes a significant reduction of neoimtma formation after balloon angioplasty. The influence of an inhibition of PDGFR on endothelial cells is not known.

In this study, we analysed the effects of two PDGFR inhibitors (Imatinib and Nilotinib) on the proliferation and migration of human coronary SMCs (hSMCs) and human coronary ECs (hECs). For this purpose, the cells were stimulated with PDGF (30 ng/ml) or VEGF (50 ng/ml) and various concentrations of imatinib or nilotinib were tested. The cellular proliferation was determined by BrdU incorporation assay and chemotaxis using a modified Boyden chamber. Protein expression and activation were investigated by Western blot analyses.

Results: Immunofluorescence and Western blot analyses demonstrated that proliferation and migration of PDGFR are induced by Imatinib and Nilotinib. Western blot analyses demonstrated that the expression and activation of PDGFR are inhibited to hSMCs while VEGF expression and activation were restricted to hECs. PDGF-induced proliferation and migration of hSMCs were completely suppressed by the inhibitors imatinib (1 μM, IC50 = 500 nM) and nilotinib (10 μM, IC50 = 1 μM). Imatinib had no effect on VEGF-induced proliferation and migration of hECs (no inhibition at 10 μM) while nilotinib caused a 50% inhibition of both cell responses at high concentrations (10 μM).

Our results indicate that inhibition of PDGFR, especially by imatinib, inhibits the proliferation and migration of hSMCs without suppressing the cellular responses of hECs. Thus, the PDGFR represents a promising therapeutic target in order to prevent restenosis following percutaneous coronary intervention.

Changes of elastic properties of large arteries in systemic sclerosis are related to endothelial activation and matrix tissue remodelling

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Introduction: Systemic sclerosis (SSc) is a connective tissue disease with characteristic fibrosis of internal organs and abnormalities of small arteries. Pulse wave velocity (PWV) is a simple and non invasive method of evaluation of elastic properties of large arteries.

Aim of the study: The aim of this study was to evaluate the changes in blood vessels wall in SSc patients and its relation with the biochemical markers of endothelial activation (endostatin-1, ADMA) and marker of matrix remodelling (TIMP-1).

Materials and methods: We prospectively examined 69 consecutive SSc patients (M: 5; F: 64, mean age 55.49±13.83 years) and a group of 21 aged and sex matched volunteers (M: 3; F: 18, mean age: 49.10±5.48 years). PWV was measured automatically (Complir Sp, Artich Medical, Pantin, France), and endothelin 1 (ET-1) (Human Endothelin-1 Immunoassay R&D Systems), tissue inhibitor of matrix metalloproteinase (TIMP-1) (Quantikine Human TIMP-1 Immunoassay R&D System) and asymmetric dimethylarginine (ADMA) (ADMA Elisa Kit Immunodiagnostic AG) serum level were assayed.

Results: PWV tended to be higher in SSc than in V. Interestingly in SSc patients PWV correlated with the TIMP-1 serum level (r = 0.3; p = 0.04) and ET-1 serum level (r = 0.3; p = 0.009). The ET-1 serum level also significantly positively correlated with TIMP-1 serum level (r = 0.4; p = 0.002).

Conclusions: SSc patients found to have higher ADMA and ET-1 serum level. ET-1 and TIMP-1 positive correlation and positive correlations between ET-1 and TIMP-1 with PWV suggest that both endothelial dysfunction and matrix remodelling are associated in the pathogenesis of large arteries in systemic sclerosis.

Angiotensin II (AngII)-induced arterial remodeling is associated with upregulation of miR-21 and downregulation of miR-29b


Materials and methods: AngII (1000ng/kg/min) was infused via osmotic pumps into 4-week-old aortic arches of Apoe−/− male mice for 7 days. Subsequently, infrarenal abdominal aortas were harvested and expression of various collagen isoforms known to be crucial determinants of arterial remodeling/stiffening was quantified via qRTPCR. We then measured expression levels of miR-21 and miR-29b.

Results: AngII stimulation resulted in a marked pro-fibrotic response as evidenced by significant increases in Col1a1 and Col3a1 expression (~3 fold) in the infrarenal aorta compared to baseline levels (p < 0.05). This increase was ac...
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Changes of vascular walls in different levels of arterial system in patients with stable coronary artery disease and type 2 diabetes mellitus

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Aim: To assess the relationship between large arterial wall remodelling and changes of microcirculation in small resistance arteries and capillaries in patients with stable coronary artery disease (CAD).

Patient and methods: In patients with CAD (n=25; male; 10; mean age: 62.7±6.7; BMI: 30.7±4.4) and 25 healthy participants (male; 11; mean age: 57.3±7.9; BMI: 26.3±4.1) digital photoplethysmography and nail fold videocapillaroscopy at resting baseline, during venous occlusion were performed. We evaluated a remodelling of large artery arterial stiffness (SI), augmentation index (AIX75) and structural changes of microcirculation in small resistance arteries (reflection index (RI)) and capillaries (maximal capillary densities (CD max), coefficient of capillary remodelling (Kvd/ad= diameter of venous part of capillary/diameter of arterial part of capillary)).

Results: Measure of remodelling of large vessels Aix 75 was significantly higher in CAD patients than in healthy controls (20.4±4.1 vs. 12.3±5.1; p<0.05). There was no different SI and RI in groups (SI CAD: 7.1±4.0 vs. 7.2±4.8; p=0.7; RI CAD: 42.4±19.1 vs. 51.7±34.5; p=0.3). As for RI, there was normal range in both groups (norm-30%).

CD max in CAD group was significantly lower than in control (49.7±6.9 vs. 58.6±12.9 cap/mm²; p<0.005). There was no significant difference of Kvd/ad between two groups (CAD vs. Control: 1.13±0.18 vs. 1.09±0.25; p=0.6). AIX75 was significantly correlated with RI (r=0.43; p<0.05). No correlation between AIX75 with CD max (r=0.17; p=0.05). RI with CD max (r=0.07; p=0.05) was observed.

Conclusions: In CAD patients presents both remodeling of large vessels and structural changes of microcirculation in small resistance arteries and capillaries (maximal capillary densities (CD max), coefficient of capillary remodelling (Kvd/ad= diameter of venous part of capillary/diameter of arterial part of capillary)).

ASSESSMENT & INTERVENTION TO IMPROVE

Relatedness between red cell distribution width (RDW) and clinical outcomes in non-ST elevation myocardial infarction and unstable angina pectoris: 3-years follow-up

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Objectives: Red cell distribution width (RDW), a marker of the variation of the size of the circulating red blood cells, was evaluated in patients with non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP).

Background: Higher RDW is associated with mortality in patients with symptomatic cardiovascular disease, heart failure, and also in the general population. We hypothesized that admission RDW would be predictive of adverse clinical outcomes in NSTEMI and UAP.

Methods: A total of 310 (mean age 59.29±11.93; 236 males, 74 females) patients with NSTEMI and UAP were prospectively enrolled into this study. Admission RDW was measured as part of the automated complete blood count. The study population was divided into tertiles based on admission RDW values. A high RDW (n=95) was defined as a value in the third tertile (≥14%), and a low RDW (n=215) was defined as a value in the lower two tertiles (≤14%). Patients were followed for clinical outcomes for up to 3 years after discharge.

Results: Kaplan-Meier survival analysis showed 3-years mortality rate of 19% in patients with high RDW versus 5.6% in low RDW group (p<0.001). In a receiver operating characteristic curve analysis, a RDW value of 14% identified as an effective cut-point in NSTEMI and UAP of 3-years cardiovascular mortality (area under curve=0.70, 95% confidence interval 0.62 to 0.79). A RDW value of ≥14% yielded a sensitivity of 60%, a specificity of 72.5%. We used proportional hazard models to examine the association between RDW and adverse clinical outcomes. A significant association was noted between high admission RDW level and the adjusted risk of cardiovascular mortality (hazard ratio: 3.2, 95% confidence interval 1.3-7.78; p=0.01). There was a good correlation between RDW levels and age (r=0.246, p<0.001), TIMI risk score (r=0.277 and p<0.001), and GRACE risk score (r=0.270, p<0.001).

Conclusion: RDW is a readily available clinical laboratory value that is associated with long-term cardiovascular mortality in NSTEMI and UAP.

Echocardiographic epicardial fat thickness is associated with arterial stiffness

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Purpose: Epicardial adipose tissue represents visceral adiposity and early de- tection of visceral adiposity could be helpful for assessing subclinical target organ damage. Although previous studies have reported the relationship between epicardial fat thickness (EFT) and carotid intima-media thickness, there is no report regarding the relationship between EFT and arterial stiffness. The present study was performed to evaluate the association between epicardial fat thickness and arterial stiffness.

Methods: We consecutively enrolled 655 subjects (445 men, 55.9 years) who underwent echocardiography and brachial-ankle pulse wave velocity (baPWV) with ankle-brachial index greater than 0.95. Echocardiographic EFT was measured from parasternal long-axis and short-axis views on the free wall of the right ventricle at the end of diastole. The subjects were divided into four quartile groups depending on EFT (≤3.45 mm, 3.45-4.95 mm, >4.95 mm, and >5.95 mm in quartile I, II, III, and IV, respectively). Subjects were also classified into two groups according to baPWV: group I (324 subjects), baPWV >1366cm/sec; and group II (331 subjects), baPWV ≤1366cm/sec.

Results: The EFT in group II were significantly higher than those in group I (4.2mm versus 3.7 mm; p<0.001). There were significant differences in baPWV value among the four quartile groups of the EFT (quartile I, 1327±148.8 cm/sec; quartile II, 1371±215.0 cm/sec; quartile III, 1434±228.3 cm/sec; quartile IV, 1507±233.1 cm/sec; p-value =0.001). In the multivariate linear regression model adjusted for age, sex, lifestyle status, systolic blood pressure, heart rate, fasting glucose, triglyceride, high-density cholesterol, homeostasis model assessment-insulin resistance, and high-sensitivity C reactive protein, the absolute values of EFT were an independent determinant of increasing baPWV in the above model (standard β=0.113, p<0.001). In the same model for logistic regression analysis, increasing quartiles of EFT showed a significant association with increased baPWV group (p for trend=0.010) and the highest quartile group of EFT had higher odds ratio (OR) for increased baPWV group compared with that of the lowest quartile group (OR [95% confidence interval (CI)]: 2.19 [1.21-3.95]).

Conclusion: This study indicates an independent relationship between epicardial fat thickness and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure and useful tool for early detection of subclinical target organ damage.

Plasma BNP versus cardiac risk scores for risk stratification after major orthopedic surgery

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Natriuretic Peptides can predict in-hospital and long term outcome of major orthopedic surgery (MOS) but they have not been validated in comparison with established cardiac risk scores.

Methods: 242 elderly patients (mean age 79.9±8.1, male 25.6%) undergoing major orthopedic surgery (MOS) were included. Preoperative B-type Natriuretic Peptide (BNP) was measured and clinical risk scores calculated. In-hospital major cardiac events (MACE) and 1-year mortality were the endpoints of the study.

Results: Twenty patients had inhosiptal MACE (8.3%) and 41 (21.9%) died within 1 year. Preoperative BNP was correlated with all indices (Spearman ρ correlation coefficient Goldman 0.325, Lee 0.76 Detry 0.492, Fleisher Eagle(FE) 0.389, Functional Capacity (FC) 0.449, all p<0.001). Logistic 14% identification for the prediction of MACE and 1-year mortality revealed for LnBNP p<0.001 and p=0.001, Goldman p=0.013 and p<0.003, Lee p=0.02 and p=0.6, Detsky p<0.001 and p=0.001, FE p=0.001 and p=0.017, FC p=0.03 and p<0.001. Sim-
Causality of inflammation related to blood leucocyte count for the progression of arterial stiffness and pressure wave reflection

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Background: It has not yet been fully clarified whether elevated serum C-reactive protein levels (sCRP) and peripheral blood leucocyte counts (BLC) are merely markers of arterial stiffening and pressure wave reflection abnormalities, which result from other factors of cardiovascular risk, or whether any causal relationship might exist between these parameters and the aforementioned cardiovascular risk factors.

Objectives: The present 3-year prospective study was conducted to examine this issue.

Methods: Measurements of sCRP, BLC, brachial-ankle pulse wave velocity (baPWV) and radial augmentation index (rAI) were conducted at the baseline and at the end of the 3-year study period in 1291 healthy Japanese men (43±8 years old).

Results: BLC, but not log-transformed sCRP, showed a significant relationship with the baPWV, but not rAI, at both the baseline and the final examinations. Elevated BLC was defined as any count in the highest tertile (BLC > 6400 cells/μl), and sustained elevation of the BLC was defined as elevated values at both the baseline and the final examinations. The delta change of baPWV (adjusted value) during the study period, but not that of the rAI, was significantly larger in the group showing sustained elevation of the BLC (54.4±23.6 cm/sec) than in the group not showing elevation of the BLC in either the baseline or the final examination (38.2±18.3 cm/sec) (p<0.05). Similar findings were not observed for sustained elevation of the sCRP.

Conclusion: The facet of inflammation related to elevated BLC, but not that related to elevated sCRP, may be causally associated with the progression of arterial stiffening of the large-to-middle-sized arteries. However, no such association with inflammation was found for progression of abnormalities of the pressure wave reflection.

Prognostic relevance of epicardial adipose tissue in patients with coronary artery disease assessed by cardiovascular magnetic resonance

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Purpose: Epicardial adipose tissue (EAT) has been correlated with the presence and severity of coronary artery disease (CAD). However, the role of EAT as a risk factor for cardiac mortality and morbidity in patients with CAD remains unclear. Therefore, we sought to investigate the prognostic relevance of indexed EAT assessed by CMR in patients with CAD.

Methods and Results: 248 patients with CAD (mean age: 64.9±7.9 yrs, 79% male, 68% were prospectively enrolled and underwent CMR). Their mean left ventricular function was 56.8±15.8%. The primary endpoint was all cause mortality. The secondary endpoints were: 1) the combination of cardiac death, heart transplantation (HTX) or adequate shock and 2) hospitalisation due to STEMI, NSTEMI, or adequate shock. During the follow-up time, 51 (20.6%) patients were hospitalised. EAT below the median of 26g/m² was a significant predictor of all cause mortality (HR 8.2, p=0.004) and cardiac mortality (HR 4.2, p=0.04). However, EAT values above the median of 26g/m² were a significant predictor of an increased cardiac mortality (HR 4.7, p=0.03). Figure 1 details the relationship between categories of indexed EAT and all cause and cardiac mortality as well as cardiac morbidity.

Conclusion: Our results suggest that the determination of EAT may help to identify CAD patients who are at higher risk of death andrehospitalisation due to heart failure. Therefore, EAT might be a useful surrogate marker to select patients who derive significant benefit from a more intense treatment.

Low-dose acetylsalicylic acid (ASA) is recommended for secondary prevention of cardiovascular events, and primary prevention in high risk patients. However, its use is associated with an increased risk of upper gastrointestinal bleeding (UGIB), although little is known about which users are at risk of developing UGIB. This study aimed to assess risk factors for UGIB in patients taking low-dose ASA.

Methods: A systematic literature analysis (1995–2011) using PubMed and Embase was performed. We reviewed randomized controlled trials and observational studies reporting UGIB in individuals receiving low-dose ASA. Studies were excluded if the ASA dose was above 325 mg/day or not reported, or if all participants were given concomitant gastroprotective medication or Helicobacter pylori eradication therapy.

Results: The searches identified 2240 unique studies, 15 of which were eligible for inclusion. The most commonly identified risk factor for UGIB was a history of peptic ulcer disease, reported in six studies (N=3353). Five of the six studies reported relative risks (RRs) or odds ratios (ORs) in the range 3.1–6.5 when assessing this relationship, while the sixth reported a much higher OR of 15.2 (95% confidence interval [CI]: 3.8–60.1). Increasing ASA dose was shown to be associated with a significantly increased risk of UGIB in users of low-dose ASA. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose ASA was also associated with a significantly increased risk of UGIB (two studies; RR: 2.30 [95% CI: 1.0–5.6]; DR: 3.8 [95% CI: 1.8–8.7]). Other factors associated with a significantly increased risk of UGIB in users of low-dose ASA were: current Helicobacter pylori infection, concomitant calcium channel blocker use, concomitant clopidogrel use and a history of dyspepsia. Two studies reported an
increased risk of UGIB with alcohol consumption among patients taking low-dose ASA. Three studies found that proton pump inhibitor (PPI) use was associated with a significant reduction in the risk of UGIB in users of low-dose ASA (OR: 0.02 [95% CI: 0.00–0.03] OR: 0.066 [95% CI: 0.00–0.73] RR: 0.56 [95% CI: 0.3–1.0]).

**Conclusions:** The risk of UGIB is increased in users of low-dose ASA who have: a history of peptic ulcer disease, Helicobacter pylori infection or dyspepsia; con- sume alcohol; or take concomitant calcium channel blockers, anti-hypertensives or NSAIDs. Increasing ASA dose is also associated with a significantly increased risk of UGIB. In contrast, patients taking a PPI in addition to low-dose ASA have a reduced risk of UGIB relative to those taking low-dose ASA without a PPI.

**Contrast-induced nephropathy (CIN) after primary percutaneous coronary intervention (PCI): the role of heat shock proteins**

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**Background:** Contrast induced nephropathy (CIN) is common complication associated with unfavourable clinical outcomes. Heat shock proteins (HSPs) comprise several families of proteins expressed by number of cell types following exposure to stressors. HSPs play essential function in cytoprotection however their role in CIN pathogenesis has never been evaluated.

**Methods:** This study included 43 selective non-diabetic patients with ischemic heart disease and normal serum creatinine undergoing PCI. CIN was defined as an increase more than 0.5 mg/dL or more than 25% of baseline value of creatinine. An enzyme-linked immunosorbent assay method was used to measure HSP27 and HSP60 levels in the plasma of patients and the controls. Serum creatinine, HSP27 and HSP60 was assessed before and 24 hours post the procedure.

**Results:** Of 43 patients 13 patients (29.5%) developed CIN. Either HSP27 or HSP60 levels were elevated in patients compared with controls (median 3.06 ng/ml (1.14 – 23.66) vs 1.35 ng/ml (0.23 – 14.65) and 254.9 ng/ml (0 – 1243) vs 10.77 ng/ml (0 – 321) respectively; p < 0.009 and p < 0.001). In CIN(-) group baseline HSP60 level was higher compared with CIN(+) group (p = 0.006). In CIN(+) group baseline HSP60 level was higher compared with CIN(-) group (p < 0.001).

**Conclusions:** HSP27 appears to play protective roles in the process of CIN. Serum HSP60 concentration seems to be a marker of increased risk of CIN development induced by PCI.

**Incidence, risk factors, and outcomes of perioperative acute kidney injury in noncardiac and nonvascular surgery**

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**Background:** Perioperative acute kidney injury (AKI) is a well-established risk factor for perioperative morbidity and mortality in patients undergoing cardiac surgery. However, predictors and outcome of perioperative AKI in patients undergoing noncardiac, nonvascular surgery is unclear. In this study, we aimed to evaluate the incidence, predictors, and outcomes of perioperative AKI in patients undergoing noncardiac, nonvascular surgery.

**Methods:** A total of 1340 consecutive patients (mean age = 65.5±13.8 years) undergoing noncardiac, nonvascular surgery were prospectively evaluated. Patients older than 18 years who underwent an elective, noncardiac case, open surgical procedure were enrolled. Patients with pre-existing renal dysfunction requiring renal replacement therapy or a preoperative serum creatinine higher than 1.4 mg/dL were excluded. The primary outcome of this study was perioperative AKI defined by the RIFLE (risk, injury, failure, loss of function, and end-stage kidney disease) criteria using the maximal change in serum creatinine and estimated glomerular filtration rate during the first 7 postoperative days compared with baseline values before surgery. Glomerular filtration rate was estimated by CKD-EPI equation. Preoperative risk factors and laboratory test results were measured and evaluated for their association with the occurrence of in-hospital perioperative adverse cardiac and noncardiac events.

**Results:** Ninety-one patients (8.0%) met AKI criteria. Univariate analysis identified age, anemia, left ventricle ejection fraction, American Society of Anesthesiologists (ASA) physical status, ischemic heart disease, congestive heart disease, diabetes mellitus (DM), and Revised Cardiac Risk Index (RCRI) score as independent preoperative determinants for perioperative AKI. Multivariate analysis identified age (OR: 1.1; 95% CI: 0.99–1.1; p = 0.001), DM (OR: 4.38; 95% CI: 2.38–8.00; p < 0.001), and RCRI (OR: 1.43; 95% CI: 0.96–2.27; p = 0.04), as independent predictors of AKI. Patients with AKI had more cardiovascular complications (30.8% vs 9.4%; p < 0.001), major bleeding (7.7% vs 3.2%, p < 0.025, stroke (8.8% vs 1.4%; p < 0.001) and in-hospital mortality (7.7% vs 9.9%; p < 0.001) compared with those who never developed AKI.

**Conclusions:** Several preoperative predictors are found to be associated with AKI after noncardiac, nonvascular surgery. Perioperative AKI is an independent risk factor for cardiovascular complications, major bleeding, stroke and in-hospital mortality.

**The association between brachial-ankle pulse wave velocity and the extent of coronary artery disease in patients with angina**

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**Purpose:** Arterial stiffness is well known as an important risk factor for cardiovascular disease. Among the variable methods for measuring arterial stiffness, brachial-ankle pulse wave velocity (baPWV) is widely used in clinical research and is a relatively simple and noninvasive test. We assessed the association between arterial stiffness, as determined by baPWV and the extent of coronary disease, as detected by conventional coronary angiography (CAG).

**Methods:** We retrospectively enrolled 651 consecutive South Korean individuals who had been admitted to our institute and had undergone baPWV and elective CAG for suspected coronary artery disease between June 2010 and July 2011. Results: By multivariable logistic regression analysis, significant predictors of coronary artery disease (CAD, diameter of stenosis >50%) were male gender, age, high density lipoprotein cholesterol, HbA1c and the level of baPWV. When we divided subjects into 3 groups according to clinical outcomes, the value of
The existence of non-obstructive plaque in carotid arteries never resulted in significant stenosis. After logistic regression, plaques cast 30-50% narrowing over the in-motion to ESRD patients on maintenance HD. Further intervention to reduce baPWV was significantly higher in patients with CAD inclading those who received revascularization than in patients without CAD (p<0.001). But there was no significant difference of baPWV between the groups of intermediate CAD and revascularization: When the extent of CAD were classified into following 4 groups: no significant CAD, 1-, 2- and 3-vessel disease, baPWV tended to correlate with the extent of CAD (p<0.01). However, there was no significant difference among the patients with CAD.

**Conclusion:** These results indicate that baPWV is significantly associated with the extent of CAD, although baPWV has limited value in identifying the patients who should receive revascularization among those patients with angina.

**Methods:**

There were 265 patients in this cohort, and the distribution of gender was nearly equal (male vs female: 49.1% vs. 50.9%). The age of this cohort is 61.2 ± 12.4 year-old, with higher fasting blood glucose (12.3 year-old), with higher fasting blood

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**Conclusion:** Type 2 diabetes mellitus has the same CV risk as a history of CHD in high-risk Japanese hypertensive patients.

**Results:**

Out of 4,703 patients, 339 (7.2%) patients experienced CV events for a rate of 15.9 per 1000 person-years during the 4.5±1.9 years of follow-up. Diabetes with a history of CHD most frequently experienced CV events among four groups (adjusted HR: 2.78; 95%CI: 1.8-4.4; P<0.001). Both non-diabetics without a history of CHD were more significantly correlated with the prevalence of coronary artery disease (CAD) and related to the existence of postprandial hyperlipidemia (PH). In patients with PH, TG-rich lipoproteins and their hydrolyzed product, remnant lipoproteins were accumulated, which were mainly apolipoprotein (apo) B-48-containing lipoproteins, such as chylomicrons and chylomicron remnants (CM-R) derived from the intestine. CM-R had highly atherogenic properties in vitro and possibly developed atherothrombotic plaques, we investigated whether the accumulation of CM-R was correlated with the development of CAD by measuring fasting apoB-48 levels.

**Methods:**

Subjects who received coronary angiography (CAG) and did not take any lipid-lowering drugs (n=189) were enrolled. Those who had angiographically significant coronary stenosis (75% or more luminal diameter stenosis) in left anterior descending artery, left circumflex artery and/or right coronary artery were treated as the patients with CAD (n=96) and age, sex and BMI-matched subjects who did not have significant stenosis were treated as non-CAD subjects (n=67). Biochemical markers for glucose and lipid metabolism including fasting apoB-48 were correlated with the prevalence of coronary artery disease (CAD) and related to the existence of postprandial hyperlipidemia (PH). In patients with PH, TG-rich lipoproteins and their hydrolyzed product, remnant lipoproteins were accumulated, which were mainly apolipoprotein (apo) B-48-containing lipoproteins, such as chylomicrons and chylomicron remnants (CM-R) derived from the intestine. CM-R had highly atherogenic properties in vitro and possibly developed atherothrombotic plaques, we investigated whether the accumulation of CM-R was correlated with the development of CAD by measuring fasting apoB-48 levels. Biochemical markers for glucose and lipid metabolism including fasting apoB-48 were correlated with the prevalence of coronary artery disease (CAD) and related to the existence of postprandial hyperlipidemia (PH). In patients with PH, TG-rich lipoproteins and their hydrolyzed product, remnant lipoproteins were accumulated, which were mainly apolipoprotein (apo) B-48-containing lipoproteins, such as chylomicrons and chylomicron remnants (CM-R) derived from the intestine. CM-R had highly atherogenic properties in vitro and possibly developed atherothrombotic plaques, we investigated whether the accumulation of CM-R was correlated with the development of CAD by measuring fasting apoB-48 levels.

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Development and psychometric properties of the Heart Failure Knowledge Scale in Japan


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2 Sakakibara Heart Institute, Tokyo, Japan

Purpose: Heart failure (HF) knowledge is considered to be a cornerstone for HF management. However, there are no valid and reliable instruments available, with a HF knowledge in Japan possibly occupying the Cath Lab for longer times. The purpose of this study was to develop a reliable and valid instrument for the measurement of HF knowledge, and to assess the relationship between HF knowledge and HF self-care behavior.

Methods: We developed a questionnaire consisting of 17 items concerning HF knowledge in reference to the previous studies, such as “HF is a condition that the heart is not able to pump sufficient amount of blood through the body”, “Diuretics remove fluids from the body”, and “HF patients had better drink more water than healthy people”. Patients responded these questions with “yes”, “no”, or “I do not know”. A correct answer was scored 1, an incorrect answer or an answer of “I do not know” was scored 0. Scores for each item were summed, giving a range of total scores from 0 to 17. A higher score indicates greater knowledge about HF. Content validity was confirmed by the expert panel including a cardiovascular nurse specialist, and a department head. Factor analysis was performed to identify any potential underlying constructs. Concurrent validity was assessed through factor validity and concurrent validity. Concurrent validity was evaluated using Pearson product-moment correlation coefficient between the HF knowledge scale and the HF comprehension scale. Reliability was assessed by internal consistency.

Results: A total of 176 patients in two independent hospitals completed the self-administered questionnaire. The mean age was 64.3±11.4 years, and males accounted for 70% of the respondents. Mean score of the HF knowledge scale was 9.6±4.5, and the percentage of correct answers ranged from 15% to 79%. Exploratory factor analysis confirmed the one dimensionality of the HF knowledge scale. The contribution to one factor was 81%. Pearson correlation coefficient for concurrent validity was 0.418 (p<0.05). Cronbach’s alpha was measured at 0.88, suggesting adequate reliability. The low HF knowledge score was significantly associated with poor HF self-care behavior, assessed by the European Heart Failure Self-Care Behavior Scale-Japanese version (r=0.256, p<0.01).

Conclusion: The HF Knowledge Scale was valid and reliable one, and this instrument can be used to gain an insight in the effects of education and counseling toward HF patients. Our data suggests that HF knowledge improves HF self-care, although further research is needed to confirm the relationship.

Short duration holter monitoring is equally as good as daily monitoring in heart rate and pause assessment

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Holter monitoring is integral to managing chronic cardiovascular disorders such as heart failure. Accurate heart rate monitoring helps guide nurses and doctors in titrating beta blocker therapy and identification of rhythm disturbances. This is usually achieved by performing 24 hour holter monitoring to assess key variables such as daily heart rate and occurrence of arrhythmias and pauses. The difficulty with this approach is the time required to wear the monitors, the limited availability of holter monitors and time spent on analysis. These factors impact upon the availability of holter monitors and time spent on analysis. These factors impact upon the availability of holter monitors and time spent on analysis.

We therefore investigated the usefulness of 2,3 or 4 hour holter monitoring in yielding similar data to the longer 16 hour daily monitoring. We analysed the holter tapes of 50 subjects attending for various cardiovascular problems. The same tape was used for each analysis and the hours selected for the 2,3 or 4 hour analysis were performed randomly during the normal 9 to 5 pm working period. We compared the mean heart rates and pause rates of the 2,3 and 4 hour observation periods with that of the longer 16 hour monitoring period. The results of this analysis are as outlined in the table below.

Comparison of 2, 3 and 16 hour holters

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>2 Hours</th>
<th>3 Hours</th>
<th>4 Hours</th>
<th>16 Hours</th>
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This study emphasizes that short duration holter monitoring, even as little as 2 hours may be useful in the clinical setting and have benefits in terms of patient convenience and costs.

Diagnostic angiography with SF catheters supports early ambulation and discharge

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Introduction: Ischaemic heart disease is mainly diagnosed through coronary angiography. Although the radial artery approach is gaining prevalence the femoral artery access is still very popular. The latter requires longer recovery times for longer times. Few studies have studied femoral artery access early ambulation and the safety of early home discharge.

Methods: An initial study with 4F catheters was conducted earlier yielding very good results. This study was published. Then data from 5F diagnostic angiography was prospectively collected over 1 year. The Cath Lab nurses managed sheath removal with manual compression targeting 1 hour bed rest time before ambulation.

Results: This study was carried out in 2009 with 262 participants. The mean time from sheath removal to discharge was 161.3 minutes. These results were obtained with minimal access site complications and without major adverse events.

Groat dressing post cardiac catheterization: traditional pressure versus transparent film

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Purpose of the study: To determine the efficacy of using a small transparent non pressure dressing compared with the traditional controlled pressure dressing applied to the femoral artery puncture wound site to maintain haemostasis following cardiac catheterization procedures.

Design: An experimental design, randomized study.

Patients: 80 post cardiac catheterization patients were randomized to have their groin dressed either with pressure dressing (N=40) or TFD (N=40). Patients am-

Assessment & intervention to improve 761
bulated 8 hours after the procedures. Outcome variables were hematoma formation or bleeding, patient discomfort, and nurse-reported ease of observation of the groin puncture site after the procedure. Five instruments were used for data collection: 1) Demographic and medical data sheet, 2) Hematoma Formation and Bleeding Scale, 3) Skin Integrity Scale, 4) Patient Discomfort and Pain Scale & 5) Nurses Ease of Assessment Scale.

Results: There were no significant differences in base line characteristics and medical data between the two groups. 100% in TFD group vs 55% in pressure dressing group reported feeling very comfortable (p value of 0.003). Hematoma formation was equal in the two dressing groups with no incidence of bleeding complications. Nurses rated the ease of assessing the groin significantly higher for TFD than for pressure dressing (p value of 0.000).

Conclusions: Dressing of the puncture site after cardiac catheterization with TFD was more comfortable than the conventional pressure dressing without any difference in hematoma or bleeding complications. So TFD can be used safely and comfortably after achieving hemostasis.

P4375
PCI in very elderly patients suffering an ACS
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There are few data on safety and outcomes of percutaneous coronary revascularization (PCI) in very elderly patients suffering an Acute Coronary Syndrome (ACS), especially those aged ≥ 85 years old.

From January 2009 to December 2011, a total of 108 very elderly patients were admitted at our coronary care unit with a diagnosis of ACS; 44% of these (n = 48) underwent PCI. The average age at intervention was 86.9 years. Most of the patients were severe chronic renal failure (26%) and COPD (13%). Most of the procedures (47%) was performed for acute myocardial infarction with ST-segment elevation (STEMI), 43% for an acute coronary syndrome without ST segment elevation with high-risk clinical features.

Coronary angiography was performed in 45% of cases with a radial approach. The rate of procedural failure was quite high, with about 20% of PCI ineffective: this finding could be consistent with the high percentage of patients with severe calcific coronary artery disease (CAD).

Complication rate in this population of ultra-elderly was 25%, with a mortality rate of 12.5%, almost entirely attributable to STEMI (63%, n=5). The cause of death was attributed to mechanical complications of myocardial infarction; in other two patients the cause of death was an arrhythmic event. The only complication attributable to revascularization was an acute contrast nephropathy, which resolved during the hospital stay. Non-fatal complications consisted of two cases of severe bleeding and five cases of severe heart failure; a matter of particular concern was the low use of intra aortic counterpulsation balloon pump: in fact, only one patient was assisted with IABP, compared with nine cases of severe heart failure.

Our study highlighted how in very elderly patients experiencing an ACS, PCI is a safe procedure, with a single complication attributable to the revascularization procedure, i.e. a case of acute contrast nephropathy. With regard to other complications these are mainly correlated to the underlying disease, especially acute myocardial infarction with ST-segment elevation. Careful nursing assessment, with a regular evaluation of main hemodynamic parameters and renal function, may facilitate early recognition of hemodynamic deterioration and its better management.

P4376
Preoperative statin use and postoperative atrial fibrillation after major noncardiac, nonvascular surgery
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Background: Perioperative beta-blockade and statin therapy have been advocated to reduce cardiac risk of noncardiac surgery. The current study investigated the effect of statin therapy with statins would reduce the incidences of perioperative myocardial infarction, atrial fibrillation, and mortality in patients undergoing noncardiac, nonvascular surgery.

Methods and Results: A total of 1750 patients, undergoing noncardiothoracic, nonvascular surgery were prospectively evaluated. Patients older than 18 years who underwent an elective, nonday case, open surgical procedure were enrolled. Electrocardiography and cardiac biomarkers were obtained 1 day before surgery, and on days 1, 3 and 7 after surgery. Patients with atrial fibrillation were excluded. Demographics, comorbidities, preoperative data (electrocardiography, echocardiography, electrocardiography-nays, laboratory results), medications, and intraoperative variables were evaluated for their association with the occurrence of perioperative cardiovascular adverse events. Patients receiving statins were generally older (68.7 vs 62.3 years; P < 0.001) and more likely to be receiving a beta-blocker (40.1 vs 19.4%; P < 0.001). Statin use was associated with a lower unadjusted rate of atrial fibrillation (2.2% vs 4.2%; P < 0.001), myocardial infarction (3.4% vs 6.4%; P < 0.001) and mortality (1.1% vs 2.4%; P = 0.01). After adjustment for patient risk factors and surgery type, odds for atrial fibrillation (adjusted odds ratio = 0.86; 95% confidence interval = 0.69-0.91; P < 0.001) and myocardial infarction (adjusted odds ratio = 0.82; 95% confidence interval = 0.67-0.98; P < 0.001) remained significantly lower among statin-treated patients.

Conclusions: Treatment with statins is associated with a lower risk for atrial fibrillation and myocardial infarction following major noncardiac, nonvascular surgery.

P4377
Carperitide can protect against acute kidney injury in patients with chronic kidney disease undergoing coronary angiography
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Purpose: Acute kidney injury remains a common complication of coronary angiography (CAG). Although previous study reported that carperitide can reduce renal protective effects after CAG, this has not been a universal finding. We evaluated whether carperitide can reduce renal damage after CAG using urinary Liver type fatty acid-binding protein (L-FABP) expressed after renal ischemia which is a novel marker detecting renal injury more sensitively than the existing marker such as serum creatinine.

Methods: We prospectively randomized 148 patients undergoing CAG who had renal dysfunction (glomerular filtration rate (GFR) < 60 ml/min/1.73m2). Patients were divided into receiving hydration alone (Hyd-group; n=74) and receiving hydration plus carperitide (ANP-group; n=74). All patients were treated with hydration for 12 hours before and after CAG. In ANP-group, carperitide (0.0125-0.025μg/kg/min) was started for 1 hour before CAG and continued for 24 hours. Patients in Hyd-group were treated by using the MDRD formula and urinary L-FABP measured at baseline, day 1 and 2.

Results: Baseline characteristics of the two groups were similar. There were no differences in serum creatinine and GFR between two groups at baseline, day 1 and day 2. However, urinary L-FABP was significantly suppressed in ANP-group, at day 1 (24.7±24.3 vs 50.4±70.0 μg/ml, p<0.001) and day 2 (15.3±23.0 vs 42.5±83.0 μg/ml, p<0.01).

Conclusions: Prolonged intravenous infusion of sodium chloride plus carperitide is more effective than sodium chloride alone for prophylaxis of acute kidney injury after CAG. Sodium chloride plus ANP may be reduced CIN, leading to improvement or prevention of long-term prognosis of CKD patients.

P4378
Effects of community-based general practitioners-led care for 12,864 patients with hypertension: study of cardiovascular risk intervention - hypertension (SCRI-HTN) in China
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Background and Objectives: Hypertension is emerging as a leading cause of cardiovascular morbidity, mortality, and disability among adults. General practitioners (GPs) working in the community health service (CHS) organizations are being positioned in the healthcare system to provide longitudinal care for hypertensive patients. This study aimed to determine the efficacy of a community-based intervention led by GPs on control of cardiovascular risk factors among patients with hypertension in China.

Methods: DESIGN: a longitudinal, pre-post study. SETTING: 98 community health centres (CHCs) in Guangzhou, the most urbanized city in southern China. Multistage cluster sampling method was adopted in identifying the study sites. The study was carried out over a 5-year period from 2007 through 2011. PARTICIPANTS: 12,864 adult patients who had diagnosed hypertension; and 196 certificate-trained general practitioners. INTERVENTIONS: cardiovascular risk reduction education; regular, long-term follow-up by general practitioners using scheduled consultations and counselling. The intensity of medication treatment was determined by the stratification of risk for cardiovascular disease (CVD).

OUTCOME MEASURES: the difference in change in systolic BP, diastolic BP, triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

Results: Sufficient data were available for 12,864 patients. The mean (SD) patient age was 52.5 (7.5) years, 53.9% were male, and the mean (SD) systolic/diastolic BP was 146.1 (19.4)/84.6 (11.3) mm Hg at baseline. Several main indicators of cardiovascular health improved over the study period: mean systolic BP decreased from 146.1 to 135.1 mm Hg (p<0.001); mean diastolic BP declined from 84.6 to 79.6 mm Hg (p<0.001); mean triglyceride level dropped from 31.7 to 30.1 mg/dl (p=0.035); total cholesterol fell from 96.4 to 74.8 mg/dl (p=0.042); mean LDL cholesterol changed from 40.5 to 22.3 mg/dl (p=0.025) and mean HDL cholesterol increased from 28.1 to 46.3 mg/dl (p=0.044).

Conclusions: This SCRI-HTN study showed that adult patients with hypertension receiving GPs-led care in the community health centres achieved statistically and clinically significant and sustained improvements on the cardiovascular indicators for as long as 5 years. It demonstrated that the participation of GPs as the core in the multi-disciplinary team to provide hypertension management care at the community health centres was effective in achieving the targeted chronic disease control.
Anxiety in patients with chronic heart failure: impact of perception of control and acceptance coping

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Purpose: The perception of lack of control has often been associated with anxiety. Studies have indicated that different coping strategies are differentially associated with mood in patients with chronic heart failure (CHF), and that maladaptive coping is generally linked to anxiety. Furthermore, it has been suggested that acceptance may potentially relieve emotional distress. The present study investigates if acceptance coping can buffer the hypothetical impact of perception of lack of control on higher degrees of anxiety. The aim is to clarify if the pattern of control, acceptance, and anxiety has relevance for nursing efforts to provide emotional support for patients with CHF.

Methods: 65 patients diagnosed with CHF in NYHA class II and III were recruited from a heart failure out patient clinic. The participants filled in forms to measure illness perception (B-IPQ), coping strategies (Brief COPE), anxiety and depression (HADS).

Results: Univariate analysis revealed correlations between Perception of control and Anxiety (r = 0.35, p < 0.05) and Acceptance coping and anxiety( r = 0.27, p < 0.05). However, upon entering both Perception of control and Acceptance coping into a path-analysis, the latter as a mediator, the effect of acceptance coping on anxiety was rendered non-significant.

Conclusion: Although the results suggest that acceptance coping inserts an influence on lower degrees of anxiety in patients with CHF, this impact seems to be dependent on the perception of control. That is, perception of control has primary over acceptance in predicting anxiety in patients with CHF. Consequently, our results suggest that the primary nursing efforts for emotional support should be directed toward an enhanced sense of control.

Depressed chronic heart failure patients have impaired autonomic function

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Background: Depression is associated with increased morbidity and mortality in chronic heart failure (CHF) patients. Sympatho-vagal balance might contribute to the relationship between depression and worse CHF outcomes. The association between depression and sympatho-vagal balance, as measured using heart rate variability (HRV), is unknown in CHF patients.

Purpose: The hypothesis of this study was that, in stable systolic CHF patients, impaired sympatho-vagal balance would be independently related to depression and to the severity of depression.

Methods: Participants completed a 30-minute electrocardiogram for HRV analysis (lying, sitting, quiet, dimly room, constant ambient temperature, no caffeine, smoking, alcohol, or exercise) and underwent a clinical interview for major or minor depression according to DSM-IV criteria. Low frequency to high frequency (LF/HF) ratio in the frequency domain, for predominance of sympathetic over parasympathetic activity, was the principal autonomic measure. Results were controlled for other co-variates (including age, sex, left ventricular ejection fraction, NYHA functional class, diabetes, renal function, beta blocker dose and other psychosocial factors) using analyses of variance (ANOVA). The outcomes were then subjected to multiple regression and pathway analysis.

Results: The sample comprised 45 participants, 35 males (78%), 10 females (22%), mean age 58.84 years (S.D. ± 12.43), NYHA Class I, N=14 (31%), II, N=26 (58%) and III, N=5 (11%), with mean left ventricular ejection fraction 41.22% (S.D. ± 11.08). Significant differences were found between patients with and without depression in all HRV frequency domain measures, with depression being significantly associated with decreased LF (nu) measures, increased HF (nu) measures, increased LF/HF ratio, and a significant increase in the LF/HF (principal outcome) measure (p < 0.001). Regression analyses demonstrated depression had a direct effect on HR. Social support had both direct and indirect effects on HRV via depression (p < 0.001).

Conclusion: In CHF patients, both minor and major depression are associated with predominant sympathetic over parasympathetic activity, a potential explanation for worse outcomes in depressed CHF patients. The apparent strong influence of social support on cardiac autonomic activity in CHF patients warrants further research.

Adherence to beta-blocker therapy in heart failure patients

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Introduction: Adherence to medical therapy is associated with patient outcome. Gender, marital status, co-morbidities, and hospitalisations have been reported to influence adherence in heart failure (HF). We aimed investigate geographical differences in adherence behaviour.

Methods: We invited patients enrolled in the CIBIS-ELD trial to participate in an observation period follow-up 1.7 to 5.5 years after the end of up-titration with beta-blockers. Self-reported beta-blocker adherence during the past month was assessed using a validated single item which has previously been shown to predict cardiovascular events in a sample of CHD patients. We used chi-square and logistic regression analyses to analyze socio-demographic and clinical variables as potential correlates for adherence.

Results: 780 patients (76 ± 5.9 years, 36.9% woman) were followed-up. 141 patients died (18.1%). Adherence data was available for 520 patients. 208 (90.4%) patients reported perfect (100%) beta-blocker adherence in the previous month. Poorer adherence (≤100%) was associated with country of residence (27.3%, 11.7% and 6% of patients were poorly adherent in Slovenia, Serbia, and Germany, respectively; p = 0.046), and with the presence of major or minor depression (20.9% of the depressed vs. 7.0% of the non-depressed patient were poorly adherent; p = 0.005). None of the other socio-demographic and clinical variables were related to adherence (all p > 0.20). Adjusting for age and sex, depression remained a significant predictor (p = 0.008). The geographical differences did not persist in multivariate analysis (p = 0.112).

Conclusion: The majority of surviving heart failure patients reported high adherence to their prescribed beta-blockers. As in previous studies, depression was a highly significant correlate of poorer adherence. To our knowledge, this is the first report of geographical differences in adherence in bivariate analyses and should be investigated further.

Effects of lifestyle factors, disease history and awareness on health-related quality of life in a Thai population

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Background: Health-Related Quality of Life (HRQoL) depends largely on individual perception of their health state, built from social norms and beliefs. Research from developed countries show that awareness of disease, as well as chronic medical conditions, play a major role in determining HRQoL. We hypothesized that, in the setting of middle-income country, such health states should have similar impacts on HRQoL. The impact of several health states on HRQoL were compared using effect sizes as part of the LIFECARE consortium.

Objective: To examine the impact of lifestyle factors, disease history, as well as awareness of diabetes and hypertension on HRQoL in a Thai population, using the Short Form Health Survey version 2 (SF-36v2).

Methods: Between 2008 and 2009, 4,850 Thais, aged 25-54 years, agreed to take part in a health survey. Impact of different health states on HRQoL were compared using effect sizes as part of the LIFECARE consortium.

Results: The mean age was 46 years and 72% were male. Physical and Mental Component Summary (PCS and MCS respectively) scores decreased as the number of chronic conditions increased monotonically (p < 0.001). Liver disease had the highest prevalence, accounting for 11.4%, followed by arthritis (10.4%), asthma (6.9%), cardiovascular disease (CVD) (3.4%) and chronic kidney disease
The sicker refuse getting healthier: cardiac rehabilitation acceptance paradox

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Aim: Early rehabilitation is a recommended early management after the acute coronary syndrome (ACS). We aimed to investigate the impact of clinical characteristics of ACS patients (pts) upon the decision to participate in early inpatient cardiac rehabilitation programme (ICR).

Methods: Consecutive pts after ACS (70% STEMI) treated with primary percutaneous coronary angioplasty were enrolled in the study. Quality of life questionnaires [EuroQol-5D with visual analogue scale (VAS)] and depression score (Beck Depression Scale) was collected at discharge from cardiac department (5-22 days after index event). All pts were proposed to participate in a 3-weeks ICR program. Depending on approval or refusal, pts were divided into two subgroups: I who participated in ICR and II-controls. Group I consisted of 98 pts [female n=25 (25.5%); mean age 66.7; years; mean BMI 28.4 kg/m²; mean average of 24.9 (149.5±24.3; p=0.0187). There was a strong trend towards lower median depression (3.8; p=0.057) but not PCS. Whether participants had significant positive effects on both PCS and MCS (p=0.08 and 0.21 respectively).

Conclusion: Despite a different social background, several health states including lifestyle factors and disease awareness showed similar impacts on HRQoL. Awareness of disease appeared to have a greater impact on mental health than having disease itself. Being physically active might help promote both physical and mental health.

The difference of QOL between older and younger patients with atrial fibrillation in Japan

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Introduction: The Atrial Fibrillation Effect on Quality-of-life (AFEQT) Questionnaire was developed and validated to measure the spectrum of quality of life (QOL) affected by atrial fibrillation (AF) and its treatment. We used this AFEQT questionnaire to investigate QOL in patients with AF in Japan. In this study we compared the QOL of Japanese patients to that of Westerners, and focused on the differences in QOL between younger and older age.

Methods: Consecutive outpatient patients (65.0±10.4 years) with AF were included (241 pts, female n=113 (47.0%); mean age 57.2±10.8, years). The AFEQT questionnaire was designed to measure the spectrum of quality of life affected by atrial fibrillation and its treatment. We compared the QOL of Japanese patients to that of Westerners, and focused on the differences in QOL between younger and older age.

Results: The scores of T reatment Concern were 75.95±84.63 and 84.63±18.25 (YG and OG, respectively, P=0.056, N.S.). The scores of Daily Activities were 80.72±19.72 and 71.72±23.57 (YG and OG, respectively, P=0.009).

The scores of Treatment Concern were 75.95±17.81 and 61.45±15.71 (YG and OG, respectively, P=0.046). The scores of Satisfaction were 75.73±18.75 and 75.99±18.05 (YG and OG, respectively, P=0.931). The score of Daily Activities was significantly higher and the score of Treatment Concern was significantly lower among YG. It means that younger patients feel less disability of daily activity, but have more concern about treatment. The score of Japanese patients tends to be higher than Westerners (the previous data showed that the score of psychological symptoms were 83.0±17.19 and 84.63±18.15 (YG and OG, respectively, P=0.566, N.S.). The scores of Daily Activities were 80.72±19.72 and 71.72±23.57 (YG and OG, respectively, P=0.009).

Conclusions: Younger patients reported less impairment of daily activities and more concern about treatment in QOL than older patients in Japan. To younger patients, we should give enough information about the treatment to remove their concern.

Dementia as an independent predictor of mortality for one year after hospital discharging of elderly subjects with cardiovascular diseases


Background: Dementia has been associated with higher overall mortality in the elderly. However, the impact of dementia in the mortality rates of those older adults who had undergone hospitalization due to cardiovascular diseases (CVD) has been less elucidated.

Aim: To evaluate the association between dementia and short-term all-cause mortality rates of older adults hospitalized with CVD during one year of follow-up.

Study design: Prospective cohort study.

Methods: We included a total of 102 consecutive patients aged 65 years or older who were discharged from a cardiology ward of a tertiary-care hospital. Mini mental state examination (MMSE) was applied. Individuals were divided into groups: group 1 with dementia diagnosis, and group 2 without dementia diagnosis. Demographic characteristics, blood analysis and cardiovascular parameters at time of discharge were recorded. Cardiac rehabilitation was not covered in this research. In the sample studied all individuals were followed up for one year or dead within this period. McNemar test was applied in order to compare the mortality rates between the groups providing the difference between the proportions with 95% confidence interval (CI). Chi-square and Kruskal-Wallis tests were applied in order to seek out differences among categorical and continuous variables between the groups, respectively. Statistical significance was set at p < 0.05.

Results: Group 1 comprised 47 subjects, and group 2 comprised 55 subjects. There were no differences between the groups regarding mean of aging nor sex distribution. Group 1 demonstrated, in relation to group 2, higher all-cause mortality rates (14.9% vs. 3.6%; p < 0.001). Obviously, there was a negative effect on PCS (p<0.001). Notably, exercise had significant positive effects on both PCS and MCS (p=0.08 and 0.21 respectively).

Conclusions: Dementia diagnosis seems to be a powerful tool for predicting poor outcomes in the elderly with CVD, thus its diagnosis scale should be applied more often in the cardiology divisions.

Anxiety, obesity and cortisol levels in patients with acute coronary syndrome

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Purpose: Previous research showed that anxiety adversely affects in hospital and long term cardiac outcomes of patients with post-acute coronary syndrome (ACS) regardless of traditional risk factors. However, the mechanisms linking anxiety to negative medical outcomes in these patients are not well known. Mechanisms could include a combination of the effect of anxiety on inflammation, catecholamines, heart rate variability, and endothelial function, along with effects on pro- and anti-inflammatory behavior. Several studies have suggested the cortisol may play an important role in cardiac health by modulating the progression of the atherosclerotic plaque and increasing the likelihood of ACS. Obesity is also an important risk factor related to heart disease. In this study, we investigated whether increasing levels of anxiety increases cortisol in patients with ACS, as well as obesity is related to higher levels of anxiety in this patients.

Methods: We recruited 115 consecutive patients (mean age 60±10; 80% male) with an ACS (76 ST-Elevation MI, 39 Non-ST-Elevation MI). During the week after the clinical event, patients completed a questionnaire measuring trait and state anxiety (STAI-R and STAI-E). In addition, we collected fasting blood samples assessing levels of basal cortisol and measured body mass index (BMI) in all patients.

Results: BMI was related to both state (r=0.02; p=0.02) and trait anxiety (r=2.7; p<0.01). In addition, levels of basal cortisol were related to trait anxiety (r=4.1; p=0.052).

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Conclusions: Obese patients suffering an acute coronary syndrome tend to be more anxious. Levels of anxiety are related to higher levels of cortisol and this might be an explanation for worse outcomes in anxious and obese patients suffering ACS. We recommend psychological therapy in patients who suffered acute coronary syndrome to reduce the impact of anxiety in their prognosis.

P4390 Clinical correlations of cognitive impairment in chronic heart failure
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Introduction: Cognitive dysfunction is known to be more common in patients with systolic heart failure than controls. The impact of heart failure severity on cerebral function remains unknown.

Methods: Fifty-three patients with systolic heart failure were included in the study. Patients have answered the Mini Mental Score and were classified as having normal cognition (25-30), mild (20-24) and moderate (10-19) cognitive impairment (CI). Patients have also completed quality of life scores (Kansas City Cardiomyopathy Questionnaire, Duke activity status index), and a depression score (Zung score). Clinical data (age, sex, NYHA class, six minute walk test) and left ventricular ejection fraction (LVEF) were also available.

Results: From the patients screened, only 14 (26%) had normal cognitive function, while 22 (41%) had mild and 17 (32%) had moderate CI. Cognitive dysfunction was strongly associated with sex, NYHA class and depressive symptoms. Nine out of 11 female vs 14 out of 42 male were classified as having moderate CI (p = 0.006). Patients with normal CI had lower zung score (41±11 vs 47±11 for mild CI, vs 54±9 for moderate CI, p = 0.05) and higher KCCQ-overall score (57±37 vs 37±23 for mild CI, vs 31±28 for moderate CI, p = 0.05). Across NYHA class deterioration, mean Minimal score decreases significantly (24.5±11 for NYHA I, 22.4±4 for NYHA II, 22.4±4 for NYHA III, 17±6 for NYHA IV, p = 0.023). LVEF, HF cause and six minute walk test did not differ significantly among the CI subcategories.

Conclusions: Cognitive dysfunction is very common in heart failure patients, affecting moderately almost one out of three HF patients. Cognitive dysfunction deteriorates along with HF deterioration and this has to be screened, especially when complex medical advice is given.

P4391 Symptom profile of hypertensive primary care patients with undiagnosed obstructive sleep apnea - a structural equation model analysis
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Background: Obstructive sleep apnea (OSA) has been linked to hypertension (HT) in sleep clinic populations, but little is known about the symptom profile of undiagnosed OSA in primary care patients with HT.

Objectives: To describe and compare (I) cardiovascular signs and risk factors associated with high and low risk for OSA, as measured by the BSAQ, in men and women with HT, as well as (II) to compare traditional sleep-related symptoms between high and low-risk patients of both genders.

Methods: Cross-sectional design, 480 patients mean age 57.8 yrs (±6.7 yrs) with HT were included at 4 primary care centres in Sweden. Clinical examinations (performed by one nurse and one physician specialized in sleep medicine), and the BSAQ, the Minimal insomnia symptoms scale, the Epworth sleepiness scale, the hospital anxiety and depression scale, as well as the International Physical Activity Questionnaire were used to collect data. Physical activity was measured with validated pedometers.

Results: 71% of the men and 61% of the women had high risk for OSA. 76% of the high-risk men expressed that others were bothered by their snoring compared to 63% of the women (p < 0.05). Men with high risk reported that breathing pauses had been noticed more commonly by others compared to women (p < 0.05). Men who demonstrated a high risk for OSA had more dyslipidaemia (p = 0.005–p < 0.001), higher mean levels of P-Crea (p < 0.001) and lower heredity of CVD (p > 0.001) than women. These men also reported more days/week of moderate (p < 0.005) and high intensity physical activity (p < 0.005), but steps/day did not differ. Medication with ACE inhibitors and angiotensin receptor blockers were more common among high-risk men (p < 0.001), but diuretics (p = 0.001) and hypnotics (p > 0.005) were more common among high-risk women compared to men. 42% vs. 62% vs. 50% (p > 0.005). The mean HADS anxiety score and the number of patients above cut-off were significantly higher among women with high risk compared to men (p < 0.05). Blood pressure, arhythmias or diabetes did not differ between the risk groups.

Conclusions: Knowledge about gender-specific symptoms, cardiovascular signs and risk factors associated with high HT might be an explanation for worse outcomes in anxious and obese patients suffering an ACS. We recommend psychological therapy in patients who suffered an ACS. We recommend psychological therapy in patients who suffered acute coronary syndrome to reduce the impact of anxiety in their prognosis.

P4392 Differences in cardiovascular signs and risk factors among hypertensive middle aged men and women with high vs. low risk on the Berlin sleep apnea questionnaire
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Background: Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder associated with hypertension (HT), increased morbidity and mortality. Difficulties to identify patients with OSA have been described in primary care, causing low referral rates to sleep clinics. The Berlin sleep apnea questionnaire (BSAQ) is a validated tool that can help to identify patients.

Aim: To describe and compare (I) cardiovascular signs and risk factors associated with high and low risk for OSA, as measured by the BSAQ, in men and women with HT, as well as (II) to compare traditional sleep-related symptoms between high and low-risk patients of both genders.

Methods: Cross-sectional design, 480 patients mean age 57.8 yrs (±6.7 yrs) with HT were included at 4 primary care centres in Sweden. Clinical examinations (performed by one nurse and one physician specialized in sleep medicine), and the BSAQ, the Minimal insomnia symptoms scale, the Epworth sleepiness scale, the hospital anxiety and depression scale, as well as the International Physical Activity Questionnaire were used to collect data. Physical activity was measured with validated pedometers.

Results: 71% of the men and 61% of the women had high risk for OSA. 76% of the high-risk men expressed that others were bothered by their snoring compared to 63% of the women (p < 0.05). Men with high risk reported that breathing pauses had been noticed more commonly by others compared to women (p < 0.05). Men who demonstrated a high risk for OSA had more dyslipidaemia (p < 0.05–p < 0.001), higher mean levels of P-Crea (p < 0.001) and lower heredity of CVD (p > 0.001) than women. These men also reported more days/week of moderate (p < 0.005) and high intensity physical activity (p < 0.005), but steps/day did not differ. Medication with ACE inhibitors and angiotensin receptor blockers were more common among high-risk men (p < 0.001), but diuretics (p = 0.001) and hypnotics (p > 0.005) were more common among high-risk women compared to men. 42% vs. 62% vs. 50% (p > 0.005). The mean HADS anxiety score and the number of patients above cut-off were significantly higher among women with high risk compared to men (p < 0.05). Blood pressure, arhythmias or diabetes did not differ between the risk groups.

Conclusions: Knowledge about gender-specific symptoms, cardiovascular signs and risk factors associated with high HT might be an explanation for worse outcomes in anxious and obese patients suffering an ACS. We recommend psychological therapy in patients who suffered an ACS. We recommend psychological therapy in patients who suffered acute coronary syndrome to reduce the impact of anxiety in their prognosis.

P4393 Is increased high-sensitive troponin T associated with severity of sleep apnea syndrome?
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Purpose: With sleep apnea syndrome (SAS) being a factor for cardiovascular
Nutritional assessment in a University Department

Methods: Retrospective analysis of 400 consecutive sleep apnoea patients with regard to hsTnT, sleep and overnight respiratory parameters, CRP, Creatinine/GFR, NTproBNP as well as pulmonary function test. Results: Of 400 patients, 65 had positive hsTnT (~<140 ng/ml). No correlation with severity of sleep apnoea syndrome as defined by apnoea-hypopnoea index (AHI), oxygen desaturation index (ODI) or lowest saturation during the night was found. Elevated hsTnT was associated with elevated NTproBNP, Creatinine and CRP as well as lower GFR and daytime PCO2. However, during positive airway pressure therapy (CPAP, AutoCPAP or Adaptive Servoventilation) hsTnT decreased significantly (p = 0.046). In patients with long-term follow-up (n=10) within the study period, the decrease of hsTnT was even more pronounced (p = 0.013).

Conclusions: SAS does not lead to elevated hsTnT per se, but co-morbidities as often seen with SAS are associated with positive hsTnT. Nevertheless, treatment of SAS leads to reduction of hsTnT, especially in patients with long-term treatment.

Adherence to the Mediterranean diet reduces the likelihood of acute coronary syndromes, even among people with high anxiety rates: a case-control study

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Purpose: Adherence to the Mediterranean diet has long been associated with beneficial effects regarding cardiovascular disease, while anxiety exerts the opposite effects. 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) in participants with and without symptoms of anxiety.

Methods: During 2009-2010, 500 participants were enrolled; 250 were consecutively patients with a first ACS and 250 population-based, control subjects, 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), while trait anxiety with the Spielberger State-Trait Anxiety Inventory form Y-2 (STAI Y-2, range 20-80).

Results: After various adjustments (i.e., age, sex, physical activity, BMI, smoking, family history of cardiovascular disease, hypertension, hypercholesterolemia and diabetes mellitus), each 1/55 increase of the MedDietScore was associated with 8% (95% CI: 0.88-0.98) lower likelihood of ACS and each unit increase of the MedDietScore was associated with 8% (95% CI: 0.86-0.99) lower likelihood of having an ACS in subjects with low anxiety and 5% (0.83-0.90) lower likelihood in participants with moderate or severe anxiety.

Conclusions: The protective effect of the Mediterranean dietary pattern regarding ACS persisted even in subjects with trait anxiety, highlighting its beneficial role.

Frequency of returning to work after ST segment elevation myocardial infarction


The aim of the study was to evaluate the occupational functioning and identify the health-related determinants of successful vocational rehabilitation in workers with a recent myocardial infarction (MI).

Material and Methods: The study group consisted of patients (pts) who under- went percutaneous coronary intervention (PCI) for first acute ST-segment elevation myocardial infarction (STEMI) and who were employed before MI. We examined the demographic, clinical and angiographic characteristics of pts who returned to employment (group 1), and those who did not returned to work (group 2). The subject mental health as well as quality of life and occupational functioning were measured using Nottingham Health Profile (NHP) scale, Beck Depression Inventory and Work Ability Index (WAI). All pts were observed during one year and cardiac events were analyzed.

Results: Among 268 pts (aged 39-64 years) 142 (53%) pts returned to work within 6 months, and 126 (47%) did not. The pts who returned to work after first MI were younger (mean age 49.2 vs 54.3 years), had higher level of education, self-rated health and quality of life than the pts who did not resume their occupational activity. In addition there was no difference in 1-year clinical events in those who returned to work and those who did not.

Conclusion: Age, sociopsychological and occupational factors have the strongest influence on the chance to return to work after myocardial infarction.
Hip fracture and risk of acute myocardial infarction: a nationwide study
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Background: Osteoporotic fractures are associated with increased mortality risk. However, few data are available on the risk of acute myocardial infarction (AMI) following hip fracture. Therefore, we investigated whether hip fracture increased the risk of AMI in a large, nationwide cohort study.

Method: We obtained data from 8,758 patients diagnosed with hip fracture from 2000 to 2009 and from 4 matched controls for each patient from the Longitudinal Health Insurance Database (LHID 2000), Taiwan. Controls were matched for age, gender, comorbid disorders, and enrollment date. All subjects were followed up from the date of enrollment until AMI, death, or the end of data collection (2009). Cox's regression model adjusted for age, gender, comorbid disorders, and medication was used to assess independent factors determining the risk of development of AMI.

Results: A total of 8,758 subjects with hip fractures and 35,032 controls were identified. Among these patients, 1,183 (257 hip fracture patients and 926 controls) developed AMI during the median 3.2 year (interquartile range, 1.4–5.8 years) follow-up period. Patients with hip fractures had a higher incidence of AMI occurrence when compared to controls (8.71/1000 person-years versus 6.82/1000 person-years). Figure exhibits the results of the log-rank test and Kaplan-Meier survival analysis. During the maximal 10-year follow-up period, the cumulative incidence of AMI was significantly higher in patients with hip fracture than controls (P < 0.001 by log-rank test). Multivariate analysis indicated that hip fracture was associated with a greater risk for AMI development (hazard ratio: 1.29, 95% confidence interval: 1.12–1.48, P < 0.001).

Conclusions: We conclude that hip fracture is independently associated with a higher risk of subsequent AMI.

Secular trends in women with acute coronary syndrome (ACS) referred to coronary artery angiography: a 15-year observation of the University Hospital Bern
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Purpose: It is suggested that the rate of young women suffering from ACS is increasing. We therefore investigated our invasive cardiology database to assess secular trends in the incidence of first ACS and CV risk factors in women classified into different age-groups over the last 15 years (1995 to 2010).

Methods: We extracted data of all women with coronary angiography between 1995 and 2010 for a first ACS event on age, presence, classification of ACS, and cardiovascular risk factors such as smoking, arterial hypertension, diabetes mellitus, dyslipidemia, family history, and obesity. In the age groups 20-49 yrs, 50-59 yrs, 60-69 yrs, 70-79 yrs, and 80-99 yrs, we calculated numbers of first ACS per year and proportion of first ACS per year with regard to the female population (according to data from the Swiss Federal Institute of Statistics) of the referring area (Cantons of BE, SO, FR, and NE). We also calculated the proportion of women with first ACS with CV risk factors. To assess temporal trends within age groups, we performed linear regressions of absolute and relative numbers of first ACS versus time, as well as risk factors versus time.

Results: Absolute and relative time trends showed significant linear increases for all age groups for absolute as well as relative numbers of first ACS events (all P < 0.01, Figure 1). While the increase in the group of the 20-49 year old women was small in absolute and relative numbers, from 1995 to 2010 it was most 5-fold, compared to a 3- and 2-fold increase in the 50-59 yrs and 60-69 yrs age groups, respectively. The increase between 1995 and 2000 in the older age-groups was most probably influenced by a change in indication with the advent of PCI. Temporal trends with regard to risk factors showed a significant increase in smoking and obesity in the 60-69 yrs age group.

Conclusions: Our results confirm that there was a small but significant increase of ACS in 20-49 year-old women which, relative to the incidence in 1995, was considerably greater than the increase in the 50-59 yrs and 60-69 yrs age groups. Increases in first ACS in the 60-69 year old women may have been linked to increased prevalence of smoking and obesity.

Physical activity attenuates subclinical atherosclerosis in subjects with chronic spinal cord injury
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Purpose: Cardiovascular diseases are the major cause of death in subjects with chronic spinal cord injury (SCI). Interestingly, SCI subjects present higher carotid intima-media thickness (IMT) than able-bodied individuals, independent of traditional cardiovascular risk factors. The present study investigated the effect of regular physical activity on carotid IMT in men with chronic (> 1 year of injury) SCI.

Methods: We studied 43 SCI men with no voluntary motor activity [20 seden- dony (40% tetraplegic), 13 subjects (69% tetraplegic)] and 24 able-bodied men by clinical, anthropometric, laboratory, blood pressure and ultrasound carotid analysis. All enrolled subjects were normotensive, non-diabetics, non-smokers and with normalistic and the studied groups presented similar age and body mass index. Data were evaluated by chi-square analysis, Wilcoxon test, 1-way ANOVA followed by Tukey test and covariance analysis and are presented as mean±standard error, P-value of less than 0.05 was considered significant.

Results: Carotid IMT in SCI athletes (0.63±0.03 mm) was lower than that of SCI sedentary individuals (0.70±0.02 mm; p=0.008), but higher than that of able-bodied subjects (0.49±0.02 mm; p=0.001). SCI athletes still presented lower IMT compared to SCI sedentary individuals (0.49±0.28 vs. 1.17±0.39 mm; p=0.037) levels in comparison to SCI sedentary individuals. Conversely, all other studied variables were similar between the SCI groups. In addition, carotid IMT analysis adjusted by triglycerides and C-reactive protein levels revealed that carotid IMT was significantly lower in SCI athletes in comparison to SCI sedentary individuals (p=0.009).

Conclusions: Regular physical activity is associated with attenuation of subclinical atherosclerosis in subjects with SCI, independent of hemodynamic, metabolic and inflammatory factors.

Vitamin D deficiency in relation to circulating inflammatory cells and inflammatory markers among apparently healthy individuals
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Purpose: Vitamin D (ViD) insufficiency is widespread all over the world. It is also known that insufficient 25(OH)D3 (vitamin D3) alters metabolite function, that has been related with the development of various clinical disorders [i.e., osteoporo- sis, diabetes, cardiovascular disease (CVD)]. This study aimed to evaluate the relationship between ViD deficiency and inflammatory cells and markers among apparently healthy adults.

Methods: During 2009, 490 volunteers (46/16 years, 40% male) were consecu- tively enrolled to the study (participation rate 85%). Biochemical analyses were performed through established procedures, at 12h fasting, and ViD (ng/mL), high-sensitive C-reactive protein (CRP, mg/dL), cytokin G (CytG, mg/L), hap- toglobin (Hp, mg/dL), haemoglobin (Hb, g/dL), platelets (PLT, 109/L) and white blood cells (WBC, 109/L) were measured. Anthropometric characteristics were also recorded to account for potential confounders. Partici- pants were classified in ViD sufficiency (i.e., >30 ng/mL) and ViD insufficiency (i.e., <30 ng/mL). Logistic regression models were used to evaluate the associa- tion of inflammation cells and biomarkers to the likelihood of having ViD insuffi- ciency.

Results: Among participants, 25% were ViD sufficient. Participants with ViD insufficiency had higher values of CRP, CytG and Hb as compared with those with ViD sufficiency (all p's <0.05). Logistic regression models, adjusted for age, sex, smoking history, family status, physical activity, body mass index and smoking, revealed a positive association between ViD insufficiency and CRP and a neg- ative association with Hb. In particular, 1 mg/dL increase of CRP increase the odds of having ViD insufficiency 3.7 times (95% CI: 1.16-12.0). On the contrary, for every 1 g/dL increase of Hb, the odds of having ViD insufficiency decrease 27% (OR=0.73, 95% CI: 0.57-0.93).

Conclusion: The involvement of ViD in the homeostasis of CVD has been re- cently evaluated. Results showed that ViD deficiency is a significant risk factor.
for the development of atherosclerosis, as it has been related with inflammation markers. Therefore, optimizing V̇O₂ max may serve as a potentially effective strategy in CVD prevention.

**P4402**

Genetic predisposition to higher blood pressure increases coronary artery disease risk


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Hypertension is a risk factor for coronary artery disease (CAD). Recent genome-wide association studies (GWAS) have identified 32 single nucleotide polymorphisms (SNPs) associated with higher blood pressure (BP) at genome-wide significance (p < 5x10^-8). If elevated blood pressure is a causative factor for CAD, these variants should also increase CAD risk. Analyzing GWAS data from 22,233 CAD cases and 43,946 controls in the CARDIoGRAM consortium showed that 88% of these BP-associated SNPs were likewise positively associated with CAD, i.e., they had an odds ratio for CAD = 1, a proportion much higher than expected by chance (p < 5x10^-10). The average relative CAD risk increase per each of the multiple BP-raising alleles observed in CARDIoGRAM was 3.0% for SBP-SNPs (95% confidence interval, CI), 1.8 to 4.3% and 2.9% for DBP-SNPs (95% CI, 1.7 to 4.1%). In sub-studies, individuals carrying most SBP- and DBP-related risk alleles (top quintile of a genetic risk score distribution) had 70% (95% CI, 50-94%) and 59% (95% CI, 40-81%) higher odds of having CAD, respectively, as compared to individuals in the bottom quintile. In conclusion, most BP-associated SNPs also confer an increased risk for CAD. These findings are consistent with a causal relationship of increasing BP to CAD. SNPs primarily affecting blood pressure contribute to the genetic basis of CAD.

**P4403**

Mitochondrial haplogroups H and J: risk and protective factors for ischemic cardiomyopathy

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Purpose: As mitochondria are the principal source of reactiveoxygen species (ROS), these organelles may play an important role in ischamiciocardioopathy (IC) development. The mitochondrial genome may influence this disease. The aim of the present study was to test the relationship between IC development and the impact of single nucleotide polymorphisms (SNPs) in mitochondrial DNA (mtDNA) defining the mitochondrial haplogroups in a population study.

Methods: The study complied with the Declaration of Helsinki. DNA samples from 731 unrelated individuals (380 healthy controls and 351 IC patients) were analysed in this study. Haplogroup analysis for the ten major European haplogroups was performed by using the single base extension technique and by polymerase chain reaction-restriction fragment length polymorphism. Frequencies and Odds Ratios for the association between IC patients (n=351) and healthy controls (n=380) were calculated.

Results: Compared to healthy controls, the prevalence of haplogroup H was significantly higher in IC patients (40.0% vs 50.4%, p-value<0.005) while the frequency of haplogroup J was significantly lower (10.8% vs 5.7%, p-value<0.015). The haplogroup frequencies for our controls did not differ substantially from those reported in previous studies that analyzed different European populations. The mitochondrial haplogroups distribution between cases and controls, stratified by the main clinical cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, smoking and alcohol consumption), was similar in both groups. The analysis of the SNPs characterizing the European mtDNA haplogroups showed that the SNP m.14766C>T (p-value<0.005) and m.14766C>T (p-value<0.005) was overrepresented in IC patients. The SNP m.7028C>T produces a non synonymous amino acid change, but the SNP m.14766C>T causes a change in cytochrome b. Furthermore, the SNP m.1038A>G, which produces a non synonymous amino acid change in NADH dehydrogenase subunit 3 (3hrenone-3-alanine), was found to be a protective factor (p-value=0.028).

Conclusions: Our results showed suggestive evidence for the association of the mitochondrial haplogroups H and J as risk and protective factors respectively for ischemic cardiomyopathy. Future analysis of the full sequenced mtDNA in these haplogroups and their phenotypic analysis will yield additional insights towards therapeutic targets for ischemic cardiomyopathy pathogenesis.

**P4404**

Prediction of ischemic events based on transcriptomic and genomic markers in patients undergoing carotid endarterectomy

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Classical risk factors, including age, smoking, serum cholesterol, diabetes and blood pressure, constitute the basis of present risk prediction models, but fail to identify all individuals at risk. The objective of this study was to investigate if genomic and transcriptional patterns improves prediction of ischemic events in patients at increased risk for cerebrovascular disease (CVD). Patients were followed for an average of 44 months and 25 ischemic events (18 ischemic strokes and 7 myocardial infarctions) occurred. Blinded leave-one-out cross-validation on Cox regression coefficients was used to assign gene expression based risk scores to each patient. When compared to classical risk factors, addition of classical and mitochondrial gene expression based risk score improved the prediction of future ischemic events from an area under curve (AUC) of 0.66 to an AUC of 0.79. The inclusion of gene expression risk score from peripheral blood mononuclear cells of or from 25 established myocardial infarction risk-SNPs only exhibited marginal effects on the prediction of ischemic events. Prediction of ischemic events is improved by inclusion of expression profiling from carotid endarterectomy patients. Gene expression profiles were obtained from carotid plaque tissue (n=126) and peripheral blood mononuclear cells (n=97) of patients undergoing carotid endarterectomy. The method may be developed to identify subjects at very high risk of ischemic events.

**P4405**

Genetic variants primarily associated with type 2 diabetes also affect coronary artery disease risk


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Multiple single nucleotide polymorphisms (SNPs) have been identified to associate with type 2 diabetes (T2DM). If T2DM is a causal risk factor for coronary artery disease (CAD), SNPs increasing T2DM risk should also increase CAD risk. We studied 29 common genetic variants previously associated with T2DM at a genomewide significant level (p<5x10^-8) in CARDIoGRAM, a genomewide data set including 22,233 CAD cases and 64,762 controls. Significant T2DM SNPs than expected by chance displayed an odds ratio for CAD >1 (20 out of 29, p<0.031). In fact, 10 T2DM SNPs were nominally significantly (p<0.05) associated with CAD in CARDIoGRAM, a proportion much higher than expected by chance. The average increase in CAD risk observed per individual T2DM risk allele was 1.27% (95% confidence interval, CI), 0.26-2.30%. Studying a weighted genetic risk score in a subgroup of 4000 cases and 5680 controls revealed that individuals in the highest quintile had an 18% higher risk (CI 4.3-4.4%) of CAD as compared to individuals in the bottom quintile of the genetic risk score. Our data indicate that multiple genetic variants associated with T2DM confer a small risk increase for CAD, strengthen the evidence that T2DM may be a causal risk factor for CAD.

**P4406**

Impact of arterial stiffness on adverse cardiovascular outcomes and mortality in peritoneal dialysis patients

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Cardiovascular (CV) disease is a major cause of morbidity and mortality in patients with end-stage renal disease. In recent years, arterial stiffness has taken on great importance in the pathophysiology of CV diseases. The independent predictive value of arterial stiffness for CV events and for all-cause and CV mortality has been demonstrated in the general population and in hemodialysis patients. Our aim in this study was to determine the relationship of arterial stiffness with mortality and fatal and nonfatal CV events in peritoneal dialysis (PD) patients.

Methods: In this prospective observational cohort study with 2 years of follow-up, we studied a cohort of 156 PD patients with a mean follow-up of 19.2±6.4 months.
At baseline, echocardiography and standard clinical and biochemical analyses were performed in all patients and in 28 healthy subjects. Aortic stiffness index beta (ASiB, a surrogate marker of arterial stiffness) was calculated as follows: 

\[
\text{ASiB} = \frac{1}{\text{Aortic stiffness index}}
\]

Results: During the follow-up period, 25 of the patients (16%) died, and 10 of those deaths had CV causes. Nonfatal CV events occurred in 15 patients. The median ASiB was greater in PD patients than in control subjects (4.2 vs. 3.5, \textit{p}<0.001). In all patients, the ASiB was related to death (p<0.001), but not all-cause mortality.

Conclusion: Our results provide the first direct evidence that arterial stiffness is independently predicted by adverse outcomes in PD patients.

**P4407**

Cardiovascular disease incidence and compliance on treatment strategy in patients with familial hypercholesterolemia

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**Introduction:** Familial hypercholesterolemics patients are considered high risk patients with a high risk of cardiovascular disease (CVD).

**Aim:** To evaluate the cardiovascular disease incidence and compliance on treatment strategy in patients with familial hypercholesterolemia.

**Methods:** We enrolled 443 consecutive patients, clinically diagnosed with heterozygous familial hypercholesterolemia (172 men), of mean age 40.4±15 years. We measured their biochemical parameters and lipid profile before and after initiation of lipid lowering therapy. We also recorded all major cardiovascular adverse events during their follow-up period.

**Results:** Mean period of follow-up was 8 years. 26.6% of the population showed poor compliance to drug therapy. The overall cardiovascular events incidence was 8% (36 events). 16 events occurred on those who showed the poorest compliance on drug therapy and 19 events on those who followed the prescribed instructions (13.5% vs 5.8%, p<0.001). Multivariate linear regression showed that increasing age was independently associated with cardiovascular events (p<0.01). The cardiovascular events decrease by 33%, independently of age, sex, body mass index, arterial hypertension, smoking habits, total and LDL cholesterol levels, pre-existing coronary artery disease and prescribed therapy.

**Conclusion:** A considerable percentage of heterozygous FH patients show poor compliance to treatment strategy and this finding consists independent prognostic factor of major cardiovascular events.

**P4408**

Association of male pattern baldness with angiographic coronary artery disease severity and collateral development

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**Purpose:** Although several epidemiological studies have shown an association between male pattern baldness and atherosclerosis, it has never been studied by investigating angiographic presence and severity of coronary artery disease. We aimed to investigate whether there is an association between male pattern baldness and angiographic coronary artery disease severity and collateral development.

**Methods:** Angiographies, coronary artery disease risk factors, lipid parameters, and presence and severity of baldness of 470 male patients were prospectively evaluated. Baldness were defined as five groups (no hair loss, frontal baldness only, frontal baldness with mild, moderate, or severe vertex baldness). Severity of coronary artery disease was evaluated with Gensini and collateral development with Rentrop scores.

**Results:** Although subjects with higher Gensini score had more frequent and severe baldness, they were older than the group with lower Gensini score (60.3±11.7 vs. 56.0±11.7, p<0.001). Bald patients had higher Gensini score when compared with their non-bald counterparts (44.7±43.3 vs. 34.1±36.4, p=0.009). In univariate analysis baldness, smoking and age more than 55 were predictors of a Gensini score more than 20. In multivariate analysis, only age more than 55 (p=0.005, odds ratio 1.392, 95% confidence interval 1.293 to 1.392), but not all-cause mortality.

**Conclusion:** Our results provide the first direct evidence that arterial stiffness is an independent risk predictor of adverse CV outcome in PD patients.

**P4409**

Risk factors for coronary plaque progression in patients with far east Asians - A serial volumetric IVUS analysis


**Backgrounds:** Far East Asians have been reported to be at lower risk of cardiovascular events than Westerners, suggesting the potential racial difference in coronary artery disease (CAD) risk factors and progression of atherosclerosis. However, few data exist correlating cardiovascular risk factors with volumetric IVUS measurements of coronary plaque progression in Asians.

**Methods:** Serial volumetric IVUS examinations (baseline and 14-months follow-up, mean measured length: 43mm) were performed for 297 Far East Asian patients with stable angina pectoris. Patients were subsequently treated with a combination of angiotension-II receptor blocking agents (ARB), β-blockers, calcium channel blockers, glycomic control agents and/or statins per physician's discretion. Serial progression rate of atherosclerosis was compared with the patients' characteristics during the follow-up period.

**Results:** In multiple linear and logistic regression test, age > 65 years, diabetes, and male gender remained as predictors of increased plaque volume by serial IVUS. On the other hand, the use of statins and ARBs were identified as factors associated with decreased plaque volume.

**Conclusions:** Advanced age, poorly controlled diabetes and male appear to be predictors of atherosclerotic progression in Far East Asians. Statins and angiotension-II receptor blocking agents may play a positive role in potential plaque regression of coronary arteries in this population.

**P4410**

Acute coronary syndrome: a serious threat even at age 40


**Purpose:** Nowadays, acute coronary syndromes (ACS) are affecting a growing number of young individuals. Are ACS in this population a different entity? Our aim was to assess the prevalence, risk profile, therapeutic approach and outcomes 40 years old and below.

**Population and Methods:** We studied 4300 patients admitted at a single coronary care unit with ACS, between May 2004 and November 2011. Two groups were considered: A - patients no older than 40 years (n=94, 2.2%), group B - patients above 40 (n=4206).

Groups were compared regarding demographic data, cardiovascular risk factors, lab results, treatment, angiographic findings and prognosis. The median follow-up was 2361 days.

**Results:** Group A had a mean age of 36.6±3.1 years and included more males (77.7% vs. 68.2%, p=0.05), smokers (59.6% vs. 14.4%, p=0.001) and patients with previous family history of coronary heart disease (25.5% vs. 10.7%, p<0.001), but less with hypertension (40.4% vs. 77.6%, p=0.001), type 2 diabetes (19.1% vs. 34.1%, p=0.002) and dyslipidemia (68.1% vs. 80.2%, p=0.004). Group A was more frequently admitted with ST elevation ACS (51.1% vs. 33.4%, p=0.001), considering laboratory data on admission, group A had lower creatinine (0.9±0.2 mg/dL vs. 1.2±0.9 mg/dL, p=0.004), but higher hemoglobin (14.7±1.2 g/dL vs. 13.4±1.8 g/dL, p=0.001) and platelet count (259.7±78.6 vs. 224.0±70.3 x 10^3, p=0.001). Blood glucose and lipid profile were not statically different. Regarding baseline therapy, group A received more GP IIb/IIIa inhibitors (48.8% vs. 30.1%, p=0.001) and less diuretics (10.6% vs. 27.3%, p<0.001). Left ventricular ejection fraction was significantly higher in this group (45.8±11.2% vs. 51.1±11.6%, p=0.007). Group A was also submitted more often to an invasive strategy (80.9% vs. 61.6%, p<0.001) and had a higher prevalence of normal coronary arteries (26.3% vs. 16.5%, p=0.024) and one vessel disease (48.7% vs. 38.3%, p=0.026). The in-hospital mortality was significantly lower for group A (0.0% vs. 5.4%, p=0.020). During the follow up, this group had a trend towards lower mortality rate (6.0% vs. 11.2%, p=0.14).

**Conclusion:** Younger ACS patients have a particular risk profile, and by being more aggressively treated, are associated with a better short term prognosis.

Long term follow-up clearly shows that this is not a benign entity, so these patients

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**Mind, body & behaviour: implications in cardiovascular risk and disease**

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require an aggressive early preventive intervention, focused on lifestyle changes, smoking cessation and medication compliance.

**RENAL DENERVATION THERAPY IN HYPERTENSION**

**P4411 One year pooled outcomes following renal sympathetic denervation in patients with resistant hypertension: From the Symplicity HTN-2 trial**

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**Purpose:** Renal sympathetic nerve activation plays an important role in the pathogenesis of essential hypertension and selective ablation of the sympathetic nerves through the renal arteries can substantially reduce blood pressure (BP) in patients with treatment-resistant hypertension. The duration of antihypertensive effect and long-term safety of renal denervation (RDN) requires further follow-up.

**Methods:** This prospective, multicentre, randomised trial evaluated the safety and effectiveness of RDN in patients with an office systolic BP of ≥160 mm Hg while taking ≥3 antihypertensive medications. The control group was managed with medication alone and at 6 months after randomisation were offered RDN treatment if eligibility was met. Data from all patients receiving RDN was pooled and change in BP at 6 and 12 months, pulse pressure, heart rate, and adverse events were analyzed.

**Results:** There were 89 patients treated with RDN. At 12 months post-procedure, data are available for 47 patients randomized to immediate RDN and 33 crossover patients. The mean age of patients treated was 58.6 years, 44% were female, mean body mass index was 31.1 kg/m², and mean heart rate at baseline was 73.7 bpm. Approximately one-third of patients had type 2 diabetes. There was one renal artery dissection. No other serious adverse events occurred.

**Conclusion:** The antihypertensive effect of RDN is durable to 12 months in patients with treatment-resistant hypertension. Additional data describing the effects of RDN on renal function, pulse pressure and heart rate through 12 months will be reported.

**P4412 Percutaneous renal sympathetic denervation exerts a chronic effect on renal hemodynamics using a novel catheter for radiofrequency ablation: data from an animal study**

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**Purpose:** To examine whether renal sympathetic denervation, performed using a novel radiofrequency ablation catheter, exerts a chronic (1 month post ablation) effect on renal hemodynamics assessed by average peak velocity (APV), renal flow reserve (RFR) and resistive index (RI).

**Method:** In 9 anesthetized female juvenile farm swines (mean age 6 months, mean weight 34.5 kg), a 0.014 inch Doppler flow wire was introduced in the main renal artery for the measurement of the APV under baseline and hyperemic condition that was induced by the bolus intrarenal administration of dopamine (50μg/kg). RFR was calculated as the ratio of hyperemic to basal peak velocity. RI was estimated as (peak systolic velocity – end-diastolic velocity)/peak systolic velocity. APV, RFR and RI were measured before and 1 month after renal sympathetic denervation. The sympathetic denervation was achieved via the lumen of the main renal artery with the novel catheter connected to a radiofrequency generator from St. Jude Medical according to pre-specified algorithm.

**Results:** In all animals, APV 1 month after ablation compared to APV before ablation was significantly higher (30.2±2.47 mm Hg; p<0.001) during the first 24 hours. Systolic blood pressure reduction appeared to be much higher at daytime (16.2±1.50 mm Hg; p<0.001) compared to night (10.61±1.47 mm Hg; p=0.001) which might indicate the role of sympathetic activity at daytime. A concordant effect on diastolic BP was observed: 6.9±1.7 mm Hg (p<0.001). Systolic BP reduction sustained at 3 (11.7±3.2 mm Hg; p<0.001) and 6 months (9.3±3.3 mm Hg, p<0.009) without further decrease – on the contrary a relapse to higher BP was seen.

**Conclusion:** Catheter-based renal sympathetic denervation augmented APV and decreased RFR and RI, persistently and significantly at 1 month post ablation in healthy swines. These results support the chronic effect of renal artery denervation by the radiofrequency ablation catheters on renal hemodynamic function even in a healthy animal setting.
Renal sympathetic denervation with brachytherapy using beta-radiation catheter. Results from a feasibility and safety preclinical study

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Background: Renal sympathetic denervation using intravascular radiofrequency ablation has demonstrated significant reduction in systolic and diastolic blood pressure in clinical trials. Local radiation therapy demonstrated the ability to damage the nervous system and is currently used for the treatment of trigeminal neuralgia. This study aimed to assess feasibility and safety of a novel approach for RSD using a clinically available beta-radiation catheter beta-cath™.

Methods: Ten naive Yorkshire swine underwent intravascular brachytherapy using a β-emitting radiation source. Dosages of 25 or 50 Gy was delivered in the proximal renal artery. Animals were followed up to 1- or 2-months and were assessed by angiography, IVUS and histology. Norepinephrine levels were measured in the renal artery and in the renal tissue of the irradiated kidneys.

Results: Renal artery intravascular brachytherapy was performed without any procedural complications. No thrombus formed on the catheter and no acute vessel injury was noted by angiography. All animals survived to the predetermined follow-up. At 1- and 2-month follow up there was no vascular injury as documented by angiography. IVUS (Figure 1A) and histology. Histology studies showed focal hypocellular fascicles with cellular degeneration and some cells having vacuolated cytoplasm as well as mild perineural inflammation with and without fibrosis (Figure 1B). Norepinephrine levels will be available at presentation.

Conclusions: Vascular brachytherapy using the beta-cath™ system in the renal artery in the porcine model is feasible and safe with evidence of sparing damage to the nerve and safety vascular parameters even at high dose of radiation. The results of this study supports clinical evaluation of brachytherapy for the treatment of resistant hypertension.

Effect of renal sympathetic denervation on blood pressure and renal perfusion in a pig model for obstructive sleep apnea

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Objective: Obstructive sleep apnea (OSA) is associated with resistant hypertension and a progression of chronic kidney disease as (CKD). Renal sympathetic innervation may contribute to either condition. We investigated the effect of renal sympathetic denervation (RDN) on blood pressure (BP), renal perfusion and neurohumoral responses during and after repetitive obstructive apneas.

Methods: Blood pressure, femoral artery and renal artery flow were measured in 22 spontaneously breathing urethane-chloralose anesthetised pigs. In 12 pigs, the effect of RDN was investigated. Repetitive tracheal occlusions for 2 min with applied negative tracheal pressure -80 mbar were performed over 3 hours.

Results: Spontaneous breathing attempts during tracheal occlusion caused a strongly intraarterial oscillating pattern of renal perfusion. Renal flow oscillations were more than twofold stronger with a gain between BP and renal flow of 2.9%/mmHg compared with femoral flow that almost showed changes proportional to the BP-oscillations (1.3%/mmHg; p<0.0001). Marked postapneic hemodynamic changes occurred in both groups (p<0.0001). Together with renal hyperfusion falling from 190±24 to 105±20/min (p<0.0001) (Figure 1A) after application of tracheal occlusion. Renal sympathetic denervation inhibited postapneic BP rises and renal hyperperfusion and attenuated increased plasma renin activity and aldosterone concentration induced by repetitive tracheal occlusions. Additionally, increased urinary protein/creatinine-ratio was significantly reduced by RDN while intraarterial hemodynamic changes were not significantly modified by RDN.

Conclusion: Renal sympathetic denervation inhibits postapneic BP rises and renal hyperperfusion and attenuates neurohumoral responses and increased protein/creatinine-ratio induced by repetitive obstructive apneas. RDN may therefore provide protection in patients with obstructive sleep apnea, hypertension and renal dysfunction.

P4417 Percutaneous renal denervation (PRD) improves central hemodynamics and arterial stiffness - a pilot study

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Background: Percutaneous renal denervation (PRD) is a novel treatment strategy for patients with resistant arterial hypertension. Since central aortic pressures and arterial stiffness are better predictors for future cardiovascular events than peripheral pressures the present study aimed at measuring central pressures and aortic stiffness parameters in patients undergoing PRD.

Methods: 27 patients (18-82 years, mean age 63.0 years) with an office systolic blood pressure of more than 150 mmHg were included. PRD was performed with an MR radiofrequency ablation catheter system. Central aortic pressure and arterial stiffness was calculated with an oscilometric blood pressure meter.

Results: 21 patients [5±1.3 antihypertensive drugs] were randomized to PRD. 6 patients [4±2.3 antihypertensive drugs] served as controls. Central systolic blood pressure (SBP) declined significantly in the therapy group after three [156±13 vs. 145±13 mmHg; p=0.05] and six months [156±13 vs. 148±17 mmHg; p=0.05]. Likewise, central systolic augmentation index (AI) reduced from 161±17 vs. 147±18 mmHg; p<0.01; six month; 161±17 vs. 151±22 mmHg; p=0.05] and pulse wave velocity (PWV) improved significantly [three month; 10.9±1.8 vs. 9.4±1.2 m/s; p<0.01; six month; 10.9±1.8 vs. 9.7±1.8 m/s; p<0.01]. Values did not change significantly in the control group. Univariate analysis of variance (F-test) showed a mean arterial pressure (MAP) independent improvement of PWV in the treatment group.

Conclusion: PRD significantly reduced central aortic pressures and arterial stiffness. Effects on PWV are only partially dependent on blood pressure changes. Thus, PRD may improve cardiovascular outcome beyond blood pressure effects in patients suffering from resistant arterial hypertension.
**P4419**

**Pleiotropic role of angiotensin-converting-enzyme inhibitors on bone remodeling biomarkers in hypertensive subjects**

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**Objectives:** In addition to their well-established efficacy in lowering blood pressure, angiotensin-converting enzyme inhibitors (ACE-I) have been shown to have an impact on reducing the risk of death, myocardial infarction, stroke and renal complications in patients with coronary artery disease (CAD). Some evidence suggests that high blood pressure is associated with abnormalities of calcium metabolism, leading to an increase in calcium loss and elevation of bone remodeling biomarkers: osteoprotegerin (OPN) and osteopontin (OPG), both in CAD patients and asymptomatic subjects. In our study, we analyzed the role of antihypertensive treatment on OPG and OPN in subjects without a history of CAD.

**Methods:** We recruited n=350 subjects using a population-based approach by combing SEER and WHO. Subjects (n=267) were considered to have hypertension because they were taking antihypertensive agents or had a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Antihypertensive drugs were used in 240 patients as a monotherapy (n=113) or in combination with two (n=95) or three (n=32) drugs. Remaining hypertensive patients (n=47) had masked (or uncontrolled) hypertension. Biochemical parameters were assessed by routine laboratory techniques. Bone remodeling biomarkers were analyzed by commercially available immunoenzymatic assays.

**Results:** Among analyzed subjects n=287 had defined hypertension, and n=240 were treated with antihypertensive drugs. We observed that both OPG and OPN levels were higher in hypertensive subjects in compare to normotensive ones: 3.49±1.85 vs. 2.83±1.32 pmol/L (p<0.007) and 88.8±95.85 vs. 56.58±69.04 ng/mL (p=0.012). Additional analysis of antihypertensive treatment showed that there was no significant difference in OPG and OPN levels between treated and untreated hypertensive subjects. However, the patients stratification according to the applied antihypertensive drugs revealed that treatment with ACE-I alone significantly reduced OPN levels in compare to patients treated with other hypertensive drugs: 79.40±88.72 vs. 139.29±124.48 ng/mL (p=0.013), or those treated with ACE-I in combination with another one drug: 73.8±64.21 vs. 101.0±58.13 ng/mL (p=0.018). OPG levels were predicted in hypertensive subjects by diabetes and ACE-I treatment, but not by age or body mass index (p=0.17 (p<0.005) and p=0.14 (p=0.017), respectively.

**Conclusions:** Angiotensin blockade inhibits OPG expression in hypertensive asymptomatic subjects, but this mechanism does not involve OPG axis. Combination therapy does not impair the effect of ACE-I on OPN levels.

**P4420**

**The Effect of sRAGE in inhibiting Angiotensin II-mediated Atherosclerosis in Apolipoprotein E deficient mice**


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**Background:** The activation of the renin-angiotensin system (RAS) signaling is a contributing factor for the development of atherosclerotic plaques. Previous studies have shown that activation RAS is associated with increased expression of the Receptor for Angiogenic Fix (RAGE) at the site of vascular inflammation. The cross talk between RAGE and angiotensin II (AngII) stimulation may be important in the development of atherosclerosis. Soluble RAGE (sRAGE), a truncated soluble form of the receptor, acts as a decoy and prevents the inflammatory response mediated by RAGE activation. In this study, we sought to determine the effect of sRAGE in inhibiting AngII induced atherosclerosis in apolipoprotein E knockout mice.

**Methods and Results:** 9 week old ApoE KO mice were infused subcutaneously with AngII (1 μg/min/kg) and saline for 4 weeks using osmotic mini-pumps. The mice were divided into 4 groups. Mice infused with saline, mice infused with saline and sRAGE IP injection for 4 weeks. Mice infused with AngII group, mice infused with saline and sRAGE IP injection for 4 weeks. The concentration of sRAGE was varied from 0.5 μg, 1 μg, 2 μg/d for each group to determine the dose response. We show that atherosclerosis in the AngII infused ApoE KO mice was increased by over 2.5-fold compared to the ApoE KO mice. The treatment of 0.5 μg, 1 μg AngII group resulted in the decrease in atheroma plaque area by 35%. In addition, the treatment with 2 μg of sRAGE resulted in 70% decrease in atheroma plaque area in the AngII group.

**Conclusion:** The results prove that blockade of RAGE activation by sRAGE prevents AngII-induced atherosclerosis. The results from this study suggest that First, RAS administration is a strong predictor of cardiometabolic dysfunction. Second, as AngII activation is a major pathway in the development of atherosclerosis, the results from this study may provide the basis for future anti-atherosclerotic drug development mediated through RAGE activation.
once weekly) for 10 weeks. The animals were treated with vehicle or three doses of BAY 94-8862 (0.1, 1 and 10 mg/kg/day) and two doses of eplerenone (30 and 100 mg/kg/day) by once daily gavage (n=7-12/group). Systolic blood pressure was measured by the tail cuff method during the treatment period of the study. At the end of the experiment, hemodynamic function was measured in the left ventricle by a Millar-Tip (2F) catheter. Plasma samples were taken for subsequent pro-BNP, creatinine, and adiponectin measurements. Organ weights were determined and tissue samples were harvested for histological characterization and gene expression profiling.

**Results:** BAY 94-8862 significantly (p<0.05) decreased cardiac and renal hypertrophy, plasma pro-BNP, and expression of several renal profibrotic and remodeling biomarker genes (PAI-1, MCP-1, osteopontin, MMP-2) vs. placebo at 1 mg/kg without significant blood pressure reduction. There was a significant reduction (p<0.05) in blood pressure, proteinuria, an improvement in diastolic function (relaxation time, tau) and decreased cardiac hypertrophy at 10 mg/kg BAY 94-8862 vs. 100 mg/kg eplerenone. In contrast, eplerenone significantly reduced blood pressure proteinuria at 30 and 100 mg/kg, but reduced pro-BNP only at 100 mg/kg and did not show an influence on the relative heart weight. Histopathological analysis of hearts and kidneys confirmed the more pronounced end organ protective activity of BAY 94-8862 versus eplerenone.

**Conclusion:** The novel MR antagonist BAY 94-8862 showed a pronounced cardiorenal protection in the DOCA/salt model. Cardiac hypertrophy, release of plasma pro-BNP and expression of profibrotic and remodeling biomarker genes were not present at a dosage which had no effect on blood pressure (BP). This blood pren was much higher dosages of eplerenone were needed to demonstrate end organ protection in this preclinical model.

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**Predictors of adequate response in spironolactone-treated resistant hypertension**

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**Background:** Primary aldosteronism (PA) is common among patients with resistant hypertension (RHTN). The aldosterone-to-renin ratio (ARR), which screens for PA, is expensive, and service patients in our government-run tertiary care facility cannot afford to pay for the test. The aldosterone antagonist spironolactone has been shown to reduce blood pressure (BP) in patients with RHTN, even in those without biochemical evidence of aldosterone excess. Without the benefit of the ARR testing, we sought to determine predictors of response to spironolactone (defined as systolic BP reduction ≥ 10 mmHg) among patients with RHTN.

**Methods:** This was an analytical cross-sectional study of patients with RHTN referred to the Hypertension Clinic of our tertiary, government run, resource-limited institution from January 2008 to November 2011. Patient demographics, clinical data, medication use, and laboratory tests were evaluated.

**Results:** Data from 94 patients with RHTN were included in the analysis. Mean age was 54.6±13.1 years, and 60.1% were females. The mean body mass index was 25.3±5.3 with 30.8% of patients overweight or obese. The average systolic BP reduction on addition of spironolactone was 38.7 mmHg among responders. Multiple logistic regression analysis revealed that concomitant diuretic use (thiazides and/or loop) predicted response to spironolactone (p=0.0409). Age, gender, family history of hypertension, body mass index, BP, serum potassium level at baseline, and estimated glomerular filtration rate did not predict treatment response.

**Conclusion:** Among patients with RHTN who did not undergo ARR testing, concomitant diuretic use predicted treatment response to spironolactone.

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**Predictors of adequate response in spironolactone-treated resistant hypertension**

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**The effect life-style education programme together with the telmisartan treatment in patients with essential hypertension**

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**Objective:** The objective of this study was to evaluate the effect of a six-month treatment with telmisartan or telmisartan-hydrochlorothiazide (HCTZ) with or without patient’s education about the blood pressure (BP). This education was focused on the reduction of body weight and healthy life-style (Life-style Programme, LSP).

**Methods:** The population of this study included 1,841 patients with essential hypertension. The inclusion criteria for the study were: essential hypertension (BP ≥ 140/90 mmHg or BP ≥ 130/80 mmHg of diabetic patients, age ≥ 18 or hypertension treatment with at least 1 anti-hypertensive drug. A total of 774 patients were treated with telmisartan and 1,067 patients with telmisartan+HCTZ. The randomization ratio for LSP was 2:1. The LSP included a 30-minute structured interview and 5 lifestyle-modified materials focused on the healthy life-style, diet and weight reduction. Each patient made 3 visits — initial visit, second one in 4th-8th week (“up-titration visit”) and third one in 24th week, the final visit.

**Results:** The decrease of BP (both systolic and diastolic) during telmisartan treatment was statistically highly significant (p<0.001). The decrease of BP below 140/90 mmHg was attained in 78.55% patients treated with telmisartan and in 66.64% patients treated with telmisartan+HCTZ. Side effects (headache 2x, vertigo 1x, nausea 1x, vomiting 1x, periferal oedema 1x) were noticed during this treatment only in 6 patients (0.32%). The final BP values (both systolic and diastolic) of patients enrolled in the LSP were not significant different from the BP values in patients without the LSP. The LSP had more “nonresistant” patients (70.7%) than the patients not-enrolled in the LSP (60.7%). The difference was not significant. The mean decrease of body weight in the LSP patients was 2.64±1.11 kg, which was significantly more than in the non-LSP patients (0.65±0.36 kg, p=0.05).

**Conclusion:** Telmisartan alone or in combination with HCTZ is an effective and well tolerated anti-hypertensive drug. The educational programme led to the decrease of body weight, but did not significantly change the BP values.

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**Blood pressure reduction with aliskiren in outpatients with hypertension in real life during 2-year follow-up. Results of the prospective 3A Registry**

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**Background and aims:** Aliskiren and Retinol-Binding Protein 4 is secreted by adipose tissue and may play a role in cardiovascular disease and insulin resistance. Telmisartan is an angiotensin receptor blocker originally developed for the treatment of hypertension. It can also partially activate peroxisome proliferator-activated receptor (PPAR-γ), which may improve insulin sensitivity. This effect may prove useful in hypertensive patients with insulin resistance or diabetes mellitus. We examined aliskiren and Retinol-Binding Protein 4 levels in patients with type 2 diabetes who treatment with the angiotensin-receptor blocker telmisartan.

**Methods:** A total of 188 patients with hypertension and diabetes mellitus were assessed at baseline and following 24 weeks treatment with the angiotensin receptor blocker telmisartan (final dose, 80 mg). Aliskiren and Retinol-Binding Protein 4 levels were measured in plasma by radioimmunoassay.

**Results:** Aliskiren levels were inversely correlated with systolic (SBP; r = -0.640, P = 0.05) and diastolic (DBP; r = -0.350, P = 0.05) blood pressure at baseline and following treatment with telmisartan. Retinol-Binding Protein 4 levels were correlated with systolic (SBP; r = -0.117, P = 0.05) and diastolic (DBP; r = 0.150, P = 0.05) blood pressure at baseline and following treatment with telmisartan. There was a significant increase in adiponectin levels (0.98 (95% confidence interval (CI), 0.57 to 1.80) microgram/mL, P = 0.01) and decrease in Retinol-Binding Protein 4 levels (5.88 (95% confidence interval (CI), 3.26 to 10.10) microgram/mL, P < 0.01).

**Conclusion:** Aliskiren and Retinol-Binding Protein 4 levels is correlated with blood pressure in patients with type 2 diabetes. Increased adiponectin and decreased Retinol-Binding Protein 4 are associated with treatment by telmisartan. Given the growing diabetes epidemic, telmisartan that can simultaneously block the angiotensin II receptor and partially activate PPAR-γ have the potential to treat both hemodynamic and biochemical features of insulin resistance.
Phytochemical drugs are the new progress in the treatment of hypertension. We compared the hypotensive effect of valsartan (VAL) and polyphenol complex (PP) and, also, we assessed the efficacy of combination consisting of VAL and PP.

Methods: Male spontaneously hypertensive rats (SHR) (n=34, weight 240-280 g) were selected for study. The experimental animals were given VAL at the doses of 5 mg/kg, 10 mg/kg and 20 mg/kg and PP at the doses of 10 mg/kg, 30 mg/kg and 100 mg/kg. The combinations of VAL plus PP at the doses of VAL 5 mg/kg plus PP 10 mg/kg, VAL 10 mg/kg plus PP 30 mg/kg, VAL 20 mg/kg plus PP 30 mg/kg were tested in animals. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were recorded with the non-invasive blood pressure monitor NIBP-8 (Columbus Instruments, USA).

Results: Our results showed the most effective dose of PP is 30 mg/kg. In 3 hours, the SBP and DBP were decreased by 18-22 mm Hg (p=0.007) and 15-19 mm Hg (p=0.002-0.003) respectively. The hypotensive effect was still present in 24 hours. The largest hypotensive effect of VAL was recorded at the dose of 20 mg/kg. The reduction was about 20 mm Hg (p=0.003) in the SBP and 15 mm Hg (p=0.009) in the DBP. The SHR rats which were given the combination of VAL 10 plus PP 30 mg/kg had the least blood pressure parameters (Fig. 1). There were not any statistically significant differences in the HR prior and after administration in all experimental animals.

Conclusions: The current study demonstrated the same efficacy of VAL 20 mg/kg and PP 30 mg/kg on blood pressure parameters. In combination the dose of VAL can be lowered in half. It will allow reaching the target blood pressure with minimal side effects caused by VAL. We propose another mechanism of action of polyphenol complex irrelevant with the AT1-receptors inhibition.

Haemodynamic effects of dapagliflozin versus hydrochlorothiazide in subjects with type 2 diabetes mellitus

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Purpose: Sodium-glucose co-transporter 2 (SGLT2) reabsorbs glucose and sodium in the renal proximal tubule. Dapagliflozin (DAPA), an inhibitor of this transporter, targets hyperglycaemia in type 2 diabetes mellitus (T2DM) by increasing renal glucose excretion. The haemodynamic profile associated with administration of DAPA remains incompletely characterised. We therefore compared the effects of DAPA and hydrochlorothiazide (HCTZ) on 24-h blood pressure (BP) and glomerular filtration rate (GFR).

Methods: In this randomised, placebo-controlled, double-blind trial, 75 subjects with T2DM aged 18–70 years (y), HbA1c 6.6%–9.5%, and seated systolic BP (SBP) 130–165 mm Hg/diastolic BP 80–105 mm Hg, on a stable dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and no other antihypertensive medications were randomly assigned to placebo (PBO), DAPA 10 mg/day, or HCTZ 25 mg/day. Change from baseline in 24-h ambulatory BP and GFR, measured by iohexol clearance, was compared with baseline after 12 weeks of treatment.

Results: Subjects’ mean age was 56 years (y), T2DM duration 6.3 y, and HbA1c 7.5%. Treatment with PBO, DAPA, or HCTZ resulted in changes from baseline in 24-h ambulatory mean SBP of -0.9 mm Hg (95% CI: -4.2, 2.4), -3.3 mm Hg (95% CI: -6.8, 0.2), and -6.6 mm Hg (95% CI: -9.9, 3.2) mm Hg, respectively, at week 12. The effects of DAPA and HCTZ on mean SBP were similar during the daytime. Night time mean SBP did not differ between DAPA and PBO, and was lower for HCTZ than DAPA. Mean changes from baseline in GFR at week 12 were -2.9% (95% CI: -6.8, 1.2), -10.8% (95% CI: -14.8, -6.7), and -3.4% (95% CI: -7.3, 0.6) ml/min/1.73m² for subjects receiving PBO, DAPA, and HCTZ, respectively.

Conclusions: SGLT2 inhibition with DAPA is associated with a reduction in 24-h mean SBP, which was somewhat less than that observed with HCTZ. While reductions in daytime mean SBP were similar with DAPA and HCTZ, the change in night time mean systolic BP with DAPA was not different from PBO, and was less than with HCTZ. Small mean decreases in GFR were noted with all treatments, which were somewhat greater with DAPA than PBO and HCTZ.
Five-year target systolic blood pressure less than 120 mmHg for more than 65 aged hypertensive patients with chronic renal disease

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Background: Many studies demonstrate that systolic blood pressure (SBP) ≤140 mmHg does not provide renal protection in renal disease with hypertension, but SBP ≤120 mmHg may be able to slow progress of renal disease. However, SBP ≤150 mmHg in elderly hypertension patients was recommended in Chinese hypertension guideline in 2005. The safety of SBP ≤120 mmHg in elderly hypertension patients with chronic renal disease is hardly reported.

Methods: In a prospective, controlled-open label study, the authors have evaluated the safety and efficacy of five-year treatment on progress of renal disease and risk of development of cardiovascular disease in 122 ≥65 aged hypertensive patients with chronic renal disease III to IV stage and macroproteinuria. Before randomization, all patients have already been treated for one-year with angiotensin converting enzyme inhibitors (ACEI) or angiotensin AT1 receptor blockade (ARBs) and other antihypertensive drugs, but their SBP are above 140 mmHg, less than 150 mmHg. Blood pressure, serum creatinine (Cr) and potas-

sium were monitored every 14 days in the period of follow-up by physician and healthcare nurse and more frequent patient-physician encounters will be improved the patients' control at least followup every day at home and adjusted their own medication according to pre-agreed rules.

Results: By the end of five year, medication possession ratio between two groups is similar (94% vs. 94%). Mean blood pressure group was 116.66 ± 6.33 mmHg and in control was 146.78 ± 13.99 mmHg, Cr clearance increased from 51.2 ± 6.4 to 63.0 ± 3.0 ml/min (P < 0.001) in the group of strict con-
trol of SBP ≤120 mmHg, while the clearance decreased significantly from 52.1 ± 1.9 to 40.2 ± 2.4 ml/min (P < 0.01) in the controls. During this time, urine protein excre-
tion decreased from 1.4 ± 0.5 to 0.2 ± 0.3 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 ± 0.6 g, P > 0.05) in the controls. Nine patients had ACS, 11 patients stroke, 18 patients had pneumonia, 8 patients renal dialysis and six patient died (4 in SCD and 2 in heart failure) in controls but one patient had ACS, four patient had strokes, five pneumonia, 1 patient renal dialysis and two patients died in non-cardiac causes in the treatment group. Incidence of hyperkalemia was similar in both two groups.

Conclusions: SBP ≤120 mmHg is safe and was more apparently in decreasing proteinuria, slowing the progress of renal disease and reducing the risk of develop-

ment of cardiovascular events and proteinuria in elderly hypertensive patients with chronic renal disease.

Cholesterol control and incident antihypertensive treatment in hypercholesterolemic subjects treated or not with statins: a pharmacoepidemiological report

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Purpose: The aim of our study was to evaluate the association between low density lipoprotein cholesterol (LDL-C) level, statin treatment and the incidence of new antihypertensive treatment in a large population sample.

Methods: A population-based cohort of 23,849 subjects from two Italian Local Health Units (LHU) aged 18 years or older with at least one LDL-C measure-
manship were included in this study. LDL-C control at baseline was followed by the LDL-C date until death or December 31, 2009. The cohort was subdivided into two groups (LDL-C ≥ target group, LDL-C < target) on the basis of their cardiovascular disease risk. The univariate data analysis was based on Pearson Chi-square to assess statistical significance of differences between frequencies and rates and analysis of variance for the comparison of means. To calculate incidence rates we divided the number of new cases of antihypertensive treatment by the total number of years that occurred before the antihypertensive treatments prescription date for the new AHT treatment cases, or the end of the follow-up period for no new antihypertensive treatment cases.

Results: A total of 7,177 patients died during the presen
ty study, 2,131 patients (10.4%) (n=1,382) of patients with LDL-C ≥ target and 13.6% (n=1,442) of patients with LDL-C < target started antihypertensive treatment. Compared with the LDL-C < target group, the LDL-C ≥ target group showed a higher overall incidence rate (7.59 vs 10.78 per 100 person-years) (P < 0.001). In the multivariable Cox regression analysis, after adjus-
tment for the potential confounding variables, compared with LDL-C < target group, the hazard ratio (HR) of AHT treatment was reduced among those with LDL-C < target (HR=0.91; 95% CI: 0.84-0.98). Significant HRs were also ob-
served for age—increasing age increases the risk of new cases of AHT treatment than the age group below 45 years –, diabetes (HR=1.32; 95% CI: 1.16-1.49) and previous CV disease (HR=0.95; 95% CI: 0.95-0.97). Gender, CV diseases and statin treatment per se were not found significant predictors of the incidence of antihypertensive treatment.

Conclusion: A better control of serum cholesterol levels seems to be associated to a significantly lower incidence of new antihypertensive treatment in a large cohort of general population.

Long-term, open-label treatment with triple olmesartan (O)/amlodipine (A)/hydrochlorothiazide (H) combination therapy in moderate-to-severe hypertensive patients (pts)

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Objectives: Analyse the effect of long-term, open-label treatment with O/A/H for 36 weeks in patients with moderate-to-severe hypertension.

Design and Method: At Week 0 (baseline), pts entered a 2-week, double-blind run in during which all received dual therapy for safety and then were randomised to 8 weeks of double-blind treatment (N=2690) with different doses of O/A or O/A/H in a factorial setting. After Week 10, all pts received 8 weeks of single-blind O/A/H 20/5/12.5 mg. Pts with controlled BP (<140/90 mmHg) <130/80 mmHg for diabetics, O/KD or CVD) then entered open-label O/A/H 20/5/12.5 mg treatment for 36 weeks. Uncontrolled pts entered two consecutive 4-week periods of re-

randomised, double-blind treatment that assessed the effects of up-titration to a maximum dose of O/A/H 40/5/12.5 or 40/5/25 mg. All pts then entered a 28- week, open-label titration phase in which therapy could be-up or down-titrated to O/A/H 20/5/12.5, 40/5/25, 40/10/25 or 40/10/25 mg (investigator's discretion) in order to get pts to and maintain their BP goal. This phase of the trial aimed to study SBP and DBP changes and sealed BP goal achievement at Week 54, as well as safety and tolerability data.

Results: By Week 54, the SBP/DBP changes were substantial and similar in three treatment groups, compared with baseline, the mean BP SBP/DBP in the O/A/H 40/5/25 mg group was reduced by 22/9.9 mmHg (Table). The mean SBP/DBP levels were <140/85 mmHg in all five treatment groups. The overall mean BP goal achievement rate for all pts at Week 54 was 78.1%. Each dose of triple therapy was well tolerated and overall hypotension levels were <1%.

Conclusions: Long-term, open-label treatment with the triple O/A/H combination, which included dose titration as required, was well tolerated and provided consistent and remarkable antihypertensive efficacy in a large group of moderate-to-

severe hypertension pts. Triple O/A/H therapy got the majority of pts to BP goal and was effective in treatment groups composed of a varying proportion of higher-risk pts.

Renoprotective effect of cilnidipine via the antioxidant activity in hypertensive patients

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Background: Cilnidipine, an L/N type calcium channel blocker (CCB), has been reported to be more beneficial on the progression of proteinuria in hypertensive pa-

tients compared with amlodipine, an L-type CCB. One of the mechanisms for this beneficial effect may be the N-type calcium channel blockade which inhibits re-
nal sympathetic nerve activity leading to a reduction of glomerular hypertension through a vasodilatation of efferent arteries. However, the precise mechanism for the renoprotective effect of cilnidipine remains unknown. Because cilnidipine showed a significantly higher antioxidant activity than amlodipine in cultured hu-

man mesangial cells, we hypothesized that cilnidipine may have a renoprotective effect by suppressing oxidative stress in the present study.

Methods and Results: Thirty-five patients with hypertension, already receiving rennin-angiotensin system (RAS) inhibitor, were randomly assigned to cilnidip-

ine or amlodipine: cilnidipine at a dose of 10mg/day that was increased up to a dose of 20mg/day (cilnidipine group; n=18) and amlodipine at a dose of 5mg/day that was increased up to a dose of 10mg/day (amlodipine group; n=17). After 6-months of treatment, systolic and diastolic blood pressures were significantly reduced in both groups which did not differ between them. The urinary albumin to creatinine ratio significantly decreased in the cilnidipine group after the treatment for 6 months (P < 0.05) whereas it did not change in the amlodipine group. The urinary 8-hydroxy-2’-deoxyguanosine (8-OHdG) level (8-OHdG to creatinine ratio) and liver-type fatty acid binding protein (L-FABP) level (L-FABP to creatinine ra-
tio) decreased significantly after the treatment of cilnidipine for 6 months whereas there was no change after the treatment of amlodipine. In addition, the rates of ur-

inary albumin, 8-OHdG, and L-FABP reduction were not correlated with the rate of change in systolic blood pressure.

Conclusions: The addition of cilnidipine rather than amlodipine ameliorated un-
Does obstructive sleep apnea affect the right heart in patients with resistant hypertension?

Echocardiographic study

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Purpose: There are limited data concerning the impact of obstructive sleep apnea (OSA) on the parameters of tricuspid inlet in patients with resistant systemic arterial hypertension (RSAH). The aim of the study was to determine the relationship between several biomarkers and echocardiographic parameters of right ventricle in patients with RSAH.

Methods: From 204 patients diagnosed with RSAH hypertension in RESIST-POL study, 155 patients (93M, 62F, mean age 47.5±10.5, range 19-69yrs) with out secondary hypertension were included into analysis. All patients underwent polysomnography and the apnea/hypopnea index (AHI) was calculated. Right ventricular end-diastolic area (RVEDA), right ventricular end-systolic area (RVESA), main pulmonary artery dimension (MPAD), FR ejection acceleration time (AcT), systolic velocity from Doppler tissue image (s', erv), early diastolic velocity (e' r) and tricuspid annular plane systolic excursion (TAPSE) were evaluated.

Results: Patients were divided into 4 groups based on AHI without OSA (AHI<5, n=43), with mild OSA (AHI 15-25, n=27), severe OSA (AHI>30, n=40); Patients with severe OSA as compared with patients without OSA had higher MPAD (62.0±12.7 vs. 23.1±3.7mm², p<0.001), RVESA (8.7±2.9 vs. 8.6±2.0mm², p=0.01), RVAD (54.4±5.3 vs. 50.3±5.3mm², p=0.03) and shorter AcT (114.2±15.7 vs. 133.4±22.1ms, p<0.001). There were no differences in RV systolic performance between patients with OSA and without RSAH. There were no differences between patients with mild or moderate OSA and patients with RSAH. The study consisted of 311 patients with angiographically documented CAD and 160 healthy controls. The 3872 A-G polymorphism was determined by PCR and the restriction enzymes HPYCHIV and SFANI respectively. C-reactive protein (CRP) levels were assessed by specific immunonephelometric method, while serum levels of interleukin-6 (IL-6) were assessed by ELISA assay.

Results: The genotype distribution for CRP polymorphism was: GG 42.1%, AG 39.8%, AA 18.2% for CAD group and GG: 48.1%, AG: 39.3%, AA: 12.6% for controls. The genotype distribution for IL-6 polymorphism was: GG: 47.4%, GC: 30.5%, CC: 22.5% for CAD group and GG: 47.8%, GC: 43.8% and CC: 8.4% for controls. Importantly, there was a significant difference in IL-6 levels (pg/ml) between the G carriers and CC homozygotes both in the CAD group (3.81±2.81 vs 6.07±3.75, p=0.001) and the control group (3.22±2.24 vs 1.82±1.57, p=0.05). Polymorphism on IL-6 gene and the AA homozygotes of 3872A-G polymorphism on CRP gene were significantly associated with greater incidence of coronary artery disease compared to the other genotypes (RR: 0.945, p=0.0101).

Conclusion: The 3872 A-G polymorphism on C-reactive protein gene is closely related to interleukin-6 levels. These findings suggest that the synergistic impact of these two different polymorphisms is capable of a significant promotion of coronary artery disease via inflammatory mechanisms.

Utility of high-sensitivity cardiac troponin T in patients undergoing elective cardiac angiography


Introduction: High-sensitivity cardiac troponin (hsTn) assays have improved diagnosis of myocardial infarction. It is unknown whether hsTn can improve the diagnosis of obstructive coronary heart disease in patients without acute coronary syndrome.

Methods: This study enrolled 1254 consecutive patients undergoing elective cardiac angiography following cardiac stress testing. Obstructive coronary heart disease was defined as a stenosis ≥75% in at least one of the main native vessels or bypass grafts. Blood samples for hsTnT testing were drawn on admission before coronary angiography and before cardiac stress test. A commercially available hsTnT assay with a 99th percentile cut-off point of 0.014 μg/L and a limit of detection of 0.003 μg/L was used.

Results: Plasma levels of hsTnT significantly correlated with the extent of coronary heart disease (r=0.14, p<0.001) but also with left ventricular function (r=0.17, p<0.001), age (r=0.09, p<0.001), and renal function (r=0.18, p<0.001). Out of 1254 enrolled subjects, 64% had a positive stress test and 61% were diagnosed with obstructive coronary heart disease during coronary angiography. The receiver operating curve (ROC) derived optimal cut-off for the diagnosis of an obstructive coronary heart disease was 0.004 μg/L. A positive stress test result was associated with a sensitivity of 69% but only a specificity of 45% for obstructive coronary heart disease. Combining stress test results with hsTnT ≥0.004 μg/L significantly improved the performance for diagnosis of obstructive coronary heart disease (c-statistics from 0.565 to 0.671, p<0.001). The sensitivity of this approach was 67% and the specificity 61%.

Conclusion: Addition of hsTnT improves significantly the performance of cardiac stress testing for diagnosing obstructive coronary heart disease.
men diameter. In OCT analysis, mild cTnI elevation before PCI was associated with the presence of TFCA (8/28: 29% vs 17/152: 11%; P=0.032), smallest thinnest cap thickness (median: 65 μm (IQR: 69-120 μm) vs 107 μm (IQR: 73-140 μm), P = 0.001) and lipid quadrants (median: 3 (IQR: 2-3) vs 2 (IQR: 0-3), P < 0.001). Post-PCI cTnI levels were greater in patients with mild baseline cTnI elevation than in those without (median: 0.52 ng/mL (IQR: 0.24 - 4.19 ng/mL) vs 0.33 ng/mL (IQR: 0.12 - 1.06 ng/mL), P=0.04).

Conclusions: Mild cTnI elevation was associated with OCT-derived unstable plaque morphology, and may help identify SAP patients at high risk for cardiovascular injury after elective stenting.

P4439 Diagnostic performance of cardiac hybrid imaging of single photon emission computed tomography and coronary computed tomography

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Background: Although cardiac hybrid imaging of coronary computed tomography (CCT) and myocardial perfusion imaging with single photon emission computed tomography (MPI) could show the ischemic myocardial area and the culprit vessel, its clinical usefulness has not been clarified. Therefore, we evaluated the clinical utility of hybrid imaging in the diagnosis of coronary artery diseases.

Method: Consecutive patients (n=96) with suspected coronary artery disease who had undergone coronary artery bypass grafting (87 cases) on CCT and equivocal myocardial ischemia on MPI were enrolled. We examined if the hybrid imaging would change the diagnosis on the culprit vessel of myocardial ischemia acquired by side-by-side analysis of CCT and MPI images (Table 1). Hybrid imaging was useful to diagnose correctly the ischemic area at the border of old myocardial infarction or at postarterial wall that had been overlooked by side-by-side analysis.

Result: In 34 (36%) of 96 patients, hybrid imaging changed the diagnosis acquired by side-by-side analysis of CCT and MPI images (Table 1). Hybrid imaging was useful to diagnose correctly the ischemic area at the border of old myocardial infarction or at postarterial wall that had been overlooked by side-by-side analysis.

Conclusion: The hybrid imaging of CCT and MPI was more useful than the side-by-side analysis for the correct diagnosis of the myocardial ischemia and its culprit vessel.

P4440 Influence of coronary plaque compositions on fractional flow reserve and epicardial stenosis resistance

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Hemodynamic effect of a coronary stenosis can be accurately determined by the assessment of fractional flow reserve (FFR) or epicardial stenosis resistance (SR). On the other hand, factors, which may potentially affect hemodynamic significance of a given coronary stenosis, such as histopathological composition of coronary plaque, are not known. The purpose of this study was to investigate the relationship between coronary plaque characteristics and hemodynamic endpoints in patients with coronary artery disease (CAD).

Methods: A Doppler and pressure sensor equipped guide wire was used for the assessment of FFR and SR in 38 coronary lesions in 38 patients. Under maximal hyperemia, SR was calculated as stenosis pressure gradient divided by average peak velocity distal to the stenosis and FFR was calculated as distal coronary pressure divided by distal arterial pressure.

Results: Means of FFR and SR were 0.6±0.14 and 1.66±0.9 respectively. In 12 lesions, FFR was above the 0.75. In lesions with FFR below 0.75, both FFR and SR were independently correlated with dense calcium volume (DCV) (r= -0.631, p= 0.015 and r= 0.69, p= 0.008 respectively) and necrotic core volume (NCV) (r= -0.661, p= 0.01 and r= 0.673, p= 0.008) respectively even after controlling for plaque burden, lesion length, minimum lumen area (MLA) and MLA/external elastic membrane area. Nevertheless, in patients with intermediate stenosis (FFR >0.75), FFR and SR were not correlated with plaque characteristics.

Conclusion: For a given stenosis geometry, FFR values decreased and SR values increased with increases in DCV and NCV in patients with hemodynamically significant stenosis. This finding implies that plaque characteristics can affect hemodynamic endpoints in patients with hemodynamically significant coronary lesions.

P4441 Plasma cyclophilin A level is a novel biomarker of coronary artery disease

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Purpose: We tested our hypothesis that plasma cyclophilin A (CyPA) levels could be a new biomarker of CAD.

Background: Oxidative stress, generated by excessive reactive oxygen species (ROS), promotes coronary artery diseases (CAD). We have recently demonstrated that ROS induces secretion of CyPA from vascular smooth muscle cells, which plays a crucial role in the pathogenesis of atherosclerosis, aortic aneurysms, and intimal thickening in mice.

Methods: In consecutive 320 patients undergoing coronary angiography, we examined the relationship between plasma CyPA levels and the severity of CAD. We measured plasma CyPA by an immunoassay based on the sandwich technique.

Results: Plasma CyPA levels were significantly higher in patients with significant coronary stenosis (>50%, n=189) compared to those without it (n=131) (P<0.001). A positive correlation was noted between plasma CyPA levels and significant coronary stenosis both by angiography and even after adjustment for age, sex, hypertension, diabetes, dyslipidemia and smoking. The average number of stenotic coronary arteries and the need for coronary intervention were significantly increased in patients with CyPA levels of both <0.001. Indeed, plasma CyPA level was a strong predictor of CAD (adjusted odds ratio for CAD, 6.20; 95% confidence interval [CI], 3.14-12.27; P<0.001). Moreover, plasma CyPA levels were significantly correlated with the number of stenotic coronary arteries, regard-
Increased rho-kinase activity in patients with vasospastic angina after the great east Japan earthquake disaster

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Purpose: We have recently demonstrated that Rho-kinase activity in circulating neutrophils is a useful biomarker for the disease activity assessment in patients with vasospastic angina (VSA). Coronary vasospastic activity is known to be enhanced by mental/physical stress. Since we experienced the Great East Japan Earthquake in our Tohoku area on March 11, 2011, we examined whether the Rho-kinase activity was increased in VSA patients after the disaster.

Methods: In 10 patients with proven VSA (one of cases with patients who were hit by the earthquake/tsunami, we examined the Rho-kinase activity in circulating neutrophils before and after the disaster as well as the influence of mental stress by using the questionnaire for post-traumatic stress disorder (PTSD).

Results: In almost all patients, Rho-kinase activity was increased after the disaster than before (phosphorylated myosin-binding subunit (MBS)/total MBS ratio 1.72±0.23 vs. 1.01±0.36, P<0.001), despite the continued treatment with calcium channel blockers (Figure). Among the 10 patients, 3 complained that the frequency of angina attack and the use of sublingual nitroglycerin were increased more than before (phosphorylated MBS/protein ratio 0.23±0.01 vs. 1.01±0.01, P<0.001) and changes in the Rho-kinase activity from the baseline (268±262% vs. 48±31%, P<0.05) were significantly higher than the remaining 7 patients without worsening symptoms. The changes in the Rho-kinase activity from the baseline were significantly correlated with the PTSD score (r=0.68, P<0.05).

Conclusions: These results indicate that Rho-kinase activity is enhanced in VSA patients by the disaster-related mental stress.

"Heart team" decision making in the management of patients with Coronary Artery Disease; structure, outcomes and reproducibility

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Purpose: Contemporary guidelines recommend that patients with stable angina and acute coronary syndromes (ACS) with multi-vessel disease are discussed by a multidisciplinary “Heart Team” (HT) to facilitate optimal evidence-based management. However, there is a paucity of data describing the workings of a HT, the acting of its recommendations and the reproducibility of its decisions.

Methods: We have utilised a HT approach since 2005. We analysed the data for 2010 and describe the HT process. A random sample of cases were scrutinised to identify whether the HT decision had been implemented. Also, cases were represented after 1 year to determine consistency and reproducibility of decision making. The HT panel for the review process excluded members involved in the original discussion.

Results: During 2010, 108 meetings were held, attended by a median of 3 interventional cardiologists, 1 non-interventional cardiologist and 2 cardiac surgeons. 1454 cases were discussed (mean 13.5 cases per meeting). 854 (58.7%) were recommended coronary artery bypass grafting (CABG), 778 (51.7%) were investigated using the questionnaire for post-traumatic stress disorder (PTSD), 442 were recommended angioplasty and stenting (PTCA), 2 (0.1%) were recommended percutaneous coronary intervention (PCI) and 2 (0.1%) were recommended medical therapy (OMT) in 264 (19.7%). In the remaining 344 cases (25.7%) further investigation was advised before a HT decision was made; most frequently a pressure wire study, in 151 cases (43.9%). Of 117 cases analysed, the HT recommendation had been fully actioned in 101 (86.3%). In the remaining 16 cases, deviation from the initial plan was due to the patient declining revascularisation (CABG, PCI), development of new comorbidity (2) or revascularisation of different vessels (6). The reason for deviation was unclear in 4 cases.

Of 50 cases re-presented, the original HT recommendation was the same in 38 (76%) cases. Different decisions in the remaining 12 (24%) included 7 cases (14%) in which further investigation had initially been suggested, and revascularisation was recommended on re-presentation.

Conclusions: A well-strucutred HT allows a large number of cases to be evaluated, while interdisciplinary discussion facilitates consensus with evidence-based and individualised advice. There is a prominent role for pressure wire assessment in the further evaluation of equivocal stenoses. The HT approach appears robust and reproducible in the majority of cases. Variation in decision making reflects the equipoise between suitability of CABG, PCI and OMT in many cases.
Nearly doubled 5-year-mortality in patients with stable coronary artery disease and prior stroke in clinical practice: results of the Star-Registry

A.K. Gitt1, F. Toivola2, C. Juenger3, A. Papp2, R. Zahn1, U. Zeymer1, on behalf of the Star-Registry Group.1Herzzentrum Heidelberg, Ludwigshafen, Germany; 2Herzenzinfarktklinikum Hamburg, Hamburg, Germany; 3Herzzentrum Ludwigshafen, Ludwigshafen, Germany. Background: Patients with coronary artery disease (CAD) often have generalized atherosclerosis with additional peripheral or cerebrovascular disease. Little is known about the impact of prior stroke 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 (50 centres). We examined the impact of prior stroke on 5-year-mortality of stable CAD in clinical practice in Germany. Results: Of 2,002 patients with stable CAD, 93 patients (4.7%) had prior stroke. These patients were significantly older, more often had concomitant diseases like hypertension, diabetes, dyslipidemia, prior myocardial infarction, peripheral artery disease and diabetes. No differences were observed in interventional treatment at the time of enrolment as well as during the 5 year follow-up, with similar rates of PCI and CABG as compared to patients without prior stroke. Patients with prior stroke had a significantly higher 5-year-mortality (36.4% vs 18.1%, univariate analysis) as well as a higher incident stroke rate. After correction for differences in baseline characteristics and treatment using multivariate analysis, prior stroke was associated with a 47% increased 5-year-mortality of stable CAD in clinical practice (OR 1.46, 95% CI 1.03–2.15). Conclusion: The use of up-to-date equipments and algorithms is associated with a significant reduction in ERD for both non-invasive and invasive strategies between the two periods. Yet, the combination of CA and FFR is still associated with a significantly lower ERD in both periods. This should be accounted for when planning diagnostic work-up in patients with suspected CAD.

Serum vitamin D levels are independently associated with severity of coronary artery disease

F. Akın1, N. Kose1, M. Sari2, M. Duran3, O. Uysal4, D. Goldsmith5, M. Karabay5, M. Uysal5, H. U. Haase6. 1Mugla University Department of Cardiology, mugla, Turkey; 2Haseki Training and Research Hospital, Istanbul, Turkey; 3Kayseri Education and Research Hospital, Kayseri, Turkey; 4Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom. Background and objectives: We hypothesized that serum vitamin D levels would be inversely associated with inflammation and with severity of coronary atherosclerosis. We therefore investigated the link between serum vitamin D levels and (i) extent of CAD assessed by the Gensini score and (ii) inflammatory parameters, including C-reactive protein (CRP) and fibrinogen. Material and Methods: We measured 25-hydroxyvitamin D (25(OH)D) and inflammatory markers in 239 patients who underwent coronary angiography. We analyzed the relation between serum levels of 25(OH)D and inflammatory markers and angiographic severity of coronary artery diseases (CAD). Gensini lesion severity score was used for the detection of severity of coronary atherosclerosis. Results: Vitamin D insufficiency were very common among the our study population and 85% had levels <30 ng/ml. Gensini score was negatively correlated with serum vitamin D level (r = 0.209, p = 0.001), and positively correlated with age (r = 0.209, p = 0.001), blood pressure (r = 0.379, p < 0.001), diabetes (r = 0.335, p < 0.001), hyperlipidemia (r = 0.300, p < 0.001) and serum CRP level (r = 0.214, p < 0.001). After adjustments for traditional and nontraditional cardiovascular risk factors, vitamin D (B = 0.345, p = 0.001) remained significant predictors of the severity of the coronary artery disease. Multiple regression models of Gensini

Prognostic impact of uric acid in patients with stable coronary artery disease

G. Ndrepepa, S. Braun, M. Hadamitzky, M. Fusan, H.U. Haase, K.A. Birkmeier, A. Schomig, A. Kastrati. German Heart Center, Hospital rechts der Isar at the Technical University of Munich, Munich, Germany. Background: The association between uric acid and cardiovascular disease is poorly studied. We undertook this study to assess whether uric acid level predicts clinical outcome in patients with stable coronary artery disease (CAD) treated with percutaneous coronary intervention (PCI). Material and Methods: This study included 814 patients with stable CAD who underwent PCI. Uric acid was measured in all patients before angiography. The primary end point was 1-year mortality. Results: Quantiles of quartiles of uric acid were: 1.4 mg/dl (1st quartile; n=2033 patients), 5.4 mg/dl (2nd quartile; n=1981 patients), 6.4 mg/dl (3rd quartile; n=2093 patients) and 21.9 mg/dl (4th quartile; n=2043 patients). There were 196 deaths during the 1-year follow-up. The number of deaths (Kaplan-Meier estimates) according to uric acid quartiles were: 35 deaths (1.8%) in the 1st quartile, 30 deaths (1.6%) in the 2nd quartile, 45 deaths (2.2%) in the 3rd quartile and 86 deaths (4.3%) in the 4th quartile (unadjusted hazard ratio (HR)=1.60, 95% confidence interval [CI] 1.38-1.86, P < 0.001 for each standard deviation (SD) increase in the logarithmic scale). Calculated for 1 mg/dl increase in the uric acid level, the unadjusted HR was 1.31 (1.23-2.40); P < 0.001, indicating a 31% increase in the unadjusted risk of 1-year mortality with each 1 mg/dl increase in the uric acid level. After adjustment for traditional cardiovascular risk factors, renal function and inflammatory status, the association between uric acid and 1-year mortality remained significant (adjusted HR=1.26, 95% CI 1.07-1.48; P=0.005 for each standard deviation SD increase in the logarithmic scale). Calculated for 1 mg/dl increase in the uric acid level, the adjusted HR was 1.15 [1.06-1.25]; P=0.01. Demonstrating a 15% increase in the adjusted risk for 1-year mortality for every 1 mg/dl increase in the uric acid level. Ur-acid improved predictivity of the multivariable model regarding mortality (P=0.040). Conclusion: In patients with stable CAD treated with PCI, elevated uric acid level predicts the increased risk of death independently from cardiovascular risk factors, status of renal function or inflammatory burden. Thus uric acid, a readily available test, has the potential to risk stratify the large group of patients with stable CAD in terms of mortality prediction.
Lack of concordance between image stress tests and invasive functional evaluation with pressure wire in patients with stable angina

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Background: Current guidelines suggest that coronary lesions should be treated when there is a previous ischemia stress test implying the involved myocardial area. However, sensitivity and specificity of non invasive stress tests (NIST) seems to be less than expected, when compared with invasive functional invasive evaluation of lesions, using a pressure wire, particularly in patients with multivessel disease.

Purpose: To investigate the diagnostic value of NIST in patients with stable angina, compared with the invasive functional study (fractional flow reserve – FFR – evaluated with a pressure wire) during coronary angiography.

Methods: Patients with stable angina admitted for coronary angiography and with ischemia identified on a previous NIST, were included. The functional relevance of identified coronary lesions was determined by FFR evaluation (Pressure-Wire®, St. Jude Medical), under adenosine coronary hyperemia. An FFR<0.75 was considered as functionally significant.

Results: 57 lesions, from 36 patients (mean age 61±8.5 years, 24 males) were included. The NIST was myocardial perfusion scan in 28 (61%) patients and stress Echo in 7 (19%). Concordance between NIST and FFR was present in only 24 (42%) of the evaluated lesions. For the defined FFR value (<0.75), NIST sensitivity was 38%, specificity 98%, positive predictive value 42% and negative predictive value 90%. There were no identifiable variables affecting the concordance between NIST and functional invasive evaluation (including age, gender, chest wall, risk factors, presence of multivessel disease or ischemia affected territory). However, there was a trend for an increase in the concordance between non invasive and invasive tests when lesion where divided according to angiographic severity: for lesions <60%, 70-80% and ≥80%, the concordance was respectively, 31%, 50% and 100% (p=0.087).

Conclusions: NIST have a low concordance with the invasive functional evaluation of lesions with a pressure wire, usually overestimating the presence of ischemia. The lack of concordance between non invasive and invasive test tends to decrease in more severe lesions. These results should be tested in larger trials, since they might change the present recommendations for coronary lesions revascularization.

A novel method for the detection of coronary artery disease using an ultrasonic microphone on the chest wall

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Background: Prior studies have associated increased amplitudes of high frequency diastolic heart sounds with Coronary Artery Disease (CAD), but these results were weak and difficult to identify in noisy clinical settings. The current study was initiated by the observation that the low frequency (≤100 Hz) of ischemic heart sounds are increased in CAD subjects. We tested a prototype of an acoustic system for non-invasive automated identification of coronary artery stenosis.

Methods: From an original group of 463 patients referred for elective coronary angiography we excluded those with potential confounders: arrhythmias (N=58); diabetes (N=21); peripheral vascular disease (N=97); women (N=230); age ≥75 years; 17% diabetic; 63% hypertension. In both the training set and the test set no significant differences among groups in baseline characteristics were observed.

Results: The 195 patients were typical for a CAD population: median age of 62.3 years; 17% diabetic; 63% hypertension. In both the training set and the test set the CAD was increased in CAD subjects compared to non-CAD subjects (32.2±21.7; p<0.000004 and 32.4±21.6; p<0.000015). In the test set the area under the receiver-operating curve was 76.8% (95% CI: 66.6-87%) Sensitivity of the test was 70.7% (95% CI: 57-82%) and the specificity 64.9% (95% CI: 42-81%).

Conclusion: This study demonstrates the potential of a new, inexpensive, non-invasive method to detect significant coronary artery disease, with accuracy comparable to many currently used diagnostic and predictive instruments. With potential improvements of the methods, such as adding an analysis of high frequency components, this method could represent a paradigm shift in the diagnosis of CAD.

Effects of ranolazine and ivabradine on exercise stress test and on coronary and peripheral vascular function in patients with refractory microvascular angina

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Purpose: Ivabradine and ranolazine are novel anti-ischemic drugs with known beneficial effects in patients with stable angina and obstructive coronary disease. In this study we assessed their effects on exercise stress test (EST), coronary microvascular function and systemic vascular function in patients with microvascular angina (MVA).

Methods: We randomized, in a double-blind way, 46 MVA patients (defined by the presence of effort angina, positive maximal EST, normal coronary arteries at angiography and coronary flow response to dipyridamole) into ester (DFP) and placebo (BID) groups. Euvardine was initiated by the observation that the low frequency (≤100 Hz) of ischemic heart sounds are increased in CAD subjects. We tested a prototype of an acoustic system for non-invasive automated identification of coronary artery stenosis.

Results: The 195 patients were typical for a CAD population: median age of 62.3 years; 17% diabetic; 63% hypertension. In both the training set and the test set no significant differences among groups in baseline characteristics were observed.

Conclusions: Ranolazine, but not ivabradine, was able to delay the appearance of ischemic ST-segment changes and improve exercise tolerance in MVA patients. This effect was not related to significant improvement in coronary microvascular function or in endothelial systemic function.

Impact of metabolic syndrome on the outcome of patients with stable coronary artery disease submitted to different types of treatment: 10-year follow-up of the MASS II Trial

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Purpose: Metabolic syndrome (MetS) is understood as a condition that promotes atherosclerosis and confers an additional risk of adverse cardiovascular events in patients with coronary artery disease. The prognosis of this syndrome in this subset of patients in a long term follow up is inconclusive. Evaluate the impact of metabolic syndrome on cardiac death in patients with symptomatic chronic multivessel coronary artery disease.

Methods: Patients randomized in MASS II study submitted to coronary artery angiography (CABG, PCI) or medical treatment (MT) were evaluated for the presence of MetS and followed prospectively for 10 years. We evaluated the incidence of overall and cardiac death in this period.

Results: Criteria for MetS were fulfilled in 263 patients of 583 (54%) randomized to three therapeutic strategies. The presence of MetS was associated with an increased cardiac related death in studied population. During a 10-year follow-up, the probability cardiac mortality free survival was significantly different among patients in the 2 groups (MetS – 81.6% x non-MetS – 91.3% P<0.004). Stratifying patients with MetS by therapeutic approach we identify a statistical difference in cardiac death free survival comparing interventional approaches (CABG and PCI) to MT: 82.4% for CABG; 86.2% for PCI and 75.9% for MT (P<0.003). Besides, there is a group with best prognosis: patients without MetS submitted to CABG presenting 98.7% of patients free of cardiac death in a 10-year follow-up.

Conclusion: MetS carries high rates of cardiac death in patients with stable coronary artery disease irrespective of therapeutic strategy used. In patients with MetS, interventional approaches (PCI or CABG) seem to confer more protection against cardiac death in a 10-year follow-up.
**P4453**

**YKL-40 is associated with long-term mortality in patients with stable coronary artery disease**

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**Objective:** We investigated whether the inflammatory biomarker YKL-40 could improve the long-term prediction of death made by common risk factors plus high-sensitivity C-reactive protein (hs-CRP) and N-terminal-pro-B natriuretic peptide (NT-proBNP) in patients with stable coronary artery disease (CAD).

**Background:** Non-hospitalized CAD patients are usually followed in general practice. There is a need for identify biomarkers which could help to foresee the prognoses of these patients. Elevated serum YKL-40 is a short-term predictor for myocardial infarction, cardiovascular mortality and all-cause mortality in patients with stable CAD.

**Methods:** Serum YKL-40, hs-CRP and NT-proBNP were measured in 4265 (97.6%) of the 4372 patients with stable CAD included in the CLARICOR trial, and death was registered in a 6-years follow-up period.

**Results:** After adjustment for type of intervention, risk factors (age, sex, hypertension, diabetes, smoking status, and previous MI) and medical treatment (diuretics, digoxin, and statin) serum YKL-40 (transformed as ln(max(82, YKL-40/μg/L))) was significantly associated with all-cause mortality [hazard ratio (HR) = 1.38, 95% CI = 1.21-1.53, p < 0.001]. After additional adjustment for ln(hs-CRP) and ln(NT-proBNP) this was still true [HR = 1.38, 95% CI = 1.21-1.53, p < 0.001].

**Conclusions:** Serum YKL-40 is a predictor of long-term mortality in patients with stable CAD independent of common risk factors and ln(hs-CRP) and ln(NT-proBNP). Serum YKL-40 can be used for prognostication in these patients.

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**P4454**

**Coronary plaque characteristics that indicate distal embolization during percutaneous coronary intervention in patients with stable angina-virtual histology intravascular ultrasound study**

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**Background:** Distal embolization (DE) is a serious complication of percutaneous coronary intervention (PCI) in patients with stable angina.

**Purpose:** The purpose of this study was to evaluate the coronary plaque characteristics that indicate DE during PCI in patients with stable angina using virtual histology intravascular ultrasound (VH-IVUS).

**Methods:** Three hundred and sixty-four consecutive stable angina patients who underwent PCI were enrolled in this study. The patients were divided into the two groups as follows: patients exhibiting DE (DE group, n=10) and patients without DE (non-DE group, n=354). The culprit coronary plaque compositions were assessed by VH-IVUS, which were classified as fibrous, fibro-fatty (FF), dense-calcium and necrotic core. The best cut-off values for predicting DE were calculated by receiver operating characteristic curve and evaluated by univariate logistic regression analysis.

**Results:** The FF ratio (28±17% vs. 11±9%, p=0.0001) was higher in the DE group compared with in the non-DE group. None of the other VH parameters were different between the two groups. The best cut-off value of FF ratio for prediction of DE was 20%, with a sensitivity of 0.80 and a specificity of 0.81 (odds ratio; 17.1, 95% confidence interval 3.56-82.5, p=0.0004).

**Conclusions:** Coronary plaques analyzing FF ratio may be the predictor of indicating DE in patients with stable angina during PCI.

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**P4455**

**Effects of ranolazine and ivabradine on angina status and quality of life in patients with microvascular angina**

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**Purpose:** Aim of this study was to assess the effects of ranolazine and ivabradine on angina symptoms and quality of life (QoL) in patients with microvascular angina (MVA: effort angina, positive exercise test, normal coronary arteries and coronary flow reserve <2.5).

**Methods:** We randomized 46 MVA patients under usual antiangina therapy to receive ivabradine (5 mg b.i.d.), ranolazine (375 mg b.i.d.) or placebo for 4 weeks. The Seattle Angina Questionnaire (SAQ) and EuroQol scale were assessed before and after treatment.

**Results:** Basal SAQ scores and EuroQol scale did not differ among groups. Both ivabradine and ranolazine improved outcome variables compared to placebo; furthermore, ranolazine was more effective than ivabradine in improving most SAQ items and EuroQol scale (table).  

<table>
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<th>Item</th>
<th>Ivabradine (n=16)</th>
<th>Ranolazine (n=16)</th>
<th>Placebo (n=17)</th>
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<tr>
<td>Physical limitation</td>
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<td>Baseline</td>
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<td>Angina stability</td>
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<tr>
<td>Baseline</td>
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<td>40.0±24.6</td>
<td>56.7±27.5</td>
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<td>50.0±25.4</td>
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<td>Angina frequency</td>
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<tr>
<td>Baseline</td>
<td>64.4±14.1</td>
<td>61.3±12.4</td>
<td>72.7±16.7</td>
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<td>Treatment satisfaction</td>
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<tr>
<td>Baseline</td>
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<td>66.8±16.4</td>
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<tr>
<td>Baseline</td>
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<td>61.3±16.8</td>
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<tr>
<td>Follow-up</td>
<td>72.5±16.8</td>
<td>79.3±12.9</td>
<td>64.3±16.6</td>
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</tr>
</tbody>
</table>

*p<0.05 for differences in changes vs. ivabradine.

**Conclusions:** Our data show that both ranolazine and ivabradine may have a therapeutic role in MVA patients. Ranolazine appeared more effective than ivabradine in achieving a better control of symptoms.

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**P4456**

**Low testosterone levels correlate with the angiographic extent of coronary artery disease in patients with stable angina and/or abnormal stress test**

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**Purpose:** Low testosterone concentration is associated with endothelial dysfunction.
Markers of prognosis, incidence of sudden cardiac death and heart failure in coronary artery disease

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Purpose: To evaluate in patients with stable angina, ST and non ST elevation acute coronary syndromes (ACS) plaque instability biomarkers and the effects on outcomes included sudden cardiac death, heart failure readmmission and left ventricular systolic dysfunction.

Methods: In 402 patients (pts) with stable angina and ACS, plaque instability biomarkers: endothelial dysfunction (Von Willebrand factor activity, flow mediated dilatation), platelets hyperactivity (ASPfitest, ADPtest by multiple electrode aggreometry), oxidative stress (Total antioxidant status, Anti Myeloperoxidase antibodies -MPO IgG ELISA), were evaluated in correlation with incidence sudden cardiac death, heart failure and other major acute cardiovascular events (MACE) for 2 years of follow up. Statistic analysis: c2 square test, multiple regression.

Results: See Table.

Conclusions: Higher aggregation values of ASPfitest/ADPtest higher Von Willebrand factor activity plasma value, lower values of flow mediated vasodilatation, lower serum levels of total antioxidant status and higher serum level of myeloperoxidase IgG antibodies, were correlated with significant increased incidence of sudden cardiac death, cardiovascular death, nonfatal AMI, heart failure and recurrent angina with readmission, significant higher incidence of left ventricular systolic dysfunction in patients with acute coronary syndromes at 2 years of follow up. Endothelial dysfunction, platelets hyperactivity and oxidative stress are the most important factors in atherosclerotic plaque instability and evolution with major acute cardiovascular events.

The prevalence of refractory angina in patients undergoing coronary angiography for stable ischemic heart disease

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Background: Epidemiological studies of refractory angina do not always take into account the number of angina episodes during a certain period of time in separate patient populations. The severity of refractory angina is not always known.

Purpose: To evaluate the prevalence and severity of refractory angina in real clinical practice in patients with stable ischemic heart disease undergoing coronary angiography.

Methods: 418 patients (301 male (72%) and 117 female (28%)) undergoing coronary angiography due to chronic stable angina were consecutively screened during a one-year period. Several aspects of ischemic heart disease were analyzed. In patients with angina refractory to medical and surgical treatment following chest pain episodes was recorded using standardized one-week diaries.

Results: Among all 418 patients 6 (1.4%) had Class 1 angina (CCS Grading Scale), 288 (68.9%) – Class II, 121 (28.1%) – Class III, 3 (0.7%) – Class IV. 29 patients (6,9%) had no detectable lesions of coronary arteries, 138 patients (33%) had non-significant lesions, 82 (19.6%) patients were diagnosed with significant single-vessel disease, 26 (6.2%) patients – with double-vessel disease, 98 (23.4%) – with multiple-vessel disease. Myocardial revascularization was indicated in 251 patients (60, 1%), 117 of them (46,6%) underwent PTCA, 79 (31,5%) – CABG. Cardiac surgeons refused to operate (due to various contraindications and/or high risk) in 26 patients (10,4%), 29 patients (11,6%) refused to be operated because of fear of operation.
Totally 55 patients were considered as having angina pectoris refractory to surgi-
cal and medical treatment, which is 21.9% of all patients with stable angina in
whom revascularization was indicated. The frequency of angina attacks in this
group varied from 0 to 24 episodes a week with median of 2 episodes. 27 patients
(49% of all refractory angina patients) had less than two angina attacks a week,
the rest 28 patients (51%) had an average of 8 attacks of angina per week. There-
fore, more than 80% of the patients considered refractory angina control and
only 28 patients had a refractory angina which is 6.7% of all 481 patients
undergoing coronary angiography.

Conclusions: Amongst all patients with stable angina undergoing coronary an-
giography 6.7% had a refractory angina which is substantial. Usage of other tools
apart from CGS Angina Grading Scale can help to evaluate severity of angina:
standardized diaries, special tools for measurement of quality of life, etc.

P4460 Prognostic value of “tight” blood pressure control in patients with coronary artery disease: evidence from the Action database

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The placebo-controlled ACTION trial examined the effects of treatment with Nifedipine GITS on clinical outcomes in patients with stable symptomatic coronary
artery atherosclerotic burden. An ad-hoc retrospective analysis of the ACTION
database demonstrated the importance of consistent blood pressure (BP) to be-
low 140/90mmHg. This further analysis evaluates the benefits of sustaining "tight" BP control at levels recommended by current guidelines for this "high risk" patient population.

The analysis was limited to those patients who had complete BP measurements
over the first year of the study (4 recordings) and excluded those who had an event during this period. The patients were then divided into 4 groups according to the proportion of visits in which BP was in controlled to <130/80 mm Hg: <25%, 25% to <50%, 50% to <75% and ≥75%. Data were analysed for the major pre-
specified ACTION outcomes by unadjusted clinical outcomes; thus, % of patients
with outcome by proportion of visits with BP control. Data were also analysed
estimating the hazard ratios (HR) for each outcome relative to the consistency of BP control with the group with BP control ≥75% of visits as reference.

Only 18.1% of patients achieved a BP control rate (<130/80 mm Hg) for more
than 75% of visits and, in the first year, 48.6% were controlled at fewer than 25%
outcomes. With the exception of coronary angiography, the rate of all of the pre-
specified cardiovascular endpoints declined as the proportion of visits with BP
control increased. The risks for primary outcome (HR: 0.63; 95% CI: 0.53 to 0.75),
all cardiovascular events (HR: 0.63; 95% CI: 0.53 to 0.76), myocardial infarction
(HR: 0.69; 95% CI: 0.51 to 0.92), and stroke (HR: 0.34; 95% CI: 0.18 to 0.63) were
less in the group with ≥75% of visits with BP control compared with the group
with <25% of visits with BP control. These findings were not significantly modified
when the data were analysed on the basis of two treatment groups (placebo
or nifedipine GITS).

These retrospective analyses highlight the importance of the current recommen-
dations for tight BP control for patients with cardiovascular disease and
provide additional supporting evidence for the same.

P4461 Impact of coronary atherosclerotic burden on clinical presentation and prognosis of patients with coronary artery disease

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Background: The impact of coronary atherosclerotic burden on prognosis and presentation of patients with coronary artery disease (CAD) is unknown. We in-
vestigated the association of coronary atherosclerotic burden with clinical out-
come and presentation as unstable angina in patients with CAD.

Methods: This study included 10647 patients with stable (n=8149) and unstable
(n=2498) CAD who underwent percutaneous coronary intervention (PCI). Coro-

nary atherosclerotic burden was assessed by Gensini score. The primary out-
come analysis was 1-year mortality.

Results: Gensini score was obtained by analysis of 13136 coronary segments.
Patients were divided into groups according to quartiles of Gensini score: <13
(1st quartile; n=2650 patients), 13 to <25 (2nd quartile; n=2661 patients), 25
to <53 (3rd quartile; n=2711 patients) and ≥53 (4th quartile; n=2665 patients).

The mean age in cases was 58.7 + 9.5 years, and 56.6 + 11.6 years in the control
group. Other characteristics like prevalence of diabetes, hypertension, coronary
artery bypass graft (CABG), percutaneous angiography (PCI) were similar in
both the groups. Clinical results demonstrated a significant improvement in exercise
time between cases and controls 6 months after treatment with CSWT (20.1 +
15.7 minutes in cases vs 10.1 + 4.2 minutes, p<0.0001). There were 43 patients in the cases only. Therapy was well-tolerated by all patients.

Conclusion: The present study shows that CSWT application to the ischemic myocardium in patients with refractory angina pectoris, improved symptoms and
reduced severity of ischemic areas at 6 months follow-up, compared to baseline.
No side-effects were observed. We recommend further studies to confirm the results.

P4463 Interleukin-6 promoter genetic polymorphism is associated with the presence and the severity of coronary artery disease

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Purpose: Interleukin-6 (IL-6) is marker of inflammatory process, closely related
to the initiation and evolution of atherosclerosis. However, it remains unclear,
whether common polymorphisms within the IL-6 gene affect the mechanisms of
atherosclerosis. In the present study we examined the impact of the common
polymorphism G-174C on IL-6 gene promoter on the severity of coronary artery
disease (CAD) as well as on endothelial function.

Methods: The study population consisted of 272 patients with angiographically
documented coronary artery disease (CAD) and 160 healthy controls. The G-
174C polymorphism was determined by PCR and digestion with SfI.

Results: The genotype distribution among the CAD patients was GG: 47.4%; GC:
30.5%, CC: 22.5%, and GG: 47.8%; GC: 43.8%; CC: 8.4% for the healthy con-
trols. Our results showed that the CC polymorphism was associated with the pres-
ence of CAD (RR=1.11; 95% CI: 1.03-1.20, p=0.05). Importantly, the present
polymorphism was also associated with the angiographic extent of CAD (X2
=11.64, p<0.001). Although, the CC homozygosity was associated with lower
FMD compared to the G allele carriers, this difference did not reach statistical
Lipoprotein-associated phospholipase A2 (Lp-PLA2) is associated with peripheral blood monocyte sirt1 expression in CAD patients, suggesting that HDL-Lp-PLA2 may significantly contribute to antiatherogenic and cardioprotective effects of HDL.

**Conclusions:**

Lp-PLA2 is a novel risk factor for cardiovascular disease. It has been postulated that the role of Lp-PLA2 in atherosclerosis may depend on the type of lipoprotein with which it is associated. We examined the prognostic value of Lp-PLA2 associated with high density lipoprotein (HDL) [HDL-Lp-PLA2] in patients with stable coronary artery disease (CAD).

**Methods:** Total plasma Lp-PLA2 and HDL-Lp-PLA2 mass and activity, lipids and cholesterol levels were measured in 524 consecutive patients with known CAD, who were followed for a median of 34 months. Primary endpoints were cardiac deaths and secondary endpoints hospitalizations for acute coronary syndrome (ACS), myocardial revascularization, arrhythmic event or stroke.

**Results:** Follow-up data were obtained by 477 patients. One hundred and twenty-three patients (25.8%) presented with cardiovascular events (24 cardiac deaths, 47 ACS, 28 revascularizations, 22 arrhythmic events, 2 strokes). The HDL-Lp-PLA2 mass and activity were associated with lower risk of cardiac death (HR=0.972, 95% CI, 0.952 to 0.993, p=0.010 and HR=0.496 to 0.957, p=0.026, respectively) after adjustment for traditional risk factors for CAD. Finally, in the subgroup of patients with low HDL cholesterol levels (men with HDL cholesterol <40 mg/dL and women with HDL cholesterol <50 mg/dL), HDL-Lp-PLA2 mass was an independent predictor of cardiovascular death after adjustment for conventional risk factors (HR=0.951, 95% CI, 0.908 to 0.996, p=0.033).

**Conclusions:** HDL-Lp-PLA2 is associated with lower risk of cardiac death in stable CAD patients, suggesting that HDL-Lp-PLA2 may significantly contribute to the antiatherogenic and cardioprotective effects of HDL.

**Memory T cells are related to microvascular obstruction in ST segment acute myocardial infarction**


**Purpose:** In ST segment elevation myocardial infarction (STEMI), successful restoration of epicardial coronary artery flow might result in microvascular obstruction (MVO). The pathophysiology of this process and its relationship with lymphocyte trafficking has not been fully defined. The aim of this study was to determine the relationship between memory T cells with MVO in reperfused STEMI.

**Methods:** We studied 30 patients with a first STEMI treated with percutaneous revascularization. Distinct subtypes of memory T cells: T naive (CD45RACD4), T effector memory (TEM) cells (CD45ROCD4CD62L-), and chemokine receptors: CXCR3 and CCR4 were serially determined by flow cytometry before reperfusion and 24, 48, 72 and 30 days afterwards; values were compared with age- and sex-matched control subjects with normal coronary arteries. Cardiac magnetic resonance was used to detect microvascular obstruction during the first week after the infarction.

**Results:** In comparison with controls, patients displayed more circulating TEM cells. In STEMI patients there was a significant increase of TEM cells during first 5 days compared with basal (p<0.05). In case of TEM cells was associated with more MVO (Figure 1). An increment of TEM cells was correlated with lymphocyte trafficking after 24 hours with further TEM cells and further CAD4CXR3 (132 ± 92 vs 243 ± 182 cells/μl) and CAD4CCR4 (132 ± 94 vs 242 ± 82 cells/μl) (p<0.001 in both cases).

**Conclusions:** Lymphocyte trafficking understood as an increase of memory T cells and chemokine receptors expression is closely related to MVO and it could be a pathophysiological mechanism to explain MVO plugging in reperfused myocardium. Further studies will be needed to determine if TEM cells number during the first stages of MI could be a useful predictor of MVO.

**Peripheral blood monocyte sirt1 expression is reduced in patients with coronary artery disease**

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**Aims:** Inflammation plays a key role in atherosclerosis. Sirt1, a longevity gene, regulates transcription factors involved in inflammatory processes and blunts atherosclerosis in mice. However, its role in humans remains to be defined. In this study, we investigated Sirt1 gene expression in circulating monocytes of patients suffering from coronary artery disease (CAD).

**Methods and results:** 48 male subjects admitted for cardiac catheterization were based on the result of the angiography, subdivided into healthy subjects and patients with stable CAD (at least one stenosis ≥75%), and those with acute coronary syndromes (ACS), with and without ST-elevation and elevated troponin. Monocytes were isolated from whole blood and Sirt1 mRNA levels were determined by quantitative real time PCR. Sirt1 mRNA levels were higher in the healthy group as compared to the CAD and ACS patients (p<0.05). Interestingly, HDL levels correlated positively with Sirt1 expression. Thus, HDL from the three patient groups was isolated by ultracentrifugation and incubated with THP-1 monocytes to determine the effects of HDL on Sirt1 protein expression. HDL from healthy subjects stimulated Sirt1 expression in THP-1 monocytes to a higher degree as compared to HDL from CAD and ACS patients (p<0.05).

**Conclusions:** HDL are associated with reduced Sirt1 expression and low plasma HDL levels. THP-1 monocytes incubated with HDL from subjects without CAD display increased levels of Sirt1 as compared to that obtained from patients with CAD and ACS suggest that HDL stimulates the expression of the longevity gene Sirt1 and that it becomes dysfunctional in CAD and ACS.

**Patients with acute myocardial infarction and severe obstructive coronary atherosclerosis display distinct peripheral blood gene expression profiles**

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**Background:** The fact that patients with severe multidivisional coronary artery disease (MV-CAD) remain stable for years without developing acute coronary events, while others develop myocardial infarction (MI) as the first manifestation of CAD despite mild coronary atherosclerosis remains poorly understood. We hypothesized that gene expression in peripheral blood differs in these two populations.

**Methods:** Peripheral blood was collected from 115 patients with angiographic MV-CAD (≥70% stenosis ≥2 vessels) but without prior MI (n=9); 2 patients with ST-elevation MI and angiographic evidence of 1- vessel disease with plaque rupture (n=14); 3 subjects with normal coronaries (NC) (n=11).

**Results:** Venn diagram of differentially expressed genes (FDR <0.2, ≥1.3 fold-change, P<0.05) demonstrated gene expression changes occurring predominately in the MV-CAD vs. NC group (n=57). These genes included atherosclerosis and inflammation-related genes including COX-2, EGR-1 and JUNB, pro-inflammatory cytokines (IL-1β, oncostatin M, visfatin), and toll-like receptors (TLR4 and TLR6). The most notable finding in an Ingenuity pathway analysis was a graded enrichment in inflammation-related pathways.
Role of CD31 and CD38 in innate and adaptive immunity in patients with chronic stable angina and acute coronary syndromes

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Purpose: CD31 is a molecule implicated in leukocyte transendothelial migration and immunomodulation by TCR inhibition. CD31 is involved in homophilic and heterophilic binding interactions with different ligands like CD38. CD38 is a functionally plectinotropic molecule implicated in transmembrane signaling and adhesion of immune cells. Recent studies have highlighted the importance of innate and adaptive immunity in acute coronary syndrome (ACS). We aim to evaluate CD31 and CD38 expressions by different monocyte and T-cell subsets in patients with ACS compared to chronic stable angina (SA). We also analyzed CD31 signaling in CD4+ T-cells after TCR stimulation.

Methods: Consecutive patients with Non-ST elevation ACS (n=12) and SA (n=16) were enrolled. CD31 and CD38 median fluorescence intensity (MFI) of different monocyte subsets, total CD4+ and CD4+CD28null T-cells was assessed by flow cytometry. In T-cells, CD31 signaling was assessed by ZAP-70 phosphorylation after TCR stimulation with CD3/CD28 and CD31 monoclonal antibody.

Results: Data are presented as mean ± SE. ASC patients had lower CD31 expression on monocyte and T-cell subpopulations as compared with SA (see Table), but there were no differences in CD38 expression. Moreover, ACS patients showed a reduced TCR inhibition after stimulation with CD31 monoclonal antibody of both total CD4+ T-cells (ACS=6±2.6% vs SA=19±2.2%; P<0.001) and CD4+CD28null T-cells (ACS=10±6.2% vs SA=29±3.2%; P=0.005). Thus, in ACS the reduced expression of CD31 is related to an impaired control of the immune response.

CD31 expression on T-cells and monocytes

Table: CD31 expression on T-cells and monocytes

<table>
<thead>
<tr>
<th>Subset</th>
<th>ASC</th>
<th>SA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD31 MFI CD4+ T-cells</td>
<td>1.25±0.12</td>
<td>1.76±0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD31 MFI CD4+CD28null T-cells</td>
<td>1.14±0.12</td>
<td>2.05±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD31 MFI CD14++CD16+ monocyte</td>
<td>23.4±2.0</td>
<td>31.9±2.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD31 MFI CD14++CD16- monocyte</td>
<td>19.5±1.9</td>
<td>25.1±1.8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Conclusions: In ACS, the altered CD31/CD38 expression and the reduced functional property of CD31 pathway suggest a defective immunomodulation which could contribute to the impaired control of inflammatory. Our data also support the importance of CD31-mediated signaling in modulating low-grade inflammation in SA.

CD3 expression on T-cells and monocytes

Table: CD3 expression on T-cells and monocytes

<table>
<thead>
<tr>
<th>Subset</th>
<th>ASC</th>
<th>SA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 MFI CD4+ T-cells</td>
<td>2.5±0.12</td>
<td>3.6±0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD3 MFI CD4+CD28null T-cells</td>
<td>1.45±0.12</td>
<td>2.6±0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD3 MFI CD14++CD16+ monocyte</td>
<td>24.8±2.0</td>
<td>31.9±2.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>CD3 MFI CD14++CD16- monocyte</td>
<td>19.5±1.9</td>
<td>25.1±1.8</td>
<td>&lt;0.05</td>
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</tbody>
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Conclusions: In ACS, the altered CD31/CD38 expression and the reduced functional property of CD31 pathway suggest a defective immunomodulation which could contribute to the impaired control of inflammatory. Our data also support the importance of CD31-mediated signaling in modulating low-grade inflammation in SA.

Erythrocyte aggregation portends worse outcomes in unstable angina patients undergoing percutaneous coronary interventions

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Background: We have previously reported a correlation between the time from symptom onset to the appearance of an inflammatory response and erythrocyte aggregation (EA) in the peripheral blood of acute coronary syndrome (ACS) patients. We now analyze the added prognostic value of EA determination in ACS patients undergoing percutaneous coronary interventions (PCI).

Methods: We performed an analysis on prospectively collected data at a tertiary health-care center in coronary intervention laboratory between 2006-2011. Cox regression models were fitted for EA and C-reactive protein (CRP) cut-offs and performed separately for myocardial infarction (MI) and unstable angina pectoris (UAP) patients. Major adverse cardiovascular events (MACE) were defined as all-cause mortality, MI and stroke. Follow-up time was defined as the time form PCI to either MACE or November 20, 2011.

Results: Included were 1055 patients (637 with MI and 418 with UAP). The median follow up in the MI and the UAP groups were 14 and 15 months, respectively (maximal follow up of 4.1 years). In the MI group, elevated CRP marginally increased the risk of MACE during follow-up with either a higher or lower EA status (HR=1.9, p=0.057; HR=1.8, p=0.129; respectively) compared to patients with low CRP and low EA. In the UAP group however, there was a significant increase in MACE for the group with high CRP and high EA (HR=4.4, p=0.005) compared to the same patients. This was not found for the group with high CRP and low EA. In general, traditional risk factors as well as coronary disease severity did not predict adverse outcomes during the follow-up period.

Conclusions: Elevated EA portends worse outcomes in UAP patients undergoing PCI who present with higher CRP concentrations.

Update on innate and adaptive immunity in coronary artery disease


Purpose: Apart from the prognostic impact of baseline renal function, small increases in creatinine during hospitalization have been demonstrated to constitute an independent prognostic marker following myocardial infarction (MI). Our aim was to identify the independent predictors of in-hospital worsening renal function (WRF) in patients with acute MI.

Methods: Our study population consisted of 522 patients admitted to the hospital with the diagnosis of acute MI (304 with ST-elevated MI and 218 with non-ST-elevated MI) within 12 hours of symptoms onset. From blood sample obtained on admission white blood count, high sensitivity C-reactive protein (CRP), brain natriuretic peptide (BNP), troponin I (TrI), plasma glucose and creatinine (Cr) were determined. Peak Cr levels were also measured throughout hospitalization. The MDRD equation was used to estimate glomerular filtration rate (GFR). WRF was defined as a 25% or more decrease in estimated GFR during hospital stay irrespective of any subsequent normalization of GFR. All patients enrolled underwent wave-tone coronary arteriography during in-hospital stay and the presence of critical underlying coronary artery disease was recorded. Ejection fraction was estimated on admission with 2D echocardiography by applying the Simpson's rule.

Results: WRF was detected in 67 pts (16.7%). Patients with WRF were significantly older (by 10 years, p<0.001), more frequently females (by 16.3%, p<0.001), hypertensives (by 14.2%, p=0.032) and exhibited significantly lower diastolic blood pressure (by 4.1 mmHg, p=0.032), ejection fraction (by 8.7%, p<0.001) as well as greater prevalence of LAD involvement (by 17%, p=0.004) and less prevalent complete revascularization (by 18%, p=0.009). Additionally, although minimum GFR during hospitalization was lower in MI patients with WRF compared to those without WRF (by 26.5 mg/dl, p<0.001), admission GFR levels did not differ between the study subgroups. Similarly, plasma glucose levels (by 26.5 mg/dl, p=0.025), white blood cell count (by 1497, p=0.024), CRP (by 18.3 g/ml, p=0.001), BNP (by 255 pg/dl, p<0.001) and TrI levels (by 1ng/dl, p<0.001) were higher in the WRF group. In the multivariate logistic regression analysis, age (odds ratio OR=1.074; 95% CI 1.041 to 1.109), ejection fraction (OR 0.951; 95% CI 0.899 to 0.961), white blood cell count (OR 1.089; 95% CI 1.004 to 1.181) turned out to be the only independent predictors of WRF.

Discussion: Admission white blood cell count, along with age and ejection fraction, predicts worsening renal failure in patients with acute MI.

Elevated plasma high sensitivity C-reactive protein and endothelin are associated with decreased flier-light induced retinal arteriolar dilatation

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Purpose: High sensitivity C-Reactive Protein (CRP) and endothelin (ET-1) are biomarkers of cardiovascular risk in patients with and without coronary artery disease. The dynamic response of retinal vessel diameter to flicker-light is a measure of endothelial function. In this study, we sought to determine the relationship of flier-light induced retinal arteriolar dilatation (FI-RAD) with CRP and ET-1.

Methods: Patients with risk factors of atherosclerosis, with and without CAD were recruited (n=258). FI-RAD was measured in both eyes after pupil dilation using the Dynamic Vessel Analyzer (DVA) and expressed as percentage increase over baseline diameter in response to flicker light. CRP was measured by the rate turbidimetry method and ET-1 by radioimmunoassay method. Pearson’s correlation and linear regression analysis were used to determine the correlation.

Results: There were 119 patients (46%) with at least two atherosclerosis risk factors but no CAD, 78 patients (30%) with stable CAD and 61 patients with an acute coronary syndrome (ACS, 24%). The mean age of the total sample was
Myocardial injury induces AIM2 inflammasome expression in neutrophil granulocytes in patients with acute coronary syndrome

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Background: Early priming and recruitment of neutrophil granulocytes (PMN) play a significant role in myocardial injury following acute coronary syndrome (ACS). Molecular mechanisms of PMN activation after myocardial ischemia and reperfusion remain largely unknown. In-vitro and animal studies could show that specific intracellular protein complexes, so-called inflammasomes (e.g. Nlrp3 or AIM2) can initiate an inflammatory response by sensing host-derived danger signals (DAMPs), such as ATP and other cellular components released during tissue injury. The aim of the present study was to investigate the inflammasome activation in PMN and its role in induction of the sterile inflammatory response in patients with ACS.

Methods: 75 patients (pts) with coronary heart disease (CHD) were included into this study. 50 pts with ACS (25 with STEMI, 25 with NSTEMI) and 25 pts with stable CHD were analyzed before and 12-24 hours after primary percutaneous coronary angioplasty (PPCI). In-vitro PMN stimulation with injury-associated DAMPs, dsDNA and ATP was performed using Western Blot analysis.

Results: Expression of mRNA for AIM2 inflammasome was significantly higher in ACS pts as opposed to stable CHD pts (RCR 88.1±7.7 vs. 59.4±5.4; p=0.02) or healthy controls (88.1±7.7 vs. 38.8±3.7; p=0.001). This ACS-related activation remained unchanged within 12-24 hours after PPCI (p=0.8; p=0.0001). AIM2 expression was higher in NSTEMI than in the STEMI group (94.1±4.7 and 83.5±8.1; p=0.009 and p=0.0001 vs. Ctrl). Protein expression analysis confirmed significant induction of AIM2 in STEMI (foldchange vs. Ctrl: 5.6±1.1; p<0.0001). In-vitro PMN stimulation (7.2±0.6; p=0.001) resulted in a 5-fold increase in AIM2 protein expression.

Conclusion: Our results identify for the first time enhanced expression of AIM2 inflammasome in PMN in patients with acute coronary syndrome. Our data suggest that inflammasome activation in PMN contributes to the early ischemia-triggered inflammatory response. Measuring inflammasome activation may therefore provide a novel clinical parameter for improved diagnosis and risk assessment in patients with ACS.

Increased YKL-40 levels in patients with isolated coronary artery ectasia

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Background: YKL-40, a new biomarker of localized inflammation, is secreted by macrophages in the atherosclerotic plaques. Coronary artery ectasia (CAE) is a clinical entity characterized with localized or diffuse dilatation, of the coronary arteries, greater than 1.5 times diameter of adjacent segments. Although the etiopathogenesis is not clearly understood, some studies have revealed that CAE may be a form of atherosclerosis that has greater inflammatory properties than atherosclerosis. The goal of this study was to investigate whether YKL-40 and C-reactive protein (CRP) are increased in patients with isolated CAE compared to non-CAE pts.

Methods: Forty-nine patients with isolated CAE (mean age: 60.1±10 years) and 30 age- and gender-matched control participants with NCA, but without CAE (mean age: 53.3±9.6 years), were included in the study. The relationship between YKL-40, CRP levels and the presence of CAE was investigated.

Results: Serum YKL-40 levels were significantly higher in CAE group compared to NCA group (144±68 vs. 110±53 μg/L, p=0.015). CRP was not significantly different between the two groups (0.67±0.63 vs. 0.53±0.39, p=NS). In addition, there were not any statistically significant differences, with respect to age, gender, the presence of hypertension or diabetes mellitus, and the smoking status (p=0.05), except creatinine levels (0.89±0.21 vs. 0.78±0.11 mg/dL, p=0.012).

Conclusion: This is the first study displaying an significantly elevated YKL-40 level in patients with isolated CAE. We believe that further studies are needed to clarify the role of YKL-40 in patients with isolated CAE.
Functional characteristics of monocytes subsets in the acute and healing phases of ST elevation myocardial infarction and their effect on ejection fraction

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Background: Monocytes are implicated in the pathogenesis of atherosclerotic disease from initiation of atherosclerotic plaque through to plaque instability and rupture. Little is known of the numerical and functional activity of the 3 monocytes subpopulations in the acute and healing phase post ST elevation myocardial infarction in humans.

Method: 96 patients (aged 64±14; 65% male) were recruited within first 24hours post percutaneous revascularization for STEMI. Peripheral blood monocyte subsets were enumerated and characterised using flow cytometry. Monocyte subsets were defined as CD14+CD16-C RCR2+ (Mon1), CD14+CD16++CR2+ (Mon2) and CD14+CD16+CR2+ (Mon3). Functional assessment of monocyte subsets was assessed by measurement of their phagocytic activity and activation of nuclear factor κappa B (NFκB). Median fluorescent intensity (MFI) of intracellular kappa-B kinase beta (IKKβ) was quantified as an index of NFκB pathway activation. Phagocytosis was measured using novel pHrodo E. Coli BioParticles phagocytized by monocytes. Monocytes characteristics were measured within 24 hours post STEMI, and at 10-14 days (i.e. initiation of healing phase). Transthoracic echocardiography was performed to assess LV systolic function. Results: Monocyte counts were significantly higher at day 1 compared to days 10-14. All monocyte subpopulations in the acute and healing phases remained functionally at the same level of activity in the acute and healing phases of ST elevation myocardial infarction in patients with STEMI. Phagocytic activity of Mon1 and Mon2 increased during the remodeling phase (Table 1).

Conclusion: Inflammation in peri-coronary adipose tissue may affect plaque destabilization in patients with NSTEMI; There is no association between amount of pericoronary fat and plaque composition; PWV SUV correlates with necrotic core component of coronary plaque and plaque volume in patients with NSTEMI; In conclusion, inflammatory activity of PVAT in patients with NSTEMI may contribute to plaque formation, vessel narrowing and plaque rupture, supporting the hypothesis of the outside-to-inside signaling.

Inflammation of innate immunity, especially monocytes, is involved in vascular disease at different stages, from initiation to vessel rupture. Instead, inflammation of adaptive immunity is not so critical at this stage, but the abundance of adaptive immunity is required for chronic plaque development. In this context, the interest is focused on the monocyte poplulations and the role of their specific markers.

In the acute phase of myocardial infarction, monocytes are involved in haemostasis and inflammation. While monocytes express markers of activation and the capacity of phagocytosis, they do not secrete pro-inflammatory cytokines.

In the chronic phase of myocardial infarction, monocytes are involved in the remodeling phase and chronic inflammation. Monocytes expressing high levels of the inflammatory markers, such as IL-1β and TNF-α, are more likely to be recruited into the vascular wall and contribute to the formation of atherosclerotic plaques.

In this study, we investigated the role of monocytes subsets in the acute and healing phases of ST elevation myocardial infarction in humans. We found that monocyte counts were significantly higher at day 1 compared to days 10-14. All monocyte subpopulations in the acute and healing phases remained functionally at the same level of activity in the acute and healing phases of ST elevation myocardial infarction in patients with STEMI. Phagocytic activity of Mon1 and Mon2 increased during the remodeling phase (Table 1).

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P4479
Monocyte-derived angiogenic/reparative cells in myocardial infarction: focus on monocyte subpopulations
E. Shantsila, A.D. Tapp, B.J. Wrigley, A. Shantsila, G.Y.H. Lip. City Hospital, Centre for Cardiovascular Sciences, Birmingham, United Kingdom

Purpose: To established levels of CXCR4+ reparative monocytes and monocyte-derived endothelial progenitor cells (EPC) derived from distinct monocyte subsets in STElevation MI (STEMI) and non-STEMI.

Methods: CXCR4+ cells and CD34+KDR+ EPCs, attributable to individual monocyte subsets (Mon1, Mon2 and Mon3), were measured by flow cytometry in patients with STEMI, NSTEMI, and stable CAD (Table). Left ventricular ejection fraction (LVEF) was measured 6 weeks after STEMI onset.

Results: CXCR4+ cells derived from Mon1 and Mon2 were increased in STEMI. CXCR4+Mon2 were increased in NSTEMI. Only EPC derived from Mon3 were increased in both STEMI and NSTEMI. In STEMI CXCR4+Mon1 and CXCR4+Mon2 decreased by 1 month, with similar trend seen for Mon3-derived EPC. After adjustment for age, sex, diabetes and troponin levels only CXCR4+Mon2 (taken as average of the 4 time points) were independently predictive of LVEF (p<0.05, p=0.024).

Conclusions: Only specific monocyte subsets contribute towards upregulation of reparative and angiogenic monocytes in MI. CXCR4+Mon2 are independently associated with cardiac recovery post MI. These cells may represent a new therapeutic target in the future.

P4480
The association of neutrophil/lymphocyte ratio with coronary flow and in-hospital mace in patients with STEMI undergoing primary PCI
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Purpose: With the growing understanding of the role of inflammation in the atherosclerosis, studies have focused on hs-CRP and other inflammatory markers in the management of ST segment elevation myocardial infarction (STEMI). In this study, we aimed to investigate the role of neutrophil/lymphocyte (N/L) ratio and in-hospital major adverse cardiac events (MACE) in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

Methods: Four hundred and eighteen consecutive patients undergoing primary PCI were enrolled to study. Patients were divided into two groups based upon the thrombolysis in myocardial infarction (TIMI) flow grade score after primary PCI. High-sensitive CRP and N/L ratio on admission were measured.

Results: There were 158 patients (mean age 62±12 years and 73% male) in no-reflow group and 260 patients (mean age 59±13 and 81% male) in reflow group. N/L ratio was significantly higher in no-reflow group compared to that of reflow group (4.6±1.1 vs. 3.1±1.1, p<0.001). In-hospital MACE was significantly higher in no-reflow group (23% vs. 7%, p<0.001). Also there was a significant positive correlation between hs-CRP and N/L ratio (r=0.675; p<0.001). In ROC analysis, N/L ratio −3.3 predicted no-reflow with an 74% sensitivity and 83% specificity.

At multivariate regression analysis, N/L ratio was still independent predictor of no-reflow (OR 1.537, 95% CI 1.343–1.759; p<0.001) and in-hospital MACE (OR 1.137, 95% CI 0.981–1.315; p=0.043).

P4481
Higher plasma levels of platelet derived growth factor and matrix metalloproteinases-9 in coronary artery disease with acute myocardial infarction
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Background: Platelet derived growth factor (PDGF) is potent mitogen and chemotactic for vascular smooth muscle cells (SMC). Oxidized low-density lipoprotein (LDL) is thought to trigger some intracellular signaling and to influence the angiogenic characteristics, the pts with high PDGF to matrix metalloproteinase (MMP), which is involved in a degradation of extracellular matrix proteins leading to the migration of SMC into the intima and to the rupture of plaques, has been reported in animal studies. However, those interactions in human in vivo studies have not been fully elucidated.

Methods: Consecutive thirty two patients (age 63±11 year-old, diabetes 35%) with ST-segment elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI) within 12-hours after the onset were enrolled in this study. Plasma levels of PDGF BB, MMP-9, malondialdehyde-modified low-density lipoprotein (MDA-LDL) and high sensitive C-reactive protein (hs-CRP) were measured from infarct-related artery (IRA) using thrombus aspiration catheter and from femoral artery (FA) during PCI. These biomarkers were measured from patients with normal coronary artery as control.

Results: Total ischemic time was 288±116 mm. In the IRA, plasma levels of PDGF BB and MMP-9 were significantly higher than those in the FA (PDGF BB: 123.1±34.8 vs. 12.3±4.1, p<0.001; MMP-9: 86.0±20.5 ng/ml vs. 34.1, p=0.03). However, MDA-LDL and hs-CRP were not different between IRA and FA during PCI (MDA-LDL: 60.2±15.9 U/L vs. 62.1±14.1 U/L, p=0.56; hs-CRP: 1735±2868 ng/ml vs. 1816±2671 ng/ml, p=0.11, IRA and FA, respectively). Plasma levels of those markers did not increase in both coronary and femoral arteries in control patients.

Conclusions: This in vivo study demonstrated that PDGF BB with MMP-9 seems to play a role in coronary plaque instability or rupture in patients with STEMI. However, oxidized LDL and hs-CRP did not increase in IRA in acute phase of STEMI.
independent predictor of ACh induced CAS (OR: 1.5, p<0.01, 95% CI: 1.1-2.0), and myocardial bridge (MB) also was an independent predictor of ACH induced CAS (OR: 3.2, p<0.01, 95% CI:2.1-4.9).

Table: Methatatic analysis of ACH induced CAS

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Positive</th>
<th>Negative</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6.99</td>
<td>1.913</td>
<td>0.999-1.825</td>
</tr>
<tr>
<td>High CRP (mg/dl)</td>
<td>0.010</td>
<td>1.504</td>
<td>1.100-2.055</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.768</td>
<td>0.993</td>
<td>0.954-1.037</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.606</td>
<td>0.788</td>
<td>0.663-1.208</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.324</td>
<td>0.768</td>
<td>0.453-1.298</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.372</td>
<td>0.820</td>
<td>0.522-1.734</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.191</td>
<td>1.699</td>
<td>0.763-3.737</td>
</tr>
<tr>
<td>Current Alcohol</td>
<td>0.662</td>
<td>1.165</td>
<td>0.777-1.738</td>
</tr>
<tr>
<td>Myocardial bridge</td>
<td>0.009</td>
<td>3.599</td>
<td>2.118-4.970</td>
</tr>
<tr>
<td>Baseline severely narrowed (30%)</td>
<td>0.661</td>
<td>1.365</td>
<td>0.985-1.919</td>
</tr>
</tbody>
</table>

Conclusion: In this study, in female pts, high hs CRP and MB were independent predictors of ACH induced CAS. Therefore, the more intensive antianginal treatment would be required in female pts with high hs CRP.

**Figure 1**

Conclusions: Intrasural administration of erythropoietin suppressed the signaling proteins on the iron metabolism pathway and improved cardiac function in patients with acute myocardial infarction.

**Figure 1. Relation between CRP/TT and CAD in EDpts.**

Conclusions: In young ED patients the diagnostic performance of CRP for the early detection of CAG is higher than that of TT. This finding underscores the pathophysiological involvement of inflammatory activation in young ED patients.

**Figure 4**

Conclusions: Transforming growth factor beta 1 (TGFbeta1) contributes to the occurrence of acute coronary syndrome (ACS)?

**Figure 4.3**

Introduction: Transforming growth factor j1 (TGFj1) is of particular interest because of its actions in relation to all the cells that build the vessel wall. The TGFj1 affects cellular processes by binding to three types of specific receptors on the cell surface. Aim of this study was to analyze the gene expression of transforming growth factor j1 (TGFj1) and its receptors (TGFjR) in peripheral blood mononuclear cells (PBMC) with quantitative QRT-PCR method.

Materials and methods: The study group consisted of 267 patients with acute coronaary syndrome (157 with STEMI, 46 - with NSTEMI and 64 patients with UA) and 25 healthy subjects, which constituted control group. The study of gene expression was performed quantitative QRT-PCR technique.

**Figure 4.4**

Conclusions: Low T3 syndrome and inflammation in patients with ST-elevation myocardial infarction

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An altered thyroid hormone (TH) metabolism known as Low T3 syndrome (LT3S) is a frequent finding in patients with severe illness and is associated with a poor prognosis. Aim of this study is to evaluate the relationship between LT3S and inflammatory status in patients with ST-elevation myocardial infarction (STEMI) Methods: 120 patients (73%; mean age 66±12.5 years) admitted for STEMI and subjected to early reperfusion therapy were included in this study. Routine biohumoral exams including haemoglobin, creatinine, TH, C-reactive protein (CRP), fibrinogen dosage and erythrocyte sedimentation rate (ESR) were performed at admission. Left ventricular ejection fraction (LVEF) was determined by echocardiography within 48 hours after admission.

Results: LT3S (T3<2.2 pg/mL) was observed in 228 (17%) patients. These subjects were older (71±12 vs 64±12 years; P<0.0001), had lower haemoglobin (12.8±1.8 vs 13.8±1.6 g/dl; P<0.0001) and higher creatinine (1.2±0.6 vs 0.9±0.4 mg/dl; P<0.0001), CRP (4.4±6.1 vs 1.4±2.8 mg/dl; P<0.0001), fibrinogen (357±120.5 vs 296±80.8 mg/dl; P<0.0001) and ESR (32.1±25.6 vs 21.4±20.1 mm/h; P<0.0001). A lower LVEF (41.5±10.7 vs 44.9±9.5%; P<0.0001) was found in LT3S patients.

Conclusions: LT3S is associated with a worse clinical status, a greater degree of inflammatory activation and a lower ejection fraction in patients with STEMI. In these subjects, an altered TH metabolism and enhanced inflammation may contribute to post-ischemic myocardial dysfunction and progression towards heart failure.

**Figure 4.5**

High C-reactive protein is a better predictor of occult coronary artery disease than low testosterone in asymptomatic men less than 60 years with erectile dysfunction

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**Purpose:** Erectile dysfunction (ED) and coronary artery disease (CAD) share common basis of etiology and progression. Links include inflammation and low total testosterone (TT) level, however the diagnostic performance of these mechanisms for prediction of CAD in young vs older ED patients is unknown.

**Methods:** A total of 115 asymptomatic at initial presentation ED patients in whom a comprehensive assessment revealed CAD were studied. They were divided into two age groups: a young group (< 60 y/o, n=57, Group A) and an elderly group (≥ 60 y/o, n=58, Group B). Two groups of 57 (< 60 y/o) and 58 (≥ 60 y/o) ED patients without CAD, matched for age and risk factors with Group A and Group B patients respectively, served as controls.

**Results:** Group A patients had higher CRP level compared to Group B patients, while TT level was significantly lower in Group B patients than that of Group A patients (all P<0.01). In both age categories CAD patients had significantly increased CRP levels and decreased TT concentration (all P<0.01) compared to non CAD subjects. ROC analysis for CAD prediction showed that in young population (CAD and non-CAD ED patients), the area under the curve (AUC) for CRP was significantly greater than the AUC for TT (difference between AUCs 18%, P<0.05, left plot). On the contrary, the diagnostic performance of CRP and TT in the elderly population was similar (right plot). In young men a CRP level of 1.73 mg/l was associated with a sensitivity of 79% and a specificity of 68% for CAD prediction.

**Figure 4.6**

High C-reactive protein is a better predictor of occult coronary artery disease than low testosterone in asymptomatic men less than 60 years with erectile dysfunction.
A gene expression was estimated by the number of mRNA copies per one microgram of total RNA sample.

**Results:** The gene expression of TGFβ1 and its receptors in peripheral blood mononuclear cells was estimated with qRT-PCR technique in the study group patients with ACS and in the control group of healthy subjects - Table 1.

**Conclusion:** Significantly reduced gene expression of TGFβ1 and its receptors in PBMC of patients with acute coronary syndrome, compared with the high transcriptional activity in the healthy control group, confirms the protective effect of high expression of this cytokine and suggests systemic disorder in its expression as an important element of pathogenesis of acute coronary syndromes.

**P4487 Early cardiac gene transcript levels in peripheral blood mononuclear cells reflect severity in stable coronary artery disease**

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**Purpose:** The early cardiac genes myocardin, GATA4 and Nkx2.5 play a role in both embryonic cardiovascular development and adult cardiovascular disease. We evaluated transcript levels of myocardia, GATA4 and Nkx2.5 in peripheral blood mononuclear cells (PBMCs) in patients with stable coronary artery disease (CAD) and we examined the relationship between these levels and the severity of the disease, estimated by the number of stenotic vessels involved.

**Methods:** 98 patients with stable CAD (aged 66±19 years) who underwent coronary angiography participated in the study, 66 healthy individuals (aged 58±13 years) were also included for comparison. Gene transcript levels were determined by quantitative real-time reverse transcription PCR.

**Results:** Patients with 3- vessel CAD had elevated transcript levels of myocardin (p<0.001, 95% CI: 1-5.8), GATA4 (p=0.015, 95% CI: 0.1-1.9) and Nkx2.5 (p<0.001, 95% CI: 4.5-23) compared to healthy controls. Patients with 3-vessel CAD also showed elevated transcript levels of myocardin (p=0.001, 95% CI: 0.49-5.5) and Nkx2.5 (p<0.001, 95% CI: 1-2.15) compared to patients with 1-vessel CAD.

**Conclusion:** Early cardiac gene transcript levels are significantly higher in PBMCs of patients with severe stable CAD than in healthy controls. Alterations in the expression profile of early cardiac genes according to the disease severity status were also observed. Our results indicate for the first time, that alterations in the early gene expression in peripheral blood of stable CAD patients, possibly reflecting alterations in circulating cardiac progenitor cells expressing these genes, may reflect the level of disease severity.

**P4488 Gamma-glutamyltransferase levels are associated with inflammatory activation, myocardial dysfunction and in-hospital mortality in patients with ST-elevation myocardial infarction**

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**Introduction:** Gamma-glutamyltransferase (GGT) is a well known prognostic marker in patients with heart failure and stable coronary artery disease. Aim of this study is to define the relationship between GGT activity, systemic inflammation, myocardial function and in-hospital mortality in patient ST-elevation myocardial infarction (STEMI).

**Methods:** 1299 patients (male: 73%; mean age: 66±12.5 years) admitted for STEMI and undergoing early revascularization were included in the study. Routine biohumoral exams, including GGT activity, fibrinogen and C-reactive protein (CRP) dosage were performed at admission. Brain natriuretic peptide BNP was determined at admission and each day during hospitalization. Ejection fraction was determined by echocardiography within 48 hours from admission.

**Results:** An elevation of GGT activity (>50 U/L) was found in 105 (8%) patients at admission. This group of subjects had also higher fibrinogen (322±5 vs 133.9 ± 289.7±92.1 mg/dL, P<0.001), CRP (4.2±6.8 vs 1.8±3.4 mg/dL, P<0.001), basal BNP (414.6±631.7 vs 298.4±18.4 ng/mL, P=0.04) and peak BNP levels (888.9±1400.7 vs 555.7±827.7 ng/mL, P<0.0005). A significantly lower ejection fraction was also found in these patients (42.0±10.5 vs 44.5±6.7%, P<0.01). At logistic regression analysis basal BNP activity resulted an independent predictor of in-hospital mortality (OR: 0.986; CI 0.976-0.996; P<0.01).

**Conclusions:** Elevated GGT activity is associated with a higher degree of inflammation, neuroendocrine activation, myocardial dysfunction and in-hospital mortality in patients with STEMI. Further studies are needed to clarify whether GGT activity may be useful in predicting the development of adverse cardiac events and mortality in STEMI patients.

**UPDATING ON CORONARY SPASM AND MICROVASCULAR DYSFUNCTION**

P4489 Predictive incremental value of combination of inflammatory cytokines (IL-6,IL-10,MIG) on impaired ventricular function at discharge and on 6-month mortality after ST-elevation myocardial infarction

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**Objective:** We investigated the ability to predict left ventricular (LV) dysfunction at discharge and fatal events at 6 months of single inflammatory cytokine and combination of cytokines measured in patients with ST-elevation acute myocardial infarction (STEMI), as first cardiovascular manifestation.

**Methods:** We studied 205 patients with STEMI and selected from the multi-ethnic First Acute Myocardial Infarction (FAMI) Study (1099 cases), that enrolled patients from urban area of Italy, Scotland and China. We assessed inflammatory genes measuring 14 cytokines (IL6, IL8, IL10, CRP,FAS-L, GM-CSF, VEGF, IL8, IP10, MCP, MIG, MIP1a, MIP1b, and eotaxin) in blood obtained before reperfusion within 6 hours from symptoms onset. We had available echocardiographic estimates of LV ejection fraction (EF) at discharge data on 113 (55%) patients and complete 6-month follow-up mortality.

**Results:** At discharge 32/113 patients (28%) had LVEF below 50%, and at 6 months 12/205 patients (5.8%) were dead. We used Receiver Operating Characteristic (ROC) curves to assess the predictive value of single cytokines and combination of cytokines in patients with STEMI, compared with single inflammatory cytokine.

**Conclusion:** The combination of IL10, MIG and IL6 showed an incremental predictive value for LVEF impairment at discharge and 6-month mortality after STEMI, compared with single inflammatory cytokine.

**UPDATE ON CORONARY SPASM AND MICROVASCULAR DYSFUNCTION**

P4490 The area of microvascular obstruction after acute myocardial infarction is determined mainly by infarct size and reduced clot permeability

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**Purpose:** The epicardial thrombus burden and distal macro- and microembolization are associated with perfusion deterioration during acute phase of ST-segment elevation myocardial infarction (STEMI) but their influence on microvascular obstruction remains poorly understood. We sought to investigate the quantitative impact of ex vivo measured fibrin clot properties and platelet function on microvascular obstruction (MVO) territory after primary coronary intervention (PCI).

**Methods:** Plasma clot permeability (Ks) was determined as clot size and clot susceptibility to lysis in assays using exogenous thrombin (t50%, min) were respectively assessed in 108 STEMI patients on admission (ADM) and 4 months after PCI (MA) whereas platelet aggregation after stimulation with 5 μM of adenosine diphosphate (ADP, %) and platelet-monocyte aggregates (PMA, %) were measured on admission (ADM) and 4 days (D4) after PCI. The MVO (expressed as % of infarct size) and infarct size were calculated as % of left ventricular mass. ADP and PMA activity were determined by magnetic resonance imaging performed 2-4 days after STEMI.

**Results:** During acute phase of STEMI pore size of fibrin clot was lower by 28% (5.6 ± 7.1 μm, P<0.001) and clot lysis time was 49% by 20% (10.7 vs 8.9 min, P<0.0001) as compared to follow-up measurements. The area of MVO was correlated with infarct size (r=0.67, P<0.0001), Ks-ADP (r=0.58, P<0.0001), epicardial blood flow after PCI measured by TIMI scale (r=0.33, P<0.001) and PMA aggregation (r=0.28, P<0.019). All clinical variables that showed the association (p<0.05) were also included in the model. The strongest independent predictor of MVO territory was infarct size (r=0.67, 27.2% of variance, P<0.0001).
Prevalence of microvascular obstruction after primary percutaneous coronary intervention is higher in male patients with hypogonadism


**Background:** Testosterone deficiency afflicts approximately 30% of Men aged from 40-79 years. Recent studies claimed that androgen deficiency contributes to the onset and progression of cardiovascular disease. Microvascular obstruction (MO) is a common event associated with a worse prognosis and unfavorable left ventricular remodeling after primary percutaneous coronary intervention (P-PCI). However mechanisms involved in MO have not been fully elucidated yet. We evaluated the importance of gonadal function in the onset of MO.

**Methods:** We studied 54 patients with stable effort angina and known positive EST: 29 patients had angiographically normal coronary arteries (MVA), whereas 25 patients showed significant (>75%) stenosis in >1 epicardial coronary artery (CAD). Patients underwent 2 maximal treadmill ESTs on 2 separate days, in a random sequence, after withdrawing all medications: one EST without any intervention (control EST) and one EST after sublingual administration of isosorbide dinitrate, 5 mg (ISDN-EST). CBF response to nitroglycerin (25 μg/ml) was assessed in only 14 (56%) patients with CAD (p=0.01). At control EST maximal STD was significantly reduced in MVA patients (1.5±0.7 vs. 1.3±0.4, p=0.01, respectively). In MVA patients, rate-pressure product (RPP) at 1 mm STD at ISDN-EST and at the control EST was 2129±5438 and 208±18428 bpm·mmHg, respectively (p=0.05); the same RPP values in CAD patients were 2260±5014 and 2073±6091 bpm·mmHg, respectively (p=0.03). In MVA patients, time to 1 mm STD at ISDN-EST and at the control EST was 308±160 and 284±136 s, respectively (p=0.19); the same values in CAD patients were 474±112 and 367±163 s, respectively (p=0.01). CBF response to NTG was significantly lower in MVA compared to CAD patients (1.4±0.3 vs. 1.7±0.3; p=0.01); in MVA patients a significant correlation was found between CBF response to NTG and heart rate at STD during ISDN-EST (r=0.4; p=0.04).

**Conclusions:** Among patients with effort angina, short-acting nitrates improve EST results in CAD, but not in MVA patients. A lower NTG-induced microvascular dilation seems to contribute to EST positivity after nitrate administration in patients with MVA.

**Agreement on coronary spasm and microvascular dysfunction**


**Background:** Previous reports showed that the index of microcirculatory resistance (IMR) after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), correlated with infarct size and recovery of left ventricular function. However, the regional differences of IMR have not been well-evaluated.

**Figure 1.** Correlation between IMR and CK-MB AUC in anterior and non-anterior STEMI.
Objective: We investigated the correlation between IMR and infarct size in ante-
rior and non-anterior STEMI.

Method: We investigated 104 patients who underwent successful pPCI for STEMI within 12 hours after onset between April 2009 and March 2011. CK-MB was measured 1, 2, 4, 6, 9, 12, 18, 24, 48, 96 hours after pPCI, and the area under the curve of CK-MB (CK-MB AUC) was calculated as the index of infarct size. We evaluated the IMR as the quantitative index of microvascular dysfunction. After successful pPCI, IMR was measured using a PressureWireTM Certus (St. Jude Medical, USA) at maximal hyperemia.

Result: There was a significant correlation between IMR and infarct size in ante-
orial STEMI. However, this finding was not observed in non-anterior STEMI.

Conclusion: IMR may predict infarct size in only anterior STEMI, but not in non-
anterior STEMI.

P4495

Quantitative analysis of microvascular obstruction is best related to clinical prognosis than clinical markers at a 1 year follow-up: a contrast-enhanced MRI study

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Objectives: To evaluate the clinical prognostic value of a cardiac magnetic res-
sonance (CMR) assessment soon after a first ST-segment elevation myocardial infarction (STEMI).

Background: Clinical factors such as gender, age, blood pressure, heart beat, heart and renal failure have already been described as related to poor clinical prognosis at follow-up. For now, the prognostic value and wording of CMR param-
eters is not well-defined.

Methods: We followed for 1 year up to 168 consecutive patients with a first STEMI treated with primary angioplasty. We performed CMR at day 5±2 and 3 months to assess LV volumes. We used delayed enhancement imaging to assess the infarct size and the presence of MVO. We defined severe MVO as MVO extent being superior to its median value (2.85 gr).

Results: 13 major adverse cardiac events (MACE) including 2 cardiac deaths, 1 nonfatal myocardial infarctions, 8 readmissions for heart failure and/or stroke were documented. In univariate analysis, the MACE was related to age, creatin kinase peak, heart failure, MVO and LV volumes. In a complete multivariate analysis, age (hazard ratio 1.075, p=0.003), end-diastolic LV volume (HR 0.74, p=0.017), end-systolic LV volume (HR 1.046, p=0.039), MVO presence (HR 8.867, p=0.041; Log rank = 9.195, p=0.002) and severe MVO (HR 8.906, p=0.002; Log rank = 18.090, p=0.001) were the only independent prognostic variables. Of note, clinical marker such as heart failure was strongly related to age and found as non significant in multivariate analysis.

Conclusion: A comprehensive CMR assessment is useful for stratifying risk soon after STEMI; baseline LV volumes and severe MVO are the stronger inde-
pendent prognosis factor. This result supports the clinical interest of a quantitative assessment of MVO.

P4496

Coronary microvascular function is impaired in diabetic patients with normal coronary arteries and correlates to renal function

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Purpose: Endothelial dysfunction is thought to represent a common pathogenetic mechanism of impaired coronary flow reserve (CFR) and renal dysfunction in pa-
patients with type 2 diabetes mellitus (DM), yet no data are available on the relation-
ship between CFR and renal function in these patients.

Methods: In the same day, while off drugs, we studied endothelial-dependent, during cold pressure test (CPT), and independent (diprydamole infusion (Dip) 0.84 mg/kg over 6 minutes) CFR using transfronar Doppler echocardiography of the left descending coronary artery in 23 DM (12 men; age 62±10) and 25 non DM patients (17 men; age 61±10), matched for all other cardiovascular risk factors. Glomerular filtration rate (GFR) was estimated by Cockcroft Gault formula in the same day of CFR studies. All patients had no significant coronary artery disease (CAD) at invasive coronary angiography performed within 7 days from CFR.

Results: CPT-CFR (1.46±0.26 in DM vs 1.70±0.33 in non-DM; p=0.007) and Dip-CFR (2.38±0.74 in DM vs 2.76±0.04 in non DM; p=0.04) were significantly lower in DM patients. GFR did not statistically differ between DM and non DM patients (85±28 vs 86±25 ml/min/1.73m², respectively; p=0.96) with 42% of pa-
patients in class I and 58% in class II-III renal dysfunction. In DM patients a significant direct correlation was found between GFR and CPT-CFR (r=0.55; p=0.007), but not between GFR and Dip-CFR. In DM patients with GFR above the median (75 ml/min/1.73m²) CPT-CFR was significantly higher (1.52±0.19) than in DM patients with GFR below the median (1.33±0.20; p=0.03), whereas no dif-
fERENCE was found for Dip-CFR (2.48±0.75 vs 2.30±0.70; p=0.57). Moreover, a weak significant correlation was found between fasting glycemia and CPT-CFR (r=0.34; p=0.016) but not with Dip-CFR.

Conclusion: In DM patients without epicardial coronary stenosis microvascu-
lar function is significantly impaired compared to non DM patients with similar risk factors. However, only endothelial dependent CFR significantly correlates to GFR. These findings support the role of endothelial dysfunction as common pathogenic mechanism of renal and myocardial dysfunction in DM patients.
artery disease who underwent the ACh test were enrolled between November 2004 and October 2010. The pts were divided into two groups according to MB (MB group: n=367, control group: n=1027).

Results: At baseline characteristics, the pts with MB had higher incidence of old age (53.3±11.6 vs 55.6±11.5, p<0.0168), male gender (59.9% vs 46.8%, p<0.0002), and hypertension (13.6% vs 16.3%, p=0.0408) than the pts in control group. At ACh provocation test, the pts with MB had higher incidence of ACh induced CAS, multivessel and diffuse spasm than the pts in control group (Table 1). Multivariate analysis showed that MB was a predictor of ACh-induced CAS, multivessel and diffuse spasm. However, at 12 month clinical outcomes, there were no significant differences between the two groups.

Table 1. 12 months clinical outcomes

<table>
<thead>
<tr>
<th>MB (n=367)</th>
<th>Control (n=1027)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE</td>
<td>5 (1.4)</td>
<td>8 (0.7)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (0.2)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>MI</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>PTCA</td>
<td>2 (0.5)</td>
<td>6 (0.5)</td>
</tr>
<tr>
<td>CVa</td>
<td>2 (0.5)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

Conclusion: In this study, MB was associated with ACh induced CAS, and multivessel and diffuse spasm. But MB was not associated with the 12-months clinical outcomes.

Impact of alcohol on coronary artery spasm as assessed with intracoronary acetylcholine provocation test

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Background: There are limited data regarding impact of chronic alcohol use on coronary artery spasm. We evaluated the impact of alcohol use on coronary artery spasm (CAS) as assessed with intracoronary acetylcholine (ACh) provocation test.

Methods: A total 3034 consecutive patients (pts, Men 1457 (48.0%), mean age 54.5±12.4 years who underwent coronary angiography with ACh provocation test were enrolled. Study population were divided into current alcoholic (912, 30.1%) vs. non-alcoholic (2101, 69.2%) groups. Significant CAS was defined as transient >70% luminal narrowing with chest pain and/or ST segment changes.

Results: Baseline clinical characteristics were balanced except non alcoholic had more hypertension (49.3% vs. 40.4%, P<0.001), diabetes (13.6% vs 12.2%, P=0.09), peripheral vascular disease (6.3% vs 3.2%, P=0.001), history of CVA (3.5% vs 2.1%, P=0.04), congestive heart failure (2.0% vs 0.5%, P=0.004) whereas alcoholic group were mostly men (76.5% vs 35.8%, P<0.001) and had more current smokers (42.8% vs 13.6%, P<0.001). Although the alcoholic group showed higher multivessel, severe coronary narrowing on QCA on univariate analysis, however, after adjusting the baseline differences, all clinical and angiographic parameters of ACh provocation test were not different between the two groups (Table 1).

Table 1. Comparison of current alcohol use vs non-alcohol use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Current Alcohol Use (n=2101)</th>
<th>Non-Alcohol Use (n=912)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE</td>
<td>5 (2.4)</td>
<td>8 (0.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (0.5)</td>
<td>3 (0.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>MI</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>PTCA</td>
<td>2 (0.5)</td>
<td>6 (0.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>CVa</td>
<td>2 (0.5)</td>
<td>2 (0.1)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Conclusion: In our study, current alcohol use was not associated with clinical and angiographic characteristics of CAS as assessed with ACh provocation test.
WKY hearts (34.5±2.3 vs 27.7±1.6, N=10-18, P<0.03), but not in SHR-SP hearts. Following exd, Akt-P was increased by 22% in exd-treated WKY, but not SHR-SP hearts snap-frozen after 3 min of reperfusion. Akt-P appeared reduced by approximately 50% in SHR-SP hearts with or without exd-treatment.

Discussion: These data suggest that hypertensive LVH might be associated with a loss of efficacy of exd postconditioning, as shown earlier for erythropoietin [3] and ischemic [4] preconditioning. Insufficient Akt-mediated signaling might contribute to this impairment.


**P4502**

Impact of ischemic postconditioning in acute myocardial infarction patients with preconditioning

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Background: Both ischemic preconditioning and postconditioning have been found to reduce myocardial damage in acute myocardial infarction (AMI). However, in animal models of ischemia and reperfusion, additive cardioprotective effects by ischemic preconditioning and postconditioning were unexpectedly uncontradicted. The present study aimed to determine whether postconditioning would provide more powerful cardioprotection in AMI patients with prodromal angina.

Method: The consecutive 82 AMI patients with single vessel occlusion, gained successful reperfusion, were recruited. Twenty-eight patients with postconditioning underwent a 60s inflation and 30s deflation of the angioplasty balloon repeated four times (PoC(+)). Both PoC(+) and PoC(−) groups were subdivided into two groups, with prodromal angina (PA(+)) and without (PA(−)). Creatine kinase-MB (CK-MB) were determined serially every 4 hours 24 hours after AMI onset. The consecutive 82 AMI patients with single vessel occlusion, gained successful reperfusion, were recruited. Twenty-eight patients with postconditioning underwent a 60s inflation and 30s deflation of the angioplasty balloon repeated four times (PoC(+)). Both PoC(+) and PoC(−) groups were subdivided into two groups, with prodromal angina (PA(+)) and without (PA(−)). Creatine kinase-MB (CK-MB) were determined serially every 4 hours 24 hours after AMI onset. The 99mTc-tetrofosmin (Tetrofosmin) and 123I-BMIPP (BMIPP) SPECT were performed within 7 days of the onset. We evaluated area at risk with BMIPP and calculated salvage ratio from severity scores of Tetrofosmin.

Results: There were no significant differences in age, time to reperfusion, collateral development, left ventricular ejection fraction, and area at risk among four groups. However, the cumulative CK-MB levels in PA(+) groups were significantly smaller than PoC(+) groups (PoC(+) PA(+): 817±489 IU/L, PoC(−) PA(+): 912±528 IU/L, PoC(+) PA(−): 1327±629 IU/L, p<0.05, respectively). Only in the group of PoC(+) PA(+), the salvage ratio was significantly greater than the groups of PoC(−) PA(+), CK-MB reperfusion: 63±13%, PoC(−) PA(+), 52±14%, PoC(+) PA(+), 48±13%, p<0.05, respectively. Surprisingly, in the groups of PoC(+), the incidence of serious reperfusion arrhythmia such as ventricular tachycardia remarkably reduced than the groups of PoC(−) (PoC(+) PA(+): 0%, PoC(−) PA(+): 8%, PoC(+) PA(−): 18%, PoC(−) PA(−): 29%, respectively).

Conclusions: We demonstrated that cardioprotective effects of ischemic postconditioning were significantly and additively enhanced in AMI patients with prodromal angina, opposite to previous experimental studies of animal models.

**P4504**

Effect of hydrogen gas inhalation on lipid metabolism and left ventricular remodeling induced by intermittent hypoxia in mice

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Background: Intermittent hypoxia (IH) relevant to sleep apnea syndrome (SAS) produces reactive oxygen species and increases cardiovascular events. Among others hydrogen radicals are highly toxic for cellular proteins and ribonucleic acids, and might affect lipid metabolism. Recently, hydrogen (H2) gas has been reported to scavenge hydroxyl radicals in rat model of cerebral infarction. The aim of this study was to examine the dyslipidemia and cardiac remodeling induced by IH in mice and to evaluate the efficacy of hydrogen gas inhalation as a novel therapeutic strategy.

Methods: Male C57BL/6J mice at 8 week of age (n = 60) were exposed to IH (repetitive cycle of 1-min periods of 5 and 21% oxygen for 8 h during daytime) for 7 days. H2 gas (1.3 v%) was given either at the time of reoxygenation, during hypoxic conditions, or throughout the experimental period. Plasma lipoproteins were analyzed using a high-performance liquid chromatography system. The heart was excised for light and electron microscopic examination, immunohistochemistry, and RT-PCR.

Results: IH significantly increased plasma levels of low- and very low-density cholesterol lipoproteins (Figure). Cardiac cross-sectional area, cardiomyocyte diameter, and percentage of perivascular fibrosis were significantly increased by IH. Further 6H-1H and the expression of TNF-α, IL-6, and BNP mRNA were significantly increased in the left ventricular (LV) myocardium.

Conclusion: H2 gas inhalation attenuated the dyslipidemia and the development of IH-induced LV remodeling at least partly through the suppression of oxidative stress. Inhalation of H2 gas during hospitalization might be potentially useful for preventing cardiovascular events in patients with SAS.

**P4503**

Second window and chronic remote ischemic preconditioning prevent endothelial injury by ischemia-reperfusion in humans

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Purpose: Remote ischemic preconditioning (RIC) by 3 times 5-minutes upper arm ischemia and reperfusion, repetitive cycle of 1-min periods of 5 and 21% oxygen for 8 h during daytime) for 7 days. H2 gas (1.3 v%) was given either at the time of reoxygenation, during hypoxic conditions, or throughout the experimental period. Plasma lipoproteins were analyzed using a high-performance liquid chromatography system. The heart was excised for light and electron microscopic examination, immunohistochemistry, and RT-PCR.

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Results: There were no significant differences in age, time to reperfusion, collateral development, left ventricular ejection fraction, and area at risk among four groups. However, the cumulative CK-MB levels in PA(+) groups were significantly smaller than PoC(+) groups (PoC(+) PA(−): 817±489 IU/L, PoC(−) PA(−): 912±528 IU/L, PoC(+) PA(+): 1327±629 IU/L, p<0.05, respectively). Only in the group of PoC(+) PA(+), the salvage ratio was significantly greater than the groups of PoC(−) PA(+), CK-MB reperfusion: 63±13%, PoC(−) PA(+), 52±14%, PoC(+) PA(+), 48±13%, p<0.05, respectively. Surprisingly, in the groups of PoC(+), the incidence of serious reperfusion arrhythmia such as ventricular tachycardia remarkably reduced than the groups of PoC(−) (PoC(+) PA(+): 0%, PoC(−) PA(+): 8%, PoC(+) PA(−): 18%, PoC(−) PA(−): 29%, respectively).

Conclusions: We demonstrated that cardioprotective effects of ischemic postconditioning were significantly and additively enhanced in AMI patients with prodromal angina, opposite to previous experimental studies of animal models.

**P4505**

APE1/Ref-1 decreases ROS generation and myocardial infarction in a mouse model of acute myocardial infarction

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Background: Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref-1) is involved in DNA base excision repair. It also controls the intracellular reactive oxygen species (ROS) production and has anti-inflammatory function against the vascular endothelial activation. To investigate the relationship between APE1/Ref-1 and cardiac cell death with apoptosis, we examined the expression of APE1/Ref-1 in a mouse model of myocardial infarction (MI).

Methods: Male (C57Bl/6J) MI models were created by ligation of the left anterior descending coronary artery. Expression of the APE1/Ref-1 protein was evaluated by Western blot. Immunohistochemistry was used for analysis of apoptosis in vivo.

Results: APE1/Ref-1 was significantly increased after MI at one week (4 folds compared to control, p<0.01) sustained until 4 weeks. To confirm the beneficial role of APE1/Ref-1 we made MI and randomly injected adeno-APE1/Ref-1 virus or null virus into the myocardium. APE1/Ref-1 injection group revealed decreased myocardial infarction size compared to control group (22.7% vs 45.8%, p<0.01) at 4 weeks later. Immunohistochemistry showed that decreased ROS generation and decreased apoptosis in the APE1/Ref-1 injection group 1 week after MI.

Conclusions: APE1/Ref-1 was significantly increased in a mouse MI model. Inhibiting APE1/Ref-1 decreased myocardial infarction size, ROS generation and apoptosis. These novel findings suggest that APE1/Ref-1 may be possible as a biomarker and has therapeutic potential for myocardial infarction.
Effect of sildenafil on mitochondria in rat myocardial infarction model - morphological and property changes utilizing atomic force microscopy


Objectives: Many studies showed that sildenafil have cardioprotective effects mediated by nitric oxide and ischemic preconditioning. Mitochondria play critical roles in both the life and death of cardiac myocytes. We tested whether sildenafil could make rat hearts resistant to infarction through mitochondrial protection using atomic force microscopy (AFM).

Methods: To prove the cardiac protective effect of sildenafil and investigate the morphologic and property analysis of mitochondria by AFM in the rat myocardium, in-vivo myocardial infarction (MI) model were used. Rat hearts were subjected to 40 min local ischemia by ligation of the left anterior descending (LAD) coronary artery and examined infarct size after 5 days of reperfusion. Isolated mitochondria were dropped onto a mica surface and AFM imaging was performed using the non-contact mode of NANOS N8 NENG (Bruker, Herzogenrath, Germany). The effect of sildenafil on myocardial protection was assessed by TTG staining, TUNEL and immunoblot analysis with anti-bax, bcl-2 and caspase-3 antibodies.

Results: Infarct area was significantly reduced in sildenafil-treated rats (7.78±3.9%) vs. 20.37±7.0% in sildenafil and control hearts, respectively, P < 0.001) as in the previous studies. Thus a relative reduction of 62% in the infarcted zone was observed in the sildenafil-treated rats. From the shape parameters of mitochondria in AFM image, it seems that myocardial infarction caused the mitochondrial swelling (1,495±1,139 nm² in normal vs. 24,150±1,289 nm² in MI, p < 0.0001). Whereas sildenafil reduced the mitochondrial area (7,428±3,682 nm² 2, p < 0.0001) by 69.23% compared to that of MI. In addition, sildenafil-mediated cardioprotection was associated with mitochondrial KATP channel.

Conclusions: In MI rat model, cardioprotective effect of sildenafil pretreatment associated with a mitochondrial protective mechanism.

DIASTOLIC DYSFUNCTION: EPIDEMIOLOGY AND MECHANISM

Prevalence and incidence of myocardial dysfunction and chronic heart failure in the patients with type 1 diabetes: a 7-year prospective cohort study

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Prevalence and incidence of myocardial dysfunction (MD) and heart failure (HF) in type 1 diabetic patients (T1DP) still remains still unresolved issue.

Objective: To evaluate the prevalence and incidence of MD and HF in long lasting (over 10 years) type 1 diabetes (T1DM) without cardiovascular disorders or with hypertension and/or coronary disease (CHD). Research design and Methods:1617 T1DP (baseline: mean age 51 years, mean diabetes duration 35 years) following initial evaluation (clinical symptoms, echocardiography,NT-pro BNP levels), underwent a 7 year follow up in terms of MD, HF (its diastolic and systolic manifestations).

Results: Baseline prevalence of HF amounted to 3.7% in the entire study group,whereas the incidence was 0.02% per year. The baseline prevalence of MD was 16.3% and the incidence was 0.26% per year. MD and HF was observed only in hypertensive and/or coronary patients. Baseline diastolic HF subjects accounted for 84.6% of all HF population, whereas the systolic HF diabetic patients accounted for 15.3% of all HF subjects. For both genders the HF incidence dropped onto a mica surface and AFM imaging was performed using the non-contact mode of NANOS N8 NENG (Bruker, Herzogenrath, Germany). The effect of sildenafil on myocardial protection was assessed by TTG staining, TUNEL and immunoblot analysis with anti-bax, bcl-2 and caspase-3 antibodies.

Results: Infarct area was significantly reduced in sildenafil-treated rats (7.78±3.9%) vs. 20.37±7.0% in sildenafil and control hearts, respectively, P < 0.001) as in the previous studies. Thus a relative reduction of 62% in the infarcted zone was observed in the sildenafil-treated rats. From the shape parameters of mitochondria in AFM image, it seems that myocardial infarction caused the mitochondrial swelling (1,495±1,139 nm² in normal vs. 24,150±1,289 nm² in MI, p < 0.0001). Whereas sildenafil reduced the mitochondrial area (7,428±3,682 nm² 2, p < 0.0001) by 69.23% compared to that of MI. In addition, sildenafil-mediated cardioprotection was associated with mitochondrial KATP channel.

Conclusions: In MI rat model, cardioprotective effect of sildenafil pretreatment associated with a mitochondrial protective mechanism.

Prevalence of increased heart rate, links with clinical status and therapy in outpatients with heart failure with preserved ejection fraction in modern Poland: results of preserved-DATA-HELP study

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Wrocław Medical University, Department of Heart Diseases, Wrocław, Poland; 1Merck, Warsaw, Poland; 2Centre for Heart Diseases, Military Hospital, Wołów, Poland

Background: Increased resting heart rate (HR) is an important cardiovascular (CV) risk factor and a potentially novel target therapy in subjects with a broad spectrum of CV disease, including those with heart failure (HF). The scope of this problem remains enigmatic in patients with HF with preserved ejection fraction (HFPEF).

Methods: Registry DATA-HELP was performed in X-XII 2009 in Poland in a representative sample of outpatients with systolic HF, whereas Preserved-DATA-HELP substudy investigated 663 outpatients with HFPEF, among whom resting HR was available in 654 subjects (99%).

Results: We analysed 488 patients with HFPEF in a sinus rhythm (74% of the whole cohort) (age: 67±1 y, BMI: 28.5±4.9 kg/m², men: 46%, systolic BP: 136±18 mmHg, NYHA class III-IV: 17%, CCS class III-IV: 15%, previous MI: 45%, hypertension: 75%; diabetes: 32%; previous TIA/stroke: 15%; COPD: 9%). In this cohort, the mean±SD of resting HR was 75±12 bpm, median with lower and upper quartiles 75 (68-80) bpm. HR >70 bpm and >75 bpm were found in 71% and 51% of patients, respectively, and these frequencies did not differ across NYHA classes (p=0.2). In a multivariable stepwise regression model, high HR was associated with higher systolic BP (p<0.001), presence of pulmonary congestion (p<0.01) and haemoptoamly (p<0.001), less advanced CCS class (p<0.01), female gender (p<0.05), younger age (p<0.05). Patients with HFPEF were treated with the following drugs: ACE inhibitor and/or angiotensin receptor blocker (59%), aldosterone antagonist (33%), ß-blocker (96%); in those receiving ß-blockers – 61% bisoprolol, 20% carvedilol, 16% metoprolol, 2% nebivolol, 1% others), calcium channel blocker (36%), digoxin (4%), loop diuretic (42%), thiazide diuretic (31%), statin (84%), antiplatelets (81%). Higher HR was found in those receiving vs not receiving loop diuretics (p<0.05) and digoxin (p<0.05), which reflected the advanced stage of HF. There were no differences in HR between those treated vs not treated with ß-blockers, and between those treated with-
fent β-blockers (all p<0.2). There were no associations between HR and daily doses of β-blockers, investigated separately in subgroups of patients receiving the particular β-blocker (all p<0.2).

Conclusion: Increased HR is common in patients with HIFPEF, regardless of NYHA class. There is no association between the most common HR reducing therapy (β-blockade) and resting HR among these patients. There is a substantial group of patients with HIFPEF in whom the classification of β-blockade on and the introduction of other HR reducing strategies could be considered.

**Relation between diastolic function in rest and during stress and peak exercise capacity among heart transplant recipients**

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Purpose: Several studies have shown that diastolic dysfunction impairs exercise capacity despite normal left ventricular ejection fraction (LVEF). This may also be a contributing factor in the limited physical performance of heart transplant recipients (HTX). We studied whether diastolic dysfunction at rest and during exercise is related to exercise capacity and the ability to improve exercise capacity after training intervention.

Methods: 23 stable HTX patients (mean age 50±14.8 years) with normal LVEF underwent maximum bicycle exercise test and semi supine exercise stress echocardiography. 13 patients underwent 6 weeks arterial interval training and had echocardiography and exercise test repeated. Standard resting echocardiography included pulsed Doppler LV inflow at apical 4 chamber (A, E, dec. time) and pulsed TDI (E' calculated as mean of lateral, septal, anterior and posterior corner of mitral annulus). Acquisitions were repeated at 30% and 60% of maximum workload and during recovery.

Conclusion: VO2peak increased from (mean ± sd): 23.8±7.0 to 28.3±6.4 ml/kg/min (p<0.001) after training. Only few of the patients exhibited diastolic dysfunction at rest, but during stress echocardiography E/E' increased and deceleration time decreased, unmasking sign of diastolic dysfunction. Diastolic dysfunction during rest and stress or the change in diastolic measures from rest to 60% did not predict workload at VO2peak at baseline or improvement in VO2peak.

Conclusions: In contrast to previous studies of other cardiac patients, we found no correlation between diastolic dysfunction in rest and during stress echocardiography and VO2peak or improvement in VO2peak after 6 weeks arterial interval training in heart transplant patients. Diastolic dysfunction may not be a limiting factor for exercise capacity when chronotropic response is impaired.

Abstract P5152 – Table 1. Measures of diastolic function at rest and during stress and their correlation with baseline VO2peak and improvement in VO2peak.

<table>
<thead>
<tr>
<th>Measure</th>
<th>VO2peak at baseline</th>
<th>Improvement in VO2peak</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>Improvement at VO2peak</td>
<td>Improvement at VO2peak</td>
<td>Improvement at VO2peak</td>
</tr>
<tr>
<td>E/e'</td>
<td>0.17 (0.43)</td>
<td>0.04 (0.90)</td>
<td>0.17 (0.43)</td>
</tr>
<tr>
<td>A wave</td>
<td>0.2 ± 0.3</td>
<td>0.17 (0.51)</td>
<td>0.34 (0.99)</td>
</tr>
<tr>
<td>E' wave</td>
<td>0.2 ± 0.3</td>
<td>0.17 (0.51)</td>
<td>0.34 (0.99)</td>
</tr>
</tbody>
</table>

VO2peak: VO2peak at VO2peak at baseline.
The association between computed tomography-derived three-dimensional pericardial adipose burden, cardiac structural alteration and diastolic dysfunction

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Purpose: Pericardial adipose tissue had been shown to exert their local effect on adjacent cardiac structures. However, data regarding three-dimensional volume measurements of such visceral adipose burden on myocardial diastolic function remained largely unknown.

Methods: We consecutively assessed pericardial fat tissue (PCF) by volume-based three-dimensional measure utilizing computed tomography (Aquarius 3D Workstation, TeraRecon, San Mateo, CA, USA) from 286 subjects after exclusion of decompensated heart failure. Diastolic parameters including left atrial (LA) diameter, early mitral inflow velocity (E), early to late-inflow ratio (E/A), isovolumetric relaxation time (IVRT), and high frame-rate tissue Doppler imaging (TDI) including lateral mitral annulus systolic (E') and early diastolic (E') velocities were all obtained. Left-sided filling pressure was estimated by E/E' ratio.

Results: Of all 286 subjects (mean age: 53.5 years, 31% female) enrolled, 81 (35.8%) had hypertension and 29 (12.9%) had diabetes with an average PCF volume of 81.4 ml. Univariate analysis showed that prolonged IVRT, reduced E’, and high frame-rate tissue Doppler imaging (TDI) including lateral mitral annulus systolic (E’) and early diastolic (E’) velocities were all independently associated with impaired diastolic function, leading to left atrial dilation and elevated filling pressures. Our study suggested the possible link between excessive pericardial fat accumulation, altered cardiac geometry and diastolic dysfunction.

Conclusion: Increasing pericardial visceral burden was independently associated with impaired diastolic function, leading to left atrial dilation and elevated filling pressures. Our study suggested the possible link between excessive pericardial fat accumulation, altered cardiac geometry and diastolic dysfunction.

A risk-factor based porcine model of heart failure with preserved ejection fraction (HFPEF)

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Background: Heart failure with preserved ejection fraction (HFPEF) results from the accumulation of cardiovascular risk factors. So far, no clearly effective treatment for HFPEF could be established, which in part relates to the lack of suitable animal models. We aimed to model HFPEF in pigs by induced hypertension and western diet.

Methods/Results: Eight landrace pigs were implanted with subcutaneous 90 day release DOCA pellets (an aldosterone analog), and subsequently fed a high salt/high lipids/high sugar diet for 90 days (DOCA). Eight weight-matched pigs (no DOCA, regular diet) served as controls. After 90 days, tail-cuff systolic blood pressure during light sedation was 138 ± 11 mmHg in DOCA vs 95 ± 6 mmHg in control (p < 0.05). Echocardiography demonstrated pronounced concentric hypertrophy in DOCA. LV function was assessed during deep anaesthesia by pressure-volume (PV) analysis. In DOCA vs control, baseline cardiac output (6.0 ± 0.2 vs 6.6 ± 0.5 l/min) and heart rate (95 ± 5 vs 84 ± 6 bpm) were not different, while LV ejection fraction (68 ± 3 vs 51 ± 3%) was higher (p < 0.05). The end-systolic and end-diastolic PV relationships (ESPVR and EDPVR) were markedly shifted leftwards in DOCA (see graph). Right atrial pacing both at baseline and during low-dose dobutamine infusion (2.5 μg/kg/h) revealed a lower increase of cardiac output in DOCA.

Conclusion: This risk factor based animal model for the first time reproduces two major characteristics of HFPEF: (i) a leftward shift of the ESPVR and EDPVR and (ii) a limited cardiac reserve.

The relation between left atrial systolic function and left ventricular performance in heart failure with preserved ejection fraction

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Background: Clinical features of heart failure with preserved EF (HFPEF) have not been well characterized. It is reported that peak atrial systolic mitral annular velocity (A’x) predicts left atrial (LA) systolic function. The aim of the present study was to investigate the relation between LA systolic function and left ventricular (LV) performance in HFPEF.

Methods: Out of 327 patients who presented to the emergency department because of acute pulmonary congestion during the last 5 years, those with EF > 50% upon admission comprised the HFPEF patients (n=56) were enrolled in this study.
Patients with atrial fibrillation or mitral valvular disease were excluded in this study. A control group (Gr-C) consisted of consecutive 30 hypertensive patients with EF of >50%. We recorded tissue Doppler-derived peak early diastolic and atrial systolic velocities (E' and A', respectively) in the chronic stage. Other echo parameters (LA diameter (LAD) and LV diastolic volume (LVDd) and E/E') were measured at the same time. The HFPEF patients, A and E were the lowest and E/E', LAD and LVDd were the highest in Gr-P (table).

Results: EF was correlated with A' (r=0.246, p=0.022). Radial dyssynchrony was detected in 12% of patients at rest which increased to 15% on exercise. E/E' was correlated with A' (y=10.92-0.24x (r=-0.4609, p=0.0069)) in the HFPEF patients. A' and E' were the lowest and E/E', LAD and LVDd were the highest in Gr-P (table).

Conclusion: The progression of LA systolic dysfunction was associated with the impairment of LV diastolic function and may play an important role in the pathogenesis of HFPEF.

**P4518**

**Radial ventricular dyssynchrony on exercise in patients with heart failure and normal ejection fraction**


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**Background:** Longitudinal dyssynchrony has been shown in patients with heart failure and normal ejection fraction (HFNEF). We hypothesised that radial dyssynchrony may also be present in these patients on exercise and contribute to LV dysfunction.

**Methods:** We studied 57 patients with the clinical diagnosis of HFNEF (39 female, age 73 ±7 years, EF 61 ±6%) and 30 healthy controls (23 female, age 70 ±7 years, EF 62 ±7%). All underwent echocardiography at rest and on supine exercise. Images were acquired and analysed off-line. Radial strain and time to peak radial strain in a six segments model were studied. Standard deviation for six radial segments was calculated (SDradial) to assess segmental radial dyssynchrony. A cut-off of 24.6 ms at rest and 18.6 ms on exercise (mean ±2SD of controls) were used to diagnose dysynchrony.

**Results:** Radial strain was comparable at rest (44.0 ±15.1% versus 48.2 ±11.2%, p=0.191) but significantly lower in patients on exercise (49.6 ±14.2% versus 58.0 ±6.0%, p=0.008). SDradial was also comparable at rest (14.1 ±13.2 ms versus 10.5 ±7.0 ms, p=0.150). Controls achieved significant reduction in SDradial on exercise (8.4 ±5.1 ms) which was not seen in patients (13.5 ±9.5 ms) (p=0.008). Radial dyssynchrony was detected in 12% of patients at rest which increased to 29% patients on exercise. SDradial on exercise correlated with Radial strain on exercise (r=-0.248, p=0.022).

**Conclusion:** HFNEF is associated with LV radial dysfunction and dysynchrony as well as longitudinal particularly on exercise and which is not present at rest. This disorganisation of ventricular function may underlie their exertional breathlessness.

**P4519**

**Prognostic significance of calibrated integrated backscatter in patients with heart failure and preserved ejection fraction**

B. D Here1, D. Stepienowski1, C. Vallet1, B. Kurtz1, V. Richard2, J.N. Dacher1, H. Eltchaninoff1, F. Bauer1. 1. University Hospital of Rouen - Hospital Charles Nicolle, Rouen, France; 2. INSERM U1036 Rouen University Medical School, Rouen, France

**Introduction:** Calibrated integrated backscatter (CIB), a surrogate for myocardial fibrosis, is deteriorated in hypertrophic, ischemic cardiomyopathy or in systolic heart failure (HF). Whether CIB may differentiate patients with heart failure and preserved ejection fraction (HFPEF) at risk of death or HF reoccurrence has never been investigated.

**Methods:** 35 patients admitted for HFPEF (Framingham criteria, EF >50% and BNP level >100 pg/ml) were imaged by echocardiography 2 months following an acute decompensation. We measured left ventricular function, atrial dimensions and calibrated Integrated Backscatter (CIB) which was obtained from parasternal long axis by subtracting pericardial CIB intensity from myocardial CIB intensity of the LV anterosetal and posterior walls (figure). Measurements of calibrated CIB, expressed in decibels, were performed at QRS complex onset. The primary endpoint was the occurrence of death or hospitalization for HF at 10-month FU.

**Results:** 10 patients reached the primary endpoint (3 deaths and 7 hospitalizations for HF). In this group at risk, patients had more chronic obstructive pulmonary disease (p=0.03) and coronary artery bypass (p=0.008). Despite similar EF (57.3 ±7.3% vs. 60.4 ±9.7%), we observed larger left atrial diameter (49.7 ±6.9 mm vs. 44.7 ±6.4 mm, p=0.050) and area (28.6 ±6.2 cm² vs. 24.5 ±5.1 cm², p=0.044) in patients with endpoint vs. no endpoint. Patients with clinical endpoint showed more anteroseptal and posterior wall myocardial ultrasound reflectivity (-12.3 ±6 dB vs. -22.7 ±8.1 dB, p=0.0024 and -14.9 ±6.1 vs. -21.1 ±8.0 dB, p=0.031) as compared with event-free patients.

**Conclusions:** LV but not RV myocardial relaxation deteriorate during follow up in patients with systemic sclerosis

M. Cizynska1, P. Bienias1, K. Izyk2, K. Kurkiewicz1, B. Lichodziejewska1, M. Kostrubiec1, Z. Rymanczyk1, A. Szewczyk2, M. Siwicka2, P. Pruszczyk1. 1. Medical University of Warsaw, Department of Internal Medicine and Cardiology, Warsaw, Poland; 2. Medical University of Warsaw, Department of Dermatology, Warsaw, Poland Systemic sclerosis (SSc) is characterized by vascular changes and fibrosis of the skin and internal organs. There are limited data on left (LV) and right ventricular (RV) diastolic function in SSc patients particularly in follow up and their relations to parameters of collagen metabolism.

**Purpose:** To analyze LV and RV diastolic function during follow up in patients with SSc and its relation to serum TIMP 1 (tissue inhibitor of metalloproteinase 1) levels, a biomarker of matrix remodeling.

**Methods:** We prospectively studied 69 consecutive pts (64F, 5M mean age 55.5 ±13.8 yrs) with SSc (mean SSc duration 9 ±12.4 yrs) at baseline and after at least 1 year of follow up (3 ±1 yrs). TTE (Philips IE 33) for assessment of LV and RV diastolic function was performed. We also measured serum TIMP –1 (Human TIMP-1 immunoassay R&D Systems) levels. At fu we observed significant deterioration of Doppler parameters of LV but no RV diastolic function. Mean TIMP-1 concentration was higher at SSc follow up patients (204 ±167.1 ng/ml, p=0.0001). In SSc fu group TIMP-1 correlated positively to mitral lateral and septal E/E' (r=0.4, p=0.0019 and r=0.32, p=0.01), and negatively to early diastolic atrial flow.

**LV and RV diastolic function in SSc patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SSc (n=69)</th>
<th>SSc follow-up (n=69)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral E/A</td>
<td>0.99 ±0.3</td>
<td>0.92 ±0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>175.6 ±36.8</td>
<td>198.6 ±36.6</td>
<td>0.001</td>
</tr>
<tr>
<td>PVF A (c/sm)</td>
<td>59.4 ±16.4</td>
<td>63.6 ±16.6</td>
<td>0.03</td>
</tr>
<tr>
<td>S/G</td>
<td>1.21 ±0.28</td>
<td>1.38 ±0.33</td>
<td>0.05</td>
</tr>
<tr>
<td>PVF A (c/sm)</td>
<td>29.5 ±7.4</td>
<td>33.3 ±8.1</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mitral E/E' lateral</td>
<td>7.5 ±3.1</td>
<td>6.9 ±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral E/E' septal</td>
<td>9.47 ±3.3</td>
<td>9.56 ±3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid E/A</td>
<td>1.05 ±0.2</td>
<td>1.02 ±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Tricuspid E/E'</td>
<td>4.75 ±1.5</td>
<td>4.83 ±1.54</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Conclusions:** LV but not RV myocardial relaxation deteriorate during follow up. TIMP-1 is significantly correlated with echocardiographic parameters suggesting a potential link for LV diastolic dysfunction and matrix remodeling in patients with SSc.
Left ventricular torsion during exercise in patients with and without increase in left ventricular filling pressures

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Left ventricular torsion (Tor) is increased in patients (pts) with diastolic dysfunction but little is known about the effect of exercise (Ex) on Tor in them. We aimed to assess Tor during Ex in pts with and without increase in left ventricular filling pressures.

Methods: We studied 132 consecutive pts with normal LV ejection fraction (LVEF)>50%, and normal Ex echocardiography. Speckle imaging was performed at rest (R) and at peak (Pk). Tor was defined as maximal apical rotation – basal rotation (/LV length (cm). Confident tracking assessment was achieved in 107 pts (81%). Volumetric LVEF and the ratios of early transmitral flow /early diastolic flow at the septal mitral annulus waves (E/e') at R and at Pk were also measured. Twenty-six pts had E/e’ratio ≥ 15 (G-HEe) and 81 pts <15 (G-NHe).

Results: G-HEe pts were older (76±9 vs 60±6, p<0.001) and achieved less ME (8±8±3 vs 7.1±1.1, n=0.02). A history of coronary artery disease was equally frequent (8% in G-HEe and 21% in G-NHe, p=0.15). LVEF at R was higher in G-HEe (70±9 vs. 66±8, p=0.04) whereas it was similar at Pk (74±9 vs. 70±11, p=0.05). E/e’values at R were 24±20.3 in G-HEe and 10±2±2.6 in G-NHe (p<0.001), whereas at Pk were 19±8.1±1.1 and 9.1±2.9, respectively (p<0.001). Rotation parameters were similar between groups except for apical rotation which was higher at R and Pk in G-HEe.

Conclusions: The results obtained suggest similar rates of ventricular-arterial uncoupling in hypertensive subjects with HHeF and asympomatic diastolic dysfunction. HHeF is associated with increased arterial stiffness.

P4542

Ventricular-arterial coupling and arterial stiffness in hypertensive subjects with diastolic heart failure

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Objective: To compare ventricular-arterial coupling (Ea/E’Lv) and arterial stiffness indices in hypertensive subjects with and without heart failure with preserved ejection fraction (HFpEF).

Methods: The study included 66 hypertensive patients with stable NYHA class II-III HFpEF (26 male, age 71.8±7.8 years, clinic BP 130±190/80±88 mmHg, EF 61±8%). HFpEF was confirmed by NTproBNP >100 pg/ml (Me 783, min 112 - max 3000 pg/ml). Control group included 20 hypertensive patients (5 male, age 71.3±7.5 years, clinic BP 128±190/80±88 mmHg, EF 61±7% or the combination of both left atrial (LA) dilatation (<3.7 cm) and raised amino-terminal pro-brain natriuretic peptide (NTproBNP) >400 pg/ml). This study aimed to examine the diagnostic utility of the deceleration time of early diastolic velocity by tissue Doppler imaging.

P4545

Deceleration time of early diastolic velocity by tissue Doppler velocity imaging: a novel index of left ventricular end-diastolic pressure

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Purpose: This study aimed to examine the diagnostic utility of the deceleration time (DT) of early diastolic velocity of mitral annulus by tissue Doppler velocity imaging, a method for the assessment of left ventricular end-diastolic pressure.

Methods: Simultaneous left ventricular catheterization and Doppler echocardiography were performed to compare the left ventricular end-diastolic pressure (LVEDP) and DT in 57 patients who were scheduled for diagnostic coronary angiography. They were admitted to our hospital for the assessment of heart disease including cardiomyopathy (n=26) and coronary artery disease (n=31). We excluded the patients with atrial fibrillation and mitral valve disease and who underwent mitral valvular surgery. Color-coded tissue Doppler images were acquired at apical 4 chamber view, and DT of early diastolic velocity measured at mitral annulus were assessed. DT was also evaluated in 15 healthy subjects.

Results: DT is successfully measured in all subjects. DT in the patients with elevated LVEDP (>18mmHg) (69±12ms, n=14) was significantly shorter than those with LVEDP<18mmHg (94±18ms, n=43) and healthy subjects (100±11ms). DT is inversely proportional to LVEDP (r=0.7, p<0.001). With a cut-off value of DT of 80 ms, which was determined by receiver operating characteristic curve, the
Impact of gender difference on the relation between arterial stiffness and left ventricular diastolic function in healthy subjects

M. Saito1, H. Okayama2, H. Higashi1, H. Morio1, T. Yoshii2, G. Hiasa1, T. Sumimoto1, K. Nishimura3, K. Inoue3, J. Higaki3,1

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Background: Diastolic heart failure has been reported to occur more often in elderly women rather than elderly men. Several studies have reported a relation between arterial stiffness and left ventricular (LV) diastolic function. Recently, it was reported that the relation was stronger in women than in men among individuals with cardiovascular risk factors. However, the impact of gender difference on this relation is still poorly understood.

Methods: Study subjects were selected from 447 who had echocardiography and examination of arterial stiffness. Among them, 95 men (mean age, 47±11 years) and 72 women (mean age, 47±10 years) without atherosclerosis risk factors (hypertension, dyslipidemia, diabetic mellitus) were analyzed. We measured brachial ankle pulse wave velocity (baPWV), carotid augmentation index (AIx) and radial AIx as arterial stiffness parameters immediately after the echocardiographic examination.

Results: Peak early diastolic mitral annular velocity (e') was significantly correlated with baPWV (Men: r = -0.42, p = 0.01, Women: r = -0.54, p < 0.001), carotid AIx (Men: r = 0.26, p = 0.01, Women: r = 0.57, p < 0.001) and radial AIx (Men: r = -0.35, p < 0.001, Women: r = -0.36, p < 0.001). E'/e' had a significant correlation with each arterial stiffness parameter in women, but not in men. Multivariate regression analysis revealed carotid AIx (β= -0.26, p= 0.02) was a significant independent predictor of E'/e' in women, but not in men.

Conclusion: Our results suggested that LV diastolic function was more affected by arterial stiffness in women than in men among healthy subjects. This might partially account for a higher incidence of diastolic heart failure in women than men.

Increased prevalence of diastolic heart failure can be identified by impaired global longitudinal strain in patients with rheumatoid arthritis

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Background: Risk of heart failure is increased in patients with rheumatoid arthritis (RA) and is more likely to occur in RA patients with a preserved ejection fraction. Until now little is known about the prevalence of diastolic heart failure (HFNEF) and related structural changes. Therefore we examined RA patients for diastolic heart failure using measurement of NT-proBNP level and echocardiography, including strain imaging.

Methods: In this prospective cross-sectional observational study we examined 155 patients (68% female, mean age 60±13 years, 56% hypertension, median BMI 28 kg/m²) with RA according to the current ACR/EULAR criteria in our outpatient clinic for rheumatic diseases. Echocardiography including strain imaging and blood sampling for NT-proBNP were done. HFNEF was diagnosed if 1) symptoms and (2) E'/e' ratio > 15 or (3) NT-proBNP > 220 pg/ml with (3) E'/e' ratio > 8 or (3) atrial fibrillation existed.

Results: There was a surprising high rate of HFNEF (21%) in our RA cohort. The systolic LVEF was reduced in only 4% of patients. LV mass index was increased in 4% of patients and 18% of patients with HFNEF, mostly due to concentric hypertrophy. In the strain imaging we found a significant reduction in the global longitudinal strain in patients with HFNEF with a threshold of -18%.

Logistic regression analysis of HFNEF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate OR</th>
<th>p</th>
<th>Multivariate OR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 65 years</td>
<td>19.0 (6.78-66.8)</td>
<td>0.001</td>
<td>21.6 (6.0-161)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>6.0 (2.0-26.3)</td>
<td>0.005</td>
<td>21.6 (3.0-140)</td>
<td>0.004</td>
</tr>
<tr>
<td>RA activity DAS28 &lt; 2.6</td>
<td>4.0 (1.7-10.2)</td>
<td>0.002</td>
<td>7.3 (2.0-34)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>5.9 (2.3-18.8)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus type 2</td>
<td>3.2 (1.9-9.4)</td>
<td>0.037</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentric LV hypertrophy</td>
<td>4.1 (1.7-9.8)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of CAD</td>
<td>7.6 (2.1-30.7)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of RA &gt; 15 years</td>
<td>3.32 (1.46-7.72)</td>
<td>0.005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: This finding in addition to the conventional echocardiographic measurements in HFNEF suggests the role of fibrotic endocardial changes in diastolic heart failure in RA. Markers of RA activity (DAS28) were significant risk factors beyond classical risk factors like age, female gender, hypertension and diabetes mellitus type 2.
DIASTOLIC DYSFUNCTION AND TREATMENT

Differing relations of the clinical responder rate to the left ventricular reverse remodelling and changes in left ventricular filling pattern in patients receiving cardiac resynchronization therapy

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Background: Clinical responder rate (CR) and left ventricular (LV) reverse remodelling (RR) are regarded valuable markers of long-term favourable effects of cardiac resynchronization therapy (CRT). Besides the aforementioned parameters, the improvement of LV diastolic function (LDF) might also be another valuable predictor of the long-term response to CRT.

Aim: To assess the relation of the improvement of the CR to the LVRP and to the improvement of LVDF evaluated by improvement in LV diastolic filling pattern (ILVFP) in pts receiving CRT. To investigate the survival of pts according to RR and ILVFP.

Patients and methods: 139 pts with CRT-P (51%) or CRT-D (49%) followed prospectively for 38.6±23.8 months. Age: 64±10.6 years, male:81.2%, ischemic:37.4%, diabetes mellitus:35.4%, atrial fibrillation:23.6%, NYHA:2.8±0.8, blood pressure:116.4±21.6/72.6±12.8mmHg. LV ejection fraction (LVEF): 20±6.2%.

RR: cardiac function improvement in T wave in E (Table 8) and T wave in V5 (Table 9). RR = 100% in Table 8. RR was found between CR and CRr. iLVFP was associated with 100% of CRr. iLVFP was improved in 16.1%. However these differences did not reach the level of significance: p=0.102. A comparison of echocardiographic variable

Variables Acute Phase Recovery Phase p value

EF % 45±16 60±6.6 <0.001

Peak E wave velocity cm/sec 66±15 78±18 0.03

E/A ratio 0.9±0.33 1.1±0.53 0.03

CRP (mg/dL) 6.3±2.5 6.7±3.1 <0.001

E/E’ 10.7±3.8 9.2±2.9 0.04

LA area cm² 16±3.3 16±3.4 0.01

LV ejection fraction 54% 67% 0.04

Normal DF stage n (%) 3 (19%) 2 (12%) 0.001

Grade 1 DD n (%) 2 (13%) 2 (13%) 1.0

Grade 2 DD n (%) 7 (44%) 3 (19%) 0.02

Grade 3 DD n (%) 3 (19%) 0.02

Conclusions: The cumulative survival rate at 1, 2 and 3 years: 97.8%, 92.5% and 78.6%, respectively. CRr (alive, improved)1 NYHA, and not hospitalized: at 6 months 82%, at 12 months 78%. RR (LVEF increases decreases 5%): at 6 months 36.8%, at 12 months 40.4%. iLVFP (deceleration acceleration) cm/sec 6.3±2.5 6.7±3.1 <0.001. E/E’ (average) cm/sec 6.3±2.5 6.7±3.1 <0.001.

A low glycemic and insulinemic diet improves diastolic cardiac function and metabolic syndrome more than the traditional low-fat diet in overweight patients with type 2 diabetes


1Bogenhausen Hospital - City Hospital Munich, Munich, Germany; 2Rehabilitation Clinic Ueberruh, Isny, Germany; 3Technical University of Munich, Institute for Medical Statistics and Epidemiology (IMSE), Munich, Germany; 4IFKE Institute, Mainz, Germany

Purpose: Diastolic dysfunction/heart failure in the metabolic syndrome and type 2 diabetes is an epidemic without evidence-based treatment strategies. While randomized controlled trials in overweight-obese patients with type 2 diabetes (D2D) have shown improved glycemic control and insulin sensitivity, the studies on dietary interventions are scarce in spite of the fact that diet may counteract the metabolic syndrome. Low-carbohydrate nutrition improves postprandial glucose control and insulin resistance more than the standard low-fat diet. We tested the hypothesis, that a low-carbohydrate diet improves cardiac function in overweight-obese patients with type-2 diabetes more than the traditionally recommended low-fat diet.

Methods: Two age and sex matched groups of 16 diabetics without overt heart disease (52±7 years, body mass index 34±6 kg/m²) were studied in a parallel and partial cross-over design during a 3-week rehabilitation program with either carbohydrate or low-fat diet. The group on low-fat diet (carbohydrate 55%, fat 25% and protein 20%) had subsequent 2 weeks on low-carbohydrate diet (25%, 45% and 30%, respectively). Cardiac function was assessed as myocardial velocity during systole and early diastole (E) using Doppler tissue imaging. Metabolic control was assessed before and 2 h after a standardized breakfast (400 kcal) with low-fat composition at baseline and with low-carbohydrate composition at the final test of the carbohydrate diet. Both groups had supervised aerobic training 2 hours a day.

Results: In the parallel groups, both diets induced similar significant reductions of weight, glycated hemoglobin and cholesterol. Low-carbohydrate diet considerably improved insulin resistance, triglycerides, systolic and diastolic blood pressure and diastolic cardiac function (E’ 9.5±1.0 to 10.4±1.5 cm/s, p=0.023). None of these variables changed on low-fat diet (E’ from 10.9±1.7 to 10.6±1.5 cm/s, but all of them improved significantly after subsequent low-carbohydrate diet (E’ from 10.6±1.5 to 11.5±1.4 cm/s, p=0.016). Intact proinsulin was unchanged with low-fat diet but decreased with subsequent low-carbohydrate diet, lasting and pp = 0.032 and 0.004.

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Conclusions: These data indicate, that a low-glycaemic/high-protein but not a low-fat/high-carbohydrate nutrition modulates diastolic dysfunction in overweight diabetics, improves insulin resistance and may prevent or delay the onset of diabetic cardiomyopathy and the metabolic syndrome.

Adaptive servo ventilation improves long-term prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep disordered breathing

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Background: Effective pharmacotherapy for heart failure (HF) with preserved left ventricular ejection fraction (LVEF) is still unclear. Sleep disordered breathing (SDB) may cause cardiac diastolic dysfunction. A high prevalence of SDB has been documented in HF patients with preserved LVEF. Adaptive servo ventilation (ASV) improves SDB including Cheyne-Stokes respiration. However, it still remains unclear whether ASV improves cardiac function and long-term prognosis of HF patients with preserved LVEF and SDB.

Methods: Twenty-five HF patients with preserved LVEF (defined as LVEF of ≥ 45%) and moderate-severe SDB (defined as apnea hypopnea index > 15/h) were enrolled. Study subjects (apnea hypopnea index 39.3±15.2/h) were divided into two groups: 10 patients treated with conventional medications for HF and ASV (ASV group) and 15 patients treated with conventional medications alone (Non-ASV group). BNP, LVEF, and right ventricular systolic pressure (RVPs) were determined before and 6 months after treatments. Patients were followed to register cardiac events after discharge (average follow-up period 728 days).

Results: Although, LVEF did not improve in both groups, BNP and RVPs significantly reduced in ASV group (BNP: 285.9±40.5 ng/ml vs. 160.5±31.6 ng/ml, p<0.01; RVP: 15.2±9.7 mmHg vs. 13.7±8.1 mmHg, p=0.05, respectively), but not in Non-ASV group. Eight events (death 5, re-hospitalization 3) occurred in this follow-up period. Importantly, event free rate was significantly higher in ASV group than in Non-ASV group (90.0% vs. 53.3%, logrank P<0.05).

Figure 1. Heart failure with preserved EF and SDB

Follow up period

Conclusions: ASV decreased cardiac overload and improved long-term prognosis in HF patients with preserved LVEF and SDB. ASV might be a promising useful tool for HF patients with preserved LVEF and SDB.

HYPERTENSION WITH PRESERVED EJECTION FRACTION: BIOMARKERS

Serum cystatin C as a biomarker of cardiac diastolic dysfunction in patients with cardiac disease and preserved ejection fraction

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Background: Systolic and diastolic functions are independently correlated with cardiac mortality. Worsening renal function also increases mortality and hospitalization, especially known as cardio-renal syndrome. Cystatin C (CysC) is a novel endogenous marker of kidney function. Recently, higher CysC concentrations were demonstrated to be associated with diastolic dysfunction in coronary artery disease and without heart failure and chronic systolic heart failure. But it is not clear whether serum CysC is associated with diastolic dysfunction in patients with cardiac disease and with preserved ejection fraction.

Methods: We measured serum CysC, Creatinine and BNP in 124 consecutive patients with cardiac disease. The patients underwent transthoracic echocardiography at rest on the same day. eGFR was determined by the MDRD formula for Japanese. Echocardiographic values were obtained by standard 2-dimensional parasternal long axis view and apical 4- and 2-chamber views. Trans Mitral Flow (TMF) patterns were categorized into two groups by their E/A ratio, mitral E velocity deceleration time and flow patterns of pulmonary veins. Results: 124 patients were classified into 5 disease groups according to their cardiac disease. There were no significant differences in serum CysC among 5 disease groups (P=NS). Serum CysC and eGFR showed a significant negative correlation (r = -0.70, P < 0.001), and serum CysC and BNP showed a significant positive correlation (r = 0.43, P < 0.001). In univariate analysis, Cardiac echo parameters (LVEF, LVdL, LVdDs, E/A, E, LAD, and TFM patterns) were significantly associated with serum CysC (p < 0.01). Multivariate linear regression analysis demonstrated TMF patterns were independent determinants of serum CysC (β = 0.286, P < 0.01). Furthermore, sub-analysis based on patients with preserved ejection fraction (LVEF ≥ 50%) and without renal dysfunction (eGFR > 60ml/min/1.73m³), in univariate linear regression analysis, LAD, E/A, E, and TFM patterns, surrogates of cardiac diastolic function, were significantly associated with serum CysC. And multivariate linear regression analysis demonstrated that LAD and TFM patterns were independent determinants of serum CysC (LAD: β = -0.362, P < 0.01; TFM patterns: β = -0.328, P < 0.05).

Conclusions: Serum CysC is associated with diastolic dysfunction in patients with various cardiac disease and preserved ejection fraction and without renal dysfunction. Our study also suggests that serum CysC become a surrogate biomarker of cardiac diastolic dysfunction in patients with various cardiac diseases and preserved ejection fraction.

Serum vitamin D and CRP levels are independently associated with diastolic dysfunction

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Background: Effective pharmaco-therapy for heart failure (HF) with preserved left ventricular ejection fraction (LVEF) is still unclear. Sleep disordered breathing (SDB) may cause cardiac diastolic dysfunction. A high prevalence of SDB has been documented in HF patients with preserved LVEF. Adaptive servo ventilation (ASV) decreased cardiac overload and improved long-term prognosis of HF patients with preserved LVEF and SDB.

Methods: Twenty-five HF patients with preserved LVEF (defined as LVEF of ≥ 45%) and moderate-severe SDB (defined as apnea hypopnea index > 15/h) were enrolled. Study subjects (apnea hypopnea index 39.3±15.2/h) were divided into two groups: 10 patients treated with conventional medications for HF and ASV (ASV group) and 15 patients treated with conventional medications alone (Non-ASV group). BNP, LVEF, and right ventricular systolic pressure (RVPs) were determined before and 6 months after treatments. Patients were followed to register cardiac events after discharge (average follow-up period 728 days).

Results: Although, LVEF did not improve in both groups, BNP and RVPs significantly reduced in ASV group (BNP: 285.9±40.5 ng/ml vs. 160.5±31.6 ng/ml, p<0.01; RVP: 15.2±9.7 mmHg vs. 13.7±8.1 mmHg, p=0.05, respectively), but not in Non-ASV group. Eight events (death 5, re-hospitalization 3) occurred in this follow-up period. Importantly, event free rate was significantly higher in ASV group than in Non-ASV group (90.0% vs. 53.3%, logrank P<0.05).

Conclusions: ASV decreased cardiac overload and improved long-term prognosis in HF patients with preserved LVEF and SDB. ASV might be a promising useful tool for HF patients with preserved LVEF and SDB.

Serum vitamin D and CRP levels are independently associated with diastolic dysfunction

Method: We measured serum 25(OH)D, CRP and fibrinogen and performed standardized LV echocardiograms. Echocardiographic data were used for classification of systolic and diastolic dysfunction. Results: 25(OH)D deficiency (≤ 30 ng/ml) was common among our study population (%78.8). Patients with severe diastolic dysfunction had a lower vitamin D levels (14.7±9.7 ng/ml, p<0.01), higher CRP levels (p<0.001), higher prevalence of hypertension (p<0.032), diabetes (p<0.011) and higher left ventricular mass index (LVMi) (p<0.021). In multivariate analysis, decreased vitamin D (β = -0.154, p<0.012) and elevated CRP (β = 0.124, p = 0.035) was associated with e/e' ratio after adjustment for potential confounders.

Conclusion: Serum levels of 25(OH)D are significantly associated with LV diastolic dysfunction suggesting that vitamin D supplementation is a promising approach in the prevention of diastolic dysfunction.

Serum Cystatin C as a biomarker of cardiac diastolic dysfunction in patients with preserved ejection fraction: biomarkers

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Background: To investigate the relationship between the amount and anatomic location of adipose tissue depots, inflammation, and left ventricular (LV) diastolic dysfunction in continuous ambulatory peritoneal dialysis patients (CAPD) patients.

Methods: Echocardiographic parameters were assessed in 173 CAPD patients. LV diastolic dysfunction was diagnosed if the mitral inflow E/A ratio was < 1, deceleration time was > 220 cm/s, or mitral inflow TDI e' < 8 cm/s. CAPD patient with LV diastolic dysfunction served as the control group. Serum levels of C-reactive protein (CRP), tumor necrosis factor-α (TNFα) and interleukin-6 (IL-6) were measured, and the location and amount of adipose tissue were assessed by computerized tomography (CT) at the level of the fourth lumbar vertebra.

Results: Subjects with LV diastolic dysfunction had higher levels of the pro-inflammatory cytokines and more visceral and peritoneal fat (all P<0.001) than control subjects. A significant correlation was found between visceral adipose tissue and pro-inflammatory cytokines (r=0.70; P<0.001). Multivariate regression...
Pulmonary hypertension and collagen metabolism in patients with heart failure and preserved ejection fraction

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Purpose: Pulmonary hypertension (PH) is a strong predictor of mortality in patients with heart failure with preserved ejection fraction (HFpEF). This study was designed to evaluate the association between circulating biomarkers of collagen metabolism and PH as assessed by pulmonary artery catheterization, in patients with HFpEF.

Methods: Plasma matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9), tissue metalloproteinase inhibitor 1 (TIMP-1) and C-terminal propeptide of type I procolagen (CIPC) values, and Doppler echocardiography images were obtained from 21 patients with HFpEF and 21 control subjects with hypertension without HF. Patients with pulmonary artery systolic pressure (PASP) > 35 mmHg were proposed to undergo a right heart catheterization.

Results: Compared to controls, HFpEF patients had higher circulating levels of MMP2 (252.6±13 ng/ml vs. 211.1±4 ng/ml, p = 0.002) and CIPC (101.6±7 ng/ml vs. 79.5±4 ng/ml, p=0.016), but no significant differences in MMP9 or TIMP1. Among the HFpEF group, PH was present in 16 patients (75%). 13 of them underwent a right heart catheterization, showing PASP 74.15±27.7 mmHg, pulmonary capillary wedge pressure (PCWP) 18.4±9 mmHg, and atrial natriuretic peptide (ANP) concentration 29.9±17.2 pg/ml. Patients with HFpEF had increased values of MMP2 and CIPC compared to hypertensive controls. Their levels showed a significant linear correlation with PASP (r=0.56, p=0.04), PADP (r=0.64, p=0.018) and with pulmonary vascular resistance (r=0.70, p=0.007).

Conclusions: Larger amounts of adipose tissue were associated with higher serum pro-inflammatory levels in CAPD patients, which could contribute or lead to the development of LV diastolic dysfunction. Modulating inflammatory reactions in CAPD patients could prove to be a novel therapeutic approach for managing LV diastolic dysfunction.

Expression of connective tissue growth factor in diabetic heart failure patients and canine models

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Background: Diastolic heart failure (DHF) is characterized by myocardial interstitial fibrosis and left ventricular hypertrophy. Connective tissue growth factor (CTGF) is an emerging marker for tissue fibrosis. The study investigated the association between CTGF and DHF from animal model to clinical indices.

Methods: A total of 120 patients with a diagnosis of DHF confirmed by echo-cardiography and 60 matched controls were recruited. Soluble plasma levels of CTGF were measured in all subjects and the associations with diabetic fraction were calculated. Canine model of DHF was induced by aortic banding. Left ventricular (LV) pressures, LV volumes, and transmural Doppler were obtained before and after pressure loading (at baseline and after 6months). Myocardium tissues were collected, and western blotting was used to detect the protein expression of CTGF for each dog. The correlation for CTGF and the severity of diastolic dysfunction was then calculated.

Results: Patients with DHF presented significantly higher CTGF levels than the controls. Significant correlations (all P < 0.05) were found for CTGF and E/e’ (r = 0.55), E/A (r = 0.5) in advanced DHF patients (E/e’ > 15). After 24 weeks in canine models, the protein expression of CTGF from LV myocardial tissue was significantly increased (p<0.01) compared with the controls (sham dogs). Moreover, the expression of CTGF paralleled the severity of LV diastolic dysfunction parameters and hemodynamic changes.

Conclusion: Both Plasma and myocardium CTGF levels had significant correlations to the severity of DHF. Our study offered the evidence to apply novel therapies for DHF patients aimed to down-regulate the overexpression of CTGF.

PHARMA THERAPY

Resveratrol, a SIRT1 activator, prevents cardiomypathy in dystrophin-deficient mice by down-regulation of p300

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Background and purpose: Heart failure is a main cause of death in patients with Duchenne muscular dystrophy (DMD), a disorder caused by defective gene for dystrophin. However, there is no effective therapy for prevention of heart failure in DMD. The aim of this study was to examine whether activation of SIRT1, an NAD+-dependent histone/protein deacetylase, by use of resveratrol prevents cardiomyopathy due to dystrophin deficiency.

Methods and results: We used dystrophin-deficient mice (mdx) as a model of DMD and C57BL/10 mice as controls. Mdx were untreated or orally treated with resveratrol (400 mg/kg/day) from 3 weeks of age. Diastolic left ventricular (LV) thickness (0.72±0.02 vs. 0.82±0.03 mm), heart-to-body weight ratio (4.1±0.6 vs. 5.4±0.8 mg/g), and atrial natriuretic peptide (ANP) mRNA level (4.3-fold) were significantly increased in 40-week-old mdx mice compared with those in the control. Echocardiography showed that diastolic LV posterior wall movement, an index of LV diastolic function, was significantly slower in the untreated mdx than in the controls (21.1± vs. 30.5±mm/sec), although LV dimension and LV ejection fraction were similar in the two groups. Ventricular fibrosis and collagen gene expressions were increased in the mdx group. These phenomena of mdx mice were significantly suppressed by treatment with resveratrol. Resveratrol reduced myocyte acetylated histone H3 levels determined by immunohistochemistry and immunoblot in mdx hearts, indicating activation of SIRT1. Phospho-ERK1/2 and TGFβ1 mRNA levels in mdx hearts were not reduced by resveratrol. However, resveratrol dose-dependently increased ANP promoter activity, which was suppressed by overexpression of wild-type SIRT1. Wild-type SIRT1, but not deacetylase inactive mutant SIRT1, reduced p300 protein level, which was blocked by the proteasome inhibitor MG132. In addition, SIRT1 was found to promote p500 deacetylation and polyubiquitination.

Conclusion: Resveratrol attenuates both cardiac hypertrophy and fibrosis and improves diastolic LV function in the mdx possibly by SIRT1-mediated down-regulation of p300. SIRT1 activation may be a novel strategy in treatment of cardiomyopathy in DMD.

Continuous infusion of the novel chimeric natriuretic peptide cenderitide in the dahl salt sensitive rat model of hypertension and renal dysfunction: evidence for renoprotection

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Purpose: Cenderitide (CD-NP) is a chimeric natriuretic peptide created by fusing the 22 amino acid human C-type natriuretic peptide (CNP) with the 15 amino acid C-terminus of Dendroaspis natriuretic peptide (DNP). The peptide was engineered to have natriuretic, diuretic, antihypertensive, and antifibrotic effects through binding of both guanylyl cyclase (GC)-B and GC-A receptors. Continuous administration of CD-NP is of interest for fluid management in patients with heart failure and impaired renal function. The purpose of this study was to deter-
mine the effect of 6-week continuous CD-NP administration on heart and kidney structure and function in the Dahl salt sensitive (DSS) rat.

**Methods:** 10-week old DSS rats were switched to a high-salt (4%) diet to accelerate the development of hypertension. Concurrently, Alzet pumps filled with CD-NP or vehicle were implanted subcutaneously. Study groups were: 1) vehicle + high salt diet (n=10); 2) 85 ng/kg/min CD-NP + high salt diet (n=9); 3) 170 ng/kg/min CD-NP + high salt diet (n=10); 4) vehicle + low salt diet (n=10). Blood and urine were collected every 2 weeks to measure albuminuria, proteinaemia, and creatinine clearance (CC). Blood pressure (BP) was measured at weeks 3 and 5 by tail cuff. Animals were euthanized after 6 weeks and a histopathological assessment of the tissues was performed. CD-NP treated groups were compared to the vehicle + high salt diet group at each time point by two way analysis of variance with a Bonferroni correction. Values are mean ± SEM.

**Results:** Continuous CD-NP administration dose-dependently decreased BP, reaching statistical significance at 170 ng/kg/min (172.4±5.2 vs. 163.8±4.4 vs. 148.9±4.7 mm Hg for groups 1, 2, and 3, respectively) at week 5. At week 6, there was a statistically significant reduction in albuminuria in both CD-NP treated groups (95.84±10.16 vs. 72.8±10.23 vs 70.15±5.44 mg/dl for groups 1, 2, and 3, respectively). Proteinaemia was similarly reduced at week 6 in the treated ani- mals. CC was increased in the CD-NP treated animals, though not to statistical significance. Histopathological assessment revealed a dose dependent trend of im- proved renal tissue morphology, specifically in terms of tubulo-interstitial changes and glomerulopathy.

**Conclusions:** Long term subcutaneous dosing of CD-NP had an antihyperten- sive effect in the DSS rat model. In addition, treated animals exhibited less renal damage and reduced proteinaemia. Further studies are warranted to understand the contributions of blood pressure lowering and direct tissue protective actions of this novel peptide.

**P4542**

**Antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase in patients with congestive heart failure: first clinical experience**

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**Background:** Antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase are a principally new classes of neurohumoral modulators. The aim of our study was to investigate the efficacy and safety of combination these antibodies (anti-AT1+E-NO-synthase) in pts with congestive heart failure (CHF).

**Methods:** 60 pts (mean age 56.9±1.3 years) with CHF (NYHA class II-IV, mean 2.7±0.07, mean ejection fraction 29.6±0.9%) were included into the randomized, single-blind, placebo-controlled study. Baseline therapy (ACE inhibitor, β-blocker, diuretics) wasn’t changed during the study. Pts with CHF were randomly assigned to anti-AT1+E-NO-synthase 3 tabs/day (group I, n=30) or placebo (group II, n=30). 2D Echo, treadmill-test (Naughton), 6-min walking test were performed before and after six months of therapy.

**Results:** After 6 months of therapy with anti-AT1+E-NO-synthase NYHA class reduced to 42.6% (p<0.008), in placebo group to 52.4% (n.s.). Significant in- crease of left ventricular ejection fraction was noted in both groups: group I +25.47% (p<0.0001), group II +6.29% (n.s.). Significant increase both exercise time (+34.7%, p<0.0005) during treadmill-test and distance during 6-min walking test (+24.9%, p=0.0002) was noted only in the group I. Adverse events related with anti-AT1+E-NO-synthase were not observed.

**Conclusions:** The adding of combination of antibodies to C-ending (intracellular) fragment of the angiotensin II type 1 receptor and endothelial NO synthase to standard therapy is a promising way for treatment pts with CHF. Large clinical trials are indicated.

**P4543**

**Systematic review of the proportion of heart failure patients reporting side effects of beta-blockers in whom the medication is genuinely causative: ethical implications for informed consent**


**Purpose:** Beta-blockers improve survival in heart failure, but patients run a gaunt- let of information about harmful effects, from doctors, drug information sheets, and media. When side-effects occur, the drug is readily blamed. We tested whether side-effect information matches reality, and provide evidence-based guidance for interpretation of side-effects in clinical practice.

**Methods:** We searched MedLine (1950 to present) up to an including November 8 2011 using keywords Beta-blocker, systolic heart failure, randomized controlled trial and RCT. We identified RCTs comparing a single beta-blocker versus placebo only; trials were excluded if they were not randomized, double-blinded studies or had a cross-over design, if they did not report side-effect data sepa- rately for both arms, and if other medications were selectively introduced.

**Results:** Only 5 of 33 alleged side-effects are actually made more commonly by beta-blockers. Out of 100 patients reporting hyperglycaemia on beta-blockers in only 17 (85% CI 2–32), is that symptom genuinely caused by the beta-blocker; in the remaining 83 it is natural or caused by the information given. Of patients reporting side-effects, the proportion in whom the drug is genuinely the cause is also low for diarrhoea (18/100, CI 5–30), and dizziness (19/100, CI 11–27). Only two side-effect symptoms were genuinely caused by the intervention in the majority of sufficient: bradycardia (67/100, CI 56–79) and intermittent claudication (59/100, CI 19–98).

**Conclusion:**_transient reduced cardiac fibrosis, renal function and blood pressure in STNx rats as well as improved diastolic function. These findings support the use of direct antifibrotic strategies in CRS.

**P4544**

**Translant reduces pathological cardiac fibrosis and improves diastolic function following kidney transplantation: implication for cardio-renal syndrome**

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**Background:** Kidney dysfunction in heart failure (HF) is associated with in- creased mortality, morbidity and cost of care, known as cardio-renal syndrome (CRS). Fibrosis plays an important role in disease progression in HF in patient with CRS. We examined the effect of the anti-fibrotic agent, tranilast, onamelio- rating these processes.

**Methods:** 5/6 subtotal nephrectomy (STNx) was induced in male Sprague Daw- ley (SD) rats. Animals were randomized to receive either tranilast (300mg/kg/day, p.o.) (n=14) or vehicle (n=16) for 12 weeks. Sham operated control animals also received vehicle (n=9). Glomerular filtration rate (GFR) was analysed with a single shot Tc99m-DTPA clearance. Blood pressure was measured by tail-cuff plethys- mography. Echocardiogram was performed to access cardiac function before cardiac tissues were harvested for immunohistochemistry analysis.

**Results:** Tranilast treatment had significant effect on blood pressure (vs STNx+Vehicle, P<0.05) and reduced collagen I and III deposition (vs STNx+Vehicle, P<0.05) in the heart post STNx. (Table)

**Conclusion:** Tranilast reduced cardiac fibrosis, renal function and blood pressure in STNx rats as well as improved diastolic function. These findings support the use of direct antifibrotic strategies in CRS.

**P4545**

**Reno-protective and diuretic therapy with low doses of natriuretic peptide and dopamine in acute heart failure patients**

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**Background/Goal:** Worsening renal function during early phase of hospitaliza- tion is related to adverse outcomes in acute heart failure (AHF). We’ve previously reported that natriuretic effect of hANP, known as renoprotective therapy with its low dose was mediated through dopamine (DA) receptors and externally added DA improved diuretic effect in rats. However, this combined diuretic effects as well as renoprotective effects have never been investigated in human AHF. Our goal was to clarify whether or not the combination therapy with DA and hANP in terms of diuresis and renoprotection is clinically beneficial for AHF patients.
Methods: Twenty-four patients (age 74 ± 17 yrs; left ventricular ejection fraction 40.2 ± 17.6%) with AHF were enrolled and were treated with intravenous low dose hANP. When adequate diuresis was not obtained by 4 hours after administration despite increasing the dose of hANP twice, low dose DA (1–3 μg/kg/min, n=12) or low dose furosemide (F, 10–30 mg injection, n=12) was randomly added. Serum creatinine did not change in both DA and F groups (137.1 ± 22.4 to 137.3 ± 19.8, P=0.007, respectively). Urine volume increased significantly in both groups (8-OHdG) were measured on admission and after additional DA or F administrations.

Results: Heart rate did not change in both groups. Systolic blood pressure decreased significantly in DA and F groups (137.3 ± 18.9 to 119.6 ± 15.8, P<0.021, 137.1 ± 29.4 to 108.3 ± 16.1 mmHg, P=0.007, respectively). Urine volume increased significantly in both groups (fig). Urinary L-FABP and 8-OHdG decreased significantly in DA but not in F (fig). Serum creatinine did not change in both groups.

Conclusion: The combination therapy with low doses of hANP and DA might be a renoprotective strategy for AHF management.

References:

Figure 1. Urine volume, L-FABP, 8-OHdG

Conclusions: In TM patients at the dosages used in the real world, combined DFP+DFO regimen was more effective in removing cardiac iron load only versus the DFP group. Combined therapy did not show an additional effect on heart function.

References:
Should we achieve the target doses of beta-blockers in chronic heart failure patients with adequate heart rate control?

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Purpose: Recent studies indicated that heart rate was an important target for Chronic heart failure (CHF) treatment, whereas the importance of doses of beta-blockers was still uncertain. We conducted the study to determine the survival prognosis of achieving the target doses of beta-blockers in CHF patients with adequate heart rate control.

Methods: We screened for symptomatic CHF patients with reduced LV ejection fraction (LVEF<40%) and newly initiated beta-blocker treatment (bisoprolol, carvedilol, metoprolol tartrate, or nebivolol) with at least 1 year follow-up in Hospital between the year 2000 and 2010. Among 2,654 CHF patients, 253 patients were eligible for the study (Figure 1). The endpoint of the study was all-cause mortality.

Results: The baseline NYHA functional class, heart rate and blood pressure were similar in all groups. The patients in group which the target beta-blocker dose was achieved had significantly more frequent history of myocardial infarction (MI) compared to placebo group (7 vs. 4%, p<0.001), had lower prevalence of hypertension (40.8% vs. 62.2%, p<0.002). The median follow-up was 50.5 months (IQR 28.7-73.0). The annual all-cause mortality was significantly lower in the group (i) than in the other groups (Figure 1). After adjusting for possible confounding factors, the difference among groups remained significant (p=0.030).

Conclusions: The CHF patients who both achieved the target doses of beta-blockers and had adequate heart rate control had the best survival prognosis. We should make an effort to achieve the target doses of the beta-blockers, even the heart rate is well controlled.

Effect of aldosterone antagonism on ejection fraction and exercise capacity is independent of NYHA classification: a meta-analysis of 1575 patients in randomized controlled trials

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Background: Current guidelines only recommend the use of mineralocorticoid receptor antagonists (MRA) in NYHA class III or IV. We used a meta-analysis to quantify the impact of aldosterone antagonism (E) with MRA therapy and to clarify whether this benefit is dependent on baseline NYHA.

Method: A MEDLINE search and examination of reference lists was used to identify randomized controlled trials of MRA. A meta-analysis was performed to compare NYHA groups.

Results: Of 14 trials, 2 included patients with average NYHA class I-II (219 patients), 9 included NYHA class III (1119 patients) and 3 included NYHA class IV (237 patients) (Table 1). Treatment duration was 7.7 months (range 2.1-9 months) and spironolactone was the predominant MRA. Baseline EF and improvement were similar in NYHA I-II (baseline EF 33%, improvement 4%), NYHA III (35% and 4%) and NYHA IV (36% and 5%). Of 6 trials reporting functional class, all reported an improvement in symptoms with MRA, with average NYHA falling from 2.2 to 1.9.

Conclusions: Improvement in EF and functional class with MRA therapy are independent of baseline NYHA.

Management of acute heart failure and adherence to guidelines in different clinical presentations

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Purpose: Data on the management of 620 patients hospitalized due to AHF at 14 centers during three months were collected. The use of therapies recommended by ESC guidelines such as intravenous (IV) nitrates, IV diuretics, IV opioids, intravenous vasopressors and continuous positive airway pressure (CPAP) support was examined. Categorical variables are presented as percentages. Comparisons between groups were performed by χ² tests for categorical variables (PASW Statistics 18, SPSS Inc., Chicago, IL, USA).

Results: Overall IV nitrates were given in 41%, IV furosemide in 76%, IV opioids in 29%, IV diuretics in 14%, IV vasopressors in 10% and CPAP in 24% of cases. Treatments given in different clinical classes are shown in table 1.

IV furosemide was the most often used treatment in all clinical classes. The use of IV nitrates, also with a class I ESC guideline recommendation, was frequent in pulmonary oedema and hypertensive AHF, but administered only to 31% of patients.
Continuous furosemide infusion versus furosemide manitol infusion in acute congestive heart failure

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Background: Loop diuretics remain the cornerstone for fluid mobilization in patients with acute congestive heart failure (CHF) although there is little evidence regarding the ideal dosing strategies and method of administration. Data on the use of mannitol for prophylaxis and/or treatment of acute CHF is controversial and the role of using mannitol in fluid mobilization is unclariﬁed, especially in pulmonary oedema.

Methods: A retrospective study of 233 patients with CHF (N=108 who received treatment with continuous furosemide–manitol infusion (FM) and N=125 with continuous furosemide–furosemide infusion) was performed. Infusions were administered intravenously for a period of 1-4 days. Dose titration was protocol-driven and based on urine output. Outcomes of diuresis achieved, death during hospitalization, dialysis requirement, length of hospital stay, effects on kidney function and electrolytes were assessed. Data are reported as mean±SD.

Results: In the comparison of continuous furosemide infusion, there was no significant difference in patients’ weight (-4.7±1.9 kg and -4.8±2.03 kg, p=0.62) or in the mean creatinine level (0.5±0.3 mg/dl and 0.4±0.2 mg/dl, p=0.39), respectively; P=0.45. There was no significant difference between these groups in the need for dialysis (9.6% and 9.2%, p=0.98), in hospital death (10.4% and 10.1%, p=0.99) and duration of hospitalization (6.0±1.5 days and 6.0±1.5 days, p=0.86). Patients who required dialysis had a lower diuretic response [FM (−0.5±0.3 kg vs 4.9±1.9 kg, p=0.02); furosemide (−0.7±0.2 kg vs 4.8±1.3 kg, p=0.00)]. Higher baseline creatinine [FM (2.8±1.6 mg/dl vs 2.5±1.2 mg/dl, p=0.05); furosemide (2.9±1.3 mg/dl vs 2.6±1.6 mg/dl, p=0.04)], higher BNP on admission (FM 2120±590 vs 1735±480, p=0.05; furosemide 2240±560 vs 1650±590, p=0.04) and a higher incidence of acute kidney injury on admission (FM 100% vs 48%, p=0.001; FM 100% vs 76%, p=0.002)

Conclusion: FM is equally efficacious as furosemide infusion in severe CHF. Superiority in terms of improved CHF persists beyond hospitalization.

Zofenopril and ramipril minus ASA in post-myocardial infarction patients receiving a higher target doses of ACE inhibitors: Insights from Studies of Left Ventricular Dysfunction (SOLVD) treatment trial

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Background: In RTCs of ACE inhibitors (ACEIs) in systolic heart failure (SHF), both ACEIs and placebo were up titrated to higher target doses if tolerated. The role of this implicit selection bias on mortality remains unclear.

Methods: In SOLVD Treatment trial, SHF (EF ≤35%) patients were randomized to placebo or enalapril. During 2-3 yrs post-randomization, study drugs were up titrated to target doses (>20 mg/day) in 61% (748/1234) and 57% (696/1224) of pts in placebo and enalapril groups, respectively. Primary outcome was all-cause mortality (median follow-up, 35 mos).

Results: When compared with overall placebo, only target dose enalapril pts had significant mortality reduction (HR, 0.79; 95% CI, 0.68–0.93; p=0.004). However, when compared with dose-specific placebo groups, both target and below-target dose enalapril pts had similar mortality reductions (5% absolute and 10% relative; p for interaction, 0.970; Table). Mortality reduction associated with target dose was similar in both treatment groups (Figure).

Conclusions: Below-target dose enalapril reduced mortality in SHF, and up titration to target dose had little additional treatment effect. Similar mortality reduction associated with target dose of both enalapril and placebo suggest selection bias associated with dose up titration.

Statin therapy and clinical outcomes in acute heart failure patients complicating acute myocardial infarction: insights from the EPHEBUS trial

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Purpose: Several clinical trials have shown that in acute and post急性 myocardial infarction (MI), statin therapy improves cardiovascular (CV) outcomes, but in these trials patients left at baseline with an acute heart failure (HF) were excluded or only few were enrolled. In patients with chronic heart failure (CHF), initiation of statin therapy reduces CV hospitalizations but not all cause or CV mortality. However, these trials did not investigate whether patients who evolved to HF while being on statin benefit from this therapy. We aimed to assess the association between statin therapy and clinical outcomes in the setting of acute HF with systolic dysfunction complicating acute MI.

Methods: We performed a post-hoc analysis in 6632 patients included in the
Efficacy of ivabradine therapy on right heart parameters in patients with severe systolic chronic heart failure

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The aim of study was to assess the efficacy of ivabradine (1 up to 5 mg) therapy on prognosis, right ventricular (RV) and atrial (RA) functional parameters, BNP, NT-proBNP and high sensitivity C reactive protein (CRP) levels in patients with III-IV NYHA FC systolic CHF in sinus rhythm.

Methods: 76 pts (age 57.4) were randomly assigned to group A (n=38, receiving I) and group B (n=38, receiving placebo), in addition to ACE inhibitors, beta-blockers, digoxin and diuretics. Assessment of RV EF, myocardial mass (MM), myocardial performance index (MPI), fractionation area change (FAC), tricuspid annulus plane systolic excursion (TAPSE), real-time of early (E) and late (A) tricuspid annulus fibrocellular septal velocities, deceleration time (DT) of E wave, overall filling time (OFT), pulmonary artery (PA) ejection (ET) and pre-ejection (PET) times, RA functional index (FI) and fractional contribution (FC), BNP, NT-proBNP and hsCRP levels was performed at baseline and 12 months.

Results: 1-year mortality, hospitalization rate and combined endpoint of mortality and hospitalization (%) were, respectively, 34.2, 55.3 and 89.5 and 21.1, 31.6 and 47.2 in groups A and B. Event-free analysis showed lower probability reduction (RR, %) of mortality at 38.3, hospitalization rate at 42.9 and mortality and morbidity at 41.2, respectively, in pts treated with I compared to group A. 1-year treatment with I increased (%) EF at 27.6, FAC at 25, TAPSE at 37.3, E/A at 27.4, DT at 21.9, OFT at 19.6, PA ET at 11.7, RA FI at 50.5, FC at 50.8, decreased MM at 28.5, MPI at 28.1, PA PET at 16.6, BNP at 65.5, NT-proBNP at 68.3 and hsCRP at 61.2 (p<0.05). Reduction from baseline of BNP NT-proBNP and hsCRP values ≥50% and HR >40% was associated with significant improvement of prognosis compared to decrease of BNP NT-proBNP and hsCRP >30% and HR >20% (RR 0.35 [95% CI 0.30-0.41], 0.36 [95% CI 0.33-0.42], 0.32 [95% CI 0.27-0.35] and 0.33 [95% CI 0.29-0.35], p<0.01), respectively. Similarly, increase of TAPSE at 50% and RA FI ≥40% was associated with significant improvement of prognosis compared to changes of EF, E/A≥15%, TAPSE >30% and RA FI ≥40%. RR 0.36 [95% CI 0.32-0.43], 0.37 [95% CI 0.34-0.44], 0.31 [95% CI 0.26-0.34] and 0.34 [95% CI 0.29-0.37], p<0.01, respectively.

Conclusions: 1) Decrease of BNP NT-proBNP and hsCRP ≥50%, HR >40% and increase of RV EF and E/A at ≥25%, TAPSE ≥50% and RA FI ≥60% identified pts with cardiac events reduction. 2) Prognostic benefit, associated with use of I, seems to be related to improvement of right heart parameters, neurohumoral and inflammation status and HR reduction.

Subcutaneous furosemide can prevent hospitalization in fluid overload decoupling of chronic heart failure

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Purpose: Chronic heart failure (CHF) is a high prevalent disease, a main cause of admission and it supposes a high economic cost. The basis of treatment for fluid overload consists of diuretics. Furosemide is the most widespread. When oral treatment is not enough, the endoveneous route is the most frequent access, but many pts require admission. Relevant differences between bolus and perfusion have not been proved. We tested ambulatory continuous infusion of subcutaneous furosemide (SF) with elastomeric pumps in order to prevent hospitalization in patients with fluid overload decoupling of CHF.

Methods: 25 patients (p) (76% male, 74±10 years-old) in 42 episodes of fluid overload were treated by subcutaneous system of furosemide continuous infusion in a heart failure department. Elastomeric pumps with UFA-filter were prepared with different dilutions of furosemide 40, 400, 4000 microns/ml during 2, 4 or 5 days of infusion. Analytical, clinical and functional data were prospectively registered.

Results: 52% suffered hypotension, 24% diabetes, 36% chronic renal failure (creatinine ≥1.5), mean creatinine 1.58±0.6, 72% atrial fibrillation and 71% were on beta-blockers therapy, 81% on angiotensin-converting enzyme inhibitors/angiotensin-receptor-antagonists II and 24% were on aldosterone-antagonist treatment. Mean duration of furosemide was 110±50 mg. 92% were in NYHA class III-IV, 52% had severe left ventricle impairment and 44% severe pulmonary hypertension by echocardiogram. Mean NT-proBNP was 4746±5762 pg/ml. After therapy (5±4 days) with furosemide (150±40 mg), mean weight loss was 2.11±2.9 kg (70.95 vs 76.90 kg, p<0.0002), creatinine levels were stable (1.58 vs 1.53, p>0.3) and no clinical relevant hypokalemia happened (2% (1p) had ≥3mEq/l (2.9 mEq/l) but no clinical events). Only 17% (3p) needed hospitalization due to fluid overload during therapy and no deaths during therapy occurred. Main adverse events were local complications at the infusion point without clinical significance (pain 5%, irritation 10%, disconnection 5%, kinked 3%, local infection 7% and local bleeding 3%). NYHA class was improved in 61% of episodes, it did not differ in 37% and it worse in just 2% (1p).

Conclusion: Ambulatory continuous infusion of subcutaneous furosemide by elastomeric pumps is effective and safe to prevent hospitalization in patients with fluid overload decoupling of CHF. No relevant renal, ionic or clinical complications occurred. Frequent minor local complications were observed. So, this alternative route of diuretic administration could have a beneficial economic impact.

Are there relationships between highest resting heart rate and not optimal doses of beta-blockers in patients with systolic heart failure in contemporary Poland? Results of DATA-HELP study

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Background: Resting heart rate (HR) is associated with poor outcome, and its reduction due to both β-adrenergic and if current blockade has provided survival benefits in patients with systolic heart failure (HF). The magnitude of contemporary European population of patients with systolic HF and high HR, and links between applied therapy and achieved HR in everyday practice are unclear.

Methods: Registry DATA-HELP was performed in X-III 2009 in Poland in a randomly selected representative sample of 5563 outpatients with clinical diagnosis of HF and LVEF<45%; resting HR was available in 5513 subjects (99%).

Results: We analysed 3820 patients with systolic HF in a sinus rhythm (65% of the whole cohort) (age: 66±11 y, BMI: 28.2±4.2 kg/m2, men: 64%, NYHA class III-IV: 31%, previous MI: 61%, diabetes: 33%). Mean±SD HR was 75±13 bpm, median with lower/upper quartiles 72 (68-80) bpm. HR >70 bpm and ≥75 bpm were found in 69% and 47% of patients, respectively, with increasing frequency along NYHA classes (I/II/III/IV - HR >70 bpm: 65%/67%/74%/77%, HR ≥75 bpm: 42%/45%/53%/60%, both p<0.001). In a multivariable stepwise logistic model, high HR was related to high syst BP (p<0.001), presence of pulmonary congestion (p<0.05) and peripheral oedema (p<0.001), advanced NYHA class (p<0.01), longer age (p<0.001), and between those not receiving β-blockers, and between those receiving β-blockers without clinical significance (pain 5%, irritation 10%, disconnection 5%, kinked 3%, local infection 7% and local bleeding 3%). NYHA class was improved in 61% of episodes, it did not differ in 37% and it worse in just 2% (1p).

Conclusion: Ambulatory continuous infusion of subcutaneous furosemide by elastomeric pumps is effective and safe to prevent hospitalization in patients with fluid overload decoupling of CHF. No relevant renal, ionic or clinical complications occurred. Frequent minor local complications were observed. So, this alternative route of diuretic administration could have a beneficial economic impact.

Do early and late nephroprotective effects differ with different inhibitors of renin-angiotensin-aldosterone system in chronic heart failure patients?

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Purpose: To compare the extent of nephroprotection in chronic heart fail-
ure (CHF) patients treated with angiotensin-converting enzyme inhibitor (ACEI), angiotensin-II receptor blocker (ARB), and direct renin inhibitor (DRI).

Methods: 155 patients with CHF of different etiology and NYHA class II or III, with chronic kidney disease (CKD) stage I to III, and with uncorrected arterial hypertension, were randomized after getting informed consent into three treatment arms: 1st – with ACEI enalapril (n=49), 2nd – with ARB losartan (n=47), and 3rd – with DRI aliskiren (n=59). The patients were evaluated at baseline, after two weeks and after one year of treatment, for systolic and diastolic blood pressure (BP), microalbuminuria (MAU), and glomerular filtration rate (GFR) by Cockcroft-Gault equation. Overall there were 6 drop-outs from groups due to patients’ decision and no cross-over of assigned treatment arms at follow-up. Mean daily doses at one year evaluation were 19.1 mg for enalapril, 65.4 mg for losartan, and 27.4 mg for aliskiren. All patients were on beta-blockers and aldosterone antagonists, and 86% on diuretics in comparable doses. ANOVA for independent and dependent samples was used for statistical analysis with 0.05 alpha-error cut-off points.

Results: After one year of treatment there was no significant difference between groups in achieving BP control: BP < 140/90 mm Hg was observed in 65.8±6.8% of patients in the 1st group, 72.6±6.5% – in the 2nd, and in 73.1±6.8% – in the 3rd. Slight decrease in MAU (by 24-27 mg per day) was already seen after two weeks of treatment; it became more pronounced and statistically significant (p<0.05) at one year evaluation within each group but more or less similar between the respective groups: by 66.2±31.3% and 71.2±15.9% vs 62.0±15.9% in treatment and control groups, respectively. A higher GFR was also noted in two weeks in all groups, and reached statistical significance in each group up to one year. At one year evaluation, however, there was a significant difference between losartan (by 11.2±1.3 ml/min) as compared to enalapril group (by 5.4±1.2 ml/min). There was only a tendency for higher nephroprotection of aliskiren over losartan after one year of treatment. Tolerability of drugs was good in all treatment arms.

Conclusion: In CHF patients with CKD and arterial hypertension the nephroprotective effects may differ due to different renin-angiotensin-aldosterone system inhibition, being somewhat greater in terms of higher GFR with aliskiren and losartan as compared to enalapril after one year of treatment.
Use of lipid lowering therapy in primary care across Europe: results from the European study on cardiovascular risk prevention in daily practice (EURIKA)

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Purpose: Current European guidelines recommend that patients free from cardiovascular disease (CVD) but estimated to be at ≥5% 10-year risk of CVD mortality should be more vigorously pharmacologically treated than those at lower risk. The recommended target level of low-density lipoprotein cholesterol (LDL-C) is <2.5 mmol/l or <1.8 mmol/l for those at very high risk (VHR; those with diabetes mellitus [DM] or ≥10% 10-year mortality risk). We examined the use of lipid lowering therapy (LLT) and achievement of LDL-C level targets in routine clinical practice in Europe.

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 from May 2009 to January 2010, recruiting 7641 patients aged 50 years who were free of clinical CVD but had at least one cardiovascular risk factor (dyslipidaemia, hypertension, DM, smoking or obesity). Ten-year CVD mortality risk was estimated using the Systematic Coronary Risk Evaluation (SCORE) algorithm. LDL-C levels were measured and use of LLT was noted, including the agents and doses used. Statin therapy was classified as low-intensity (LIS; pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin <40 mg or rosuvastatin <20 mg) or high-intensity (HIS; atorvastatin ≥40 mg or rosuvastatin ≥20 mg).

Results: We identified 3278 individuals who were receiving any form of LLT, of whom 3040 (92.7%) were receiving a statin. Of the 4363 patients not receiving LLT, 1741 (39.7%) had DM or a SCORE risk ≥5%. LDL-C levels were available for 3151 participants receiving LLT, for whom LDL-C levels were not at target (<2.5 mmol/l) in 1931 (61.3%). Only 8.9% of patients on LLT were receiving HIS. Of those receiving LIS, only 39.8% had LDL-C levels <2.5 mmol/l. A subset of 2970 patients were at VHR, of whom only 1469 (49.5%) were receiving any form of LDL-C targets were at target (<1.8 mmol/l) in 1717 of these patients. Only 17.1% of VHR patients on LLT were receiving HIS: of the VHR patients receiving LIS, only 17.1 had achieved LDL-C levels <1.8mmol/l.

Conclusion: Approximately 40% of patients aged >50 years with at least 1 cardiovascular risk factor who are not currently receiving LLT are at high risk of CVD and treatment with LLT was noted, including the agents and doses used. Statin therapy was classified as low-intensity (LIS; pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin <40 mg or rosuvastatin <20 mg) or high-intensity (HIS; atorvastatin ≥40 mg or rosuvastatin ≥20 mg).

P4657

Fasting and postprandial triglycerides are independent cardiovascular risk markers in non-obese coronary artery disease patients with normal glucose tolerance

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Background: Risk prediction with fasting triglycerides (TG) in high cardiovascular risk patients with coronary artery disease who are overweight or obese remains uncertain. The role of postprandial serum triglycerides as a risk modifier in secondary prevention is unknown. We hypothesized that the postprandial TG increase is a superior risk predictor compared to fasting TG in patients with coronary artery disease (CAD).

Methods: An oral triglyceride load (OTL, 750 mg fat) and glucose tolerance test (OGT, 75g glucose) was developed to obtain standardized measurements of postprandial TG in an observational, prospective study on 514 consecutive patients at high risk for CVD who were free of clinical CAD but had at least one cardiovascular risk factor (dyslipidaemia, hypertension, DM, smoking or obesity). Ten-year CVD mortality risk was estimated using the Systematic Coronary Risk Evaluation (SCORE) algorithm. LDL-C levels were measured and use of LLT was noted, including the agents and doses used. Statin therapy was classified as low-intensity (LIS; pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin <40 mg or rosuvastatin <20 mg) or high-intensity (HIS; atorvastatin ≥40 mg or rosuvastatin ≥20 mg).

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Conclusion: Approximately 40% of patients aged >50 years with at least 1 cardiovascular risk factor who are not currently receiving LLT are at high risk of CVD and treatment with LLT was noted, including the agents and doses used. Statin therapy was classified as low-intensity (LIS; pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin <40 mg or rosuvastatin <20 mg) or high-intensity (HIS; atorvastatin ≥40 mg or rosuvastatin ≥20 mg).

P4656

Low levels of IgM antibodies against phosphorylcholine (anti-PC) increase the risk of ischemic cardiovascular events among European men at high risk of cardiovascular events

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Purpose: IgM antibodies against phosphorylcholine (anti-PC) reduce the uptake of oxidized LDL and inhibit the effect of-inflammatory phospholipids, thereby exerting cardioprotective effects. Previous studies have shown that low levels of IgM serum levels increase the risk of cardiovascular (CV) events. The aim of the present study was to investigate the association of low levels of anti-PC with the incidence of CV events and the progression of intima media thickness (IMT) in a large prospective cohort of men at high risk of cardiovascular diseases contained in the IMPROVE study, a prospective multicenter European study.

Methods: 3711 subjects (age 54-79) with at least three established cardiovascular risk factors at enrollment. Serum levels of anti-PC were measured at baseline and at each 10 years of follow-up. The risk of ischemic cardiovascular events and IMT progression was analyzed by a Cox regression and a logistic regression analysis, respectively. Risk estimates were adjusted by center, gender, age and the conventional cardiovascular risk factors. Results: Absolute levels of IgM were classified into quartiles [Q1 ≤ 0.115 (≤90th percentile), Q2 = 0.116-0.15 (90-92.5th percentile), Q3 = 0.151-0.20 (92.5-95th percentile), Q4 > 0.20 (≥95th percentile)] of the fasting IMT progression, i.e. the segment showing the fastest progression over 30 months in the whole carotid tree, with an OR of 1.42 (95%CI:1.03-1.98). No significant associations were found in women.

Conclusions: These results suggest that low anti-PC serum levels increase the risk of cardiovascular events in men partly through effects on progression of atherosclerosis.

P4658

The effect of plant stanol esters on blood flow in adults

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Purpose: LDL cholesterol can be reduced by about 10% with dietary means by consuming 2 g of plant stanols daily, but their effect on cardiovascular health is controversial. The aim of this study was to evaluate the long-term effects of plant stanol ester consumption on arterial stiffness and endothelial function in 92 adults with mild to moderate hypercholesterolemia in a placebo-controlled, randomized, double-blind intervention lasting for six months.
Methods: The subjects replaced 20 g/d of their regular fat intake with the test spread with (stakest group) or without (controls) plant stanol esters (3 g/d of plant stanols). Compliance was verified with measuring serum plant stanols. Arterial stiffness was measured using the pulse wave velocity and the obtained variables were carotid-ankle vascular index (CAVI) and augmentation index (AI), and endothelial function was measured as reactive hyperaemia index (RHI) using peripheral arterial tonometry. Serum sterols were analyzed with gas-liquid chromatography. The study was performed according to the principles of the Declaration of Helsinki of the World Medical Association, and the Ethics Committee of the Hospital District of Helsinki and Uusimaa had accepted the study protocol.

Results: The mean age of the study population was 50.8 ± 1.0 (SEM) years with 38% of males. At baseline, mean LDL cholesterol was 3.5 ± 0.1 mmol/L, HDL cholesterol and serum triglycerides were within the reference values, CAVI was 8.7 ± 0.1, AI 9.1 ± 1.9, and RHI 2.2 ± 0.1, respectively. The intervention was well tolerated without any side-effects, and compliance was good. LDL cholesterol was reduced in the stakest group by 7.9 ± 1.6% from baseline and by 10 ± 2.7% from controls (P < 0.05 for both). AI changed significantly differently between the groups: it was increased in the controls and decreased in the stakest group (P = 0.04 between groups). CAVI was decreased in men with stakest by 1.1 ± 1% and increased in control men by 3.2%, so that the difference was significant (P < 0.001). In the stakest group, the change in RHI was inversely related to the change in LDL cholesterol level suggesting that the more LDL cholesterol was reduced, the more AI fell. No correlation was found between the change in CAVI and the change in LDL cholesterol in either group.

Conclusions: Six-month consumption of 3 g plant stanols as esters decreased arterial stiffness and increased endothelial function by reducing LDL cholesterol by 10% compared to controls. This study is dedicated to the memory of Professor Tatu A. Miettinen.

P4659 Reduced blood pressure and risk of future cardiovascular disease from structured care algorithm in primary care patients with persistent hypertension: a multicentre randomised controlled trial

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Purpose: To determine the impact of reduced systolic and diastolic blood pressure (BP) on the risk of cardiovascular disease achieved in primary care patients with persistently elevated BPs randomised to enhanced usual care (UC) or an algorithm to optimise risk profiling and BP control in the Valsartan Intensified Primary Care: Reduction of Blood Pressure (VIPER-BP) Study.

Methods: Prospective, multi-centre randomised controlled trial involving 119 primary care clinics and 2185 patients. The VIPER-BP intervention comprised automated risk profiling and standardised guideline-based, stepwise pharmacological treatment (initial angiotensin receptor blocker (ARB) mono-therapy or two forms of single pill ARB combination therapy) and computer assisted intensified follow-up and treatment titration. Using 26 week follow-up data (intention to treat) we used - a) change in risk profile (age as a constant) and b) age, initial systolic and diastolic BP and change in BPs, we calculated the impact of VIPER-BP intervention on absolute 5 year cardiovascular risk score (ACVRS) and relative risk (RR) of a future coronary artery disease (CAD) or stroke event.

Results: Overall, 1962 patients (aged 59±12 years, 62% men, 67% prior hypertensive history and BP >140/90 mmHg) who remained above the individualised BP target (national guidelines) were randomised (1:2 ratio) to UC (n = 524) or VIPER-BP intervention (n = 1438). During follow-up, BP changed from 150±7/87±8 to 136±5/81±11 mmHg in the VIPER-BP group vs. 149±7/88±7 to 139±5/81±10 mmHg in the UC group. Accordingly, at 26 weeks 72.1% UC vs. 81.4% VIPER-BP patients had a lower systolic BP (<90 mmHg) in favour of VIPER-BP – p < 0.001. For both systolic (R2 = 0.39) and diastolic (R2 = 0.28) BP there was a strong linear relationship with greater falls (r = 0.75 mmHg) in those with the highest initial BP. Mean falls in calculated ACVRS from baseline were greatest in VIPER-BP patients (-3.7% ± 4.5% vs. -2.6% ± 4.5%, adjusted mean difference -1.13 95% CI -1.63 to -0.64%, p < 0.001). Similarly, the adjusted risk of CAD (RR 0.75 ± 0.36 vs. 0.81 ± 0.39; p < 0.001) and stroke (RR 0.69 ± 0.49 vs. 0.86 ± 0.52; p < 0.001) was attenuated most in the VIPER-BP group.

Conclusions: VIPER-BP is one of the largest studies of its type ever undertaken and reflects real-world practice. In those patients with persistently elevated BP being managed in primary care, a structured care algorithm not only results in lowered BP (those with higher BPs benefiting most) but reduces absolute and relative risk of future cardiovascular disease.

P4660 Successful weight loss following gastric sleeve surgery improves vascular function in obese individuals

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Background: The risk of premature atherosclerosis rises with obesity and previ-ous studies have shown that obese individuals have stiffer arteries than those of normal weight. Vascular dysfunction is probably related to the long term prognosis of these patients. There are no papers about vascular function evaluation after a recently used bariatric intervention: laparoscopic gastric sleeve (GS).

Purpose: To investigate whether weight loss is associated with changes in aortic (Ao) vascular function 6 months after GS.

Methods: 34 consecutive obese subjects (mean age 39 ± 11 years, 35.2% men) scheduled for GS were prospectively studied before and 6 months after intervention.

Aortic vascular function was assessed by following indexes, calculated using systolic and diastolic ascending Ao diameters and blood pressure values: Ao Strain, Ao distensibility (Ao Stiff) (Ao Stiff).

Results: Baseline Ao vascular function parameters correlated with body mass index (BMI), Waist Circumference (WC), systolic hypertension stage and blood glucose level and not with age, sex, blood lipid profile or smoking status - see table.

Correlation coefficients (r) Ao Dis Ao Strain Ao Stiff

| BMI | -0.6** | -0.5** | 0.3 |
| WC | -0.6* | -0.5* | 0.3* |
|Blood glucose level | -0.3 | -0.4** | 0.4* |

*p < 0.05, **p < 0.01.

At 6 months follow up, compared with baseline subjects had very significant reduction of: BMI (32.3 ± 7.4 vs. 43.6 ± 11.9 kg/m²), WC (101.7 ± 26.4 vs. 124.9 ± 23.3 cm), levels of total cholesterol (183.3 ± 29.5 vs. 222.3 ± 39.3 mg/dl), LDL-cholesterol (100.1 ± 38.5 vs. 138.2 ± 73.3 mg/dl), triglycerides (103.2 ± 36.7 vs. 167.7 ± 86.4 mg/dl), blood glucose (87.4 ± 12.6 vs. 119.5 ± 52.4 mg/dl) (all p < 0.01). HDL-cholesterol level increased at 50.4 ± 10.9 mg/dl from 45.9 ± 10.3 mg/dl (p = 0.02).

The proportion of hypertensives decreased from 35.3% to 8.6% (p < 0.01).

6 months after GS surgery, patients had also increased Ao Dis (2.1 ± 0.9 vs. 1.0 ± 0.7; 10.6 cm² dynes⁻¹) Ao Stiff (22.9 ± 8.3 vs. 12.2 ± 8.6%) and decreased Ao Stiff (2.6 ± 0.8 vs. 6.2 ± 4.1) (all p < 0.01).

Conclusion: By successful weight loss, 6 months after bariatric surgery-gastric sleeve vascular function parameters improve, in association with favorable metabolic and blood pressure changes.
CARDIAC MAGNETIC RESONANCE ACROSS THE SPECTRUM OF CARDIOMYOPATHY

P4662 Comprehensive assessment of diastolic function from velocity-encoded cardiac magnetic resonance in patients with hypertrophic cardiomyopathy

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Purpose: To elucidate the role of cardiovascular magnetic resonance (CMR) in the diagnosis and management of constrictive pericarditis

Methods: In 47 patients with a clinical diagnosis of constrictive pericarditis a complete CMR exam was performed to assess biventricular volumes, function, myocardial thickness, T1, T2-weighted signal intensity, and post-gadolinium T1-weighted delayed enhanced. A CMR diagnosis of pericardial constriction was based on pericardial thickening, subepicardial fibrosis, and on the presence of early gadolinium enhancement within the pericardium. The CMR diagnosis was compared with echocardiography and the final diagnosis (based on clinical, multimodality imaging, catheterization, as well as the opinion of a team of both cardiologists and surgeons) was considered as the gold standard. The primary end point of the study was to determine the diagnostic accuracy of CMR in the diagnosis of constrictive pericarditis. The telephonic follow-up of all patients was performed to assess the incidence of major events (surgery and death)

Results: CMR resulted as specific as echocardiography (100%) but significantly more sensitive (91.2% vs 50%) in the diagnosis of constrictive pericarditis. The positive predictive value was 100% in both techniques, but the negative predictive value was significantly higher for CMR (97.2%) than for echocardiography (50%). The most sensitive and specific parameter resulted related to pericardium thickness >3 mm. Sigmoid motion of the interventricular septum was a specific (97.1%) but not sensitive (51.6%) parameter. A CMR diagnosis of pericardial constriction was a significant predictor of mortality (p = 0.039).

Conclusions: CMR yielded a high sensitivity and specificity for the diagnosis of constrictive pericarditis. CMR provides useful information in the clinical suspicion of constrictive pericarditis as second-level study, adding significant more information over echocardiography. Its diagnostic and prognostic role allows to reserve an invasive diagnostic (cardiac catheterization) and therapeutic approach (pericardietomy).

P4665 Role of cardiovascular magnetic resonance in the diagnosis and management of constrictive pericarditis

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Purpose: To assess the state of myocardial energy metabolism in patients with ventricular hypertrophy by 31P magnetic resonance spectroscopy

Methods: The study included 52 people: group I - patients with AH and LVH (16), group II - patients with HCM (16), group III - relatively healthy volunteers (20). The average age in the groups I and II was 57±5.9 years and 54±6.3 years, respectively, which were not significantly different from each other and group III - 56±6.7 years (p = 0.05).

ECG-synchronized single voxel 31P MRS was performed on high field MRI system (3T – Philips Achieva, using an adiabatic pulse and iterative shimming. The ECG-synchronized single voxel 31P MRS was performed on high field MRI system (3T – Philips Achieva, using an adiabatic pulse and iterative shimming. The ECG-synchronized single voxel 31P MRS was performed on high field MRI system (3T – Philips Achieva, using an adiabatic pulse and iterative shimming.

Results: Mean age was 47±20.2 years in HCM pts and 47.5±16.1 in HV (p = NS). LV mass, mass/end-diastolic volume and LA volumes were increased in HV group, but the ratio between areas of IVS peaks was found at 20 HCM pts. While there was no significant difference in E/A in IVS, myocardial longitudinal velocity E and LA emptying fraction were markedly lower in HCM pts. Furthermore, E/E ratio and LV ejection time (DT) were higher in HCM pts. There was a linear relationship between increased LV mass and increased LA volumes (p < 0.001), IVRT (p = 0.003), DT (p = 0.002), E/E (p = 0.002) and decreased E (p = 0.003) independent of age, gender and BSA.

Conclusion: Comparison of HCM pts with HV by CMR showed significantly altered LV diastolic function and increased LA volumes related to increased LV mass. Assessment of diastolic function may be considered for routine comprehensive evaluation of left heart function in HCM.

P4663 High energy myocardial metabolism in patients with different causes of left ventricular hypertrophy by 31P magnetic resonance spectroscopy

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Purpose: To assess the state of myocardial energy metabolism in patients with arterial hypertension (AH) and left ventricular hypertrophy (LVH) and patients with hypertrophic cardiomyopathy (HCM) compare with healthy volunteers by 31P magnetic resonance spectroscopy.

Methods: The study included 52 people: group I - patients with AH and LVH (16), group II - patients with HCM (16), group III - relatively healthy volunteers (20). The average age in the groups I and II were 6,3 years, respectively, which were not significantly different from each other and group III - 5,5 years (p < 0.05).

ECC-synchronized single voxel 31P MRS was performed on high field MRI system (3T – Philips Achieva, using an adiabatic pulse and iterative shimming. The localisation was done by ISIS. Voxel size was fixed on 92 mm3. The standard protocol was consist 128 repetitions and repetition time was 10 000 ms.

Results: In group I all patients showed symmetrical hypertrophy of the left ventricle, interventricular septum (IVS) thickness (18.7 ± 0.24 mm) was significantly different from group II, p < 0.05. The IVS thickness in group III was 7.8 ± 0.12 mm. The lowest index value of Pcr/ ATP was detected in patients with HCM - 1.32 ± 0.35, which was significantly lower than the index in patients with AH and LVH - 1.76 ± 0.29, p < 0.05. The highest index value was recorded in a group of healthy volunteers - 2.18 ± 0.32, which was significantly higher than the values in the groups I and II.

Conclusions: 31P MRS revealed signs of myocardial energy metabolism alterations in patients with LVH. The greatest changes are detected in HCM; patients with AH and LVH also demonstrate a significant reduction in the energy index.

P4664 The left atrium build-up: amyloid in patients with cardiac amyloidosis (CA) is associated with left atrium dysfunction: morphological and functional evaluation by cardiovascular magnetic resonance

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Purpose: The Amyloidosis is a systemic disease that can affect the heart, (cardiac amyloidosis or CA). Ventricular biopsy is the diagnostic gold standard but it is an invasive test, then the diagnosis is made by echocardiography (ECHO) and/or cardiac magnetic resonance (CMR) and confirmed by non-cardiac biopsy. CMR study made with gadolinium (CMRGad) is able to detect CA at both left ventricle (LV) and left atrium (LA) levels. Atrial dilatation (AD) detected by ECHO may be an early marker of an AD for those who later present with diastolic dysfunction. In order to test whether CMR can be a substitute of CA that can affect only the LA called Isolated Atrial Amyloid (IAA).

Methods: We evaluated by CMR gad 106 patients with confirmed CA. Patients with atrial fibrillation and/or with pericardial effusion were excluded. In all patients we found LGE at LV at a zebrafish heart typical for CA; in 73 patients we found LGE at the LA (group Atria+); in 33 patients we did not found LGA at LA (Atria−) (figure1). By cine sequences we measured major and minor atrial diameters both in systole and in diastole in a four chamber view (FCV). We then calculated: fractional shortening of the major diameter (FSL%), of the minor diameter (FSR%) and fractional area change (FAC%). We also estimated LV stroke volume (SV), ejection fraction (EF) and mass by CMR tools.

Results: Atria+ patients showed FSAP FSRL and FAC significantly reduced compared to Atria−(p = 0.000000001, 0 = 0.0000000000001, p = 0.0000003). LA is more dilated in Atria+ compared to the Atria−. LV function is worse in Atria+ (EF = 51% vs 63% Atria− p = 0.001).

Conclusions: Our results suggest that the atrial build-up of CA may lead to structural and functional changes. The LA dysfunction, may induce LV function worsening due to impaired atrial systole. It is unclear why some patients have LA involvement and some others do not. Probably, LA involvement may represent a different subtype or stage of CA. Preliminary data suggest that the mortality in Atria+ is higher than Atria−. If these data are confirmed, LA involvement detected by CMR may be considered as a diagnostic and prognostic marker of CA.
Late gadolinium enhanced cardiac magnetic resonance in lamin A/C, cardiac troponin T and myosin binding protein C gene mutation related cardiomyopathies: characteristics and clinical associations

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Purpose: To investigate the correlation between characteristics of late gadolinium enhancement (LGE) in asymptomatic and symptomatic carriers of known cardiomyopathies. Methods: Thirty-eight patients with known gene mutations of lamin A/C (LMNA), cardiac troponin T (TNNT2) or myosin binding protein C (MYBPC3) were recruited. All TNNT2 carriers and 1/5 LMNA carriers with midwall patterns of LGE located at the basal or mid-ventricular septal wall were the most commonly seen pattern in all gene mutations (57% of all LGE data). The presence of LGE was assessed by a 1.5 T clinical scanner to determine presence, pattern and location of LGE. Associations between clinical characteristics, gene mutation and LGE were analyzed. Results: LGE was present in 19/30 (63%) MYBPC3 carriers, all TNNT2 carriers and 1/5 (20%) LMNA carriers; midwall patterns of LGE located at the basal and/or mid-ventricular septal wall were the most commonly seen pattern in all gene mutations (57% of all LGE data). Conclusion: LGE is a common finding in cardiomyopathy patients with known gene mutations, most prominently expressed with basal and/or mid-ventricular septal midwall patterns. Its presence seems to be independent of the symptomatic stage of the disease or its phenotypic manifestation.

Diffuse myocardial fibrosis by post-contrast T1-time

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Introduction: Myocardial fibrosis is a histological hallmark of heart failure and an independent predictor of adverse outcome. Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) is a standard noninvasive tool for the identification of focal fibrosis. Diffuse fibrosis, however, cannot be quantified by LGE. Recently, it was shown that diffuse myocardial fibrosis is strongly related to post-contrast longitudinal relaxation (T1) time. The aim of our study was to assess diffuse myocardial fibrosis by CMR T1 mapping in patients with known heart failure. Methods: Late gadolinium enhancement (LGE) was performed 10 minutes after a gadolinium bolus using an inversion recovery sequence. Myocardial T1 mapping was performed 10 minutes after a gadolinium bolus using an inversion recovery sequence. Results: Serum NT-proBNP levels in patients ranged from 126 to 4239 pg/ml (mean 763±64 pg/ml). Areas with LGE indicating local fibrosis in 5 patients were excluded from T1 analysis. Post-contrast T1 was significantly shorter in patients with NT-proBNP levels >125 pg/ml of preserved left ventricular ejection fraction (EF>50%). Conclusion: T1 mapping may be used as a noninvasive tool for the assessment of diffuse myocardial fibrosis.

Relation of myocardial fibrosis to left ventricular and mitocondrial dysfunction in nonischemic dilated cardiomyopathy—a comparison focal and interstitial fibrosis

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Purpose: Mitochondrial dysfunction plays an important role in ventricular dis-
P4690
Ranolazine modifies the electrophysiological effects of acute myocardial stretching
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Purpose: Mechano-electrical feedback is an arrhythmogenic factor and several mechanisms have been implicated in this effect, involving the stretch-activated ion channels, autocrine/paracrine events or the activation of beta-adrenergic receptors as a result of the stretch-mediated release of catecholamines from intramyocardial nerve endings. Ranolazine inhibits the late inward Na+ current, but we do not know whether it also modulates the electrophysic responses to myocardial stretch in acute ventricular stretching produces modifications on the cardiac electrophysiological properties such as an increase of dominant frequency (DF) during ventricular fibrillation (VF). The aim of this study is to analyze and to compare the acute effects of ranolazine in the stretch-activation frequency under deformation of this drug.

Methods: In eighteen Langendorff-perfused rabbit hearts VF recordings were obtained using epicardial multiple electrodes on the left ventricle free wall under control conditions (n=9) and during perfusion of ranolazine (5 μM) (n=9). VF was induced using pacing at increasing frequencies, without interrupting coronary perfusion. After the induction of VF, stretching was applied and maintained for ten minutes and after this period, local stretching was suppressed. DF during VF was determined using spectral techniques and spectral concentration (SpConc) was calculated as a percentage of the total energy contained in the interval of DF = 0 Hz.

Results: In control series, myocardial stretch increased DF of VF from 13.6 ± 2.3 Hz to 19.1 ± 3.1 Hz (p=0.001), with a SpConc that decreased from 29.9 ± 8% to 18.3 ± 2% (p=0.001). These parameters returned to baseline values 3 minutes after stretch and perfusion with saline (9 μM NaCl). DF increased from 13.1 ± 2.4 Hz (n=9, and SpConc 24.6 ± 2.7%, n=9). In ranolazine group, DF prior to stretch was 11.4 ± 1.6 Hz (p=0.053 vs control), and the SpConc was 25.4 ± 4% (n=3 vs control). During myocardial stretch DF increased to 14.5 ± 2.4 Hz (p=0.012 vs baseline and p=0.001 vs control), with a SpConc of 23.4% (ns vs baseline and p=0.01 vs control). After suppressing stretch, DF returned to values similar to baseline state (10.6 ± 1.3 Hz, ns vs baseline, and p=0.034 vs control), with a SpConc of 28.4 ± 4% (ns vs baseline and vs control). The maximum DF percentage increment obtained in the control group during stretch was 41% versus 23% in the ranolazine group, being the latter percentage significantly lower than in control group.

Conclusion: The inhibition of the late inward Na+ current with ranolazine reduces the ventricular electrophysiological modifications produced by acute myocardial stretching.

P4691
Novel electrophysiological properties of dronedarone: Inhibition of human cardiac two-pore-domain potassium (K2P) channels
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Purpose: Dronedarone is currently used for the treatment of paroxysmal and persistent atrial fibrillation (AF). Pharmacological inhibition of cardiac two-pore-domain potassium (K2P) channels results in action potential prolongation and has recently been proposed as novel antiarrhythmic strategy. We hypothesized that blockade of human K2P channel contributes to the electrophysiological efficacy of dronedarone in AF.

Methods: Two-electrode voltage clamp electrophysiology was used to record K2P currents from Xenopus oocytes.

Results: All functional human K2P channel were screened for dronedarone sensitivity, revealing significant and concentration-dependent inhibition of cardiac K2P2.1 (IC50 = 26.7 μM) and K2P3.1 channels (IC50 = 18.7 μM) with maximum current reduction of 60.3% and 65.5%, respectively. The molecular mechanism of action was studied in detail. Dronedarone block was voltage-independent and affected open and closed channels. K2P3.1 currents were reduced in frequency-dependent fashion in contrast to K2P2.1, Mutagenesis studies revealed that amino acid residues implicated in K2P3.1 drug interactions were not required for dronedarone blockade, indicating a novel pharmacological binding mode.

Conclusions: The class III antiarrhythmic drug dronedarone targets multiple human cardiac two-pore-domain potassium channels, including atrial-selective K2P3.1 currents. K2P current inhibition by dronedarone represents a previously unrecognized mechanism of action that is expected to suppress AF by prolonging atrial refractoriness in vivo.

P4692
Mechanisms of antiarrhythmic activity of new class III agent Niferidile in patients with supraventricular arrhythmias

Background: Niferidile (NI) is a new potassium channel blocker that inhibits transient outward and delayed rectifier currents. Preclinical studies showed that NI increases effective refractory periods (ERP) in atria more than in ventricles. High affinity of NI to atrial myocardium is thought to contribute to high efficacy in supraventricular arrhythmias and to low risk of ventricular proarrhythmia.

Aim: To evaluate electrophysiological mechanisms of antiarrhythmic effect of NI in patients with paroxysmal supraventricular tachycardia (PSVT).

Materials and methods: Effects of NI (20 μg/kg intravenously) were studied in 24 patients (14 males) with PSVT (12 orthodromic tachycardia in WPW syndrome, 8 AV-nodal reenterant tachycardia, 4 orthodromic tachycardia due to concealed bypass tract) during endocardial electrophysiological study. Termination of sustained paroxysms of SVT by NI could be investigated in 18 patients and prevention of reinstitution of PSVT in 22 patients.

Results: NI terminated PSVT in 77.77% and prevented reinstitution in 72.72% of patients. NI increased ERP of right atrium by 22.88% (p<0.001), left atrium by 20.09% (p<0.05), right ventricle by 12.33% (p<0.05) and accessory pathways (antegrade by 21.47%, retrograde by 32.83%). NI did not affect sinus node and atrioventricular conduction. NI significantly increased relative refractory period (RRP) of His-Purkinje system (33.41%), NI prolonged QT (by 24.5%, p<0.01) and QTc (by 17.31%, p<0.05) intervals. One patient developed short runs of torsade de pointes shortly after injection of drug.

Conclusions: Prolongation of ERP, predominantly in atria and accessory pathways, and ERP in His-Purkinje system are main electrophysiological effects of NI. New drug showed high antiarrhythmic efficacy and good safety profile in patients with PSVT.

P4693
Flecainide improves exercise testing parameters in patients with catecholaminergic polymorphic ventricular tachycardia

Purpose: Despite recent basic and clinical evidence, F is not included in current guidelines for CPVT management. We present a single-centre experience of flecainide (F) addition in patients (P) on maximal betablockers dose (BB) exhibiting catecholaminergic polymorphic ventricular tachycardia (CPVT).

Methods: 17 phenotype and genotype positive CPVT P from 2 different families were enrolled. Maximal arrhythmia (MA) in exercise testing (ET, Bruce protocol) was defined as the worst of: none, 1) isolated ventricular extrasystoles (VE) or <5 binomial VE, 2) ≥5 binomial VE, 3) ≥1 ventricular couplet, 4) ≥1 run of non-sustained ventricular tachycardia and 5) sustained ventricular tachycardia. The ventricular and atrial pacing (VP) was assessed by the total VEs manually checked by the operator to discard artifacts and by the area under the curve

Abstract P4693 – Table 1. Effect of flecainide on exercise testing

<table>
<thead>
<tr>
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<th>On BB (N=10)</th>
<th>Same patients but on BB plus flecainide (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minutes of exercise</td>
<td>9.2 ± 2.2</td>
<td>10.7 ± 3.3</td>
</tr>
<tr>
<td>Maximal arrhythmia</td>
<td>3.0 ± 0.8</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>VP/BBVC and total ventricular extrasystoles</td>
<td>24.6 ± 221.0 and 464.5 ± 51.3</td>
<td>12.3 ± 13.3 and 5.6 ± 6.4</td>
</tr>
<tr>
<td>Threshold of any ventricular arrhythmia: bpm and stage</td>
<td>114 ± 4.9 and 2.7 ± 1.3</td>
<td>124 ± 18.4 and 4.0 ± 0.7</td>
</tr>
<tr>
<td>Threshold of maximal ventricular arrhythmia: bpm and stage</td>
<td>122 ± 11.4 and 3.2 ± 0.9</td>
<td>123 ± 10.6 and 4.0 ± 0.9</td>
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Arrhythmia mechanisms and antiarrhythmic drugs / Arrhythmia mechanisms 815

Value-based pricing for dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation in Germany

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Warfarin effectively reduces the incidence of ischemic stroke in patients with non-valvular atrial fibrillation (AF) but increases the risk of major and intracerebral bleeding, mortality and myocardial infarction. To assess the benefits and risks of the NOACs, based on the available trial evidence, a network meta-analysis (NMA) was performed to compare dabigatran (75 mg bid, 110 mg bid), rivaroxaban (20 mg od, 30 mg bid) and apixaban (5 mg bid, A5) showed equivalent or superior efficacy and safety compared to warfarin in these patients. We aimed to analyse the value-based price (in Euro) for Germany for these NOACs from a social health perspective. The data of the outcomes of ischemic cerebral and non-cerebral embolism, major and intracerebral hemorrhage, myocardial infarction, and mortality were taken from dabigatran’s RE-LY (D110 and D150), rivaroxaban’s ROCKET (R20), and apixaban’s ARISTOTLE trials (A5). All were randomized and prospective trials and compared the NOAC with dose-adjusted warfarin including more than 6,000 patients. The quality-adjusted life-years (QALYs), costs (in Euro 2012 for Germany), and incremental cost-effectiveness ratios (ICER) for the NOACs were calculated with adjusted-dose warfarin as comparator. The societal willingness to pay was set conservatively at 50,000 Euro per QALY. A Markov decision model was adopted using the Tree Age Pro 2011 program. The current daily cost of D110, D150, and R20 in Germany account for about 3.20 Euro/patient/day. The relation of QALYs was 11.53/11.41 for D110/warfarin, 11.66/11.41 for D150/warfarin, 12.32/12.05 for R20/warfarin, and 11.74/11.5 for A5/warfarin. Total costs were higher for all NOACs compared to warfarin. With this calculations ICER was found for all NOACs in a range of about 50,000 Euro per QALY. Provisionally calculated daily dose-based prices for the NOACs compared to dose-adjusted warfarin ranged from 1.25 Euro to 2.50 Euro per day. Our results are robust in a wide range of sensitivity analyses. The daily value-based price for D110, D150 and R20 are markedly lower than those conservatively effective in Germany. The data should be seen as preliminary and need further adaptation to current German methodological standards. The model can be used to calculate such prices for every community and country.

Network meta-analysis of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation

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The three new oral anticoagulants (NOAC) dabigatran (two doses), rivaroxaban, and apixaban showed equivalent or superior efficacy and safety compared to warfarin in patients with non-valvular atrial fibrillation. A head-to-head clinical trial comparison of these NOACs is highly unlikely to be performed given the expense of such an investigation. Therefore, there is a need for an unbiased comparative assessment of the benefits and risks of the NOACs, based on the available trial data. Appropriate statistical tools for such an analysis is mixed treatment comparison -based network meta-analysis (NMA). A NMA of the 3 new oral anticoagulants was performed extracting the data of the RE-LY study of dabigatran 110 mg bid and dabigatran 150 mg bid, the ROCKET trial of rivaroxaban and the ARISTOTLE trial of apixaban for the composite outcome of ischemic stroke and systemic embolism with the same rate of intracerebral bleeding, mortality and myocardial infarction. The NMA was performed to compare these endpoints using odds ratios and confidence intervals. Dabigatran (150 mg bid) showed superior efficacy in preventing ischemic stroke plus systemic embolism to dabigatran (110 mg bid, p=0.036) and rivaroxaban (p=0.038). Apixaban had equivalent efficacy with rivaroxaban and dabigatran (either dose). Apixaban was safer (less major bleeding) than dabigatran (150 mg bid, p=0.036) or rivaroxaban (p=0.005). Intracerebral hemorrhage occurred more frequently for all agents and regimens except for rivaroxaban (higher risk than dabigatran 110 mg bid, p=0.0076). Myocardial infarction occurred less frequently with rivaroxaban and apixaban compared to either dose of dabigatran (all p<0.05). All-cause mortality was not different for any agent or regimen. In the absence of head-to-head comparisons, this network meta-analysis suggests that apixaban and dabigatran 110 mg bid may offer the best benefit-risk balance for stroke prevention in non-valvular atrial fibrillation. Dabigatran 150 mg bid may be preferred for patients with a high risk for embolism.

ARRHYTHMIA MECHANISMS

Administration of vernakalan in a highly sensitive model of proarrhythmia caused prolongation of myocardial repolarization without increased vulnerability to arrhythmias

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Purpose: Vernakalan (VER) is a novel and relatively atrial-selective antiarrhythmic drug that inhibits potassium and sodium channels frequency-dependent. Previous studies demonstrated conversion of atrial fibrillation (AF) to sinus rhythm (SR) by VER. The present study investigated whether VER in escalating high doses in a highly sensitive rabbit model of proarrhythmia.

Methods: Eightendo- and epicardial monophasic action potentials (MAP) and action potentials of atrial and ventricular cells from 12 rabbits treated with VER, compared to 13 rabbits treated with sotalol (SOT).

Results: Administration of VER (10 μM and 30 μM) showed a significant prolongation of QT-interval compared to baseline (10 μM: +25 ms, 30 μM: +51 ms, p<0.05) and an enhanced action potential duration (APD90, 10 μM VER: +18 ms; 30 μM VER: +20 ms). APD90 prolongation was accompanied by a distinct increase in effective refractory period (ERP, 10 μM: +40 ms, 30 μM: +50 ms, p<0.05) leading to a significant increase in postrepolarization refractoriness (PRR) defined as the difference between the ERP and APD90. Dispersion of repolarization was not altered by VER. In trabeculae carnaress hearts with mechanical activation, reduced potassium concentrations did not lead to early afterdepolarizations (EAD) or polymorphic ventricular tachycardia despite significant QT-prolongation. Application of SOT (100 μM) caused prolongation of QT-interval (+52 ms and APD90 (+33 ms) along with an increased ERP (+49 ms) and PRR (+15 ms). In contrast to VER, SOT enhanced dispersion of repolarization (+19 ms, p<0.05) and evoked EAD in 12 of 13 rabbits and torsades de pointes (Tdp) in 9 of 13 rabbits after lowering of potassium level.

Conclusions: The present study showed that administration of VER and SOT caused comparable prolongation of myocardial repolarization. PRR was increased by both drugs. In contrast to SOT, VER did not affect dispersion of repolarization nor generate EAD and thus did not provoke ventricular tachyarrhythmias. In summary, administration of VER seems to be safe despite significant prolongation of QT-interval.
Zooming in on the focus: flecainide inhibits atrial fibrillation maintained by aconitine

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Background: The contribution of focal discharges for the maintenance of atrial fibrillation (AF) is under discussion. Aconitine (ACO) is used in a model for focal atrial fibrillation. The aim of the present study was to investigate the influence of flecainide on ACO-induced focal discharges.

Methods and results: In open chest experiments in goats (n=6), we performed high density epicardial mapping to investigate the interaction of focal tachycardia induced by ACO with activation pattern during AF. The topical application of ACO-crystals on the left atrium in the middle of the mapping area induced rapid focal discharges with radial spread of activation exactly at the place of ACO-application. Epicardial cycle length (CL): 242±15 ms. Local electrograms at the site of earliest activation did not show R-waves. S1S1-stimulation (basic cycle length (BCL): 200ms) from two different directions showed no blocklines and no change of conduction velocity (CV) (80±3 cm/s vs. 80±3 cm/s, p.<0.05). During experimental period of 30 min. after ACO-application, neither atrial effective refractory period (BCL=200ms: 135±2 ms vs. 135±2 ms, n.s.) nor left atrial electrical activity was changed significantly. Episodes of burst-induced AF became longer (470±65 sec. vs 100±10 sec., p.<0.01), but AFCL was not changed significantly (131±5 ms vs. 134±5 ms, n.s.). During AF the number of breakthroughs increased more than 10 fold (1.4±0.14 per cycle vs. 0.08±0.03 per cycle, p.<0.01). However, breakthroughs occurred remote from the site of ACO-application. The mean of epicardial coupling intervals of breakthroughs and dominant interval at the side of ACO-application were slightly shorter than the mean of AFCL (131±3 ms and 131±2 ms respectively vs. 133±5 ms, p.<0.05). During AF more than 80% of all local electrograms at the site of breakthroughs showed R-waves, but just 44% of them could be explained by transmural conduction (contralateral activation within 8ms). Flecainide inhibited ACO-induced rapid focal discharges at the site of ACO-application. After flecainide, AF was not inducible anymore. Summary: Topical application of ACO on the left atrium in the middle of the mapping area induced rapid focal discharges with radial spread of activation exactly at the place of ACO-application. The use of flecainide reduced the number of breakthroughs. Since the atrial effective refractory period or the local electrograms did not change significantly, it seems that flecainide inhibited the focal discharges without a change in refractoriness or conductivity. This indicates a modulation of the automaticity of focal discharges by flecainide.

Absentence of cyclase-associated protein 2 leads to marked atrial and ventricular conduction delays and ventricular arrhythmias

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Purpose: Cyclase-associated protein 2 (CAP2) is an evolutionarily conserved protein that plays a major role in regulating the actin cytoskeleton and in signal transduction. CAP2 is predominantly found in the nucleus of undifferentiated cardiomyoblasts and at the M-line of adult cardiomyocytes. Recent studies showed that the expression of CAP2 by a gene trap approach (CAP2/gt) results in right ventricular cardiomyopathy and increased mortality in a mouse model. We hypothesised that CAP2 also has a major impact on cardiac electrophysiological parameters.

Methods: We performed in vivo electrophysiological studies using right heart catheterisation in 25 mice (8 CAP2/gt, 8 CAP2+/- and 9 wild type control mice (WT)) at the age of 14 weeks. We analysed standard ECG- and electrophysiological parameters and the inducibility of arrhythmias.

Results: In comparison to WT, CAP2/gt showed a reduction in basal heart rate (403±9/99 ms vs. 445±3/39 ms, p<0.05), prolongation in PQ time in PQ (45.4±5.6 ms vs. 39.0±6.3 ms, p<0.01), QRS time (15.0±1.1 ms vs. 12.7±1.5 ms, p<0.01) and QT time (35.3±3.9 ms vs. 30.7±3.0 ms, p<0.01). Functional testing revealed an extension in atrio-ventricular refractory period in CAP2/gt+/- (53.1±4.09 vs. 41.7±1.2 ms, p<0.01). The ventricular effective refractory period (VERP) was slightly prolonged in CAP2/gt (33.1±12.2 ms) and significantly in CAP2/gt (36.7±5.8 ms) compared to WT (26.7±5.2 ms, p<0.01). The probability of induction of ventricular tachycardias (VTs) was significantly raised in CAP2/gt+/- (16% vs. 5% in WT; p<0.01). Interestingly, in CAP2/gt the probability of induction of VTs (7%) was as low as in WT. The inducibility of atrial fibrillation (AF) did not differ among the groups.

Conclusions: Loss of CAP2 results in marked changes in heart rate, atrial and ventricular conduction times and refractory periods. This points towards a significant involvement of CAP2 in a normal sinus node function as well as a normal conduction system. CAP2/gt+/- leads to a modification of further increase in the incidence of VTs in CAP2/gt may originate from a further prolongation of VERP with antiarrhythmic effects. Cases of right ventricular cardiomyopathy with no real cause of an underlying disease may be due to dysfunction of CAP2, so further evaluation of its influence on cardiomyopathy and arrhythmogenesis should ensue to fully understand its functioning.

Decreased connexin43/Nav1.5 expression and reduced sodium current through downregulation of desmoplakin by small RNA interference in HL-1 cardiomyocytes

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Purpose: Desmosomes and gap junctions are situated in the intercalated disk and ensure the integrity of mechanical coupling and electrical impulse conduction between cells. Addition to these cell-cell junctions, there are other molecules such as voltage-gated sodium channel (Nav1.5) located in the intercalated disc. Some cardiac disorders, such as arrhythmogenic right ventricular cardiomyopathy (ARVC), have mutations in genes encoding proteins of the desmosome and gap junctions leading to the occurrence of fatal arrhythmias. Desmoplakin, one of the major desmosomal components, plays an important role in the stability of the desmosomal components interconnecting. The mutant proteins in ARVC may lead to the loss of desmosomal integrity, but it cannot be explained why life-threatening arrhythmias occur early in the course of the disease before cardiomyocyte replacement has taken place. We here sought to characterize whether the presence of DSP is necessary for the normal function and localization of the gap junction protein connexin (Cx) 43 and Nav1.5.
Methods: We used small RNA interference to downregulate DSP specifically in myofibroblasts. This resulted in an increase of connexin43 and Nav1.5 without changes in other connexins or sodium channels. Immunofluorescence studies showed that DSP silencing led to a decrease in distance between connexons. Furthermore, a decrease in connexin43 and Nav1.5 was observed under laser scanning confocal microscopy. The function of Cx43 and Nav1.5 were evaluated by immunofluorescent staining and western blot. The location and distribution of Cx43 and Nav1.5 were significantly decreased following DSP silencing. This was confirmed by an increase in peak current density, a shift in voltage dependence of steady-state inactivation, and a prolongation of time-dependence of recovery from inactivation of sodium current.

Results: A Tp-T e interval in limb leads does not add some further information. A Tp-T e max value according to the symptoms and cardiac events and independently ECG parameter related to symptoms and cardiac events and independently ECG parameter related to symptoms and cardiac events can be useful in risk stratification.

Conclusion: In a few recent works including a limited number of patients with structural cardiac abnormalities, the apparent electrophysiological safety and the ability to use it in patients where other sodium channel blockers are contraindicated could have enormous economic implications. This is the first experimental evidence to propose new mechanisms for the antiarrhythmic benefit of Ran application in chronic heart failure.

Methods: ECGs from 325 BS patients (259 men, 46±13 yo) were reviewed. Base line ECG (n=123) or ECG after provocative test (n=202) showing the BS pattern and the highest T wave in the selected patient. TP-te were measured in each lead at the 12-lead surface ECG and compared between asymptomatic patients and pts with syncope and asympomatic pts with SD or with and/or appropriate ICD therapy.

Results: 228 pts were asymptomatic (70%), 71 presented with unexplained syncope and 12 with SD. 135 pts were implanted with an ICD. 14 implanted pts with SD in heart failure. The contribution of myofibroblasts to the substrate of atrial fibrillation was studied in 7 female rabbits. CHF was induced by 4 weeks of rapid atrial pacing.

Conclusion: In the present study, Ranolazine (RAN) was reported to be effective and safe in converting atrial fibrillation (AF) to sinus rhythm by intake of a single dose ("pill in the pocket") in patients with structural cardiac abnormalities. The apparent electrophysiological safety and the ability to use it in patients where other sodium channel blockers are contraindicated could have enormous economic implications. This is the first experimental evidence to propose new mechanisms for the antiarrhythmic benefit of Ran application in chronic heart failure (CHF).

Methods and results: In 7 female rabbits CHF was induced by 4 weeks of rapid ventricular pacing leading to a significant decrease in ejection fraction. 12 rabbits were sham-operated and served as controls. Isolated failing and sham hearts were perfused with the Langendorff method and were paced with cycle lengths from 350 to 150ms in the atrium. In addition, burst pacing was used to induce atrial fibrillation. Two monophasic action potential recordings on the left- and right-epicardium showed an increase of atrial action potential duration (aAPD) and effective refractory period (aERP) in CHF hearts as compared with controls. Additional infusion of acetylcholine (1μM) and isoproterenol (1μM) led to a significant decrease in aERP and aAPD in CHF hearts in comparison with controls. Moreover, RAN application significantly increased conduction velocity in sham (+14ms) - and failing (+16ms) hearts, respectively. RAN suppressed AF in 55% of sham- and 57% of failing hearts. RAN had no effect on aAPD but led to a significant increase of aERP (sham: +28ms; CHF: +24ms) lead to a significant increase of aERP (sham: +28ms; CHF: +24ms) and effective refractory period (aERP) in CHF hearts as compared with controls. Additional infusion of acetylcholine (1μM) and isoproterenol (1μM) led to a significant decrease in aERP and aAPD in CHF hearts in comparison with controls. Moreover, RAN application significantly increased conduction velocity in sham (+14ms) - and failing (+16ms) hearts, respectively.

Conclusion: In the present study, administration of RAN has been shown to be effective in suppressing AF not only in sham- but also in failing hearts. The antiarrhythmic effect is due to development of aPRR and a marked effect on conduction velocity. RAN might be a new safe option to reduce the burden of AF in CHF, where other antiarrhythmic drugs are contraindicated. The described electrophysiological mechanism should be adopted as a fascinating novel antiarrhythmic option in heart failure.

Methods: The present model, risperidone and sertindole have antiarrhythmic effects. The absence of afterdepolarizations in Purkinje fibers after T-peaks and a1AR stimulation caused con- siderable QT prolongation (188±7 to 509±82 ms, p<0.05) and TdP in 8 of 10 rabbits. Pretreatment with antiarrhythmics with various combinations of a1R-block and a1AR blocking properties reduced the incidence of drug-induced TdP to 0/10 (risperidone) and 2/10 (sertindole), p<0.05; whereas haloperidol (4/10, p=0.2) and olanzapine (5/10, p=0.3) did not reduce TdP incidence at the tested dose. There was a statistically significant positive correlation between a1AR antagonism and antiarrhythmic efficacy (Spearman’s correlation, p<0.05) independent of QT intervals.

Conclusions: a1-Adrenergic stimulation causes APOD prolongation in vivo and contributes to TdP in vivo. In the present model, risperidone and sertindole have antiarrhythmic effects. The absence of afterdepolarizations in Purkinje fibers after T-peaks and a1AR stimulation causes considerable QT prolongation (188±7 to 509±82 ms, p<0.05) and TdP in 8 of 10 rabbits. Pretreatment with antiarrhythmics with various combinations of a1R-block and a1AR blocking properties reduced the incidence of drug-induced TdP to 0/10 (risperidone) and 2/10 (sertindole), p<0.05; whereas haloperidol (4/10, p=0.2) and olanzapine (5/10, p=0.3) did not reduce TdP incidence at the tested dose. There was a statistically significant positive correlation between a1AR antagonism and antiarrhythmic efficacy (Spearman’s correlation, p<0.05) independent of QT intervals.

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Contribute to the AF substrate and that administration of LatB increases CV in the left atrial appendage (LAA) of patients with AF.

Methods: The LAA of patients undergoing thoracoscopic surgery for AF was excised. The LAA preparation was superfused with Tyrode's solution in a tissue bath and optical mapping was performed with di-4-ANEPPS. The LAA was paced at 100 bpm and exposed to LatB for 1 hour and CV was measured every 5 minutes. Immunohistochemical staining for alpha-SMA and connexin 43 was performed to identify myofibroblasts in tissue preparations and differentiate myofibroblasts from vascular smooth muscle cells.

Results: A total of 21 LAAs were studied (0.1 and 1 micromol LatB and control, 7 per group). No spontaneous activity was observed. Longitudinal CV was 0.27-1.43 mm/ms and transversal CV was 0.04-1.11 mm/ms. LatB did not affect CV irrespective of the type of AF. Run down of the model, characterized by a reduction of CV in time, was observed. Concordantly with the outcome of the electrophysiological experiments, myofibroblasts were not detected with immunohistochemical staining of LAA.

Conclusions: Exposure of human LAA preparations to LatB does not change CV. Furthermore, immunohistochemical staining does not reveal the presence of myofibroblasts in LAA of AF patients. These data suggest that myofibroblasts do not play a major role in the pathophysiological substrate of human AF.

P4706 Cervical vagal nerves contain sympathetic ganglion cells

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Background: Cervical vagal nerve stimulation (VNS) has been applied to treat patients with heart failure. The VN is considered part of the parasympathetic portion of the autonomic nervous system. However, we have recorded bilateral cervical vagal nerve activity (VNA) from ambulatory dogs with atrial fibrillation (AF). The studies showed that when cervical VNA does not co-activate with the inferior vena cava-inferior atrial ganlionated plexus, the VNA does not reduce the ventricular rate during AF. These findings suggest that VNA is not purely parasympathetic. We hypothesize that sympathetic nerve structures are present in the cervical VN.

Methods and Results: We harvested the left cervical VN from 4 normal dogs under isoflurane general anesthesia. The tissues were processed routinely, paraffin embedded and cut into 5-μm thick sections and stained for tyrosine hydroxylase (TH) to identify sympathetic nerves and cholineacetyltransferase (ChAT) to identify cholinergic nerves. The results show that cervical VN contain both sympathetic and parasympathetic components. While CHAT positive nerves formed a majority of the cervical VN, a small amount of TH-positive nerves were also present most likely at the edge but also in the center of the nerve bundles. Most unexpectedly, we identified sympathetic neurons in the VN, indicating that the cervical VN was a source of sympathetic innervation. Because these dogs did not undergo cervical VN recording, these changes could not have been caused by either manual manipulations or electrical stimulations.

Conclusions: Cervical VN contains sympathetic ganglion cells and sympathetic nerve fibers in addition to parasympathetic nerve fibers. Cervical VNS may achieve its therapeutic effects by activating both branches of the autonomic nervous system.

P4707 EUK-8, an antioxidant suppresses the electrical remodeling induced by hyperglycemia in heart/muscle-specific manganese superoxide dismutase-deficient mice

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Background: We have previously reported that the myocyte-deriving primary oxidative stress under hyperglycemic (diabetes mellitus: DM) condition would promote cardiac electrical remodeling without causing structural changes in heart/muscle-specific manganese superoxide dismutase-deficient (H/M-Sod2−/−: d/W) mice which demonstrates a normal phenotype but limited mitochondrial function in response to reactive oxygen species (ROS). In the present study, we evaluated the effect of EUK-8, the SOD/catalase mimetic, on the process of the electrical remodeling in d/W mice under hyperglycemia.

Methods: DM (blood sugar >400mg/dl on days 3–8) was induced by intraperitoneal injection of streptozotocin (STZ 250mg/kg body weight) on day 0 in d/W and wild-type (WT) mice. EUK-8 (15mg/kg body weight) was injected on days 1 and 4 in randomly selected DM mice. The same amount of saline was injected in the control. They were divided into 6 groups; 1) d/W DM (n=11), 2) WT DM (n=11), 3) WT DM-EUK-8 (n=10), 4) WT DM-EUK-8 (n=10), 5) d/W control, (n=7), and 6) WT control (n=11). On day 8, the following parameters were evaluated and compared among the 6 groups; serum derivatives of reactive oxygen metabolites (d-ROM), the left ventricular end diastolic dimension (LVEDD) and ejection fraction (LVEF) in the echocardiography, the effective refractory period (ERP) and the monophasic action potential duration (MAPD) in the open-chest study. With the excised ventricles, Hematoxilin-Eosin (HE) and Azan staining were performed.

Results: The d-ROM level was higher in d/W DM than control groups, and d-ROM levels in d/W DM-EUK-8 and WT DM-EUK-8 groups were lower than those in DM groups without EUK-8 (p<0.05). No group exhibited LV hypertrophy. There was no difference in the histological findings among the 6 groups. The ERP and MAPD90 were mostly prolonged in d/W DM in comparison with the other groups, but these prolongations were partially suppressed in d/W DM-EUK-8 group (p<0.05). (ERP: 70±5 vs. 58±7 ms, MAPD90: 108±2 vs. 68±4±4 ms, p<0.05). The prolongations of ERP and MAPD90 were obvious in WT DM group, but they were almost completely suppressed in WT DM-EUK-8 group.

Conclusion: The STZ induced hyperglycemia caused electrical remodeling characterized by prolongation in ERP and MAPD prominently in H/M-Sod2−/− mice. However, EUK-8 treatment suppressed these changes independently to the hyperglycemic condition, but possibly through diminishing ROS production and oxidative stress. This result may indicate the importance of oxidative stress in promotion of the electrical remodeling in acute hyperglycemic state.

P4708 An in vitro model of early or late reperfusion-scars to explain antiarrhythmic and anti-arrhythmic potential of pharmacologic or electric defibrillation

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Purpose: Early-reperfusion causes patchy myocardial scars, whereas late-reperfusion causes solid scars. Patchy scars show lower reentry inducibility, shorter cyclelength and more polymorphic VTs compared to solid scars. Despite the greater-early-reperused patient population, its arrhythmic mechanisms have not been thoroughly investigated. We investigated the applicability of in vitro model of patchy or solid scarcompositions to gain a mechanistic understanding of their arrhythmic characteristics.

Methods: Neonatal Rat Ventricular Monolayers were locally ablated at day 3 by laser-cut stamps of one ø6mm circle to mimic late-reperfused, solid scars (solids). A circular arrangement (four ø2mm circles with outer diameter of 6mm mimicked early-reperused, patchy scars (patchies). Alday 4, optical mapping was performed.

Results: Inducibility of reentry was lower in patches (30%, n=23 vs 72%, n=11) and cyclelength was 252±33ms vs 325±43 ms, p<0.05) compared to solids. Spiral-wave attachment to obstructions was 100% in solids, but only in 50% obstructions. Polymorphic arrhythmias were more prevalent in patches, due to increased meandering and un/re-pinning, and excitability gradients were largerdur- ring arrhythmias. High-frequent electrical stimulation terminated arrhythmias less frequently in patches (3 out of 6 vs 6 out of 6 in solids) and couldinduce arrhythmia characteristics due to wavebreaks. Nav1.5 blockade terminated 8% of arrhythmias in patches but 25% in solids.

Conclusions: An invitro model of patchy or solid obstructions reproduces arrhythmia characteristics of early- or late reperused hearts. Furthermore, it may provide
The anatomic relationship between the right and left ventricular outflow tracts: its relevance in catheter ablation

**Methods:** Fifteen structurally normal human hearts (10m, 47±5 years) were carefully studied by sagittal and horizontal histological sections. The junction between the LVOT and RVOT were serially sectioned at 10-μm thickness, and stained with Goldner and Masson trichrome methods. By light microscopy, the myocardial thickness at the level of the RVOT and LVOT may be greater than 10 mm. An endocardial ablation approach of idiopathic outflow tract tachycardias can be unsuccessful due to this anatomic finding, suggesting the need of an epicardial approach in selected cases.

**Conclusions:** The myocardial thickness at the level of the RVOT and LVOT may be greater than 10 mm. An endocardial ablation approach of idiopathic outflow tract tachycardias can be unsuccessful due to this anatomic finding, suggesting the need of an epicardial approach in selected cases.

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The acute anodal block of Kv1.5 channels by DHA increases rabbit atrial refractory period

**Methods:** Among, mono-, poly-unsaturated and saturated fatty acids, DHA exerted the most powerful inhibition of IKv1.5 that appears to be sufficient to significantly increase AERP in anesthetized rabbit. Such a lengthening of AERP may be of therapeutic benefit in atrial fibrillation.

**Conclusions:** The fastest AERP was related with the heart rate with the anterior INP at the highest heart rates. During sympathetic stimulation, the anterior INP became the fastest conduction pathway with the superior EAS in most patients. Finally, the fastest AERP was closely associated with the location of EAS.

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Depletion of connexin45 and connexin30.2 deteriorates AV-nodal conduction in the murine heart

**Methods:** We interbred a transgenic mouse line cardiacly depleted for Cx45 mice (C45-/-) with Cx30.2 knock out (KO) mice (C30.2-/-), resulting in Cx45-/-C30.2-/- double KO offspring. In these and control wildtype (WT) littermates, we performed percutaneous ECGs and in vivo electrophysiological investigations (IEP) using transvenous catheterization to assess standard EPI-parameters (n=14).

**Results:** AV nodal conduction was impaired in Cx45-/-; PQ-intervals were significantly prolonged in the Holter ECG-recordings of Cx45-/- compared to their WT littermates (41.0±2.2 ms vs. 36.4±3.1 ms; p<0.05). When Cx30.2 was additionally deleted in Cx45-/-C30.2-/- mice, PQ was more prolonged as compared to Cx45-/- (43.5±1.6 ms vs. 41.0±2.2 ms; p<0.05). In vivo IEP showed prolongation of the A-His interval as surrogate of supra Hisian conduction disturbances in Cx45-/- versus WT (33.3±5.3 ms vs. 26.9±2.1 ms; p<0.05), which was more pronounced in the double KO versus their WT littermates (48.3±4.6 ms vs. 33.3±5.3 ms; p<0.02). AVNRP was shortened in the double KO. Spontaneous AV-blocks did not occur in none of the genotypes. Inducibility of atrial and ventricular arrhythmias was equal among the groups.

**Conclusions:** Our data show prolonged AV-intervals and impaired AV-nodal conduction under fast heart rates in mice with conditional cardiac deletion of Cx45. These findings support the thesis of Cx45 as a provider of basal AV-nodal conductivity. When Cx30.2 is additionally missing, AV-nodal conductivity is more severely impaired as in the Cx45 single knock out. These results point that predominantly expressed Cx45 and Cx30.2 are crucial for maintaining AV-nodal conductivity.
Dexmedetomidine and clonidine inhibit ventricular tachyarrhythmias in a rabbit model of acquired long QT syndrome

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Purpose: We hypothesized that alpha-2 AR agonists have an inhibitory effect on abnormal repolarization-related ventricular tachyarrhythmias (VTs).

Methods: Effects of dexmedetomidine and clonidine on the occurrence of VTs were assessed in a methoxamine-sensitized rabbit model of acquires long QT syndrome (n=45). To verify that VTs in this model animal were triggered by early afterdepolarization (EAD), monophasic action potential on the left ventricular surface was recorded in 28 open-chest rabbits.

Results: Incidence of VT significantly decreased during the treatment with dexmedetomidine (1 μg/kg/min; 5/12 (p<0.01 vs. control)) or with clonidine (33.3 μg/kg/min; 10/18 (p<0.001)), as compared with that in control rabbits (14/15). EAD-like bump, less frequently detected during EAD-scan in control or with clonidine or dexmedetomidine (2/14) than insulin-treated rabbits (9/10, p<0.005). Presence of hump was significantly related with the advent of VTs (p<0.05).

Conclusion: Alpha-2 AR agonists have an inhibitory effect on VTs in the rabbit long QT model.

Lymphocytic cell infiltration of myocardium is associated with the episode of ventricular fibrillation in patients with Brugada syndrome

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Purpose: Brugada syndrome is a disease known to cause ventricular fibrillation (VF) with a structurally normal heart and is linked to SCN5A gene mutation. The existence of myocarditis on endomyocardial biopsy samples in patients with Brugada syndrome is still debated. The aim of the present study was to investigate by endomyocardial biopsy whether the presence of lymphocytic cell infiltration on myocardium and its association with clinical features in patients with Brugada syndrome.

Methods: We studied consecutive 73 patients (71 males; mean age 48±11 years) with Brugada syndrome. All patients underwent cardiac ultrasonography, coronary and ventricular angiography, endomyocardial biopsy from right ventricular septum, electrophysiological (EP) study, and DNA screening of the SCN5A gene. The lymphocytic cell infiltration of myocardium was determined by the presence of over five inflammatory cell infiltration by C4D5R0 immunohistochemical staining associated with necrosis or degeneration of adjacent myocytes in high power field image.

Results: SCN5A mutation was detected in 15 patients. VF episode was detected in 17 patients. Lymphocytic cell infiltration of myocardium was detected in 7 patients (2 patients with SCN5A mutation and 5 without SCN5A mutation) out of all patients and was detected in 4 patients out of 17 patients with episode of VF. The existence of lymphocytic cell infiltration was associated with the VF episode in patients with Brugada syndrome (P<0.047), but not with SCN5A mutation, syncope, family history, or VF induction in EP study.

Conclusion: Lymphocytic cell infiltration was detected in patients with Brugada syndrome in both of SCN5A positive and negative group. And the existence of lymphocytic cell infiltration is associated with VF episode in patients with Brugada syndrome.

False tendons are possibly associated with genesis of J-waves: prospective study in young healthy men

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Background: Recent studies showed that J-wave was associated with vulnerability to ventricular fibrillation. While J-waves are also observed in the healthy population, the mechanisms responsible for J-wave are still under investigation. On the other hand, the possible association of false tendon (FT) with fascicular tachycardia suggested the presence of the arrhythmogenic slow conduction zones in FT. Recently, we reported the association between the FT and J-waves in the general population (Heart Rhythm, in press).

Methods: We prospectively studied 30 young healthy men. The FTs were detected by the echocardiogram and classified into 3 types on the basis of their points of attachment: type 1 (longitudinal type), type 2 (diagonal type) and type 3 (transverse type) as shown in figure. 12-lead ECG and the signal averaged ECG were recorded. J-wave was defined as terminal QRS notching or slurring. Presence of hump was significantly related with the advent of VTs (p<0.05).

Results: The FT was detected in 70% of all subjects. The incidence of J-wave was significantly higher in the subjects with type 1 and 2 FTs than type 3 FT and without FT (100, 50, 20%, respectively, p<0.005). Latent potential was not recorded in all subjects, however, the presence of J-wave was significantly longer in the subjects with type 1 or 2 FTs than the others (p<0.05).

Conclusion: These results suggested that FT was related to the genesis of J-waves and may have a potential arrhythmogenic property with conduction abnormality.
Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension

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Background: Renal sympathetic denervation (RDN) reduces sympathetic activity and blood pressure (BP) in patients with resistant hypertension. The present study was aimed to investigate the effects of RDN on HR and other electrophysiological parameters.

Methods: 136 patients aged 62.2 ± 0.8 years (58% male, BP 177 ± 293/1 mm Hg) with resistant hypertension underwent RDN. BP and a 12-lead electrocardiogram (ECG) were recorded before, 3 months (n = 122), and 6 months (n = 84) after RDN.

Results: After 3 months (3M) and 6 months (6M), systolic BP was reduced by 25.5 ± 2.4 mm Hg (p < 0.001) and 28.1 ± 3.1 mm Hg (p < 0.001). HR at baseline was 66.1 ± 1.1 beats per minute (bpm) and was reduced by 2.6 ± 0.8 bpm after 3 months (p = 0.001) and 2.1 ± 1.1 bpm after 6 months (p = 0.046). Change of HR correlated with HR at baseline: patients with HR at baseline between 60-71 bpm and ≥ 71 bpm had a reduction of 2.9 ± 7.6 bpm (p = 0.008) and 9.0 ± 8.6 bpm (p < 0.001), respectively, whereas in patients with baseline HR > 60 bpm HR increased after 3 months (2.6 ± 4.4 bpm; p = 0.035). Neither baseline HR nor change of HR correlated with changes of systolic BP. The PR interval was prolonged by 11.3 ± 2.5 ms (p = 0.001) and 10.3 ± 2.5 ms (p = 0.001) at 3 and 6 months after RDN. Patients with a PR-change < 10 ms had a shorter baseline PR duration (159.7 ± 3.6 ms vs. 171.4 ± 4.4 ms; p = 0.043) and a greater reduction of heart rate (3M: 41.1 ± 1.5 bpm vs. 0.1 ± 1.1 bpm; p = 0.022). Duration of ventricular de- or repolarisation was not significantly affected by RDN.

Conclusion: RDN significantly reduced heart rate and PR interval, as indicators of cardiac autonomic activity, in patients with resistant hypertension. The changes did not correlate to BP reduction.

Distribution of J waves on 87-lead body surface map in patients with inferolateral early repolarization syndrome

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Purpose: J waves in the inferior lead reportedly relate to poor prognosis in patients with inferolateral early repolarization syndrome (ERS). However, little is known about the body surface distribution of J waves and the significance of J wave localization in ERS patients with inferolateral J wave (VF).

Methods: This study consists of 15 patients (13 males, mean age 33.6 ± 9.5 years) with ERS and a prior VF who underwent multiple recordings of 12-lead electrocardiogram (ECG) and 87-lead body surface map (BSM) during sinus rhythm. Locations of J waves on ECG were compared with distributions of J waves on the body surface and the clinical characteristics of patients. J wave was defined as an elevation of at least 1 mm (0.1 mV) of the J point in at least 2 leads, either as QRS slurring or notching in the inferior lead (II, III, aVF), lateral lead (V4-V6), and high lateral lead (I, aVL) followed by ST elevation. Type 1 Brugada syndrome was excluded from this study.

Results: J waves were noticed on extensive body surface area, not only in the lower anterior chest but also in the lower back where the excitation of left ventricle is reflected in 9 patients with inferior J waves. In contrast, they were noted in the restricted area of left mid lateral chest in 11 patients with lateral J waves, and in the left upper chest in 5 patients with high lateral J waves. Two patients with J waves in global leads had much wider J wave distribution on BSM. During 11.5 ± 4.14 years follow-up, 14 patients received implantable cardioverter-defibrillator and 7 of 15 (47%) patients had recurrences of VF with a rate of 80%, 46%, and 33% in patients with high lateral, lateral, and inferior J waves, respectively.

Conclusion: Patients with J waves in the inferior or global leads on ECG exhibited wider distribution of J waves on the body surface, although high lateral J waves tended to link with poor outcome in ERS patients with VF.

QT peak prolongation predicts cardiac death following stroke

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Introduction and Hypothesis: Cardiac death has been linked in many populations to the presence of mitral regurgitation, atrial fibrillation, and hypertension. However, little is known. This study aims to assess whether QT peak duration prolongation predicts cardiac death.

Methods and Results: ECGs were recorded from 296 stroke patients (152 male, mean age 67.2 (SD11.6) approximately 1 year after the event. These ECGs were digitised by one observer who was blinded to patient outcome. The QT peak duration (TP) was measured from the onset of the QRS complex to the end of the T wave. The TP was measured in three groups: isoelectric ST segment elevation and in those with isoelectric ST segment and differences among the three groups were statistically tested.

Results: The magnitude of ST segment elevation was lower (P < .001) in patients with pericarditis (0.1 ± 0.06 mV) than in patients with STEMI (anterolateral: 0.2 ± 0.16 mV; inferior: 0.2 ± 0.15 mV). However, the number of leads with ST segment elevation was larger (P < .001) in pericarditis (6.5 ± 2.01) than in STEMI (anterolateral: 5.8 ± 2.14; inferior: 4.8 ± 1.78). Patients with pericarditis showed comparable QRS duration in leads with isoelectric ST segment and in leads with elevated ST segment (80.4 ± 12.20 ms vs 81.4 ± 11.36 ms; P = .281). However, patients with STEMI showed a significant longer QRS duration in leads with ST segment elevation than in leads with isoelectric ST segment (anterolateral: 83.3 ± 13.15 ms vs 78.1 ± 12.58 ms, p < .0001), which was followed up for a median of 4.3 years. The primary endpoints were cardiac death and cardiac death from any cause. A prolonged heart rate corrected QT peak (QTPc) of lead I carried the highest relative risk of death from all cause as well as cardiac death, when compared with the other more conventional QT indices. In multivariate analyses, when adjusted for conventional risk factors of atherosclerosis, a prolonged QTc of lead I was still associated with a 3-fold increased risk of cardiac death. (adjusted relative risk 3.0 (95% CI 1.1-8.5), p = 0.037).

Conclusion: QT peak prolongation predicts cardiac death in stroke survivors. Further studies are required to elucidate the mechanism that may lead to cardiac death, and test the hypothesis that interventions might reduce the risk of cardiac death in these patients.

Distribution of J waves on 87-lead body surface map in patients with inferolateral early repolarization syndrome

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Results: J waves were noticed on extensive body surface area, not only in the lower anterior chest but also in the lower back where the excitation of left ventricle is reflected in 9 patients with inferior J waves. In contrast, they were noted in the restricted area of left mid lateral chest in 11 patients with lateral J waves, and in the left upper chest in 5 patients with high lateral J waves. Two patients with J waves in global leads had much wider J wave distribution on BSM. During 11.5 ± 4.14 years follow-up, 14 patients received implantable cardioverter-defibrillator and 7 of 15 (47%) patients had recurrences of VF with a rate of 80%, 46%, and 33% in patients with high lateral, lateral, and inferior J waves, respectively.

Conclusion: Patients with J waves in the inferior or global leads on ECG exhibited wider distribution of J waves on the body surface, although high lateral J waves tended to link with poor outcome in ERS patients with VF.
Early repolarization patterns in young healthy individuals: prevalence, morphological characteristics and impact of gender, ethnicity and physical activity

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Purpose: Early repolarization (ER) is commonly observed in athletes and young healthy individuals. Recently, ER in the inferior and lateral leads has been associated with sudden cardiac arrest from idiopathic ventricular fibrillation. We studied the prevalence, distribution and morphology of ER patterns in inferior and lateral leads in young healthy individuals.

Methods: 12-lead electrocardiogram (ECG) was performed at rest in 20 young healthy individuals (age range 13-38 years) between February and September 2011. We evaluated the impact of gender, ethnicity and physical activity on ER. Individuals were divided into physically-active (exercise >2 hours/week) and sedentary. Early repolarization was defined as notched or slurred J-point elevation of at least 0.1 mV from baseline, in ≥2 contiguous inferior or lateral leads; anterior ER patterns were not considered in this study. The morphology of ST-segment was classified as rapidly ascending/up sloping or horizontal/descending.

Results: The mean age of participants was 17.9 (±4.4) years, of which 140 (73%) were male, 1557 (80%) were physically active and 1780 (82%) were Caucasians. ER pattern in inferior and lateral leads was present in a total of 382 (19.8%) cases; of these 40% were in the inferior leads, 35% in lateral leads and 25% in both. Notched ER pattern was more prevalent compared to slurred morphology, and more commonly associated with ascending/up sloping ST-segment elevation. ER was significantly more prevalent in males compared to females (20% vs. 12%, p=0.003), in physically-active people compared to sedentary (20.4% vs. 14.8%, p=0.013), and in Afro-Caribbeans compared to Caucasians (31.2% vs. 19.9%, p=0.012). In addition, voltage criteria for left ventricular hypertrophy and sinus bradycardia were a common associated finding in individuals with ER pattern compared with those without (p=0.0001 and 0.0001 respectively). Only 5% of individuals with ER had J-point elevation of >0.2 mV.

Conclusion: Early repolarization is a common finding in young healthy individuals, and is more prevalent in males, physically-active individuals and those with Afro-Caribbean ethnicity. The inferior leads were more commonly involved but the difference was not statistically significant. Notched ER pattern with ascending ST-segment elevation was the most commonly observed morphological pattern. More research is required to understand precise long term implications of such repolarization changes in young individuals.
Screening for arrhythmogenic myocardial substrate by 12-lead ECG, high resolution ECG and T-wave alternans in patients with low to intermediate sudden cardiac death risk

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Aims: Increased QRS score, wide spatial QRS-T angle, T-wave alternans (TWA), and late potentials by signal averaged electrocardiogram (SAECG) are independent predictors of cardiovascular mortality in the general population. We analyzed whether these electrocardiographic (ECG) parameters enable screening of patients for myocardial scar features implicated in sudden cardiac death risk.

Methods and results: We screened a 6-month period of the entire 20-month ECG database of 6629 patients at Johns Hopkins Hospital and identified 802 patients aged >70 years from non-cardiac care areas and no record of reduced life expectancy who had QRS >50 ms and spatial QRS-T angle >10° as well as left ventricular ejection fraction (LVEF) ≥35%. All individuals were invited to participate, of whom 77 enrolled in the study and underwent clinical examination, SAECG, 30-minute ambulatory ECG recording for TWA, and complete late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) study to determine scar presence and pattern as well as to characterize gray zone, core, and total scar size. The mean patient age was 60-10 years, with 70% males and no known heart disease in 43% of the study population. Patients’ mean LVEF was 58±8%. Previously unreported myocardial scar was present in 41 (53%) patients, of whom 19 (48%) exhibited a typical ischemic pattern. Median and Inter-quartile range for scar, core scar, and gray zone extent were 8% [4; 12%], 5% [5; 9%], and 2% [1; 7%] of left ventricle (LV), respectively. QRS-T angle was not QRS score was associated with the presence of scar and ischemic scar pattern. QRS score was related to total scar size and gray zone size (R2=0.18; P=0.001) and core scar extent (R2=0.12; P=0.005, respectively). There was a significant independent association between TWA level with total scar size (R2=0.13; P=0.001), but not with the presence of late potentials on SAECG (OR=1.04, 95%CI [0.99; 1.08]; P=0.10). Presence of late potentials was significantly related only to LVEF (OR=0.97, CI [0.93; 1.01]; P=0.01), but not with the presence of late potentials on SAECG (OR=1.04, 95%CI [0.99; 1.08]; P=0.10). The fQRS was determined primarily in Inferior leads (16/52, 31%) and followed by precordial (9/52, 17%) and lateral leads (15/52, 29%). During the mean follow-up of 10.4±2.3 years, fQRS was defined by the presence of ≥1 notch in the R or S wave in ≥2 contiguous leads.

Results: The fQRS was more frequently detected in patients with IVF compared to the controls (25/52, 48% versus 21/156, 13%; P<0.001). The fQRS was detected primarily in Inferior leads (16/52, 31%) and followed by precordial (9/52, 17%) and lateral leads (15/52, 29%). During the mean follow-up of 10.4±2.3 years, fQRS was defined by the presence of ≥1 notch in the R or S wave in ≥2 contiguous leads.

Conclusions: ECG screening by QRS score ≥5, QRS-T angle ≥10°, and TWA identifies patients with preserved LVEF but previously unreported myocardial scar with arrhythmogenic potential.

Various morphological ventricular premature beats with fragmented QRS waves on a 12 lead Holter ECG had a positive relationship with the left ventricular fibrosis on CT in hypertrophic cardiomyopathy

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Purpose: Various morphological kinds of ventricular premature beats (VPB) with fragmented QRS waves are often observed in subjects with hypertrophic cardiomyopathy (HCM) but its significance is not clear.

Methods: Retrospective analysis acquired from a total of 24 consecutive HCM subjects (17 male, mean 64±12 yrs) who underwent enhanced ECG gated CT (Aquilion one or Light Speed Ultra 16) and a 12 lead Holter ECG (RAC-2103, Nikon Kodak) within 3 months. Evaluation of coronary artery and characteristics of left ventricular myocardium were performed. If there was a contrast defect in myocardial early phase, late phase acquisition was added, and if abnormal late enhancement was observed in the corresponding site, we diagnosed myocardial fibrosis.

Results: Correlation coefficients (CCs) of numbers of morphological kinds of 1) all VPB (blue bar) and 2) fragmented VPB (red bar) against the patient’s characteristics and CT findings are represented in the Figure. Positive CCs were observed between numbers of kinds of both all VPB and fragmented VPB and the frequency of diabetes mellitus and fibrosis in left ventricular myocardium on CT and negative CCs were observed between numbers of kinds of both all VPB and fragmented VPB and luminal stenosis ≥50% in any coronary arteries and each coronary artery on CT. There were no significant differences between numbers of kinds of all VPB and fragmented VPB concerning their relationship with the patient’s characteristic factors and CT findings.

Conclusion: Numbers of morphological kinds of fragmented VPB on a 12 lead Holter ECG may have a positive relationship with the occurrence of fibrosis in left ventricular myocardium but a negative relationship with coronary arteries stenosis on CT in HCM subjects as well as those of all VPB.

Prevalence, electrocardiographic characteristics and variations of early repolarization syndrome on a population of healthy subjects

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Background: Infero-lateral repolarization has been considered benign for a long time, however recent studies have demonstrated a possible association with sudden death.

The aim of this study is to estimate the prevalence of early repolarization, demonstrate the associated electrocardiographic abnormalities and fluctuations of this syndrome in a population of healthy subjects.

Patients and methods: Electrocardiograms of 1963 patients undergoing routine medical examination at the Principal Centre of Medical Expertise of Flight Crew for french Army from earlyJanuary to late March 2000 were described. Early repolarization was defined as an elevation of J wave of at least 0.1 mV in the inferior and posterior leads. In patients with early repolarization, retrospective analysis of electrocardiograms from the following ten years (2000-2010) was carried out. Clinical and electrocardiographical characteristics were statistically analyzed.

Results: The prevalence of early repolarization was estimated at 5.7% (CI 95%, 4.7-6.7%). 3 patients presented with ECG severity criteria (intralateral early repolarization. J wave>0.2 mV and notching). For 20% of patients early repolarization was intermittent and 56.5% had substantial variations in J wave amplitude, morphology or territory. Early repolarization was commonly associated with ST-segment elevation, prominent T-waves, slower cardiac heart rate and shorter corrected QT duration. No malignant ventricular arrhythmia nor sudden death occurred among the 3 patients presenting with ECG severity criteria during the 10 years follow-up.

Conclusions: Our data are consistent with previous studies concerning early repolarization syndrome. Given the high prevalence and important fluctuations of early repolarization, every patient who presents with this syndrome cannot be considered to be at risk of sudden death. Further research is needed to identify the electrocardiographic forms of this syndrome which are associated with an increased risk of mortality.
in Eastern Europe. Several studies have investigated the effect of seasonality and sudden cardiac death (SCD). Less commonly investigated has been the short-term effects of change in ambient temperature and SCD. We investigated the association between hourly and mean daily change in ambient temperature and SCD.

**Methods:** We evaluated the effect of ambient temperature and the risk of SCD, comparing data from the Heart Start registry with local hourly measurements of atmospheric temperature in Scotland from January 1995 to December 2004, using a case crossover design.

**Results:** 29,954 victims suffered a SCD in the studied time frame. Across all distances and all time lags, there was an increase in risk of SCD with lowering of ambient temperature. There was a 7.6% (95% CI 2.7% - 12.3%) increase in the risk of SCD per 10 degree lowering of the ambient temperature. The association with temperature remained up to 24hours (Lag 0-1 days) prior to the SCD with sensitivity analysis showing patients < 65 years and those with known heart disease (Figure 1) being more vulnerable.

**Conclusion:** These preliminary results of a prospective registry show that MFI based QRS-fragmentation in addition to the ejection fraction is able to identify patients who are more likely to get a life-threatening ventricular tachycardia. Further studies to evaluate the use of this parameter for pts. with only moderate ejection fraction are planned.
clinical symptoms. The disadvantage of the ivabradine is the lack of approval for IST therapy and the contraindication during pregnancy. During ivabradine treatment there was no indication for sinus node transcatheter ablation. Before the ablation of the sinus node the inherent risk of pacemaker implantation a clinical trial with ivabradine is suggested.

**P4733** The role of non-invasive methods in determining the arrhythmic risk in myotonic dystrophy type 1

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**Purpose:** In myotonic dystrophy type 1 (MD1) the risk of cardiac death is higher than in the general population and atrial or ventricular arrhythmias are frequent. The aim of this study was to assess the determinants of arrhythmic risk in patients with MD1 using non-invasive methods.

**Methods:** Eighty-four patients (82% males; age 41±15 years) with a clinical-genetic diagnosis of MD1 (class E1=11%; E2=75%; E3=14%) were enrolled. All patients underwent cardiological evaluation, 12-lead ECG, echocardiography, 24-hour ECG/Holter with heart rate variability (HRV) and neurological assessment at entry. During a mean follow-up of 46±28 months (±2 visits) echo-ECG-Holter data and arrhythmic events were collected.

**Results:** During the follow up 8 patients (9%, incidence 2/100-year) died (age at death 48±11 years). Six (75%) of the deaths were cardiac: 2 cardiac deaths (SD), 1 aborted SD i.e. ICD shock on ventricular fibrillation (VF), and 3 deaths due to heart failure. Four patients (5%) developed major arrhythmic events (SD/aborted SD, VF, sustained or non-sustained ventricular tachycardia), and 7 patients (8%) atrial flutter/fibrillation (AF). According to current guidelines, 7 patients received pacemaker and 2 ICD. The incidence of cardiac death was associated with prolonged PR and QRS intervals at baseline ECG (544±48 msec vs 189±34, p=0.003 and 126±23 msec vs 96±21, p=0.002 respectively), with presence of AF (50% vs 11%, p=0.009) at baseline or during follow up, with lower SDNN (100±22 vs 32±14, p=0.06) and SDANN (81±15 vs 132±41, p=0.04) values at HRV. Patients who developed major arrhythmic events had a trend toward a longer QRS duration at baseline ECG (118±13 msec vs 97±23, p=0.07) and more frequent premature ventricular beats/PVEs at ECG/Holter (2692±4817 vs 490±1579, p=0.018). Patients who developed AF were characterized by older age (51±17 years vs 39±14, p=0.047), longer PR interval at baseline ECG (237±49 msec vs 198±32, p=0.03), and higher HRV (RR mean 968±1578 vs 837±84, p=0.008; SDNN 176±45 vs 139±39, p=0.04; RMSSD 89±53 vs 43±21, p=0.001).

**Conclusions:** In MD1 patients cardiac deaths are associated with conduction disturbances at baseline ECG, presence of AF and HRV data suggesting increased sympathetic activation. Major arrhythmic events are associated with intraventricular disturbances at ECG and frequent PVBs at Holter. Atrial fibrillation is more frequent in patients with baseline atrio-ventricular conduction disturbances and vagal prevalence. Non-invasive cardiological evaluation is important for arrhythmic risk assessment, identifying patients who can develop major tachyarrhythmic events.

**P4734** Exploring the origin of J-wave with magnetocardiographic (MCG): depolarization or repolarization?

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**Purpose:** The mechanism of J-wave is not definitely known. There are still controversies over whether J-wave is derived from depolarization or repolarization.

**Methods:** We recorded 64-channel MCG simultaneously with digitalized ECG (II, V5) during sinus rhythm in 60 subjects (men 46 and women 14, mean age 49.5±19.5) with either notched or slurred J-point elevation (<19.5) with either notched or slurred J-point elevation (<19.5) with either notched or slurred J-point elevation (<19.5) with either notched or slurred J-point elevation (<19.5) with either notched or slurred J-point elevation (<19.5). For J-wave analysis, we used the following criteria: J-point elevation of 0.1 mV or more, the duration of J-wave of more than 30 ms, and the J-wave direction opposite to the QRS complex. The depolarization phase of the J-wave was calculated from the beginning of the J-wave to the end of the J-wave, and the repolarization phase of the J-wave was calculated from the end of the J-wave to the end of the T-wave. The J-wave depolarization phase and repolarization phase were compared between patients with and without J-wave, and between patients with and without arrhythmia.

**Results:** 24 of 60 subjects had organic heart diseases (cardiomyopathy: 6, ischemic heart disease: 5, and other cardiac abnormalities: 13) and 12 had history of VT or VF events (organic heart disease: 4, idiopathic: 9). J-wave was noticed in inferior leads in 58 subjects and lateral leads in 6. The direction and distribution of current flow during J-wave was similar to that of depolarization phase before J-wave and totally different from that of mid ST to T period in 59 subjects. 20 out of 58 subjects with J-wave in inferior leads on ECG had the flow of current in components of inferior direction on MCG, although others showed no consistent distribution during J-wave period.
Conclusion: Prolonged PQ interval was the best predictor of VT and may help arrhythmic risk stratification in Lamin A/C mutation carriers. Myocardial function was most decreased in the septum and correlated to prolonged PQ interval. These findings indicate that reduced septal function and AVB are involved in mechanisms of ventricular arrhythmias in Lamin A/C mutation carriers.

P4738

T-wave alternans is helpful for predicting recurrence of fatal arrhythmias in ventricular fibrillation survivors

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Backgrounds: T-wave alternans (TWA) is useful for predicting the occurrence of ventricular tachyarrhythmias in various heart diseases. However, little is known about the clinical significance of TWA measurement in patients with past history of ventricular fibrillation (VF).

Methods: We studied 22 VF survivors (15 males, mean age 58 years) who received implantable cardioverter-defibrillator implantation. The patients of J-wave syndrome were excluded from this study. We measured plasma B-type natriuretic peptide (BNP) and assessed left ventricular ejection fraction (LVEF) by echocardiography. Additionally, QRS duration and QTc interval were measured in electrocardiogram. TWA value was calculated by the time-domain moving average method. All subjects were divided into two groups based on whether TWA value was above 65 μV (n=11, Group-A) or not (n=11, Group-B). We compared these parameters and the appearance of ventricular arrhythmias requiring appropriate shock therapy in the observation term (8.8±5.9 months) between two groups.

Results: BNP and LVEF were not different between two groups (BNP: 213±292 pg/ml vs. 275±154 pg/ml; LVEF: 42.4±14.8% vs. 46.6±16.2%). QRS duration and QTc interval were not different between two groups (QRS duration, 121.3±23.2 msec vs. 107.2±16.1 msec; QTc interval, 454.8±292 msec vs. 431.6±54.1 msec). However, ventricular arrhythmias requiring appropriate shock therapy occurred more frequently in Group-A than in Group-B (P<0.05). In Kaplan-Meier actuarial curves for arrhythmic event-free rates, Group-A had lower event-free than Group-B (P<0.05).

Conclusions: These results suggest that T-wave alternans is useful for predicting the recurrence of ventricular arrhythmias or adverse outcomes in patients with past history of VF.
Utility of magnetocardiography for detection of delayed potentials, epsilon waves, with arrhythmogenic right ventricular cardiomyopathy

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Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by hypokinetic areas involving the free wall of the right ventricle, with fibro-fatty replacement of the right ventricular myocardium, with associated arrhythmias originating in the right ventricle. Diagnostic ECG finding includes epsilon wave, which is interpreted as a delayed potential in RV. Some cases are difficult to identify the delayed potentials. The aim of this study was to visualize the delayed potentials and compare the delayed potential point using magnetocardiography (MCG).

Methods: This study included 14 cases with ARVC who were diagnosed by Task Force of WHO/ISH (1996) and biopsy, echocardiography and imaging, they were examined 64-channel MCG waveforms.

64-channel MCG waveforms were examined before electrophysiological study and ablation for ventricular premature contraction or ventricular tachycardia. 6 of them showed typical abnormal potential representing the epsilon wave at the end of QRS complex and right in front of T wave on electrocardiography (ECG). 8 cases were difficult to detect the delayed potentials by 12-leads ECG. A current arrow map (CAM) depicted the propagation of the delayed potentials. The locations of the delayed potentials identified by MCG were compared with ablation successful site tagged on the electroanatomical map.

Results: 6 of 8 (75%) with undetectable delayed potential cases could identify the delayed potentials at the end of QRS complex. using MCG. The origins of the delayed potentials deduced CAM agreed with that from the invasive study in 12 of 14 patients.

Conclusion: Magnetocardiography was useful for detecting the presence of delayed potential, epsilon wave, and estimating delayed potential points before the catheter ablation.

SYNCOPE

Home orthostatic training is not effective in elderly patients with vasovagal syncope - a prospective randomised controlled trial

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Objective: To assess the effect of home orthostatic training (HOT) on autonomic reflexes in elderly patients with vasovagal syncope (VVS).

Design: A single blind randomised control trial.

Setting: Eastbourne District General Hospital, East Sussex NHS Trust.

Interventions: The over 65 group were randomised 1:1 to active HOT (O65+) or sham HOT (O65-). The U65 group received active HOT. Participants performed HOT/sham HOT and recorded their training and symptoms. Patients had a repeat tilt test at 3 months.

Main outcome measures: Time to syncope at repeat tilt test, low-frequency heart rate variability (LF-HRV), high-frequency HRV (HF-HRV), mean upstroke baroreflex sensitivity (BRS) and mean downslope BRS were assessed.

Results: Symptomatic benefit occurred in 4 (31%) of the O65+, 4 (29%) of the O65-, and 6 (50%) of the U65. None of the autonomic measures changed significantly in any group (table 1.). 50% of the O65+ group stopped training due to back pain. Time constraint (25%) was the most common reason for cessation in the U65 group.

Conclusions: Despite good tilt training compliance no improvement in autonomic measures in any group was shown. The most common reason for cessation of training was back pain the elderly groups. This study does not support the use of the HOT in elderly patients.

Vasovagal syncope mediated by emotional distress associated with increased risk of cardiovascular events

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The aim of the study was to assess whether vasovagal syncope mediated by emotional distress (emotional-VVS) is associated with an increased risk of cardiovascular events (CVEs).

Methods and results: The study group consisted of consecutive 2248 Cardiology Clinic outpatients aged 61.4±12.1 years (604 patients with and 1644 patients without CVE). 28.3% of the studied population reported at least one episode of syncope, 8.7% had emotional-VVS. The median age of CVE was 59, the interquartile range 52-66 years. The median time between the first emotional-VVS and diagnosis of CVE was 70 years (604 patients with and 1644 patients without CVE). 26% of diagnoses were made after 18 months. The diagnostic yield was independent of sex, age, and gender; the median time to diagnosis of ISSUE type 1 patients was shorter than other patients (4 weeks vs 16 [6-23] months). During the observation period, 3 patients (1.9%) died and none suffered arrhythmic death.

Conclusions: Prolonging observation up to 4 years increased the diagnostic value of ILR in syncopal patients and was safe. A quarter of patients diagnosed needed more than 18 months of follow-up. As consequence, when a strategy of prolonging monitoring is chosen, monitoring should be maintained even for several years until diagnosis is established.

Electrocardiogram/non invasive studies/syncope / Syncope

Patients: 106 patients with recurrent syncope underwent tilt table testing between August 2007 and October 2009. 45 patients (30 over 65 and 15 under 65 controls (U65)) with at least 2 syncopal episodes and tilt test proven VVS were recruited.

Interventions: The over 65 group were randomised 1:1 to active HOT (O65+) or sham HOT (O65-). The U65 group received active HOT. Participants performed HOT/sham HOT and recorded their training and symptoms. Patients had a repeat tilt test at 3 months.

Main outcome measures: Time to syncope at repeat tilt table testing, low-frequency heart rate variability (LF-HRV), high-frequency HRV (HF-HRV), mean upstroke baroreflex sensitivity (BRS) and mean downslope BRS were assessed.

Results: Symptomatic benefit occurred in 4 (31%) of the O65+, 4 (29%) of the O65-, and 6 (50%) of the U65. None of the autonomic measures changed significantly in any group (table 1.). 50% of the O65+ group stopped training due to back pain. Time constraint (25%) was the most common reason for cessation in the U65 group.

Conclusions: Despite good tilt training compliance no improvement in autonomic measures in any group was shown. The most common reason for cessation of training was back pain the elderly groups. This study does not support the use of the HOT in elderly patients.
Classification and Regression Trees (CART) analysis revealed that emotional-VVS is a factor of increased risk of CVE in men.

**Conclusions:** Emotional-VVS is associated with an increased risk of CVE, independently of other risk factors and seems to be a risk factor only in men. 2. The survival curves between patients with and without emotional-VVS begin to drift apart at the age of 50.

3. The causal relationship between emotional-VVS and CVE requires further studies.

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**P4743**

Two-year diagnostic yield of implantable loop recorder in patients with neurally-mediated syncope enrolled in the ISSUE3 trial

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Since the diagnostic yield of implantable loop recorders (ILRs) is a function of the length of observation, this rate increases by prolonging the observation period. We assessed the diagnostic yield among the 284 patients (pts) enrolled in ISSUE3 trial who completed the planned 2-year follow-up period. Eligible pts were ≥18 years of age; suffered ≥3 severe syncopal episodes of suspected or certain neurally-mediated syncope (NMS) in the prior 2 years significant electrocardiographic and cardiac abnormalities. Within 2 years from implantation, 76 pts (27%) had syncopal recurrence with asymptomatic pauses ≥ 4 (67%) or asymptotic pauses ≥ 6 without syncope (419). 49 pts (17%) had a diagnosis of tachycardia or syncope due to non-arrhythmic cause and 159 pts (56%) had no diagnosis. No baseline clinical variables (table 1) was able to predict the outcome except a positive HITT (NMS) response as a predictor of adverse outcome. The aim of this meta-analysis is to establish the incidence and aetiology of adverse outcomes as well as the predictors.

**Methods:** Studies reporting multivariate predictors of adverse outcomes in patients presenting with syncope to the ED were included and pooled, when appropriate, using a random-effect method. Adverse events were defined as ‘incidence of death, or ophthosialization and interventional procedures because of arrhythmia, ischemic heart disease or valvular heart disease’.

**Results:** 11 studies included. Pooled analysis showed 42% (CI 95%; 35-52) of patients were admitted to hospital. Risk of death was 4.4% (CI 95%; 3.1-5.1) and 1.1% (CI 95%; 0.7-1.5) had a cardiovascular etiology. One third of patients were discharged without a diagnosis, while the most frequent was syncope, orthostatic or vasovagal syncope in 29% (CI 95%; 12-47). 10.4% (CI 95%; 7.8-16) were diagnosed with heart disease, the most frequent type being bradyarrhythmia, 4.8% (CI 95%; 2.2-6.4) and tachyarrhythmia 2.6% (CI 95%; 1.1-3.1). Patellations preceding syncope, exertional syncope, a history consistent of heart failure, arrhythmic heart disease, and evidence of bleeding were the most powerful predictors of an adverse outcome.

**Conclusion:** Syncope carries a high risk death, mainly related to cardiovascular disease. This large study which has established the most powerful predictors of adverse outcomes, may enable care resources to be better focused at high risk patients.

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**P4744**

Incidence, etiology and predictors of adverse outcomes in 43315 patients presenting to the emergency department with syncope: an international meta-analysis

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**Background:** Syncope remains challenging for Emergency Department (ED) physicians due to difficulties in assessing the risk of future adverse outcomes. The aim of this meta-analysis is to establish the incidence and aetiology of adverse outcomes as well as the predictors.

**Methods:** Studies reporting multivariate predictors of adverse outcomes in patients presenting with syncope to the ED were included and pooled, when appropriate, using a random-effect method. Adverse events were defined as ‘incidence of death, or ophthosialization and interventional procedures because of arrhythmia, ischemic heart disease or valvular heart disease’.

**Results:** 11 studies included. Pooled analysis showed 42% (CI 95%; 35-52) of patients were admitted to hospital. Risk of death was 4.4% (CI 95%; 3.1-5.1) and 1.1% (CI 95%; 0.7-1.5) had a cardiovascular etiology. One third of patients were discharged without a diagnosis, while the most frequent was syncope, orthostatic or vasovagal syncope in 29% (CI 95%; 12-47). 10.4% (CI 95%; 7.8-16) were diagnosed with heart disease, the most frequent type being bradyarrhythmia, 4.8% (CI 95%; 2.2-6.4) and tachyarrhythmia 2.6% (CI 95%; 1.1-3.1). Patellations preceding syncope, exertional syncope, a history consistent of heart failure, arrhythmic heart disease, and evidence of bleeding were the most powerful predictors of an adverse outcome.

**Conclusion:** Syncope carries a high risk death, mainly related to cardiovascular disease. This large study which has established the most powerful predictors of adverse outcomes, may enable care resources to be better focused at high risk patients.

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**P4745**

The risk of clotting induced by orthostatic stress patients with vaso-vagal syncope

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**Aim of study:** Analysis of prevalence of endothelium-dependent clotting and fibrinolysis, as a response to orthostatic stress during head up tilt test (HUTT) in patients with vaso-vagal syncope (VVS).

**Study population:** 40 pts (15 men, 25 women) aged 18-72 yrs (median of age: 35 yrs. IQR 23.7-55.6) with VVS referred to HUTT. Cardio- and neurogenic reasons of syncope were previously excluded in all pts.

**Methods:** All pts underwent HUTT acc. to standard Westminster protocol. Before HUTT and at the onset of HUTT provoked syncope blood sample was collected for analysis of clotting and fibrinolysis parameters. We measured: prothrombin time APTT, serum concentrations of: fibrinogen (FIB) d-dimer (d-Dim) serum, tissue plasminogen activator (tPA) plasminogen activator (inhibitor-1 (PAI-1) and V-on-Willebrand factor (VWF:Ag) described as % of normal values.

**Results:** Significant decrease of APTT (30.9 to 25.6 s; p<0.0001), INR (1.1 vs 1.03; p<0.00) and PAI-1 (4.6 vs 3.1 mg/l; p<0.03) as well as increase of serum levels of FIB (3.1 to 3.33 g/l; p=0.006), D-dimer (263.0 to 379.0 ug/l; p=0.001), vWF:Ag (57.1 vs 81.6%; p<0.01) and IPA (5.0 vs 9.8 mg/ml; p<0.001) were observed in patients subjected to HUTT. APTT showed >25% decrease of pts, FIB in 63%, tPA-1 in 60%; d-Dimer in 62% of pts, and PAI-1 decreased in 75% of patients. Fibrinogen concentration rises during HUTT in 76% of pts, d-Dimer – in 86.6% of pts, vWBI – in 69.2% of pts ant IPA – in 71.8% of patients. In patients with negative HUTT only significant decrease of PAI-1 serum level was observed (6.8 vs 4.4 ng/ml; p<0.04). Changes of values of measured parameters during HUTT did not correlate with age of pts. Observed changes in clotting related to the orthostatic stress resembles changes occurred during haemorrhage. Only activation of fibrinolysis simultaneously to
Incidence of permanent atrioventricular block in patients with syncope and bifascicular block

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Introduction: In patients with syncope and bifascicular block (BBF), syncope is likely to be attributable to paroxysmal atrioventricular block (AVB). Therefore, a pacemaker implantation is recommended by current guidelines. However, it remains unclear if and at which time point a permanent blockade of atrioventricular (AV) conduction occurs and if pacemaker with AV management are useful in these patients.

Methods: 106 patients with either syncope with bifascicular block (group 1, n = 34) or paroxysmal AVB with (group 2, n = 51) or without BBF (group 3, n = 21) were included in the study. All patients received a pacemaker with AVM (AAI-SafeR-, Symphony®, Sorin SPA, Milano, Italia) and were follow-up in a six-months-interval (mean follow-up 20 ± 12 months). The primary end-point was the time to permanent switch to DDD-, DDI-, or VVI-mode.

Results: 46% of patients in group 1, compared to 70% in group 2 and 77% in group 3 had episodes of intermittent switches to ventricular pacing modes (p = 0.05). Proportion of ventricular pacing was significantly higher in group 2 (40%) and group 3 (32%) compared to group 1 (17%) (p = 0.02). The primary end-point occurred in 16% patients in group 2, 53% patients in group 3 (p = 0.001). Time to primary end-point was not significantly different between the groups (17.5 ± 12.3 vs. 11.3 ± months; p = 0.633). Documented paroxysmal AVB before pacemaker implantation was a significant predictor of the primary end-point (hazard ratio 4.86; 95% confidence interval 95% CI: 1.88-12.5; p = 0.01). No other clinical or electrophysiological variables were predictive for the primary end-point.

Conclusion: Only 16% of patients with syncope and bifascicular block lose permanent AV conduction compared to 55% of patients with paroxysmal AVB.

Prevalence of depression syndrome in patients with vaso-vagal syncope

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The aim of study was analysis of factors influencing on the prevalence of depression syndrome (DS) in patients with vaso-vagal syncope (VVS).

Study population: We observed 650 pts (386 women, 264 men) aged 18-72 (median of age 41.5) yrs, with VVS referred to head-up tilt test (HUTT).

Methods: All pts underwent HUTT performed acc. to standard Westminster or Italian protocols. Before HUTT the Depression Beck Score questionnaire was applied to all pts for evaluation of presence of DS. Mild DS was diagnosed if Beck Score ranged between 10 and 19, mild 20-25 and severe SD – with Beck Score ≥ 26 and higher.

During HUTT regional saturation (rSO2) of frontal lobes of brain was measured using INVOS cerebral oximeter in all pts. Changes of rSO2 during HUTT was expressed as a relative decrease (in%) of rSO2 in left and right channels in relation to the baseline value of rSO2. Univariate and multivariate analysis were performed for evaluation of the influence of age and gender, number of syncope and presyncope episodes, duration of disorder, CSSS results, type of vaso-vagal response during HUTT and duration of total, passive and active phases of HUTT on the occurrence of depression syndrome in patients with VVS.

Results: Depression syndrome was diagnosed in 275 pts (42.3%). Mild DS was observed in 30.9% of cases (201 pts), moderate DS – in 32 (4.9%) persons and severe DS was noticed in 63 (9.6%) pts. Significant influence of older age (p = 0.05; p = 0.01), higher number of syncope (F = 4.1; p = 0.04), longer time from first syncope (F = 16.9; p = 0.0001) and type of vaso-vagal response during HUTT (F = 3.8; p = 0.04) on prevalence of depression syndrome in patients with VVS was proved.

Conclusions: There were no significant influence of gender, number of presyncope episodes, duration of HUTT (all phases), oxygen saturation of brain during HUTT and CSSS results on DS occurrence in patients with vaso-vagal syncope.

The CHADS2 risk score predicts long-term outcome after first admission for syncope - A nationwide study

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Background: The CHADS2 score is an important risk stratification tool for risk of stroke in patients with atrial fibrillation and may also be predictive for other major cardiovascular events. We investigated if CHADS2 score could be applied as a risk stratification tool for predicting cardiac events after an episode of syncope.

Methods and results: All patients admitted with a first time diagnosis of syncope from 2001 to 2009 where identified from nationwide administrative registers in Denmark. Risk of major cardiovascular events (acute myocardial infarction or implantation of pacemaker/ICD) and all-cause or cardiovascular death according to CHADS2 score was analyzed by multivariable Cox proportional-hazard models. A total of 88,355 patients were included (median age 64 years (IQR: 47.5-80.5) and 47.6% were females. There were a total of 19,011 deaths of which 10,389 (54.6%) were cardiovascular. The event rate of cardiovascular death was 5.25 per 1000 person-years for the group with CHADS2 score ≤ 0. The risk of cardiovascular death was significantly increased with increasing CHADS2 score when adjusted for sex (CHADS2 score = 1.2 HR 10.25 [CI: 9.60-10.94]), (CHADS2 score = 2.4 HR = 23.59 [CI: 21.96-25.35]), (CHADS2 score = 3.6 HR = 36.82 [CI: 32.08-42.25]), p < 0.0001. This pattern was similar for all-cause mortality and major cardiovascular events.

Conclusion: The CHADS2 score significantly predicts risk of cardiovascular death, all-cause mortality and major cardiovascular events in patients admitted with syncope, and may be used for risk stratification in combination with other risk score systems. A CHADS2 score of 0 is associated with a very low long- and short-term mortality.
Pictureconomics: a micro-costing analysis of diagnostic investigations for unexplained syncope

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Transient Loss of Consciousness (TLoC) and syncope are areas of increasing resource use. UK claims data analyses placed TLoC/Syncope in the Top-20 reason for hospital admission – more common than myocardial infarction, chronic obstructive pulmonary disease and migraine.

**Purpose:** To quantify the resource use associated with unexplained syncope in a real-world setting, before a clinical decision to implant an implantable loop recorder (ILR) was made.

**Methods:** PICTURE is a prospective, observational registry on Implantable Loop Recorders (ILR), and diagnostic tests for unexplained syncope, carried out in 570 patients at 83 sites in 11 EU countries. PICTUREEconomics is based on PICTURE and a UK micro-costing study to quantify the burden of investigation and understand actual “bottom-up” costs of each test. The previous history of healthcare contacts and investigations were captured. Types and volumes of 17 predefined diagnostic tests were recorded. Patients then received ILRs and were followed until a symptomatic event or a clinically scheduled visit (35-65 months after implant).

**Results:** The mean number of tests before ILR implant was 17 (95% CI 16.08 – 17.04) while the median was 13 (IQ Range 9 – 20). The minimum number of diagnostics observed was 0 while the maximum was 203. Among the top 25% of healthcare resource users, the median tests were 27 (IQ Range 22–36). Based on the tag-on micro-costing study, the mean expenditure per patient was £1,613.15 (€1,879.20). The median was £1,113.86 (€1,297.77 – IQ Range 558.97 – €226.42), while the costs could escalate up to £7,417.89 (€8,642.66). The cost of a patient receiving every type of the 17 investigations once, including e.g. ECG, Holter, blood pressure provocation, TILT test, neurological evaluation, coronary angiography, MRI, CT, invasive testing etc., would have been £5,007.81 (€5,696.54). Should ESC Guidelines have strictly been adhered to (as was the case in 12% of the PICTURE Study population), the mean diagnostic test cost per patient per admission would be £710.32 (€827.58). In the remainder of patients, the same cost was £1,348.47 (€1,571.12).

**Conclusions:** Most patients were more thoroughly investigated before ILR implant than suggested in guidelines. PICTUREEconomics showed the costs of investigations to be highly significant and most patients having moderate consumption while others consumed several times more. Identification of resource intensive patients can be an algorithm for choosing a more cost-effective approach before an ILR implantation.

Remote monitoring of implantable loop recorders: high artefact in the early phase following implant

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**Purpose:** Implantable loop recorders (ILRs) are increasingly used in the investigation of unexplained syncope. Remote monitoring of ILRs has recently become available. We report our initial experience with the practical aspects of remote monitoring of ILRs.

**Methods:** During August 2011, patients were offered remote monitoring using the Medtronic Carelink system at the time of Reveal XT ILR implant. Scheduled transmissions were planned weekly for 8 weeks, then monthly. Patients were asked to make phone calls after a symptomatic event. Time taken to download, review and report results to patients was recorded. Data from existing patients using Carelink after Reveal implant was also analysed; these patients made ad-hoc transmissions.

**Results:** 19 patients were enrolled, mean age 49.5 years. 18 successfully made a test transmission; there were technical difficulties in 1 patient resulting in 4 missed transmissions. 2 other patients missed a total of 3 transmissions. 134 scheduled transmissions were made; 2039 automatically detected episodes were recorded, all false positives. The majority of the episodes occurred in 2 patients. 1570 episodes of asystole were recorded in 1 patient due to artefact as a result of the autogain feature. In another patient, 401 episodes were detected as AF due to frequent atrial ectopics. Staff time requirements are shown in Table 1. Three patients made recordings after symptoms but no abnormality was identified.

Nine patients already using Carelink sent ad-hoc/symptom transmissions only. 44 transmissions were received; 23 VT episodes in 1 patient and 2575 AF episodes in another patient; all were artefact. 9 symptomatic recordings were made; 1 patient received a pacemaker, all others were artefact.

**Conclusions:** Our data show a high incidence of artefact in the early phase after ILR implantation resulting in multiple recordings. Staff time to process, report and communicate data was 5.3 minutes per transmission.

In patients with vasovagal syncope the increase of adrenomedullin during the positive head-up tilt test correlates with HRV parameters

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**Background:** The mechanism regulating adrenomedullin (ADM) secretion - a strong vasodilating peptide - is little known. The activation of sympathetic nervous system causes rise of blood pressure due to increase of peripheral vascular resistance, what can be the impulse for ADM secretion. The strong activation of sympathetic nervous system is considered as a cause of syncope in vasovagal patients. The aim of the study was to assess the relation between the changes of ADM plasma level during HUTT and heart rate variability parameters in patients with vasovagal syncope due to cardiodepressive reaction after nitroglycerin provocation.

**Material and methods:** The studied group consisted of 17 patients (pts) with vasovagal syncope (vvs) due to cardiodepressive reaction during active phase of HUTT (after NTG provocation). In all studied pts blood samples for ADM level assessment were drawn before the test, after 30 minutes supine rest, and immediately after the syncope. Adrenomedullin plasma level was assessed using radioimmunological assay. The patients had 24-hour ECG Holter monitoring and time domain HRV analysis was performed for 24 hours, night and day time.

**Results:** In the study group there was no correlation of HRV parameters and mRR with age of pts. The mRR was significantly shorter in women than in men (p<0.05), after the adjustment for sex there was no correlation of HRV parameters and mRR with age of pts. There was significant negative correlation between ADM level changes during HUTT (ADM2/ADM1) and mRR during the all 24 hours (r=-0.55 p<0.05), night (r=-0.52 p<0.05) and day time (r=-0.54 p<0.05), negative correlation with pNN50 (r=-0.50 p<0.05), SDNNnight (r=-0.51 p<0.05) and pNNnight (r=0.54 p<0.05).

**Conclusions:** In the studied population mRR and HRV parameters do not correlate with age of pts. 2. In pts with vasovagal syncope the ADM2/ADM1 correlates with HRV parameters in the time period in which the patients remain free from any signs of neurocardiogenic reactions and gravitational stress.

The influence of the menstrual cycle on the tilt testing result

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The fluctuation of the female sex hormones level may change the susceptibility to the neurocardiogenic reflex provocation throughout the menstrual cycle.

The aim of the study was to assess the distribution of the positive tilt testing (TT) results through menstrual cycle as well syncope and presyncope and finally to determine if the phase of menstrual cycle contribute to the duration of the loss of consciousness during TT induced syncope.

**Material and methods:** The study group consisted of 18 premenopausal women aged 29.5±9.8 years. The menstrual cycle was divided into 4 phases based on the first day of the last menstrual period (Menstrual (M), Periovulatory (F), periervulatory (O) and postovulatory (L)). The clinical characteristics and TT results are shown in the table:

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Premenstrual phase (M) n=49</th>
<th>Preovulatory phase (F) n=54</th>
<th>Periovulatory phase (O) n=39</th>
<th>Postovulatory phase (L) n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30±4.5</td>
<td>29±1.2</td>
<td>30±1.3</td>
<td>28±4.7</td>
</tr>
<tr>
<td>Syncope spells</td>
<td>2±1.5</td>
<td>3±1.5</td>
<td>4±1.1</td>
<td>4±1.1</td>
</tr>
<tr>
<td>Positive TT (%)</td>
<td>62</td>
<td>89</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Syncope duration (sec)</td>
<td>41±26</td>
<td>30±15</td>
<td>20±15</td>
<td>25±12</td>
</tr>
</tbody>
</table>

*p<0.05 vs group M.

**Conclusions:** 1. The distribution of the positive and negative TT results as well syncope and presyncope as a TT result does not differ throughout the menstrual cycle. 2. The duration of the loss of consciousness is longer during perimenstrual phase of the menstrual cycle independently from the higher syncope score and lower heart rate at TT termination. 3. The fluctuation of the female sex hormones levels does not change the susceptibility to the neurocardiogenic reflex provocation but when provoked influence on its course.
Percutaneous coronary intervention: invasive imaging/devices and technique

P4754
Head to head comparison of fully drug-free biodegradable PLA and bare metal stents in normal porcine coronary: a six-month angiography and OCT follow-up study

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Background: The concept of fully biodegradable polyactic (PLA) stent is now perceived as a potential attractive alternative to metallic stent. The aim of this study is therefore to evaluate a drug-free PLA stent in the porcine model as compared to a bare metal stent (BMS).

Methods: Twenty-nine BMS (Vision®, Abbott, Inc; 3X12 mm) and 29 PLA stents (ART, Noisy le Roi, France; 3X11mm) were implanted in porcine coronary arteries. QCA and OCT analysis were performed immediately after stent implantation, and repeated 1 (n=22), 3 (n=28), and 6 (n=6) months later. The primary end-point was in-stent diameter by OCT, and the secondary end-points were acute recoil and late lumen loss (LLL).

Results: Acute recoil was not significantly different between PLA and BMS groups (3.6±1.1% vs. 4.7±5.3%, respectively; p=NS). In-stent diameter was closely similar immediately after stent implantation in PLA and BMS groups (2.99±0.08 mm vs. 3.05±0.18 mm, respectively). BMS in-stent diameter remained constant through 6-month follow-up (2.99±0.21, 2.95±0.21, 3.14±0.21 mm at 1, 3, and 6 months, respectively). In contrast, in-stent diameter significantly increased at 3 and 6 months in the PLA group indicating late positive remodeling (2.87±0.19, 3.27±0.21, 3.24 vs. 3.14±0.21 mm, p=0.01). The lipid volume was independently correlated with area of captured debris. The lipid volume of patient with FFD was significantly higher those without FFD (160.0±90.2 mm3 vs. 93.0±56.0 mm3, p=0.01). The lipid volume was independently correlated with area of captured debris in multivariate regression analysis after adjustment for clinical, procedural parameters and other plaque components.

Conclusions: The volume of lipid-rich plaque associated with amount of procedure-related released debris captured by filter device. These findings provide insight into the mechanisms of distal embolism during PCI.

P4757
Nine months optical coherence tomography evaluation of neointimal coverage of a strategy of paclitaxel-eluting balloon plus bare metal stent

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Background: Drug-eluting balloon (DEB) predilatation followed by bare metal stent (BMS) implantation represents an innovative treatment for coronary artery disease. Yet, the safety of this strategy has still to be demonstrated.

Methods: Frequency-domain optical coherence tomography was performed at 9 months in a registry of 30 consecutive patients who underwent elective stenting with a BMS (Prokine, Biortikon) after predilatation with a DEB (Elutax, Aachen Resonance). Patients with clinical restenosis (n=3), or with suboptimal images (n=4) were excluded. Quantitative strut level analysis was performed at 0.4-mm intervals (every other frame) along the entire target segment. A total of 23 lesions in 23 patients were analyzed. The center of the luminal surface of the strut blooming was determined for each strut, and its distance to the lumen contour was calculated automatically to determine strut-level intimal thickness (SIT). Struts covered by tissue had positive SIT values whereas uncovered or malapposed struts had negative SIT. The number of struts without coverage was counted for each frame analyzed, and the total number of frames with uncovered struts was recorded. Strut malposition was determined when the negative value of SIT was higher than 100 micron (60 μm). Prokinetic strut thickness, plus a correction factor of 40μ, to account for strut blooming.

Results: A total of 4304 struts were analysed. In total, 131 struts (3%) in only 2 lesions (123 in one, 8 in the other) were found to be uncovered. Malapposed struts were 105 (2.4±3.2%). Percentage net volume obstruction was 30.2±15.6%.

Conclusions: BMS implantation plus DEB is a safe strategy, as it is associated with a percentage of malapposed/uncovered struts which compared favourably with BMS historical controls. Neointimal regrowth (after the exclusion of clinical restenosis patients) is also comparable to historical data.

P4755
The volume of lipid-rich plaque, measured by integrated backscatter IVUS was associated with amount of captured plaques by filter-type distal protection device during coronary intervention

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Background: The atherosclerotic plaque disruption caused by balloon or stent expansion and distal embolism may major cause of peri-procedural myocardial injury during percutaneous coronary intervention (PCI). However relationship between details of lesion characteristics and amount of released plaque particle during procedure is unclear.

Methods: From April 2010 to December 2011, thirty consecutive patients who underwent PCI with filter-type distalprotection device (Filtrap™) following integrated backscatter intravascular ultrasound (IB-IVUS) analysis were enrolled. The volume of each plaque component (lipid, fibrous and calcified) within target lesion was calculated. Area of captured debris of protection filter was measured by microscopic evaluation (Figure). The coronary flow disturbance (TIMI 0/1/2) during distal protection was defined as filter-related flow disturbance (FFD).

Results: The lipid volume of target lesion significantly correlated with area of captured debris (r= 0.41, p= 0.02). The fibrous volume and calcified volume did not correlate with area of captured debris. The lipid volume of patient with FFD was significantly higher those without FFD (160±3.190.2 mm³ vs. 93.0±56.0 mm³, p=0.01). The lipid volume was independently correlated with area of captured debris in multivariate regression analysis after adjustment for clinical, procedural parameters and other plaque components.

Conclusions: The volume of lipid-rich plaque associated with amount of procedure-related released debris captured by filter device. These findings provide insight into the mechanisms of distal embolism during PCI.

P4758
Intravascular ultrasound guided everolimus eluting stent implantation resolves the disadvantage of thin strut cobalt chromium platform in patients with diabetes


Background: Though efficacy of everolimus-eluting stent (EES; Xience V) is well-established by many clinical evidences, several trials failed to show superiority in diabetic subset. We hypothesized that inappropriate stent expansion in complex lesion of diabetes due to thin cobalt chromium platform may be one of the reasons. The purpose of this study is to investigate this hypothesis using intravascular ultrasound (IVUS).

Method: Consecutive 130 de-novo lesions (61 EES and 69 paclitaxel-eluting stent (PES; Taxus Express2, stainless steel thick platform)) treated by elective IVUS-guided PCI for stable patients were recruited in this study. Stent size was determined according to pre-procedural IVUS findings. After stent deployment using standard technique, IVUS procedure was repeated and stent diameter and cross-sectional area (CSA) were measured. If stent expansion was inadequate,
post dilation was performed using short-length high pressure balloon and again IVUS was performed. IVUS findings were then compared with estimated diameter and CSA calculated from each stent compliance chart.

**Result:** In EES, there were significant differences of stent expansion and symmetry index between diabetic and non-diabetic just after stenting. However, these findings were not observed in PES. According to IVUS findings, 75% of diabetic cases in EES group required post balloon dilation to obtain optimal stent expansion. After post dilation, difference between diabetic and non-diabetic did not appear in EES.

**Conclusion:** In EES, asymmetrical stent underexpansion was observed in diabetic patient after stent deployment, however, IVUS-guided post-dilation resolved this disadvantage. IVUS-guided EES implantation can improve clinical outcome in patients with diabetes.

**P4759**

**Feasibility and efficacy of ex-vivo stent fracture detection by optical coherence tomography (OCT) and microcomputed tomography (microCT)**

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**Purpose:** Coronary stent fracture (SF) is recognized as a contributor to adverse clinical events like stent restenosis. However, the true prevalence of coronary SF remains uncertain with clinically observed fracture rates of up to 8% in vivo utilizing fluoroscopic detection and up to 70% at autopsy using high resolution x-ray and microCT. There is limited data to suggest that intravascular ultrasound may improve the sensitivity of in-vivo stent fracture detection, however, to our knowledge there are no controlled studies to demonstrate the sensitivity of cross-sectional intra coronary imaging for SF detection.

**Methods:** A bench top fracture model was created by manually cutting stent crowns or interconnectors (Abbott Multilink Vision 3.0 x 12 mm and Biotronik, PRO-Kinetik, 3.0 x 10). A total of 7 stents with varying extent of fracture were implanted in silicone tubes and analyzed with optical coherence tomography (OCT) (100 bps, 10 mm/sec, Dragonfly, St. Jude) and microCT (xPlore, GE). Two experienced, blinded interventional cardiologists reviewed the 2D-OCT pullback scans, 2D-3D OCT reconstructions looking for SF. The review procedure was limited to 5 minutes per stent/modality to simulate a realistic clinical decision time. The sensitivity and specificity of each modality was determined based on the known fracture sites as visualized through the clear silicone tubes.

**Results:** Review of the 2D OCT images accurately identified 4/9 SF (sensitivity 44.4%) with no false positive SF detection (specificity 100%). Review of the 2D microCT images accurately identified 8/9 SF (sensitivity 88.9%) with no false positive SF detection (specificity 100%). Review of the 3D microCT renders accurately identified all of the SF (sensitivity100%) with no false positive SF detection (specificity 100%). The superimposed variability was moderate for OCT and perfect for 2D microCT (0.55 and 1.00 respectively).

**Conclusion:** Based on this small bench top series, clinically available 2D cross-sectional imaging with OCT is inadequate to reliably detect coronary SF. The vast superiority of microCT to detect SF explains the gap between the clinically reported prevalence of SF as compared to autopsy studies. We chose OCT over IVUS given the improved temporal and spatial resolution, however, even with OCT wire artifacts may have limited SF detection. Given the 100% sensitivity of 3D microCT for SF detection there remains the potential for high-resolution axial imaging like OCT to be rendered in 3D to improve SF discrimination and ultimately may garner a more comprehensive understanding of the natural history and impact of SF.

**P4760**

**Neointimal appearance of late clinical event related lesions after bare-metal stent and sirolimus-eluting stent implantation assessed by Optical Coherence Tomography**

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**Background:** Late clinical event such as very late stent thrombosis (VLST) and late in-stent restenosis (ISR) after bare-metal stent (BMS) and drug-eluting stent (DES) is an important clinical issue. However, the difference of underlying mechanisms in late clinical event between BMS and DES has not been fully evaluated yet. The aim of the present study was to compare neointimal tissue appearance between these lesions within BMS and sirolimus-eluting stent (SES) by using optical coherence tomography (OCT).

**Methods:** We examined the neointimal tissue appearance in 34 late clinical event lesions after BMS (n=15) and SES (n=19) implantation by OCT. Late clinical event was defined as VLST and late ISR (>1 year after initial procedure).

**Results:** Results were shown in the table described below.

<table>
<thead>
<tr>
<th></th>
<th>BMS</th>
<th>SES</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of OCT imaging after stent implantation, month*</td>
<td>100±23</td>
<td>34±14</td>
<td>0.001</td>
</tr>
<tr>
<td>Lipid-rich neointima, n (%)</td>
<td>13 (87)</td>
<td>15 (79)</td>
<td>0.558</td>
</tr>
<tr>
<td>TCFA-like neointima, n (%)</td>
<td>73 (79)</td>
<td>73 (79)</td>
<td>0.839</td>
</tr>
<tr>
<td>Micro-channels, n (%)</td>
<td>11 (12)</td>
<td>12 (13)</td>
<td>0.521</td>
</tr>
<tr>
<td>Neointimal disruption, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.089</td>
</tr>
<tr>
<td>Thrombus, n (%)</td>
<td>0 (0)</td>
<td>6 (6)</td>
<td>0.096</td>
</tr>
<tr>
<td>Stent malaposition, n (%)</td>
<td>0 (0)</td>
<td>5 (5)</td>
<td>0.032</td>
</tr>
<tr>
<td>Calcification within neointima, n (%)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

**Values are given as n (%) or *mean±SD. BMS = bare-metal stent; OCT = optical coherence tomography; SES = sirolimus-eluting stent; TCFA = thin-cap fibroatheroma.**

**Conclusions:** In late clinical event related lesions, atherosclerotic change such as TCFA formation and calcification within neointima is often demonstrated in BMS and stent malaposition might be related in DES.
Sex-related differences in percutaneous coronary interventions for chronic total occlusions

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Purpose: The aim of this study was to assess sex-differences in percutaneous coronary intervention (PCI) for chronic total occlusions (CTO).

Methods: The study included all consecutive patients undergoing PCI for CTO at 3 tertiary PCI centres between January 2004 and December 2011. A multivariable mixed effect logistic regression for clustered data was used to assess the impact of female sex on PCI success after adjustment for clinical and procedural characteristics, CTO lesion difficulty, vessel site, and procedural techniques. CTO lesions were graded as easy (score of 0), intermediate (score of 1), difficult (score of ≥2), and "very difficult" (score of ≥3), according to the J-CTO score on the basis of the lesion location. The presence of calcification, branching, and vessel quality were also taken into account. The primary endpoint was PCI success, defined as the restoration of TIMI 3 coronary flow, as assessed by visual inspection of cineangiograms, and as confirmed by late phase creatinine kinase (CK) release.

Results: Among 1261 patients, median age 63 yrs-old (25th-75th percentile, 55-72), undergoing PCI for 1418 CTO, 176 (13.9%) were women. Women, as compared to men, were significantly older (70.5 yrs-old (61-77) vs 62 (55-72), p<0.001) and more likely to be on aspirin (89% vs 82%, p=0.01). The prevalence of CTO-J score ≥2 was lower among women than in men (34.9% vs 43.6%, p=0.02). No differences between the two groups in the prevalence of bridging or side branch at the occlusion site, in Rontrop collateral circulation were present, although the use of retrograde approach tended to be lower in women (6.8% vs 10.6%, p=0.1). Success rate was higher in women (77.1% vs 70.1%, p=0.049). However, at multivariable logistic regression female sex was not found to be a significant predictor of PCI success (odds ratio 1.31, 95% confidence interval 0.89-1.94, p=0.17).

Conclusions: In this registry of patients undergoing PCI for CTO, women presented a higher PCI success rate as compared to men that could be largely explained by a lower lesion complexity. Indeed, female sex did not emerge as an independent predictor of PCI success.

Impact of final kissing balloon in distal left main bifurcation lesions treated with single or two stents

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Background: The optimal revascularization strategy for unprotected left main coronary artery disease (ULCMD) is the subject of ongoing debate. Further, optimal strategy for distal left main (LM) bifurcation is still matter of controversy.

Methods: A total 181 consecutive patients (pts) who underwent percutaneous coronary intervention (PCI) for distal LM bifurcation lesions with DESs were enrolled for the study. We compared 6-month angiographic and 12-month clinical outcomes no FKB group (n=114) to FKB group (n=67).

Results: Baseline characteristics were similar between the two groups. At six months angiographic follow up, FKB group showed a trend towards higher late loss. At twelve months follow up, there was no difference in major clinical outcomes between the two groups (Table).

Table. 12 months clinical outcomes

<table>
<thead>
<tr>
<th>Variables, n (%)</th>
<th>No FKB</th>
<th>FKB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DES</td>
<td>52 (45.6)</td>
<td>27 (40.3)</td>
<td>0.378</td>
</tr>
<tr>
<td>FKB</td>
<td>62 (53.8)</td>
<td>38 (56.7)</td>
<td>0.378</td>
</tr>
</tbody>
</table>
| FKB group showed similar mid-term angiographic and one-year clinical outcomes as compared with those without FKB.

Conclusions: In patients with distal LM bifurcation lesion undergoing PCI with DES, FKB group showed similar mid-term angiographic and one-year clinical outcomes as compared with those without FKB.

P4765 Very late stent thrombosis in diabetic patients on long-term dual antiplatelet treatment after 1st generation drug-eluting stent implantation: comparison with patients on single antiplatelet treatment

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Background: Despite encouraging short and mid-term results after drug-eluting stents (DES) implantation in diabetic (DM) patients (pts), the long-term safety and efficacy is controversial. We assessed the influence of long-term dual antiplatelet treatment (DAPT) with aspirin and clopidogrel on clinical outcome of DM pts treated with DES.

Methods: In this study, 598 (male 80%, mean age 65.6±9 years) consecutive DM pts (insulin dependent 22%) that had been treated with 1st generation DES (Cypher 81%, Taxus 11%, combination 8%) were included. Five years clinical follow-up (FU) obtained in 576/598 (96%). Early and late (up to 12 months) stent thrombosis (EST) and very late stent thrombosis (VLST) were assessed according to ARC definition. As Hard-end point (HENP) was considered the combination of all cause mortality (D), myocardial infarction (MI), and cerebrovascular accident (CVA).

Results: At 12 months (MO) 89% of pts were on DAPLT; the incidence of definite/probable EST (median time 6.5 MO) was 0.7% (one D, and 3 MI), and all pts were on DAPLT when the event occurred. The incidence of definite/probable VLST at 5 years (median time 34.5 MO) was 0.7% (2 D, 2 MI); two pts were on DAPLT when the event occurred. The incidence of HENP year according to APLT treatment is shown in the Table. In a Cox regression model age (p<0.001) and EF (p<0.001) were predictors for HENP at 5 years. At 5 years 340 (65%) remained continuously on DAPLT and 187 (35%) on SAPLT. The comparison between these two groups regarding HENP and ST did not reveal significant differences.

Conclusions: Long-term DAPT in DM pts treated with 1st generation DES is not associated with lower risk of ST or HENP.

P4766 Predilection with drug eluting balloon followed by bare metal stent implantation versus drug eluting stent in the treatment of simple de-novo coronary stenosis

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Background: Paclitaxel-coated balloons (DEB) represent a promising alternative to drug-eluting stent (DES) in the treatment of coronary stenoses. The aim of our study was to compare 9-month restenosis rate between a strategy of predilation with a paclitaxel eluting balloon (PEB) (Eliutax, Aachen Resonance, Aachen, Germany) versus the conventional approach of a drug eluting balloon (DEB) (Abiomed, Danvers, MA) (Table).

Conclusion: The newly developed covered stents performed well in terms of creating less intramural hyperplasia and in the embolization effect without disturbing branching vascular flow.

Conclusion: In patients with distal LM bifurcation lesion undergoing PCI with DES, FKB group showed similar mid-term angiographic and one-year clinical outcomes as compared with those without FKB.
Germany) followed by bare-metal CoCr stent implantation (Prokinitic, Biotronik, Berlin, Germany) (PEB-CoCr-stent group) versus implantation of everolimus-eluting stent (Xience, Abbott Vascular, Redwood City, CA) (DES group) in the treatment of de-novo stenosis in native coronary artery.

Methods: The study, randomized, single center, was planned to enroll 366 patients, 188 patients per arm, with stable angina, undergoing percutaneous coronary intervention of a de-novo stenosis less than 15mm in length in a native coronary artery. Primary endpoint, in a non inferiority study design, was 9-month binary angiographic restenosis. Combined antiplatelet treatment was to be continued for 3 months in PEB-CoCr stent group and 12 months in DES group.

Results: The study was stopped after enrollment of 125 patients, 59 in the DEB group and 66 in the DES group, due to excess of Target Lesion Revascularization (TLR) in the PEB group (14% in the PEB vs 2% in DES group; p=0.001). No significant differences in terms of clinical or angiographic characteristics were observed among the two study groups. No stent thrombosis occurred in both study groups.

Conclusion: In the treatment of de-novo coronary stenosis, a strategy of predilatation with Elutas PEB prior to bare-metal CoCr stent implantation was significantly inferior to implantation of Xience stent in terms of 9-month target lesion revascularization.

P4771 An angiographic outcomes of everolimus-eluting stent as compared to sirolimus-eluting stent: a sub-study of the RESET trial

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Objective: This study is aimed to clarify the difference in the angiographic findings of Everolimus-eluting stent (EES) as compared to the first generation Sirolimus-eluting stent (SES).

Methods: RESET is a prospective multicenter randomized open label trial comparing EES with SES in Japan. The trial was designed as “all-comers” trial. Out of 3197 patients of total cohort, 571 patients were enrolled in the angiographic sub-study. Angiograms were assessed qualitatively and quantitatively both at procedure and at 8-12 month in the independent corelab.

Results: Baseline demographics were not different except for stent length, and follow-up results were not different between the 2 groups except for the late loss of proximal edge (table). Edge restenosis was mainly observed in SES group. Stent fracture was only observed in SES group (1.7% vs. 0%) in 3197 patients of total cohort. No stent thrombosis occurred in both groups.

Conclusions: Angiographic outcomes of EES and SES were similar. However, restenotic pattern and detrimental findings such as stent fracture and PES were different between the 2 groups.
(WH) stent designs with only the delivery balloon size changing to cover different diameters. Cut-off diameters between the different workhorses are not commonly provided by manufacturers. Knowing cut-off diameter and maximal expansion capacity of each stent is, however, critically important when major changes in vessel diameter are present along the target vessel, necessitating post-dilatation with larger non-compliant balloons.

We analysed the differences in workhorse designs of 6 Drug Eluting Stents (DES): the Promus Element (4WH), Taxus Liberte (3WH), Xience V (2WH), Resolute Integrity (2WH), Biomatrix (2WH) and Cypher stent (2WH). Furthermore, we tested maximal expansion capacities of all workhorse stent with successive post-dilatation using 4.0, 5.0 and 6.0 mm balloons inflated at pressure <14 ATM and analysed stent expansion using high resolution micro Computed-Tomography. Maximal inner lumen diameter (MLD) achieved with full expansion of the largest Workhorse was on average 5.4 mm for the Element, 5.7 mm for the Xience V, 5.75 mm for the Taxo, 4.7 mm for the Taxo2, 5.4 mm for the Xience V, 5.7 mm for the Biomatrix and 5.75 for the Cypher. At their maximal expanded diameter, struts were severely distorted with shortening at the stent edges and with differences depending on workhorse and connector design.

P4773 Is there an advantage in using second vs. first generation drug eluting stents in acute coronary syndromes?

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Purpose: Registry series and RCTs show that DES have an overall better performance than BMS in patients treated in the clinical context of an acute coronary syndrome (ACS), both STEMI and NSTEMI/UA, mainly by reducing TLR. Whether or not the use of 1st generation DES (DES1g) versus 2nd generation DES (DES2g) differs in this particular setting is largely unknown.

Methods and results: In a single-center prospective registry, 3266 patients were submitted to PCI with at least 1 DES from January 2003 to December 2009. Of these, 1423 (43.6%) were treated in the setting of ACS with either DES1g only (pactolix or sirolimus; n=903 [64.9%]) or DES2g only (n=500 [35.1%]). The primary outcome measure was the occurrence of death, myocardial infarction (MI) or target vessel failure (TVF), whichever came first; repeat revascularization of the index lesion (TVL) and the occurrence of definite stent thrombosis (according to the ARC definition) were assessed as secondary outcomes. At a median follow-up of 598 days (IQR range 453; 1206), the incidence of death was 8.8% (286), 220 pts (6.7%) had MI and TVF events occurred in 349 (10.7%). Disparity of follow-up duration was accounted for by considering only one year of patients included in the analysis. Whether or not the use of 1st generation DES (DES1g) versus 2nd generation DES (DES2g) differs in this particular setting is largely unknown.

P4775 The anti-proliferative effect of atorvastatin is dependent on stent surface material

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The proliferation and migration of arterial smooth muscle cells (SMCs) are key events in the formation of neointima that frequently follows percutaneous coronary intervention (PCI). Beside the clinical benefit, Statins have an anti-proliferative effect on SMCs and stabilize arteriosclerotic plaques. To optimize controlled drug delivery and release, new biodegradable polymer stent coatings are currently being developed. The impact of Statins on cell proliferation of endothelial cells (ECs) and SMCs on biodegradable polymers has not been studied yet.

Thus, we assessed EC and SMC proliferation, viability, and uptake of 14C-Atorvastatin by BniU-ELISA, AlamarBlue®-Assay, and Radio-Assay, respectively. Primary endothelial cells (HCAEC) and smooth muscle cells (HCASMC) were incubated with concentrations of Atorvastatin ranging from 0.01 μM up to 10 μM for 48 hr. Additionally, HCAEC and HCASMC were cultured on different polymer surfaces. Comparable evaluation was performed with polymers similar to those utilized in DES that are currently being marked (PEVA, PBMA, and PLLA).

Atorvastatin showed a dose-dependent inhibition of EC and SMC proliferation. At a concentration of 0.1 μM the proliferation of HCAEC remains unaffected whereas the proliferation of smooth muscle cells is significantly reduced. However, increasing Statin concentrations also affect endothelial cell proliferation. At a concentration of 2 μM Atorvastatin was measured 20 min in HCAEC and HCASMC. Data show a 1.6-fold higher Atorvastatin uptake in HCAEC (p=0.05). Interestingly, we found that HCAEC and HCASMC cultured on different polymer surfaces and incubated with Atorvastatin showed a material-dependent effect of the Statin rather than a dose-dependent. On PEVA and PBMA (Cypher stent) proliferation of HCAEC is significantly decreased by nearly 90% (p=0.05). On PLLA HCASMC proliferation is reduced by 50%. Furthermore, PLLA-Copolymers seem to promote Atorvastatin proliferation and somehow inhibit the impact of Atorvastatin on SMC proliferation.

We demonstrate for the first time a material-dependent effect of Atorvastatin on the proliferation of HCAEC and HCASMC. It seems that recently designed polymers for new stent technologies do not support the anti-proliferative effect of Atorvastatin on SMCs. The development process of new stent surfaces, particularly bioabsorbable polymers should comprise the analysis of interactions of frequently used drugs with the material.

P4776 One-year outcome after PCI for distal left main stenosis treated with single stenting or with T-stenting


Background: Percutaneous treatment (PCI) of distal left main bifurcation may involve stenting of the main branch including final kissing balloon of the side branch (single stenting) or stenting of both branches. There is only limited data comparing single stenting including final kissing-dilatation versus T-stenting regarding the long term clinical follow-up.

Hypothesis: We tested the hypothesis that the lesions that were treated with the single stent have a lower target lesion revascularisation (TLR) 1 year after PCI than lesions treated with T-stenting.

Methods: We established a bifurcation registry of 394 consecutive patients undergoing percutaneous catheter intervention (PCI) for distal left main stenosis in our institution between January 2002 and december 2009. One stent approach was performed in 229 patients and T-stenting in 165 patients. The need for double stenting to achieve best angiographic result was 42%. Complete 1 year clinical follow-up of all patients is available for the analysis.

Results: Baseline clinical characteristics were well matched between 2 groups. Target lesion revascularisation (TLR) after 1 year was performed in 11.7% of patients treated with single stenting and final kissing and in 13.5% treated with T-stenting (p=0.16). The combined endpoint of death and myocardial infarction (MI) as marker for safety was reached by 10.5% of patients in the single stent group and in 11.5% in the T-stenting group (p=0.56). Death occurred in 8.7% in the single stent group and in 7.9% in the T-stenting group (p=0.57).

Conclusions: PCI of de-novo distal left main stenosis using single approach (single stenting with final "kissing balloon"-dilation) is associated with similar 1 year outcome as compared with T-stenting.
Drug eluting stents with microporous polymeric covering as a scaffold for acquisition of extremely thin neoointimal lying without disturbing branching vascular flow

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Objective: As new generation of drug eluting stents, we developed microporous polymeric-covered stents, whose design concept was utilization of covering for a scaffold for extremely thin neoointimal lying. The effectiveness was demonstrated in this study for long-term animal experiments.

Methods and Results: Two types of covered stents based on different stent platforms of self-expandable stents (Luminexx from Bard Co.; 3 mm x 20 mm) and balloon-expandable stents (Momo from Japan Stent Technology Co.; 3 mm x 20 mm) were prepared in three steps, that is 1) dip-coating of polyurethane for covering, 2) laser-induced microporing, and 3) drug coating with argatroban. The stents had structural advantage with flat luminal surface impregnating strut completely into the cover film. The stents were placed at carotid or subclavian arteries of beagle dogs or rabbits. Even at 1 month of implantation (n=5) the luminal surface was fully endothelialized. Extremely thin neoointima (n=19, thickness; 187±39 nm) was observed at 1 year of implantation, which was about half of that in non-covered bare stents. The thin and stable neoointima continued up to 3 year of implantation (n=15). The covered stents could maintain the branching microvascular flow perfectly due to microporing of cover film. Argatroban had strong anti-thrombogenic and anti-inflammation potentials.

Conclusion: Argatroban-loaded microporous covered stents developed here were effective for in short-term lying of extremely thin neoointima with long-term highly reliability.

Comparison of 3-year clinical outcomes between classic crush and modified mini-crush technique in coronary bifurcation lesions

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Objective: We aimed to compare long-term outcomes of modified mini-crush (modi-MC) technique with classic crush (Crush) technique for treating coronary bifurcation lesions. Modi-MC technique showed excellent procedural success immediately and good 9-months clinical outcomes. We compared 3-year clinical outcomes between 2 techniques.

Methods: From Jan 2000 to Nov 2009, we enrolled de novo bifurcation lesions treated with modi-MC (n=112 lesions in 111 patients) and crush technique (n=69 lesions in 67 patients). Primary end-point was major adverse cardiac events (MACE), composite of all-cause death, myocardial infarction (MI), target lesion revascularization (TLR), and stent thrombosis at 3 years.

Results: There were no significant differences in baseline characteristics. After 3 years, MACE was significantly lower in modi-MC group (25.4 vs 13.5%, p=0.046). The incidence of all-cause death was 7.5% vs. 2.7% (p=0.16), MI was 4.5% vs. 1.8% (p=0.63) in Crush and modi-MC group, respectively. However, MACE of left main (LM) lesion was significantly higher than non-LM bifurcation (25.7% vs. 12.9%, p=0.001) in entire cohort. Cox regression analysis showed LM location (p=0.002, odds ratio[OR] 3.031, 95% confidence interval[CI] 1.526-6.021), and crush technique (p=0.044, OR 2.035, 95% CI:1.018-4.069) were independent predictors for MACE.

Conclusions: Modified mini-crush technique was more favorable 3-year clinical outcomes comparing with classic crush technique. However, both classic crush and modified mini-crush techniques are cautiously applied in LM bifurcation lesion.

Assessment of an asymmetrical coating stent with sirolimus released from abluminal matrix in porcine model

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Purpose: Delayed endothelialization contributes to stent thrombosis (ST) of current drug eluting stents (DES). Asymmetrical coating technique is considered to perform antiproliferative effect as well as enhance surface endothelialization. We developed an asymmetrical coating stent with sirolimus released from abluminal matrix and assessed its efficacy in a porcine model.

Methods: Layer-by-layer self-assembled chitosan/heparin (C/H LBL) was ever proved to promote re-endothelialization. A novel stent system, C/H LBL coated luminally and sirolimus released abuminally (C/H LBL-SES), was fabricated. Bare metal stents (BMS), traditionally circumferential sirolimus-eluting stents(SES), and C/H LBL-SES were implanted into porcine coronary arteries. At 7, 14 and 28 days follow-up, angiography, intravascular ultrasound (IVUS), vasomotor function analysis, scanning-electron microscopy (SEM) and histopathology were performed. The study protocol followed the “Principles of laboratory animal care” (NIH Publication no. 85-23 revised 1985) and was approved by the Animal Care and Use Committee of Zhongshan Hospital.

Results: At 28 days after implantation, the diameter stenosis of C/H LBL-SES by quantitative coronary angiography was 18.76±2.48%, the area stenosis by histomorphometry was 24.17±2.94%, which were comparable to that of SES and superior to BMS. At 14 days, re-endothelialization of C/H LBL-SES almost completed while only about 50% of surface of SES was covered by endothelium. During 28 days follow-up, although C/H LBL-SES suffered a greater vasoconstriction (3.5±1.5%) than BMS, it behaved better than SES. No sign of stent malposition was detected in all three groups by IVUS. Remodeling index was within the normal range. No acute or subacute thrombotic events occurred.

Conclusions: With pro-healing C/H LBL membrane luminally coated on stent struts and sirolimus released from abluminal matrix, the asymetrically designed C/H LBL-SES reduced in-stent stenosis as effectively as traditionally coated SES during 28 days follow-up. Comparing with circumferential coating of SES, the asymmetrical coating significantly promoted rapid re-endothelialization in the early stage of follow-up. No sign of LSM or paradoxical remodeling was detected by IVUS at the end of observation. No acute or subacute thrombotic events occurred. This finding highlighted asymetrically designed DES may be a promising stent platform superior to traditionally DES.

The ulnar puncture technique: lessons from experience

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Background: The Ulnar Artery (UA) could be a valuable approach for cardiac catheterization, but the "how to do" of the puncture have not been follow up, the "how and where" to puncture to the UA to reduce the incidence of complications.

Methods: We evaluated all patients (pts) in which the UA approach was at OCA from May 2002 to October 2011. All studies were performed in 113 pts (73% radial approach) 1127 (5%) were performed via UA, of a total of 22425 pts attended, (73% radial approach) 1127 (5%) were performed with experience in transradial approach. Follow-up was achieved in 95% pts at 24 hours and 91% at 3 months after procedure. Haematomas (H) and neurological complications related to the UA puncture were recorded.

Results: A total of 22425 pts attended, (73% radial approach) 1127 (5%) were performed via UA (mean aged 67±14 years. 65% males). Risk factors were the usual in the non-selected populations. UA was punctured at or near the wrist’s skin folds, or more proximal at 3-4 cm (the 2 sites where the artery can be best felt). Study was completed in 1025 pts (91% of attempted). In 113 pts (11%) UA was used after failure of radial puncture in the same wrist. The main cause of crossover to other artery was puncture failure (65% of cases). Out to 1513 procedures performed (77% by right UA), 661 (45%) were PCI. A total of 65 H > 10 cm were documented; 12 (12%) of them, within the first 100 cases done, and 50 (3.3%) in the following 955 pts (5.3%) (p<0.05). There were 3 temporary neurological complication related to the nerve compression by big H and 15% of unintentional nerve punctures without sequel at follow up (ulnar nerve runs slightly below the artery). In a Multi-Variable analysis, H was related to a proximal puncture site, that difficult the compression of UA.

Conclusion: Ulnar puncture must be done above the carpal bones (at the level of the wrist’s skin fold). Needle should be directed from lateral to medial (45º) in order to avoid unintentional ulnar nerve puncture. The high incidence of UA puncture failure is due to the difficulty to felt the artery in many pts, but when UA pulse is stronger than radial, could be even better option than radial for cardiac catheterization.
The impact of circadian variations on long-term clinical outcomes in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Purpose: The circadian rhythm influences a number of cardiovascular physiological processes including the incidence of acute myocardial infarction. A circadian variation in infant size has recently been shown in rodents, but there is no clinical evidence of its influence on long-term outcomes. The aim of this study is to investigate whether circadian rhythm could cause differences in long-term clinical outcomes in patients with STEMI.

Methods: A total of 3,581 STEMI patients with less than 12 hours of symptom onset were obtained from the Korea Acute Myocardial Infarction Registry and divided into 4 time groups based on time of symptom onset (period I: 00:00-05:59, period II: 06:00-11:59, period III: 12:00-17:59, and period IV: 18:00-23:59). The primary outcome was the composite of major adverse clinical events (MACE), defined as death, non-fatal myocardial infarction, and revascularization, at one-year follow-up.

Results: There was no difference regarding baseline patient characteristics, angiographic findings, and procedural results. There was significant difference between groups regarding symptom-to-door time and door-to-balloon time with highest levels in patients with symptom onset of period I (251.7±182.1 min, p<0.001; 107.4±62.6 min, p<0.001, respectively). However, there was no significant difference between groups regarding maximum CK-MB and left ventricular ejection fraction. Total death and MACE were not different between groups during hospitalization (period I: 4.9%, period II: 5.1%, period III: 3.7%, period IV: 5.1%, p=0.410; period I: 5.9%, period II: 5.4%, period III: 4.4%, period IV: 5.2%, p=0.562, respectively) and at one-year (period I: 8.0%, period II: 8.6%, period III: 5.8%, period IV: 7.7%, p=0.103; period I: 14.6%, period II: 14.6%, period III: 12.0%, period IV: 14.0%, p=0.321, respectively).

Conclusions: This study showed that a circadian difference in symptom onset of STEMI did not influence in-hospital and long-term clinical outcomes. More data are needed to clarify the role of circadian variations on the long-term outcomes in patients with STEMI.

High preprocedural total adiponectin levels are associated with poor long-term cardiovascular outcome after percutaneous coronary intervention

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Objective: Adiponectin is considered to possess antiatherogenic and cardio-protective properties. In patients undergoing percutaneous coronary intervention (PCI), the prognostic value of preprocedural total adiponectin is unknown. The present study was designed to address this issue.

Methods: From March 2006 to September 2007, pre-procedural total adiponectin levels were measured in 477 consecutive PCI patients who underwent PCI for primary PCI or PCI for patients with STEMI. There was no significant difference in the incidences of death or MI, target lesion revascularization between two groups. The incidence of revascularizations for new lesions was significantly higher in patients with MIA than those without MIA (13.6% vs 38.5%, p<0.019). Independent predictor of cardiac events identified by Cox proportional hazard model was MIA (hazard ratio 2.54;95% CI. 1.203-5.352; p=0.014) after adjusted for age, gender, and conventional risk factors.

Conclusions: The elevated urinary albumin excretion rate is an independent predictor of adverse cardiovascular outcomes in patients with mild renal dysfunction who underwent coronary intervention.

Impact of microalbuminuria on cardiovascular outcomes in patients with mild renal dysfunction who undergo elective PCI

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Background: Microalbuminuria (MIA) is considered an independent predictor for one-year mortality (Hazard ratio 0.98, 95% confidence interval 0.92 – 1.06, p=0.76). Conclusion: While adiponectin is associated with in-hospital and one-year mortality in STEMI patients undergone p-PCI, body mass index is not a independent predictor for in-hospital and 1-year mortality. This can be explained by multiple comorbidities in overweight group and younger age, more aggressive treatment in overweight group.

Prognostic significance of body mass index for in-hospital and long-term mortality in patients undergoing primary percutaneous coronary intervention

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Purpose: Prognostic significance of body mass index for in-hospital and long-term mortality in overweight and underweight population with ST elevation myocardial infarction (STEMI) is well-defined. However, cause of this relation has not yet understood well.

Method: 2007 patients in 36 months period admitted to our hospital emergency service within first 12 hours of chest pain and undergone primary percutaneous coronary intervention (p-PCI) were our study population. Patients were divided in four groups according to body mass index. <18.5 (n=182), 18.5 – 24.9 (n=732), 25 – 29.9 (n=768), >30 (n=325).

Results: Advanced age, anemia, renal functional impairment and nonspecific inflammation (baseline C-reactive protein) were more common in underweight group. Final TIMI 3 flow was lowest in underweight group and highest in overweight group (82.9% vs 89.5% vs 89.5% vs 90.2%, p=0.038, respectively). In-hospital mortality was lowest in obese group (6.0% vs 5.3% vs 3.1% vs 2.5%, p=0.034, respectively) and one-year mortality was highest in underweight group (13.5% vs 9.5% vs 6.7% vs 7.8%, p=0.006, respectively). After adjusting for potential confounding variables by Cox proportional hazard model, BMI was not a independent predictor for one-year mortality (Hazard ratio 0.98, 95% confidence interval 0.92 – 1.06, p=0.76).

Conclusions: In contrast to studies in the general population, high preprocedural total adiponectin levels may be associated with increased risk of mortality, MI or stroke in patients undergoing PCI.
Comparison on 1-Year MACE of everolimus-eluting stent Xience vs sirolimus-eluting stent cypher in diabetic patients

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Background: To expand the paucity of data on the efficacy of sirolimus-eluting stents (Cypher, Cordis, Bridgewater, NJ) vs everolimus-eluting stent (Xience, Abbott Vascular, Redwood City, CA) in diabetic patients.

Methods: Due to Tuscany Region Medical Authority, Cypher stent was no more available after December 2008 and replaced by Xience stent. We collected the data of all consecutive type 2 diabetic patients presenting with de novo or in-stent restenosis lesions in native coronary arteries treated in our institution from January 2003 to November 2008 (Cypher period) and from December 2008 to May 2010 (Xience period). The primary end point was the 1-year composite of major adverse cardiac events (MACE), including cardiac death, myocardial infarction (MI), and clinically driven target vessel revascularization (TLR).

Results: During the study periods, 440 lesions in 256 patients were treated with Cypher stent and 420 lesions in 212 patients with Xience stent (p=0.2). There were no significant differences among the two study groups except for previous myocardial surgical revascularization (8.6% in Cypher group vs 4% in Xience group, p=0.03) and stent length (22.4±8.7 mm vs 30.1±8.7 mm, respectively, p=0.004). MACE-free survival was 89% in the Cypher group and 88% in the Xience group (p=0.7). Cardiac death occurred in 3 (1.2%) Cypher vs 4 (1.9%) Xience patients (p=0.7). MI in 4 (1.9%) vs 4 (1.9%) respectively. TLR in 37/440 (8%) Cypher vs 25/420 (6%) Xience lesions (p=0.2). Sient Thrombosis (ST) confirmed by angiography occurred in 2 (0.8%) Cypher vs 1 (0.5%) Xience patients (p=0.7).

Conclusions: The present study suggests that in diabetic patients, the Cypher stent is associated with a similar 1-year MACE rate when compared with Xience stent. Longer follow-up will evaluate the impact of the two stent in the occurrence of ST.

EPC capture stent and CD34+ mobilization in acute myocardial infarction

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Background: Percutaneous revascularization is the gold standard for the treatment of acute myocardial infarction (AMI), with the main limitation of in-stent restenosis for BMS and late stent thrombosis (ST) for both BMS and DES. Endothelial progenitor cells (EPC) CD34+ capture stents, promoting vascular healing, may be advantageous in preventing ST. The role of EPC on restenosis and atheromasis disease progression is unclear. The aim of the study is to evaluate the outcomes of AMI patients treated with EPC CD34+ capture stent and describe the mobilization kinetics of CD34+ and their clinical correlation.

Methods: 50 AMI patients underwent primary PCI with EPC CD34+ capture stent. Serial assays of CD34+ were performed by flow-cytometric analysis. Primary outcome was occurrence of death, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), stent thrombosis, and major adverse cardiac events (MACE).

Results: Procedural success rate was 100%. At six months follow-up cardiac death, MI, TLR and TVR occurred respectively in 2%, 4%, 10% and 12% of patients. No case of ST was observed. The MACE-free survival was 82%. The mean peak value of plasmatic CD34+ was 4.69±3.76 cells/μL. A positive correlation was found between CD34+ concentration, age and infarct area. No correlation was detected between CD34+ concentration and occurrence of TVR, TLR and MACE.

Conclusions: EPC capture stent implantation seems to be safe and effective in the clinical setting of AMI, representing a possible alternative to BMS and DES. CD34+ cells plasmatic concentration seems not to correlate to coronary restenosis and atheromasis disease progression.

Developments in the last ten years - LHC and PCI

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Background: In 1996 German Cardiologists in Private Practice started to collect all their diagnostic procedures (LHC) and interventions (PCI) in a quality assurance registry. With only eight cath-labs in 1996 participants in the registry increased to 127 in 2010. We report changes since the beginning and compare the results of 2010 to the ones of the year 2000.

Multivessel versus culprit lesion percutaneous coronary intervention in ST-elevation myocardial infarction: is more worse?

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Introduction: Existing data on the benefits of multivessel versus culprit lesion PCI during acute STEMI elevation myocardial infarction (STEMI) are conflicting. Methods: We compared outcomes between STEMI patients with multivessel disease treated with multivessel PCI versus those treated with culprit lesion only PCI who were enrolled in the national AMIS Plus registry of Switzerland from 2005 to 2011. Baseline characteristics of these groups were assessed using Student t-tests and chi-squared tests while multivariable logistic regression models were used to evaluate differences in in-hospital outcomes.

Results: From 11,099 STEMI patients who presented during this study period, we identified 4559 patients (41%) with multivessel disease (including 5.6% with main stem) who underwent PCI. Among these, 3541 patients (78%) were treated with multivessel PCI and 1018 patients (22%) received only culprit PCI. Overall, 21 patients died in the 30-day follow-up period, 14 had multivessel PCI during their STEMI. Patients who underwent multivessel PCI had higher rates of cardiopulmonary resuscitation prior to admission (8.3% versus 5.6%; p=0.007) and Killip class >2 (12.0% versus 5.9%; p<0.001). Immediate drugs, such as glycoprotein IIb/IIIa inhibitors, beta-blockers, ACE inhibitors or angiotensin receptor blockers, and statins were used less frequently in this group. Unadjusted rates of in-hospital events were higher among patients treated with multivessel PCI with nearly double the rate of cardiogenic shock (7.5% versus 4.7%; p=0.001) and in-hospital mortality (7.4% versus 4.4% p=0.001).

Conclusion: STEMI patients with multivessel disease undergo multivessel PCI are sicker than those who undergo culprit lesion PCI only. After multivariable adjustment, multivessel PCI was not independently associated with worse in-hospital mortality.
Impact of successful thrombus retrieval during primary percutaneous coronary intervention with thrombus aspiration on the infarct size and microvascular obstruction: a magnetic resonance imaging study


Background: Thromboaspiration (TA) during primary percutaneous intervention (PCI) is effective in opening the infarct-related artery in patients with ST-segment elevation myocardial infarction (STEMI), leading to better reperfusion and improved outcome. However, the effect of positive macroscopic efficacy of TA remains unknown. We aimed to evaluate the impact of positive thrombus retrieval during PCI with manual TA on infarct size (IS) and microvascular obstruction (MVO) as assessed by contrast-enhanced magnetic resonance imaging (CE-MRI) in a subset of patients with STEMI.

Methods: Inclusion criteria were patients aged <75 years, with first STEMI referred for PCI within 12 hours of onset of symptoms, infarct-related artery ≥2.5 mm in diameter, thrombus score ≥3 and no prior history of coronary disease. All patients underwent TA before stenting and were categorized according to positive or negative TA. Clinical and procedural characteristics of the study population and CE-MRI were performed at 5 days and 6 months to evaluate MVO and IS.

Results: 88 patients were enrolled, with mean age 55±10 years; 43.1% in the positive TA group. Main results are presented in the table. Clinical and procedural characteristics (90-min total ischemic time, STE-segment resolution, post-procedural TIMI flow grade and post-stenting myocardial blush grade, and peak troponin) did not differ significantly between groups. Independent predictors of final IS were: positive TA (OR 0.34, 95%CI 0.03-0.71), MVO (OR 1.75, 95%CI 1.28-0.71) and IS at 5 days (OR 2.06, 95%CI 1.87-3.32).

Conclusion: Positive thrombus retrieval during primary PCI with manual TA in STEMI reduces MVO and IS at 5 days and 6 months and represents a powerful predictor of final infarct size.

P4789

Intra-procedural stent thrombosis: a new risk factor for adverse outcome in patients undergoing percutaneous coronary intervention for acute coronary syndrome

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Background: Stent thrombosis (ST) is a rare complication of percutaneous coronary intervention (PCI). It is more common in the setting of acute coronary syndromes (ACS). It is not known whether intra-procedural ST (IPS) carries the same prognosis as post-procedural ST.

Objective: To examine the incidence, correlates and consequences of IPS.

Methods: We combined two large ACS studies—ACUTY and HORIZONS AMI. The angiograms were independently reviewed frame-by-frame for the occurrence of IPS. Patients with and without IPS were compared with respect to clinical and angiographic characteristics, and adjudicated events at 30 days and 1 year.

Results: Among 6,591 patients, there were 47 cases of IPS (49 lesions, 0.7%). There were no important differences in baseline characteristics between the two groups. Patients with IPS had significantly more often biventricular lesions treated, revascularization of anterior ST at baseline. Death occurred significantly more often among IPS patients at 30 days (12.9% vs. 1.4%, P<0.0001) and at 1 year (12.9% vs. 3.1%, P<0.0001). ST occurred significantly more often among IPS patients at 30 days (12.9% vs. 1.4%, P<0.0001) and at 1 year (12.9% vs. 3.1%, P<0.0001). Table), ST occurred significantly more often among IPS patients at 30 days (12.9% vs. 1.4%, P<0.0001) and at 1 year (12.9% vs. 3.1%, P<0.0001). Table), ST occurred significantly more often among IPS patients at 30 days (12.9% vs. 1.4%, P<0.0001) and at 1 year (12.9% vs. 3.1%, P<0.0001).

Conclusion: IPS is a rare complication of PCI in ACS, correlated with procedural factors. It is associated with an increased incidence of ST particularly in first 30 days and is an independent predictor of cardiac death at 1 year. IPS should be considered as a distinct category of ST.

P4788

P4790

Real-world use of the second-generation cobalt-chromium sirolimus-eluting stent: 12-month results from the prospective multicentre FOCUS registry

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Background: The second-generation Firebird-2 cobalt-chromium alloy sirolimus-eluting stent (CoCr-SES) has been widely used in the world. The FOCUS registry is a prospective, international, and web-based program designed to collect clinical and angiographic outcome data from real-world patients receiving the CoCr-SES.

Methods: From March 2009 through February 2010, a total of 5,084 patients from 83 clinical centers in 3 Asian countries eligible to receive a Firebird-2 CoCr-SES were enrolled in the FOCUS registry. Baseline characteristics and procedure results from the prospective multicentre FOCUS registry were recorded and CE-MRI was performed at 5 days and 6-months to evaluate microvascular obstruction (MVO) in a subset of patients with STEMI.

Results: One year data were available for 5,013 (98.6%) of the 5,084 patients enrolled. The primary endpoint, MACE at 12 month follow-up, occurred in 174 (3.47%) of 5,013 patients, consisting of 43 (0.86%) cardiac death, 132 (2.63%) MI, and 46 (0.92%) TVR. According to the Academic Research Consortium definition, definite and probable stent thrombosis (ST) occurred in 0.52% (26/5,013) of the patients, with a 12-month MACE rate of 3.73% and 6.06% for extended- and standard-use patients, respectively (p=0.002).

Conclusion: The second-generation CoCr-SES was associated with low rates of 12-month MACE and ST in a broad spectrum of patients, thereby confirming the clinical safety and efficacy of this stent in a real-world setting. (FOCUS Registry: NCT00886829)

Polymer-Free Sirolimus- versus Polymer-Based Paclitaxel-eluting stents. An individual patient data analysis of randomized trials

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Aims: The efficacy of polymer-free sirolimus-eluting stents (PF-SES) and polymer-based paclitaxel-eluting stents (PF-PES) was recently debated, mainly in high-risk subsets. We investigate outcomes of PF-SES versus PB-PES with an individual patient data analysis of randomized trials.

Methods: Patients included in the randomized trials Intravascular Stenting and Angiographic Restenosis - Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST) and LIPSIA Yukon trials were pooled. Primary endpoint was in-stent late loss (LUS) at 9-month angiography. Secondary endpoints were: death or myocardial infarction (MI), cardiac death or MI, target lesion revascularization (TLR) and MI. Interaction of treatment effect with subgroups (gender, age, insulin/non insulin treated diabetes, stable/unstable presentation and small/large vessels) was addressed.

Results: A total of 686 patients (PF-SES, n=345 versus PB-PES, n=341; diabetes 55.9% versus 51.0%, p=0.19) and 751 lesions (PF-SES, n=383 versus PB-PES, n=368; B2/type 62.1% versus 67.1%, p=0.15) were included. Control angiography (606 lesions) showed comparable in-stent LUS for PF-SES versus PB-PES (0.53±0.59 mm versus 0.46±0.57 mm, p=0.15). Clinical follow-up (median 30.4 months) confirmed no significant difference between PF-SES versus PB-PES regarding death or MI (12.4% versus 12.6%, Relative Risk 95% Confidence intervals) 0.89 [0.49-2.00]; p=0.71), cardiac death or MI (10.7% versus 9.0%, RR=1.17 [0.72-1.89]; p=0.50), TLR (13.6% versus 13.7%, RR=0.98 [0.65-1.47]; p=0.93) and MI risk (5.7% versus 3.2%, RR=1.79 [0.85-3.76]; p=0.12) without treatment-effect modification among subgroups.

Conclusions: Polymer-free SES is comparable to polymer-based SES with respect to angiographic and clinical efficacy. No difference exists among gender, age, clinical presentation, insulin/non insulin treated diabetes and vessel diameter subgroups.
Lack of gender difference and improved in-hospital mortality rates in patients with cardiacogenic shock following primary percutaneous coronary intervention: a UK tertiary cardiac centre registry study

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Background: Despite substantial recent improvement in mortality from cardiovascular disease, due primarily to success of primary and secondary prevention strategies, it remains the leading cause of death in the developed world. Among those patients hospitalized with acute myocardial infarction (AMI), cardiogenic shock (CS) is the foremost cause of death complicating up to 10% of admissions. Introduction of early revascularisation strategies and mechanical ventricular support have seen short-term mortality due to CS fall from 70-80% in the 1970s to around 50-60% in the 1990s. Previous studies suggest that women experience more CS than men (11.6% vs. 8.3%) in the setting of ST elevation MI. Whether primary percutaneous coronary intervention (PCI) for AMI has resulted in further reduction in in-hospital mortality and whether there are gender differences in outcomes due to CS is not known.

Aims: The aim of this study is to determine the rate of in-hospital mortality following primary PCI in the setting of CS and examine the gender differences in the incidence of CS and the rate of in-hospital mortality.

Methods: Data were collected prospectively among all patients presenting with AMI to a large UK tertiary cardiac centre and undergoing PCI between April 2008 and October 2011.

Results: In total 2866 patients (male: 2023 [70.6%] vs. female: 843 [29.4%]) underwent PCI. In total, 141,286 (4.9%) had percutaneous coronary procedures (balloon angioplasty only or stenting) in the setting of cardiogenic shock. There were 81/2023 (4%) male patients and 60/843 (7%) female patients with CS undergoing PCI. There were no significant differences in the baseline characteristics between male and female patients except female patients were older than men (male: mean age 64.1 years vs. female: 69.9 years, p=0.004). The overall unadjusted in-hospital mortality rate was 35.4% with no difference in the genders (male: 35.8% vs. female: 35%, p=0.730).

Conclusion: The present analysis demonstrates that in the PCI era, there is reduction in the incidence of cardiogenic shock with reduced unadjusted in-hospital mortality rates following primary PCI. The unadjusted in-hospital mortality rates did not differ between the genders despite the fact that there were more women that had presented with cardiogenic shock.

In-hospital clinical outcome of patients with definite stent thrombosis

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Background: The outcome of patients with angiographically proven stent thrombosis is only insufficiently known. We sought to evaluate presentation and outcome of patients with angiographically proven stent thrombosis.

Methods: 76 consecutive patients (mean age 69±12 years; 58% male) with 81 angiographically proven stent thrombosis between 2003 and 2010 were included in the analysis. The time interval between initial stent implantation, rate of dual antiplatelet therapy (DAPT) at presentation with stent thrombosis, frequency of death during hospitalisation, predictors of death as well as frequency of recurrent stent thrombosis were evaluated.

Results: A total of 18 (48%) had early ST, 3 patients (4%) had late ST and 12 patients (16%) had very late ST. 59 patients (78%) were on dual antiplatelet therapy at the time of stent thrombosis. 60 patients (79%) presented with STEMI while 16 patients (21%) presented with other forms of acute coronary syndrome. 13 patients (17%) died during hospitalization. Univariate predictors of death were presentation with cardiogenic shock (OR 1.61, 95% CI 1.32-1.97, p<0.001), LV ejection fraction (EF) ≥ 30% at presentation (OR 1.35, 95% CI 1.06-1.71, p<0.010), and discontinuation of clopidogrel administration at presentation (OR 1.35, 95% CI 1.06-1.71, p<0.010). Cardiogenic shock (OR 1.46, 95% CI 1.24-1.72, p<0.001) and discontinuation of clopidogrel administration (OR 1.22, 95% CI 1.04 - 1.43, p<0.020) remained independent predictors of death during hospitalization. 5 patients (7%) had recurrent ST during hospitalization.

Clinical outcome after stent thrombosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>13 (17%)</td>
</tr>
<tr>
<td>STElevation myocardial infarction</td>
<td>60 (79%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>24 (32%)</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>81 (100%)</td>
</tr>
<tr>
<td>Recurrence stent thrombosis</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

Conclusion: Stent thrombosis is associated with a detrimental acute prognosis with severe systolic left ventricular dysfunction (EF ≤30%), cardiogenic shock and discontinuation of clopidogrel being predictors of death. Recurrent stent thrombosis is not unfrquented.

Cost-effectiveness of drug-coated balloon angioplasty and drug-eluting stent implantation for treatment of coronary in-stent restenosis

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Purpose: In-stent restenosis (ISR) is a persistent problem limiting the long-term success of percutaneous coronary intervention. Recent studies have demonstrated safety and efficacy of drug-coated balloon (DCB) angioplasty for the treatment of corony ISR. The cost-effectiveness of this practice is unknown.

Methods: A Markov state transition decision analysis model was used to assess the comparative cost-effectiveness of two common treatment strategies for BMS-ISR: stenting with paclitaxel-eluting DES versus paclitaxel-coated balloon angioplasty (SeQuent Please, B. Braun Melsungen AG, Berlin, Germany). The model accounted for varying procedural efficacy rates, complication rates, and cost estimtates. Data on procedural outcomes associated with both treatment strategies were derived from the literature, and the cost analysis was conducted from a healthcare payer perspective. Effectiveness was expressed as life-years gained. Cost-effectiveness was calculated by dividing the difference in mean costs (costs – costs for DES implantation) by the difference in effectiveness (life expectancy in the DCB arm – life expectancy in the DES arm). All simulations were performed using Monte Carlo simulations with 100,000 random trials.

Results: In the base-case analysis, incremental cost-effectiveness was τ≤ 3,604.14 for DCB angioplasty and to τ≤ 3,309.66 for DES implantation. Over a 12-month time horizon, the DCB strategy was found to be less costly (€1,430.38 versus €5,305.30) and slightly more effective in terms of life expectancy (0.983 versus 0.976) than the DES strategy. Extensive sensitivity analyses indicated that, in comparison with DES implantation, the cost advantage of the DCB strategy was robust to clinically plausible variations in the values of key model input parameters. The variables with the greatest impact on base case results were the duration of dual antiplatelet therapy with acetylsalicylic acid and clopidogrel after DCB angioplasty, the use of generic clopidogrel, and variations in the costs associated with the DCB device.

Conclusion: DCB angioplasty is a cost-effective treatment option for coronary BMS-ISR. The higher initial costs of DCB are more than offset by later cost savings, predominantly as a result of reduced medication costs. Health care payers

Twelve-month safety and performance results of the paclitaxel-eluting bioabsorbable magnesium scaffold in the prospective, multicenter first-in-man trial - BIOSOLVE-I

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Purpose: Absorbable metal scaffolds (AMS) are developed to overcome limitations of current permanent bare or drug-eluting coronary stents like stent thrombosis despite prolonged dual antiplatelet therapy (DAPT), caged vessel segment not allowing vasoconstriction and remodelling or chronic vessel wall inflammation. Magnesium is an essential element of the human body, thus Magnesium is considered as a potential alloy for absorption. To overcome the limitations associated with the first generation of a bare AMS a Drug (Paclitaxel) Eluting Absorbable Magnesium Scaffold was developed (DREAMS).

Methods: Between July and December 2010, 46 subjects were enrolled in the first-in-man BIOSOLVE-I study, and assigned to two different cohorts with different follow-up schedules. Clinical follow-up for both cohorts is scheduled at 1, 6, 12, 24 and 36 months, angiographic follow-up for cohort 1 at 6 months and for cohort 2 at 12 months. Angiographic assessment was performed by an independent core laboratory. The primary endpoint is Target Lesion Failure (TLF), defined as the composite of cardiac death, target vessel myocardial infarction and clinically driven target vessel revascularization at 6 months for cohort 1 and at 12 months for cohort 2.

Results: Of the 46 subjects 34 were male and 12 were female subjects with a mean age of 65.3±9.7 years ranging from 42 to 80 years. Hyperlipidemia (89%), hypertension (87%) and history of myocardial infarction (33%) were the major risk factors. Type A (25.5%), Type B1 (57%) and Type B2 (8.6%) lesions were treated with a 3.25/16 mm (48.9%) or a 3.5/16 mm (51.1%) DREAMS. The target lesion failure rate at 12-month is 7.0% with no cardiac death, one periprocedural target vessel non-viable myocardial infarction and two clinically driven target lesion revascularizations (TLR). There was no scaffold thrombosis. The angiographic results of 33 patients consenting for the 12-month follow-up will be available upon presentation.

Conclusion: DREAMS showed an excellent safety profile and a low TLF rate up to one year follow-up.
would benefit from a wider adoption of this technology, as DCG angioplasty can be regarded as one of the rare innovative medical interventions that are cost-saving at equal or even increased effectiveness.

**P4796**

**Difference of vascular response between everolimus- and paclitaxel-eluting stents for small coronary artery diseases: optical coherence tomography analysis**

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**Background:** The aim of this study is to evaluate the differences of chronic vascular response following small coronary stenting between everolimus-eluting stent (EES) and paclitaxel-eluting stent (PES) evaluated by optical coherence tomography (OCT).

**Methods:** SACRA and PLUM registries are prospective, multicenter registry to assess the efficacy of single paclitaxel (PES) or everolimus-eluting stents (EES) in patients with small coronary artery diseases. Inclusion criteria of both registries were: 1) significant stenosis in vessels <2.5mm in reference diameter, 2) lesion length <30mm. From these two registries (506 patients with 533 lesions), non- restenotic 50 EESs and 50 PESs were imaged with OCT at 9-month follow-up and analyzed at interval of 1 mm.

**Results:** Average intimal hyperplasia thickness was not different between the two groups. Exposed struts and layered intima were observed more frequently in PES group than EES group.

**OCT results**

<table>
<thead>
<tr>
<th>EES</th>
<th>PES</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of stent</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>No. of observed cross-sections</td>
<td>899</td>
<td>825</td>
</tr>
<tr>
<td>Homogenous intima</td>
<td>803 (93%)</td>
<td>737 (89%)</td>
</tr>
<tr>
<td>Heterogenous intima</td>
<td>38 (4.4%)</td>
<td>28 (3.4%)</td>
</tr>
<tr>
<td>Layered intima</td>
<td>18 (2.1%)</td>
<td>60 (7.3%)</td>
</tr>
<tr>
<td>Peri-stent low signal</td>
<td>30 (3.5%)</td>
<td>100 (12.5%)</td>
</tr>
<tr>
<td>Peri stent ulcer like appearance</td>
<td>53 (6.2%)</td>
<td>106 (12.8%)</td>
</tr>
<tr>
<td>No. of analyzed strut</td>
<td>3360</td>
<td>7600</td>
</tr>
<tr>
<td>Exposed strut</td>
<td>26 (0.27%)</td>
<td>130 (1.7%)</td>
</tr>
<tr>
<td>Malapposed strut</td>
<td>9 (0.10%)</td>
<td>22.0</td>
</tr>
<tr>
<td>Percent neointimal hyperplasia area,</td>
<td>20.4±8.6</td>
<td>22.0±10.7</td>
</tr>
<tr>
<td>Average NIT, μm</td>
<td>0.04±0.06</td>
<td>0.15±0.08</td>
</tr>
<tr>
<td>Maximum NIT, μm</td>
<td>0.22±0.06</td>
<td>0.28±0.12</td>
</tr>
<tr>
<td>Minimum NIT, μm</td>
<td>0.07±0.04</td>
<td>0.07±0.05</td>
</tr>
<tr>
<td>Minimum NIT - minimum NIT, μm</td>
<td>0.15±0.04</td>
<td>0.21±0.09</td>
</tr>
</tbody>
</table>

EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; NIT: neointimal thickness.

**Conclusions:** This study suggested that characteristics of neointimal hyperplasia after EES implantation were more stable compared with PES although neointimal growth was similar between the two groups.

**P4798**

**Second vs. first generation DES are associated with a better safety profile in real world coronary intervention: analysis of 3266 procedures from a single centre prospective registry**

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**Background and Aims:** When compared to their first generation counterparts, second generation DES have been associated with better clinical outcomes in recent RCTs, which, together with safety concerns (mostly stent thrombosis [ST]), led to a progressive abandonment of the latter in most clinical settings. Our goal was to assess whether or not newer devices translate into higher safety in a real world population. For that purpose, our main outcome measure was the occurrence of definite ST.

**Methods and Results:** Between January 2003 and December 2009, 3266 patients/lesions were submitted to PCI with at least one DES. Of these, 2260 (69.2%) were known to be an important predictor of early stent thrombosis and restenosis in the DES era. Recently, a large retrospective study demonstrated that post-dilatation after DES implantation reduced the restenosis rate. However, the population of the study did not include patients with acute myocardial infarction (AMI). The aim of present study was to 12-month patients with AMI.

**Methods:** We studied 474 (343 men, 65±12 years old) patients who underwent DES implantation for AMI including 358 with postdilatation (253 male, 66±12 years old) and 116 with un-postdilatation (90 male, 63±12 years old). Rate of cumulative 12-month events, such as cardiac death, target-vessel related MI, revascularization, or stent thrombosis were compared between groups.

**Results:** Compared with the postdilatation group, the un-postdilatation group had younger, less calcified lesion, and obtained postprocedural TIMI-3 flow. They also had significant benefit on composite events in 12 months (5.6% vs. 9.9%, p < 0.045) (Figure). However, Cox regression survival analysis showed the Killip Class ≥ 3 (odds ratio 17.271, 95% CI 5.433-54.906, p < 0.001) and age (odds ratio 1.061, 95% CI 1.005-1.119, p < 0.03) to be independent predictors of 12-month composite events rather than postdilatation itself.

**Conclusion:** Postdilatation after DES implantation in patients with AMI does not seem to have a benefit on the 12-month clinical outcomes. Age and Killip Class rather than postdilatation itself would be more predictive of 12-month clinical outcomes.

**P4800**

**Bare-nitrolin stent versus paclitaxel-coated balloon for femoro-popliteal revascularization. An adjusted indirect comparison meta-analysis of randomized trials**

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**Aims:** In femoro-popliteal artery (FPA) disease, Bare-Nitrolin Stent (BNS) and Paclitaxel-coated balloon (PCB) improved outcomes as compared to Uncoated-Ballon (UCB) angioplasty. Nevertheless, the relative efficacy of BNS vs. PCB remains unknown, due to the lack of head-to-head comparisons. We performed an adjusted indirect comparison meta-analysis of randomized trials to evaluate outcomes of BNS versus PCB in FPA disease.

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After correcting for clinical differences and the Syntax Score, the use of 1ndGEN DES was associated with a significant 2.3 fold increase in the risk of definite ST (95% CI 1.02-5.12; p=0.046) and implantation of paclitaxel-DES only (but not sirolimus-DES) was an independent predictor of the occurrence of definite ST (corrected HR 1.8; 95% CI 1.01-3.4; p=0.047). Although slightly numerically superior in patients treated with 1stGEN DES (3.5% vs. 3.4%), total mortality was not statistically different between groups (HR 1.16; 95 CI 0.77-1.74; p=0.48).

**Conclusions:** Our data suggests that in the real world clinical practice, the use of first generation DES should be restricted to very specific subsets of patients, and that newer devices actually appear to exhibit a better safety profile when broadly used for PCI with DES.
Methods: A systematic literature search (PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, scientific session abstracts and relevant websites) through December 2011 was performed. Selected search words were: superficial-femoral artery, popliteal artery, angioplasty, self-expanding stent, nitinol-stent, bare-stent, drug-eluting balloon, and randomized trial. Inclusion criteria were: randomized trial design, intention to treat analysis, ≥6-month follow-up (FU). Exclusion criteria were: other arterial segments treated than FPA, comparison other than BNS/PCB vs. UC, irremovable, duplicated or incomplete data. Odds ratio (OR [95% confidence intervals]) and z scores (z), with corresponding p values, were used as summary statistics. Main outcomes were target lesion revascularization (TLR), binary restenosis and all cause mortality.

Results: We identified 8 eligible trials, enrolling a total of 1,008 patients randomized to BNS/PCB or UC B (N=342, PCB n= 196, n= 480). Median FL was 11.5 months. Angioplasty with BNS was found inferior to PCB with respect to TLR (OR= 2.60 [1.27–5.32], z= 2.63, p =0.008), with a trend toward higher binary restenosis (OR = 2.03 [0.99–4.18], z= 1.93, p= 0.052). No significance in mortality was evident among study groups (OR=1.79 [0.37–8.55], z= 0.73, p =0.46; BNS vs. PCB comparison).

Conclusions: In diseases of femoro-popliteal artery, PCB offers superior freedom from repeat revascularization as compared to BNS. Both revascularization strategies appeared safe. Adequately powered, randomized, head-to-head comparisons are needed.

MANAGEMENT OF CORONARY ARTERY DISEASE AND PERCUTANEOUS CORONARY INTERVENTION COMPLICATIONS

P4801 Bivalirudin Vs Unfractionated Heparin during Percutaneous Coronary Intervention in High Risk Patients for Bleeding, AntiCoagulant Regimen In high risk Patients for Bleeding - ACRIPAB Trial

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Introduction: In low to medium risk population undergoing PCI Bivalirudin (BIV) exhibited significantly lower rate of bleeding compared to unfractionated heparin (UFH). However, clinical outcome and bleeding complications in high risk population was not established yet.

Aim: Randomized double blinded prospective trial comparing efficacy and safety of BIV vs. UFH on top of dual antiplatelet therapy during PCI among patients with NSTEMI or angiography pectors and with high risk for bleeding.

Methods: There were 100 consecutive patients (66.6±12.3 years old, 69 males) enrolled in our study with 1:1 distribution between BIV and UFH groups. With starting of PCI BIV or UFH were administered in acceptable dozes. The study end points were: major, minor bleeding, death, renal complications, MACCE in hospital and after 30 days follow up.

Baseline characteristics: There were 87% patients with diabetes mellitus, 98% with hypertension, 22% with chronic renal failure, 30% older than 75 years, 21% with haemoglobin plasma level <11 mg% and 58% with systolic blood pressure >160 mm Hg. 24% of participants were catheterized due to NSTEMI. Femoral approach was used in 16% of patients. There were significantly more PCI’s accomplished via radial approach in BIV group (90% vs. 78%, p=0.05). BIV group was represented with higher male’s rate (78% vs. 60%, p=0.05).

Results: At day 3 of PCI, there was case of major GI bleeding in BIV group and 7% rate of minor bleeding complications in both categories. There was twice higher rate of periprocedural AMI in BIV group compared to UFH group (20% vs.10%, p=0.016).

In hospital MACCE rate was higher in BIV patients too (12% vs. 2%, p=0.01). In UFH group, there was 1 case of urgent CABG and another 1 case of death after PCI. In univariate analysis, no one factor was found to be predictor of worse outcome. After follow up, there were no differences in end points between the groups.

Conclusions: In patients with high risk for bleeding undergoing PCI, BIV was found non-superior to UFH in categories of all bleeding complications, early and late clinical outcome.

P4802 Triple over Dual anti-Platelet therapy was not mandatory in Acute Coronary Syndrome Patients with 2nd Generation Drug eluting Stent Implantation


Purpose: Triple antiplatelet therapy with clopidogrel has been known to be superior to dual antiplatelet therapy in the era of 1st generation DES in terms of clinical outcome. However, it remains to be cleared whether triple antiplatelet therapy also has the same significance after implantation as compared to dual generation DES even in patients with acute coronary syndrome (ACS) Methods: In CO-ACT registry, the study subjects were 644 patients who underwent PCI with Everolimus eluting or Zotarolimus eluting stent (Endeavor, Xience V or Promus) with ACS were analyzed retrospectively. The patients were divided into 2 groups after propensity score matching: those treated with triple antiplatelet drugs (aspirin, clopidogrel, and clobazolid; group 1, n=208, M=116 (55.7%), mean age=60.7±14.6 years) and those with dual antiplatelet drugs (aspirin and clopidogrel; group 2, n=636, M=407 (63.9%), mean age=67.8±11.3 years). The incidences of various clinical outcomes were compared between two groups.

Results: The mean follow-up duration was 17.6 ± 6 months (median=13.4).There was no significant difference in the incidence of major bleeding between two groups. Compared with group 1, group 2 showed no significant difference of cardiac death and MI (OR, 1.12; CI, 0.78-1.37; p=0.43), MACCE (cardiac death, MI and TLR) (OR, 1.55; 95% CI, 0.77-1.85; p=0.33). Kaplan-Meier curves for MACCE did not show any survival benefits in triple anti-platelet therapy.

Conclusions: Triple antiplatelet therapy has no beneficial effect in clinical outcome compared to dual antiplatelet therapy in patients with 2nd generation DES even in ACS patients.

P4803 Brain natriuretic peptide during coronary intervention prevents endothelial dysfunction post PCI via NP-cGMP activation

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Background: Percutaneous coronary intervention (PCI) is associated with endothelial dysfunction (ED) and systemic vascular injury induced by contrast media (CM). According to our previous study, brain natriuretic peptide (BPN) administration 24 hours post PCI decreases ED.

Aims: The purposes of this study: 1. To evaluate the ability of human BNP (hBNP) infusion during PCI, to prevent ED in patients with acute coronary syndrome (ACS) post the PCI. 2. To investigate the effect of contrast medium (CM) administration on human coronary microvascular endothelial cells (HCMEC).

Methods and Results (in vivo): One hundred eleven patients who underwent PCI were randomized into 2 groups: a group who received BNP infusion during the procedure (n=44), and another control group who received nitroglycerin (n=67) according to standard protocol. The endpoints were: the rate of decreased flow mediated dilatation (FMD) (by ≥2.5%), the increase in BNP, urine sodium creatinine (sCr) and decrease of estimate Glomerular Filtration Rate (eGFR), 24 hr after, compared to pre operative value. There was no significant difference in baseline FMD. The patients were divided in control group (p=0.05) but increased non-significantly in the hBNP group (p=0.16). FMD was significantly higher in the hBNP group (p=0.04). BNP, sCr increased significantly in the control group (p=0.001, 0.003, 0.0002 respectively) but not in hBNP group (p=0.09, 0.07, 0.18). eGFR decreased significantly in the control group (p=0.02), no change in the hBNP group (p=0.4).

Methods and Results (in vitro): HCMEC were treated with CM (10%) in the presence and absence of BNP, eNOS, corin and cGMP levels were measured by ELISA and the results were compared to untreated cells. In both treatments eNOS was significantly reduced (p<0.001) and corin was significantly increased (p=0.002), to the same levels. cGMP was not affected by CM, treatment (p=0.278), but was increased significantly (p=0.001) by BNP combination. cGMP immuno-fluorescence staining of HCMEC showed distorted cellular cGMP appearance by CM treatment, that was corrected in the combination with hBNP with accentuated subcellularmembrane staining.

Conclusions: These data show that CM reduces eNOS in endothelial cells in vitro. Therefore, reducing the NO-cGMP pathway probably is the mechanism that induces ED in-vivo. BNP treatment reduces FMD and kidney injury post PCI. A compensatory rise in corin that increases BNP as well the administration, maintains cytosolic cGMP via NP-cGMP, and compensates for NO-cGMP loss, which prevents ED.

P4804 Why is the posterior myocardial infarction the most frequent cause of acute mechanical complications?

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Background: The prevalence of ramus circumflexus (LCX) and its branches as an infarct related artery (IRA) in STEMI patient populations is low, around 10-15%. LCX is the most frequent IRA among patients with mechanical complications of AMI.

Objective: To estimate the reason for high involvement of LCX as IRA in patients with mechanical complication of AMI.

Methods: Registry of patients with acute coronary syndromes treated in the tertiary cardiac centre.

Results: In the group of 809 STEMI patients treated in period 2008-2011, the LCX, LAD, and RCA were detected as IRA in 133 (16%), 347 (43%) and 308 (38%) patients respectively. In the parallel group of 709 NSTEMI-ACS patients the localization of LCX, LAD and RCA was performed in 209 (31%), 323 (33%) and 209 (29.5%) respectively. The difference of LCX involvement in STEMI (16%) compared to NSTEMI-ACS patients (31%) was highly significant (p<0.001). From the group of 7 patients hospitalized for the acute mitral regurgitation due to rupture
of papillary muscle the LCX was identified as IRA in 3 (60%) patients. The hospital mortality was 29%. In the group of 5 patients hospitalized with the rupture of free left ventricle wall post AMI, the LCX was culprit in 3 (60%) patients. The hospital mortality was 40%. None of the 9 patients received immediate reperfusion therapy for acute LXC occlusion as they all were initially identified and treated as NSTE-ACS.

Conclusions: In the present era of catheter based reperfusion therapy, the posterior AMI due to LCX occlusion is the most frequent cause of serious mechanical complication of AMI because of improper reperfusion therapy. The incorrect evaluation of patients with posterior AMI as being NSTE-AMI is also the cause of low prevalence of LCX as culprit in the groups of STEMI patients treated with immediate reperfusion therapy. We showed that about 30% of patients with acute LCX occlusion are not receiving needed timely reperfusion therapy.

P4805 Effect of high dose statin pretreatment on endothelial progenitor cells after percutaneous coronary intervention (Hipocrates study)

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Background: Pretreatment with high-dose statins given before percutaneous coronary intervention (PCI) has been shown to have beneficial effects. The mechanism of these lipid-independent statin effects is unclear. Circulating endothelial progenitor cells (EPCs) have an important role in the process of vascular repair, by promoting re-endothelialization following injury. We hypothesized that statins can limit the extent of endothelial injury induced by PCI and promote re-endothelialization by a positive effect on EPCs.

Methods: Included were patients, either statin naïve or treated chronically with low-dose statins, with stable or unstable angina who underwent PCI. Patients were randomized to receive either high-dose atorvastatin (80 mg the day before PCI and 40 mg 4 hours before PCI) or placebo. EPCs profile was examined before PCI and 24 hours after it. Circulating EPC levels were assessed by flow cytometry as the proportion of peripheral mononuclear cells co-expressing VEGFR2, CD34 and CD38.

Conclusions: In these preliminary results, there is a trend towards higher EPC counts (mean±SEM: 4.6±0.8 vs. 3.5±0.8 cells/mm³) in the high-dose statin-pretreated group as compared to placebo (p=0.1).

P4807 Onset-to-needle times in patients with ST-segment elevation myocardial infarction: shortest referral route to a primary coronary intervention facility

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Introduction: Primary percutaneous coronary intervention (PCI) is the preferred therapeutic strategy for patients with acute ST-elevation myocardial infarction (STEMI). However, several referral routes between onset of symptoms and PCI exist namely: Pre-hospital diagnosis and direct transfer to PCI, emergency room visit and on-site transfer to PCI, or emergency room visit and secondary transfer to PCI. We compared the delays between onset and PCI associated with each referral route.

Methods: Data was obtained in a retrospective analysis of randomly selected STEMI patients from 64 hospitals in France. For each patient, the referral route and onset-to-needle time was obtained. Onset-to-needle time was defined as time from onset of symptoms to time of arterial puncture for PCI. We used a Cox proportional-hazards model to compare delays between referral routes.

Results: In total, 1217 patients were included in the analysis. Median onset-to-needle time was 186 min (Q1:133; Q3:292) for the pre-hospital diagnosis route, 237 min (Q1:165; Q3:368) for the on-site transfer route and 305 min (Q1:230; Q3:570) for the secondary transfer route. There was no difference in median onset-to-needle times between hospital types or volume of activity. After adjusting for age, year of admission and history of cardiovascular disease, pre-hospital diagnosis was associated with the shortest delay as compared to onsite-transfer (Hazard ratio [HR] 0.71 [0.59 - 0.86]) and secondary transfer (HR 0.67 [0.52 - 0.86]).

Conclusion: Pre-hospital diagnosis with direct transfer to PCI leads to shorter delays in patient care. In France, this management pathway requires the presence of an emergency physician at first medical contact.

P4808 Improved prognosis of weekends/holidays admission for acute myocardial infarction and a decreasing weekend-effect from 2005 to 2010

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Purpose: Many hospitals provide routine care on weekdays and only emergency or urgent care on weekends. Accordingly, hospital staffing is reduced on weekends and this difference may result in different outcome in patients with acute
myocardial infarction (AMI). Implementation of national quality improvement program may have the potential to obliterate the "weekend-effect" in patients with AMI.

Methods: Between November 2005 and December 2010, 25,233 patients (18.025 men; mean age = 63.3±12.8 year-old) were included from Korea AMI Registry. Exposure was defined as admission on a Saturday, Sunday, or a holiday. The study period was stratified according to three time-periods: 2005.11.1 – 2006.12.31 (KAMIR I; n=7,077), 2007.11.1 – 2008.11.1 (KAMIR II; n=13,911) and 2008.11.2 – 2010.12.31 (KorMI; n=4,605).

Results: Proportions of weekend-admissions were 27.4%, 27.9% and 28.2%, respectively. Patients admitted on weekend were younger and had more typical chest pain, inferior MI, ST-segment elevation MI, higher Killip class, and higher serum glucose, CK-MB, and triglyceride levels. Current smokers were more frequently observed in patients admitted on weekend. Cardiopulmonary resuscitation were more frequently performed in patients admitted on weekend. From KAMIR I 6.5% of patients admitted on weekends died compared to 5.2% of those admitted on weekdays (p=0.037). During the two following periods the apparent difference between weekends and weekdays decreased: KAMIR II (7.1% versus 7.8%, p=0.436) and KorMI (6.2% versus 5.8%, p=0.367). Accordingly, in the adjusted multivariate analysis an increased all-cause mortality in patients admitted on weekends was observed only in KAMIR I with a weekend-weekday hazard ratio (HR) of 1.320 (95%CI: 1.001-1.741, p=0.049) but was not found in KAMIR II (HR: 0.945, 95%CI: 0.688-1.299, p=0.728) and KorMI (HR: 0.904, 95%CI: 0.744-1.198, p=0.307).

Conclusions: We showed that a weekend-effect on mortality in patients with AMI has previously been present, but it has decreased over the past five years.

Methods: CIN was defined as an absolute increase in serum creatinine ≥0.5 mg/dl, or an increase ≥25% from baseline within 72 hours after the administration of contrast medium. AUC for CIN score was calculated by adding 1 point to the Age/EF ratio if the eGFR was >60 mL/min per 1.73 m². Logistic regression analysis, receiver-operating characteristic (ROC) curve analysis and Hosmer-Lemeshow χ² statistic were performed to assess accuracy and calibration of AUC score, EuroSCORE and MRS as predictors of CIN, with the AUC as a measurement of accuracy. The best cutoff value for each score was identified according to the Youden index.

Results: Overall, the incidence of CIN was 5.2%. AUC score was an accurate (OR 5.19, 95% CI 3.13-8.62, p<0.0001, AUC 0.88) and calibrated (Hosmer-Lemeshow χ²=6.24, p=0.62) predictor of CIN with a 100% sensitivity for AGET score >1.5 points; all patients developing CIN were in the highest tertile of AGET score (p<0.0001). When considered linear, continuous variables MRS (OR1.27, 95% CI 1.17-1.39, p=0.0001, Hosmer-Lemeshow χ²=3.18, p=0.05) and EuroSCORE (OR1.61, 95% CI 1.36-1.91, p<0.0001, Hosmer-Lemeshow χ²=5.39, p=0.50) predicted the risk of CIN as well.

Both MRS (AUC 0.80, p<0.15 vs AGET score) and EuroSCORE (AUC 0.82, p<0.14 vs AGET score) were less accurate, though not significantly, than AGET score. The cutoff for MRS was 5, with 72% sensitivity and 73.5% specificity, and coincided with the upper boundary of the lowest risk category in the original Mehan study. The cutoff for EuroSCORE was 6, with 92% sensitivity and 92% specificity, and coincided with the lower boundary of the high risk category.

Conclusions: In patients undergoing primary PCI for STEMI, a linear risk score based on age, ejection fraction and eGFR can predict the risk of CIN at least as accurately as more complex non-linear risk scores. Simple models based on pre-procedural, readily obtainable objective variables, such as the AGET score, are well suited to the acute settings. Complex risk models may be over fitted, at least in populations with a low rate of events.

Methods: This prospective cohort study included 56,426 consecutive PCI procedures performed from September 2005 to July 2010 at the New York University Medical Center. Patients who were discharged alive and had a complete follow-up, were included in the study. The primary endpoint of the study included 30-day mortality and MACE (cardiovascular death, MI, stroke). The AUC was calculated for the CSS and MACE as a measurement of accuracy. The best cutoff value for each score was identified according to the Youden index.

Results: The area under the receiver operating characteristic (AUC) curve for the CSS was 0.88 (p<0.0001), the Hosmer-Lemeshow χ² statistic 9.45 (p=0.28) and the calibration of CSS as a predictor of in-hospital and 30-day mortality was good (OR 5.36, 95% CI 3.56-7.89, p<0.0001). The AUC for the MACE was 0.92 (p<0.0001), the Hosmer-Lemeshow χ² statistic 6.95 (p=0.41) and the calibration of MACE as a predictor of in-hospital and 30-day mortality was also good (OR 9.34, 95% CI 6.30-13.88, p<0.0001).

Conclusions: The CSS and MACE scores are more accurate than the EuroSCORE in predicting the risk of in-hospital mortality and MACE.
received protamine after procedure and GII with 436 DES who did not receive this drug.

Results: Six patients (0.24%) had subacute stent thrombosis in the group receiving protamine (256 DES) and only one patient (0.05%) in the group who did not receive this drug (436 DES) (p-value = 0.96; odds ratio: 0.96; 95% confidence limits).

Conclusion: Immediate reversal of heparin anticoagulation by protamine after coronary drug eluting stent implantation in our study was safe and did not predispose to stent thrombosis. This finding has important clinical consequences.

Impact of Mehran Risk Score for the prediction of Contrast-Induced Nephropathy in the Japanese patients undergoing Percutaneous Coronary Intervention

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Background: Contrast-induced nephropathy (CIN) is associated with the increase of the risk of the cardiovascular event. We sought to investigate the association with Mehran risk score (MRS) and the incidence of CIN in the Japanese population undergoing PCI.

Methods: Study subjects consisted of 2198 consecutive patients who were treated with PCI for stable angina, unstable angina or myocardial infarction, except for the patients who were receiving heparinolysis and died within seven days (n=34). We categorized them into 4 groups according to MRS (low risk group: <5, medium risk group: 6-10, high risk group: 11-16 and very high risk group: 16+).

Results: A total of 192 patients (8.7%) developed CIN. The incidence rate of CIN were as follow: 7.2%, 8.3%, 12.9% and 37.5% for low, medium, and very high risk group (p<0.0001). At multivariate analysis, the odds ratio for CIN was 4.09 (95% confidence interval [C.I], 1.72-9.17; P=0.002) in the very high risk group, 1.49 (95% CI, 0.86-2.42; P=0.120) in the high risk group, and 1.08 (95% C.I. 0.74-1.54; P=0.693) in the medium risk group, as compared with the low risk group.

Conclusion: MRS might be potentially useful information for a prediction of the incidence of CIN in the Japanese patients undergoing PCI.
Functional syntax score improves stratification of risk in patients with left main coronary artery disease

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The Functional Syntax Score (FSS) is obtained including in the computation of the Syntax Score (SS) only FFR positive lesions (i.e. FFR>0.80). FSS has demonstrated better prognostic value as compared with SS in patients with multivessel disease (lesions of left main excluded) treated with DES implantation. The purpose of the present analysis is to assess whether FSS is better to discriminate the potential PCI-related risk in patients with left main (LM) lesions as compared with SS.

Methods and results: Patients (pts) with angiographically equivocal LM stenosis (n=209) undergoing FFR measurement were enrolled. Pts with (n=138) LM FFR <0.80 with either deferred to optional medical treatment or to PCI of other significantly stenotic lesions. Pts (n=75) with LM FFR <0.80 underwent bypass surgery. SS was calculated on all angiographies, FSS was calculated by excluding from the computation LM stenosis with FFR >0.80. Based on the SS, patients were classified in the following tertiles: 68 pts in the low (<14 SS), 69 pts in the intermediate (15-21 SS), and 72 pts in the high (≥22 SS). After calculation of FSS, 67 out of 209 patients (32%) were reclassified to lower SS tertile. More specifically, out of 69 patients with intermediate SS (15-21), 37 (54%) were reclassified to low tertile (<14). While out of 72 patients with high SS (22-44), 13 (18%) pts were reclassified to the intermediate tertile and 17 (24%) to the low tertile.

Conclusion: The present study demonstrates that FSS is particularly useful in the risk stratification of patients with equivocal LM stenosis, allowing to downsize coronary artery disease severity in up to one third of the cases. Further studies assessing the prognostic significance of FSS in LM disease are warranted.

Impact of real time 3d-echocardiography in the assessment of right ventricular volumes and function in patients with pulmonary hypertension

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Background: Right ventricular (RV) function is taking last years a higher relevance as a clinical and prognostic marker in many pathological conditions. The aim of the study is to point out the incremental value of real time three dimensional echocardiography (RT3DE) and Tissue Doppler imaging (TDI) in the evaluation of patients affected by pulmonary hypertension (PH).

Methods: We enrolled 42 subjects affected by PH who underwent 2D and Doppler echocardiography, RT 3D Echocardiography and TDI evaluation of RV, and an healthy control group. PH can induce itself severe functional and structural abnormalities of RV, such as RV hypertrophy, RV dilatation, RV systolic and diastolic dysfunction.

Results: RV fractional area contraction (RV FAC) and tricuspid annular plane systolic excursion (TAPSE) showed marked alterations in patients with PH compared to control group (C): RV FAC (PH:0.30±0.08 vs C:0.50±0.05%, p<0.001; TAPSE (PH)15.4±3.1 vs C:21.0±2.5 mm, p<0.0001). 3D RV End Diastolic Volume was significantly higher in PH than in C (PH)136.5±25.1 vs. C:83±12.6 ml, p<0.0001) as well as 3D RV End Systolic Volume (PH) 97.7±21.4 vs (C) 39.4±9.6 ml, p<0.0001. 3D RV EF was significantly lower in pulmonary hypertension than in healthy subjects (31.6±6.8 vs C:52.7±4.6%, p<0.0001).

Discussion: RV systolic, volumetric and ejection fraction evaluation by RT3DE showed a higher discriminating power in comparison respectively with 2D RV diastolic area and the relative fractional area changes in patients with pulmonary hypertension compared with controls.

Purpose: Right Ventricular (RV) diastolic functional assessment is often limited and underreported in comparison to the LV. RV diastolic function has shown changes with age similar to that of the LV. However the routine reporting of RV diastolic function is hampered by a lack of concise measurements. Strain Rate (SR), calculated via speckle tracking, is an angle and load independent measure of myocardial adverse event. Analysis of one- or two-probability matched pairs showed a significantly higher risk of access site complication in patients receiving additional anticoagulation (13.1 vs. 5.7%, p=0.049).

Conclusions: Therapeutic warfarin treatment seems to provide sufficient anticoagulation for PCI. Additional heparins are not needed and may increase access site complications.

Right ventricular dP/dt in normal subjects: feasibility and normal values

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Recently published guidelines for the Echocardiographic Assessment of the Right Heart in Adults, point out that because of the limited data in both normal subjects and pathologic conditions, RV dP/dt cannot be recommended for routine uses. Our aim was to assess the feasibility of obtaining the dP/dt value in normal subjects with mild incruspid regurgitation and to determine the normal values in this specific population.

Methods: Four hundred and thirty nine consecutive patients were enrolled. Patients were eligible if they were 18 years or older and their echocardiograms were performed as normal with the presence of mild incruspid regurgitation. The highest tricuspid regurgitation (TR) velocity obtained from a sinus beat was measured to obtain the peak systolic RV-right atrial gradient. TR velocity-time integral (VTI) was manually traced in order to obtain a high quality border to define the exact position of the pointer at 0.5 m/s, 1 m/s and 2 m/s. dP/dt measurements were repeated in 20 patients by the same investigator and by a second investigator. 49 patients had a normal echocardiogram with mild TR (11.2%) and RV dP/dt was measurable in 22 patients in this group (44.9%). The reasons for not calculating it in the remaining subjects were: 1) Peak TR velocity inferior to 2.3 m/s and 2) poor Doppler registry at the beginning of the TR slope. Intraclass correlation coefficient for the dP/dt measurement from 0.5 to 2 m/s was 0.197 (p = 0.196) for the intra-observer agreement and 0.173 (p = 0.227) for the inter-observer agreement.

Discussion: RV dP/dt is measurable in a small proportion of normal subjects with mild tricuspid regurgitation (44.9%). Mean value from 0.5 to 2 m/s was 52.7 mmHg/s with a minimum of 75 mmHg/s. The methodology used offers only a poor intra and inter-observer agreement.
Pulmonary artery stiffness and right ventricular directional changes in right ventricular preload, which can guide in fluid management Doppler parameters may provide a simple and non-invasive means to assess predict volume responsiveness during hypotensive states. These easily accessible obesity.

Methods:

Methods: Several patients in critical conditions, like cardiogenic or septic shock, can have hypervolemia as a contributory factor to cardiovascular failure by decreasing cardiac preload. Assessment of fluid status, however, might be controversial in spontaneously breathing, non-ventilated patients, in which quantitation data have been scarce. Although widely used, cardiac filling pressures do not reliably predict responsiveness to fluid challenge. Excessive volume loading can even increase

Results: Increased PAS was observed in children who were at risk for over-weight compared with children (P < 0.001). The children who were at risk for overweight have subclinical diastolic right ventricular dysfunction (P < 0.05 and P < 0.001 for E/A ratio and svolumentic relaxatio time (IVRT) respectively) and higher levels of hs-CRP (P < 0.01) compared to controls. RV function was significantly correlated with WC, RV wall thickness, PAS, and hs-CRP. Waist circumference and CRP (P < 0.001) were the main predictors of PAS in children at risk for obesity.

Conclusion: Increased PAS, subclinical RV dysfunction and inflammation indices were observed in children who were at risk for overweight. The data suggest that appropriate treatment strategies for weight control are essential not only for obese children but also for those at risk for overweight.

Non-invasive assessment of right ventricular preload by Doppler echocardiography

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Several patients in critical conditions, like cardiogenic or septic shock, can have hypervolemia as a contributory factor to cardiovascular failure by decreasing cardiac preload. Assessment of fluid status, however, might be controversial in spontaneously breathing, non-ventilated patients, in which quantitation data have been scarce. Although widely used, cardiac filling pressures do not reliably predict responsiveness to fluid challenge. Excessive volume loading can even increase

Methods: 19 young healthy volunteers, aged 20-46 years (mean 30.8 ± 4.1 years), were observed in children who were at risk for overweight. The data suggest that appropriate treatment strategies for weight control are essential not only for obese children but also for those at risk for overweight.

Results: Increased PAS was observed in children who were at risk for overweight compared with children (P < 0.001). The children who were at risk for overweight have subclinical diastolic right ventricular dysfunction (P < 0.05 and P < 0.001 for E/A ratio and svolumentic relaxatio time (IVRT) respectively) and higher levels of hs-CRP (P < 0.01) compared to controls. RV function was significantly correlated with WC, RV wall thickness, PAS, and hs-CRP. Waist circumference and CRP (P < 0.001) were the main predictors of PAS in children at risk for obesity.

Conclusion: Increased PAS, subclinical RV dysfunction and inflammation indices were observed in children who were at risk for overweight. The data suggest that appropriate treatment strategies for weight control are essential not only for obese children but also for those at risk for overweight.

Impact of untreated obstructive sleep apnea on left and right ventricular myocardial function and effects of CPAP therapy


Background: Obstructive sleep apnea (OSA) has deteriorating effect on LV function, whereas its impact on RV function is controversial. We aimed to determine the effect of OSA and continuous positive airway pressure (CPAP) treatment on left and right ventricular (LV, RV) function using transthoracic echocardiography (TTE) and 2 dimensional speckle tracking (2D ST) analysis of RV deformation capability.

Methods and results: 82 patients with OSA and need for CPAP therapy were prospectively enrolled and underwent TTE at study inclusion and after 6 months of follow up (FU). Multivariate regression analysis revealed an independent association between baseline apical RV-Si, BMI and the severity of OSA (apical RV-Si: P =0.0002, BMI: P =0.02). After CPAP therapy, LV func- tion parameters (LVF: P =0.0001, LV performance index: P=0.03, stroke volume: P=0.042), and apical RV-Si (P=0.001) improved significantly. The effect of CPAP therapy was related to severity of OSA (LVF: AHI 5-14, 66.4±8.8%, 65.5±10.6% [P=ns]; AHI 15-30: 59.6±7.7%, 66.8±6.9% [P=0.002]; AHI >30: 54.1±12.4%, 40.8±13.9% [P=0.001]; apical RV-Si: AHI 5-14: P=0.014; AHI 15-30: 16.0±10.8% [P=ns]; AHI 15-30: 9.8±6.0%, -15.4±10.9% [P=0.028]; AHI >30: -6.3±5.7%, -17.9±11.2% [P<0.0001].

Conclusions: OSA seems to have deteriorating effect on LV and RV function. We found a beneficial effect of CPAP on LV and RV functional parameters predominately in patients with severe OSA. 2D speckle tracking might be of value to determine early changes in global and regional right ventricular function.

Biomarkers and imaging in early diagnosis of right ventricular dysfunction


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Background: While left ventricular dysfunction has been intensely studied, knowledge regarding the right ventricular dysfunction in diabetic patients is still incomplete.

Aims: To evaluate inflammatory biomarkers: high sensitivity C- reactive protein (hsCRP), tumor necrosis factor-alpha (TNF-alfa), lipoprotein associated phospholipase A2 (Lp-PLA2) and their correlation with right ventricle strain and strain rate parameters in patients with diabetes mellitus type II.

Methods: We studied 51 patients with type 2 diabetes mellitus (DM), divided into two groups: group 1 with coexisting cardiovascular complications (coronary artery disease) and high blood pressure only, with no coexisting cardiovascular complications (29 patients) and group 2 DM and co- controlled high blood pressure only, with no coexisting cardiovascular complications (22 patients). We conducted the analysis of right ventricular (RV) function through Vector Veloc- ity Imaging and determined the inflammatory profile (hsCRP, TNF-alfa, Lp-PLA2) for each patient.

Results: In group 1, patients with type 2 diabetes and cardiovascular disease, the Lp-PLA2 activities were significantly higher, with mean value 419.46 UI, compared to group 2, where Lp-PLA2 activity mean value was 207.22 UI. In addition, we identified significant differences between groups for hsCRP and HDL cholesterol (p < 0.01).

A higher impairment of right ventricular longitudinal systolic function was noticed within group 1, compared with group 2, being statistical significant for SbasalRV, SmidRV and SmidRdV and SrmidRDV (p < 0.01). Lp-PLA2 activity was statistically positively correlated with RV strain and strain rate (p < 0.01). TNF-alfa and hsCRP did not correlate with any RV echocardiographic parameters.

Conclusion: By assessing the inflammatory profile of diabetic patients, it has been revealed that, even those asymptomatic for cardiovascular diseases, have a continuous inflammatory state, together with a decrease in RV systolic function, which should be screened as well in each diabetic patient. Lp-PLA2 was the best correlated marker with RV parameters, nevertheless due to the cross-sectional design, data collected could not provide prognostic value for the investigated inflammatory markers and it is necessary to extend the study with a follow-up pe- diate.

Echocardiographically derived tricuspid dp/dt as a marker of right ventricular function

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Purpose: Right ventricular (RV) systolic function assesses prognostic significance in various disease states. RV geometry is not readily amenable to volumetric assessment by 2-dimensional echocardiography. Intraventricular pres- sure rate of rise (dp/dt) predicts myocardial contractility and adjusting dp/dt for the maximal regurgitant velocity (Vmax) eliminates the effect of preload. We ex-
amined the relationship of echo derived tricuspid dP/dt and dP/dt/Vmax with RV ejection fraction (EF) by cardiac magnetic resonance imaging (MRI) as a measure of RV systolic function.

**Methods:** Fifty cardiac MRI and echocardiograms performed within 30 days were included in the study cohort. The tricuspid regurgitation (TR) spectral doppler trace was analyzed offline. TR dP/dt calculated using simplified Bernoulli (dP/dt between 1m/s and 2m/s), dP/dt/Vmax was calculated as a ratio of dP/dt and TR Vmax. RV end diastolic and end systolic volumes obtained from contouring of steady state free precession axial stack MRI images; RVEF was calculated as (RV end diastolic volume - RV end systolic volume) / RV end diastolic volume x 100. RV EF - 44% was considered normal.

**Results:** A majority (78%) of studies were adequate for measurement of dP/dt and included in the final analysis. Median age of the study population was 48 years (IQR = 36-63); 56.4% were female (n=22/59). There was moderate correlation between dP/dt and RVEF (r = 0.51, p < 0.01) which improved with dP/dt/Vmax (r = 0.59, p = 0.01). Using 400mmHg/s as the lower limit of normal for RV function, TR dP/dt had a positive predictive value of 91% and a sensitivity and specificity of 74% and 84% respectively. Interobserver agreement and repeatability analysis of dP/dt by Pelman's variance ratio test showed no significant difference (ratio of standard deviation = 0.95, 95% CI 0.90-0.99, t = -1.8, p = 0.06).

**Conclusion:** Tricuspid dP/dt is a reproducible measure of RV function and correlates significantly with MRI RV EF. A dP/dt of more than 400mmHg/s strongly predicts normal RV EF. Adjusting for preload (dP/dt/Vmax) further improves this correlation.

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**Tricuspid annular plane systolic excursion obtained in the right ventricle modified apical four chamber view shows strong correlation with right ventricular fractional area change**

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**Purpose:** Analysis of right ventricular (RV) function is considered to be difficult because of the complex structure. Tricuspid annular plane systolic excursion (TAPSE) is easily obtainable method for assessment of RV function. However, conventional TAPSE obtained in apical four chamber view (cTAPSE) has a disadvantage of angle dependency. The purpose of this study is to evaluate the superiority of TAPSE obtained in RV modified apical four chamber view (mTAPSE) over cTAPSE in assessment of RV function.

**Methods:** This study consisted of 67 patients (39 females, 55±19 years) who underwent the standard transthoracic echocardiography. Our exclusion criteria is the presence of myocardial infarction, interventricular septal hypertrophy, LV dysfunction, cardiomyopathy, mitral valve pathologies, mitral regurgitation, and atrial fibrillation. A total of 150 patients (80% males; 58.5±10.7 years) with AMI and treated with primary percutaneous coronary intervention underwent echocardiography within 48 hours of admission, in order to evaluate conventional parameters of RV function index and diastolic function of RV. RV function index (including tricuspid annular plane systolic excursion –TAPSE) and valvular function. In addition, RV strain was assessed by speckle-tracking analysis and myocardial contrast echocardiography was performed to evaluate LV segmental and global perfusion. 6-month follow-up, echocardiography was repeated for LV function reassessment. Plasma BNP level was also assessed in patients without (versus with) RV function improvement after AMI.

**Results:** Improvement in RV function was defined as an improvement of TAPSE follow-up, echocardiography was repeated for LV and RV function reassessment. At 6-month RV function index (including tricuspid annular plane systolic excursion –TAPSE) and valvular function. In addition, RV strain was assessed by speckle-tracking analysis and myocardial contrast echocardiography was performed to evaluate LV segmental and global perfusion. At 6-month follow-up, echocardiography was repeated for LV and RV function reassessment. Plasma BNP level was also assessed in patients without (versus with) RV function improvement after AMI. In all patients, Multivariable linear regression analysis indicated that only LV ejection fraction (standardized coefficients of 0.44) were independent determinants of RV function. Plasma BNP level was also assessed in patients without (versus with) RV function improvement after AMI.

**Conclusion:** RV dysfunction can progress as remote remodeling in patients with previous myocardial infarction and high plasma brain natriuretic peptide levels. K. Konishi1, K. Dohi1, Y. Sato1, E. Sugiyura1, T. Sawai1, H. Nakajima1, S. Nakamori1, K. Onishi1, M. Nakamura1, M. Ito1, 1Mie University Graduate School of Medicine, Department of Cardiology and Nephrology, Tsu, Japan; 2Mie University Graduate School of Medicine, Department of Molecular & Laboratory Medicine, Tsu, Japan

**Background:** Although right ventricular (RV) dysfunction often coexists with left ventricular (LV) dysfunction after myocardial infarction (MI), the underlying mechanisms responsible for RV dysfunction have remained unclear in the clinical setting.

**Methods:** We analyzed 82 patients with previous MI with no history of LV infarction (LV ejection fraction 45±17%) and 28 age-matched normal controls (LV ejection fraction 65±5%). All patients underwent complete echocardiography including speckle-tracking strain measurements both in the LV and RV. Global RV longitudinal peak systolic strain (RV-strain) was assessed from apical 4-chamber view using by speckle-tracking strain imaging. Global left ventricular longitudinal peak strain (LV-strain) was assessed from apical 2-, 4-, and 5-chamber views and was calculated by averaging three strain values by using speckle-tracking strain imaging. Plasma BNP level was also assessed in patients without (versus with) RV function improvement after AMI.

**Results:** RV-strain and LV-strain were significantly reduced in patients with MI as compared to normal controls (RV-strain: -18.6±25.6%, LV-strain: -12.6±13.2%, p<0.05 vs. normal) in all patients. Multivariable linear regression analysis indicated that only LV ejection fraction (standardized coefficients of 0.44) were independent determinants of RV-strain. When patients were divided into 3 groups according to plasma BNP levels (group A: BNP < 100 pg/ml; n = 32, group B: 100 < BNP < 500 pg/ml; n = 31, and group C: BNP > 500 pg/ml; n = 18), only group C had strong correlation between RV-strain and LV-strain (r = 0.63, p < 0.05).

**Conclusion:** Longitudinal RV systolic function highly depends on longitudinal LV systolic function after MI especially in patients having high plasma BNP levels. These results may indicate that RV dysfunction can progress as remote remodeling which regulated in response to the increase in loading conditions after MI.
Comparison of strain measurements with speckle tracking echocardiography and velocity vector imaging in detection of RV dysfunction in patients with ischemic cardiomyopathy: a validation study with Ca

J.H. Park, D.H. Kwon, T.H. Marwick. Cleveland Clinic, Cleveland, United States of America

Background: Though strain measurement has been introduced and used to measure LV function, it has been used to estimate RV function. However, variations in strain measurement by different vendors have limited the application of these techniques for assessment of RV dysfunction. We sought to compare two methods for the assessment of RV function, compared with cardiac magnetic resonance imaging (CMR).

Methods: We studied 25 patients (21 men, 66±12y) with ischemic cardiomyopathy who underwent both echocardiography and CMR. Global longitudinal strain of RV with velocity vector imaging (GLS-V; Siemens Medical systems) and GLS with speckle tracking echocardiography (GLS-STE; GE Medical Systems) were measured on the same set of echo images. RV dysfunction was defined by RV ejection fraction (EF) < 50% by CMR.

Results: GLS-V and GLS-STE were correlated (r=0.76, P<0.001) and showed significant correlation with conventional echocardiographic parameters of RV (Table). APSE correlated better with VVI (r=0.75, P<0.001) than STE (r=-0.56, P=0.004). The best cutoff of GLS-V for detection of RV dysfunction was 16.9% (area under the curve = 0.89, P<0.001) with a sensitivity of 81.3% and specificity of 75%. The best cutoff of GLS-STE was 13% (area under the curve = 0.70, P=0.101), sensitivity 75% and specificity 68%.

Comparison of correlations between GLS-V

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GLS-V</th>
<th>GLS-STE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation Coefficient (r)</td>
<td>P-value</td>
<td>Correlation Coefficient (r)</td>
</tr>
<tr>
<td>CMR RVF</td>
<td>-0.748</td>
<td>-0.555</td>
</tr>
<tr>
<td>RV FAC</td>
<td>-0.701</td>
<td>-0.619</td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.675</td>
<td>-0.574</td>
</tr>
<tr>
<td>RV Tei index</td>
<td>0.605</td>
<td>0.491</td>
</tr>
</tbody>
</table>

Conclusion: Although GLS-V and GLS-STE show significant correlations with CMR RVF and other conventional echocardiographic parameters of RV function, GLS-V appears superior to GLS-STE in the detection of RV dysfunction.

Right ventricular regional systolic function and dysynchrony in patients with pulmonary hypertension evaluated by three-dimensional echocardiography

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Objective: Right ventricular (RV) function is of diagnostic and prognostic importance in patients with pulmonary hypertension (PH). The purpose of the present study was to evaluate RV regional systolic function and dysynchrony in patients with PH using real-time three-dimensional echocardiography (RT3DE).

Methods: A total of 70 patients with PH and 26 age-matched controls were enrolled. RT3DE images were acquired and analyzed to obtain RV regional (flow, body, outflow) function (EF and Tmsv) and E/e’ (aortic outflow). RV systolic function was evaluated with the Tei index. Dysynchrony was assessed with the standard deviation of Tmsv in three RV segments corrected by heart rate (Tmsv-SD). RV regional longitudinal strain (GLS-V) and global peak systolic pressure (PASP) were measured.

Results:

- Basal echo: PASP 41±18 mmHg, Tmsv 2.9±0.8 cm/seg, TAPSE 14.4±2.5 cm, Tei index 0.605±0.002
- PH: PASP 308±107 mmHg, Tmsv 3.8±1.0 cm/seg, TAPSE 11±2.5 cm, Tei index 0.49±0.04
- APSE –0.675
- Evolution of RV echo parameters in HTx

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline (n=26)</th>
<th>PH (n=70)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV FAC (%)</td>
<td>41±18</td>
<td>308±107</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDI S (cm/seg)</td>
<td>2.9±0.8</td>
<td>3.8±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>14.4±2.5</td>
<td>11±2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tei index</td>
<td>0.605±0.002</td>
<td>0.49±0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV Lateral strain (%)</td>
<td>6.6±1.6</td>
<td>16.6±1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV Septal strain (%)</td>
<td>6.6±1.6</td>
<td>16.6±1.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: Serial echocardiograms are useful and feasible to monitorize the evolution of RV function after HTx. Most patients improve RV function 1 year after HTx. New techniques such as RV longitudinal strain offer an alternative to evaluate RV normalization.

AORTA AND AORTIC VALVE

A new morphological and quantitative approach of aortic atheroma: a preliminary 3D transesophageal echocardiography study

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Transesophageal echocardiography (TEE) is the reference method for characterization of aortic atherosclerotic plaques (AAP) at risk of stroke. To evaluate the feasibility and contribution of 3D TEE in the evaluation of AAP, we prospectively included 82 patients referred for TEE. In addition to 2D, 3D study of AAP of the descending and horizontal thoracic aorta was performed. 308 AAP were identified in 2D. 98% of them were analyzed using 3D. We identified 3 morphological 3D types of plaques (figure). 2D characteristis of the 3D types were different: type I are thin and rarely calcified; type III are thicker and often calcified; type II have intermediate characteristics (Table). All AAP ulcerations seen in 2D were identified in 3D. Thickness measurements from 3D correlated with intimal thickness measurements performed on the 2D acquisitions (r=0.91; P<0.001). Area measurements of AAP were feasible in 58%, 14% and 23% of 3D types I, II and III, respectively. The areas of type I AAP were not correlated with those of thickness in 2D.
method to measure AA diameters, however other approaches have been proposed (inner to inner or outer to outer). Our aim was to analyze the accuracy of TEE by different methods in the evaluation of aortic dimensions in comparison with multidetector gated computed tomography (MSCT).

Methods: 80 patients with a severe aortic valvular disease (stenosis or regurgitation) were evaluated with a transesophageal echocardiography and MSCT to measure the thoracic aorta at different levels: sinuses of Valsalva, sinotubular junction and ascending aorta. Three different echocardiographic methods were used: leading edge to leading edge, inner to inner and outer to outer and then compared to the ones obtained from MSCT. The interobserver and intraobserver variability was also performed.

Results: Transthoracic echocardiographic diameters were obtained in all patients but 3 (4%) because of poor acoustic window. The three methods showed an excellent interobserver and intraobserver variability, however, the inner to inner method presented the best reproducibility. Also, the inner to inner method showed the best correlation with MSCT for the assessment of thoracic aorta diameters (intraclass correlation coefficient): sinuses of Valsalva 0.83, sinotubular junction: 0.87, and ascending aorta: 0.88. Mean difference between TTE and MSCT in measuring the ascending aorta were: by inner to inner 0.25±0.6 mm, leading to leading -0.77±0.43, and outer to outer -3.2±1.23.

Conclusions: Transthoracic echocardiography is an accurate technique for the assessment and follow-up of thoracic aortic diameters in valvular patients. The inner to inner approach is the method that shows the best agreement with MSCT measurements of aortic root dimensions.

### Table 1. 3D morphological types of plaques

<table>
<thead>
<tr>
<th>Type I (n=115)</th>
<th>Type II (n=97)</th>
<th>Type III (n=89)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descending Aorta (n)</td>
<td>77</td>
<td>63</td>
<td>49</td>
</tr>
<tr>
<td>Horizontal Aorta (n)</td>
<td>98</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Plaque thickness (mm)</td>
<td>1.2±0.5</td>
<td>2.6±1.2</td>
<td>3.2±1.5</td>
</tr>
<tr>
<td>Net calcified plaques (%)</td>
<td>103 (88.5)</td>
<td>22 (17.2)</td>
<td>9 (2.3)</td>
</tr>
<tr>
<td>Vary calcified plaques (%)</td>
<td>3 (4.2)</td>
<td>13 (18.3)</td>
<td>55 (77.5)</td>
</tr>
</tbody>
</table>

In conclusion, 3D TEE is a feasible method and provides a new morphological and quantitative approach of AAP.
and 6 months after operation in 47 patients, 28 women and 19 men, undergoing aortic valve replacement for isolated aortic stenosis.

Results: Preoperatively, women and men had similar ejection fraction (56 and 59%) and left ventricular mass (142 and 148 g/m²). Postoperatively, there was no difference in effective valvular orifice area index, mean transvalvular pressure gradient between men and women. Two weeks after operation, increased LV mass persisted in men (131 g/m²) although LV hypertrophy in women (119 g/m²) re-gressed to the similar level of 6 months (121 g/m²). LV mass in men was similar to those in women in 6 months after operation.

Conclusion: Women adapt to pressure overload quickly than men, while men caught up to women in 6 months after operation.

Purpose: To examine the possible associations of aortic stiffness with LV longitudinal myocardial function and ventricular-arterial coupling in both systolic and diastolic phase in normal subjects.

Methods: A cohort of 134 subjects without clinical CV disease and atherosclerotic risk factors (69 males; mean age 39±13 years, range 18-61, LV EF >55%) was studied. Aortic stiffness was estimated by carotid-femoral pulse wave velocity (PWV) measured by Compil (Alam, Vincennes, France).

Results: PWV was related to CV disease (r=0.35, p<0.0001), systolic BP (r=0.47, p<0.0001) and age related to PWV in the same way (r=0.71, p<0.0001) with aortic distensibility 3.61±2.54 cm²/dyns 10⁻⁶ and aortic stiffness index (ASI) (4.08±0.79) was normal range, as well as basal (2.42±1.43 degrees) and apical LV rotation (5.6±1.43 degrees) and LV twist (11.01±5.19 degrees). Apical LV rotation correlated with aortic distensibility (r=0.36, p<0.05), and ASI (r=-0.41, p<0.05), while LV twist showed similar correlation with ASI (r=-0.42, p<0.05).

Conclusions: Significant recovery of left ventricular systolic function after transcatheter aortic valve implantation (TAVI) in aortic stenosis measured by longitudinal 2D strain echo after 1 year.

Purpose: Transcatheter aortic valve implantation (TAVI) is becoming an established treatment for patients with severe aortic stenosis (SA) and at high risk for conventional heart surgery. We aimed to measure left ventricular systolic function by a novel and sensitive method, the longitudinal 2D strain analysis, to detect even discrete changes after TAVI.

Methods: A total of 25 patients (9 male, 16 female) undergoing transfemoral TAVI (4 Edwards Sapien, 21 CoreValve prosthesis) were analysed. Echocardiography was performed at baseline, after 7 days, 3 months and 1 year. The analysis included standard 2D and Doppler echocardiography, assessment of global systolic and diastolic function as well as 2D Strain and Tissue Doppler echocardiography.

Results: The left ventricular ejection fraction (LVEF) was 51±12% at baseline, the mean pressure gradient was 44.4±17.4 mmHg, and the valve area was 0.75±0.24 cm². After 12 months global longitudinal systolic 2D strain increased significantly from -14.2±3.8% to -17.9±3.0%. This improvement of left ventricular function was seen in the apical four chamber baseline -14.6±4.1% vs. -17.2±3.0% after 12 months), the apical three chamber (-14.0±4.1% vs. -18.7±4.4%) and the apical two chamber view (-13.9±4.2% vs. -18.2±3.7%). There was no significant difference in increased longitudinal function concerning particular left ventricular segments.

Conclusions: Our results show a significant improvement of the longitudinal systolic myocardial function as measured by 2D strain. The assessment of 2D strain appears to be a helpful and very sensitive novel technique to detect distinct improvement of myocardial function after TAVI.
without CAP (n=118, 63±13years). Vs and Vd were compared between groups and with conventional vessel parameters including carotid-ankle vascular index (CAVI), calculated from blood pressure and pulse wave velocity), ankle brachial pressure index (ABPI), and carotid plaque score (PS, a composite index based on carotid artery plaque thicknesses).

Results: Comparing patients with vs. without CAP, Vs and ABPI were significantly decreased (2.9±1.2 vs. 3.8±1.1 cm/sec, p<0.001; 1.6±0.5 vs. 2.0±0.8 cm/sec, p<0.001, 0.88±0.23 vs. 1.10±0.12, p<0.001), and AoJ and PS were significantly increased (17.4±12.5 vs. 12.3±6.8, p<0.01; 9.0±5.0 vs. 5.3±3.8, p<0.001; respectively). Furthermore, Vs and Vd were significantly correlated with AoJ (r=0.381, p<0.001 and r=0.348, p<0.0001; respectively), CAVI (r=0.328, p<0.001 and r=0.396, p<0.0001; respectively), ABI (r=-0.219, p<0.001 and r=0.269, p<0.001; respectively) and r=0.228, p<0.05 and r=0.358, p<0.001; respectively), although there were no significant correlations with blood pressure, or heart rate.

Conclusions: Evaluation of Vs and Vd using PW-TDI in the aortic arch wall may be a novel and easily acquired indicator of aortic arch stiffness, and also correlate with several conventional vessel parameters.

ATRIAL FIBRILLATION AND ATRIAL FUNCTION

The relation between the CHADS2, CHA2DS2-VASc score and echocardiographic parameters of thromboembolism in patients with atrial fibrillation

M.N. Kim1, D.H. Choi1, S.A. Kim1, Y.H. Kim2, J.I. Choi1, S.M. Park1, S.W. Park1, Y.H. Kim1, W.J. Shim1, 1Korea University Hospital, Seoul, Korea, Republic of; 2Korea University Anam Hospital, Seoul, Korea, Republic of

Background: CHADS2 score has been revised as CHA2DS2-VASc score for better embolic risk stratification in patients with AF. The aim of this study was to evaluate the relation between 2 clinical risk scores and echocardiographic parameters of embolism in AF patients.

Methods: 365 (M=305, mean age=65±10.4) patients with non-valvular AF who had trans-oesophageal echocardiography and trans-esophageal echocardiography were enrolled. CHADS2 and CHA2DS2-VASc scores were calculated and correlated to echocardiographic findings. LA volume, LA emptying fraction(EF), LA anterior wall thickness, and presence of non-thrombotic atrial septal defect (ASD) were assessed.

Results: Increased LA(LAVi)≥35ml/m² was found in 143 patients, impaired LAAEF(≥30%) in 130 patients, decreased LAA emptying velocity(≤20cm/s) in 46 patients, decreased LAA EF(≤30%) in 136 patients, SECO in 100 patients and LA thrombus in 1 patient. The patients with higher than 2 CHADS2 and CHA2DS2-VASc score was 65 and 182 respectively. Higher than 2 CHADS2 and CHA2DS2-VASc score was related with increased LAV, low LAAEF, the presence of LHV. But low LAA EF and low LAA emptying velocity was related with higher than 2 CHA2DS2-VASc score only.

Conclusion: The presence of SEC was related with higher than 2 CHA2DS2-VASc score. But the presence dense SEC and thrombus was associated with higher than 2 CHA2DS2-VASc score only(Table 1)

**Table 1**

<table>
<thead>
<tr>
<th>CHA2DS2</th>
<th>CHA2DS2-VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio</td>
<td>95%CI</td>
</tr>
<tr>
<td>Increased LAV</td>
<td>2.29</td>
</tr>
<tr>
<td>Impaired LAAEF</td>
<td>5.27</td>
</tr>
<tr>
<td>LHV</td>
<td>2.70</td>
</tr>
<tr>
<td>Decreased LAA emptying velocity</td>
<td>1.76</td>
</tr>
<tr>
<td>Decreased LAA EF</td>
<td>1.58</td>
</tr>
<tr>
<td>The presence of SEC</td>
<td>1.80</td>
</tr>
<tr>
<td>The presence of significant SEC and thrombus</td>
<td>1.09</td>
</tr>
</tbody>
</table>

Conclusion: Higher CHADS2 and CHA2DS2-VASc scores were correlated with echocardiographic markers of LA dysfunction. But LAA dysfunction was associated with higher than 2 CHA2DS2-vasc score only. CHA2DS2-vasc score appears to be more sensitive than CHADS2 score in detecting high-risk patients.
Assessment of left atrial deformation and dysynchrony by three-dimensional speckle tracking imaging: comparative studies in healthy subjects and patients with atrial fibrillation


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Background: Here we examined whether left atrial (LA) strains and synchrony are assessable by three-dimensional speckle tracking (3DS) and how the 3DS parameters are modified by atrial fibrillation (AF).

Methods: LA peak longitudinal, circumferential and area strains in systole (LSs, CSs, ASs) and those in late diastole (LSa, CSA, ASa) were determined by 3DS, and standard deviations (SD) of times to peaks of regional LA strains were calculated as indices of LA dysynchrony. LA strain and synchrony in AF patients were compared with those in age-matched healthy subjects (controls).

Results: 3DS could measure LA strains in 75 (97%) of 77 healthy subjects and all 30 patients with AF (20 with paroxysmal AF (PAF) and 10 with permanent AF). The mean time of analysis was 3.3±1.9 min for 3DS analysis, which was 18% shorter than for two-dimensional speckle tracking (2DS) analysis (4.0±2.3 min, P<0.05). In 3DS, inter-observer and intra-observer variabilities of LA strain were less than 10% and 12%, respectively. LSs (15.8±6.9 vs 25.7±7.2%, P<0.05), CSs (19.2±11.9 vs 27.1±10.2%, P<0.05), ASs (39.2±23.0 vs 74.2±20.2%, P<0.05), and 2DS-LSs (22.3±9.2 vs 32.6±6.5%, P<0.05) were significantly reduced in PAF than in age-matched controls (n=15), and further reduction of all of the parameters was observed in permanent AF. SDs of LSs, CSs, ASs were similarly larger in PAF and permanent AF than in controls. CSA (6.2±4.1 vs 12.0±4.1%, P<0.05), CSs (10.0±8.0 vs 22.8±8.1%, P<0.05), and ASs (16.6±7.2 vs 38.2±14.4%, P<0.05) were also reduced in PAF than in controls. SDs of CSA and CSs were larger in PAF than in controls. Multivariate analysis, CSs (odds ratio (OR) 0.77, P=0.043), ASs (OR 0.90, P=0.011), SD of ASA (OR 1.15, P=0.039) and 2DS-LAs (OR 0.71, P=0.045) were independent factors for identifying PAF patients. ROC analysis indicated that optimal threshold to predict PAF was <28% for CSs, <57% for ASs, >22% for SD of ASA and <26% for 2DS-LSs. Using these thresholds, sensitivity and specificity of prediction of PAF were 80% and 95%, respectively, for CSs, 97% and 85% for ASs, 75% and 80% for SD of ASA and 100% and 75% for 2DS-LAs. Conclusions: 3DS is feasible for measurement of both LA strain and synchrony in both PAF and permanent AF patients. 3D LA strain appears to be comparable to the 2D LA strain for identifying PAF patients.

Atrial fibrillation and atrial function

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Figure 1

Left atrial dysynchrony in patients with paroxysmal atrial fibrillation - three-dimensional speckle tracking analysis

A. Furukawa, H. Hoshiba, C. Miyazaki, H. Sato, T. Nagai, E. Tada, K. Kataoka, Y. Seino, K. Ishii, Kansai Electric Power Hospital, Osaka, Japan

Background: Left atrial (LA) enlargement is commonly known to be associated with the presence of atrial fibrillation and we have already reported about decreased LA compliance in patients with paroxysmal atrial fibrillation (PAF) using the parameter of the peak global strain and LA emptying fraction (LAEF) as assessed with three-dimensional (3D) speckle tracking imaging. The purpose of this study was to investigate LA wall mechanical synchrony in patients with PAF.

Methods: A total of 150 subjects (96 males; mean age 61±14 years) including 50 PAF patients, 50 hypertension (HT) patients and 50 control were enrolled. All the subjects were in sinus rhythm during examination. LA volume, LAEF and LA wall strain were analyzed by 3D area tracking imaging and the maximal value of global area strain curve was defined as peak global strain. Time-to-peak standard deviation (TP-SD) was calculated as the standard deviation of the time from R-wave on electrocardiogram to peak positive value of the segmental strain curve in six mid LA segments to assess LA dysynchrony.

Results: 84% of PAF patients had hypertension. Early diastolic mitral annular velocity (Ea) was lower in HT (P<0.0001) and PAF (P<0.0001) than in control and the ratio of early diastolic transmural flow velocity to Ea (E/Ea) was higher in HT (P<0.0002) and in PAF (P<0.0001) than in control. The maximal LA volume index was larger in HT than in control (P<0.0001) and was larger in PAF than in HT (P<0.0007). LAEF and peak global strain was lower in PAF than in HT (P<0.0001) and P<0.0001, respectively) and in control (P<0.0001 and P<0.0001, respectively). TP-SD was higher in PAF than in HT (P<0.0006) and in control (P<0.001). Conclusion: LA dysynchrony is developed in patients with PAF and it may have a potential to predict the incidence of PAF.

Measurement of left and right atrial volume in patients undergoing ablation for atrial arrhythmias: comparison of different algorithms of real-time 3D echocardiography


Purpose: Real-time full-volume 3D echocardiography (3DE) allows rapid and non-invasive measurement of left (LA) and right atrial (RA) volume. Different algorithms from different commercial providers are available. Older software requires manual tracing of endocardial contours. Recently software with semiautomated endocardial contour finding algorithm has become available, which considerably speeds up the procedure. Our aim was to compare, in the same data set, LA and RA volume determined by an algorithm involving manual tracing to values obtained by a software algorithm with semiautomated contour detection.

Methods: 88 patients were studied by real-time 3D E. Atrial volume was measured using a multiplane interpolation method algorithm (CardioView v1.3, Tomtec) with manual planimetry of 8 equidistant slices. These volumes were compared with atrial volume determined by the QLAB 7.1 software (Philips) using a semiautomated border detection method.

Results: Linear regression showed for both LA and RA an excellent correlation between volumes determined by Tomtec and QLAB software (r²=0.91 and 0.89 respectively, P<0.001). Bland-Altman analysis of Tomtec versus QLAB volume determination showed rather narrow 95% limits of agreement (-12 to +16 cc for LA volume and -12 to +14cc for RA volume) with a minimal slight bias of +1.9 ± 6.5 cc and +0.8±6.5 cc respectively by the Tomtec method.

Echocardiographic assessments of left atrial function in patients with chronic primary mitral regurgitation by two-dimensional speckle tracking

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Background: In conjunction with left atrial (LA) volume, the evaluation of LA performance, including reservoir, conduit, and booster pump function, provides incremental information pertaining to LA function. The aim of this study was assess the hypothesis that global LA function is altered in patients with chronic primary mitral regurgitation (MR).

Methods: Two-dimensional speckle tracking of the left atrial was acquired from the apical 4-chamber view in 49 normal and 72 subjects with chronic MR. Maximum LA volume and minimal LA volume and the LA volume before atrial contraction were measured. Similarly, global atrial longitudinal strain was measured by averaging all atrial segments. Reservoir (S-LAs), conduit (S-LAe), and contractile (S-LAa) phase strain were obtained.

Results: To explore the effects of MR severity on LA function, subjects were divided into two groups: mild MR group (n=52) and moderate/severe MR group (n=20). Reservoir (total LA emptying fraction), and booster pump function (active LA emptying fraction) were impaired in the moderate/severe MR. S-LAs was significantly reduced in the moderate/severe MR group than in the mild MR group and the controls. Similarly, S-LAs was significantly reduced in the mod-
Reference values of right atrial area and volume in healthy adults by two-dimensional echocardiography

Table 1

<table>
<thead>
<tr>
<th>Function</th>
<th>Controls (n=27)</th>
<th>Mild MR (n=47)</th>
<th>Moderate/severe MR (n=25)</th>
<th>P-value 1</th>
<th>P-value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA total area</td>
<td>42.6±9.4</td>
<td>41.3±7.5</td>
<td>34.7±10.1</td>
<td>0.005</td>
<td>0.01</td>
</tr>
<tr>
<td>S-LAs (%)</td>
<td>20.3±6.5</td>
<td>19.9±4.3</td>
<td>15.3±4.6</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Conduit function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA passive emptying</td>
<td>22.9±10.8</td>
<td>20.8±6.6</td>
<td>20.6±8.9</td>
<td>0.42</td>
<td>0.63</td>
</tr>
<tr>
<td>S-LAs (%)</td>
<td>15.5±5.4</td>
<td>9.3±4.0</td>
<td>8.7±4.1</td>
<td>0.48</td>
<td>0.03</td>
</tr>
<tr>
<td>Booster pump function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA active emptying</td>
<td>15.7±7.3</td>
<td>25.7±7.4</td>
<td>17.6±10.1</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>S-LAs (%)</td>
<td>2.7±3.5</td>
<td>10.1±3.3</td>
<td>6.1±4.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P-value 1, controls vs. moderate/severe MR; P-value 2, mild MR vs. moderate/severe MR.

P8484

Reference values of right atrial area and volume in healthy adults by two-dimensional echocardiography

P. Henn1, E. Gruenig2, A. D’Andrea3, M. Claussen2, C. Nagel1, N. Ehnlken1, F. Maier1, F. Prange1, E. Bosson4, C. Fischer1

1 University of Naples, Naples, Italy; 2 Clinic Grosshansdorf, Grosshansdorf, Germany; 4 University of Salerno, Salerno, Italy

Background: Right atrial (RA) size is important in several indications as for screening, diagnosis and follow-up assessment in patients with pulmonary hypertension. The objective of this paper was to define normolical cut-off values for RA area by echocardiography in healthy subjects.

Methods: In this prospective study 880 healthy adult subjects (mean age 28±5.9 years, 38% female, 395 top-level endurance athletes, 255 strength athletes and 230 non-athletes) were examined by echocardiography. For comparison we performed a meta-analysis of 9 previously published studies (1979-2010) describing RA area in healthy subjects (n=624). Statistical analysis included the calculation of 95%-quantiles for defining cut-off values and the identification of possible confounding factors.

Results: Mean RA area was significantly larger in endurance athletes as in strength- and non-athletes (15.4±2.0 cm² vs. 12.8±1.6 cm² and 12.3±2.0 cm², p<0.001). RA area correlated significantly with age, gender, body surface area and endurance exercise training and was similar in previously described 624 healthy adults (12.6±3.8 cm²). 95%-quantiles for RA area of all investigated non-endurance-trained subjects was 15.2 cm² (95%-confidence interval 14.7-15.7 cm²) in females and 16.2 cm² (95%-confidence interval 15.8-16.6 cm²) in males.

Conclusion: To our knowledge, this is the largest data set described RA size in adult healthy subjects (aged below 50 years). Cut-off values for RA area were significantly different in females (15 cm²) and males (16 cm²). This is clinically relevant. Age, gender, body surface area and high level endurance exercise training were confounding factors of RA area. Further investigations in subjects aged >50 years should be performed.

P8489

Reduced atrial reservoir function in fabry disease using doppler strain imaging

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Purpose: Fabry disease is associated with progressive concentric left ventricular hypertrophy (LVH), with subsequent diastolic dysfunction and left atrial enlargement. Atrial strain rate measures myocardial deformation and may be used to quantify phasic atrial function. The aim of this study was to evaluate the impact of Fabry disease, if any, on left atrial function using Doppler derived strain.

Methods: Transthoracic echocardiograms were performed on 24 Fabry patients; without LVH (n=10) and with LVH (n=14), and were compared to age and gender matched Normals. Doppler derived atrial strain (SI) and strain rate (S-r) were measured from 4 segments in the apical 4 and 2 chamber views of the left atrium and mean global strain and strain rate calculated. Systolic and diastolic SI, systolic strain rate, strain rate at the onset of early diastole (E-sr), and strain rate at the end of atrial contraction (A-sr) were assessed.

Table 1

<table>
<thead>
<tr>
<th>SI</th>
<th>Normals (n=50)</th>
<th>Fabry: no LVH (n=10)</th>
<th>Fabry: with LVH (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV mass (g/m²)</td>
<td>70±18</td>
<td>79±16</td>
<td>127±23*</td>
</tr>
<tr>
<td>Left atrial volume (m³)</td>
<td>23±4</td>
<td>25±7</td>
<td>28±5</td>
</tr>
<tr>
<td>Systolic SI (%)</td>
<td>69±16</td>
<td>66±11</td>
<td>64±12</td>
</tr>
<tr>
<td>Diastolic SI (%)</td>
<td>42±7</td>
<td>42±8</td>
<td>39±11</td>
</tr>
<tr>
<td>S-sr [cm/s]</td>
<td>3.0±0.8</td>
<td>2.4±0.5*</td>
<td>2.3±0.6</td>
</tr>
<tr>
<td>E-sr [cm/s]</td>
<td>3.3±1.2</td>
<td>2.9±0.8</td>
<td>2.3±1*</td>
</tr>
<tr>
<td>A-sr [cm/s]</td>
<td>3.0±0.7</td>
<td>3.0±0.8</td>
<td>2.9±0.6</td>
</tr>
</tbody>
</table>

P<0.05 compared to Normals.

P8450

Evaluation of left atrial appendage dysfunction by strain imaging using transthoracic echocardiography


Background: Left atrial appendage (LAA) thrombus is common cause of cardioembolic stroke. LAA dysfunction, which can induce thrombus formation, is usually evaluated by LAA peak flow velocity measured by transesophageal echocardiography (TEE), but it is a semi-invasive procedure. Therefore we investigated whether LAA dysfunction can be evaluated by recently developed speckle tracking strain imaging using noninvasive transthoracic echocardiography (TTE).

Methods: Consecutive 55 patients, who underwent TEE to rule out thrombus or evaluate valvular disease, were enrolled. Immediately before TEE, we observed LAA by parasternal short-axis view using TTE. A following TTE parameter was evaluated as LAA dysfunction in this study: LAA shortening fraction which was defined as the difference between maximum and minimum longitudinal strain of LAA. We compared LAA shortening fraction with classical TEE parameter, LAA peak flow velocity and also analyzed the parameter in sinus or atrial fibrillation group separately.

Results: LAA shortening fraction was significantly correlated with LAA peak flow velocity measured by TEE (r=-0.641, P<0.001). In addition, LAA shortening fraction was significantly higher in sinus rhythm group (35.6±15.3% vs 25.3±15.7%, P<0.001). LAA thrombi were found in three patients, whose rhythm were all atrial fibrillation and they were all on adequate anticoagulant therapy. LAA shortening fraction of these three patients showed significantly worse value than the other patients in atrial fibrillation group (10.5±3.9% vs 26.7±15.7%, P<0.001).

Conclusion: LAA dysfunction including possible thrombus formation can be evaluated noninvasively by strain imaging using transthoracic echocardiography.

P8451

Comparison between two-dimensional and real-time three-dimensional speckle tracking echocardiography in the assessment of left atrial structure and function

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Purpose: Two-dimensional speckle tracking echocardiography (2-DSTE) using Simpson’s method has been recently used to assess left atrial (LA) volume (LAV) and function. To evaluate the accuracy of 2-DSTE, we compared 2-DSTE with 3-DSTE as a reference standard because major advantage of 3-DSTE is the improvement of accuracy in the evaluation of cardiac chamber volume without any geometrical assumption.

Table 1

<table>
<thead>
<tr>
<th>LA parameter</th>
<th>2-DSTE</th>
<th>3-DSTE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAV (mL)</td>
<td>32±8</td>
<td>33±8</td>
<td>0.82</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>22±4</td>
<td>22±4</td>
<td>0.75</td>
</tr>
<tr>
<td>LA perimeter (cm)</td>
<td>56±6</td>
<td>56±6</td>
<td>0.75</td>
</tr>
</tbody>
</table>

P-value 0.05 compared to 3-DSTE.
Methods: We measured phasic LAV (max., min. and pre-atrial contraction (AC) volume) and emptying function (EF) (total, passive and active EF) and LA peak strain by 3-DSTE (Artila) which can provide time-LA volume curve with volume rates 35-40mLs and by 2-DSTE from apical 2, 3, and 4-chamber views in 61 sub-
jects. Parameters were compared between 2-DSTE and 3-DSTE.

Results: LAV and function were easily and rapidly obtained by 3-DSTE. There was a good correlation between LAV by 3-DSTE and LAV in 2, 3, and 4-chamber views and the average of these three views by 2-DSTE (r = 0.76, 0.80, 0.76 and 0.84, p<0.001, respectively). LA total and passive EF in 4-chamber view by 2-
DSTE was increased compared to 3-DSTE despite no difference in LA peak strain. Phasic LAV in 3-chamber view by 2-DSTE was decreased and LA phasic function was increased compared to 3-DSTE (table).

Table 1. LA function and structure assessed by 3-D and 2-D speckle tracking

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2-DSTE</th>
<th>3-DSTE</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. LAV, ml</td>
<td>52.2±13.4</td>
<td>53.3±18.0</td>
<td>48.4±15.6*</td>
</tr>
<tr>
<td>Min. LAV, ml</td>
<td>28.0±9.4</td>
<td>28.2±11.9</td>
<td>28.1±11.9</td>
</tr>
<tr>
<td>Pre AC LAV, ml</td>
<td>41.6±12.2</td>
<td>42.9±16.0</td>
<td>43.9±14.0*</td>
</tr>
<tr>
<td>Total EF, %</td>
<td>46.5±9.1</td>
<td>47.3±14.0</td>
<td>50.3±12.5</td>
</tr>
<tr>
<td>Passive EF, %</td>
<td>20.8±9.1</td>
<td>21.5±11.9</td>
<td>21.5±11.9</td>
</tr>
<tr>
<td>Active EF, %</td>
<td>31.7±10.3</td>
<td>36.4±13.7</td>
<td>36.5±11.8</td>
</tr>
<tr>
<td>LA strain</td>
<td>19.7±5.7</td>
<td>22.9±6.8</td>
<td>21.6±7.5</td>
</tr>
</tbody>
</table>

Conclusions: Although LA volume and function assessed in 3 and 4-chamber view by 2-DSTE was increased compared to 3-DSTE, it was more promising method in assessment of LA structure and function than 2-DSTE.

P4852 Prolonged atrial electromechanical conduction in hypertrophic cardiomyopathy and cardiac amyloidosis

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Left atrial (LA) remodeling is characterized by atrial dilatation, depressed contraction and interstitial fibrosis. Particularly, hypertrophic cardiomyopathy (HCM) and cardiac amyloidosis are representative disorders of left ventricular hypertrophy to progress LA remodeling. Recently, atrial electromechanical conduction time (EMT) measured by tissue Doppler method was reported as the useful parameter of recurrence of atrial fibrillation after cardioversion. However, this method has limitations having angle dependency and tethering effects by adjacent cardiac motion.

Methods: This study was aimed to clarify the impact of EMT measured by speckle tracking echocardiography on LA remodeling and outcomes in 38 patients with HCM (mean 59 years), and 20 age-matched healthy control subjects. Echocardiographic images were acquired and processed in Qlab7.1. Using multiplanar reconstruction (MPR) the end-faces view LAA orifice was identified. The longest and shortest dimensions of the LAA ostium were measured. The LAA working depth was measured perpendicularly from the ostium to the back wall of the LAA. The data was further analyzed for differences in means between the 2D and 3D technique.

Results: All LAA orifices were oval in shape. The mean LAA orifice diameter on 2D imaging was significantly smaller at 17.9mm (4.3mm, 11.0-22.8mm) in comparison to 3D MPR diameter of 25.1mm (6.5mm, 11.7-46.8mm). The working LAA depth was similar using both methods: 2D 18.3mm (5.0mm, 7.8-36.0mm), 3D 18.8mm (6.3mm, 7.8-36.0mm).

Conclusions: Accurate LAA orifice measurement is important for successful implantation and complete occlusion of the LAA. The LAA orifice is oval in shape and 2D TOE may significantly underestimate the diameter of the LAA orifice by 2-3mm. 3D TOE and images obtained for full visualization should be used for final measurement of the LAA orifice. Such improved measurement techniques facilitate accurate device selection during LAA occlusion.

P4854 Evaluation of right atrial dysfunction using 3D echocardiography in patients with pulmonary artery hypertension


Purpose: In patients with pulmonary artery hypertension (PAH), right ventricular pressure overload causes right heart failure (RHF). In these patients, right atrial pressure (RAP) increased, and cardiac index (CI) decreased. RAP CI, and serum brain natriuretic peptide (BNP) were independent predictors to evaluate the prognosis. We sought to investigate the degree of right atrial (RA) overload and the severity of RHF using 3-dimensional (3D) right atrial volume index by 3D echocardiography.

Methods: We performed 3D echocardiography and right heart catheterization in 53 PAH patients (age 41±15 years). We measured right atrial end-diastolic volume index (3DRAEDI), right atrial end-systolic volume index (3DRAEVI), and right atrial ejection fraction (3DRAEF) by 3D-echocardiography. Mean right atrial pressure (mRAP) and cardiac index (CI) by right heart catheterization, and serum BNP were measured.

Results: mRAP was 8.7±6.0 mmHg (range 1 to 30mmHg), 3DRAEDI was 21.4±20.1 ml, 3DRAEVI was 37.2±28.6 ml, and 3DRAEF was 55.2±15.3%.
There were significant positive correlations between mRAP and 3DRAEDVI (r=0.6, p < 0.01), 3DRAESVI (r=0.7, p < 0.01). There were significant negative correlations between mRAP and 3DRAEF (r=-0.6, p < 0.01). There were significant positive correlations between mRAP and 3DRAEDVI (r=0.3, p=0.02), 3DRAESVI (r=0.35, p < 0.02). There were significant positive correlations between CI and 3DRAEF (r=0.39, p < 0.01). There were significant positive correlations between BNP and 3DRAEDVI (r=0.58, p < 0.01), 3DRAESVI (r=0.64, p < 0.01). There were significant negative correlations between BNP and 3DRAEF (r=0.70, p < 0.01).

**Conclusions:** 3D echocardiography was useful for noninvasive evaluation of RA overload and severity of RHF in patients with PAH.

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**P4856**

**Supranormal diastolic function in elite endurance athletes is related to left atrial geometry and function**

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Endurance-training is associated with specific structural and functional cardiac changes. "Supranormal" diastolic function in athletes was demonstrated previously, but data on left atrial (LA) geometry and function are lacking. Our aim was to investigate complex changes in LA structure and deformation assessed by 2D speckle-tracking imaging (STI), and their relation with left ventricular (LV) diastolic properties in elite endurance-athletes.

**Methods:** 64 subjects (21±4 years, 44 male) were enrolled: 40 endurance athletes and control group of 24 age- and sex-matched sedentary subjects. LA geometry was assessed by volumes at the MVO (MVOV), MVC (MVCV), and at the beginning of the P wave (PV), while LA function by passive EF (pEF) as MVOV/MVCV, expansion index (EIv) as MVOV/MVCV/MVOV, and active EF (aEF) as PV/MVOV/PV. LA deformation was measure by STI: contraction from peak negative strain (PNS) and strain rate (PNSR); relaxation from peak positive strain (PPS) and strain rate (PPSR), and global strain (GS). LV diastolic function was assessed by E/A ratio, flow propagation velocity (FPV), E/FPV, S/D (from pulmonary vein flow), long-axis early diastolic velocity (E), and E/E'.

**Results:** Athletes had "supranormal" LV diastolic function (E/A=2.3±0.5 vs 1.5±0.2; PVJ=7±14 vs 37±9 cm/s; EPPVJ=3.1±0.7 vs 18±1.1; S/D=0.7±0.2 vs 1.3±0.1; E/E<4.8±1.2 vs 5.9±2.1, all p<0.05). There were changes in LA geometry and optimized LA deformation in athletes (see table). Univariate analysis showed that GS was correlated with E, E' and FPV (r=0.71, p<0.02; and r=0.58, all p<0.05) and with E/E' and S/D (r=0.64 and r=0.68, both p<0.01). By multiple stepwise regression analysis, best independent determinant of GS was E/E' ratio (r=0.62, r²=0.48, p<0.01).

**Conclusion:** Elite endurance-athletes had a "supranormal" LV diastolic function, related to improved LA deformation. Assessment of complex changes in LA geometry and function may help to understand the role of LA in the cardiac changes induced by endurance training.

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**P4857**

**Dependence of atrial strain and strain rate on ventricular function - implications for the assessment of left atrial function**

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**Background:** Speckle tracking echocardiography (STE) has been used to determine left atrial (LA) strain (S) and strain rate (SR) in order to measure intrinsic LA function (booster, reservoir, conduit). However, LA deformation is influenced by LV function since both chambers are connected through the mitral annulus. Our aim was to estimate how much of the variability of LA S and SR can be accounted for by LV S and SR in subjects without cardiovascular symptoms.

**Methods:** Global longitudinal S and SR were determined by STE from 3 apical planes in 50 asymptomatic subjects aged 31±7 yrs. In LA and LV, using the same cardiac cycle and the P-wave onset as reference, we measured peak amplitude and timings of S and SR during LA contraction (Sa, SrA) and SR during LV contraction (Sa, SrA), and SR during LV early diastolic relaxation (SrE). By conventional echo, we also measured LA and LV volumes at P-wave onset, end-diastolic and end-systolic, estimated arterial elastance (Ea); LV stroke work – SV; and diastolic function (E, A, E' DT, Vp).

**Results:** Peak SrA occurred on average 9 ms earlier in the LA compared with LV (p<0.001); all other events occurred at the same time in both chambers. LA S and SR had higher absolute values compared with corresponding LV S and SR values (p<0.001 for all). Sa correlated with changes in LA length (r=0.39, p=0.006) and volume (r=-0.30, p=0.035) during LA contraction. LA Sa correlated with changes in LA length (r=0.63, p<0.001) and volume (r=0.44, p<0.001) during LV contraction. Multiple stepwise regression analysis revealed that the strongest independent predictor of LA Sa and SR was the corresponding LV S and SR. This was not the case during A contraction (r<0.13) when compared with the events during LV contraction and LV early relaxation (r<0.5, r<0.027). Additionally, LA Sa, SrA, and SrE were also predicted by LA end-diastolic volume. There was no significant correlation between LA Sa and LV stroke volume at P-wave onset; LA Sa, and LV EDV; between LA Sa, SrA, and SrE; and between LA Sa and Vp. A, and Sa and LV and LV volume at P-wave onset; between LA Sa and E, LV ESV and E; and between LA Sa, SrA, and Vp. A, and Sa and LV and LV volume at P-wave onset; between LA Sa, SrA, and E, LV ESV and E; and between LA Sa, SrA, and LV and Sa. and LV and LV volume at P-wave onset; between LA Sa, SrA, and E, LV ESV and E; and between LA Sa, SrA, and LV and Sa. and LV and LV volume at P-wave onset; between LA Sa, SrA, and E, LV ESV and E; and between LA Sa, SrA, and LV and Sa. and LV and LV volume at P-wave onset.

**Conclusions:** There is substantial interaction of LA Sa and SR on the corresponding LV S and SR through the shared mitral annulus, most pronounced when the LV is the driving chamber. Thus, STE may be useful to assess only the LA booster function, rather than assessing intrinsic LA reservoir and conduit function, because of its less dependence on corresponding LV Sa and SR during LA contraction.

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**NEW ULTRASOUND TECHNOLOGY**

**P4859**

**Detection of pulmonary congestion using the newly-developed pocket-sized transthoracic echocardiographic imaging device in patients with suspected heart failure**

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**Background:** Ultrasound lung comets (ULCs) assessment is simple, fast and clinically useful for the evaluation of pulmonary congestion in patients with heart failure (HF). Recently-developed pocket-sized transthoracic echocardiographic (pTEE) imaging device has allowed performing pTEE study in a variety of clinical settings. The aim of this study is to investigate the feasibility and usefulness of pTEE for the evaluation of ULCs in patients with HF.

**Methods:** This prospective study consisted of 51 consecutive patients (25 female, 66±15 years) with known or suspected HF who underwent the standard TTE (sTEE) and pTEE. Exclusion criteria included the following: patients with hemodialysis, recent cardiac surgery, known pulmonary diseases. The examination of pTEE was performed with the VSCAN (GE Medical Systems). Immediately after TTE study including the assessment of ULCs, all patients underwent sTEE and pTEE assessment by another sonographer blinded to the results of pTEE study. We defined ULC score according to the number of ULCs observed in each 4 segments (right upper & lower, left upper & lower) of chest wall as follows: None 0, Mild (the number of ULCs; 0-5): 1, Moderate (6-10): 2, Severe (11-): 3. The sum of these scores in each 4 segments is defined as total ULC score (0-12 points). Clinical diagnosis of congestive HF was based on the Framingham criteria, with all corroborative information reviewed by 2 cardiologists blinded to the information of ULCs in each patient. The sum of score was well correlated with ULC score evaluated by pTEE and the diagnosis of HF (AUC=0.93). The ULC score of 2 was found to maximize the diagnostic accuracy with a sensitivity of 88% and a specificity of 83%. The ULC score of 4 had a sensitivity of 60% and a specificity of 100%.

**Conclusion:** Detection of pulmonary congestion using the newly-developed pTEE imaging device in patients with HF is feasible and accurate.

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**P4859**

**Test accuracy of hand-held echocardiographic imaging**

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**Aims:** To investigate intra- and inter-rater variability of expert-users interpreting hand-held echocardiographic studies (HAND).

**Methods:** We scanned 330 consecutive patients both with HAND and high-end scanners (HIGH). Imaging studies were interpreted independently by two blinded level III echocardiographers. HIGH readings served as gold-standard. Segmental endocardial-border delineation was scored to describe image quality. Assessment
of LV-dimensions, regional/global LV-function and grading of valve disease were compared.

**Results:** We found correlations of r = 0.8 (p < 0.01) for intra-rater variability for both expert-readers analysing HAND and HIGH studies for image quality, wall-motion abnormalities and left ventricular measurements. For intra-rater variability of LV-EF assessment correlations were at least moderate (r = 0.6, p < 0.01). Inter-rater variability for HIGH studies was r = 0.9 (p < 0.01) for all parameters. Inter-rater variability for all parameters assessed by HAND was less favourable, but still at least moderate for all parameters (r = 0.6, p < 0.01). Pericardial effusion was detected in each case. The agreement for the detection and grading of mitral and aortic regurgitation was at least moderate (κ = 0.6, p < 0.01). Detection of tricuspid regurgitation was less favourable, however only mild regurgitations were missed. Each aortic stenosis was detected by both readers.

**Conclusions:** The test accuracy for hand-held echocardiographic study interpretation focusing on basic assessment of cardiac morphology and function as compared to standard echocardiography is moderate to very good for experienced echocardiographers. However, training in interpreting hand-held echocardiographic findings is desirable.

**P4860**

**Effect of through plane motion for the accuracy of two-dimensional circumferential strain analysis**

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**Purpose:** Measurements of 2D circumferential strain (CS) is affected by loss of speckles due to through plane motion, raising the doubt regarding its accuracy. 3D speckle tracking echocardiography (STE) may eliminate this limitation. If through-plane motion affects 2D speckle tracking analysis, we hypothesized worst correlation and largest mean difference of CS were observed at basal level, and best correlation and least difference of CS were noted in the apical level between 2DSTE and 3DSTE measurements.

**Methods:** We obtained 2D basal, middle and apical short-axis images, and 3D full-volume datasets (GE, Vivid E9) in 44 patients with various cardiovascular diseases (mean age 62 ± 19 years, 23 men). Using 2D/3D speckle tracking software, segmental CS at end-systole was measured. Global CS and average CS at each of 3 LV short-axis levels were calculated in both modalities. Using anatomical M-mode, we measured mitral annular displacement (MAD) on apical 4-chamber view, and patients were divided into two groups according to the median value of MAD (9.4 mm) for investigating the effect of through plane motion.

**Results:** Although a good correlation of global CS was noted between the two methods (r = 0.80, p < 0.01), mean values were significantly higher in 3DSTE compared to 2DSTE (-18.4 ± 6.3 vs. -14.7 ± 5.0, p < 0.001). Correlation of averaged CS and their mean bias between the two methods were 0.66/± 0.61 at basal level, 0.78/± 0.17 at middle level and 0.60/± 0.23 at apical level, respectively. Correlation of global CS between the two methods was higher in group of patients who showed MAD less than 9.4 mm (r = 0.81) compared to group of patients with MAD >9.4 mm (r = 0.61).

**Conclusions:** Our results suggest that through plane motion affects CS measurements using 2DSTE, especially in subjects with normal longitudinal function.

**P4861**

**Diagnostic accuracy and cost-effectiveness of pocket-sized transthoracic echocardiography**

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**Background:** A pocket-sized portable transthoracic echocardiography (pTTE) imaging device has been recently introduced. Although the ability of pocket-sized pTTE in the assessment of cardiac chamber size and function, and valvular disease has been reported, its diagnostic accuracy and cost-effectiveness remains unknown. This study therefore was aimed to investigate the diagnostic accuracy of pocket-sized pTTE as well as to examine its screening cost-effectiveness in different at-risk patients.

**Methods:** This study consisted of 200 consecutive patients (104 males, mean age 70 ±16 years) who had standard TTE (sTTE). Patients were then divided into low- and high-risk groups based on the clinical characteristics. Pocket-sized pTTE was performed using the Vscan (GE Medical Systems). Standard parasternal long- and short-axis views and the apical 2-, 3-, 4-chamber views were obtained. These views were then repeated with the color Doppler method. The results of pTTE were compared to those with sTTE.

**Results:** Echocardiographic measurements were completed for sTTE and pTTE in all 200 patients (feasibility 100%). Of the 200 patients, echocardiographic abnormalities were observed in 150 (75%) patients. Normal sTTE finding was observed in 22 (11%) patients in high-risk group, and 28 (14%) patients in low-risk group, respectively. In 28 (14%) patients, pTTE findings missed abnormalities detected by sTTE also. Despite of the agreement between sTTE and pTTE results, further detailed sTTE examination was necessary in 63 (31.5%) patients. As a result, pTTE provided sufficient information on 109 (54.5%) patients in overall group, on 68 (50.8%) patients in high-risk group, and on 43 (61.4%) patients in low-risk patients, respectively. Due to decreasing the number of the referral of sTTE, the use of pTTE would result in 54.3% cost reduction in overall population, 50.5% in high-risk population, and 61.2% in low-risk population, respectively.

**Conclusions:** This study demonstrated that pocket-sized pTTE was feasible and accurate in the diagnosis of cardiac abnormalities. The use of pocket-sized device would be cost-effective by reducing the number of the referral of sTTE, especially in low-risk populations.
Results: A total of 104 patients were studied. There was excellent agreement between the Vscan and the high-end echocardiograph for left ventricular systolic function and pericardial effusion (Kappa 0.89 and 0.81 respectively), and agreement was good or moderate for evaluating aortic, mitral and tricuspid valve function and left ventricular size (Kappa 0.55-0.66). Visualization of the Vscan images in full-screen format on a PC did not in general confer added value.

Conclusion: The Vscan used by a trained cardiologist has good diagnostic accuracy in the emergency setting compared to a high-end echocardiograph, despite small screen size and lack of pulse-wave and continuous Doppler.

P4863 Inter-vendor variability for measurements of left ventricular strain using two-dimensional speckle tracking analysis: a study of Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE)

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Purpose: Two-dimensional speckle tracking analysis of the left ventricular (LV) strain has been widely used for the evaluation of the LV mechanics. However, controversy exists regarding the inter-vendor agreement of LV strain. We aimed to determine inter-vendor variability of LV 2D strain in healthy subjects.

Methods: Among 817 healthy subjects enrolled in JUSTICE, inter-vendor variability was determined by acquiring echocardiographic images in 193 subjects using systems from 2 of 3 different vendors (V1 vs. V2=47, V1 vs. V3=96; V2 vs. V3=50). The acquired images included 3 short axis views and 3 apical views. With the 2D speckle tracking software from each vendor, radial, circumferential and longitudinal strain were measured using an 18-segment model, and global 2D strain values were determined. Agreement was assessed by intraclass correlation coefficient (ICC) with its limit of agreement (LOA) and Bland-Altman analysis.

Results: Global 2D strains were significantly different between the two vendors in majority of comparisons. In each two-vendor comparison, the ICCs of global longitudinal strain was -20%. Concordance between each diagnostic method and the reference standard, represented by coronary angiography, was evaluated by kappa score and Kendall’s tau coefficient. Furthermore, the agreement between two observers with different experience in DSE was assessed by using Cohen’s k coefficient.

Results: Prevalence of significant CAD (more than 50% of luminal narrowing) was 70% and prevalence of single vessel disease was 60%. Mean GLS significantly decreased from rest (-17.4±4.2% to peak DSE -15.1±4.4%, p<0.001). Sensitivity, specificity, PPV and NPV for WMSI were respectively: 50%, 67%, 83% and 28%. However, combination GLS and WMSI had the highest sensitivity (70%), specificity (70%), PPV (87.5%) and NPV (40%). Furthermore GLS showed higher concordance with coronary angiography (k = 0.75; Kendall’s tau = 0.78) than WMSI (k = 0.11; Kendall’s tau = 0.14). In addition, there was a good agreement between a trainee and an expert observer by using GLS in comparison with WM analysis for images interpretation at rest (k = 0.61 for WM, k = 0.57 for GLS) whereas the agreement significantly improved for images interpretation at peak stress (k = 0.50 for WM, k = 0.70 for GLS).

Conclusions: Combination of GLS and WMSI resulted in significant increase in the accuracy of DSE to detect myocardial ischemia, especially with regard to the test sensitivity. Besides, GLS analysis provides an increase of the agreement for images interpretations between experienced and non-experienced observer, especially at peak stress. Hence, adding routinely GLS analysis during DSE could probably be helpful for more accurate patient risk stratification.

P4864 Usefulness of automated function imaging to detect myocardial ischemia during dipyridamole stress echocardiography

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Purpose: Dipyridamole stress echo (DSE) is currently used as an alternative to dobutamine stress echo in detecting coronary artery disease (CAD). However, the lower sensitivity, especially in single-vessel disease and the high inter-observer variability of wall motion (WM) analysis are two major drawbacks of DSE. We aimed in this study to investigate the usefulness of global longitudinal strain (GLS) by automated function imaging (AFI, Echopac GE Horten, Norway) to improve diagnostic accuracy and reproducibility of DSE in detecting myocardial ischemia.

Methods: 37 patients (18 men, 67±9 years), with intermediate/high pre-test CAD probability underwent DSE followed by coronary angiography within one week. Diagnostic accuracy in the identification of CAD, evaluated through sensitivity, specificity and positive/negative predictive values (PPV/NPV), was analyzed for wall motion score index (WMSI) and GLS. Optimal cutoff value to define normal GLS was -20%. Concordance between each diagnostic method and the reference standard, represented by coronary angiography, was evaluated by kappa score and Kendall’s tau coefficient. Furthermore, the agreement between two observers with different experience in DSE was assessed by using Cohen’s k coefficient.

Results: Prevalence of significant CAD (more than 50% of luminal narrowing) was 70% and prevalence of single vessel disease was 60%. Mean GLS significantly decreased from rest (-17.4±4.2% to peak DSE -15.1±4.4%, p<0.001). Sensitivity, specificity, PPV and NPV for WMSI were respectively: 50%, 67%, 83% and 28%. However, combination GLS and WMSI had the highest sensitivity (70%), specificity (70%), PPV (87.5%) and NPV (40%). Furthermore GLS showed higher concordance with coronary angiography (k = 0.75; Kendall’s tau = 0.78) than WMSI (k = 0.11; Kendall’s tau = 0.14). In addition, there was a good agreement between a trainee and an expert observer by using GLS in comparison with WM analysis for images interpretation at rest (k = 0.61 for WM, k = 0.57 for GLS) whereas the agreement significantly improved for images interpretation at peak stress (k = 0.50 for WM, k = 0.70 for GLS).

Conclusions: Combination of GLS and WMSI resulted in significant increase in the accuracy of DSE to detect myocardial ischemia, especially with regard to the test sensitivity. Besides, GLS analysis provides an increase of the agreement for images interpretations between experienced and non-experienced observer, especially at peak stress. Hence, adding routinely GLS analysis during DSE could probably be helpful for more accurate patient risk stratification.

P4865 Changes in left ventricular strain during exercise stress echocardiography in healthy subjects: a speckle tracking echocardiography study

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Background: Stress echocardiography is widely used but its major limitation is the subjective interpretation of wall motion changes. Speckle tracking echocardiography (STE) offers a quantitative method with the semiautomatic evaluation of the different components of myocardial deformation. The aim of our study was to evaluate changes in left ventricular (LV) systolic performance during the different steps of exercise stress echocardiography (ESE) in a population of healthy subjects.

Methods: ESE was performed in 25 healthy subjects (mean age 26±3.1) in the semi-supine position on a tilting cycloergometer: the workload was increased every 2 minutes by 25W, up to the achievement of 100W. Echo was performed at each stage of the physical exercise and during the recovery phase. LV global longitudinal strain was calculated averaging values of all myocardial segments in apical 2-, 3- and 4-chamber views; radial, circumferential strain and LV twisting obtained from the parasternal short-axis views at basal and apical levels.

Results: Mean heart rate of 164±21 bpm was reached. All LV parameters explored increased significantly, reaching the maximum value at peak exercise. Subjects showed a relative increase of strain values respect to baseline of 48.2±14.1% for LV global radial strain (baseline: 23.8±8.6, peak value: 35.4±10.1%), 43.8±12.2% for LV twisting (baseline: 10.5±3.6, peak value: 15.5±4.7%), 34.9±8.6% for global circumferential strain (baseline: 24.3±6.6, peak value: 32.6±9.6%) and 13.4±4.9% for global longitudinal strain (baseline: 20.1±5.9, peak value: 22.8±5.8%).
Hypertrophic cardiomyopathy in Iceland: MYBPC3 founder mutation?

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The aim of this study was to investigate Hypertrophic Cardiomyopathy (HCM) in Iceland, identify sarcomeric mutations causing HCM and understand the phenotype consequences of these mutations. Iceland, an island with the population of 300,000 offers a great opportunity to investigate this heterogeneous disease in a whole population.

Methods: The study cohort consisted of all patients having clinical diagnosis of HCM in Iceland in the period from 1997-2010. Patients were searched through medical records and echocardiographic database at the main hospitals and cardiologists private clinics. All HCM patients were invited to have genetic testing and an interview. Samples were screened for the MYBPC3 c.927-2A>G mutation previously described in two Icelandic families. If negative, targeted sequencing of 8 HCM genes and the GLA gene was performed. Information on phenotype and clinical outcomes was obtained from medical records that were mined and reviewed.

Results: 177 patients with HCM diagnosis were identified, 156 were still alive. 12 had already been genotyped and 119 accepted to participate in the study. 72 (55%) had the c.927-2A>G mutation in MYBPC3. In addition, 4 had other variants in MYBPC3, one was diagnosed with a variant in MYH7. 5 were diagnosed with variants in the GLA gene. Fabry disease has been confirmed in three of these five patients. Clinical data on patients with c.927-2A>G mutation in MYBPC3 are shown in the table 1.

Table 1

<table>
<thead>
<tr>
<th>Age at diagnosis (mean, range)</th>
<th>Average LV thickness (mm)</th>
<th>Age at first adverse event</th>
<th>Ad IPablation</th>
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<tr>
<td>40.4 (9-72)</td>
<td>21.7</td>
<td>51 (17-72)</td>
<td>12 (16.2%)</td>
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</table>

*Sudden cardiac death (SCD), ICD implant, myectomy, alcohol septal ablation.

Conclusions: The c.927-2A>G mutation in MYBPC3 is the leading cause of HCM in Iceland, accounting for 55% of cases. The c.927-2A>G mutation causes serious disease with an average age of onset of 40 yrs. We hypothesize that all 72 individuals with the c.927-2A>G mutation are offspring of a common ancestor. At present, we cannot estimate when this common ancestor lived in Iceland, but we expect from inheritance studies, that he/she lived more than 5 generations ago.

cause of hypertrophic cardiomyopathy in muscular dystrophy: genetically caused structural weakness vs. acquired myocarditis? Answers based on a siblings study


Background: Muscular dystrophy type Duchenne (DMD) and type Becker (BMD) represent the most common X-linked genetic diseases. Apart from progressive proximal skeletal muscle weakness, DMD and BMD are characterised by cardiac muscle involvement with a characteristic pattern of myocardial damage affecting the subepicardium of the left ventricular (LV) free wall. The molecular pathomechanism leading to cardiomyopathy is still unclear: the fragility of the cell membrane caused by genetically deficient dystrophin – but not the extent of LGE was 0.5% and 1.1%, respectively. The age of sibling pair no.4 (BMD) was 49yrs and 43yrs, LV-EF was 58% and 63%, and the extent of LGE was 3.7% and 5.1%, respectively. All siblings demonstrated the same localization of LV in the subepicardium of LV free wall (+/- septal wall).

Conclusions: The similar results in LV-EF, extent of LGE and localization of LGE in siblings with the same dystrophin gene mutation clearly suggest that the fragility of the cell membrane caused by genetically deficient dystrophin – but not acquired myocarditis[(i)] – is the cause of the characteristic cardiomyopathy in DMD/BMD patients.

Phenotype-genotype correlation in patients with mutations in the beta-myosin converter domain

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Purpose: Our main purpose was to evaluate the genotype-phenotype correlation of mutations located in the beta-myosin converter domain. This region, located between aminoacids 299 and 777, is responsible for the elasticity of the protein which allows strain to develop within the motor before the cargo is actually moved. Several mutations affecting this important and highly conserved domain have been previously described.

Methods: Identification of mutations in the converter domain on MYH7 was performed in a cohort of more than 800 cases diagnosed either with Hypertrophic Cardiomyopathy (HCM) or Dilated Cardiomyopathy (DCM). Additionally, a single case of cardiomyopathy was added. We also reviewed the published data about all missense mutations located within this domain.

Results: In our centre, mutations were identified in 11 families comprising 59 relatives and 30 carriers, all diagnosed with HCM except 1 family (LVNC and DCM). These mutations were G716R (2 families), G741R (1 family), G768R, (1 family), G730N (1 family, novel mutation), 7367G (5 families) and R719Q (1 family). Taking into account our data and data from literature, a total of 21 pathogenic mutations have been identified within this domain. They were distributed in 143 families comprising 470 relatives (in half of those families more than 1 member was described). Of these relatives, 424 were affected or possibly affected (11 of them diagnosed with DCM and the rest with HCM) and 382 were mutation carriers. We observed an early onset of disease with a mean age at the diagnosis of 27±18 years (range 1 to 77, 56% males). Thirteen of 21 mutations were associated with a severe adverse event affecting at least one member in 52/143 families (36%). These serious events occurred in 151 affected or possible affected relatives (36%), distributed as follow: sudden death occurred in 96 patients (22.6%) and at least 54 of them were younger than 45 years old, heart failure death in 35 (8.2%), cardiac transplantation in 18 (4.2%) and fatal stroke in 6 (1.4%). Finally, 61 patients (16%) presented an impairment in the left ventricular systolic function.

Conclusions: Data from our families and from the extensively reviewed publications indicates that mutations located within the beta-myosin converter domain presented an early onset of disease. A significant proportion of mutations were associated with the occurrence of a severe adverse event and also left ventricular dysfunction, in a high proportion of families.

Is the gene MYOM2 encoding myomesin 2 involved in the pathogenesis of hypertrophic cardiomyopathy?

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Background: Hypertrophic cardiomyopathy (HCM) is the most frequent genetic myocardial disease with a prevalence 1/500. Although twenty mostly sarcomeric genes have been shown to cause HCM, it is anticipated that additional so far unknown disease genes exist. In a candidate gene approach, we did a genetic screening of myomesin 2 (MYOM2), a M-band protein expressed in cardiac sarcomeres.

Methods: We clinically evaluated a cohort of fifty-eight HCM patients on the basis of medical history, physical examination, echocardiography, and 12-lead ECG, after obtaining informed consent. Using PCR and direct automated Sanger sequencing, the thirty-six coding exons of MYOM2 were analyzed. The study was approved by the institutional review board of the Charité.

Results: As expected, a number of known mutations were identified. Three single nucleotide polymorphisms (SNPs) were detected. Interestingly, we identified three novel mutations (M269T, S466R, R1078X) in three unrelated HCM patients. All mutations were heterozygous and were not detected in 570 control alleles. Furthermore, they are not registered in the SNP database, although more than 200 variations are known in MYOM2. The mutations affect different domains of the protein. Whereas the affected residue of codon 466 is highly conserved in different species from chimp to fish, the codon 269 is conserved only in mammals. While M269T and S466R are missense mutations affecting one residue, the mutation R1078X created a premature stop and is predicted to lead to a truncated protein from immunoglobulin-like domain 10. The two most common HCM disease genes, MYH7 and MYBPC3, as...
Unravelling mutation effects from secondary adaptations in cardiomyocytes of Familial Hypertrophic Cardiomyopathy patients

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New genetic determinants of disease phenotype in hypertrophic cardiomyopathy: high-throughput sequencing reveals unexpected complexity

Missense mutations in titin-associated proteins identified in patients with dilated cardiomyopathy

Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications

Results: The prevalence of thromboembolic complications was higher in the cohort of LMNA mutation carriers than in DCM patients (22 vs 11%, p=0.05), after adjustment for left ventricular ejection fraction, which was lower in LMNA mutation carriers than in DCM patients (p=0.04). A majority of patients carried multiple rare variants, questioning the role for extra-sarcomere variants as possible modifiers.

Purpose: About 1/3 of genetically FHC patients carry missense mutations in the β-cardiac myosin heavy chain (β-MHC). Yet, at the sarcomere level of cardiomyocytes, the primary functional effects of these mutations are still largely unknown. We aimed to characterize the effects of the highly malignant β-miomyosin heavy chain (β-MHC) missense mutation R722G in myocardial tissue and to compare the data with previous findings in M. soleus fibres with the same mutation. This allows to differentiate (1) the primary functional effects of the mutation and (2) adaptational processes in the myocardium.

Methods: In left ventricular cardiomyocytes from explanted hearts of patients with the β-miomyosin mutation R722G and in donor cardiomyocytes we determined force generation, force-calcium relations, and cross-bridge kinetics. We also determined the relative expression of mutated vs. wildtype β-MHC at the mRNA and protein level and analyzed the phosphorylation of sarcomeric proteins. To assess cardiomyocyte structural properties, histology and electron microscopy was also performed.

Results: Measurements revealed reduced maximum force generation but unchanged calcium-sensitivity of the myocytes. Yet, previous studies on slow skeletal muscle fibres with the same mutation showed reduced calcium-sensitivity and increased maximum force. The expression of mutated β-MHC-mRNA and β-miomyosin in LV tissue was found to be 68% and 64% of total β-MHC-mRNA and β-miomyosin, respectively, which is the same fraction as in M. soleus. Get electrophoresis of the HCM cardiac tissue showed reduced phosphorylation of troponins I and T, myosin binding protein C, and myosin light chain 2 compared to donor tissue, which is similar to previous findings for failing human heart. Treatment with protein kinase A (PKA) to adjust phosphorylation of TnI and MYBP-C in donor and HCM myocytes, however, uncovered reduced calcium-sensitivity, similar to what was observed previously in M. soleus, while maximum force was not affected by PKA. Electron microscopy showed lower myofibril density and disorganization of myofibrils in the cardiac tissue samples which most likely accounts for the reduced force.

Conclusions: (1) The primary effects of HCM related mutations might obscure typical adaptations commonly seen in end stage heart failure due increased calcium-sensitivity due to changes in protein phosphorylation. (2) To identify primary functional effects of a mutation in myocardial tissue an advanced stage of the disease, posttranslational modifications like protein phosphorylation and ultrastructural alterations must be taken into account.

Purpose: Lamin A/C (LMNA) mutation carriers suffer from a variety of clinical phenotypes, including dilated cardiomyopathy (DCM). Although it has been suggested that carriers are at risk for thromboembolic complications, it is unknown whether this risk is higher than can be expected from the underlying cardiac abnormalities.

Methods: We compared a cohort of 76 LMNA mutation carriers with a cohort of 60 unrelated and consecutive DCM patients without a LMNA mutation, with respect to the prevalence of arterial and venous thromboembolic complications. Furthermore, we carried out a case-control study to explore whether a prothrombotic phenotype was present in LMNA mutation carriers without DCM or atrial tacharyrhythmias (n=14) and compared this with mutation negative relatives (n=13).

Results: The prevalence of thromboembolic complications was higher in the cohort of LMNA mutation carriers than in DCM patients (22 vs 11%, p=0.05), after adjustment for left ventricular ejection fraction, which was lower in LMNA mutation carriers than in DCM patients (p=0.04). A majority of patients carried multiple rare variants, questioning the role for extra-sarcomere variants as possible modifiers.

Methods: We aimed to characterize the effects of the highly malignant β-miomyosin heavy chain (β-MHC) missense mutation R722G in myocardial tissue and to compare the data with previous findings in M. soleus fibers with the same mutation. This allows to differentiate (1) the primary functional effects of the mutation and (2) adaptational processes in the myocardium.

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Results: Measurements revealed reduced maximum force generation but unchanged calcium-sensitivity of the myocytes. Yet, previous studies on slow skeletal muscle fibres with the same mutation showed reduced calcium-sensitivity and increased maximum force. The expression of mutated β-MHC-mRNA and β-miomyosin in LV tissue was found to be 68% and 64% of total β-MHC-mRNA and β-miomyosin, respectively, which is the same fraction as in M. soleus. Get electrophoresis of the HCM cardiac tissue showed reduced phosphorylation of troponins I and T, myosin binding protein C, and myosin light chain 2 compared to donor tissue, which is similar to previous findings for failing human heart. Treatment with protein kinase A (PKA) to adjust phosphorylation of TnI and MYBP-C in donor and HCM myocytes, however, uncovered reduced calcium-sensitivity, similar to what was observed previously in M. soleus, while maximum force was not affected by PKA. Electron microscopy showed lower myofibril density and disorganization of myofibrils in the cardiac tissue samples which most likely accounts for the reduced force.

Conclusions: (1) The primary effects of HCM related mutations might obscure typical adaptations commonly seen in end stage heart failure due increased calcium-sensitivity due to changes in protein phosphorylation. (2) To identify primary functional effects of a mutation in myocardial tissue an advanced stage of the disease, posttranslational modifications like protein phosphorylation and ultrastructural alterations must be taken into account.

Purpose: Lamin A/C (LMNA) mutation carriers suffer from a variety of clinical phenotypes, including dilated cardiomyopathy (DCM). Although it has been suggested that carriers are at risk for thromboembolic complications, it is unknown whether this risk is higher than can be expected from the underlying cardiac abnormalities.

Methods: We compared a cohort of 76 LMNA mutation carriers with a cohort of 60 unrelated and consecutive DCM patients without a LMNA mutation, with respect to the prevalence of arterial and venous thromboembolic complications. Furthermore, we carried out a case-control study to explore whether a prothrombotic phenotype was present in LMNA mutation carriers without DCM or atrial tacharyrhythmias (n=14) and compared this with mutation negative relatives (n=13).

Results: The prevalence of thromboembolic complications was higher in the cohort of LMNA mutation carriers than in DCM patients (22 vs 11%, p=0.05), after adjustment for left ventricular ejection fraction, which was lower in LMNA mutation carriers than in DCM patients (p=0.04). A majority of patients carried multiple rare variants, questioning the role for extra-sarcomere variants as possible modifiers.

Methods: We aimed to characterize the effects of the highly malignant β-miomyosin heavy chain (β-MHC) missense mutation R722G in myocardial tissue and to compare the data with previous findings in M. soleus fibers with the same mutation. This allows to differentiate (1) the primary functional effects of the mutation and (2) adaptational processes in the myocardium.

Methods: In left ventricular cardiomyocytes from explanted hearts of patients with the β-miomyosin mutation R722G and in donor cardiomyocytes we determined force generation, force-calcium relations, and cross-bridge kinetics. We also determined the relative expression of mutated vs. wildtype β-MHC at the mRNA and protein level and analyzed the phosphorylation of sarcomeric proteins. To assess cardiomyocyte structural properties, histology and electron microscopy was also performed.

Results: Measurements revealed reduced maximum force generation but unchanged calcium-sensitivity of the myocytes. Yet, previous studies on slow skeletal muscle fibres with the same mutation showed reduced calcium-sensitivity and increased maximum force. The expression of mutated β-MHC-mRNA and β-miomyosin in LV tissue was found to be 68% and 64% of total β-MHC-mRNA and β-miomyosin, respectively, which is the same fraction as in M. soleus. Get electrophoresis of the HCM cardiac tissue showed reduced phosphorylation of troponins I and T, myosin binding protein C, and myosin light chain 2 compared to donor tissue, which is similar to previous findings for failing human heart. Treatment with protein kinase A (PKA) to adjust phosphorylation of TnI and MYBP-C in donor and HCM myocytes, however, uncovered reduced calcium-sensitivity, similar to what was observed previously in M. soleus, while maximum force was not affected by PKA. Electron microscopy showed lower myofibril density and disorganization of myofibrils in the cardiac tissue samples which most likely accounts for the reduced force.

Conclusions: (1) The primary effects of HCM related mutations might obscure typical adaptations commonly seen in end stage heart failure due increased calcium-sensitivity due to changes in protein phosphorylation. (2) To identify primary functional effects of a mutation in myocardial tissue an advanced stage of the disease, posttranslational modifications like protein phosphorylation and ultrastructural alterations must be taken into account.
these mutations were found in healthy subjects. Immunohistochemical analysis of endomyocardial biopsies demonstrated an abnormal distribution of myofibrillin in cardiac myocytes from the p.P961L mutation carrier, while the periodic localization of myofibrillin in sarcomeres was unchanged in the p.R950W carrier and four other DCM patients used as controls. Interestingly, in cardiac myocytes from the p.P961L patient we also observed a disturbed localization of α-actinin, which is a known binding partner for myofibrillin. In the ANKR1G1 gene we identified only one novel synonymous mutation in a DCM patient, which was a mononucleotide substitution in exon 2 (c.108C>T), but failed to detect non-synonymous mutations.

Conclusions: Taken together, we have identified novel point mutations in the third immunoglobulin-like domain of myofibrillin. One of these missense mutations, a substitution of a highly conserved prolyl residue in position 961, was associated with structural alterations in the sarcomere organization. These findings point to the role of myofibrillin in myofibrillogenesis with impact on the pathogenesis of dilated cardiomyopathy.

**Figure 1. NT-proBNP increases with age in men and women**

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**P4874**  
Tei index, a useful indicator for right ventricular involvement in fabry disease  
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**Aim:** Fabry disease is an X-linked lysosomal storage disorder caused by a deficiency of α-galactosidase A. Besides renal failure and strokes, cardiomyopathy and cardiac arrhythmia are frequent complications of the disease. The cardiomyopathy can be characterized by left and right ventricular hypertrophy and cardiac fibrosis. The Tei index, a marker for combined diastolic and systolic function, has been investigated in Fabry disease to assess left ventricular dysfunction and correlates with left ventricular hypertrophy. Whether right ventricular involvement is accompanied by systolic and diastolic dysfunction in Fabry patients is as yet unknown. The aim of this study was to investigate if right ventricular hypertrophy is accompanied by right ventricular dysfunction, using Tei index.

**Methods:** A total of 83 (30 males, mean age 43 years) genetically confirmed consecutive Fabry patients and 21 (9 males, mean age 43 years) healthy controls were included in this study. Standard echocardiography was performed in all patients, including Tei-index of the lateral annulus off the right ventricle, left ventricular mass index (LVMI), tricuspid annular plane systolic excursion (TAPSE) and tricuspid lateral annular systolic velocity (Sa). 49 Patients receiving enzyme replacement therapy (ERT) and 34 patients had natural history.

**Results:** TAPSE (22.6±0.8) and Sa (12.4±0.4) were significantly lower in the Fabry patients compared to controls (TAPSE 24.8±1.63, p<0.001, Sa 13.6±0.8, p<0.001). The Tei-index was significantly higher in the Fabry patients (0.51±0.03) compared to the controls (0.28±0.03, p<0.001). The LVMI was significantly higher in the Fabry patients (124.8±11) compared to the controls (94.3±7, p<0.001). The Tei-index of the right ventricle correlated significantly with LVMI and the Tei-index (r 0.542, p<0.001).

**Conclusion:** In comparison to healthy controls, Fabry patients display right ventricular dysfunction as measured by Tei-index. The right ventricular dysfunction correlates to the degree of left ventricular hypertrophy.

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**P4875**  
Role of serum NT-proBNP measurement in the diagnosis of early cardiac involvement in patients with Fabry disease  
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**Purpose:** NT-proBNP has an established role in the diagnostic and prognostic assessment of heart failure. Cardiac involvement in AFD is common, however detection of early disease is challenging. The aim of this study was to determine the relation between serum NT-proBNP concentration and cardiac abnormalities in patients with Anderson Fabry disease (AFD).

**Methods:** NT-proBNP was measured using resting conditions in 117 patients with AFD (48±15 years old, 46.2% male). All patients underwent clinical evaluation including ECG and echocardiogram.

**Results:** NT-proBNP concentrations ranged from 5pmol/L to 6059pmol/L. Eighty six (74%) patients had cardiac involvement (defined as an abnormal ECG or echocardiogram). A cut off of 230pmol/L had a 69% sensitivity and 94% specificity for detecting cardiac involvement in AFD with area under a receiver operator characteristics curve of 0.85 (95% CI 0.79-0.92). In multiple regression analysis the following were independently associated with logNT-proBNP levels: age, creatinine, LA volume index, E/Ea and the presence of an abnormal ECG (R 0.67, p<0.05).

**Conclusion:** NT-proBNP concentrations are raised in patients with Anderson-Fabry disease and cardiac involvement and correlate with non-invasive markers of diastolic dysfunction. These findings suggest that measurement of NT-proBNP may assist in decisions on the timing of enzyme replacement therapy.

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**P4876**  
Advanced left heart disease in cystic fibrosis: a distinct form of cardiomyopathy  
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During decades, occasional cases of cardiomyopathy (CMP) have been described in patients with cystic fibrosis (CF). Necropsies of children with CF who died of sudden death showed dilated left ventricles with patchy fibrosis. Currently, patients with CF usually reach adulthood, and the incidence and features of CMP in them are unknown.

**Methods:** We describe cardiologic findings of 9 adult patients with CF and left ventricular (LV) systolic dysfunction, 3 of them referred to our centre for cardiac transplantation and 6 found in a study of 120 CF patients without known cardiovascular disease (5% prevalence). We report data of clinical evaluation, blood tests, ultrasound and magnetic resonance (MRI) studies. Histological findings of the three explanted hearts are described. The remaining 114 patients without CMP served as control group.

**Results:** The mean age of the 9 CMP patients was 31±7 years and 6 were male. Four of them had del508 mutation and 2 had a rare mutation of other CF-related genes. Their mean LV ejection fraction was 36% (vs 66±8% in controls, p<0.01); 55% had also diastolic dysfunction (vs 5% in controls, p<0.01). Four patients (44%) showed moderate mitral regurgitation. Right ventricle was affected in 1 patient (11%) and was normal in all control patients. Mean NT-proBNP in CF patients with CMP was 1498±3219 pg/mL (vs 58±45 pg/mL in controls, p<0.001). MRI showed a patchy delayed myocardial gadolinium uptake in 43% of CMP patients, vs 0/04 among controls, p<0.05. Pathology of the 3 hearts explanted at transplantation showed patchy myocardial fibrosis in all cases, a finding similar to the autopsies of Keshan syndrome (CMP due to selenium deficiency). Eighty patients (89%) with CMP had pancreatic exocrine deficiency, needing high-dose pancreatic enzyme supplements (vs 50% in the control group, p<0.05), and 6/9 (67%) had a body mass index <20 kg/m² (vs 53 among controls, p=0.07). From the pulmonary standpoint, the mean FEV1% for the 9 patients was 45±16% (vs 60±20% for controls, p=0.08). All of them had a permanent airway colonization by Pseudomonas (vs 58% among controls, p=0.04). In fact, 4/9 (44%) patients with cardiac involvement required lung transplantation (vs 1% in controls, p<0.05).

**Conclusions:** A small percentage of adult CF patients show a distinct CMP with a characteristic patchy myocardial fibrosis, a finding similar to the autopsies of children with CF and other malnourishment syndromes. CMP should be suspected in CF patients with significant malnutrition and more severe pulmonary involvement. ProBNP levels could serve as a screening tool for this form of CMP.
Desmin null mice (des−/−) develop dilated cardiomyopathy with myocardial de-
generation, extensive calcification and fibrosis which leads to arrhythmias and
sudden cardiac death. Our aim was to investigate the cardiac autonomic nervous
system function in the des−/− mouse by measuring heart rate variability (HRV)
indices.

Methods: We generated des−/− mice by gene targeting via homologous recom-
bination in 129Sv genetic background. Twenty four hours ECG recordings were
obtained from 6m old des−/− and wild type (WT) mice, using a telemetry sys-
tem (DSI) and all RR intervals were recorded. The following linear and non-linear
HRV indices were calculated: Approximate Entropy (ApEn) modified to avoid self-
ocurrences, Detrended Fluctuation Analysis (DFA) and the beta-Spectral Expo-
ntion. Poincare map measures were used to extract 3D measures of spread and
maximum and the 2D distances axis sD1 and sD2. Time domain (SDNN, SDNNI,
RMSSD, pNN50) and frequency domain (LV, HF) indices were also calculated.

Results: Results are presented in Table 1.

Conclusion: Desmin null mice show a global autonomic nervous system dys-
function which affects both the sympathetic and the parasympathetic compo-
nents. This may explain the presence of arrhythmias and sudden cardiac death in
these mice. Further investigations are needed so as to clarify whether this dysfunc-
tion is a result of the extended myocardial fibrosis and calcification caused by the
absence of desmin.

MYOCARDITIS

Left ventricular mechanics in acute myocarditis

Correlation of 20 specie tracking deformation and rotation imaging with troponin release and cardiac magnetic resonance findings

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P.E. Vardas; 1University of Heraklion, Department of Cardiology, Heraklion, Greece.

Background: Acute myocarditis with normal ejection fraction (EF) represents a
diagnostic challenge for conventional echocardiography. Cardiac magnetic reso-
nance imaging (CMRI) is the current non-invasive reference standard for diag-
nosis. Speckle tracking imaging (STI) allows measurement of left ventricular (LV)
torsion and deformation. Abnormalities of these parameters may contribute to
earlier diagnosis of myocardial inflammation.

Aim: The purpose of this study was to explore the longitudinal, circumferential, and
torsional mechanics of the LV in patients with acute myocarditis.

Methods: Longitudinal, circumferential and torsional mechanics of the LV were
quantified at baseline in 30 patient consecutive cases of myocarditis based on clini-
cal, laboratory and CMRI findings and 50 healthy age-matched controls. All
patients had chest pain, abnormal ECGs and preserved EF (>45%) whereas
coronary artery disease was angiographically excluded.

Results: In comparison with controls, global longitudinal strain values in myocarditis
group (17.35±3.08% vs. -20.08±2.63%, p= NS) were not statistically different, reflecting the preserved longitudinal contractility. On the contrary, myocarditis patients showed decreased LV torsion (10.30±4.92 vs 14.28±4.30 degrees, p<0.01), apical rotation values (4.74±3.73 vs 8.73±2.05 degrees, p<0.003) and circumferential strain in the mid posterior (7.5±6.5% vs -18.2±7.4%, p<0.001), mid lateral (-7.1±7.3% vs -16.4±11%, p<0.001) and mid inferior wall (11.5±4.6% vs -20.5±4.7%, p<0.001) compared to controls. Tropinin elevation was found in 25 patients (50%) with mean values 14.8±23.79 ng/ml and was correlated with both LV tor-
sion (r=0.584, p<0.001; and the number of affected segments in CMRI (r=0.57, p=0.04). A circumferential strain cut off below -12.5% for mid lateral and below
-10.5% for mid inferolateral segment yielded a sensitivity of 75% & 87.5% and a
specificity of 60% & 60% respectively, in predicting late enhancement (LGE) at
CMRI in these segments.

Conclusion: STI assessment revealed abnormal LV torsion and circumferen-
tial strain in acute myocarditis. Torsion impairment was strongly correlated to the
level of troponin release. On the contrary, longitudinal strain and conven-
tional echocardiographic parameters were not significantly affected. Circumfer-
enzial strain yielded only modest specificity in predicting the segments with LGE at
CMRI

Adiponectin promotes coxsackievirus B3 myocarditis by controlling viral infection within the heart

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Klinikum (CVK), Medical Immunology and BCRT, Berlin, Germany; 3University of Tübingen, Department of Molecular Immuno-
logy, Tübingen, Germany.

Purpose: Adiponectin (APN) is an adipokine that is expressed in cardiac cells
and mediates immunomodulatory and cardioprotective effects. High APN
expression promotes favorable outcome in patients with virus-negative inflamma-
tory cardiomypathy and in mice with autoimmune myocarditis. Interestingly, APN
also controls antigen-specific T cell responses and viral replication during hepa-
titis. Coxsackievirus B3 (CVB3) is cytopathic for cardiac myocytes and causes
severe myocarditis, which might progress to dilated cardiomyopathy. Here, we
investigate whether APN modulates cardiac inflammation and injury in CVB3
myocarditis.

Methods: Myocarditis was induced by infection of APN−/− and WT mice with
CVB3. Viral load was determined by qRT-PCR, plaque assay and in situ hybridiza-
tion. I&H stained heart sections were used for histological analysis. Gene ex-
pression was analysed by qRT-PCR. Matrix metalloproteinase (MMP) activity was
measured by Western blot. Results: APN−/− mice displayed significantly reduced CVB3 load in the my-
ocardium. This was accompanied by decreased myocarditis severity designated by
reduced number and size of inflammatory infiltrates and diminished expres-
sion levels of immune cell markers NKp46, CD3, CD4, CD11b and CD45. Cor-
respondingly, APN−/− mice displayed significantly decreased cardiac expression
tests of IL-10, IFNgamma, TNFalpha, IL-1β, IL-6 and IL-12. However, in APN−/− mice, cardiac resident macrophages exhibited an in-
creased M1/M2 phenotype ratio. Histological analysis of the heart revealed less
severe necrotic lesions in APN−/− mice after CVB3 infection. Accordingly, CVB3 induced cardiac remodeling was significantly dimin-
ished in APN−/− mice. The expression levels of Collagen type I, Collagen type III and MMP-13 as well as activ-
ities of MMP-2 and MMP-9 were attenuated. In contrast, APN−/− mice displayed unchanged expression levels of Coxackie-Adenovirus receptor, TLR3 and TRIF.

In cell culture APN treatment resulted in significantly increased CVB3 replication in cardiac myocytes accompanied by enhanced TNFalpha expression.

Conclusions: Our observations indicate that APN promotes myocardial inflam-
mation and injury in CVB3 myocarditis by facilitating viral infection of cardiac
myocytes. Invasive viral replication might be enhanced by APN mediated dif-
ferentiation of cardiac resident macrophages towards an immunosuppressive M2
phenotype. Thus, in contrast to other models of inflammatory heart disease the
immunomodulatory effects of APN result in increased myocardial damage follow-
ing CVB3 infection.

Adiponectin promotes coxsackievirus B3 myocarditis by controlling viral infection within the heart

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Background: Acute myocarditis (AM) clinical onset can span from subclinical
disease to acute heart failure (AHF) ventricular fibration (VF) or sudden car-
diac death in young adults. Myocarditis can cause arrhythmias both in the acute
and chronic phases. As a consequence, diagnosis of myocarditis based on clini-
cal, laboratory and CMRI findings and 50 healthy age-matched controls. All
patients had chest pain, abnormal ECGs and preserved EF (>45%) whereas
coronary artery disease was angiographically excluded.

Results: In comparison with controls, global longitudinal strain values in myocarditis
group (17.35±3.08% vs. -20.08±2.63%, p= NS) were not statistically different, reflecting the preserved longitudinal contractility. On the contrary, myocarditis patients showed decreased LV torsion (10.30±4.92 vs 14.28±4.30 degrees, p>0.01), apical rotation values (4.74±3.73 vs 8.73±2.05 degrees, p<0.003) and circumferential strain in the mid posterior (7.5±6.5% vs -18.2±7.4%, p<0.001), mid lateral (-7.1±7.3% vs -16.4±11%, p<0.001) and mid inferior wall (11.5±4.6% vs -20.5±4.7%, p<0.001) compared to controls. Tropinin elevation was found in 25 patients (50%) with mean values 14.8±23.79 ng/ml and was correlated with both LV tor-
sion (r=0.584, p<0.001) and the number of affected segments in CMRI (r=0.57, p=0.04). A circumferential strain cut off below -12.5% for mid lateral and below
-10.5% for mid inferolateral segment yielded a sensitivity of 75% & 87.5% and a
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Conclusion: STI assessment revealed abnormal LV torsion and circumferen-
tial strain in acute myocarditis. Torsion impairment was strongly correlated to the
level of troponin release. On the contrary, longitudinal strain and conven-
tional echocardiographic parameters were not significantly affected. Circumfer-
enzial strain yielded only modest specificity in predicting the segments with LGE at
CMRI
In vivo delivery of adenoviral vector containing Interleukin-17 receptor A reduces cardiac remodeling and improves myocardial function in CVB-3-induced chronic myocarditis

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Purpose: Th17 cells have been implicated in the pathogenesis of myocarditis. Interleukin (IL)-17A produced by Th17 is dispensable for viral myocarditis but essential for the progression to dilated cardiomyopathy (DCM). This study investigated whether adenoviral transfer of the IL-17 receptor A would reduce myocardial remodeling and dysfunction in chronic viral myocarditis.

Methods and Results: In a mouse model of Coxsackievirus B3 (CBV3)-induced chronic myocarditis, delivery of adenovirus containing IL-17 receptor A (Ad-IL17R:Fc) reduced IL-17A production and decreased the mortality rate compared with a control adenovirus null (Ad-null) 3 months after first CBV3 infection (56% versus 76%). Cardiac function was significantly improved in Ad-IL17R:Fc compared with Ad-null treated mice. The Th17 cell was one of the major sources of IL-17 in the heart, suggesting an important role of IL-17A in fibrosis. These effects of Ad-IL17R:Fc correlated with a decrease of Th17 cells in the spleen and heart, and a reduction of systemic TNF-α and IL-6 productions. In cultured cardiac fibroblasts, IL-17A induced expression of ADAMTS-1, MMP-2, collagen subtypes I and III, and increased fibroblast proliferation in chronic viral myocarditis and DCM. Thus, blockade of IL-17A by adenoviral transfer of IL-17 receptor A may represent an alternative therapy for chronic viral myocarditis and its progression to DCM.

Conclusion: IL-17A inhibits beneficial effects of IL-17 receptor A in reducing myocardial fibrosis.

Injectable collagen implant improves survival and early cardiac remodeling after fulminant myocarditis in rats

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Purpose: Acute myocarditis can lead to massive cell death, destruction of extracellular matrix, left ventricle (LV) dilatation, dysfunction and death. We sought to test the hypothesis that injection of collagen-based implant into the infarced myocardium would stabilize LV and prevent adverse remodeling and dysfunction.

Methods and Results: Autimmune myocarditis was induced in 42 male Lewis rats. Fourteen days after immunization, sick animals were randomized into either injectable-collagen implant or saline injection, into anterior infarmed myocardium. LV remodeling and function were assessed by serial echocardiography and cardiac magnetic resonance (CMR) scans; before immunization, before collagen implantation and 17 days after implantation. Thirty one days after immunization rats were euthanized and subsequently underwent histopathological examination. Notably, 30 day survival rate was significantly higher in collagen-treated group compared with control (87.5% vs. 50%; p<0.03). CMR imaging of control animals showed epicardial late gadolinium enhancement, as marker of fibrosis, LV wall motion abnormalities, and in some cases pericardial effusion. The injectable collagen implant increased systolic and diastolic wall thickness, 10 days after treatment, compared with control (p=0.07, p=0.05). Furthermore, while injectable collagen implant attenuated the LV systolic and diastolic dilatation and preserved LV ejection fraction, control animals developed significant LV dilatation (p=0.02, p=0.04) and dysfunction (p=0.01). However, these favorable effects disappeared within 17 days after treatment.

Conclusion: Injectable collagen implant improves survival in a rat model of fulminant myocarditis. However, while the effect on survival was sustained, the early protective effect on LV remodeling and function was limited to the early period after treatment.

Matrix Metalloproteinase-13 is beneficial in viral myocarditis not only by preventing cardiac inflammation but also reducing cardiac inflammation due to regulating chemokines

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Myocarditis is an important cause for cardiac failure especially in younger patients followed by the development of cardiac dysfunction and death. The present study investigated whether gene deletion of matrix metalloproteinase-13, an important enzyme which influences cardiac inflammation and remodeling in murine coxsackievirus B3 (CBV3) induced myocarditis.

Methods and Results: MMP-13 knockout mice (MMP-13-/-) and their controls (WT) were infected with CBV3 to induce myocarditis and 7 days later LV function was analyzed invasively. CBV3 induced significant cardiac inflammation (increased CD3 (+18 fold) and CD68 (+25 fold) cells) as well as cardiac dysfunction (decreased cardiac output (-24%) in WT CBV3 animals. Interestingly, deletion of MMP-13 increased the protein level of the chemokine MCP-1 (4 fold). This increas...
ment of a potent chemokine due to MMP13 KO aggravated cardiac inflammation (3 fold) as well as cytokine levels (increased TNF-alpha 6 fold and IL1 beta 3 fold) compared to infected WT animals. Moreover, this excessive cardiac inflammation was associated with an increased transdifferentiation of fibroblasts to pathological activated myofibroblasts (10 fold), which are known to be induced by inflammatory cells. This was associated with detrimental cardiac remodeling leading to severe cardiac dysfunction when MMP-13/- were compared to WT animals after CVB3 infection. Interestingly, also viral load was increased in MMP-13/- mice with significantly more cardiac apoptosis being present in the infected myocardium.

Conclusions: Loss of MMP-13 increased the inflammatory response after CVB3 infection, which impaired cardiac remodeling, apoptosis and function during CVB3 infected myocarditis due to an increment of the chemokine MCP-1. MMP-13, similar to other MMPs like MMP-2 might be more than just a degrada-
tion system for cardiac collagen but may modulate inflammation by processing chemokines as MCP-1 and therefore being one negative feedback loop in card-
diac inflammation.

No evidence of adenoviral genome in endomyocardial biopsy specimens in patients with new-onset unexplained dilated cardiomyopathy

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Background and aim of the study: Dilated cardiomyopathy (DCM) may rep-
resent a sequela of acute or chronic myocarditis, either due to persistence of infectious agent (mostly virus) or to a secondary autoimmune myocardial in-
flammation. Several studies reported adenovirus as an important causative agent in the pathogenesis of myocarditis and DCM in children and adults. Therefore, we aimed to prospectively evaluate the presence of genomes of several cardiotropic pathogens including adenovirus and Borrelia burgdorferi (Bb) in myocardium of patients with new-onset unexplained DCM.

Methods: In 58 consecutive patients (53±11 years, 42 men) with new-onset un-
explained DCM (left ventricular ejection fraction 30±3%, endomyocardial biopsy (EMB) specimens were studied by immunohistochemistry (HLA expression) and polymerase chain reaction (PCR) techniques.

Results: The genome of cardiotropic infectious agent was found in EMB speci-
mens (35%) in 6 patients suffering from a recent viral myocarditis infection. Namely, Bb genome was present in 13 subjects and adenovirus parovirus B19 in 10, enterovirus in 5, human herpes virus 6 in 5, and cytomegalovirus in 3. Adenovirus and herpes simplex virus 1 genome were not detected in any subjects. Myocar-
dial inflammation was found in 18 patients (31%), of which in 7 subjects (12%) the presence of viral or Bb genome was also revealed.

Conclusions: The genome of cardiotropic infectious agent, viral or Bb, is present in the myocardium of more than half of the patients with new-onset unexplained DCM. Notably, Bb genome can be detected in almost one quarter of these subjects, which may have important therapeutic consequences. However, adenovirus infection does not seem to play an important role in the pathogenesis of new-onset unexplained DCM. Therefore, it is not necessary to perform adenovirus PCR assay of EMB specimens in patients with new-onset unexplained DCM.

Clinical, ECG and echocardiographic criteria are insufficient to to reach a definite diagnosis in patients with myocardial injury and normal coronary angiogram: insights from magnetic resonance-based


Purpose: Some patients (p) with troponin-positive chest pain have no coronary obstruction on angiography, leading to diagnostic uncertainty. Cardiac magnetic resonance (CMR) is able to determine causative aetiology in most p. The aim of this study was to analyse whether clinical, ECG or echocardiographic criteria could be useful for diagnostic assessment using CMR as gold standard.

Method: 59 consecutive p referred for CMR after admission in our institution for typical chest pain and normal coronary arteries or non-flow-limiting CAD in coronary angiography were analysed. CMR studies were performed with a 1.5 T Philips Intera and included SSFP sequences, T2-weighted black-blood, first pass perfusion and late enhancement. P were classified as AMI, myocarditis, apical ballooning or un conclusive study. Clinical data including age, sex, type of chest pain, troponin levels, ECG recordings, echocardiography and coronary an-
giogram were reviewed and compared between different groups defined by CMR.

Results: Mean age was 45±15 years and 43 (72%) were male. P with AMI showed a non significant trend towards more frequent non significant stenosis in comparison with myocarditis (39% vs 9%) and compared to myocarditis (p > 0.01) or apical bal-
looning (0 p). All with apical ballooning recalled a previous stressing event and showed a typical distribution of wall motion abnormalities. 17 p (50%) with my-
ocarditis had evidence of a recent infection, whereas no p from the other groups had (p =0.001). Characteristics of different subgroups are displayed in table 1.

Conclusions: In p admitted for troponin-positive chest and no coronary obstruc-
tion on angiography which do not recall a recent infection, clinical, ECG and echocardiographic data are unreliable to differentiate between AMI and myocardi-
etanercept treatment improves acute chagas disease myocardial mechanics for the early detection of death or heart transplantation (hazard ratio 9.2; 95% confidence interval 1.7-50; p=0.011). The peak of CRP was at 7 dpi and decreased until 21 dpi in all groups, but the levels were significantly lower in treated animals. TNF relative levels peak occurred at 7dpi and there was no differences between treated and untreated animals. Vertical and horizontal motility reduction and hyperalgesia in infected animals was reversed by etanercept treatment. Finally, the infected animals showed T-wave height and repolarization slope reduction during the first and second week post-infection. ECG was taken weekly with surface electrodes coupled to a Blip amplifier.

Results: The survival of treated animals was increased significantly with respect to infected untreated animals (20 vs 24 days, p=0.0048). According to EMB 6 patients were diagnosed with acute myocarditis (37.4±16.6) vs 9 patients (14±14) never had acute myocarditis (p=0.042). During follow-up, no significant differences existed between the groups. The concentration of hs-TnT compared to other groups (AM 262.9 pg/ml (61.4-4225 ng/ml) was predictive for cardiac death or heart transplantation (hazard ratio 9.2; 95% confidence interval 1.7-50; p=0.011).

Conclusions: Acute and viral myocarditis are characterized by elevated concentrations of hs-TnT. However, these biomarkers do not replace EMB for diagnosis of myocardial inflammation.

MYOCARDIAL INVOLVEMENT IN SYSTEMIC DISEASES

Measurement of interatrial dysynchrony using tissue doppler imaging predicts functional capacity and cardiac involvement in systemic sclerosis

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Background: Heart involvement in systemic sclerosis (SSc) is associated with poor prognosis, and early detection is crucial. SSc may affect all heart structures, including conduction pathways: interatrial block is considered common and may reflect atrial involvement, but has been so far poorly evaluated. Echocardiography may detect interatrial dysynchrony, using either M-mode or strain modalities.

Method of the study: 1) To assess the prevalence of interatrial dysynchrony (IAD) by measuring the interatrial electro-mechanical delay (IAMD) in SSc patients using TDI. 2) To evaluate the correlation between IAMD and other usual follow-up parameters.

Methods: Patients with SSc were selected if there were in sinus rhythm and were able to walk. The following data were collected: NYHA functional class and distance walked in 6 minutes (6'WD), P wave duration on ECG, serum creatinine and Na proBNP levels. Echo-Doppler study comprised: left ventricular (LV) mass, LV systolic and diastolic function, right ventricular (RV) function, pulmonary artery pressure (PAP), left atrial (LA) volumes and function. IAMD was assessed using colour TDI study, by measuring the delay between annular tricuspid and mitral a' waves. A cut off value of 35 ms was chosen to define the presence of IAMD.

Results: Forty patients were studied. Forty-nine patients were found to have IAD. These patients were significantly older. Using age-adjusted analysis, patients with IAMD had more severe symptoms, lower 6'WD, higher NT proBNP and creatinine levels, and longer P wave duration than patients without IAD. No difference was found regarding LV dimension and UEF. LV mass was higher, E/A and E/E' ratio were significantly different, LA volume was significantly higher, TAPSE was lower, and PAP was higher. Most importantly, IAMD correlated well with 6 WD (r = 0.72, p = 0.0001). During a 1-year follow-up, 5 patients died or had severe events: all of them were in the dysynchrony group.

Discussion: The prevalence of interatrial dysynchrony among SSc patients is high (40%). IAMD was found to be associated with lower exercise capacities, altered LV diastolic function, decreased LA and RV function, increased pulmonary pressure, and increased natriuretic peptides. This finding suggests that IAMD may represent a marker of myocardial involvement and may indicate a poorly compliant left atrium.

Conclusion: IAMD is a simple parameter showing good correlations with all other usual indices of heart involvement. We believe that it should be added to the routine echocardiographic evaluation of SSc patients, and that its prognostic value should be evaluated.

Diagnostic and prognostic value of biomarkers in suspected myocarditis

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Background: Myocarditis can be associated with increased markers of myocardial injury. However, data on novel biomarkers as high-sensitive troponin (hs-TnT) or Copeptin are lacking. The aim of this study was to determine the diagnostic and prognostic utility of biomarkers in patient with suspected myocarditis.

Methods: Seventy patients with suspected myocarditis (age 43.4±14 years, 76% male, creatinine fraction 36.9±17.8%, 76% in NYHA class III/IV) underwent endomyocardial biopsy (EMB) and were follow-up for 7.5 (2-21) months. At the time of EMB, concentrations of hs-TnT, Copeptin, NT proBNP and proadrenomedullin (M,N-A/adrenomedulin) were evaluated. Values were given as mean± standard deviation or median (interquartile range).

Results: According to EMB 6 patients were diagnosed with acute myocarditis (AM) and 36 patients with chronic myocarditis (CM). In 28 patients, EMB revealed no myocardial inflammation (NM). Acute myocarditis was associated with high concentrations of hs-TnT compared to non-viral myocarditis (37.4±16.6) vs 9 patients (14±14) never had acute myocarditis (p=0.042). During the first and second week post-infection, ECG was taken weekly with surface electrodes coupled to a Blip amplifier.

Conclusions: TNF blocker etanercept on inflammation parameters, ECG recordings and survival in an acute infection with a wild T. cruzi virulent strain.

P4892 Measurement of interatrial dysynchrony using tissue doppler imaging predicts functional capacity and cardiac involvement in systemic sclerosis

P4893 Myocardial mechanics for the early detection of cardiac sarcoidosis

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Purpose: Speckle tracking has emerged as valuable tool for a more comprehensive assessment of regional myocardial function, providing angle-independent measurements of strain. The aim of this study was to evaluate left ventricular (LV) function in patients with newly diagnosed sarcoidosis, utilizing the novel method of 2D speckle tracking.

Methods: 67 patients with newly-diagnosed sarcoidosis and with unremarkable medical history of cardiovascular disease, as well as 29 healthy age-and gender-matched controls underwent echocardiographic study. Apical 4-, 2-, 3- chamber and rotational indices, implying elevated filling pressures of the left ventricle. This could represent an early sign of myocardial involvement in patients with newly-
pattern on MR ($P < 0.05$ for all cases). The subgroup with left ventricular systolic dysfunction showed patchy proBNP in systolic dysfunction was 53 pg/ml (range 22 - 8000 pg/ml).
Purpose: Echocardiography with tissue Doppler annular measurements decreased the abnormalities in 83.3% of young asymptomatic or oligosymptomatic survivors of Hodgkin's lymphoma 5 years after mediastinal irradiation. Mean age at the time of treatment was 19.6 ± 6.0 years, mean mediastinal irradiation dose = 36 ± 5.5 Gy, anthracyclines in 83.3% patients. Echocardiographic measurements above or below ±2SD age specific normal mean were considered abnormal.
Results: 26 patients were asymptomatic, 34 had mild nonspecific symptoms (cardiac arrhythmias). Any cardiac abnormality was found in 59 (83.3%) patients. 2 had mitral regurgitation grade 2, 3- aortic regurgitation grade 1, 1- tricuspid regurgitation grade 2. Pericardial impairment was found in 6 cases (1% overall). 8 patients had increased right DT and 14 Doppler LA; lateral wall tissue Doppler early annular diastolic velocity (e') was reduced in 31 (51.7%) and septal e' in 19 (15%) Patients. Peak exercise VO2 and aerobic threshold correlated with EDV/BSA (Spearman correlation coefficient $R=0.75$, septal and average £ (R=0.53-0.74) and lateral annular (R=0.52-0.75), and negatively correlated with E/e' (R=0.60, $p < 0.05$ for all cases).
Conclusion: Echocardiography with tissue Doppler annular measurements detected the abnormalities in 83.3% of young asymptomatic or oligosymptomatic survivors of Hodgkin's lymphoma ≥5 years after mediastinal irradiation. Early signs of restrictive/constrictive impairment were present and correlated with exercise limitations.

Prevalence of cardiomyopathy in an unselected population of adult patients with cystic fibrosis
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Purpose: Cystic fibrosis (CF) is characterized by an obstructive pulmonary pat- tern and a pancreatic exocrine deficiency, frequently associated with malabsorp- tion and complications. Cardiomyopathy (CMP) has been described in children with CF since the 1950's, with histologic features similar to those seen in malnutrition-related CMP, such as Keshan's disease. Our aim in this study was to describe the prevalence and features of CMP in a population of unselected adult CF patients.
Methods: As part of an investigation the prevalence and causes of CMP in CF, we studied a series of unselected adult CF patients without known cardiac disease. After obtaining clinical and genetic information, we performed a blood test, a proBNP, and an echocardiographic study. We defined systolic dysfunction as left ventricular ejection fraction less than 55% (Simpson's method). Diastolic dysfunction was defined by pathological patterns in mitral flow as classically ob- tained by doppler ultrasound. Patients with data of CMP were also studied with magnetic resonance (MR).
Results: Studied population included 120 adult CF patients recruited from 4 spe- cialized outpatient clinics. Mean age was 31±8.9 years, and 55% were male. Pancreatic disease was present in 80% of them, and low levels of vitamins and trace elements were common in spite of receiving dietary supplements. Left heart disease was present in 12 patients, with prevalence of 10%. Systolic dysfunction was evident in 6 patients (5%), and diastolic dysfunction in 9 patients (7.5%). There was a 2.5% that had both systolic and diastolic dysfunc- tions. Systolic dysfunction was significantly associated with a patchy myocardial enhancement pattern on MR ($P<0.05$), as well as with a higher frequency of Pseudomonas aeruginosa airway colonization ($p<0.04$) and a trend to having a lower body mass index ($22.6±4.9$ vs $20.9±1.6$, $p=0.07$). Median value for proBNP in systolic dysfunction was 53 pg/ml (range 22 - 8000 pg/ml).
Conclusions: The prevalence of CMP in an unselected group of adults with CF was 10%. The subgroup with left ventricular systolic dysfunction showed patchy fibrosis, similar to that described in malnutrition-related CMP. This form of heart disease should be included in the spectrum of organic involvement in CF patients and should be ruled out, especially in those with severe malabsorption or under evaluation for pulmonary transplant.

Impaired vascular elasticity and diastolic dysfunction in pseudoxanthoma elasticum
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Purpose: Pseudoxanthoma elasticum (PXE) is an autosomal recessive connec- tive tissue disorder of the skin and the arterial wall, caused by a genetic defect in the vascular system caused by homozygous mutations in the ABCC6 gene. The histological hallmark of PXE is degeneration of elastic fibers of the skin, which display progressive fragmentation. Similar histological findings have been observed in the endo-, myo- and pericardium and in the intima and media layers of medium sized blood vessels. Though cardiovascular involvement has been suggested in heterozygous carriers, controversy exists on the characteristics and relevance. We conducted an echocardiographic and vascular imaging study to determine whether these lesions influence ventricular function and the elastic properties of the middle-sized arteries in PXE patients and carriers.
Methods: 35 PXE patients, 22 carriers and 28 matched healthy subjects, aged between 18 and 70 years, were enrolled in this study. Measurements of global and local arterial stiffness (Pulse Wave Velocity (PWV) and carotid distensibility, and PWV) and elastic properties of the middle-sized arteries in PXE patients and carriers. Population: 35 PXE patients, 22 carriers and 28 matched healthy subjects, aged between 18 and 70 years, were enrolled in this study. Measurements of global and local arterial stiffness (Pulse Wave Velocity (PWV) and carotid distensibility, and PWV) and elastic properties of the middle-sized arteries in PXE patients and carriers.
Results: The left ventricular diastolic dysfunction was impaired in PXE patients and carriers, with a significantly higher deceleration time (118±5ms vs. 48.5±192.4ms ± 43.4; 138±36s ± 36.5; $p<0.001$, $p<0.001$, respectively), significantly lower Em ($9.5±2.7$ vs. $9.9±2.6$, $p=0.01$, $p=0.025$, respectively) and significantly higher $E$/Em ratio ($4.9±2.6$ vs. $8.4±1.8$, $p<0.01$, $p=0.04$, respectively) in both patients and cariers when compared to the control group. PXE patients older than 35 years had a significantly higher PWV (8.5±2.7 versus 6.6±1.8; $p=0.04$), which was independent of the presence of cardiovascular risk factors as determined by multiple logistic regression analysis. In the carriers we found a non signifi- cant increase in PWV. The distensibility of the middle sized arteries did not differ between groups. The Intima Media Thickness was significantly higher in both patients and carriers versus healthy controls (0.5±0.002 mm ± 0.13, 0.5±0.001 mm ± 0.12; $p<0.001$, $p=0.003$, respectively).
Conclusions: The results of this study clearly indicate the presence of left ven- tricular diastolic dysfunction as well as impaired elastic properties of middle-sized
arteries in PXE patients independently of the presence of cardiovascular risk factors. In heterozygous carriers, diastolic ventricular function is also abnormal, indicating cardiovascular involvement and the need for cardiovascular assessment in this specific group.

**P4989**

**Differential effect of antiretroviral drug regimens on aortic elastic properties in HIV infected individuals**

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**Purpose:** Aortic elastic properties mediate cardiovascular performance. Pulse wave velocity (PWV), an index of aortic stiffness, is an independent predictor of future outcomes. HIV infection is linked to higher cardiovascular risk and certain classes of antiretroviral therapy (ART) drugs, i.e. protease inhibitors, increase this risk disproportionally. The aim of the study was to assess the interplay of ART and arterial stiffness. Moreover, we sought to investigate how different ART regimens are linked to arterial stiffness.

**Methods:** 51 HIV infected patients were studied (50 men, age 40±10 y.o.). 12 were naïve to treatment, 29 were on ART. Among the ART treated, 22 were on a combination of nucleoside reverse transcriptase inhibitor plus non-nucleoside reverse transcriptase inhibitor (NRTI/NNRTI) and 17 were on a combination of nucleoside reverse transcriptase inhibitor plus protease inhibitor (NRTI/PI). Carotid-femoral PWV was measured non-invasively with a validated device (Complior). 

**Results:** Naïve patients had lower values of PWV compared to patients on ART (6.68 m/sec vs. 7.45 m/sec, P=0.05). Regarding drug regimens, those on NRTI/PIs had higher levels of PWV compared to those on NRTI/NNRTIs and to naïve to treatment patients (7.98±1.83 m/sec vs 7.04±1.21 m/sec vs 6.68±0.98 m/sec respectively, P=0.037 for overall ANOVA) (Figure).

**Figure 1.** PWV across ART drug regimens

**Conclusions:** HIV patients on ART have higher levels of aortic stiffness compared to naïve patients. Moreover, NRTI/PIs lead to heightened levels of PWV compared to NRTI/NNRTIs. These findings suggest that the detrimental effect of PIs on cardiovascular outcomes may be mediated through mechanisms of aortic dysfunction. Measurements of aortic stiffness in the setting of HIV infection can aid in risk stratification.

**P4990**

**Right ventricular 2D-strain: a new tool to follow up pulmonary hypertension patients under vasodilator therapy**


In patients with pulmonary hypertension (PH), progression of the disease and survival are related to the capability of the right ventricle (RV) to adapt to the chronically elevated pulmonary artery pressure (sPAP). Recent studies have successfully applied speckle-tracking derived strain (S) to quantify RV dysfunction in PH. Little is known about RV deformation evolution under pulmonary vasodilator (PV) treatment.

**Methods:** We performed echocardiographic follow-up of 17 patients with PH (Groups I and IV of the Dana Point classification) during 13.2±5.8 months and measured RV longitudinal systolic S from 6 RV segments. All cases were under PV treatment according to their physician’s criteria.

**Results:** We found a significant improvement in most conventional echocardiographic measurements as well as global and regional S during follow-up (table 1, figure 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>TAPSE</th>
<th>FAC</th>
<th>Global S</th>
<th>Lateral S</th>
<th>Septal S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo 1</td>
<td>17.2±3.9</td>
<td>0.05</td>
<td>0.005</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Echo 2</td>
<td>18.3±4.8</td>
<td>30.9±2.6</td>
<td>14.5±3.6</td>
<td>17.1±5.7</td>
<td>11.8±3.2</td>
</tr>
<tr>
<td>Echo 3</td>
<td>26.2±3.6</td>
<td>37.9±13.4</td>
<td>17.3±3.8</td>
<td>22.1±7.4</td>
<td>14.8±3.8</td>
</tr>
</tbody>
</table>

**Table 1.** Echocardiographic parameters

**Figure 1.** Global S evolution

**Conclusion:** RV performance as measured by S significantly improves during follow-up in PH patients who are under PV treatment. Further investigation is needed to find out whether this improvement is secondary to a functional recovery of the RV or to a decrease in RV afterload. We suggest routine measurement of RV S to follow up the disease progression.
Results: With regards to 2DE indices, it seems that after initiation of therapy, they improved significantly except right atrial volume which further increased. On the third follow up, 2D indices deteriorated and described eventually RV failure by the end of follow up. At the last follow up, there was excellent agreement between the two modalities for RV end-diastolic and RV end-systolic volume: r = 0.98, p < 0.001, mean bias = -1.95 ml, SD of bias = 10.4 ml and r = 0.99, p < 0.001, mean bias = -0.3 ml, SD of bias = 6.2 ml respectively. There was also significant agreement for RV stroke volume: r = 0.9, p < 0.001, mean bias = -2.2 ml, SD of bias = 8.2 ml as well as for RV ejection fraction: r = 0.9, p < 0.001, mean bias = -1.1%, SD of bias = 3%. However, there was no agreement between the two modalities for RV mass. With regards to clinical deterioration, stable patients had an RVEDV less than 200 ml through follow up, while patients who clinically deteriorated further increased RVEDV. RVEF was increased for both groups, however it increased more rapidly in patients who clinically deteriorated. An RVEF less than 23% together with regression of RV mass indicated clinical deterioration.

Conclusions: As a conclusion, PAH is an aggressive disease which in the majority of patients caused further RV dilatation and reduction in RV function. 3DE and CMR have excellent agreement for volumes and ejection fraction, but not for RV mass. Furthermore, both modalities have significant intra and inter-observer reproducibility.

Purpose: The aim of this study was to assess pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients’ survival in relation to a prospective, protocol-based collection of echocardiographic data in pre-capillary pulmonary hypertensive patients, referred to the National Pulmonary Hypertension Centre in London. All patients received the guideline-indicated best medical therapy.

Methods: All patients referred to the National Pulmonary Hypertension Service from 2002 until 2010 were included in the study. The patient cohort was solely composed of inoperable (PAH) and chronic thromboembolic pulmonary hypertensive patients, referred to the National Pulmonary Hypertension Centre in London. All patients received the guideline indicated best medical therapy.

Results: The overall survival was best determined by the severity of tricuspid regurgitation (p < 0.001, HR=10.98), the presence of pericardial effusion (p=0.0003, HR=1.714) and the composite score of RV systolic function (p=0.0002, HR=1.37), followed by left atrial diameter (p=0.0349, HR=1.04), the diameter of inferior vena cava (p<0.001, HR=0.896) and the echocardiographic measurement of pulmonary vascular resistance (p<0.0002, HR=0.822) that were the strongest predictors of mortality.

Conclusion: In a large group of consecutive pre-capillary pulmonary hypertensive patients, the severity of tricuspid regurgitation, RV systolic function and the presence of pericardial effusion may indicate poor survival. Inoperable CTEPH patients had worse survival when compared to patients with pulmonary arterial hypertension.
Improving echocardiography estimation of right atrial pressure: comparison among several models and a new one based on right atrial echocardiography

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Purpose: The estimation of right atrial pressure (RAP) has a great impact on the non-invasive evaluation of pulmonary hemodynamics. Several models have been developed to estimate RAP based on the inferior vena cava (IVC) diameter and collapsibility. However, IVC evaluation is not reliable for intermediate RAP values, young athletes, patients on ventilators or bad subcostal window.

The aim of this study was to compare several known models of RAP estimation against the invasive RAP (iRAP) and develop a new one to overcome the limitations of IVC analysis.

Methods: Echocardiography was performed on 75 patients within 60 minutes from cardiac catheterization. IVC was evaluated in long and short-axis view. Images of right chambers, tricuspid Pulsed and Tissue Doppler, and hepatic vein flow were acquired. RAP was estimated using 5 different known models based on IVC evaluation and a new one based on right atrium analysis.

All RAP models were compared to iRAP by Bland-Altman analysis.

Results: A population of 75 patients was evaluated (age: 62±14 years; iRAP: 9.5 mmHg [7-12], range 1 - 22 mmHg). IVC measured by MMode in long-axis view showed better correlation with iRAP. Among the 5 models based on IVC, the most recent one performed better (ρ̂ = 0.29; p = 0.04), but had a wide confidence interval (-13.0, 11.6 mmHg). Right atrial total ejection fraction (ToEF) and systolic volume (sVol) showed a strong positive (sVol) and inverse (ToEF) linear association with iRAP (p = 0.0001). Our model based on these parameters performed significantly better (ρ̂ = 0.48; p = 0.001) and had a narrower confidence interval (-8.9, + 8.4 mmHg) (see figure).

Conclusion: RHC remains the gold standard for the diagnosis of PH. Nevertheless, an easy and integrated echo score allows pathophysiologic insight along a hemodynamic spectrum in a mixed PH cohort providing a good pre-test probability of having a pre-capillary rather than post-capillary PH.

Echo features for pre-capillary PH

<table>
<thead>
<tr>
<th>RA-LA</th>
<th>RV-LV</th>
<th>Apex RV</th>
<th>LV</th>
<th>PE</th>
<th>RVOT</th>
<th>E/e'</th>
<th>Dyskinesis</th>
<th>LVEF</th>
</tr>
</thead>
</table>
| RA > LV Apex RV > LV e' < 9 PE > 0.4 EF > 40% Moderate to severe aortic and/or mitral disease (score for yes = 1, no = 0). The echo range scored from -2 to 7. Patients were arbitrarily divided in 3 groups: low score (-2 to 0), medium score (1 to 2) and high score (3 to 7) probability of having pre-capillary PH.

Results: Twelve 135 patients did not have pulmonary hypertension at RHC. 84 patients showed pre-capillary PH (54 group 1, 22 group 3 and 8 group 4) and 39 post-capillary PH (group 2) at RHC. The probability of having pre-PH was 37% in presence of low, 86% in presence of medium and 95% in presence of high echo score. No patient with LV-EF < 40% had pre-PH (specificity for post-PH 100%). The majority of echo features showed an high specificity but a low sensitivity for pre-PH (table).

P4907 Pulmonary artery trunk dilation in symptomatic subjects referred for coronary artery calcium scoring by means of a 64-row cardiac computed tomography

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Non-contrast cardiac computed tomography is as established method for coronary artery calcium determination in both asymptomatic and symptomatic subjects. We aimed at assessment of the prevalence of ancillary findings, including pulmonary artery dilation.

1075 females and 484 males examined between March 2010 and January 2012 were examined for CAC scoring by means of cardiac MDCT (64-row Aquilion). A retrospective analysis of the data for evaluation of pulmonary artery trunk diameter (PAD), mm), was performed. Gender-dependent upper normal limits were established in 74 women and 50 men with normal CT scanning, zero CAC score, who were never smokers, non-obese, non-diabetic and not-hypertensive. Proportion of subjects with abnormal PAD was determined separately in women and men.

Abnormal PAD was detected in 209 women (19%), while increased PAD:AAD ratio in 57 women (5%). In total, the PA dilation was found in 219 women (20.3%) including 172 with one measure abnormal, and 47 with both measures abnormal. Among men, abnormal PAD was detected in 89 subjects (18%), while abnormal PAD:AAD ratio in 9 men (2%). In total, any PAD increase was found in 82 men (17%) and both measure abnormal was found in 8 subjects (2%). Logistic regression analysis revealed that independent predictors of PAD increase in females were a positive CACS (OR 2.78) and obesity (1.83). Similar determinants were recognized in men (a positive CACS OR 2.34) and obesity (1.36). Conclusion: Pulmonary artery trunk dilation is relatively frequently observed in subjects referred for coronary artery calcium determination. Presence of coronary atherosclerosis and obesity were found as independent predictors of PAD enlargement. Detection of PAD abnormality might help to optimize diagnostic and therapeutic approaches in symptomatic subjects referred for CAC scoring.

P4909 Pulmonary vasculopathy assessed by intravascular ultrasound in patients with severe chronic respiratory failure evaluated for lung transplantation: comparison to pulmonary arterial hypertension


Purpose: The aim of the study is to assess pulmonary vasculopathy (wall fibrosis, pulmonary arterial pulsatility and elastic modulus) in patients with chronic respiratory failure evaluated for lung transplantation, by means of intravascular ultrasound (IVUS) in medium sized pulmonary arteries, and to compare it to pulmonary arterial hypertension (PAH) and healthy controls.

Methods: We studied 37 patients, 9 Group 1 (pre-lung transplantation, COPD, pulmonary fibrosis, NYHA 3-4), 18 Group 2 (PAH, NYHA 2-3) and 10 in Group 3 (healthy controls). Group 1: 2 females, 59±8 years. Group 2: 14 females, 56±14 years and Group 3: 6 females, 51±5 years. All patients were submitted to left and right heart catheterization, and IVUS in medium sized elastic PA (2-3 mm diameter) of the inferior lobes.
Studied variables were: Mean pulmonary artery pressure (PAPm), pulmonary wedge pressure, aortic pressure, cardiac output (CO), pulmonary vascular resistance (PVR), IVUS pulsatiliy (IVUSp) and elastic modulus (EM). Local arterial pulstaility was estimated by IVUS: (systolic/diastolic lumen area) × 100. PA stiffness was assessed by the EM (pulse pressure/IVUSp).

Results: Age was similar in the 3 groups. As expected, in group 3 all variables were significantly different from the other 2 groups. PAPm was higher in group 3 than in group 1. Despite this finding no significant differences were found in IVUSp and EM between Groups 1 and 2, although EM tended to be higher in Group 1.

Conclusions: Patients with severe chronic respiratory failure, even in the absence of severe pulmonary hypertension, suffered from a severe pulmonary arteriole vasculopathy with a high degree of structural and functional PA wall remodelling similar to that of PAH patients.

PULMONARY HYPERTENSION: MECHANISMS

Egr-1 expression is specific for neointimal development in both human and experimental PAH

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Objectives: In Pulmonary Arterial Hypertension (PAH) due to congenital heart disease, increased pulmonary blood flow is an essential trigger for neointimal formation. Using micro-array analysis, we recently identified that transcription factor Egr-1 is upregulated in experimental flow-associated end-stage PAH. Its role in neointimal development in PAH is unknown.

Here, we aimed to assess in both human and rats alveolar expression of Egr-1 in neointimal (flow-associated) PAH compared to non-neointimal Pulmonary Hypertension (PH).

Methods: In rats, flow-associated PAH was created by combining monocrotaline with an aortocaval shunt (MCT+Flow); and compared with a non-neointimal PH model (MCT-only). Animals were sacrificed 1 day before increased flow and at multiple time points after flow addition (1 day, 1 week, 4 weeks). Egr-1 expression was assessed using laser-dissection, qRT-PCR and immunohistochemistry.

Results: In rats, MCT+Flow rats developed, within 4-5 weeks, severe PAH (P<0.001 as compared to MCT-only) (p<0.001); and compared with normal non-neointimal (p<0.05) with a high degree of structural and functional PA wall remodelling.

Conclusions: Patients with severe chronic respiratory failure, even in the absence of severe pulmonary hypertension, suffered from a severe pulmonary arteriole vasculopathy with a high degree of structural and functional PA wall remodelling similar to that of PAH patients.

A female model of severe neointimal pulmonary hypertension: evidence for increased susceptibility in a female rat following pneumonectomy and monocrotaline

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Pulmonary arterial hypertension (PAH) is an enigmatic, fatal disease with few treatment options. Decades of important animal studies in pulmonary hypertension have utilized male rats, exposed either to chronic hypoxia or monocrotaline (MCT), to define disease mechanisms and test novel treatment strategies. However, females represent 70-80% of the afflicted human population, and a female rat model with the key features of human disease would be useful for testing hypotheses about sex and the susceptibility to PAH. Previous studies exposed female rats to MCT did not demonstrate significant pulmonary hypertension.

We sought to establish a female rat model of PAH with neointimal formation and right ventricular (RV) failure. 7 days after left pneumonectomy, we administered 40-60 mg/kg of MCT to young rats (male or female); early signs of RV dysfunction were present by day 10 after MCT using a Visusonics 2100 echo. In some animals, echo measures were made at day 21 after MCT before the rats were sacrificed for lung micro-CT and histology; other rats were allowed to progress to death. At 60 mg/kg, female rats experienced mortality at least as severe as males, perhaps worse. In contrast to previous findings, micro-CT illustrated more severe vascular pruning in female rats receiving 40 mg/kg MCT as compared to male rats receiving 50 mg/kg suggesting that female rats in this model are more sensitive to MCT. Male and female rats had severe RV dilation and loss of fractional shortening at day 21 after MCT. In a separate group, RV gene expression profiling in rats (n=4 each) sacrificed at day 10 illustrated greater magnitude RNA difference for females as compared to males in functional clusters controlling cellular hypertrophy, sarcomere contraction, cell-cell adhesion, cytokine regulation, and calcium signaling. There was no apparent renal or liver disease in males or females as assayed by urine, blood chemistry, and tissue histology on days 7, 14, and 21 after MCT. We will also present exciting qualitative data from the micro CT which details length, radius, and branching of the individual vessels in the micro CT images.

Young female rats treated with relatively low dose MCT following left pneumonectomy develop severe, neointimal pulmonary vasculopathy with vascular pruning and RV failure. This model offers a unique opportunity to explore hormonal or sex chromosomal influences on the susceptibility to PAH. It also affords the opportunity to examine sex-specific differences in the response to an experimental PH therapy and the potential to analyze sex-specific RV adaptation to increased afterload.

Increased pulmonary blood flow causes perivascular macrophage infiltration in experimental PAH

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Background: In Pulmonary Arterial Hypertension (PAH) due to congenital heart disease, increased pulmonary blood flow is an essential trigger for neointimal formation. Inflammatory processes have been suggested to play a role in the development of these lesions.

Objectives: Here, we aimed to investigate the role inflammation, specifically macrophage infiltration, during neointimal development due to increased blood flow in experimental PAH.

Methods: Flow-associated PAH (with neointimal formation) was created in Sprague-Dawley rats by combining monocrotaline (MCT) with an aortocaval shunt (MCT+Flow) and Rats that received monocrotaline MCT-Only (non-flow, non-neointimal Pulmonary Hypertension) and sham operated rats (Con) served as control. After invasive hemodynamic measurements, animals were sacrificed 1 day before the addition of 1 day, 1 week, 4-5 weeks after flow addition for biomolecular analysis.

Results: In rats, MCT+Flow rats developed severe PAH (P<0.001 as compared to MCT-only) (p<0.001) and compared with normal non-neointimal (p<0.05) with a high degree of structural and functional PA wall remodelling.

Conclusions: We show that in both experimental human and rat, but not in non-neointimal PH, Egr-1 is upregulated and associated with neointimal development. This suggests that Egr-1 is an important regulator in the development of pulmonary neointimal lesions in PAH.

Nitrated fatty acids attenuate right ventricular dysfunction in hypoxia-induced pulmonary hypertension in mice

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Background: The pathophysiological hallmarks of pulmonary arterial hypertension (PAH) are centered around vasoconstriction, vascular hypertrophy and fibrosis. So far, the molecular mechanisms underlying consecutive righthear failure re-
main only incompletely understood. Besides the increase in afterload, inflammation and oxidative stress have been identified as important cofounders for induction of right heart dilatation and failure. Nitrated fatty acids (NO2-FA) represent endogenously generated biomolecules, which convey potent anti-inflammatory and anti-oxidative effects. We have shown recently that these molecules are strongly cardioprotective. Whether NO2-FA modulate the development of right heart failure in PAH however remains unknown.

Methods and Results: Wild-type C57BL6J mice were housed under hypoxic conditions (10% oxygen concentration) and treated for 4 weeks with vehicle or nitro-eic acid (OA-NO2, 6 mg/kg bodyweight, n=8) via subcutaneous minipumps. Animals treated with OA-NO2 displayed a reduced right ventricular pressure as assessed by in vivo-right heart catheterization (RVP= 48.67±2.05 vs. 54.0±1.30 mmHg, p=0.01) and relative right ventricular hypertrophy (RVLV weight= 0.25±0.01 vs. 0.37±0.02 sec, p=0.01) as compared to vehicle-treated animals. This translated in significantly reduced right heart failure as determined by BNP (p<0.05). Leukocyte infiltration as well as oxidative stress superoxide bioavailability in the right ventricle were significantly reduced following OA-NO2 treatment. In addition, picrocruorin red staining revealed attenuated ventricular fibrosis in response to OA-NO2 (1.22±0.01 vs. 54.0±0.33, p<0.05).

Conclusions: The current findings not only underscore the significance of inflammation and oxidative stress in the pathophysiology of right ventricular dysfunction in pulmonary hypertension, but reveal that nitrated fatty acids may provide a novel therapeutic option in pulmonary arterial hypertension.

Right ventricular hypertrophy and failure abolish cardioprotection by ischemic preconditioning

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Purpose: To investigate whether hypertrophy and failure of the right ventricle changes the response to ischemia and ischemic preconditioning.

Materials and Methods: Male Wistar rats were subjected to moderate pulmonary trunk banding (mPTB), severe PTB (sPTB) or SHAM operation. The degree of right ventricular hypertrophy and failure (RHF) were evaluated with measurement of the infarct size/area-at-risk (IS/AAR) of global ischemia) or no preceding ischemia (CON) followed by 40 minutes of reoxygenation (R/O).

Results: IPC did not improve IS/AAR or hemodynamic recovery (fig.1). mPTB hearts measured by a decrease in IS/AAR and improved hemodynamic recovery of RV contractile function. In sPTB hearts with hypertrophy and failure RV caused an increase in infarct size in hearts from mPTB and sPTB animals versus CON. Hypertrophy of the ventricular myocardium of the rat.

Conclusions: The untargeted GWAS approach provides an opportunity to identify novel biologic pathways related to platelet activation and to direct future studies of candidate genes that hold the most promise for relevance to platelet activation and aggregation.

Impact of clinical and genetic factors on acenocoumarol dose requirements in Polish patients - dose calculation algorithm

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Purpose: Widespread use of warfarin in Western Europe allowed extensive studies of warfarin dose determining factors. We present the first large Eastern European study looking at another oral anticoagulant from the vitamin K antagonist group - acenocoumarol (AC). Our aim was to establish the prevalence of CYP2C9 and VKORC1 polymorphisms in Polish population and factors determining dose requirements of AC.

Methods: We included 321 patients attending our outpatient cardiology clinic: 207 receiving long-term AC for atrial fibrillation (65.7%) and artificial valve (34.3%), aged 36-89 (mean 71), 54.5% women, and 114 control patients matched by demographic characteristics not receiving AC.

Results: Prevalence of CYP2C9 polymorphisms is shown in the table. Dose requirements in patients carrying CYP*2 and *3 polymorphic alleles were significantly lower compared to wild-type homozygotes CYP*1/*1, 2.3±0.7 mg/day and 3.5±1.2 mg/day respectively (p<0.001). Additional determinants identified were age (negative correlation) and body mass (p<0.004). Genetic and clinical factors explained 48% of the variance of dose. Using multivariate regression analysis we created an algorithm for calculation of dose of AC (mg/day): 3.298 +
1.477 (VKORC1 G/G) + 0.476 (VKORC1 G/A) + 0.451 (CYP2C9 *1/*1) – 0.043 × age (years) + 0.0169 × body mass (kg). The algorithm was tested on a validation group of 33 patients. The accuracy of dose calculation was 66.6%. The algorithm will be evaluated on a larger group of patients.

Conclusions: Prevalence of VKORC1 and CYP2C9 polymorphisms in Polish population is similar to that of other Caucasians. Genotype, age and body mass are independent determinants of dose requirements for Acenocoumarol.

P4916 Low-frequency intermediate penetrance variants in the ROCK1 gene predispose to congenital heart disease

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Background: Epidemiological studies indicate a substantial excess familial recurrence of non-syndromic Tetralogy of Fallot (TOF), implicating genetic factors that remain largely unknown. The Rh induced kinase 1 gene (ROCK1) is a key component of the planar cell polarity signaling pathway, which plays an important role in normal cardiac development. The aim of this study was to investigate the role of genetic variation in ROCK1 on the risk of TOF.

Methods: ROCK1 was sequenced in a discovery cohort of 93 non-syndromic TOF probands to identify rare variants. TagSNPs were selected to capture common variation in ROCK1. Novel variants and TagSNPs were genotyped in 458 TOF cases and 1920 healthy controls.

Results: A novel rare SNP (c.807C>T) was associated with TOF risk (OR 4.29 [95% CI 1.91-9.60]; p = 0.004). The minor allele frequency of c.807C>T in the controls was 0.003, and the variant accounted for 2% of the population attributable risk (PAR) of TOF. There was also significant association with TOF for an uncommon SNP in ROCK1, rs898979 (OR 1.76 [95% CI 1.15-2.70]; p = 1.5x10^{-5}) and 3146G>A at 0.034, and the variant accounted for 11% of the PAR of TOF. These association signals were independent of each other.

Conclusions: We conclude that low frequency intermediate penetrance (LFP) variants in the ROCK1 gene predispose to the risk of TOF.

P4917 Influence of genetic polymorphisms of alpha-adrenergic receptors, endothelial nitric oxide synthase and bradykinin receptor B2 on treadmill exercise test responses

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Purpose: Treadmill exercise testing responses have been associated with cardiovascular prognosis in individuals without overt heart disease. Neurohumoral and nitric oxide responses may influence cardiovascular performance during exercise. The aim of this study was to evaluate associations between genetic polymorphisms of alpha-adrenergic receptors (ADRA1A, ADRA2A and ADRA2B), endothelial nitric oxide synthase (eNOS) and bradykinin receptor B2 (BKGR) with treadmill exercise test responses in individuals without overt heart disease.

Method: We enrolled 766 (417 women and 349 men) asymptomatic subjects. We selected the following variables during a maximal symptom-limited treadmill exercise test: exercise capacity, chronotropic reserve, maximum heart-rate achieved, heart-rate recovery, exercise systolic blood pressure, exercise diastolic blood pressure and systolic blood pressure recovery. Genotypes for the ADRA1A Arg347Cys (rs1048101), ADRA2A C1780T (rs553668), ADRA2B Del 301-303 (rs2886503), eNOS T786C (rs207044), eNOS Glu298Asp (rs1799893) and BKGR (rs5810761) polymorphisms were assessed by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis. Laboratory and demographic data were collected for all participants. Statistical analysis was performed with multiple regression models for women and men.

Results: The genotype frequencies were under Hardy-Weinberg equilibrium, except for the ADRA2B Del301-303 polymorphism. In the multivarilated analysis the ADRA2A C1780T polymorphism was significantly associated with exercise diastolic blood pressure in both sexes. Exercise diastolic blood pressure was higher in individuals with TT genotype than in C allele carriers (P = 0.003 for women; P = 0.007 for men) (Table 1). The other polymorphisms did not influence significantly the treadmill exercise test responses.

Table 1: Genetic associations of exercise diastolic blood pressure in men and women

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<tr>
<td>Women</td>
<td>ADRA1A C1780T</td>
<td>(TT) 9.123</td>
<td>(T) 10.75</td>
<td>(C) 8.69</td>
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<td></td>
<td>ADRA2A C1780T</td>
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<td>Men</td>
<td>ADRA1A C1780T</td>
<td>(TT) 9.123</td>
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<td>ADRA2A C1780T</td>
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Conclusion: The ADRA2A C1780T influenced the exercise diastolic blood pressure in both sexes. This finding suggests that this polymorphism may be a marker of blood pressure response during exercise.

P4918 Association between a genetic variant near adrenomedullin gene with left ventricular mass index

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Purpose: Adrenomedullin (ADM), is a multifunction peptide that has been reported to prevent myocyte and fibroblast hypertrophy. Its plasma concentrations are correlated to cardiovascular risk factors and hemodynamic compromise. We assessed the relationship between genome-wide association study-identified variants associated with MRproADM levels and left ventricular mass index (LVMi).

Methods: LVMi was measured using ASE recommendations on 4 axis view from the apical window 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 (Affymetrix SNP array 6.0) were analyzed to identify correlates of LVMi. The methods were corrected for multiple testing.

Results: Two variants, rs2957692 (p = 1.54 × 10^{-13}) and rs2957717 (p = 2.24 × 10^{-8}), located 39Kb and 53Kb upstream the ADM gene were previously identified as independent correlates of MRproADM plasma levels. The minor allele of rs2957717 (T) was associated with higher levels of LVMi in men as well as women (4.55 mm) in the general population. The effect on left ventricular mass index was independent of MRproADM plasma levels.

Conclusion: These findings support the hypothesis of a possible causal relationship between the variant and ventricular mass warranting further investigation.

P4919 Systematic testing of literature reported genetic variation associated with restenosis after percutaneous coronary intervention: results of the genetic determinants of restenosis study

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Purpose: Despite all medical advances, coronary restenosis after percutaneous coronary intervention still is a significant problem. Unraveling the mechanisms leading to restenosis development remains challenging. Although many studies have identified genetic markers associated with restenosis, consistent replication of the reported markers is scarce, mainly due to small sample sizes, heterogeneity of the phenotype and lack of proper replication cohorts. The aim of the current study was to analyze the joined effect of previously in literature reported candidate genes for restenosis using the gene-set analysis of GENetic DEterminants of Restenosis (GENDER) database.

Methods: Candidate genes were selected using a search on MEDLINE including the terms ‘genetic polymorphism’ and ‘coronary restenosis’. The final set included 36 genes. All single nucleotide polymorphisms in the genomic region of each gene, including a 10Kb window, were analyzed using set-based analysis in PLINK in the GENDER databank, containing genotypic data of 2,575,000 SNPs of 295 patients who developed restenosis (cases) and 571 matched controls.

Results: The set including all candidate genes was significantly associated with

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restenosis, p=0.041. Subsequent analyses of the individual genes demonstrated that the observed association of the complete set was determined by 7 of the 36 genes. Removing these 7 genes from the complete set and subsequent analysis of the subset of the other 29 genes did not demonstrate a remaining joined effect, p=1.0 (subset1).

Conclusion: Despite the overt inconsistencies of individual candidate gene studies, this study demonstrates that the joint effect of all these genes together, indeed is associated with clinical restenosis.

Synergistic effects of genetic variants of the apolipoprotein A-V gene and the butyrophilin, subfamily 2, member A1 gene on dyslipidemia in East Asian populations

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Purpose: The genes underlie genetic susceptibility to dyslipidemia in East Asian populations remain to be identified definitively. We previously showed that the rs1131113C→G polymorphism (rs662799) of the apolipoprotein A-V gene (APOA5) and the G→T polymorphism (rs9628946) of the butyrophilin, subfamily 2, member A1 gene (BTN2A1) were significantly associated with increased serum concentration of triglycerides (TG) and a decreased serum concentration of HDL–cholesterol in Japanese individuals. The purpose of our study was to examine whether these polymorphisms synergistically affect serum lipid profiles and the prevalence of dyslipidemia in East Asian populations.

Methods:

1. A cohort of 4431 Japanese or Korean individuals
2. Genotype distribution of rs11333040 in coronary arteries was the follow: 4 had no plaques was in between (p=0.00013).

Results: Genotype distribution of rs11333040 in atherosclerotic plaques was the follows: 5 had no risk allele (CC), 10 had one (CT) and 15 had two (TT). The expression of CDKN2A/B2 genes was significantly lower in the TT plaques than in the plaques without the risk allele (CC), whereas their expression in the CT plaques was in between (p=0.0013). Genotype distribution of rs11333040 in coronary arteries was the follow: 4 had no risk allele (CC), 2 had one (CT) and 14 had two (TT). Genotype analysis on VSMC was concordant, showing that CDKN2A/2B genes are both expressed according to the rs11333040 genotype (p=0.001 for both genes). Immunohistochemistry on coronary artery section localized the CDKN2A/B2 protein expression with the VSMC population.

Conclusion: Our findings show a link between rs9213 genotype and CDKN2A/B2 gene expression in disease human coronary arteries, which support the hypothesis that sequence variations in the CAD risk interval on 9p21 may act as distant regulatory sequences and be required for the correct vascular expression of CDKN2A/B2.

Genotype expression profiling in patients with myocardial infarction at young age

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Myocardial infarction (MI) is one of the main causes of mortality. It is usually a disease of the middle-aged and elderly population and is a rare phenomenon. Explanations about the molecular mechanisms of the genetic predisposition of MI at young age remain elusive. Transcriptome analysis by large-scale gene expression profiling is a promising tool to explore disease-related genes and biological pathways. The aim of this study was to survey differentially expressed genes in young MI individuals, to functionally characterize these genes by pathway analysis and to investigate the relation to the underlying pathophysiology. Using Affymetrix GeneChip Human Exon ST1.0 gene expression data we performed linear regression analysis to identify differentially expressed genes between 235 young MI individuals and 419 population-based controls. After adjustment for classical cardiovascular risk factors age, gender, hypertension, smoking, BMI, diabetes, LDL/HDL ratio we identified 217 genes being differentially expressed in the young MI group. Most significantly de-regulated was GPR15, an orphan G-protein-coupled receptor (p = 5.96*10-17, up-regulation) with a fold change of 1.78. Pathway analysis revealed key signaling processes (G-protein signaling, including P2RY2, DSP1, GPR107, GPR133, PKR2GAK, PK2CD, ADCY2, ADCY7, GNAL) and lipid metabolism (including ABCA1, ABCG1, FDF1, GALNT2, LIGP) to be affected in MI patients at young age. Our results provide novel insights in the genetic basis and pathways involved in myocardial infarction and expand our current understanding of the pathophysiology of early onset CAD.
Results: After conditional analysis, among 34 variants exceeding significance threshold and located all near the adenomediullin gene, GWAS identified 2 variants, rs2957692 (p=1.5x10^-13) and rs2957717 (p=4.2x10^-8) independently associated with all-cause mortality, encoding GNAS. Together the 2 SNPs of the epigenetic lncRNA PHANR accounted for 1.4% [0.7-2.2] of the variability before and 4.5% [3.2-5.8] after adjusting for non-genetic correlates.

Conclusions: PHANR expression levels increase in association with endothelial activation, astrocytic growth, vascular risk factors, hemodynamic status and inflammatory processes. Although PHANR expression levels' dominance is related to non-genetic factors, genetic variants near the ADAM gene also affect such levels.

P4924 Genetic polymorphisms of CYP2C19 and effect of CYP2C19*2 allele on clopidogrel P2Y12 inhibition in healthy Malaysian volunteers Y.N. Sanii, S.C. Lim,1 L.H. Lim,1 N.E.Y. Edwin,1 N. Abdul Karim1, T.H. Goht,1 C.V. Seneeratnam,1 School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia;2 Loh Guan Lye Specialist Centre, Penang, Malaysia;3 Johns Hopkins University, Towson, Maryland, United States of America.

Purpose: CYP2C19*2 allele may be associated with reduced antипlattlet effect of clopidogrel and potentially worsened clinical outcomes. We assessed the prevalence of CYP2C19 polymorphisms, namely CYP2C19*2 and CYP2C19*3 alleles in healthy Malaysian volunteers and we linked the CYP2C19*2 allele with platelet reactivity after administration of 300-mg oral dose of clopidogrel.

Methods: 90 volunteers (34 Malays, 49 Chinese, 7 Indians) were genotyped for CYP2C19*2 and CYP2C19*3 alleles in healthy Malaysian volunteers and we linked the CYP2C19*2 allele with platelet reactivity after administration of 300-mg oral dose of clopidogrel.

Results: The study group included 237 subjects, members of two-generation families, recruited from the general population. At baseline and after on average 6.8±1.4 years of follow-up, we used the same methods for phenotyping. To observe information about ambulatory BP, SpaceLabs 90207 oscillometric monitors were programmed to measure BP each 15 min time point (8:00 – 22:00) and 30 min night time (22:00-8:00). Venous blood samples were drawn for measurement of serum creatinin and for further genotyping. Estimated glomerular filtration rate (eGFR) was calculated using MDRD formula. The analyses of genotype-phenotype relations were adjusted for covariables and relatedness of study participants.

Conclusions: The study group included 108 men and 129 women. Mean age at base-line was 50.6 years in 113 parents and 24.1 years in 124 offspring. The genotype frequencies were: AA – 16.1%, GA – 48.5%, GG – 34.6%, and did not deviate from Hardy-Weinberg equilibrium (P=0.98). In 2 volunteers and 66 patients, CYP2C19*2 allele was detected in 2 volunteers and 36 patients respectively. Among carriers of CYP2C19*2 allele, CYP2C19*2/2 carriers had significantly higher mean PRU than CYP2C19*1/2 and CYP2C19*1/1 (213.3±81.4 vs. 147.4±87.2 PRU, P<0.001). Of 15 volunteers, 7 of 15 (46.7%) were found to be non-responders with PRU>330 (2 were CYP2C19*1/1, 11 were CYP2C19*1/2 and 7 were CYP2C19*2/2).

Conclusions: CYP2C19*2 allele is commonly found in Malaysian population and is associated with marked decrease in platelet responsiveness to clopidogrel. A high proportion of Chinese volunteers appeared to carry this allele. The results of the present study show that genotyping or phenotyping may be useful in clopidogrel therapy.

P4925 Matrix metalloproteinase-1 gene polymorphism in patients with proteinuria as effective factor in myocardial infarction A.S. Tabatabaei Panah1, R. Akbarzadeh Najari2, SM.H. Ghadernia2.

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Purpose: Current evidence indicate that extracellular matrix (ECM) remodeling is involved in progression of acute myocardial infarction (AMI) and matrix development (MMP) has a role in early atherosclerosis, plaque rupture and myocardial infarction (MI). The necessity of inhibition of ECM remodeling and subsequent injuries in patients with AMI suggests that MMP might be involved in this task. Therefore, we measured the activities of MMP-1, -2, -3, and -9 which play an important role in AMI.

Methods: Plasma and peripheral blood mononuclear cells (PBMCs) of 50 patients with AMI were isolated from peripheral blood after the onset of AMI within 24 hours, comparing with 50 control subjects. The active form of MMPs was measured by enzyme-linked immunosorbent assay (ELISA); MMP proteins presence and expression by immunoblotting and zymography analysis; and mRNA expression by qRT-PCR. MMP-1, -2, -3, and -9 of 2 patients carried the polymorphism and the MMP-1 mRNA expression was found.

Conclusions: To our knowledge, it is the first monitoring of MMP gene and protein expression and also circulating active MMPs in Iranian patients with AMI and normal subjects. Up-regulation of MMPs activity is common in the failing myocardium and missing up-regulation of transcription indicates that protein levels of MMPs were regulated at the post translational level.
Influence of rs5065 atrial natriuretic peptide gene variant on Coronary Artery Disease

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Either modified ANP plasma levels or peptide structural alterations have been involved in development of cardiovascular events. To investigate the impact of rs5065 atrial natriuretic peptide (ANP) gene variant on coronary artery disease (CAD) and its outcomes and to gain potential mechanistic insights on the association with CAD.

Methods: 1000 patients undergoing coronary angiography for suspected CAD [432 stable angina (SA), 572 acute coronary syndrome (ACS)] were genotyped for rs5065 ANP gene variant. Data in SA and ACS groups were replicated in an independent population of 482 SA patients (rSA) and of 675 ACS patients (rACS), respectively. Clinical follow-up was available for both SA and rSA patients. Plasma NT-proANP, myeloperoxidase (MPO), lipoprotein-associated phospholipase A2 (Lp-PLA2), oxidized low density lipoprotein (oxLDL) were assessed in a subgroup of rSA patients.

Results: rs5065 minor allele (MA) was an independent predictor of ACS (OR=1.90; 95% CI: 1.42-2.58; p=0.001). At follow-up, rs5065 MA was independently associated with significantly higher rate of major adverse cardiovascular events (MACE) in SA group, p<0.001. Data were replicated in rSA group at follow-up (p=0.03). Cox proportional hazard analysis tested by 4 models confirmed association with CAD.

Conclusions: The MA of rs5065 ANP gene variant associates with increased susceptibility to ACS and has unfavorable prognostic value in CAD.

Coronary artery disease risk polymorphisms in Latvian patients and population controls

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Purpose: Genome-wide association studies (GWAS) have discovered multiple single nucleotide polymorphisms (SNP) associated with coronary artery disease (CAD). These results are generally based on populations of Northern and Western European ancestry and importance and informativeness of the results may be limited for researchers studying patients of other ethnic backgrounds. Our aim was to validate findings of European CAD GWAS in Latvian population which is of Eastern European ancestry. We focused on six loci: 1p13.3, 2q28.3, 4q25.1, 9p21, 10q11.21 and 15q25.33 characterized by SNPs rs998960, rs2943634, rs692269, rs1333049, rs501120 and r7122812 respectively.

Methods: All six SNPs were genotyped in a case-control study consisting of 1100 clinically diagnosed CAD cases and 452 population controls with no history of cardiovascular manifestations. Written informed consent was obtained from all participants of this study. Genomic DNA was extracted from white blood cells by chloroform-preserved method and genotyped using fluorescently labeled hydrolysis probes with the use of Taqman system.

Results: Two of the investigated polymorphisms rs2943634 and rs1333049 were significantly associated with CAD. Allele C of the rs2943634 had frequency 0.634 in cases and 0.573 in controls (CAD OR=1.29; 95% CI: 1.10-1.51; P=0.002) while allele C of the rs1333049 had frequency 0.522 and 0.437 in cases and controls respectively (CAD OR=1.40; 95% CI: 1.20-1.64; P=2.12e-5). None of other four SNPs reached significance level of P=0.05 even before correction of results.

Conclusion: Our data suggest that rs1333049 is strongly associated with CAD risk in Latvian population and that rs2943634 also increases risk of CAD.

Secretoneurin gene therapy reverses the impairment of hindlimb post-ischemic recovery in Apo E-/- mice

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Introduction: Hypercholesterolemia (HC) is a major risk factor for peripheral arterial disease (PAD) and has been shown to impair the angiogenic response in the unilateral mouse hind limb ischemia (HLI) model. The impairment of up-regulation of angiogenic factors seems to be one of the underlying mechanisms for reduced vessel formation. Since previous studies revealed an angiogenic potential of secretoneurin (SN) we tested the hypothesis if SN-gene therapy might also improve neovascularization in a mouse model associated with impaired vascular response.

Results: To simulate HC in vitro, endothelial cells were treated with 50 µg/ml oxidized low-density-lipoprotein (oxLDL). Under these experimental conditions we found a significant induced proliferation was impaired. Secretoneurin gene therapy improved oxLDL induced proliferation SN vs. ctr: no oxLDL: 1.59±0.032; n=5; P<0.001; with oxLDL: SN 1.36±0.024; n=5; P<0.01. Similarly, in the matrigel assay the effect of SN in promoting capillary tube formation was reduced but couldn't be abolished by addition of
oxLDL (rel. tube formation SN vs. ctr.: no oxLDL 1.71±0.02; n=5; P<0.01; with oxLDL 1.44±0.03; n=5; P<0.05). Moreover, the SN-induced activation of signal transduction pathways like ERK 1/2 wasn’t abrogated by addition of oxLDL. SN induced effects were similar to vascular endothelial growth factor.

To evaluate the therapeutic effect of SN in vivo we performed the HLI model in Apo E−/− mice set on western diet for 12 weeks. HLI was induced by ligation of the common carotid artery and 50 μg of SN plasmid (p-SN/control plasmid (p-ctr)) was injected. The groups showed no significant difference regarding body weight and levels of cholesterol. Blood flow recovery (BFR) was assessed using a laser Doppler perfusion-imaging (LDPI) machine. Interestingly, p-SN injection increased capillary (capillaries/high power field 200x: p-SN 35.64±4.14 vs. p-ctr 20.84±7.86; n=10; P<0.001) and arteriolar (arterioles/high power field 200x: p-SN 5.69±0.52 vs. p-ctr 3.16±0.24; n=10; P<0.001) density in ischemic muscles and ameliorated BFR (p-LDPI ratio ischemic/non ischemic limb after 4 weeks: p-SN 0.78±0.04 vs. p-ctr 0.64±0.02; n=10; P<0.019). Moreover, SN-treatment resulted in a significant necrosis reduction (necrosis score: p-SN 1.55±0.2 vs. p-ctr 2.5±0.3; n=10; P=0.03).

Conclusion: Our data suggest therapeutic potential of SN under hypercholesterolemic conditions and open up new therapeutic options for the treatment of PAD.

Early AAV9-mediated over-expression of S100A1 ameliorates myocardial hypertrophy in dystrophin-deficient mice

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Mutations of dystrophin leading to a complete loss of the protein cause x-chromosomal Duchenne muscular dystrophy (DMD), frequently associated to severe cardiomyopathy (CM). However, although cardiac complications increase the mortality of these patients, strategies to efficiently treat the CMP are not well established. It has been suggested that the loss of cardiomyocyte Calcium (Ca2+) cycling integrity plays a key role in the development and progression of CMPs, although so far its role in dystrophin-associated CMPs is unclear. In this context, the cardiomyocyte EF-hand Ca2+ sensor protein S100A1 plays a critical role in regulating Ca2+ cycling integrity and has been considered to be a target for gene therapy approaches to treat CMP. We have investigated the efficiency of Adeno-associated virus serotype 9 (AAV9) - mediated cardiac over-expression of S100A1 to prevent the development of CMP in dystrophin-deficient (mdx) mice. Therefore, AAV-9 vectors containing S100A1 cDNA under transcriptional control of a CMV-MLC promoter (AAV9/S100A1) were created. 1012 AAV9/S100A1 vector particles were intra venously injected into 8 week-old mdx mice before the onset of CMP. AAV9 harbouring an enhanced green fluorescent protein reporter (AAV9/EGFP) was used as a control vector. At the age of 1 year histological examinations, echocardiography and PV-loops were performed to assess myocardial morphology and contractility (cardiomyocyte cross-sectional areas (csa), μm2), enddiastolic posterior wall thickness (PWTd; mm), fractional shortening (FS; %) and left ventricular maximum pressure rate of change (dp/dmax; mmHg/sec).

Uninjected and AAV9/EGFP-treated mdx mice showed distinct myocardial hypertrophy and reduced contractility (csa 860±71 and 871±39 μm2; PWTd 1.7±0.1 and 1.53±0.06 mm; FS 49±4% and 51±4% and dp/dmax 5624±230 and 5259±304 mmHg/sec, respectively) compared to age-matched wildtype mice (csa 329±13 μm2; PWTd 1.1±0.1 mm; FS 74±3% and dp/dmax 1235±933 mmHg/sec) (values ± standard error). AAV9/S100A1/1-treated mdx mice showed significantly reduced myocardial hypertrophy (csa 585±33 μm2 and PWTd 1.41±0.07 mm, respectively). PV loops showed improved contractility (dp/dmax 7493±406 mmHg/sec; p<0.05) in AAV9/S100A1/1-treated mdx mice, whereas fractional shortening did not improve significantly (FS 54±2%).

Our data suggest that AAV9-mediated cardiac overexpression of S100A1 attenuates myocardial hypertrophy in mdx mice thereby representing a valuable tool to limit cardiac dysfunction in dystrophin-deficient cardiomyopathy.

Adenovirus-mediated gene transfer of a luciferase reporter gene by a cardiac-specificpromoter through direct injection into the left ventricular wall

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Purpose: Localized administration of a highly efficient gene transfer system in combination with a cardiac-specific promoter may provide a biologically safe strateg- ey in the cure of ischemic cardiac disease. We hypothesized that such expres- sion could be restricted to the heart after local direct injection by packaging an adenovirus carrying the luciferase cDNA driven by the cardiac troponin-I promoter.

Methods: Adenoviral vectors carrying the firefly luciferase gene under the control of the cardiac troponin I (Ad-Tnluc) or CMV promoter (Ad-CMV-luc) packaged into adenovirus serotype 6 were directly injected into the left ventricular wall of SD rats via thoracotomy. Luciferase expression was monitored for 28 days through in vivo bioluminescence imaging system (IVIS, Xenogen) and in vitro luciferase assays. Myocardial infarction was induced immediately before direct injection.

Results: Luciferase expression was evident within 12 hours after Ad-Tnluc or Ad-CMV-luc injection. Adenovirus- mediated increased luciferase expression 100x higher in the CMV promoter group whereas there was difference in luciferase expression between these two groups at 72 H. At Day 28, light output from hearts was 100x higher in the Ad-Tnluc group (Panel A). In addition, myocardial infection induced higher luciferase expression in the Ad-Tnluc group but not the Ad-CMV-luc group. Luciferase assays in multiple organs in vitro confirmed that luciferase expression was higher in the CMV group (Panel B ‘‘p<0.01 vs Tnluc group).

Identification of AAV6 as most efficient vector for transvascular gene transfer into porcine myocardium based on an in vitro model for prediction of the cardiac gene transfer performance

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Background: Adenovirus mediated gene transfer is a widely used method for myocardial gene transfer. The efficiency of different viral vectors is different and depends on the type of the specific promoter used. Adeno-associated virus (AAV) mediated gene transfer into diseased myocardium holds high promises for numerous gene therapy applications. While high transfer efficiencies are achieved in small rodents, gene transfer to the hearts of larger animals appears to be limited. Aim of our work was the devel-
Penetrance study in SCN5A-mutations in brugada syndrome

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Introduction: Brugada syndrome (BS) is an inherited channelopathy associated with mutations in SCN5A gene and up to 7 genes more. The disease is inherited in autosomal dominant manner, although with variable penetrance.

Aim: To evaluate the penetrance of the disease in a unselected population.

Material and Methods: Seventy six non-related patients with BS were studied. Clinical characteristics and family risk profile were recorded. Direct sequencing of the SCN5A gene for identification of mutations and familial genetic study of parents was performed.

Results: Eight patients (10.5%) had point mutations (R27H, E901K, G1743R, V281I, N1443S, E1152X), and 19 additional carriers (10 male and 9 female) could be identified. Index patients with mutations had more frequently spontaneous type I Brugada pattern (87.5% vs 52.9%, p = 0.06) and evidence of familial disease (62.5% vs 23.5%, p = 0.03). Symptoms and risk profile of the proband carriers (146 patients) is shown in figure 1.

The prevalence of spontaneous type I ECG varied according to sex in carriers, with 8 cases among 18 men (44.4%) and no cases among 9 female (p=0.2). However, after the flecainide test, the rate of type I ECG was 66.7% vs 62.5%, p = 0.9. Flecainide test unmasked a higher proportion of females (66.7% vs 25.0%, p = 0.4).

The penetrance of type I ECG in carriers was 29.6%, and rise to 63.2% after drug challenge test. Percentage of carriers who expressed type I ECG varied among different mutations (figure 1). A 36.8% of carreiis who underwent a complete study, had normal ECG despite the drug challenge test.

Conclusion: About one third of the SCN5A mutations’ carriers presented a normal baseline ECG and drug challenge test. Drug challenge test allowed to unmask a higher proportion of female silent carriers.

Age-related penetrance in genetic carriers of hypertrophic cardiomyopathy

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Introduction and Purpose: Hypertrophic cardiomyopathy (HCM) was initially considered to have an early onset in the life. The last advances in genetic area have showed new carriers without clinical diagnosis. The aim is study the age-related penetrance of HCM in patients with different MYBPC3, MYH7 and TNN2 mutations to determine whether the age at diagnosis depends on genetic background.

Methods: We included 195 HCM causal mutations carriers (55% males, age 40±16 years); 64.8% had clinical manifestations of the disease. All patients were diagnosed in inheritance cardiomyopathy consultation, in a reference hospital. All patients were carriers of at least one mutation in MYBPC3 (IVS2-1G->A, II270fsX116, A107fsX116, 26, A126T (11), V696M (4), 21 were carriers of a mutation in MYH7 (T1377M (21), D968N (4), E1349Q (8), E1356Q (4), E1367D (4)), of which 1382Q (4) were carriers of R255H in TNN2. IVS2-1G->A, the most prevalent mutation, was present in 18 unrelated families. We performed time-to-diagnosis analysis according to the affected gene and the most prevalent mutations.

Results: No differences in time to diagnosis were detected between the most prevalent mutations. Median age at diagnosis was 46±2 years for IVS2-1G->A, A44+3 years old (Arg861Val), 44±7 years old (T1377M) and 51±9 years old (A216T); log rank p=0.963 (figure 1). Similarly, there were no differences according to the 3 analyzed genes (log rank p>0.935). Median age at diagnosis for the whole was 47±2 years.

Conclusions: Mutations in MYBPC3 encoding myosin binding protein C could be considered more benign form of HCM than initially was considered. Now, genetic diagnosis reveals that HCM-phenotype can appear later in life, reaching near full penetrance in the elderly.
Association of a matrix metallopeptidase 1 gene polymorphism with long-term outcome of thoracic aortic aneurysm

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Objective: Although genetic variants are thought to contribute to the development of thoracic aortic aneurysm including dissection (TAA), it remains unclear whether gene polymorphisms are associated with the long-term outcome of TAA. The identification of genetic variants related to the long-term outcome of medically treated TAA may lead to a better understanding of the factors relevant to the progression or rupture of TAA, and consequently may better inform the selection of patients as candidates for surgical therapy because of a higher risk of rupture. The purpose of the present study was to identify genetic variants associated with the long-term outcome of medically treated patients with TAA.

Methods: A total of 103 medically treated patients with TAA (age, 63.3±11.9; mean±SD; range, 13 aneurysms and 90 dissections) were retrospectively studied for their outcomes (mean follow-up period, 24 months). An unfavorable outcome was defined as: (1) death from cardiovascular causes or aneurysm rupture, (2) surgical repair, or (3) occurrence of cardiovascular events after initial hospitalization. The genotypes for 95 polymorphisms of 89 candidate genes were determined by a method that combines the polymerase chain reaction and sequence-specific oligonucleotide probes with suspension array technology.

Results: The prevalence of Stanford A, hypertension, prior cardiac surgery, shock, and a maximum aortic diameter were greater in subjects with the unfavorable outcome than those with the favorable outcome of this condition. Evaluation of genotype distribution by the chi-square test and subsequent multiple logistic regression analysis with adjustment for covariates revealed that the –340A>G polymorphism (rs514921) of the matrix metallopeptidase 1 gene (MMP1) was significantly (P = 0.0288) associated with the outcome of TAA, with the minor G allele being related to a favorable outcome. The aneurysm diameter was significantly (P = 0.0167) smaller in the combined group of the AG and GG genotypes for this polymorphism (42.3±14.0 mm) than in subjects with the AA genotype (48.8±11.2 mm). Kaplan-Meier survival curves constructed according to MMP1 genotypes showed a more favorable outcome of TAA (log-rank P = 0.0146) in subjects with the AG or GG genotypes.

Conclusion: The G allele of rs514921 in MMP1 is associated with favorable long-term outcome of TAA. Determination of genotypes for this polymorphism may prove informative for assessment of the long-term outcome of TAA.

The onset of type 2 diabetes protects the heart against ischaemia-reperfusion injury by shutdown of mitochondrial metabolism during early reperfusion

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Purpose: To investigate whether sensitivity towards ischaemia-reperfusion (IR) injury in the type 2 diabetic heart is dependent on the stage of the disease. Inhibition of mitochondrial metabolism during ischaemia and initial reperfusion confers protection against IR-injury. We hypothesized that the acute metabolic alterations present at onset of T2DM entails cardioprotection by metabolic shutdown during IR, and that chronic alterations seen in late T2DM cause increased IR-injury. Methods: Isolated perfused hearts from 6 (prediabetic), 12 (onset of T2DM) and 24( late T2DM) weeks old Zucker diabetic fatty rats (ZDF) and their age-matched heterozygote controls were subjected to 40 min ischaemia/120 min reperfusion. IR-injury was assessed by TTC-staining. Myocardial glucose metabolism was evaluated by glucose tracer kinetics (glucose uptake-, glycolysis- and glucose oxidation rates), myocardial microdialysis (metabolomics), coronary effluent measurements and tissue metabolite measurements.

Results: At onset of T2DM ZDF hearts had a significant decrease in infant size (A) and complete shutdown of glucose oxidation during initial reperfusion (B). Correlation analyses showed that the protection at onset coincided with the emergence of hyperglycaemia (C). At late T2DM ZDF hearts suffered significantly larger IR-injury. Myocardial Metabolomics, effluent measurements and tissue metabolite concentrations supported the role of metabolic shutdown during IR in the presence of cardioprotection at onset of T2DM.

Conclusion: The acute metabolic alterations at onset of T2DM induce protection towards IR-injury due to a shutdown of mitochondrial metabolism during ischaemia and initial reperfusion - alterations that become detrimental in late diabetes. These findings explain previous conflicting results on IR-injury in T2DM.

Obesity and metabolic syndrome aggravates myocardial diastolic dysfunction in obese spontaneously hypertensive rat

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Purpose: The additive effects of obesity and metabolic syndrome on left ventricular (LV) maladaptive remodeling and function in hypertension are not characterized. We compared an obese spontaneously hypertensive rat model (SHR-ob) with lean spontaneously hypertensive rats (SHR-lean) and normotensive controls (Ctr).

Methods: LV-function was investigated by cardiac magnetic resonance imaging and invasive LV-pressure measurements. LV-interstitial fibrosis was quantified by glucose tracer kinetics (glucose uptake-, glycolysis- and glucose oxidation rates), myocardial microdialysis (metabolomics), coronary effluent measurements and tissue metabolite concentrations supported the role of metabolic shutdown during IR in the presence of cardioprotection at onset of T2DM.
in SHR-ob than in SHR-lan when compared to Ctrl (4.3±1.1mmHg and 8.8±0.62mmHg, respectively, p<0.0001 for all). Increased LV-fibrosis, collagen1 and TGFβ gene expression together with increased myocyte diameters and ANG gene expression in SHR-ob were associated with increased GLUT1/α2/2 protein levels in SHR-ob suggestive for an upregulation of the GLUT1/α2/2-JNK and GLUT1/TGFB-axis. Serca2α protein levels were decreased in SHR-lan but not altered in SHR-ob compared to Ctrl, while PLB-phosphorylation was not modified.

**Conclusion:** In addition to hypertension alone, metabolic syndrome and obesity adds to the myocardial phenotype by aggravating diastolic dysfunction. Upregulation of the GLUT1/α2/2-JNK and GLUT1/TGFB-axis may lead to metabolic rearrangements to structural cardiac remodeling in the state of insulin resistance and obesity on the background of hypertension.

### Subclinical hyperthyroidism and cardiovascular mortality


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**Background:** It is still uncertain if subclinical hyperthyroidism and "high-normal" thyroid function is a risk-factor for cardiovascular mortality.

**Objectives:** To examine the risk of cardiovascular mortality in relation to subclinical hyperthyroidism.

**Methods:** Patients consulting their general practitioner from 2000–2009 in Copenhagen, Denmark, who underwent thyroid blood tests, were identified by individual-level linkage of nationwide registries. Patients with a history of thyroid disease or related medication were excluded. Risk of cardiovascular mortality was analyzed using Kaplan-Meier curves and Poisson regression models to estimate Incidence Rate Ratios (IRR).

**Results:** Of 525,100 individuals in the study population (mean age 51.7 years [SD 18.0]; 39.5% males) 504,113 (96.0%) were euthyroid, 1,474 (0.3%) had clinical hyperthyroidism and 8,833 (1.7%) had subclinical hyperthyroidism. The prevalence of MetS in Japanese individuals with the C allele of APOA5 and any genotypes of BTN2A1 revealed that the prevalence of MetS was significantly (P<0.05) higher in Japanese individuals than in those with the T allele of APOA5 and the C allele of BTN2A1.

**Conclusions:** Subclinical hyperthyroidism and "high-normal" thyroid function is a significant risk-factor for cardiovascular mortality.

### Endothelial Microparticles derived under high glucose concentrations increase monocyte adhesion on endothelial cells through upregulation of adhesion proteins in a p38 dependent way

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**Background:** Circulating endothelial microparticles (EMP) are increased in diabetic patients, but their role in the progression of atherosclerosis is unclear. We tested the hypothesis if EMP isolated from glucose treated human coronary endothelial cells (HCAEC) influence adhesion protein expression in target endothelial cells and thereby increase adhesion of monocytes to the endothelium, an important step in the development of atherosclerosis.

**Methods and results:** We created a hyperglycemic condition by treating HCAEC for 72h with 30mM glucose and generated EMP after 24h starvation. These modified EMP were defined as "injured" EMP (IEMP). Confocal microscopy, flow cytometry and electron microscopy were used to characterize size (~1um) and cellular origin of IEMP. The effects of IEMP were compared with EMP generated from untreated HCAEC. EMP, but not EMP, induced upregulation of ICAM-1 and VCAM-1 in target HCAEC demonstrated by Western Blot and real-time RTPCR. Moreover, Western Blot experiments revealed that HCAEC treated with EMP expressed ICAM-1 and VCAM-1 in a time- and dose-dependent way. Following experiments showed increased monocyte adhesion on IEMP-treated HCAEC compared to EMP-treatment and control (47.3% vs. 26.9% vs. 8.4%, p<0.05). We next investigated how EMP activate endothelial cells and found that pro-inflammatory cytokines IL-8, IL-6, TGF-β and MCP-1 were detectable in IEMP. EMP contain higher level of TGF-β (807 ng/ml vs. 1647ng/ml, p<0.05) and IL-8 (115 pg/ml vs. 335 pg/ml, p<0.05) than EMP. As cytokines mentioned above activate p38 into phosphorylated p38 (phospho-p38), expression of p38 activity was analyzed in HCAEC after IEMP stimulation. Time dependent experiments revealed that IEMP induced activation of p38 into phospho-p38 in HCAEC within 30 min. Inhibition of p38 in IEMP abrogated IEMP-dependent induction of adhesion proteins on HCAEC and promotion of monocyte adhesion on target cells.

**Conclusion:** Endothelial Microparticles from glucose treated cells increase monocyte adhesion by altering adhesion protein expression in endothelial cells. Activation of p38 through proinflammatory cytokines containing MP might be a possible pathway.

### Effects of combined genotypes for polymorphisms of the apolipoprotein A-V gene and the butyrophilin, subfamily 2, member A1 gene on metabolic syndrome in East Asian populations


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**Purpose:** Although recent genome-wide association studies have implicated several loci and genes in predisposition to metabolic syndrome (MetS) in Caucasian populations, the genes that confer susceptibility to this condition in Asian populations remain to be identified definitively. We previously showed that the −1137T→C polymorphism (rs662799) of the apolipoprotein A-V gene (APOA5) and the C→T polymorphism (rs692846) of the butyrophilin, subfamily 2, member A1 gene (BTN2A1) were significantly associated with an increased serum concentration of triglycerides, a decreased serum concentration of HDL–cholesterol, and the prevalence of MetS in Japanese individuals. The purpose of this study was to examine whether these polymorphisms synergistically affect the prevalence of MetS in East Asian populations.

**Methods:** The study population comprised 3474 Japanese (2744 subjects with MetS, 730 controls) and 1671 Korean (1294 subjects with MetS, 377 controls) individuals. Subjects with MetS had three or more of the five components of criteria for MetS, whereas control individuals had none of the five components. Bonferroni’s correction was applied for statistical significance of association.

**Results:** Comparison of allele frequencies by the chi-square test revealed that rs662799 of APOA5 was significantly (P=0.025) associated with MetS in Japanese and Korean individuals, whereas rs692846 of BTN2A1 was significantly associated with MetS in Japanese individuals, but not in Korean individuals. Similar analysis of combined genotypes for rs662799 of APOA5 and rs692846 of BTN2A1 revealed that the prevalence of MetS was significantly (P<0.0056) increased in Japanese individuals with the C allele of APOA5 and any genotypes of BTN2A1 compared to those with the TT genotype of APOA5 and the CC genotype of BTN2A1. No relation was detected between combined genotypes and MetS in Korean individuals. Multivariable logistic regression analysis with adjustment for age and sex revealed that rs662799 of APOA5 and rs692846 of BTN2A1 were significantly (P<0.001) associated with MetS in Japanese individuals, but not in Korean individuals. Similar analysis of combined genotypes with adjustment for age and sex revealed that individuals with the C allele of APOA5 and the T allele of BTN2A1 had a 2.87-fold increased risk for MetS compared to those with the TT genotype of APOA5 and the CC genotype of BTN2A1 in Japanese individuals. There was no relation between combined genotypes and MetS in Korean individuals.

**Conclusions:** Genetic variants of APOA5 and BTN2A1 may synergistically affect the prevalence of MetS in Japanese individuals.

### Clinical and prognostic implication of advanced glycation in acute coronary syndromes


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**Aims:** Advanced glycation end products (AGEs) are molecules with important
pathophysiologica impact in cardiovascular pathology. The aim of our study was to evaluate the prognostic value of AGEs and its soluble receptor (sRAGE) in the context of acute coronary syndrome (ACS), both in in-hospital phase and follow-up period.

Methods: AGE and sRAGE were analyzed by fluorescence spectroscopy and competitive ELISA (respectively) in 215 consecutive ACS patients admitted to coronary care unit (62.7 ± 13.0 years, 24.2% female). 47.4% had a diagnosis of ST segment elevation myocardial infarction. The end-points were the development of cardiac events (cardiac deaths, reinfarctions and new-onset heart failure) during in-hospital phase and follow-up period (366 days, interquartile range: 273-519 days).

Results: The mean fluorescent AGEs and sRAGE levels were 57.7 ± 45.1 AU and 1045.4 ± 850.9 pg/mL, respectively. 19 patients presented cardiac events during in-hospital phase and 29 during the follow up. In-hospital cardiac events were significantly associated with higher sRAGE levels (P<0.001), but not long-term cardiac events (P=0.365). Regarding fluorescent AGE the opposite was happen. After multivariate analysis correcting for sex, left ventricular ejection fraction, glucose levels, hemoglobin, GRACE and SYNTAX scores, sRAGE was significantly associated with higher sRAGE levels (P=0.001), but not long-term cardiac events (P=0.05).

Conclusion: We have shown that genetic Crh deficiency is characterized by improved myocardial FA metabolism, most likely through inhibition of the PPAR α pathway.
Stress-induced adipose inflammation promotes a procoagulant state and impairs insulin sensitivity by adipocyte-derived monocyte chemotactic protein-1

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Objective: Stressors contribute to thrombosis and perturbation in glucose metabolism. Since adipose inflammation is also involved in obesity-induced insulin resistance and thrombotic disease, we tested the hypothesis that stress correlates with adipose inflammation.

Research Design and Methods: Male mice were subjected to daily restraint stress for 2 weeks. Inguinal white adipose tissue (WAT) was collected from control and stressed mice to examine CD11b-positive cells and expression of macrophage markers (CD68 and F4/80), proinflammatory cytokines (MCP-1, TNF-α, and IL-6), adiponectin, and coagulation factors (PAI-1 and tissue factor (TF)) using immunohistochemistry and RT-PCR, respectively. Glucose metabolism was assessed by glucose (GTT) and insulin tolerance tests, and expression of IRS-1 and GLUT4 in WAT. To examine the effects of MCP-1 blockade, animals were intraperitoneally transfused with control- or 7ND (dominant negative form of MCP-1)-overexpressing adipose-derived stromal cells (ADSCs). Plasma free fatty acid (FFA), mouse MCP-1, TNF-α and IL-6 levels were measured.

Results: Stress increased accumulation of CD11b-positive cells and expression of CD68 and F4/80 in WAT. The stressed mice also showed a higher frequency of smaller adipocytes in the inguinal adipose tissue compared to the control mice. Chronic stress also induced proinflammatory cytokine expression including MCP-1, TNF-α, and IL-6 and reduced adiponectin. Furthermore, stressed mice showed increase in FFA, MCP-1, TNF-α, and IL-6 concentration. The stress-induced adipose inflammation worsened the prothrombotic state through induction of PAI-1 and TF. Without any changes in GTT, stress worsened insulin sensitivity and decreased IRS-1 and GLUT4 in WAT. 7ND-ADSCs reversed the stress-induced adipose inflammation with reduction of CD11b-positive cells, macrophage markers, and proinflammatory cytokines. Moreover, 7ND-ADSC treatment rescues the stress-induced decline in insulin sensitivity and the prothrombotic state.

Conclusions: Restraint stress over a 2-week period evoked the expression of MCP-1 and other inflammatory adipokines in adipose tissue and a low-grade chronic state of adipose inflammation that exacerbated insulin resistance and induced the procoagulant factors through the expression of MCP-1. MCP-1 inhibition with 7ND-ADSCs reversed adipose inflammation and these pathological consequences. Increased lipolysis and FFA would be also involved in stress-induced adipose inflammation.

Chronic consumption of reheated vegetable oils increases cardiometabolic risk factors


Purpos: To establish whether the chronic ingestion of re-used vegetable oils contributes to the development of cardiovascular risk.

Methods: A canola commercial vegetable oil was used to fry corn flour dough in a proportion of 1g per 10 mL. Cooking temperature was kept between 190 and 250°C. The oil (1 cycle oil, 1CO) was stored up to one week under nitrogen atmosphere (N2) until utilisation. The same heating protocol (1.12, 0.69-1.81) of MetS and CHol(T)/HDL (1.22, 0.84-1.78) and all adipocytokine profiles (adiponectin 1.32, 0.89-1.98; leptin 1.19, 0.96-2.22) of MetS components, CHol(T)/HDL (1.12, 0.84-1.78) of lipid profile, and adiponectin leptin and IL-6, and decreased adiponectin leptin (1.06, 0.71-1.60). However, CYP27A1 rs4674344 was not significantly associated with MetS after adjusting for all the other significant non-MetS components (1.12, 0.69-1.81).

Conclusion: The vitamin D metabolism gene CYP27A1 rs4674344 is significantly associated with both cholesterol and adipokine homeostasis and may contribute to the development of MetS.

The heme oxygenase system reduces pericardial adiposity and improves diabetic cardiopathy in Zucker diabetic fatty rats

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Visceral adiposity adversely affects many vital organs including the heart. We investigated the effects of the heme oxygenase (HO) inducer, hemin on pericardial adiposity and diabetic cardiopathy in Zucker diabetic fatty rats (ZDF), and age-sex-matched Zucker-lean controls.

Hemin administration normalised glyceric levels in ZDF rats and suppressed pericardial adiposity with the reduction of pro-inflammatory oxidative mediators including, NF-κB, c-Jun-N-terminal kinase (cJNK), endothelin (ET-1), TNF-α, interleukin (IL)-6, IL-1β, and β-isoprostane. Similarly, hemin reduced the pro-inflammatory macrophage-M1 phenotype, but increased the M2-phenotype that dampens inflammation in the heart, and improved cardiac hemodynamics by enhancing ejection fraction, stroke volume, cardiac output, while reducing to- tal peripheral resistance. Hemin improved glucose metabolism by potentiating insulin-signalising agents like the insulin-receptor substrate-1 (IRS-1), phosphatidylinositol-3-kinase (PI3K), glucose-transporter-2 (GLUT2) and PKC-ε, and PKB (PKB). The hemin effects were accompanied by increased HO-activity, whereas the HO-blocker, stannous-mesoporphyrin (SnMP) nullified the effects. Interestingly, the hemin effects were less-pronounced in Zucker-lean controls with healthy status, suggesting greater selectivity in ZDF with disease. Since NF-κB activates TNF-α IL-6 and IL-1β, while TNF-α and JNK impair insulin signalling, the high levels of these cytokines in obesity/diabetes would create a vicious circle that together with β-isoprostane and ET-1 exacerbates tissue injury, compromising its function. Therefore, the concomitant reduction of proinflammation cytokines and macrophage infiltration coupled to increased levels of IRS-1, GLUT2, PI3K, PKB and cardiac hemodynamics may account for enhanced glucose metabolism and improved cardiac function in ZDF rats.

We conclude that HO-inducers may be explored against the co-morbidity of impaired insulin-signalising, visceral adiposity and diabetic cardiopathy

Synergistic effect of human immunodeficiency virus and the metabolic syndrome on arterial stiffness

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Purpose: Patients with Human Immunodeficiency Virus (HIV) on combination antiretroviral therapy have a high incidence of the metabolic syndrome (MS) and cardiovascular (CV) disease. To determine the contribution of HIV infection and the MS to vascular disease, we investigated aortic stiffness using aortic pulse wave velocity (PWV) in HIV patients with and without the MS.
Methods: Subjects were divided into: 1) HIV-/MS-ve (n=84), 2) HIV+/MS-ve (n=35), 3) HIV+/MS-ve (n=73) and 4) HIV+/MS-ve (n=17) according to the National Cholesterol Education Program-Adult Treatment Panel III guidelines. Magnetic resonance imaging was used to assess aortic PWV between the ascending aorta at the level of the pulmonary artery (PA) and descending aorta 11 cm below the PA. PWV was calculated as Δx (distance between the 2 imaging levels)/Δt (time delay between the arrival of the pulse wave between these imaging levels). To compare PWV in groups 1-4, one-way ANOVA analysis was performed with post hoc Bonferroni correction.

Results: PWV was 16% higher in HIV+/MS-ve and 14% higher in HIV+/MS-ve compared to HIV-/MS-ve subjects (6.26±1.73 vs 5.38±1.00 m/s, p=0.042 and 6.14±1.91 vs 5.38±1.00, p=0.032 respectively, Figure 1). HIV+/MS-ve subjects had 21% higher PWV compared to HIV+/MS-ve subjects (7.43±1.93 vs 6.14±1.93, p=0.028).

Conclusion: HIV patients without the MS have increased PWV compared to controls. The increase in PWV observed with HIV alone is similar to that seen with the MS alone. The detrimental impact of HIV and the MS on PWV appears to be synergistic. Given the increased prevalence of the MS in HIV patients, therapeutic interventions aimed at controlling this increased risk may reduce HIV-related vascular disease.

The metabolic syndrome significantly affects the association between resting heart rate and all cause as well as cardiovascular mortality

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Purpose: Epidemiological studies suggest that the resting heart rate (RHR) is an independent predictor of cardiovascular and all cause mortality. However, the potential of the RHR to predict cardiovascular events in patients with the metabolic syndrome (MetS) is not known.

Methods: We prospectively investigated the relationship between RHR and cardiovascular events in 766 consecutive patients undergoing coronary angiography for the evaluation of coronary artery disease (CAD) over a follow-up period of 7.1±0.1 years. The MetS was defined according to NCEP-ATPIII criteria.

Results: In the total study population, both all cause and cardiovascular mortality were increased with an increasing RHR (standardised adjusted HRs 1.03 [1.01-1.04], p=0.001 and 1.15 [1.03-1.47], p=0.001, respectively). From our patients, 357 (47.2%) had the MetS and 399 did not have the MetS. Among patients without out the MetS, a higher baseline RHR indicated a significantly higher risk of total mortality (HR=1.14 [1.11 –1.16], p=0.001) after multivariate adjustment. However, the RHR did not significantly affect total mortality (p=0.120) or cardiovascular mortality (p=0.244) in patients with the MetS. Interaction terms RHR*MetS were significant for both total and cardiovascular mortality (p=0.027 and p=0.037, respectively), indicating that the respective risks conferred by a high RHR were significantly higher in patients without the MetS than in patients with MetS.

Conclusions: We conclude that among angiographically characterized coronary patients, the metabolic syndrome status significantly affects the association of the RHR with total and cardiovascular mortality: RHR is a strong predictor of both total and cardiovascular mortality among subjects without the MetS, but not among MetS patients.
Multi compartment body composition analysis in chronic heart failure: air displacement plethysmography, body impedance analysis, dual-X-Ray-absorptiometry, and 3D-white light scan analysis

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Purpose: Chronic Heart Failure (CHF) is characterized by impaired body fluid distribution and associated with obesity and cachexia. Early recognition of changes in body composition is vital for optimal adjusted medical therapy and has high prognostic relevance for patients suffering from CHF. Prospective data on body composition in CHF is sparse. We investigated whether Body composition can be assessed by Air-Displacement Plethysmography (ADP) and Bioelectrical Impedance Analysis (BIA) as by the current gold-standard Dual-X-Ray-Absorptiometry (DXA).

Methods: In this single centre, prospective, observational study we included 52 consecutive symptomatic NYHA I/II, outpatients who presented with HFREF and left ventricular ejection fraction <40%. Mean age was 75±4, mean BMI was 30.0±5.5, mean BMI 34.8±5.6. Lin’s Concordance Correlation Coefficient (CCC) for FM in DXA vs ADP was 0.76 (95% CI 0.64-0.85) and for FM BIA 0.85 (95% CI 0.54-0.94).

Results: 52 CHF patients participated (11 female). In HFREF (n=33) mean age was 66±4, male BMI was 26.7±4.5, mean FM 32.0±9.1 in men (n=19) mean age was 70±4, mean BMI was 30.0±5.5, mean FM was 34.8±5.6. Lin’s Correlation Concordance Coefficient (CCC) for FM in DXA vs ADP was 0.76 (95% CI 0.64-0.85) and for FM BIA 0.85 (95% CI 0.54-0.94).

Conclusion: Body composition can be accurately assessed by ADP and BIA in heart failure with reduced and preserved ejection fraction and healthy volunteers. Further studies reveal body composition differences in HFREF vs HFREF and HFrEF vs healthy volunteers.

Early-induced overweight causes rapid changes in heart genomic expression and long-term cardiovascular, metabolic and oxidative alteration

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Several studies in rodent have shown that postnatal overfeeding (OF) induces permanent moderate increase of body weight in the adult; however, cardiovascular and oxidative repercussions of postnatal OF are less known. Immediately after birth, litters of C57BL/6 mice were either maintained at 10% OF or HFREF with end systolic left atrial dimension ≥ 40mm (parasternal long-axis). For comparison, 20 healthy controls were studied. FM analysis was obtained by DEXA, ADP, and BIA. Intra- and inter-observer variations were assessed by IA and Intraclass Correlation Coefficients were performed with 3D-ful-bodied-surface-white-light scan (3DBS).

Results: 52 CHF patients participated (11 female). In HFREF (n=33) mean age was 66±4, male BMI was 26.7±4.5, mean FM 32.0±9.1 in men (n=19) mean age was 70±4, mean BMI was 30.0±5.5, mean FM was 34.8±5.6. Lin’s Correlation Concordance Coefficient (CCC) for FM in DXA vs ADP was 0.76 (95% CI 0.64-0.85) and for FM BIA 0.85 (95% CI 0.54-0.94).

Conclusion: Body composition can be accurately assessed by ADP and BIA in heart failure with reduced and preserved ejection fraction and healthy volunteers. Further studies reveal body composition differences in HFREF vs HFREF and HFrEF vs healthy volunteers.

These results show that OF induces metabolic, oxidative and functional disturbances but also a higher susceptibility to cardiac functional damage after ischemia reperfused. Complementary data are required to understand the cellular pathways involved in these cardio-metabolic and oxidative modifications.

Longitudinal study of Advanced Glycation End product plasma levels in patients undergoing coronary artery bypass grafting surgery: effects of statin treatment, gender and type-2 diabetes

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The accumulation of advanced glycation end products is thought to be a key factor in the initiation and progression of type 2 diabetes. Despite studies demonstrating a beneficial rate of statins in reducing cardiovascular morbidity/mortality risk with type 2 diabetes, statins may also raise the risk type 2 diabetes in the elderly. We aimed to show an association between plasma AGE levels and statin therapy in 17 diabetic patients (11 male, 6 female) mean age 63.59 years ± 5.79 (SD) and 10 non-diabetic patients (8 male, 2 female) mean age 65.60 years ± 6.39 (SD) all in sinus rhythm undergoing coronary artery bypass grafting (CABG) surgery with no bypass grafting (SBP).

Our longitudinal model (pre- and post- CABG) was adjusted for cross – clamp time (non-significant) and for differences in diabetes status, gender and treatment with statin. Blood plasma was taken before aortic occlusion and after reperfusion. Plasma AGE (μg/mL) was assayed by enzyme-linked immunosorbent assay (ELISA).

AGE plasma levels were higher in non diabetic compared to diabetic patients pre- (64.1±26.2 vs 46.7±21.1 μg/mL, p < 0.05) and post- (33.1±12.6 vs 14.7±5.1 μg/mL, p < 0.05) CABG. Taking into account gender differences, non diabetic females vs males had increased AGE plasma levels pre- (108±70.8 vs 39.5±12.4 μg/mL, p<0.05) and post- (57.5±39.8 vs 21.9±3.9 μg/mL, p<0.05) whereas, diabetic males had higher AGE plasma levels pre- (54.6±27.4 vs 22.4±21.6) and post- (16.6±6.5 vs 10.1±4.3 μg/mL, p<0.05).

CABG induced a drop in AGE plasma levels independent of diabetes or gender. Non diabetic and diabetic pts on statin therapy vs no therapy had higher AGE plasma levels pre- and post- CABG. Female diabetics experienced a significant drop in plasma AGE concentrations after CABG while significant drop happens after CABG in female patients non treated with statins. In pts not under statin treatment the post CABG drop in AGE plasma concentrations was significantly higher in non diabetics vs diabetic patients, a reduction 3- to 4- fold higher than the significant reduction for pts treated with statins (diabetic and non-diabetic). AGE plasma levels significant reduction post-CABG in patients with statins was on average almost 50-fold the post-CABG reduction in patients not submitted to statin treatment. The significant mean reduction of post-CABG AGE plasma levels was not different in magnitude between diabetic and non diabetic pts.

Statin treatment and diabetes may contribute to gender differences in AGE plasma levels pre- and post- CABG. Reversal of a similar effect in limiting the post CABG drop of AGE plasma levels in female patients.

Full appraisal of glycemic risk

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Purpose: Patients with acute coronary syndromes (ACS = unstable angina/myocardial infarction) and newly detected impaired glucose tolerance (IGT) or type 2 diabetes (T2DM) have beta-cell dysfunction. The hypothesis that a DPP-4 inhibitor can be safely instituted soon after an ACS and will improve beta-cell function was tested.

Methods: ACS patients with IGT or T2DM (n=71), screened by oral glucose tolerance tests (OGTT) 4-23 days (median 6) after admission were randomised to sitagliptin 100 mg (n=34) or placebo (n=37) during 12 weeks. All patients received lifestyle advice but no other glucose lowering drugs. The endpoints were beta-cell function assessed through OGTT expressed as insulinogenic index (IGI = ΔIns/ΔG10min) and Acute Insulin Response to glucose (AIRg) by a frequently sampled intravenous glucose tolerance test (FSIGT).

Results: Sitagliptin was well tolerated. Fasting glucose (Figure 1c) and insulin resistance (Figure 1d) did not change during the 12 weeks of treatment in either group. Significantly more patients in the sitagliptin group normalised their post load glucose metabolism than in the placebo group (26 vs. 16; p=0.004). The IGI- and AIRg at baseline did not differ between the sitagliptin and placebo groups (69.8 vs. 66.4 pmol/mmol and 1394 vs. 1106 pmol/l min1). After 12 weeks the IGI was 85.0 in the sitagliptin and 58.1 pmol/mmol in the placebo group (p=0.019).
Detection of subclinical left ventricular dysfunction in asymptomatic young adults with type-2 diabetes: a cardiac magnetic resonance study

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Introduction: There is an epidemic of obesity and Type 2 diabetes (T2DM) in the developed world. Although diabetic cardiomyopathy is well documented in older adults with T2DM there is very little data on younger adults and no published CMR data.

Objective: To use CMR to assess whether asymptomatic young adults with T2DM have evidence of subclinical left ventricular (LV) dysfunction compared to healthy lean and obese controls.

Methods: 40 asymptomatic subjects (20 T2DM, 10 obese non-diabetic controls, 10 lean non-diabetic controls) underwent CMR assessment of the LV on a Siemens Avanto 1.5T system. LV function and volumes were assessed using SSFP. Circumferential strain was assessed using a multi breath-hold CSPAMM tagging sequence at 3 slices (basal, mid-cavity, apical). Perfusion was assessed on first-pass contrast imaging during adenosine stress.

Results: Subjects were matched for age, height and blood pressure. Global peak early diastolic strain rate (PEDSR) was significantly lower in T2DM, compared to lean and obese controls (Table 1). There was no evidence of coronary artery disease on perfusion testing.

Conclusions: This is the first CMR study demonstrating subclinical diastolic dysfunction in young adults with T2DM. The significant difference between the T2DM and obese groups suggest that T2DM in early adulthood has detrimental effects on cardiac function, additional to those associated with obesity.

Heart rate variability, postprandial responses of glucose and insulin and beta-cell function: the NEO study

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Introduction: Low heart rate variability (HRV) is associated with diabetes mellitus (DM). We hypothesize a negative association of HRV with insulin resistance in fasting state (IR) and postprandial responses of glucose and insulin and a positive association with beta-cell function.

Methods: Baseline analysis of the Netherlands Epidemiology of Obesity (NEO) study, including 6000 individuals aged 45-65y with a BMI ≥27kg/m². HRV was calculated as SDNN (ms), RMSSD (ms), LF (ms²) and HF (ms²). Blood was sampled fasting, 30min and 150min after a mixed meal (400 ml, 600 kcal). We calculated Homeostasis Model Assessment of insulin resistance (HOMA2-IR) as a measure IR. Area under the curve (AUC) for glucose and insulin were used as measures of the postprandial responses. Beta-cell function was calculated with the insulinogenic index (IGI): Insulin(t30-t0)/glucose(t30-t0) and AUC(Ins)/AUC(Glu). Linear regression analysis was used to assess the association of HRV with IR, postprandial responses and beta-cell function, stratified by day/night and adjusted for sex, age, BMI, waist circumference, ethnicity, education, smoking, medication, hypertension, beats per minute and activity.

Results: Of 4562 included participants, 639 had HRV measurements. Participants with recordings >72h (n=75), CVD (n=33) or DM (n=47) were excluded, resulting in 489 participants (46% men, mean age (SD): 56 (6) years, BMI: 31 (4) kg/m², fasting glucose: 5.6 (0.78) mmol/L. We found no association of lnSDNN (ms) during daytime with lnHOMA2-IR (β=0.15, 95%CI: -0.032, 0.30).

National cardiovascular risk assessment in type 2 diabetes in China

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Objectives: The China Cardiometabolic Registries (CCMR), is designed to establish systematic evaluation of cardiovascular disease (CVD) prevention and progression and influencing factors. The CCMR-3B is a cross sectional study designed to assess the level of CVD risk control in patients with type 2 diabetes (T2D).

Methods: Patients were recruited from cardiology, endocrinology, nephrology, and internal medicine clinics across China. Patients’ demographics, socioeconomic status, health behaviors, medical history, current medication, physical characteristics, and recent laboratory tests were collected.

Results: A total of 25,454 patients with the mean age of 62.6 years were enrolled from 104 hospitals; 53% were females, 72.1% had HTN and/or DLYP. Patients with T2D+HTN+DLYP had the highest proportion of CVD compared to T2D-HTN, T2D+DLYP, and T2D only (27.6% vs. 13.8%, 9.0% and 4.1%) and the highest proportion of BMI>24 kg/m² (Figure 1). While 47.7%, 28.4%, and 36.1% of the population achieved the appropriate targets of blood glucose (HbA1c<7%), blood pressure (SBP/DBP <130/80 mmHg), and total cholesterol (<4.5 mmol/L), respectively; only 5.6% achieved all three targets. Older age (<65 years), male sex, BMI>24 kg/m², no smoking or drinking, higher education, and less than 5 years of diabetes were independent predictors of better achieving the CVD risk control.
Diabetes is related to higher central blood pressure

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Background: Central blood pressure (BP) is directly related to LV overload as well as blood supply to the heart and brain. It may also directly damage coronary and cerebrovascular walls being one of the most important causes of atherosclerosis.

Several studies have shown closer correlation between end-organ damage and central than peripheral BP. Central BP was also shown to better predict cardiovascular (CV) risk. Diabetes is related to at least two-fold increased in CV risk. The influence of diabetes on central BP values is unknown.

Aim: To assess the independent influence of diabetes on the ascending aortic BP values.

Methods: BP in the aorta was measured using fluid-filled filter in 400 patients (200 with type 2 DM and 200 without DM matched for age and gender) undergoing emergency coronary angiography. Brachial BP was measured using a sphygmomanometer. Both groups did not differ in respect of age and sex. General regression model (age, sex, mean BP, risk factors, LVEF, creatinine level, and drugs were included into the model) was used to assess the independent influence of diabetes on BP.

Results: Systolic, diastolic, and mean brachial BP did not differ between the study groups (138.6±21.3 vs. 133.7±20.3 mmHg; p=0.06; 83.4±12.0 vs. 82.6±10.7 mmHg; p=0.81; 109.1±14.0 vs. 99.6±13.0 mmHg; p=0.07) in diabetics and non-diabetics, respectively, but brachial pulse pressure was higher in diabetics (55.4±15.3 vs. 51.1±14.2; p=0.02). Central BP values are shown in the Table. In multivariable analysis diabetes was related to higher ascending aortic systolic BP by 2.7 (95% confidence intervals: 1.7-3.8 mmHg) and pulse pressure by 4.1 (2.5-6.7) mmHg as well as higher brachial pulse pressure by 1.8 (0.2-3.3) mmHg. The differences in mean and diastolic (both brachial and central) BP as well as brachial systolic BP were not significant in multivariable analysis.

Conclusions: Diabetes is independently related to higher values of systolic and pulse pressure in the ascending aorta. This may partly explain the higher CV risk in diabetics.

Omentin-concentrations predict 10-year incidence of diabetes in Thai: the EGAT study, 1998-2008

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Background: Obesity has reached pandemic proportions and is an established risk factor for insulin resistance, type 2 diabetes (T2D) and cardiovascular disease. Alterations in the secretion of adipokines in obesity are believed to contribute to the undesirable changes in glucose metabolism that ultimately result in the development of T2D. Omentin-1 is a novel adipokine preferentially produced by adipose tissue with insulin-sensitizing effects, where the circulating levels are decreased in insulin-resistant state.

Objective: To investigate whether baseline omentin-1 concentrations were associated with 10-year incidence of diabetes in Thais.

Materials and Methods: Nested case-control study was conducted in a population-based cohort: the Electricity Generating Authority of Thailand study, 1998-2008. The baseline demographic, anthropometric and clinical data were collected in 1998. The resurvey was done 10 years later in the same participants. one hundred and sixty eight individuals with newly diagnosed diabetes and 168 age-, sex-, and clinic-matched non-diabetic individuals were enrolled to the study. baseline serum omentin-1 concentrations were measured by ELISA.

Results: Baseline socioeconomic status, educational background BMI, and waist and hip circumferences were significantly higher in incident cases compared with control. Omentin-1 concentrations were significantly negatively correlated with BMI (r=-0.196, p<0.0001) and waist circumference (r=-0.168, p=0.002). newly diagnosed diabetes group had significantly lower omentin-1 concentrations compared with control group (437.4±149.4 vs. 485.0±172.1 ng/mL, p=0.007) even after further adjusting for family income, educational background, smoking, drinking, family history of diabetes, and waist circumference (p=0.019).

Hazard ratios (95%CI) for developing diabetes for those in the highest tertile vs. lowest tertile of omentin-1 concentrations were 0.506 (0.297-0.863) and 0.528 (0.298-0.935) in unadjusted and multivariate adjusted model, respectively. Diabetes: Methods: Diabetes family history, obesity markers (waist to hip circumference ratio - WHR, body mass index - BMI), glycemic parameters (fasting glucose, glycated haemoglobin - HbA1c, fasting insulin, insulin resistance indices (homeostasis model assessment - HOMA, quantitative insulin sensitivity check index - QUICKI), McAuley) and the prevalence of IGH were all determined in a large cohort of 11540 hypertensives (mean age 56.8 years, 51.7% males, mean office blood pressure 164.0/98.8 mmHg) who were referred to the hypertensive units of our institutions.

Results: Positive DM family history was associated with elevated glycated haemoglobin, BMI and insulin resistance index (HOMA) in every subgroup of WHR and BMI (Figure).

Conclusions: Non-diabetic hypertensives with positive diabetes family history present with higher prevalence of impaired glucose homeostasis and worse glycemic indices levels compared to those with negative family history.

Current smoking and prediabetes in young and healthy adults

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Purpose: Several studies have shown a strong relationship between smoking and type 2 diabetes. However, it is unclear whether smoking is related to changes in glucose homeostasis in young adults without prevalent type 2 diabetes and with a relatively short smoking history. We therefore aimed to assess the association between smoking and prediabetes in young and healthy adults.

Method: The Genetic and Phenotypic Determinants of Blood Pressure and Other Cardiovascular Risk Factors (GAPP) study is a population based cohort of healthy adults aged 25-40 years in the Principality of Liechtenstein. Individuals with diabetes, body mass index >35 kg/m2 and prevalent cardiovascular disease were excluded. Smoking behaviour was assessed by self-report. Pack years of smoking were calculated by multiplying the number of years smoked by the average number of cigarettes packs smoked per day. Glycosylated haemoglobin (HbA1C) was assayed from fasting venous blood samples using high-performance liquid chromatography (Bio-Rad D-10). Prediabetes was defined as an HbA1C between 5.7 and 6.4%.
Membrane type 1-matrix metalloproteinase correlates with the coronary plaque stability in patients with postprandial hyperglycemia

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Background: We reported pericellularly localized membrane-type matrix metalloproteinases (MT-MMPs), which are main activator of secreted latent type MMPs, were highly expressed on circulating peripheral blood mononuclear cells (PBMCs) from patients with acute myocardial infarction (AMI). Although, postprandial hyperglycemia (PPH) is an independent risk for development of cardiovascular disease, there are few knowledge about predictor of coronary plaque in type 2 diabetic patients with PPH.

Methods: Fifty eight outpatients with type 2 diabetes whose glycated hemoglobin (HbA1c) ranged between 5.5 and 8.0 (%DS,), and 1.5-arthydrocorticul as a short-term marker for PPH did not exceed 14 μg/mL, were enrolled. Subjects underwent 64-multidetector computed tomography to analyze the plaque. Vulnerable plaque was defined as positive remodeling (remodeling index < 1.05), low-attenuation plaque (< 39 Hounsfield Units), and/or adjacent spotty calcification. PBMCs were examined for the frequencies of CD14 pentraxin-3 were measured by using ELISA methods.

Results: MT1-MMP expression on PBMCs in all patients with PPH was significantly elevated in patients with active smokers (p = 0.012), but no differences in HbA1c, serum MMP-2,-9, and plasminogen activation were identified between patients with and without active smoking.

Conclusion: MT1-MMP expression on PBMCs correlates with active smoking, but not with postprandial glycemia.

A dipeptidyl peptide-4 inhibitor, alogliptin, improves postprandial triglyceridemia and postprandial endothelial dysfunction

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Background: Postprandial hyperlipidemia, especially hyper-triglyceridemia, has been shown to impair endothelial function and play an important role in the development of atherosclerosis. We investigated the postprandial effects of a DPP4 inhibitor, alogliptin, on endothelial dysfunction and lipid profile.

Methods: A randomized double-blind cross-over trial design in 10 healthy subjects (9 males and 1 females, 35 ± 10 years) was performed. Lipid profiles, levels of apolipoprotein B48 (apoB-48), glucose, glucagon, insulin, glucagon-like peptide (GLP-1) and endothelial function, assessed by brachial artery flow-mediated dilatation (FMD) during a fasting state and at 2, 4, 6 and 8 after a standard meal loading test, were determined before and after treatment for one week.

Results: In control group, the maximum reduction in postprandial %FMD was significantly correlated with the maximum increases in postprandial triglyceride (r = -0.663, p = 0.012), but no differences in HbA1c, serum MMP-2,-9, and plasminogen activation were identified between patients with and without active smoking. Alogliptin treatment significantly suppressed postprandial elevation in serum triglyceride (area under the curve [AUC], from 8.3±26 to 7.6±14 mg/dl, p = 0.05, Figure A) and apoB-48 (AUC; from 29.4±7.8 to 21.9±4.8 μmol/l, p = 0.05). Secretion of GLP-1 was significantly increased after alogliptin treatment (AUC; from 38.2±16.7 to 61.5±13.3 pmol/l, p = 0.05).

Conclusion: Administration of alogliptin significantly improved postprandial endo-thelial dysfunction and increase in triglyceride, suggesting alogliptin may be a promising anti-atherogenic agent.

Reference:
1. National Cholesterol Education Program (NCEP) Adult Treatment Panel III.}

Prognostic impact of coronary artery involvement of postprandial metabolic syndrome and chronic kidney disease in patients undergoing coronary intervention; involvement of coronary plaque morphology

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Background: Both metabolic syndrome (MeS) and chronic kidney disease (CKD) have been reported to be risk factors of cardiovascular events. Objective: The aim of this study was to assess the synergistic effect of MeS and CKD on atherosclerotic plaque and cardiovascular outcomes. Methods and Results: A total of 204 consecutive patients who underwent percutaneous coronary intervention (PCI) were enrolled. They were divided into four groups according to the presence or absence of MeS and CKD. MeS was defined by following criteria of the National Cholesterol Education Program in Adult Treatment Panel III. CKD was defined as an estimated GFR < 60 ml/min/1.73 m². We analyzed the incidence of major adverse cardiac events (MACE) including cardiovascular death, nonfatal myocardial infarction, target lesion revascularization, and revascularization for new lesion as well as coronary plaque characteristics using integrated backscatter intravascular ultrasound (IBIVUS). Major adverse cardiac events occurred more frequently in patients with both MeS and CKD (46.2%) as compared to the other three groups during follow-up period (Log rank p = 0.029). In the IB-IVUS analyses, patients with both MeS and CKD showed a greater plaque burden (p = 0.001) with larger lipid cores (p = 0.048) as compared to the other three groups. In Cox analyses, patients with both MeS and CKD proved to be an independent predictor of MACE even after adjustment of confounding factors (hazard ratio 1.739; 95% confidence interval 1.011-2.991; p = 0.046).

Conclusion: Coexistence of MeS and CKD would predict higher MACE, which may attributes to the worse coronary plaque morphology in these patients.

Purpose: An elevated resting heart rate has previously been reported to predict new onset diabetes (NOD). Pre-diabetic autonomic nervous system dysfunction
has been suggested to be the mediating mechanism. We tested if change in maximum heart rate (ΔMHR) through seven years predicts NOD over 28 years.

Methods: Exercise MHR was measured among 1,387 healthy men at two separate examinations, in 1979 and in 1997. The men were divided into quartiles (Q1-Q4) by ΔMHR. NOD events were registered in a nationwide survey of all participants' hospital charts through 2008. Relative risk of NOD in the quartiles was calculated using Cox proportional hazard regression adjusting for baseline MHR, maternal diabetes, smoking status, systolic blood pressure, fasting triglycerides, fasting blood glucose, age, BMI, physical fitness and change in physical fitness.

Results: A total of 124 NOD events were registered. Median MHR at baseline was 165 and 160 seven years later. The incidence of NOD was the highest among the men who decreased their MHR the most (Q1) and lowest among those who increased their MHR (Q4). Q1 was associated with an 82% increased NOD-risk compared with Q4.

Conclusion: These findings indicate that a reduction of MHR of more than 15 BPM over seven years is independently associated with a significantly increased long-term risk of new onset diabetes. We suggest that a marked fall in maximum heart rate could be associated with autonomic nervous system dysfunction. This observation could be helpful when identifying individuals at high risk of developing diabetes.

P4974 Metabolic syndrome in the Czech population. Current status and trends
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Purpose: The prevalence of the metabolic syndrome is perceived as high and increasing among Czech adults. Our objective was to determine its exact prevalence, incidence trends since 1997/8 and to assess the control and treatment of the metabolic syndrome in the Czech population.

Methods: A total of 3196, 3249 and 3537 men and women aged 25-64 years from 1997/8, 2000/1 and 2006-9 Czech post MONICA cross-sectional population surveys (1% random representative population sample of nine districts of the Czech Republic) were included in the analyses. We used the definition of the metabolic syndrome developed by the Joint Interim Statement of several major scientific organizations (Circulation 2009;120:1640-1645.).

Results: The prevalence of the metabolic syndrome was 37.1% in 1997/8 and 32% in 2006-9 among women (P=0.002, a significant decrease) and 50.5 and 48.2%, among men (P=0.218). The prevalence of the metabolic syndrome increased with the age in all surveys. In 2006-9 survey in men 25-34 years old 55-64 years old 67.1%; among women the prevalence was 5.8%, 18%, 36.5%

Conclusions: The prevalence of the metabolic syndrome is perceived as high and increasing among Czech adults. The prevalence has increased with the age in all surveys. In 2006-9 survey in men 25-34 years old 67.1%; among women the prevalence was 5.8%, 18%, 36.5%

P4975 Autonomic neuropathy is independently associated with new heart failure and atrial fibrillation in diabetic patients with preserved ejection fraction: prognostic significance of heart rate recovery
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Purpose: Atrial fibrillation (AF) and heart failure (HF) are important and interacting complications of type 2 diabetes mellitus (T2DM), and may be predicted by left atrial volume index (LAVI). Diabetic autonomic neuropathy may be an important contributor to AF, and may be evidenced by attenuated heart rate recovery (HRR). We sought whether HRR had an association with HF and AF in T2DM, independent of LA size.

Methods: We enrolled 814 consecutive uncontrolled patients with T2DM (56±11 yrs, 508 men) who had negative stress echocardiography from 2004 to 2007. Patients with prior cardiac surgery, AF, > mild valvular disease, HF, ejection fraction <50% or any cancer at enrollment were excluded. Demographics, clinical assessment, standards of diabetes care, comorbidities, and treatment with insulin, diuretics, beta-blockers, statins, ace-inhibitors and aspirin were collected prospectively of 124 NOD events were registered. Median MHR at baseline was 165 and 150 seven years later. The incidence of NOD was the highest among the men who decreased their MHR the most (Q1) and lowest among those who increased their MHR (Q4). Q1 was associated with an 82% increased NOD-risk compared with Q4.

Hazard ratios

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<th>Quartiles (ΔMHR)</th>
<th>N=340</th>
<th>N=335</th>
<th>N=361</th>
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<tr>
<td>Q1 (15-69)</td>
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<td>Q2 (7-14)</td>
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<td>Q3 (1-6)</td>
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<td>Q4 (10-21)</td>
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ΔMHR (median) 49.5% NOD, n (%) 40 (11.8) 28 (8.4) 31 (8.6) 25 (7.1)

Quartiles (ΔMHR) | N=340 | N=335 | N=361 | N=351 |
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<td>Q1 (&lt;15)</td>
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<td>Q2 (15-69)</td>
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<td>Q3 (7-14)</td>
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<td>Q4 (10-21)</td>
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Multiple adjusted 1.82 (1.07–3.17) 1.21 (0.68–2.15) 1.33 (0.78–2.32) 1.0

Conclusions: These findings indicate that a reduction of MHR of more than 15 BPM over seven years is independently associated with a significantly increased long-term risk of new onset diabetes. We suggest that a marked fall in maximum heart rate could be associated with autonomic nervous system dysfunction. This observation could be helpful when identifying individuals at high risk of developing diabetes.

P4976 Tight glycemic control after cardiac surgery reduces the incidence of post-surgical atrial fibrillation regardless of existence of diabetes mellitus

Purpose: Atrial fibrillation is a common occurrence after cardiac surgery. However, there remains some uncertainty surrounding the relationship between onset of atrial fibrillation and pre-existing diabetes mellitus as well as the role of tight glycemic control after cardiac surgery. The purpose of this study was to clarify the relationship between incidence of atrial fibrillation after cardiac surgery and diabetes mellitus, and the effect of tight glycemic control.

Methods: Consecutive 60 subjects after cardiac surgery were divided into two groups, tight glycemic control group (Group T, n=30) and usual control group (Group C, n=30). In Group T, glycemic status was aimed to be between 80-150mg/dL. Incidence of atrial fibrillation was compared between two groups, as well as the effect of diabetes status on occurrence of atrial fibrillation was investigated.

Results: Atrial fibrillation occurred in 24 patients. There was no significant difference in the occurrence of atrial fibrillation between patients with or without diabetes mellitus (p=0.90). Incidence of atrial fibrillation was greater in Group C (50.0%) than in Group T (30.0%).

Conclusion: It is revealed that tight glycemic control after cardiac surgery reduces the incidence of post-surgical atrial fibrillation regardless of the diabetic status.

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lipoprotein (oxLDL), and IgM antibodies against PC (anti-PC) are present as natural antibodies in humans. Low levels of IgM anti-PC have been shown to be inversely correlated with the prevalence of DM(OR=0.554, 95%CI: 0.281-1.00), compared with rare coffee consumers; while high coffee consumption showed no benefit, as they both increase the plasma levels of VEGF in patients with diabetes mellitus.

We have found that neither pioglitazone (p=0.09), nor perindopril (p=0.5) affected plasma levels of CRP (p=0.85). Interestingly, we have found that perindopril had a superior effect than that of pioglitazone considering Delta1/DM prevalence even in elderly individuals. However this protective effect is lost with higher amount of coffee consumption.

Conclusions: Moderate coffee consumption seems to have beneficial effect on DM prevalence even in elderly individuals. However this protective effect is lost with higher amount of coffee consumption.

Copein and adrenomedullin in a large cohort of cathepsin laboratory patients with newly detected diabetes or impaired glucose tolerance: the Silent Diabetes Study

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Purpose: Endothelial progenitor cells (EPCs) play a significant role in neovascularization of ischemic tissues and in re-endothelialization of injured blood vessels. The purpose of this study was to investigate if the administration of pioglitazone or perindopril in diabetic patients can modify the number of EPCs in the peripheral blood and alter the endothelial function and inflammatory status of these patients. Methods: Fifty type 2 diabetic patients were recruited and were randomly assigned to receive either pioglitazone (15mg/day) or perindopril (4mg/day) for a one-month period. Blood samples were obtained in order to count EPCs and inflammation markers such as C-reactive protein (hsCRP), vascular endothelial growth factor (VEGF) and asymmetric dimethylarginine (ADMA). Circulating EPCs were defined by the surface markers CD34+KDR (CD34 and VEGFR2 expressing cells) and analyzed by flow-cytometry. Moreover the endothelial function of the patients was evaluated both on admission and after treatment with flow-mediated dilation (FMD). Results: We have found that neither pioglitazone (p=0.09), nor perindopril (p=0.5) affected the number of EPCs. Importantly, we have shown that pioglitazone reduced CRP (2.5±2.4 vs 1.8±1.5 mg/dL, p=0.04) and ADMA levels (0.8±0.5 vs 0.7±0.5 pmol/L, p=0.02) in addition, pioglitazone improved FMD (0.05±0.02 vs 0.07±0.04, p=0.04) and increased plasma concentrations of VEGF (102.7±70.6 vs 169.3±120.7 pg/mL, p<0.001). On the contrary, perindopril had no significant effect on CRP (p=0.57), FMD (p=0.61) as well as on ADMA (p=0.09). However, perindopril administration increased significantly plasma levels of VEGF (126.3±100.0 vs 163.2±121.5 pg/mL, p=0.03), Moreover, both agents did not differ regarding to their effect on ∆ADMA (p=0.34), ∆FMD (p=0.70), ∆VEGF (p=0.27) and ∆CRP (p=0.85). Interestingly, we have found that perindopril had a superior effect than that of pioglitazone considering ∆ADMA levels (0.16±0.15 vs 1.5±0.01), despite the non significant effect on ADMA levels resulting solely from the differences in ∆ADMA.

Conclusions: Our results support the beneficial role of pioglitazone in terms of inflammation and oxidative stress. In addition, the combined administration of pioglitazone and perindopril could be proved beneficial with respect to angiogenetic effects, as they both increase the plasma levels of VEGF in patients with diabetes, which may confer important pathophysiological and clinical implications.
fartion (MI), adrenomedullin as a marker for congestive heart failure (CHF). Both hormones may be involved in the pathophysiology of metabolic syndrome.

**Methods:** Sera of 920 patients (pts) were eligible for this analysis, 777 pts had undergone elective coronary angiography (CA), 143 pts CA in acute coronary syndrome. All pts underwent an oral glucose tolerance test (OGTT). Pts with previously known diabetes mellitus were excluded from the study. Definition of glucometabolic state (OGTT): NGT = normal glucose tolerance; IFG = impaired fasting glycaemia; IGT = impaired glucose tolerance; DM = diabetes mellitus. Definition of coronary anatomy: no CAD = normal; minor CAD = lesions < 50%; 1-VD, 2-VD, 3-VD = 1-, 2-, or 3-vessel disease. In pts with elective CA 59 pts had no coronary artery disease (no CAD), 152 pts only lesions -50% (minor CAD), 164 pts 1-vessel disease (1-VD), 172 pts 2-vessel disease (2-VD), and 230 pts 3-vessel disease (3-VD). In OGTT 393 pts had normal glucose tolerance (NGT), 279 pts impaired glucose tolerance (IGT), and 105 pts diabetes mellitus (DM). Copeptin and MP-pre-adrenomedullin (ADM) were measured by ELISA (Germany). Usual statistical analyses were performed by ANOVA and Kruskal-Wallis methods.

**Results:** Pts with no CAD had significantly lower copeptin levels compared to pts with beginning CAD (p = 0.02), 1-VD (p = 0.03), 2-VD (p = 0.012) or 3-VD (p = 0.001). Concerning ADM, only pts with 3-VD (p = 0.001) and beginning CAD (p = 0.009) had higher ADM levels compared to no CAD pts. Interestingly, both pts with DM (p = 0.0001) and IGT (p = 0.0003) had higher copeptin levels compared to pts with NGT; there was no significant difference between pts with DM and IGT. Similarly, pts with NGT had lower ADM levels compared to pts with IGT (p = 0.001) or pts with DM (p = 0.005). And again there was no difference in ADM levels with DM and IGT (p = 0.085).

**Conclusions:** Copeptin was elevated in pts with CAD compared to those with no CAD, but there was no grading based on severity of CAD. Similarly, ADM was elevated mainly in pts with advanced CAD (3-VD), but also in pts with minor CAD compared to no CAD pts. Both markers were elevated in pts with IGT and previously unknown DM. The fact that both hormones were already elevated in newly diagnosed IGT may be an argument for their early involvement in the pathophysiology of the metabolic-vascular syndrome.

**Impact of exercise training on waist circumference, glucose metabolism and endothelial function in pre-diabetic, adipose patients with severe coronary heart disease**

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**Purpose:** Certain fat-tissue-derived adipokines are thought to contribute to impaired glucose metabolism and endothelial dysfunction, which is a predictor of future cardiovascular events. The aim of our study was to elucidate the association between obesity and endothelial function of the left internal mammary artery (LIMA) in pre-diabetic patients with severe coronary heart disease (CHD), who were scheduled for elective coronary bypass grafting (CABG), and to investigate the influence of 4 weeks of regular physical exercise training (ET) in these patients.

**Methods:** 29 patients with CHD (age ≤ 75 years), obesity (BMI = 28 kg/m²) and impaired glucose tolerance were randomized to 4 weeks of ET (in-hospital basis, 6 times a day for 20 min on a bicycle and rowing ergometer) (n=15) or sedentary lifestyle (C) (n=14). At begin and after 4 weeks ET, waist circumference, oral glucose load decreased from 10.2 ± 0.4 to 7.7 ± 0.5 mmol/l (p < 0.05). LDL- and HDL-cholesterol levels, maximum oxygen uptake (VO2max) and average peak velocity (APV) in response to LIMA selective intraarterial infusion of increasing doses of acetylcholine (0.072, 0.72 and 7.2 µg per minute) and nitroglycerin (200 µg as bolus) were assessed by Doppler velocimetry (Cardio- metrics, USA).

**Results:** Compared to C exercise training was associated with a reduction in waist circumference by 4.4 ± 0.1 cm (p < 0.01). Blood glucose levels two hours after oral glucose load decreased from 10.2 ± 0.4 to 7.7 ± 0.5 mmol/l (p < 0.01). LDL-cholesterol level declined from 2.87 ± 0.28 to 2.36 ± 0.17 mmol/l (p < 0.05), whereas HDL-cholesterol level increased from 1.11 ± 0.05 to 1.20 ± 0.04 mmol/l (p < 0.05). VO2max during cardiopulmonary exercise testing increased from 20.2 ± 1.0 to 23.9 ± 1.4 ml/min/kg body weight (p < 0.01). Additionally, four weeks of ET resulted in an increase in APV in response to acetylcholine compared to intraarterial saline infusion by 87%, 50% and 25%, respectively (p < 0.05). In contrast, endothelium-independent alteration of APV in response to nitroglycerin remained unchanged. All these parameters remained virtually unchanged in C.

**Conclusion:** Four weeks of exercise training lead to a reduction in body weight, waist circumference and LDL-cholesterol and an increase in HDL-cholesterol in obese patients with severe coronary heart disease. This is associated with a normalization of glucose tolerance and improved endothelial function of the left internal mammary artery. Further analysis will link these findings with adipokine expression patterns in peripheral subcutaneous fat and peri-arterial fat from the chest wall (LIMA) and the pericardium (coronaries), which was harvested during CABG.

**Higher incidence of hypoglycaemia under oral anti-diabetic therapy in patients with type 2 diabetes and manifest vascular disease: 12-months follow-up**

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**Background:** Patients with type 2 diabetes and manifest vascular disease (VD) were at higher risk for hypoglycemic complications in a 12-months retrospective analysis of DiaRegis. We examined if the incidence of hypoglycaemic events in diabetics with manifest vascular disease did change after adjustment of anti-diabetic therapy in clinical practice.

**Methods:** In the ongoing DiaRegis registry, 3,740 consecutive outpatients with type 2 diabetes and insufficient glycaemic control under chronic oral antidiabetic mono- or dual combination therapy were enrolled to document patient characteristics, medical treatment as well as the prevalence of hypoglycaemia. We examined differences between diabetics with and without vascular disease (VD), defined as known coronary artery disease (CAD) or prior stroke or peripheral artery disease (PAD) in the prevalence of hypoglycaemia during a 12 months prospective follow-up.

**Results:** A total of 909 patients had known VD (17.9%,CAD, 4.7% prior stroke, 6.0%,PAD). Type 2 diabetes outpatients with manifest VD were older, less often female and already had a significantly longer duration of diabetes as compared to patients without manifest VD. No difference was found in baseline HbA1c as indicator of long-term glycaemic control, but patients with VD more often suffered from hypoglycaemia during the 12 months prior to enrolment. The retrospective data collection even underestimated the incidence of hypoglycaemias, as in the prospective 12 months follow-up the rate of hypoglycaemia increased to 22.8% in VD patients. Independent predictors of hypoglycaemia in VD were the treatment with sulfonylureas as well as with insulin.

**Conclusion:** High-risk outpatients with type 2 diabetes and VD suffer from significant hypoglycaemias as complication of anti-diabetic therapy. Even after adjustment for differences in baseline characteristics and treatment, patients with VD have a significantly higher incidence of hypoglycaemia.
Hyperglycaemia-induced oxidative stress mediates monocyte dysfunction in diabetes mellitus

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Purpose: Monocytes play a very vital role in the biological processes which increase the diameter of the existing arterial vessels. This process, also known as arteriogenesis, is essential for maintaining vascular integrity. Circulating monocytes are recruited to the sites of collateral growth where arteriogenesis is mediated through VEGF1 signaling pathways, among others. The impaired monocyte function in hyperglycaemia, due to the reduced ability of monocytes to respond to VEGF stimulation, has been implicated in reduced arteriogenesis in diabetes patients. Molecular mechanisms leading to this VEGF-specific signal transduction defect in monocytes is incompletely understood.

Methods: Human monocytes were isolated from peripheral blood through gradient centrifugation and subsequent negative immunological magnet isolation.

Results: The monocyte cell line THP-1 and primary monocytes isolated from healthy donors were subjected to normoglycaemia (5.5 mM glucose) or hyperglycaemia (25 mM glucose) for 7 days and 72 hours, respectively. Hyperglycaemia induced reactive oxygen species in the cells leading to a reduction in total PTP activity. Induced oxidative stress resulted in reduced VEGF-A-induced chemotaxis. RT-PCR analysis indicated that NADPH oxidase 2 (NOX2) is upregulated in hyperglycaemia, and NOX2 inhibition by pyrrolidine dithiocarbamate (PDTC) and by a general NOX inhibitor diphenyleneiodonium (DPI) showed that all patients with CAD should have an OGTT, since it's not possible to predict the risk of glucose metabolism abnormalities (GMA) in patients with previous percutaneous coronary intervention (PCI).

Conclusions: Despite the high risk of subsequent cardiovascular events in type 2 diabetes less than half of the patients were treated with a statin. In very high risk diabetes with already manifest VD only 12.1% did reach the recommended target values of LDL <70 mg/dl in clinical practice.

Can we predict the risk of glucose metabolism abnormalities in patients with previous percutaneous coronary intervention?

S.B. Baptista, P. Magno, C. Monteiro, E. Lourenco, P.F. Abreu, V. Gil, Hospital Fernando Fonseca, Amadora, Portugal

Background: Oral glucose tolerance test (OGTT) is recommended in all patients with coronary artery disease, since glucose metabolism abnormalities (GMA) adversely impact their prognosis. However, there are no risk models developed for the assessment of GMA in CAD patients. These models would be useful to identify patients with higher risk and to obviate the need of an OGTT in lower risk patients.

Purpose: To identify CAD related risk factors for GMA in patients with previous percutaneous coronary intervention (PCI).

Methods: 294 patients (mean age 60.9±10.9 years, 222 males), with previous PCI and without known diabetes were included. OGTT was performed according to WHO protocol and patients were classified, according to ADA criteria in normal (N), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM). The relation between main epidemiological and CAD related factors was then evaluated.

Results: The OGTT identified 63 patients (21.4%) with IFG, 61 patients (20.7%) with IGT and 48 (16.3%) with DM, leaving only 122 (41.5%) patients with a normal OGTT. Comorbidity was more frequent in patients with GMA, involving hypertension, hypercholesterolaemia and obesity; cardiovascular and metabolic risk factors were more frequent in patients with GMA, involving hypertension, hypercholesterolaemia and obesity; cardiovascular risk factors were more frequent in patients with GMA, involving hypertension, hypercholesterolaemia and obesity; cardiovascular risk factors were more frequent in patients with GMA, involving hypertension, hypercholesterolaemia and obesity; cardiovascular risk factors were more frequent in patients with GMA, involving hypertension, hypercholesterolaemia and obesity.

Conclusions: In patients previously submitted to PCI and without known DM, GMA are very frequent (58.5% of patients). Age, previous hypertension, diabetes and BMI (all included in most risk models for the prevention of diabetes in non-CAD populations) were not useful in this CAD population. These results suggest that all patients with CAD should have an OGTT, since it’s not possible to identify lower risk groups.

The impact of diabetes mellitus according to gender difference on acetylcholine induced coronary artery spasm

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Background: Thegender difference is known to be a strong predictor of coronary artery spasm(CAS). Diabetes mellitus (DM) is also known to reduce risk factors of atherosclerosis and endothelial dysfunction. However, the impact of DM according to gender difference on CAS during acetylcholine (Ach) provocation test has not been defined.

Methods: A total of 2504 consecutive patients without significant coronary artery disease who underwent the Ach provocation test were enrolled between November...
The incidence of anemia on long-term prognosis in patients with acute myocardial infarction and concomitant glucose abnormalities

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Background: Anemia deteriorates the prognosis in patients (pts) with myocardial infarction. However, the prognostic value of anemia in subjects with different glucose abnormalities (GA) and acute myocardial infarction (AMI) treated invasively remains unclear.

Aim: To assess the incidence and impact of anemia on clinical outcomes in subjects with different GA and AMI treated with percutaneous coronary intervention (PCI).

Methods: A prospective registry of 2154 consecutive AMI subjects treated with PCI was analyzed. In all hospital survivors, GA was significantly different in patients with DM (27.9%, n=99; new onset DM (23%, n=498); IG (18%, n=480); IFG DM was found in 854 (35.0%), a history of hypertension in 663 (27.2%), a history of DM in 366 (15.0%), and a history of both disease entity in 555 (22.8%). Rate of MACE were significantly higher in patients with DM in comparison with pts with no DM or with other concomitant disease entity. The rate of MACE was significantly higher in male patients in comparison with female patients (51% vs. 28.8% vs. 37.0, Log-rank P < 0.001). Further analysis with 15 and 24 months follow-up indicated that the effect of DM on MACE was significant in men (HR 1.79; 95% confidence interval = 1.313-2.422; P < 0.001).

Conclusion: Acute MI patients with a history of DM or hypertension had a higher mid-term mortality than acute MI patients without such a history. The combination of DM and hypertension appeared to be more strongly associated with mortality than DM or hypertension alone.

Table 1

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized</th>
<th>Standardized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>B 0.065 0.016</td>
<td>0.594 4.034 0.001</td>
</tr>
<tr>
<td>Mean Blood Glucose (mg/dl)</td>
<td>-0.001 0.000</td>
<td>-0.496 -0.726 0.472</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.036 0.038</td>
<td>0.653 0.954 0.346</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>-0.037 0.065</td>
<td>-0.098 -0.563 0.576</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.000 0.001</td>
<td>0.041 0.264 0.793</td>
</tr>
<tr>
<td>BMI</td>
<td>0.003 0.002</td>
<td>0.169 1.249 0.218</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>0.000 0.000</td>
<td>-0.011 -0.080 0.936</td>
</tr>
</tbody>
</table>

| CPR (mg/dl) | 0.002 0.026 | 0.008 0.060 0.953 |

Boys with T1D had higher cIMT than girls; moreover cIMT correlated with weight and glycemia dependent parameters in girls but not in boys. Our pilot study suggests an important sex-dependent difference from the very beginning of atherosclerosis in patients with type 1 diabetes.
Genetic variability of sCD40L reveals a novel pathophysiological role of sCD40L in insulin resistance, in advanced atherosclerosis

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Purpose: Soluble CD40 ligand (sCD40L) is an inflammatory marker released by activated platelets and inflammed adipose tissue. Recent evidence suggests that sCD40L levels are higher in patients with metabolic syndrome. We sought to examine the relationship between chronically elevated sCD40L levels and insulin resistance by using the functional single nucleotide polymorphism (SNP) A3459G of the sCD40L gene.

Methods: The study population consisted of 265 individuals. After an overnight fast, a sample of blood was collected and used for biochemical measurements and genotyping. Plasma sCD40L levels were determined by ELISA. Plasma insulin levels were used to calculate insulin resistance by means of the Homeostatic Model Assessment (HOMA-IR). DNA was extracted from whole blood by using a commercially available kit and genotyping for the A3459G SNP of the sCD40L gene was performed by restriction fragment length polymorphism PCR method.

Results: In the study population, 188 individuals were carriers of the AA genotype, 44 of the AG and 33 of the GG genotype. Subjects exhibiting the GG genotype had significantly higher sCD40L levels when compared to AA and AG individuals (A). A higher risk profile of the GG genotype was not significantly associated with fasting glucose levels (B), it was associated with higher insulin resistance, as calculated by HOMA-IR (C).

Conclusions: Our data show that chronically increased activation of platelets and the related inflammation of the adipose tissue releasing sCD40L, are associated with increased insulin resistance. Therefore, our study shows novel links between the CD40/CD40L axis and insulin resistance, providing novel insights into the pathophysiology of diabetes mellitus.

Genetic susceptibility to type II diabetes in a Portuguese population

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Recently, variants in the transcription factor 7-like 2 (TCF7L2) gene have been reported to be associated with susceptibility to type 2 diabetes mellitus (T2DM) across multiple populations. There is no still replication in the Portuguese population, though.

Purpose: To investigate the genetic and environmental risk factors and their interactions increasing the susceptibility of T2DM, in the Portuguese population.

Methods: Case-control study with 1337 individuals, 467 diabetes and 1113 controls not significantly different in terms of age and gender. We investigated the markers, TCF7L2 C/T (rs7903146), FTO C/A (rs9903108) and HNF4A C/G (rs1884613). T Student or c2 tests with the OR and 95% CI, were used as indicated. Afterwards, multivariate analyzes and a 4x2 table approach, as well as summary statistics in additive (Si) and multiplicative (SIM) models were used.

Results: The TCF7L2 TT genotype was more incident among diabetics (16.7%) vs. controls (11.0%) with an OR= 1.63 (1.18-2.24) p=0.002 and FTO AA was more in diabetic (18.6%) vs. controls (15.7%), but without statistical significance. sCD40L levels were higher in patients with TCF7L2 TT variant compared with an OR= 1.8 (1.28-2.66); p=0.001. FTO AA and HNF4A/G variants did not represent T2DM risk in our population. The TCF7L2 TT variant interacted with dyslipidemia (Si=2.5; SIM=1.6; RERI=1.30; AP=0.40) and sedentarism ((Si=2.03; SIM=1.36; RERI=1.03; AP=0.34) enhancing the diabetes risk.

Conclusion: Our study provides the first significant evidence that the TCF7L2 TT polymorphism is a strong independent risk factor for T2DM in a Portuguese population. The subjects carrier of this variant must have early primary prevention for tackling these risk factors.
Predictors of long-term cardiovascular outcomes in patients with type 2 diabetes mellitus

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Introduction: Type 2 Diabetes mellitus (T2DM) is a public health problem associated with several complications, such as hypertension, dyslipidemia and obesity. Prevalence of cardiovascular events in T2DM is twice the observed in non-diabetic subjects, even after adjustment for classic risk factors. Early detection of predictors of hard outcomes are needed to try to avert this scenario. Objectives: To identify biomarkers associated with higher rates of clinically relevant events in a prospective cohort of patients with T2DM.

Materials and Methods: A random selected cohort of 1825 men and women, 50 or 60 years old were invited to the screening study. DM was defined as the use of anti-diabetic medication or fasting plasma blood glucose level ≥7.0 mmol/l on two different days. Traditional risk factors were obtained and for the non-diabetics HeartScore was calculated. A non-contrast CT-scan was performed to assess the CAC score (Agaston score >400 was considered high).

Results: A total of 1226 subjects without previous cardiovascular disease participated. Five % (59 subjects) had DM while 92% (1167 subjects) were non-diabetics. Among patients with DM the prevalence of males, 60 years old, smokers, hypertension and statin treatment were 49%, 38%, 37% and 55% respectively, while 47%, 50%, 25% and 10% for the non-diabetics. Also CAC was more frequent in diabetics (63% versus 44%; p=0.006), as well as severe calcification (9% versus 5%; p=0.02). HeartScore was higher for diabetics in multivariate logistic regression results only in a non-significant increased risk for calcification in diabetic patients (OR=1.3; p=0.44).

Discussion: We found that one-third of patients with DM did not have any coronary calcification and thus a better prognosis, while few had severely calcified coronaries. These data suggest that also in diabetics preventive therapy should be individualized based on CAC.
Arterial elastic wall properties are similarly impaired in first degree relatives and diabetic patients on the grounds of significant insulin resistance.


Conclusions: In UK patients at high CV risk, LDL-C goal attainment with ATORVA monotherapy was suboptimal, with over 60% not achieving an LDL-C <1.8 mmol/l even at the highest dose. This suggests that more effective lipid-lowering strategies such as, more aggressive dose titration or add-on therapy, are required to achieve LDL-C goals in these patients.

Type 2 diabetes and the progression of visualized atherosclerosis to clinical cardiovascular events.

Results: Of 2,403 high-risk patients (65% males, mean age 69 yrs [SD 10]) who Of 2,403 high-risk patients (65% males, mean age 69 yrs [SD 10]) who were enrolled into the study. Trans thoracal echocardiography was used for the transthoracal echocardiography and blood pressure. The relationships between parameters were analysed by linear regression model. Statistical analysis was performed by SPSS program.

In 60 subjects without known diabetes a standard 75-gr OGTT was performed and plasma glucose and serum insulin levels were measured at 0, 30, 60, 90 and 120min after glucose loading. At the same time intervals, we measured the carotid-femoral pulse wave velocity (PWVc) using the Compurral apparatus and aortic PWV (PWVap) and augmentation index (AI) using an oscilometric method (Arteriograph). We measured insulin resistance after fasting, using homeostatic model index and hepatic insulin sensitivity (HISb) during OGTT using within 45 days of LDL-C measurement, and (HOMA).

Results: Of the 60 subjects, 20 who were first degree relatives of diabetics had normal OGTT (relatives), 20 had normal OGTT and no family history of diabetes (normals), 20 had pre-existing atherosclerosis and abnormal wave reflection compared to normals with no family history of diabetes.

Conclusions: In normals, 56% of subjects had an LDL-C reduction of 1.5 mmol/l by 30% in normals and relatives (p < 0.01). The % decrease in AI at 30 min was related to the corresponding %increase in insulin levels (r = -0.46, p < 0.01). The % decrease in AI at 30 min was related to the corresponding %increase in insulin levels (r = -0.46, p < 0.01). The % decrease in AI at 30 min was related to the corresponding %increase in insulin levels (r = -0.46, p < 0.01).

The baseline prevalence of CAD (87.8% vs. 80.4%; p = 0.029) and of significant coronary stenoses (50% vs. 43.5%; p = 0.010) as well as the extent of baseline CAD pred cated vascular events independently from T2DM (HRs 3.29 [95%CI: 1.93-5.4]; p = 0.001 and 1.37 [1.23-1.53]; p < 0.001, respectively). However, the overall risk increase conferred by T2DM was driven by an extremely high 53.3% (p = 0.001) in first degree relatives and diabetic patients on the grounding of insulin resistance. In diabetes the effect of insulin on AI is blunted likely because of severe insulin resistance.

Suboptimal LDL-cholesterol control by atorvastatin therapy in high-risk patients with coronary heart disease or atherosclerotic vascular disease in the UK.
P5004 Preliminary observations of passive exercise using whole body periodic acceleration on coronary microcirculation and glucose tolerance in patients with type 2 diabetes

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Purpose: Whole body periodic acceleration (WBPA) system is recently developed as a passive exercise device by providing increased pulsatile shear stress for improvement of peripheral and coronary endothelial function (Figure left). This study aimed to investigate the acute effects of WBPA on coronary microcirculation and glucose tolerance in patients with type 2 diabetes (T2D).

Methods: The study subjects were 8 patients with T2D who underwent transthoracic Doppler echocardiography (TTDE) for the assessment of coronary flow reserve (CFR) before and immediately after 45-min session of WBPA. The flow velocity in the distal portion of the left anterior descending coronary artery was measured at baseline and during adenosine infusion. The CFR represented the ratio of hyperemic to basal mean diastolic flow velocity.

Results: WBPA were completed and well-tolerated in all patients, and no significant hemodynamic or mechanical complications were observed during the procedure or follow-up. WBPA increased CFR from 2.3±0.3 to 2.6±0.4 (p<0.02) (Figure right). WBPA decreased serum insulin level from 26±19 μU/ml to 19±15 μU/ml (p<0.01) and increased total adiponectin from 11.6±7.3 μg/ml to 12.5±8.0 μg/ml (p<0.02). The high molecular weight adiponectin from 4.9±3.6 μg/ml to 5.3±3.9 μg/ml (p<0.03), whereas the serum glucose level was stable from 207±66 mg/dl to 203±56 mg/dl (p=0.8).

Conclusions: This study demonstrates that a single session of WBPA treatment simultaneously improved coronary microcirculation and glucose tolerance in patients with T2D, providing the mechanical insights into the relationship between exercise and adiponectin.

P5005 A novel anti-inflammatory adipokine, secreted frizzled-related protein 5, is associated with coronary artery disease in non-elderly population

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Background: Secreted frizzled-related protein 5 (Sfrp5) has been reported to be a novel anti-inflammatory adipokine. Sfrp5 deficient mice fed a high-calorie diet showed severe glucose intolerance and hepatic steatosis, leading to the inflammation in adipose tissue. Those evidences suggest that sfrp5 would be involved in the development of atherosclerosis; however, the clinical relevance of sfrp5 remains unknown. We investigated whether reduced serum sfrp5 level can be associated with the presence of coronary artery disease (CAD) in human subjects.

Methods: The consecutive 185 patients (68±11 years, 79% male) were enrolled from inpatients who underwent coronary angiography (CAG). The subjects were divided into two groups on the basis of the CAG findings: patients with significant coronary stenosis defined as 50% or greater luminal diameter narrowing (CAD) and without significant coronary stenosis (non-CAD). Serum sfrp5 levels were measured by ELISA.

Results: In all subjects, serum sfrp5 levels in CAD patients tended to be lower than those in non-CAD patients (48.9±26.9 vs. 52.4±31.5 ng/ml, median ± IQR, p=0.08 by Mann-Whitney test). There were no significant difference in serum sfrp5 between two groups according to gender, the presence of diabetes, hypertension and dyslipidemia. Serum sfrp5 levels were significantly associated with body mass index (r = -0.15, p = 0.03) and HDL-cholesterol (r = 0.15, p = 0.03), but the associations of other biochemical parameters with sfrp5 levels were not significant. In sub-analysis of subjects aged <65 years (n=79), serum sfrp5 levels in CAD patients were significantly lower than those in (45.6±24.8 vs. 52.4±24.5 ng/ml, p = 0.03); however in subjects aged =65 years (n=10), serum sfrp5 did not differ between CAD and non-CAD patients. In subjects aged <65 years, serum sfrp5 levels were significantly correlated with body mass index (r = -0.35, p < 0.01), HDL-cholesterol (r = 0.32, p < 0.01) and tended to be correlated with LDL-cholesterol (r = 0.21, p<0.08), HOMA-R (r = 0.21, p < 0.08) and eicosapentaenoic acid/arthachidonic acid (r = -0.19, p = 0.11).

Conclusion: Serum sfrp5 levels are significantly associated with coronary artery disease in subjects aged <65 years. Low sfrp5 levels may contribute to coronary atherosclerosis.
Serum adiponectin is a negative predictor of incident metabolic syndrome: a population-based follow-up study

S.V. Ahn, J.Y. Kim, J.K. Park, S.B. Koh, Wonju College of Medicine, Yonsei University. Wonju, Korea, Republic of

Objective: Growing evidence suggests that increased adiponectin levels may play a protective role in the development of metabolic abnormalities, but prospective studies of adiponectin levels and incident metabolic syndrome are lacking. We investigated whether serum adiponectin predicts incident metabolic syndrome and its components in a population-based longitudinal study.

Methods: We analyzed data from 2,068 adults (838 men and 1,230 women) without metabolic syndrome, aged 40 to 70 years, who participated in a health survey in 2005. Serum adiponectin concentrations were measured by radioimmunoassay. Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III report.

Results: During an average of 2.6 years of follow-up, 154 men (16.4%) and 206 women (16.8%) developed metabolic syndrome. Median baseline adiponectin levels in subjects who developed metabolic syndrome were significantly lower than in those who did not, both in men (7.09 vs. 8.63 μg/ml, p < 0.001) and women (10.96 vs. 12.16 μg/ml, p < 0.001). In multivariable adjusted models, the odds ratio (95% confidence interval) for incident metabolic syndrome comparing the highest to the lowest quartiles of adiponectin levels was 0.26 (0.14 – 0.48) in men and 0.27 (0.10 – 0.70) in women. Serum adiponectin levels were also associated with the number of metabolic syndrome components developed by study participants over follow-up (P trend <0.001 in both men and women).

Conclusion: Our findings suggest that increased serum adiponectin could be a negative predictor of incident metabolic syndrome and its components.

Impact of a cardiac diabetic nurse in reducing the incidence of hypoglycaemic events in cardiac patients with type 2 diabetes mellitus

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Introduction: Hypoglycaemia is a potential lethal complication of hypoglycaemic medications for patients with diabetes mellitus (DM), as was demonstrated in the Diabetes Control and Complication Trial (DCCT). United Kingdom Prospective Diabetes Study (UKPDS) reported an annual incidence of major hypoglycaemic events of 2.3% in that receiving insulin therapy.

Objective: To evaluate the effectiveness of the Cardiac Diabetic Nurse in Reducing the Incidence of Hypoglycaemic Events in Cardiac Patients with Type 2 DM at KACC.

Methodology: In this prospective study, we implemented two interventions. The first focused on an intensive educational strategy for 140 cardiac nurses, and the second intervention addressed timely of patient snippets and a pre and post audit instigated to evaluate any improvement in deficit areas.

Results: In September and October, 2010 in KACC, 40 (11/83 (2.4%) patients had developed Hypoglycaemic events. In December 2010 and Jan 2011 after the intervention phase only 5/1408 (0.4%) patient had documented hypoglycaemic events, P value >0.0001.

Conclusion: Focused educational interventions by cardiac diabetic nurses are effective in reducing the incidence of hypoglycaemic events in cardiac patients with Type 2 DM.

Non-dipping heart rate and microalbuminuria in a type 2 diabetic population

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Purpose: There is increasing interest in the association between non-dipping heart rate and target organ damage. However, this has not been adequately studied in diabetic patients. The aim of the study is to identify factors that are independent predictors of non-dipping heart rate in a type 2 diabetic population who is at high risk of cardiovascular disease.

Methods: One hundred eighty six type 2 diabetic subjects with mean diabetes duration of 18.3 ± 9.5 years were recruited. All participants had proliferative retinopathy, thus enabling analysis of factors independent of glycemic control. All underwent 24-hour BP and heart rate monitoring, and were assessed for markers of inflammation (erythrocyte sedimentation rate and high-sensitivity C-reactive protein), insulin resistance as well as albuminuria, presence of peripheral neuropathy (as assessed using vibration perception thresholds) and peripheral vascular disease. Data were analysed using SPSS version 20.0.

Results: Both systolic and diastolic blood pressure on ABPM. Groups were similar for rest SBP, DBP, heart rate, exercise blood pressure on ABPM. Groups were similar for SBP and DBP on office measurements.

Conclusion: Non-dipping heart rate might give us an indication of underlying generalized atherosclerosis in diabetic patients. This merits further study.

Cost-effectiveness of cardiac resynchronization therapy in combination with an implantable cardioverter defibrillator in mild heart failure based on Markov modeling using UK cost approach in MADIT CRT

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Purpose: To evaluate the cost-effectiveness of CRT-D in mild heart failure LBBB or female patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT).

Methods: A decision analytic Markov model was created to evaluate the costs, gained life-years and quality-adjusted life years (QALYs) associated with CRT-D compared to ICD treatment. Analysis was performed in 1281 LBBB patients and in 453 CRT-D women enrolled in MADIT-CRT. Costs were measured using the perspective of the United Kingdom National Health Service. Costs and utilities were discounted at 3.5% per year. Base-case analysis and multiple one-way sensitivity analyses were performed.

Results: Compared with ICD treatment, CRT-D gained 1.51 QALYs having a cost of £19,855 in LBBB patients, resulting in an incremental cost-effectiveness ratio (ICER) of £13.147 per QALY gained when using a life-time horizon of 35 years. The female population gained 3.81 QALYS at an additional cost of £30,088 resulting in an ICER of £7.898. ICER implemented for a 10-year time-period was £14,392 for LBBB patients, £8,313 for female patients, respectively. One-way sensitivity analyses revealed the discount rate and the utility per cycle without heart failure events to be the most sensitive variables for cost-effectiveness.

Conclusions: CRT-D treatment is cost-effective in mild heart failure LBBB or female patients with severely depressed left ventricular ejection fraction and wide QRS compared to ICD only, for a 10-year and 35-year time horizon.

Cost-effectiveness of the molecular autopsy in sudden unexplained death in the young

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Purpose: Sudden unexplained death (SUD) accounts for 30% of young sudden cardiac deaths under the age of 35 years. The underlying cause is suspected primary arrhythmogenic disease in such cases, including long QT syndrome (LQTS). The “molecular autopsy” (genetic testing of postmortem DNA) can clarify both the cause of death, and the genetic status of asymptomatic family members. This study sought to determine the incremental cost-effectiveness of a family management strategy including the “molecular autopsy” in addition to traditional clinical screening, compared to clinical screening alone.
Methods: A decision model was developed to depict the two strategies: (i) clinical screening including the “molecular autopsy” and (ii) the conventional approach of clinical screening alone. Input data were based on published research where available and expert opinion (Table 1). Costs were from a third-party payer perspective, and presented in Australian dollars ($A = $0.8086). Effectiveness was measured using life-years gained (LYG). One-way sensitivity analysis was carried out to assess the impact of each input variable on the overall incremental cost-effectiveness ratio (ICER).

Results: Assuming a 35% mutation pick-up rate (cost $A30500/€2829 to screen 4 genes with HERG, SCNIA, RyR2 and 4 family members per decedent), the addition of the “molecular autopsy” to conventional family management was found to be cost-saving, dominating the clinical screening strategy. One-way sensitivity analysis found the key variables to be the cost of the “molecular autopsy” and the mutation detection rate. If the cost of genetic testing was more than $A3988 (€3224), or the mutation detection rate below 28% then it became the less cost-effective strategy.

Conclusions: The addition of the “molecular autopsy” to the conventional approach of clinical screening is a cost-saving strategy. There is significant cost-saving benefit in predictive genetic testing of the surviving family members, particularly for those who tested gene negative. The “molecular autopsy” is expected to become even more cost saving as newer genetic technologies facilitate testing more genes, at lower cost, with higher mutation detection rates.

Purpose: Guidelines, to be accepted and commonly used by practitioners, should be short, clear, and non-controversial. The aim of the study was to evaluate how frequently different levels of evidence and classes of recommendations are used in currently published Guidelines of the European Society of Cardiology.

Methods: A retrospective cohort study was conducted in the Premier Hospitalization database between January 2006 and June 2011. The Premier database includes data on 200 hospital and healthcare systems accounting for 37 million hospitalizations per year. Patients were included if they had a primary diagnosis of any ischemic stroke (IS) (ICD-9: 433.xx, 434.xx) or hemorrhagic stroke (HS) (ICD-9: 430.xx, 431.xx, 432.xx) and a secondary listed diagnosis of AF (ICD-9: 427.3x). Demographic information, Charlson comorbidity index (CCI), comorbid conditions and discharge status stratified by stroke type were evaluated.

Results: In sum, 107,818 hospitalizations met the inclusion criteria. IS accounted for 83% and HS for 17% of hospitalizations. The sample had a mean age of 78 years, 55.5% were female, and the mean CCI was 5.7. The most frequently identified individual comorbidities were hypertension (63%), diabetes (30%), and congestive heart failure (29%). The in-hospital mortality rate was 6.6% for IS and 24.0% for HS; for both stroke types the mortality rate was positively correlated with the CCI. A minority of all admitted patients were discharged home (IS: 28.1%; HS: 13.6%). Most patients were discharged to a center requiring additional care and resources (IS: 61.4%; HS: 59.7%); more specifically, a skilled nursing facility (IS: 22.9%; HS: 19.5%), another rehabilitation facility (IS: 15.7%; HS: 15.3%), home health care (IS: 10.9%; HS: 7.1%), hospice care (IS: 5.8%; HS: 4.0%), or any other center providing additional follow-up care (IS: 6.0%; HS: 11.7%). Unknown discharge status was reported for IS: 1.9% and HS: 0.7%.

Conclusion: Among patients with AF, one in twelve experiencing an IS and one in four experiencing a HS did not survive the index hospitalization. Patient care was extended beyond the initial hospitalization in more than half of all patients. To what extent post-discharge care actually increases the direct medical cost associated with stroke events in AF patients could be evaluated in further research.

Purpose: Taking into account the economic crisis in cardiology / The use of statistics to improve cardiovascular care

The incidence of acute myocardial infarction (AMI) has been shown to decrease in countries where the prevalence of CV disease is high, such as the USA or Northern European countries. Little is known, however, on the evolution of the incidence of AMI in countries with a low prevalence of the disease, such as France. In addition, whether the trends are uniform according to gender and age groups is not known.

Aim: To assess the trends in the annual incidence of hospitalisations for AMI in France from 2002 to 2008 in men and women, according to age groups.

Methods: Data were extracted from the national administrative database of patients admitted for acute hospital stays from 2002 to 2008 in France. Hospital stays for AMI were selected on the basis of principal diagnosis codes from the ICD 10 (I21 to I23). Only first hospital stays each year were retained. Annual rates were standardized on the European population and annual trends in subgroups (according to age and sex) were analysed using Poisson regression.

Results: On a nationwide scale, the absolute number of patients admitted for AMI decreased by 7.4% and the standardised rate decreased by 15.3%. This global trend to a decreased incidence, however, differed according to gender and age groups. In men, there was an homogeneous decrease in the incidence of AMI whatever the age group. In women, the incidence of AMI decreased in the >65-year age group and paralleled that observed in men in the same age group (standardized rates decreased -22.5% in men and -23.4% in women), while in women aged 35 to 54 years, the incidence of AMI significantly increased during this time period (age 25-34 years: +8.3%; 35-44 years: +14.6%; 45-54 years: +17.9%).

Conclusion: In a country with comparatively low rates of coronary artery disease, the overall incidence of hospitalized AMI has consistently decreased over the past decade. These results are in keeping with results from the French MONICA centres. The increase in the incidence of AMI in younger women, however, appears highly perplexing and will deserve further study.

Purpose: Discharge status of atrial fibrillation patients hospitalized for ischemic or hemorrhagic stroke in the United States

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Purpose: Limited information is available on the proportion of patients with atrial fibrillation (AF) that continue to require follow-up care post stroke. Our aim was to describe the clinical characteristics and discharge status in AF patients hospitalized for a first stroke event.

Methods: A retrospective cohort study was conducted in the Premier Hospitalization database between January 2006 and June 2011. The Premier database includes data on 200 hospital and healthcare systems accounting for 37 million hospitalizations per year. Patients were included if they had a primary diagnosis of either ischemic stroke (IS) (ICD-9: 433.xx, 434.xx) or hemorrhagic stroke (HS) (ICD-9: 430.xx, 431.xx, 432.xx) and a secondary listed diagnosis of AF (ICD-9: 427.3x). Demographic information, Charlson comorbidity index (CCI), comorbid conditions and discharge status stratified by stroke type were evaluated.

Results: In sum, 107,818 hospitalizations met the inclusion criteria. IS accounted for 83% and HS for 17% of hospitalizations. The sample had a mean age of 78 years, 55.5% were female, and the mean CCI was 5.7. The most frequently identified individual comorbidities were hypertension (63%), diabetes (30%), and congestive heart failure (29%). The in-hospital mortality rate was 6.6% for IS and 24.0% for HS; for both stroke types the mortality rate was positively correlated with the CCI. A minority of all admitted patients were discharged home (IS: 28.1%; HS: 13.6%). Most patients were discharged to a center requiring additional care and resources (IS: 61.4%; HS: 59.7%); more specifically, a skilled nursing facility (IS: 22.9%; HS: 19.5%), another rehabilitation facility (IS: 15.7%; HS: 15.3%), home health care (IS: 10.9%; HS: 7.1%), hospice care (IS: 5.8%; HS: 4.0%), or any other center providing additional follow-up care (IS: 6.0%; HS: 11.7%). Unknown discharge status was reported for IS: 1.9% and HS: 0.7%.

Conclusion: Among patients with AF, one in twelve experiencing an IS and one in four experiencing a HS did not survive the index hospitalization. Patient care was extended beyond the initial hospitalization in more than half of all patients. To what extent post-discharge care actually increases the direct medical cost associated with stroke events in AF patients could be evaluated in further research.
Ambulatory blood pressure monitoring affects sleep

A retrospective cohort of long-term all-cause mortality and recurrent cardiovascular events in patients with acute coronary syndrome in Thailand

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Objectives: To assess the long-term outcome of patients presenting with acute coronary syndrome (ACS); ST-segment elevation myocardial infarction (STEMI), non-STEMI and unstable angina (UA) in Thailand.

Methods: This is a retrospective cohort study. The data of admission and the vital status were obtained from the records of ICD 10 and ICD 9CM systems of central office for healthcare information and bureau of policy and strategy of Thailand. All patients admitted to the hospitals using 2 health security services of Thailand; national health security (UC) and civil servant (CS) due to ACS in 2005 (from January 1st-December 31st) were collected and followed through 2010. Primary outcome was 5 years all-cause mortality.

Results: A total of 31,087 patients with ACS in 2005 were collected. In-hospital death rate was 14%. A total of 26,722 patients (86%) survived at discharge (UA 51.6%, MI 48.4%). The post-discharge overall all-cause mortality was 11.3% and 40.6% at 1 and 5 years, respectively. At 5 years, post-discharge all-cause mortality of patients presenting with MI was significantly higher than that of UA (43% vs. 38.4%), HR 1.18; 95% CI 1.14-1.23, P < 0.001). Among the patients with MI, those with NSTEMI died after hospital discharge more than those with STEMI (48.7% vs. 37.5%, HR 1.42; 95% CI 1.31-1.53, P < 0.001), despite in-hospital mortality was higher in STEMI. The composite endpoints of death or recurrent MI, death or stroke, death or heart failure were 15.4%, 11.7% and 17% at 1 year. Multivariable analysis of age, sex, diabetes, history of coronary artery disease, co-morbid diseases (ischemic stroke, atrial fibrillation, heart failure, chronic kidney disease), history of in-hospital cardiac arrest showed all these factors were independent risk of death. Patients using CS security service died less than those using UC. Revascularization and CS security service were significantly independent protective factors of death (HR 0.58; 95% CI 0.54-0.63, P < 0.001) for revascularization and HR 0.83; 95% CI 0.79-0.86, P < 0.001 for CS security service).

Conclusion: The post-discharge all-cause mortality and subsequent morbidity burden of ACS in Thailand are still high when compared to other countries. These findings will be useful for the improvement of treatment and health systems in Thailand.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.997</td>
<td>0.974-1.019</td>
<td>0.69</td>
</tr>
<tr>
<td>Gender (male, %)</td>
<td>51.12</td>
<td>1.282-20.38</td>
<td>0.02</td>
</tr>
<tr>
<td>Total mean BP (mmHg)</td>
<td>1.243</td>
<td>1.071-1.396</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day mean BP (mmHg)</td>
<td>1.050</td>
<td>0.986-1.115</td>
<td>0.15</td>
</tr>
<tr>
<td>CF-PWV (mm)</td>
<td>1.004</td>
<td>0.952-1.059</td>
<td>0.87</td>
</tr>
<tr>
<td>24-hr BP</td>
<td>1.992</td>
<td>1.240-3.188</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Conclusion: Our results suggest that diminished nocturnal decline in BP is independently associated with PWV and nocturnal BP rather than day-time BP. Non-dipper pattern, mainly related to increased pulse wave velocity and impaired modulation of vascular smooth muscle tone during the night, may justify an increased cardiovascular risk in these patients.

AMBITUARY BLOOD PRESSURE MONITORING: FOCUS ON NOCTURNAL BLOOD PRESSURE

Non-dipping pattern in untreated hypertensive patients is related to increased pulse wave velocity independent of raised nocturnal blood pressure

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Background: Non-dipper pattern, characterized by diminished nocturnal decline in blood pressure (BP), is associated with an increased risk of cardiovascular events. In this study, we investigated the association between pulse wave velocity as the surrogate of arterial stiffness and non-dipper pattern in untreated hypertensive patients.

Methods: Eighty-four hypertensive patients, consulted for initial evaluation of hypertension, were included in the study. Of the hypertensive patients, 28 were classified as dippers and 28 as non-dippers based on nocturnal BP drops of >10 mmHg and <10 mmHg, respectively. Thrombocyte serotonin levels, serum uric acid, and C-reactive protein (CRP), and urinary albumin/creatinine ratios were analysed.

Results: There is a positive, significant change in the guidelines of the ESC towards the reduction of guidelines based on the expert opinion (Level C) and on divergence in opinion (Class I). Despite many randomized studies published in last years, still less than 25% of current recommendations is based on the strongest evidence (Level A) and an effort should continue to obtain a significant increase in this section.

Table 1. Multivariate logistic regression analysis: Predictors for non-dipping blood pressure pattern among individuals with essential hypertension.

<table>
<thead>
<tr>
<th>Dependent variable: non-dipper hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Gender (male, %)</td>
</tr>
<tr>
<td>Total mean BP (mmHg)</td>
</tr>
<tr>
<td>Day mean BP (mmHg)</td>
</tr>
<tr>
<td>CF-PWV (mm)</td>
</tr>
<tr>
<td>24-hr BP</td>
</tr>
</tbody>
</table>

Conclusion: Our results suggest that diminished nocturnal decline in BP is independently associated with PWV and nocturnal BP rather than day-time BP. Non-dipper pattern, mainly related to increased pulse wave velocity and impaired modulation of vascular smooth muscle tone during the night, may justify an increased cardiovascular risk in these patients.

The use of statistics to improve cardiovascular care / Ambulatory blood pressure monitoring: focus on nocturnal blood pressure
Circadian variation of blood pressure is impaired in dipper status, which is characterized by augmented nocturnal blood pressure decrease in hypertensive patients. In non-dipper hypertensive patients, thrombocyte serotonin levels and CRP were significantly correlated with increased benzodiazepine’s administration, impaired arterial stiffness, and diastolic dysfunction.

**Conclusion:** In non-dipper hypertensive patients, thrombocyte serotonin levels and CRP were significantly correlated with increased benzodiazepine’s administration, impaired arterial stiffness, and diastolic dysfunction.

**Methods:** This cross-sectional study included 230 consecutive patients with never-treated hypertension who presented to our institution for initial evaluation of hypertension. Restless legs syndrome was assessed by a self-administered questionnaire based on the International Restless Legs Study Group criteria.

**Results:** Of the study group, 133 patients were diagnosed as hypertensive (53.4% nondippers) and 81 patients as normotensive (54.3% nondippers). The prevalence of RLS, globally, was significantly higher in nondippers compared with dippers (34.7% vs 21.2%, respectively; p=0.028). Logistic regression analysis showed that the RLS is an independent determinant for both hypertension (odds ratio=0.43 [95% confidence interval (CI)=0.21–0.83; P=0.013]) and the nondipping blood pressure pattern (odds ratio=1.96 [95% confidence interval (CI)=1.05–3.67; P=0.035]).

**Conclusions:** In conclusion, non-dippers compared to dippers hypertensives are microalbuminuric characterized by increased benzodiazepine’s administration, impaired arterial stiffness and more pronounced activation of prothrombotic mechanisms. In addition, they exhibit higher c-PWV values (8.5 vs 7.6 mmHg, p<0.05), increased hs-CRP (2.8±0.8 vs 2.1±0.6 mL, p<0.05) and homocysteine levels (14.6±6.8 vs 11.9±5.4 mmol/L, p<0.05). Benzodiazepine’s administration as anxiolytic was significantly more prevalent among non-dippers compared to dippers (78% vs 23%, p<0.05).
nocturia, and duration in bed. In a multivariate mixed model controlling simulta-
neously for the former confounders, log-transformed UME was significantly asso-
ciated with nocturnal SBP (regression coefficient: -3.6, 95% confidence intervals
[CI] from -7.1 to 0.042). Moreover, to explain this association more prac-
tically, nocturnal SBP was estimated to decrease by 3.2 mmHg (95% CI from 0.1
to 6.4 mmHg) when UME increased from 4.7 μg (1st quartile value) to 11.5 μg
(3rd quartile value; Figure).

Conclusion: An inverse dose–response association exists observed between
UME and nocturnal SBP among elderly individuals.

**CHARACTERIZATION OF ISOLATED NOCTURNAL HYPERTENSION IN ADOLESCENTS**

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Venezuela

Objective: To determine the prevalence and characteristics of isolated nocturnal
hypertension (INH) in adolescents from Maracaibo, Venezuela.

Methods: It was conducted a prospective and transversal study that included
621 subjects, 264 males and 357 females, mean-age: 14.6 ± 1.7 years, who were
underwent 24-h ambulatory blood pressure (BP) monitoring (ABPM) to obtain
BP during awake and sleep periods. The presence of INH was defined as sleep
BP higher or equal than 95th percentile and awake BP less than 95th for age
and gender. Demographic (age, gender), anthropometric data [weight, height, waist
circumference (WC) and hip circumference (HC)] and office blood pres-
sure were registered. Also, serum glucose, lipids, fibrinogen and insulin, as well
as C-reactive protein (CRP) were determined. The prevalence of INH and its 95%
confidence intervals (95% CI) was calculated in all adolescents and by gender.
The ANOVA test was used to study the effects of all factors included in the study
on the INH.

Results: The INH prevalence was 15.8% [n=98; 95%CI: 12.9-18.7] in all sub-
jects, 15.5% [n=41; 95%CI: 11.1-19.9] in males and 16.0% [n=57; 95%CI: 12.2-
19.8] in females (p: NS). Adolescents with INH showed significant higher val-
es than normotensives in the following factors: weight (60.7±16 vs. 54.8±13 kg,
p=0.0001), height (161.7±9 vs. 159.7±10 cm, p= 0.0001), WC (75.1±12
vs. 71.0±10 cm, p=0.0001), HC (93.2±10 vs. 89.3±9 cm, p=0.0001), office
BP (118/74±12±2.9/16 vs. 102.9±11/58.6±6.6 mmHg, p<0.0001) and triglycerides
(89.5±44 vs. 77.7±36 mg/dl, p=0.0001). Age and gender did not show statisti-
cally significant effects on INH.

Conclusions: There is a very high INH prevalence in adolescents. In this age
group, the anthropometric measures are important factors to be evaluated in order
to establish the presence of INH. This condition is extremely important because
from the early age the subjects could be in cardiovascular risk.

**ABNORMAL BLOOD PRESSURE RISE POST MILD EXERCISE PROTOCOL IN NEWLY DIAGNOSED HYPERTENSIVE SUBJECTS IS ASSOCIATED WITH SIGNIFICANT CARDIOVASCULAR FUNCTIONAL/STRUCTURAL ABNORMALITIES**

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Purpose of the study: In previous publications we reported positive correlation
between cardiovascular disease risk and abnormal (Abn.) blood pressure (BP)
rise post mild exercise (PME).

The purpose of this study was to assess whether abnormal BP rise PME in
subjects with newly diagnosed Hypertension (HTN) is associated with func-
tional/structural cardiovascular (CV) abnormalities, which might require more ag-
gressive therapeutic approach.

Methods: We evaluated 2174 consecutive asymptomatic subjects, who pre-
sented to our Center for Cardiovascular Disease (CVD) risk assessment, using
the Early Cardiovascular Disease Risk Score (ECVDRS), age range from 20 to
83 years. The majority of these subjects were self-referred. The ECVDRS con-
sists of 10 non-invasive tests: large (C1) and small (C2) artery stiffness, BP at rest
and PME according to a pre-specified protocol, carotid and abdominal aorta ultra-
sound, retinal photography, Microalbuminuria, ECG, LV ultrasound, and pro-BNP.
We defined HTN according to JNC VII.

Results: Among the subjects screened1277 were not receiving any CV medica-
tions, 198 of them met criteria for HTN: 90 female (45.5%) and 108 male (54.5%).
Among the 198 subjects 36 females (40%) and 40 males (37%) had no other
comorbidities. Detailed results are outlined on table 1.

Conclusion: 1. Asymptomatic newly diagnosed hypertensive subjects with Abn.
BP and PME have significantly higher CV functional/structural abnormalities re-
gardless of sex, than those with normal BP rise PME; 2. Hence we propose that
asymptomatic subjects with newly diagnosed HTN should be screened for ev-
idence of any functional/structural CV abnormalities; which will mandate more
aggressive therapeutic interventions
Combined effects of blood pressure and aldosterone on cardiac left ventricular mass - ethnic differences between Han, Kazakh and Uygur subjects

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Purpose: Hemodynamic factors such as blood pressure have been established to be major determinants of cardiac left ventricular structure. However, factors other than blood pressure have also been shown to influence cardiac mass. We performed a medical survey and found that cardiac left ventricular mass index (LVMI) in an ethnic group of China with higher blood pressure was smaller than in another ethnic group with lower blood pressure. Here, such contradictions were analyzed with regard to blood pressure, LVMI and chemical parameters of blood and urine.

Methods: In a medical survey conducted in Xinjiang, China, 303 subjects (age, 65-70 years) from 3 ethnic groups (Han, Kazakh and Uygur) from two separate regions provided tripotassium and urinary samples, and underwent echocardiography and 24-h ambulatory blood pressure monitoring (AB-PM). The Ethics Committee of Xinjiang Medical University approved all study protocols. All subjects provided informed consent.

Results: Systolic and diastolic blood pressure obtained by AB-PM were significantly higher in the Kazakh than in the Han and Uygur groups. However, LVMI in Kazakh was lower than in other 2 groups. Plasma aldosterone (PA) and plasma renin activity (PRA) were significantly lowest in Kazakh. Values for LVMI in all ethnic groups were positively correlated with both blood pressure and PA. An inverse correlation was observed between PA and urinary sodium excretion value. Although highest blood pressure was seen in Kazakh subjects, LVMI was lower than those of Han and Uygur, who showed lower blood pressure.

Conclusion: These results suggest that blood pressure is not always a determinant of LVMI value. It is possible that relatively low PA resulting from higher sodium intake suppressed the increase in LVMI caused by higher blood pressure in Kazakh subjects.

Ambulatory blood pressure monitoring in hypertensive patients with chronic kidney disease

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Chronic kidney disease (CKD) is predictor of cardiovascular (CV) events in hypertensive patients. But the parameters of ambulatory blood pressure monitoring (ABPM) in hypertensive patients with CKD have not been fully examined. We investigated ABP in a group of non-diabetic hypertensive patients with CKD. Patients with diabetes, a body mass index (BMI) of more than 35 kg/m², CV diseases and a glomerular filtration rate (GFR) of less than 30 ml/min per 1.73 m² were excluded. 120 patients were included into the research. According to the classification of the European cardiology society (2007), all of them suffered from stage I and II arterial hypertension (AH). Of these, 60 patients suffered from AH and CKD who underwent surgery of the upper urinary tract. They made up the first (basic) group in which there were 31 males and 29 females, the mean age was 54.5 ± 12.2 years and the duration of AH was 11.7 ± 1.2 years. The other 60 patients suffered from AH without CKD and they made up the second (control) group in which there were 27 males and 33 females, the mean age was 55.2 ± 1.2 year and duration of AH was 11.1 ± 0.9 years. The patients in both groups were similar in sex, age, duration of AH. The analysis of the results of the 24-hour ABPM revealed that systolic and diastolic blood pressure time indices were more significant in hypertensive patients with CKD than in patients without CKD (69.0 ± 3.1 vs 53.2 ± 3.2 and 63.8 ± 3.6% vs 51.1 ± 3.8%, respectively, p < 0.05). The number of patients with increased 24 hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) variability was more among hypertensive patients with CKD (49.1 ± 3.2 vs 41.6 ± 3.2, respectively; p = 0.005). The number of patients with increased 24 hour SBP and DBP variability was more among hypertensive patients with CKD than in patients without CKD (55.9 ± 3.1 vs 55.3 ± 3.3 mm Hg in hypertensive patients with CKD vs 55.5 ± 3.9 mm Hg in hypertensive patients without CKD). The analysis of distribution of patients according to daily SBP values showed that the amount of non-dipper and night-peaker patients was significantly higher in the basic group than in the control one (48.8% vs 25.4%, respectively, p = 0.05). It was established that the number of patients with DBP daily value ≤ 10 was more significant in hypertensive patients with CKD versus hypertensive patients without CKD (34.1% vs 18.2%, respectively). Hypertensive patients with CKD who underwent surgery of the upper urinary tract in comparison with patients suffering from AH without CKD have significantly more pronounced changes of a daily BP profile.

The association of mean platelet volume levels with subclinical target organ damage in asymptomatic hypertensives

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Background: Significant numbers of asymptomatic hypertensives are attacked by subclinical target organ damages (TOD) such as proteinuria, increased left ventricular mass (LVM) and carotid atherosclerosis because of inadequate treatments. There is increasing evidence that platelets get activated in uncomplicated hypertension and have a crucial role in the increased thrombotic tendency. Mean platelet volume (MPV) is one of the markers that correlate closely with platelet activity.

In our study we aimed to investigate relationship between MPV levels and subclinical early period of TOD in asymptomatic hypertension patients.

Methods and results: Between 901 hypertensive patients (46 male, mean age: 51.8 ± 0.8) with primary hypertension attending the outpatient clinic of our institution were included to the study. 24-hour ambulatory blood pressure monitoring, Echocardiography, carotid ultrasoundography was performed to all patients. MPV was measured from tripotassium EDTA based anticoagulated blood samples and urine albumin/creatinine ratio (UACR) was measured from spot urine samples. The average value of MPV levels, UACR, LVMI and C-reactive protein (CRP) was 5.6 ± 0.42 l/liter and 90.0 ± 0.8 mmo/1.2 ± 2.9 g/m² and 0.94 ± 0.13 mm, respectively. MPV is significantly correlated with 24-hour systolic and diastolic blood pressure (r = 0.51, p< 0.001 and r = 0.55, p< 0.001, respectively). Correlation analyses related to early period of TOD; proteinuria levels (r = 0.50, p< 0.001), LVMi (r = 0.55, p< 0.001) and CRP levels (r = 0.60, p< 0.001). The other significant correlation was determined between MPV and no-CRP levels (r = 0.69, p< 0.001). Multivariate stepwise linear regression analyses identified that MPV levels independently associated with severity of proteinuria (r = 0.45, p< 0.001), CIMT (r = 0.49, p< 0.001) and LVMI levels (r = 0.46, p< 0.001).

Conclusion: These results call to mind that MPV levels could be used as a simple and cheaper marker to interrogate adequacy of anti-hypertensive therapy during 24-hour, to anticipate early period of TOD and intensify therapy to prevent TOD development.

Diastolic but not systolic blood pressure was more significantly affected by the gender in newly diagnosed hypertensive patients with obesity

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Background: Obesity is associated with an increased risk of cardiovascular morbidity and mortality as well as life of quality. Body mass index (BMI) provided the most useful parameter of obesity. The aim of this study, we tried to search the differences in certain well-defined blood pressure pattern according to gender between newly obtained non-obese and non-obese group.

Methods: Total 773 hypertensive patients (442 male, 481yr) enrolled from Korean Hypertension Network II were evaluated in this study. The patients were no history of antihypertensive medication. BP was checked by nurse or doctor in office, self measurement in home and ambulatory monitoring. The study population was divided into two groups based on their BMI (obese group ≤ 24kg/m² and non-obese group II > 24kg/m²). The mean systolic and diastolic BP for both male and female categories of patients were compared between two groups.

Results: In female, there was no significant difference of systolic and diastolic BP measured in office, home and ambulatory monitoring between groups. In male gender, there was no significant systolic BP difference measured in office, home and ambulatory monitoring between groups. Mean diastolic BP in office (97.1± 12.9 vs 94.1± 11.8mmHg, p=0.016), average diastolic BP in AH at home (92± 14 vs. 86± 11mmHg, p=0.001), average diastolic BP in PM at home (92± 14 vs. 86± 11mmHg, p=0.010) and mean diastolic BP in home (91± 12 vs. 87± 11mmHg, p=0.005) were significantly higher in obese group than non-obese group. There was no significant difference between male non-obese and obese groups patients obtained from ambulatory monitoring. Although there was no clinical significance, diastolic mean BP from all measurement included office, home and ambulatory monitoring was higher in obese group than non-obese group.

Conclusions: Diastolic but not systolic blood pressure was more affected by the gender in newly diagnosed hypertensive patients with obesity.
Antihypertensive treatment less efficacious when evaluated by Ambulatory Blood Pressure Monitoring

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Ambulatory blood pressure monitoring (ABPM) is now widely used not only for a better diagnosis of hypertension, but also for considering of antihypertensive treatment.

**Purpose:** We aimed to study the efficacy of antihypertensive drug treatment by analyzing office and ABPM recorded values.

**Methods:** From a database of more than 1000 ABPM recordings we have selected 146 pts whose BP was monitored twice, first without and then 2 weeks after beginning of standard antihypertensive treatment. Office measured, peak and mean (systolic/diastolic) values were selected for comparison. Treatment was considered efficacious when BP values (either systolic or diastolic) were reduced >10 mm Hg, or when were returned to normal (<130/80 mm Hg).

**Results:** At first evaluation Office (syst/dia) BP values were significantly reduced to 138±16 (<p=0.001) and 91±11 mm Hg (<p=0.001). Peak BP values to 167±19 (<p=0.001) and 107±15 (<p=0.001) mm Hg and Mean BP values to 133±14 (<p=0.001) mm Hg, respectively. Office-measured BP values (syst/dia) were reduced >10 mm Hg in 121/146 pts (83%) and were found normal in 82/146 pts (56%).

Peak BP values were reduced >10 mm Hg in 101/146 pts (69%) and were within normal limits in only 40/146 pts (27%). Mean BP values were returned to normal in 110/146 (75%) pts.

**Conclusion:** These data indicate that when evaluated by ABPM antihypertensive treatment results less efficacious than when traditionally evaluated.

AMBULATORY BLOOD PRESSURE MONITORING

**P5032**

Masked hypertension and atherogenesis: the impact of nocturnal continuous positive airway pressure therapy on ambulatory blood pressure in patients with obstructive sleep apnea and prehypertension

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**Purpose:** Recent evidence demonstrates that masked hypertension (MH) is a significant predictor of cardiovascular disease, while hypoapelinemia and hyporelaxinemia may contribute to vascular damage accelerating atherogenesis. Recent evidence demonstrates that masked hypertension (MH) is a significant predictor of cardiovascular disease, while hypoapelinemia and hyporelaxinemia may contribute to vascular damage accelerating atherogenesis.

**Methods:** We aimed to investigate the short term effects of CPAP treatment on blood pressure (BP) and nondipper or dipper status in OSAS patients without a prior diagnosis of hypertension (HT). We included a total of 24 patients (19 male, mean age: 48.7±10.4 years). The study group was divided into 2 groups; group 1 with mild-moderate OSAS (AHI<30) and group 2 with severe OSAS (AHI ≥30). Patients with OSAS were assigned treatment with CPAP. An overnight polysomnography was performed by a computerized system. A 24-h ambulatory monitor (was used to record BP in all patients.

**Results:** Mean ambulatory 24 hour systolic and diastolic BPs were 126.6±9.4 mm Hg and 79.5±10.2 mm Hg respectively. CPAP treatment significantly decreased 24 hour mean BP after 12 weeks irrespective of AHI (89.8±8.4 mm Hg baseline vs 82.9±7.3 mm Hg after 12 weeks, p<0.0001). After 6 weeks CPAP treatment, non-dippers reduced to 16.6% and at the end of 12 week CPAP treatment 12.5% of the patients were non-dipper (p<0.008). Multiple linear regression analysis revealed that male gender, Epworth sleepiness scale, apnea-hypopnea index, smoking and mean 24 hour BP were the predictors of BP reduction in patients between baseline and after 12 week CPAP (p<0.05)

**Conclusion:** Effective CPAP therapy reduces BP levels in OSAS patients without hypertension and improves dipper-nondipper status.

**P5033**

Masked hypertension and atherogenesis: the impact of nocturnal continuous positive airway pressure therapy on ambulatory blood pressure in patients with obstructive sleep apnea and prehypertension

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**Purpose:** Our findings suggest that subjects with masked hypertension have significantly lower apelin and relaxin levels compared to healthy individuals. This observation may have prognostic significance for future cardiovascular events in subjects with masked hypertension and needs further investigation.

**Methods:** Ambulatory blood pressure monitoring (ABPM) is now widely used not only for a better diagnosis of hypertension, but also for considering of antihypertensive treatment. ABPM enables the identification of MH. Previous reports have demonstrated the role of MHT in the outcome of hypertensive patients. However, the true prevalence of MHT in Rtx is still unknown.

**Results:** The prevalence of MHT and nocturnal hypertension in our group were 49% and 61%, respectively. Fifty-four (54%) patients had a history of HT. Fifty-eight (58%) were being treated with antihypertensive medications. Non-dipping was present in 81.5% of patients. There were no significant differences regarding demographic and clinical features between patients with and without MHT (Table).

**Table 1**

<table>
<thead>
<tr>
<th>Age, years</th>
<th>With MHT (n=50)</th>
<th>Without MHT (n=50)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40±11</td>
<td>42±11</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>123±12</td>
<td>122±11</td>
<td>0.79</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>79±5</td>
<td>80±5</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±5</td>
<td>26±4</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>30</td>
<td>24</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>8</td>
<td>4</td>
<td>0.18</td>
</tr>
<tr>
<td>CCB, n</td>
<td>30</td>
<td>28</td>
<td>0.41</td>
</tr>
<tr>
<td>BB, n</td>
<td>13</td>
<td>10</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Conclusion:** We demonstrated an increased prevalence of MHT and BP variability in Rtx population. These results may explain high cardiovascular events in Rtx patients. Therefore routine recommendation of ABPM in Rtx patients may be reasonable.
Metabolic syndrome increases morning blood pressure surge

E. Chatziemmanouil1, G. Moustakas1, E. Androulakis1, D. Tououli1, A. Avgouropouli1, N. Kaloudovius1, M. Dvani1, G. Liakos1, C. Stelfanakis1, I. Malkazaros1, 1Hippokration General Hospital, Cardiology Department, Athens, Greece; 2Ippokration Hospital, University of Athens, 1st Department of Cardiology, Athens, Greece

Purpose: Large scale studies suggests that systolic blood pressure morning surge is an independent predictor of target organ damage. Aim of our study was to investigate associations between 24hr ambulatory blood pressure (ABPM) levels and morning surge in never-treated essential hypertensive (EH) patients with and without metabolic syndrome (MS).

Methods: We studied 366 consecutive newly diagnosed EH patients stage I-III (age 51±12 years, 60% males) without prevalent cardiovascular disease. In all participants anthropometric data were recorded. Also, all subjects underwent a 24-hour ambulatory blood pressure monitoring (ABPM) and morning surge index was calculated as: the mean systolic blood pressure (SBP) during the 2 hours after awakening minus mean SBP during the 1 hour that included the lowest sleep BP. Heart rate variability was calculated as the ratio of day-night mean heart rate difference normalized to mean day heart rate. According to ATP III criteria, the study cohort was divided in two groups: group A (n=210, MS+) and group B (n=156, MS-).

Results: The two groups did not differ regarding age, sex, smoking and snoring status, alcohol and coffee consumption, serum cholesterol, office systolic and diastolic blood pressure and 24h ABPM blood pressure levels. Group B compared to A exhibited increased BMI (31±4 vs. 26±3, p<.001), 24h average (74±9 vs. 72±8, p=.019) and night (66±8 vs. 63±8, p=.002) heart rate, heart rate variability (12±7 vs. 15±7, p=.037) and morning surge index (23±13 vs. 19±12, p=.009).

Conclusion: In never-treated EH patients, the presence of metabolic syndrome unfavourably affects autonomic function as expressed not only by decreased HR variability, but also by increased blood pressure morning surge. These autonomic disturbances may be the link between MS, subclinical target organ damages and prevalent CVD.

A novel non-invasive continuous system for estimating arterial blood pressure: first-in-man clinical results

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Purpose: There was growing interest on noninvasive technologies for arterial blood pressure (BP) measurement on beat-to-beat basis. Our aim was to clinically evaluate the accuracy of a novel device for estimating real-time BP using an algorithm based on pulse-wave transit time (PTT).

Methodology: This device measures PTT between ECG R wave and the onset of photoplethysmography (PPG) and is estimated using an improved technique first reported by Heath. BP estimation involves the delay between R wave and the inflection point of positive slope of PPG and the instantaneous heart rate. PPG sensor was attached to the right index finger. R wave was registered using lead I. Values obtained with this method were compared with a validated oscillometric device (Omron) and were compared with the left arm.

Results: 10 subjects (3healthy/7patients) were evaluated, 5 female. Baseline systolic BP (SBP) was 121.0±8.0/77.0±4.5mmHg, diastolic BP (DBP) was 66.0±5.0/27.0±3.0mmHg and heart rate was 60.0±3.0/56.0±2.5bpm in healthy/patients.

Conclusions: The present study is the first to establish reference and normal values of central BP estimated by Omron HEM-9000AI. This noninvasive estimation shows close correlation with that by SphygmoCor device, but the Omron device requires its own reference values because of technological differences between SphygmoCor and Omron. Thus, the present study was designed to establish normal and reference values for central BP estimated by the Omron device.

Methods: Consecutive 10756 subjects (55.3±12.5 years) who visited our hospital for a health checkup were enrolled in this study. Of these, 7348 subjects received no anti-hypertensive, anti-diabetic, or lipid-lowering drug treatment, constituting the reference value population. Subjects with no cardiovascular risk factors and that were in the optimal or normal brachial BP categories (n=2072) were selected to establish normal values.

Results: Estimated central BP was higher than brachial BP and was significantly correlated with age and brachial BP. Reference and normal values of central BP were established according to age decade (table) and brachial BP categories. Reference values (mmHg, mean±SD) were 113.5±18.6 in optimal, 128.6±14.6 in normal, 138.4±16.8 in high normal, and 155.3±27.9 in hypertension categories and normal values were 112.6±19.2 in optimal and 120.2±14.9 in normal BP categories.

Enhanced external counterpulsation has no lasting effect on blood pressure

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Background: Enhanced external counterpulsation (EECP) has been reported to reduce blood pressure (BP) using clinic BP readings. Purpose: To assess the effect of a course of EECP on BP using ambulatory BP (ABP) measurements.

Methods: Patients referred for EECP due to refractory angina pectoris were consecutively included in the study and treated with EECP for 1 hour 5 days a week in 7 weeks. The ABP were measured for 24 hours using a SpaceLab Ultrafire 90217 device 2 months before an EECP course, just before the EECP course, just after, 3 and 12 months after EECP. The anti-hypertensive medication was held constant during the study period. Changes in BP were tested by repeated measure analyses and changes in anti-hypertensive medication by Friedmans test for related samples.
Results: Fifty patients were included, 72% were males, mean age was 63 years, mean BMI was 29.7 kg/m² and 64% had hypertension. The mean baseline clinic BP was 118/75 mm Hg. Fifty two percent were treated with ACE/ARB, 90% betablocker, 66% calcium antagonist, 92% long acting NTG and 42% with diuretics. The CCS class improved from mean 2.6 to 1.5. No significant change was found in medication. The mean daytime and night time ABP did not change significantly during the study period (p>0.05), see table. Further, when controlling for the variables of baseline ABP level no interaction was found between ABP and baseline level.

Conclusion: EECP treatment has no lasting effect on blood pressure.

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of investigation</th>
<th>Age</th>
<th>y (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive</td>
<td>10/28</td>
<td>175</td>
<td>0.24±0.19 (0.27±0.38)</td>
</tr>
<tr>
<td>Non-Dipper</td>
<td>199/99</td>
<td>61.3±13.18</td>
<td>0.08±0.14 (0.30±0.31)</td>
</tr>
<tr>
<td>Dipper</td>
<td>162/77</td>
<td>55.8±15.70</td>
<td>0.05±0.18 (0.10±0.20)</td>
</tr>
<tr>
<td>Exposed Dipper</td>
<td>16.7</td>
<td>58.1±16.34</td>
<td>0.44±0.21 (0.01±0.26)</td>
</tr>
<tr>
<td>All</td>
<td>448/201</td>
<td>60.4±14.43</td>
<td>0.27±0.19 (0.21±0.29)</td>
</tr>
</tbody>
</table>

r: correlation coefficient; p-value <0.05 = statistical significance.

Conclusion: Systolic BP in ABPM is related to AP in 58.8% of study population. Pts with labile HA and evidence of sensitivity to changes in AP should monitor BP (3.8%).

Figure 1. ROC curves

Conclusions: The CRUSADE and ACUITY-HORIZONS risk scores showed an excellent predictive value for in-hospital bleeding in our cohort of STEMI patients. The CRUSADE risk score seemed to perform better than the ACUITY-HORIZONS risk model for bleeding prediction.
Real-world primary PCI with bivalirudin: a report from the prospective, multi-center EUROVISION registry

U. Limbruno1, A. Picchi2, S. Hassanì3, S. Galli4, B. Cortese5, K. Huber6, J. Lipiecik6, F. Pagani7, M. Sanguinì8, M. Hamon9 on behalf of EUROVISION investigators.1 米色, 2 イタリア, 3 イタリア, 4 イタリア, 5 イタリア, 6 イタリア, 7 イタリア, 8 イタリア, 9 イタリア

Purpose: In primary PCI, bivalirudin (BIVA) is superior to heparin+ GPI/IIa inhibitors (GPI) as shown in the HORIZONS-AMI trial (HOR) due to significant reduction in bleeding and improved survival. However, a higher incidence of acute stent thrombosis was observed in BIVA-treated patients. The purpose of this analysis was to evaluate 30-day outcomes from a real-world STEMI population from the EUROVISION (EUR) registry treated with a BIVA alone strategy.

Methods: Among the 2018 EUR BIVA-treated patients, 663 underwent primary PCI for STEMI. Outcomes measures were 30-day death, re-infarction (MI), stroke, stent thrombosis, urgent revascularization (URV), bleedings, and thrombocytopenia. The net adverse cardiovascular events (NACE) rate combining death, MI, URV and major bleeding was also calculated.

Results: Baseline data from HOR, in EUR patients BIVA infusion was frequently continued post-PCI (62%, median 122 min, 60-296 IQR). Pre-PCI thienopyridine loading was performed in 95%, GPI used in 5%, and radial approach performed in 30% of cases. STEMI patients in EUR were older (p<0.001), but with similar 30-day mortality rate to HOR BIVA-treated patients. Thirty-day outcomes (MI, URV or bleedings) were lower in EUR resulting in lower NACE rates compared with HOR (Table 1). In EUR patients there were no acute (<24 hrs) stent thrombosis cases and no cases of thrombocytopenia.

Conclusions: Real world data from EUR confirm the HOR trial results with a favorable impact of a BIVA alone strategy on STEMI patients’ outcome. Prolongation of BIVA infusion after the end of PCI seems a safe strategy that may further contribute to improve patient’s outcome.

Impact of one versus multiple heparins administration on clinical outcome after primary PCI for STEMI: a prespecified analysis of the ATOLL trial

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Background: The ATOLL trial evaluated the efficacy and safety of IV enoxaparin versus UFH in primary PCI. Patients who had received any antiocoagulation before randomization were not enrolled. Cross over to a different antiocoagulant after randomization was not allowed.

Objective: To evaluate the impact of antiocoagulant cross over on clinical outcome. The primary endpoint was reduced by 11% after anticoagulation with one versus more than one anticoagulant administration as well all its individual components. Conclusively, major and minor bleed was significantly reduced.

Conclusions: In primary PCI for STEMI, crossover to the other antiocoagulant (treatment violation) resulted in significant higher rates of both ischemic and bleed- ing events and should be discouraged.

Thrombus aspiration reduces plaque volume in non-ST elevation acute coronary syndromes: the reduction of myocardial necrosis achieved with nose-dive manual thrombus aspiration study

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Purpose: Thrombus and plaque microembolization is the main cause of myocardial damage during percutaneous coronary intervention with stenting (S-PCI). Thrombus aspiration (TA) has proven useful in limiting myocardial damage in ST-elevation myocardial infarction (STEMI), but its role in non-ST elevation acute coronary syndromes (NSTE-ACS) is not yet defined. We hypothesized that TA reduces the atherothrombotic burden in such patients before S-PCI, thus having the potential of limiting periprocedural myocardial damage.

Methods: Patients with ≥1 “high-grade” (>90%) lesions at coronary angiography subjected to PCI for a NSTE-ACS were submitted to TA before S-PCI. Exclusion criteria were the presence of visible thrombus, total occlusion, degein vened vein graft, restenotic lesions. TA successfully crossed the lesion in 38/45 patients. We evaluated the impact of TA on thrombus burden and lesion characteristics by angiography and intravascular ultrasound (IVUS) before and after TA and after S-PCI. The aspirated material was also processed for histology.

Results: Mean patients’ age was 65±10 years; 82% were male; 34% underwent PCI for a recent STEMI; 66% for a NSTE-ACS. Mean lesion and stent lengths were 25±11 and 26±9 mm, respectively. Drug-eluting stents were used in 5 of cases. Peak CK-MB and cardiac troponin-I were 23.5±9 mg/L and 9.26±23.13 ng/mL, respectively. Main findings as related to the effects of TA are summarized in the Table. The aspirated material was composed of fibrin in 45% of cases, red thrombus in 19%, plaque fragments in 25%, with a lymphocyte infiltration in 16%, and signs of intraplaque hemorrhage in 16%.

Effects of TA on angiographic and IVUS

Conclusions: TA reduces the "mobilizable” atherothrombotic plaque burden and may be safely performed before S-PCI in high-risk NSTE-ACS pts as an alternative to balloon predilation. Data are encouraging for a beneficial role of TA in reducing peri-procedural myocardial damage also in S-PCI in the setting of NSTE-ACS.

Evidence of ischemic post-conditioning in patients with myocardial infarction

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Purpose: Ischemic post-conditioning (PC) has been shown to reduce myocardial
infarction (MI) size. The objective of our study was to determine whether PC has a long-term benefit on left ventricular (LV) remodelling and function in optimally treated patients with MI.

Methods: Patients presenting, within 12h of the onset of chest pain, with a first STEMI, and for whom the clinical decision was made to perform revascularization by percutaneous coronary intervention, were eligible for enrolment. After reperfusion by direct stenting, 47 patients were randomly assigned to either a control (no intervention; n=23) or a post-conditioned group (repeated inflation and deflation of the angioplasty balloon; n=24). MI size was assessed by cardiac enzyme release during 72h after reperfusion. At 3 days and 6 months after MI, LV size and function was evaluated by echocardiography.

Results: The 2 groups had similar ischemic duration, area at risk and medical treatment during and after reperfusion. PC significantly reduced MI size (p=0.02) and no significant improvement on LVEF or wall motion score index (Figure 1). In contrast, PC patients displayed no LV enlargement (90±28 vs. 95±35 mL, respectively; p=0.02) and improved both their LVEF and wall motion score index compared to the initial echocardiography (Figure 1, p<0.05 vs baseline).

Conclusions: Ischemic PC on top of optimal therapy reduces MI size in patients with acute MI and improves remodelling at 6 months compared to controls.

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**Enoxaparin is superior to unfractionated heparin in primary PCI for STEMI: results of the prespecified per-protocol analysis of the ATOLL trial**

J.-P. Collet1, P. Eccotill1, U. Zeymer2, M. Cohen3, P. Goldstein4, C. Pollack5, K. Huber6, E. Vicaut7, G. Montalescot8 on behalf of ACTION. 1AP-HP - Hospital Pitié-Salpêtrière, Paris, France; 2Heart Center Ludwigshafen, Cardiology, Research Institute for Heart Attack, Ludwigshafen, Germany; 3Newark Beth Israel Medical Center, Newark, United States of America; 4Hospital Regional University of Lille, SAMU, Lille, France; 5University of Pennsylvania Medical Center, Philadelphia, United States of America; 6Wilhelminen Hospital, 3rd Department of Internal Medicine, Cardiology and Emergency Medicine, Vienna, Austria; 7AP-HP - Hospital Fernand Widal, University of Medicine Paris 7, Paris, France

**Background:** The ATOLL trial evaluated the efficacy and safety of intravenous enoxaparin versus unfractionated heparin (UFH) in the contemporary interventional management of STEMI. Patients who had received any anticoagulation before randomisation could not be enrolled. Cross over to a different anticoagulant after randomisation was not allowed. Enoxaparin was shown to be significantly better than UFH for all ischemic endpoints without safety issue but the 17% risk reduction of the primary endpoint of death, complication of MI, procedure failure or major bleeding was not significant (p=0.06).

**Objectives and methods:** To present the results of the pre-specified per-protocol analysis excluding patients that received more than one heparin (protocol violation). A total of 850 patients (87.8%) were treated according to the protocol with consistent anticoagulation using enoxaparin (n=463) or UFH (n=387). The per-protocol analyses as for the intent-to-treat analysis were performed in this cohort of patients.

**Results:** Enoxaparin resulted in significantly reduced rates of the primary endpoint and main secondary endpoint (table). The net clinical benefit of death was also reduced with enoxaparin (table). There were favorable trends for enoxaparin on bleeding complications and blood transfusion as well.

**Conclusions:** The per-protocol analysis of the ATOLL trial confirms and reinforces the main findings of the study. Intravenous enoxaparin was superior to UFH on both the primary and secondary endpoints. Most of the benefit is observed on ischemic endpoints. However, in a study with predominant radial access, bleedings tended also to be less frequent on enoxaparin than on UFH. The net clinical benefit was significantly improved with enoxaparin.

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**Effect of mechanical ischemic post-conditioning and microbubble aspiration on microvascular obstruction in patients with acute ST-segment elevation myocardial infarction**

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**Aims:** Mechanical postconditioning during primary percutaneous coronary intervention (PCI) may cause thrombus dislodgement with distal embolization and its combination with thrombus aspiration on microvascular obstruction (MVO) and infarct size (IS) have not been assessed. We assessed the short-term effects of mechanical ischemic postconditioning with or without thrombus aspiration on early and late MVO size, IS and left ventricular ejection fraction (LVEF) in acute STElevation myocardial infarction (STEMI) patients.

**Methods and results:** Fifty-one patients undergoing PCI for a first STEMI with TIMI grade flow 0–1 and no collaterals were randomized to ischemic postconditioning (n=26) or controls (n=25). Ischemic postconditioning consisted in the application of four consecutive cycles of 1 minute balloon occlusion, each followed by 1 minute deflation at the onset of reperfusion. Thrombus aspiration was applied at the discretion of the treating physician. MVO size, IS, LVEF and volumes were assessed by contrast enhanced cardiac-MRI 72 hours after reperfusion. Postconditioning was associated with smaller early (3 minutes post-contrast) and late (10 minutes post-contrast) MVO size (5±6.7 vs. 11.3±11.0 g in controls for early MVO; P<0.02; and 2.5±4.6 vs 5.9±6.1 g in controls for late MVO; P<0.03) even after adjustment for thrombus aspiration. Overall, there was a non-significant
IS reduction in the postconditioning group (29±15 vs. 37±19 g; P = 0.16), but there was a significant IS reduction in infarcts of the anterior territory (35±14 vs. 48±18 g; P = 0.05). No significant difference in LVEF was found between groups but there was a significant dilatation of the LV end-diastolic volume in the control group (P = 0.02). Thrombus aspiration did not have any significant effect on IS or MVO (P = 0.34 and P = 0.42).

Conclusion: Mechanical postconditioning reduces MVO in patients with acute STEMI treated with PCI. The impact of postconditioning seems to be independent of thrombus aspiration and our data suggest that it does not increase distal embolization.

P5050

Addition of ivabradine during beta-blockers titration improves systolic and diastolic LV function in patients with recent Q-wave myocardial infarction

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Heart rate (HR) is a powerful predictor of mortality and heart failure (HF) in pts with acute myocardial infarction (AMI). β-blockers are the first line treatment for these pts but time is needed for their titration and side effects can limit their use in appropriate dose. Ivabradine may be a good alternative for HR reduction during β-blockers titration. 80 pts with recent (36–72 h after symptom onset) Q-wave AMI and HR > 80 bpm were studied; β-blockers were initiated in all the pts. 40 pts were randomized for ivabradine 5mg bid in addition to standard treatment and 40 pts were controls. Dosage of ivabradine was increased to 7.5 mg bid if HR remained > 70 bpm after 24 h of treatment. 69 (86.3%) pts had anterior AMI and 55 (68.8%) pts had symptoms of acute heart failure (Killip II). Study and control groups did not differ in terms of baseline, clinical characteristics, reperfusion and initial treatment. Standard two-dimensional, M-mode, spectral, color and tissue Doppler were performed at baseline and day 7.

Ivabradine significantly decreased HR after the first 24 h of treatment and helped to keep HR 7-10 bpm lower than in control group throughout the period of investigation. Addition of ivabradine to standard recommended treatment improved LV systolic and diastolic function. By day 7, early diastolic velocity of lateral LV corner (E) was significantly higher in ivabradine group than in controls. Ivabradine also prevented left atrial dilatation.

Table 1

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct mass (g)</td>
<td>Infarct thickness (mm)</td>
<td>Infarct length (# slices)</td>
</tr>
<tr>
<td>Infarct mass (g)</td>
<td>Infarct thickness (mm)</td>
<td>Infarct length (# slices)</td>
</tr>
<tr>
<td>EDI, mm²</td>
<td>58.8±1.6</td>
<td>59.3±1.4</td>
</tr>
<tr>
<td>EF, %</td>
<td>39.3±0.8</td>
<td>44.4±0.7</td>
</tr>
<tr>
<td>LA, mm</td>
<td>36.2±0.5</td>
<td>37.5±0.6</td>
</tr>
<tr>
<td>E/A</td>
<td>1.09±0.1</td>
<td>0.98±0.1</td>
</tr>
<tr>
<td>DT, ms</td>
<td>153±17.5</td>
<td>169±3.7</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>87.9±3.9</td>
<td>94.3±5.4</td>
</tr>
<tr>
<td>E', cm/s</td>
<td>6.8±0.4</td>
<td>8.1±0.5</td>
</tr>
<tr>
<td>E/E'</td>
<td>10.9±0.1</td>
<td>9.0±0.4</td>
</tr>
</tbody>
</table>

In patients with recent Q wave AMI and HR > 80 bpm ivabradine can be used during β-blockers up titration for LV systolic and diastolic function improvement.

P5051

The utility of thrombectomy and distal protection in patients with ST-segment elevation myocardial infarction showing poor coronary artery flow prior to primary percutaneous coronary intervention

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Introduction: Previous studies had shown that poor coronary artery flow prior to primary percutaneous coronary intervention (PCI) for STEMI is associated with exacerbated clinical outcomes, although the positive clinical results of the facilitated percutaneous coronary intervention have not been shown. The aim of this study was to evaluate the efficacy of thrombectomy and/or distal protection device in PCI for STEMI patients showing poor pre PCI grade.

Methods: Out of 696 STEMI patients enrolled either in the two multicenter randomized trials (VAPiR trial: tested the efficacy of thrombectomy or aspirin or ASGAVI trial: tested the efficacy of distal protection device), 185 lesions in 185 patients who underwent the primary PCI for proximal or mid left anterior descending coronary artery lesion and have complete sets of angiographic data (Ejection fraction (EF) evaluated by left ventriculography, myocardial blush grade (MBG) and TIMI grade) at baseline and 6-months follow-up were evaluated. Delta EF was calculated by (follow up - baseline).

Results: Table shows the results. MBG 3 was achieved more frequently at pre TIMI 0-1 and 2-3 group. However, in patients who underwent aspiration and/or distal protection, the difference in MBG. 3 rate was insignificant between pre TIMI 0-1 and 2-3 group.

Conclusions: In the present study cohort, poor pre TIMI grade seemed to result to the late exacerbated microcirculation. In patients with STEMI showing poor pre-PCI TIMI grade, thrombectomy and distal protection may be promising remedies for the myocardial salvage with lower risk of bleeding complication.

Table 1

<table>
<thead>
<tr>
<th>TIMI 0-1 (N=128)</th>
<th>TIMI 2-3 (N=57)</th>
<th>p</th>
<th>TIMI 0-1 (N=128)</th>
<th>TIMI 2-3 (N=57)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF baseline (%)</td>
<td>48.4±11.4</td>
<td>48.6±12.4</td>
<td>0.97</td>
<td>48.6±10.6</td>
<td>51.3±11.7</td>
</tr>
<tr>
<td>LVEF follow up (%)</td>
<td>54.3±12.7</td>
<td>56.2±11.2</td>
<td>0.49</td>
<td>56.3±11.8</td>
<td>59.1±10.0</td>
</tr>
<tr>
<td>LVEF delta (%)</td>
<td>6.9±12.6</td>
<td>7.7±10.4</td>
<td>0.53</td>
<td>8.1±12.9</td>
<td>7.1±10.6</td>
</tr>
<tr>
<td>TIMI Grade</td>
<td>3 at post PCI (%)</td>
<td>60.0</td>
<td>82.5</td>
<td>0.036</td>
<td>71.2</td>
</tr>
<tr>
<td>MBG Grade</td>
<td>3 at post PCI (%)</td>
<td>31.3</td>
<td>50.9</td>
<td>0.12</td>
<td>40.9</td>
</tr>
<tr>
<td>MBG Grade</td>
<td>3 at follow up (%)</td>
<td>45.3</td>
<td>68.4</td>
<td>0.003</td>
<td>54.6</td>
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</tbody>
</table>

Conclusions: Despite early revascularization strategies, left ventricular (LV) remodeling and dysfunction after myocardial infarction (MI) remain of clinical significance. Intermittent pacing therapy (IPT) has been shown to limit infarct size and subsequent LV remodeling when applied during early reperfusion. Here we investigated the effects of chronic IPT on global and regional LV function and infarct composition in a preclinical porcine model of reperfused infarction.

Methods: Fourteen pigs underwent proximal LCx ligation for 2h followed by reperfusion to induce a transmural infarction, and were instrumented with a pacemaker connected to an epicardial LV lead positioned in the anterior peri-infarct zone. Three days later, LV function and infarct-size were assessed with 3.0-Tesla cardiac MRI and animals were stratified into Control therapy and IPT groups (after which all pigs survived). IPT consisted of LV pacing twice daily for 3 x 5 min separated by 5 min of normal sinus rhythm until 5 wk post-implantation, after which follow-up cardiac MRI was obtained and myofibroblasts were quantified in the infarct zone, using a muscle mass actin staining.

Results: Although IPT had no significant effect on global LV remodeling or function (data not shown), or infarct mass, it markedly influenced infarct geometry (Table). Thus, in control pigs the reduction in infarct mass over time was principally due to infarct thinning. In contrast, in the IPT pigs it was principally due to decreases in circumference and longitudinal length (both p < 0.05) with no significant change in infarct thickness. Subsequently, histological scoring of myofibroblasts in the infarct zone revealed an increase in myofibroblasts in IPT animals (10.9±2.1%) compared to controls (5.4±1.6%, p < 0.05).

Conclusions: IPT favorably modified infarct remodeling, likely by enhancing myofibroblast numbers in the infarct zone.

ST-elevation myocardial infarction – from risk stratification to therapeutic strategies 907
P5053 Gender differences in major bleeding with bivalirudin: results from the HORIZONS-AMI trial

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Purpose: Previous studies have shown that women are at increased bleeding risk post PCI and primary PCI. Bivalirudin (BIV) has been shown to reduce bleeding complications compared with heparin plus glycoprotein IIb/IIIa inhibitor (HEP + GPI). The purpose of this study was to examine the differential impact of BIV on short- and long-term outcomes (> 1 year) in women vs. men.

Methods: We examined 3-year outcomes from the HORIZONS-AMI trial according to sex and assignment to BIV vs. HEP + GPI. We used Cox proportional-hazards methods with stepwise selection using entry and exit criteria of p < 0.1 to determine the independent predictors of major bleeding among women. Candidate variables tested were assigned to BIV vs. HEP + GPI, age, a history of hypertension, history of smoking, prior MI, prior PCI, prior CABG, Killip class > 1, baseline creatinine, creatinine, radial vs. femoral access, and symptom onset to balloon time.

Results: Women (n=842), as compared with men (n=2760), were significantly older and had higher prevalence of hypertension and hyperlipidemia but were less likely to have a prior history of MI, PCI, CABG or smoking (all p < 0.05). BIV was associated with reduced in-hospital and 30-day major bleeding in both men and women (all p < 0.05). At 3 years, men receiving BIV compared with HEP + GPI had reduced major bleeding (5.3% vs. 1.9%, p = 0.0002), however the difference among women did not reach statistical significance (12.3% vs. 15.1%, p = 0.16). After multivariable analysis, randomization to BIV vs. HEP + GPI showed a trend towards reduced major bleeding among women (Figure 1).

Figure 1. Predictors of 3-year bleeding

Conclusions: In the HORIZONS-AMI trial, BIV significantly reduced short-term and long-term bleeding in men and women, and 3-year bleeding in men. Among women, BIV was associated with a trend towards reduced 3-year bleeding.

ADVANCES IN NON-ST ELEVATION MYOCARDIAL INFARCTION ACUTE CORONARY SYNDROMES – DIAGNOSTICS AND TREATMENT

P5054M Prospective evaluation of the diagnostic accuracy of the novel ESC 2011 guidelines for rapid rule-out of NSTEMI using high sensitive cardiac troponin T


Purpose: High-sensitive cardiac troponin (hs-cTn) assays have been shown to significantly improve the early diagnosis of acute myocardial infarction. The novel 2011 ESC guidelines for the management of acute coronary syndromes in patients with persistent ST-segment elevation contain for the first time a new fast track rule-out protocol including hs-cTn. We intended to verify the safety of this fast track protocol in our prospective study setting.

Methods: Out of our ongoing prospective international multicenter study 1871 consecutive patients who presented with symptoms suggestive of acute myocardial infarction and absence of significant ST-elevations in the ECG were included. The final diagnosis was adjudicated by two independent cardiologists using all available informations including high sensitive cardiac Troponin T (Roche). We examined the diagnostic accuracy of the novel ESC rapid rule-out protocol using the Roche high sensitive cardiac troponin T (hs-cTn, 99th percentile defined as 0.014 μg/L) performed on blood samples obtained in the emergency department at presentation and after 3 hours according to the novel guidelines. All patients were divided in line with the ESC algorithm into the subgroups of late presenters with chest pain onset maximum (COPM) ≥ 6 hours and early presenters with COPM < 6 hours. In the former group rapid rule-out was based on a single measurement using hs-cTnT, and in the latter group on two hs-cTnT values, at presentation and at 3 hours.

Results: Of all late presenters (n=169), 19% (n=117) received the final diagnosis of NSTEMI, compared to 17% (n=214) of early presenters (n=1252). Six late presenters and two early presenters with the final diagnosis of NSTEMI had hs-cTnT levels below the cutoff of 0.014 μg/L. The overall negative predictive value (NPV) applying only the hs-cTnT criteria was for CP: 69.8% (95% CI 96.6 to 99.4%) and for CP: 69.9% (95% CI 97.9 to 99.9%). As one of late presenters had a GRACE Score > 140 and the other was not free of symptoms when the troponin became available after one hour, the NPV increased to 99.2%.

Conclusions: Using a high sensitive assay for troponin T, the novel ESC guidelines provide an effective way of rapid rule-out of NSTEMI with a very high however not perfect negative predictive value. These results indicate some room for formal improvement of the algorithm.

ClinicalTrials.gov number, NCT00470587.

P5055 Usefulness of a 3-hour compared to a 6-hour blood sampling protocol using high-sensitivity cardiac troponin T for rule-out and rule-in of non-STEMI in an unscreened emergency department population

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Background: Current European guidelines recommend use of more sensitive or highly sensitive cardiac troponin assays to reduce the minimal sampling interval from 6 to 3 hours. We evaluated the utility of a shortened sampling protocol using high-sensitivity cardiac troponin T for rule-out and rule-in of non-ST-elevation myocardial infarction (NSTEMI) compared to 17% (n=214) of early presenters (n=1252). Six late presenters and two early presenters with the final diagnosis of NSTEMI had hs-cTnT levels below the cutoff of 0.014 μg/L. The overall negative predictive value (NPV) applying only the hs-cTnT criteria was for CP: 69.8% (95% CI 96.6 to 99.4%) and for CP: 69.9% (95% CI 97.9 to 99.9%). As one of late presenters had a GRACE Score > 140 and the other was not free of symptoms when the troponin became available after one hour, the NPV increased to 99.2%. In this subgroup:

Conclusions: Using a high sensitive assay for troponin T, the novel ESC guidelines provide an effective way of rapid rule-out of NSTEMI with a very high however not perfect negative predictive value. These results indicate some room for formal improvement of the algorithm.

ClinicalTrials.gov number, NCT00470587.

P5056M Who funds the evidence in the ESC guidelines: government or industry? Analysis of class I acute coronary syndrome recommendations from 2011

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Background: There is ongoing heated debate regarding the influence of pharmaceutical industry on clinical guidelines, which has raised questions about whether industry-sponsored trials impact guidelines negatively (or positively). To analyze this issue, we evaluated funding sources for the evidence base of all Class I recommendations put forth by the ESC Guideline committee on Acute Coronary Syndromes (ACS) in 2011.

Methods: After importing all citations listed in summary tables in the ESC ACS guidelines into EndNote citation manager, we excluded those that were not primary publications (e.g. consensus or summary statements) (n=13). Information on financial support was unavailable, either in EndNote or the primary publication, for 2 of 80 citations. For the remaining 78, funding source was determined from the PubMed database in EndNote (or if not specified, the primary publication); for meta-analyses, primary publications were referenced. Based on EndNote category, research support was divided into 3 categories: governmental (gov’l), non-gov’l (typically industry), or mixed. Recommendations were reviewed to determine what percentage of the supporting evidence was funded by gov’l vs. non-gov’l, weighting those in the mixed category equally between the two other categories. Fisher’s exact tests were used to statistically compare these percentages.

Results: Overall, 84% of studies cited to support Class I recommendations were sponsored by non-gov’l/industry sources. Among these, 60% of Class I recommendations, including diagnosis and intervention, pharmaceutical ther-apy, secondary prevention, and special populations had ≥70% of the supporting studies funded by non-gov’l/industry rather than federal sources. Among these,
recommendations on secondary prevention (9 studies) and pharmacological in- terventions (29 studies) were based on the largest amount of non-gov't/industry sponsorship (100% and 93%), compared with bleeding complications (9 studies) and risk stratification (14 studies) (67%, 86%, respectively) (p<0.05 for risk stratification vs. pharmacological intervention). There were no categories of rec- ommendations that relied on a majority of studies funded by gov't.

Conclusion: Based on this categorization, it appears that the funding for the major- ity of the evidence base guiding ESC ACS recommendations comes from non- gov't/industry-sponsored trials. This finding suggests that industry-sponsored tri- als provide an important and positive impact on clinical guidelines in identifying many new strategies and treatments for ACS.

P5059
Performance of high-sensitivity troponin T in the early diagnosis of non-ST-elevation myocardial infarction in elderly patients presenting to an emergency department

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Purpose: Age >65 years has been reported to be the dominant factor associ- ated with elevated high-sensitivity troponin T (hs-cTnT) levels in emergency room (ER) patients. We hypothesized that a protocol implementing a serial hs-cTnT measurement on admission and after 3 hours - as proposed by the latest ESC guidelines - could be beneficial in the rapid rule-out of non-ST-elevated myo- cardial infarction (NSTEMI) in the elderly. Therefore, we examined the accuracy of hs-cTnT for an early diagnosis of NSTEMI in elderly patients presenting to our ER.

Methods: During a 6-month period, we included all consecutive patients pre- senting to our hospital emergency department with an age ≥70 years. Patients with ST-elevation acute coronary syndrome (STEMI), heart surgery or percutaneous coronary intervention within 3 months prior to the index hospital stay were excluded. Measurement of hs-cTnT [Elecys Troponin T high-sensitive, Mannheim, Germany] was performed in a blinded fashion on admission and after 3 hours. Echocardiography was used to rule in or rule out differential diagnosis in all patients. The final diagnosis was adjudicated by two independent cardiologists after reviewing all available medical records.

Results: Among 307 recruited patients (mean age 81±6 years), 206 (67%) pa- tients had elevated hs-cTnT levels ≥0.014 μg/L. 45 (15%) of all patients had a NSTEMI and 161 (52%) were diagnosed as having a non-ACS-condition. The median time from symptom onset to admission was not significantly different in both groups (4.1 vs. 4.7 h, p=0.06). 36% of non-ACS-patients had heart failure, 20% rhythm disorders, 19% severe renal insufficiency, 11% hypertensive heart disease, 6% valve disease, 4% endo/myocarditis and 4% sepsis. Using hs-cTnT levels obtained at 3 hours after admission, the sensitivity was 93.6% and the negative predictive value was 97.1% to rule-out NSTEMI. The diagnostic perfor- mance for the absolute hs-cTnT concentration - as quantified by the area under the receiver operating characteristic curve (AUC) - significantly improved for se- rial measurements from 3 hours after admission (AUC 0.80 vs. 0.84, p=0.0167). The diagnostic delta-changes tended to be better than relatives changes in the entire study population (AUC 0.58 vs. 0.53, p=0.054).

Conclusions: Many elderly patients presenting to the emergency department revealed elevated hs-cTnT mainly due to non-ACS conditions. In elderly patients, a serial measurement in hs-cTnT from admission to 3 hours after admission was beneficial for an early diagnosis of NSTEMI.

P5060
Direct comparison of absolute and relative changes in high-sensitive cardiac troponin I in the early diagnosis of AMI


Background: The current guidelines for the diagnosis of acute myocardial infarction (AMI) require, especially in non-ST-elevation infarction, a rise and/or fall in the levels of cardiac troponin T (cTnT). We evaluated whether absolute or relative changes in high-sensitive cTnI have a higher diagnostic accuracy.

Methods: In a prospective, observational, multicenter study, we analysed the di- agnostic performance of absolute and relative changes in high-sensitive cTnT as measured with a novel pre-commercial prototype assay [Siemens: LioT 0.5ng/l, 99th percentile 9ng/l and <10% CV at 3ng/l] in 1127 patients presenting to the emergency department with symptoms suggestive of AMI. Blood samples were collected at presentation and after 1, 2, 3 and 6 hours in a blinded fashion. The final diagnosis was adjudicated by two independent cardiologists using all available information including hs-cTnT (Roche) levels.

Results: Baseline high-sensitive cTnI levels were higher in patients with AMI (16.4% of the cohort) than in patients with other diagnosis of chest pain (p<0.001).

Figure 1. FFR in acute phase of NSTEMI

Conclusions: These data are consistent with the hypothesis that active vasocon- striction contributes to the coronary obstruction at the level of the culprit lesion in ACS (non-STEMI) patients.

P5058
Release kinetics of cardiac biomarkers in patients with acute myocardial infarction

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Purpose: High sensitivity cardiac troponin T (hs-cTnT) assays have been shown to improve diagnostic sensitivity in patients presenting with symptoms suggestive for an acute coronary syndrome (ACS). However, the release kinetics of cardiac troponin T in patients with acute myocardial infarction (AMI) are difficult to establish.

Therefore, in the present study we aimed to analyze the release kinetics of cTnT in patients with hypertrophic obstructive cardiomyopathy (HOCM) undergoing transcoronary ablation of septal hypertrophy (TASH) as a method uniquely offering a clear-cut definition of myocardial infarction.

Methods: We analyzed the release kinetics of cTnT measured by the 4th gen- eration assay and high-sensitivity assays in patients with HOCM undergoing TASH, a model of acute myocardial infarction (AMI). cTnT measurement (99th percentile (KB)-mass and myocardin were performed additionally. Consecutive patients (n=21) undergoing TASH were included. Serum and EDTA-plasma samples were collected prior to and at 15, 30, 45, 60, 75, 90, 105 mm, and 2, 4, 6, and 24 h after TASH. The blood specimens were sent to the laboratory for centrifugation and frozen storaged at –80 °Celsius until assayed.

Results: Using the 99th percentile cut-off point for a healthy population, hs-cTnT levels raised steadily after induction of myocardial infarction and were significantly increased already after 15 minutes (21.4 ng/L [13.9-39.7] vs. 11.3 ng/L [6.0-18.8]; p<0.03). In comparison, cTnT levels showed the first significant in- crease only after 60 min (30.0 ng/L [18.0-30.0] vs. <1.0 ng/L [<1.0-3.0]; p<0.01). CK-MB mass levels showed a continuous increase with a signifi- cant rise over the upper normal limit after 90 minutes (8.4 μg/L [6.9-14.4] vs. 0.9 μg/L [0.4-1]; P<0.01) and myoglobin at 30 minutes (188.0 μg/L [154.0-230.0] vs. 38.6 μg/L [28.0-56.0]; P<0.01).

Conclusions: hs-cTnT values measured by the hs-assay were significantly increased after TASH at all time points with a doubling at 15 min after induction of AMI, proving earlier evidence of myocardial injury compared to the 4th generation cTnT assay and CKMB and myoglobin.
The area under the receiver operating characteristic curve for diagnosing AMI was significantly higher for 1-, 2-, 3- and 6 hour absolute versus relative changes in hs-TnI (Delta abs: AUC 0.840 (95% CI 0.790-0.890), 0.683 (0.634-0.932), 0.848 (0.790-0.909) and 0.866 (0.802-0.930); Delta rel: AUC 0.711 (95% CI 0.667-0.754), 0.759 (0.709-0.809), 0.732 (0.672-0.792) and 0.744 (0.676-0.812); p < 0.001 for the comparison). The receiver operating characteristic curve-derived cutoff values for 1-, 2-, 3- and 6-hour absolute changes were 8.5, 7, 8.2 and 9.6ng/l, all near the 95th percentile of the hs-TnI assay. Absolute changes at 2 hour were superior to relative changes in patients with both low and elevated baseline troponin levels. Combining the baseline troponin I levels with absolute and relative changes in a logistic regression performed even better in diagnosing AMI for absolute changes (1h: AUC 0.921 vs 0.864, 2h: 0.919 vs 0.866, 3h: 0.923 vs 0.858, 6h: 0.922 vs 0.860; p<0.001 for all comparisons).

Conclusions: Absolute changes of high-sensitive cTnT levels showed a significantly higher diagnostic accuracy for AMI than relative changes, and seem therefore superior in the interpretation of the changes of elevated troponin levels regarding AMI.

**P5063**

**Complementary intravenous Enoxaparin during percutaneous coronary interventions and NSTEMI. Is it necessary?**


**Objectives:** To assess the incidence of thrombotic complications during percutaneous coronary intervention (PCI) in patients (p) with non ST elevation acute coronary syndrome (NSTEMI) pretreated with subcutaneous (sc) enoxaparin (ENX) with two different anticoagulation strategies.

**Methods and Results:** We analyzed two retrospective cohorts of patients with NSTEMI pretreated with sc ENX 1mg/kg and PCI performed within 8 hours after the last dose of ENX. Cohort 1 (C1) includes 48p with additional doses of ENX during PCI from 05/2009 to 12/2010. Cohort 2 (C2) includes 41p with additional doses of ENX at the beginning of PCI from 01/2011 to 01/2012. We evaluated baseline, (10 minutes and 2 hours after iv ENX) activated clotting time (ACT) and antiXa activity (antiXa). Thrombosis was defined as the detection of angiographically visible thrombus not present previously or macroscopic thrombus observed in the material in contact with the visceral blood (guiding catheter angioplasty guidewires) during the procedure that required specific treatment. The primary endpoint was the incidence of thrombosis (including catheter thrombosis). Secondary endpoints were: incidence of bleeding complications, in-hospital and 30 days death and non fatal acute myocardial infarction (AMI). Both groups had comparable baseline characteristics. There were no differences in baseline levels of ACT or antiXa. The incidence of thrombosis was 37.5% (18/48p) in C1 versus 2.4% (1/41p) in C2 (p=0.007; OR 0.058). There were no bleeding complications in either group nor any differences in mortality (2.2% C1 vs 2.4% C2) or AMI (0.2% C1 vs 0% C2) at 30 days. There was a greater need for additional doses of unfractionated heparin and/or ENX during PCI in C1 (31% C1 versus 2.4% C2). In C2 antiXa level 10 minutes after bolus administration was 145±0.55 and 2 hours after was 1.13±0.40. In C2 ACT level 10 minutes after bolus administration was 189±49 sec. In the multivariate analysis, the administration of bolus of ENX (p=0.011; OR 0.019) showed a protective effect while the total duration of the procedure (p=0.014; OR 1.034) was related to thrombotic complications.

Conclusions: A high incidence of thrombotic complications occurs during PCI performed within 8 hours after the last dose of sc ENX in patients with NSTEMACS. The intravenous administration of an additional ENX bolus of 0.5mg/kg at the beginning of the PCI significantly reduces the incidence of such complications while AntiXa levels observed after this extra bolus are within the safety range reported in previous studies.

**P5064**

**Early diagnosis of acute myocardial infarction in patients with kidney disease using more sensitive cardiac troponin assays**

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**Purpose:** The rapid and reliable diagnosis of acute myocardial infarction (AMI) is a major unmet clinical need, particularly in patients with kidney disease (KD), who are known to have elevated levels of cardiac troponins (cTn) already in the absence of AMI, which may lead to a lower diagnostic value of cTn in this high-risk subgroup.

**Methods:** We conducted an international multicenter study to examine the diagnostic accuracy of new, more sensitive cTn assays in 1291 consecutive patients presenting to the ED with symptoms suggestive of AMI, of whom 186 (14%) were patients with kidney disease (KD). The performance of the NIH consensus-operated NSTEMI patients and MVO and papillary muscle involvement correlate with infarct size. Further studies are warranted to prove clinical significance of described characteristics.
greater for the sensitive cTn-assays compared to the standard assay (AUC for hs-TnT, 0.88; TnI Ultra, 0.89; and TnI Abbott, 0.89 vs. AUC for the standard assay, 0.83, p<0.05 for all comparisons). In patients presenting within three hours after the onset of chest pain, TnI Ultra (AUC 0.90) and TnI Abbott (AUC 0.93) were superior to hs-TnT (AUC 0.82; p=0.05 and p=0.015 for comparisons, respectively) and TnT4 (AUC 0.73; p<0.01 for both comparisons), whereas hs-TnT no longer performed superior to TnT4 after (p=0.07). Using the predefined 99th-percentile cutoff of the sensitive cTn-assays, specificity and diagnostic accuracy was significantly reduced in KD-patients compared to the subgroup with normal kidney function, whereas sensitivity remained similar.

Conclusions: Sensitive cTn-assays have high diagnostic accuracy also in KD and are superior to conventional cTn-assays. In addition, there seems to be a difference among the sensitive assays in the early presents with a higher diagnostic accuracy of TnI Ultra and TnI Abbott as compared to hs-TnT. Mild elevations are common in non-AMI patients and test-specific optimal cut-off levels tend to be higher in KD-patients than in patients with normal kidney function.

**Use of troponin testing in internal emergency medicine**

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Purpose: Troponin is recommended as the preferred biomarker for the diagnosis and risk stratification of non-ST myocardial infarction (NSTEMI). Per definition, the diagnosis AMI requires not only a positive test result but also corresponding signs and symptoms. We analyzed the association of chief complaint, cardiac main hospital diagnoses and troponin testing in two large EDs over a one-year period to evaluate its use in Emergency Medicine.

Methods: Data of all 34,333 patients who presented to either one of the two EDs were retrieved from the hospital information system. The patient’s chief complaint was documented in the electronic ED form by the treating physician.

Results: Troponin testing was performed in 38.1% (n=13,071) of all patients. Of these, 23.3% presented with chest pain, 10.4% with dyspnea, 5.8% with abdominal pain, 3.3% with headache. The vast majority (57.1%) presented without one of these pre-specified chief complaints. Of all patient tested, 10.4% had a positive test result at admission, of these 24.6% with chest pain, 22.1% with dyspnea, 2.5% with abdominal pain, 0.6% with headache and 50.2% with none of these symptoms. Even though 52.3% had a cardiac main hospital diagnosis, only 4.6% were diagnosed with a NSTEMI and 2.5% with a STEMI.

Conclusion: Troponin was tested in almost 40% of the patients at admission to the ED, a quarter of those tested presented with chest pain. A total of 10% of patients tested had a positive troponin result at admission and only 7% were Finally diagnosed with acute myocardial infarction. Troponin testing requires a clear indication and should not be used as a screening test in patients without a well justified reason to suspect ACS.

**Early strain echocardiography may exclude high-grade coronary artery stenosis in suspected non-ST-elevation acute coronary syndrome**

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Purpose: Many patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS) do not have significant coronary artery disease. Current diagnostic approach with repeated ECG and cardiac biomarkers requires observation for >6-12 hours. The aim of this study was to investigate whether global strain by echocardiography measured at admission may exclude high-grade (>75%) coronary artery stenosis in patients presenting with inconclusive ECG and normal cardiac biomarkers.

Methods: Patients with suspected NSTE-ACS were consecutively enrolled. 12-lead ECG, Troponin T assay and echocardiography were performed on admission. Patients underwent coronary angiography after 27±18 hours. Conclusively ECG was >1 mm ST-segment change in any lead and Troponin T >0.03 μg/L was considered abnormal. Global peak systolic longitudinal strain (GLS) was measured using speckle tracking echocardiography in the 3 apical image planes and calculated from a 16 segment model.

Results: Out of 134 patients admitted with suspected NSTE-ACS, 41 patients presented without known coronary artery disease, inconclusive ECG and Troponin T <0.03 μg/L. GLS was -18±3% in those with high-grade stenosis (n=22) and -22±2% in those without high-grade stenosis (n=19). In a receiver operator characteristic curve analysis, GLS (AUC=0.90) was significantly better than both WMSI (AUC=0.72) and EF (AUC=0.65) at discriminating between no high-grade and high-grade coronary artery stenosis (p<0.01). A GLS of <20% excluded high-grade coronary artery arteriostenosis with 90% sensitivity and 96% specificity.

**The diagnostic accuracy of novel biomarkers of myocardial injury in the unsolicited emergency room population**

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Objective: To examine the diagnostic accuracy of novel biomarkers of myocardial injury compared to highly sensitive troponin assays for the diagnosis of myocardial infarction using the universal definition of myocardial infarction.

Methods: The study was a sub study of the point of care arm of the RATPAC trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers), set in the emergency departments of six hospitals. Prospective admissions with chest pain and a non-diagnostic echocardiogram were randomised to point of care assessment or conventional management. Blood samples were taken on admission and 90 minutes from admission for measurement of a panel of cardiac markers. An additional blood sample was taken at admission and 90 minutes from admission, separated and the serum stored frozen until subsequent analysis. Samples were analysed for high sensitivity cardiac troponin I (cTnI) by the Stratux CS (CS) for cardiac troponin I (cTnI) by the Roche high sensitivity cardiac troponin T assay, for heart fatty acid binding protein (hFABP) and copeptin. Diagnostic accuracy was compared by construction of receiver operator characteristic curves against the universal definition of myocardial infarction utilising laboratory measurements of cardiac troponin performed at the participating sites together with measurements performed in a core laboratory.

Results: Admission samples were available from 838/1132 patients enrolled in the study. There were 66 patients with a final diagnosis of myocardial infarction. Areas under the curve were as follows (confidence intervals in parentheses) cTnI CS 0.94 (0.90-0.98), cTnT 0.92 (0.98-0.96), FABP 1.04 (0.77-0.90) copeptin 0.62 (0.57-0.68). Both hFABP and copeptin were diagnostically inferior to troponin. The combination of hFABP(at the 95th percentile) and either troponin (at the 99th percentile) increased diagnostic sensitivity to cTnI CS 0.794 (0.673-0.885) to cTnI CS + hFABP 0.921 (0.824-0.974), cTnT 0.778 (0.655-0.873) to cTnT + hFABP 0.857 (0.746-0.933) with a small loss in specificity, cTnI CS from 0.980 (0.967-0.989) to 0.923 (0.901-0.941) cTnT from 0.962 (0.946-0.975) to 0.916 (0.894-0.935). Addition of copeptin (from an optimised decision level) increased sensitivity for cTnI CS to 0.905 (0.804-0.964) but reduced specificity to 0.591 (0.555-0.626) and for cTnT to 0.841 (0.727-0.921) but reduced specificity to 0.596 (0.561-0.631).

Conclusions: Additional measurement of copeptin is not useful in the chest pain population. Simultaneous measurement of hFABP improves sensitivity.
Reduction of medical consumption in low risk chest pain patients

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Background: Patients with chest pain are often admitted for clinical observation, and treated as ACS awaiting final diagnosis. Consequently, unnecessary diagnostics and treatment are common. The HEART score serves the making of a quick diagnosis and consists of five elements: History, ECG, Age, Risk factors and Troponin.

Methods: This study was performed in 260 patients in three hospitals in the Netherlands. These patients were participating in a prospective validation study of the HEART score in 2388 chest pain patients in the ED of ten hospitals. Numbers of hospitalization days, exercise tests, echocardiography and various other cardiac investigations were counted.

Results: Chest pain patients visiting the ED were classified as low-risk, based on the HEART score, in 102/280 (36.5%) of the cases. MACE did not occur in these patients.

Conclusion: When a policy would be made to withhold redundant medicine in low-risk chest pain patients, with a HEART score ≤3, hospitalizations would be saved in one fifth and various examinations in half of the patients. Improved risk stratification in chest pain patients may result in a reduction of medical consumption.

Mitrail annular excursion in patients with suspected non-ST-elevation acute coronary syndromes

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Background: Many non-ST-elevation acute coronary syndrome (NSTE-ACS) patients have coronary occlusions but do not receive acute reperfusion therapy as the occlusion is not readily identified. Identification and closer follow up of high-risk patients may reduce mortality. Mitral annular excursion (MAE) reflects the global longitudinal shortening deformation of the left ventricle (LV). We therefore hypothesized that MAE may differentiate between coronary occlusion and non-occlusion in NSTE-ACS patients, and predict mortality.

Methods: 167 patients were examined in relation to NSTE-ACS at two Scandinavian centers. 47 healthy individuals were used as controls. Tissue Doppler by echocardiography was done at the mitral level of the LV in three apical planes, and a mean MAE value was acquired from a newly developed software (Gripping Heart AB, Stockholm, Sweden). Mortality data was collected over a mean period of 1477 days.

Results: MAE was significantly reduced in NSTE-ACS patients as compared to healthy individuals (9.5±2.1mm vs. 13.1±2.0mm, p<0.001). Median Peak CK rise was higher in group A than group C (940IU/L vs 571 IU/L; P=.01), but was similar 74% for group B (P=.93), and 63% for group C (P=.11). Median Peak CK rise changes/within normal limits.

Conclusion: A significant minority of ECG protocol negative cases were found to have an acute vessel occlusion with comparable biomarker rises to the protocol positive group suggesting significant myocardial infarction.

Risk stratification in non-ST-elevation Acute Coronary Syndromes: utility of using both GRACE and CRUSADE models

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Background: According to ESC guidelines, patients (pts) presenting with non-ST-elevation acute coronary syndromes (NSTE-ACS) should have their prognosis and bleeding risk determined using established risk scores (RS), namely GRACE RS for in-hospital mortality and ischemic events and CRUSADE RS for bleeding. However, the clinical implications and utility of combining both risk scores is less well established.

Aim: Evaluate how risk stratification combining GRACE and CRUSADE performs in pts with NSTE-ACS

Methods: Analysed 1425 pts (66±13 years, 72% male) with NSTE-ACS, consecutively included in a nationwide registry. CRUSADE RS and CRUSADE RS at hospital admission were calculated for each patient and tested, respectively, for group B (940IU/L vs 925IU/L; P=.28). Age, vessel treated, and mortality are shown in the table. Cardiovascular risk factor prevalence did not differ between groups.

Conclusion: A significant minority of ECG protocol negative cases were found to have an acute vessel occlusion with comparable biomarker rises to the protocol positive group suggesting significant myocardial infarction.
predicting in-hospital death and major bleeding (defined using CRUSADE crite-
rion). Pts were divided according to low, intermediate or high risk of fatal events, using GRACE RS (≤ 108, 109-140 or >140, respectively) and then sub-stratified into low, intermediate or high risk of major bleeding, according to CRUSADE RS (≤31, 31-40 or >40, respectively). In-hospital pharmacological treatment, pro-
cedures and events were compared between groups.

Results: GRACE and CRUSADE had a good performance in predicting in-
hospital death (AUC 0.880, p<0.001) and major bleeding (AUC 0.755, p<0.001), respectively. Only 53% of pts had a concordant risk by both RS (table). Sub-
stratification using CRUSADE was useful for identifying major bleeding risk across all categories of GRACE RS. Use of ibi/IIa inhibitors, fondaparinux and radial ac-
cess for catheterization diminished with increasing bleeding risk (p<0.001).

Conclusion: Both GRACE and CRUSADE RS have good performance for pre-
dicting in-hospital death and major bleeding, respectively. Half of NSTE-ACS pts have a discordant fatal and bleeding risk. CRUSADE RS can be used for identi-
ifying pts at risk of bleeding events, independently of risk estimated with GRACE RS.

P5072 Rapid rule-out of NSTEMI by using a high sensitive prototype assay for troponin I: a prospective evaluation of the safety of the novel ESC 2011 guidelines

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Purpose: High-sensitive cardiac troponin (hs-cTn) assays have been shown to significantly improve the early diagnosis of acute myocardial infarction. The novel 2011 ESC guidelines for the management of acute coronary syndromes in pa-
tients without persistent ST-segment elevation contain for the first time a new fast track rule-out protocol including hs-cTn. We intended to verify the safety of this fast track protocol in our prospective study setting.

Methods: Out of our ongoing prospective international multicenter study 1102 consecutive patients who presented with symptoms suggestive of acute myocardial infarction and absence of significant ST-elevations in the ECG were included. The final diagnosis was adjudicated by two independent cardiologists using all available informations including high sensitive cardiac Troponin T (Roche). We examined the diagnostic accuracy of the novel ESC rapid rule-out protocol using the pre-commercial Beckman Coulter high sensitive cardiac troponin I assay (hs-
cTnI, 99th percentile defined as 9.2 ng/l) performed on blood samples obtained in the emergency department at presentation and after 3 hours according to the novel guidelines. All patients were divided in line with the ESC algorithm into the subgroups of late presenters with chest pain onset/maximum (CPM) ≥ 6 hours and early presenters with CPM ≤ 6 hours. In the former group, rapid rule-out was based on a single measurement using hs-cTnI and in the latter group, on two hs-cTnI values, at presentation and at 3 hours.

Results: Of all late presenters (n=393), 17% (n=67) received the final diagnosis of NSTEMI, compared to 15% (n=104) of early presenters (n=708). Three late presenters and three early presenters with the final diagnosis of NSTEMI had hs-cTnI levels below the cutoff of 9.2 ng/l. The overall predictive negative value (NPV) appeared only the hs-cTnI criteria was for CPM ≤ 6h 98.7% (95% CI 98.6 to 99.9%) and for CPM ≤ 6h 98.7% (95% CI 96.3 to 99.7%). All missed patients had a GRACE Score below 140. As two late and two early presenters were not free of symptoms at the point of time when the decisive troponin became available, the NPV increased to 99.6% in both subgroups.

Conclusions: Using a novel high sensitive prototype assay for troponin I, the ESC rapid rule-out protocol provides an effective way of rapid rule-out of NSTEMI with a very high however not perfect negative predictive value. (ClinicalTrials.gov num-
ber, NCT00470587)

P5073 The nature and clinical outcomes of total occlusion in non-ST-elevation myocardial infarction: is it bad or good?

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Background and Objectives: Non-ST-Elevation MI is a different disease entity from ST-elevation MI. But while undergoing coronary angiography, there are les-
sions in NSTEMI with TIMI grade 0,1 showing near total occlusion. Therefore the definition of occlusion in non-ST elevation MI is still uncertain. The purpose of this study was to compare the baseline characteristics, treatment strategies, and clinical outcomes of patients with and without occluded culprit arteries.

Subjects and Methods: In 2011, 5649 patients were registered in COREA-AMI (Convergent Registry of Atherothrombosis and chronic MI for AAMI) registry. 2324 patients were NSTEMI, and we divided these patients into two groups, based on TIMI flow. Occluded lesion was defined as a lesion with TIMI 0 or 1, 1099 patients had occluded lesion, and 1315 patients had non-
occluded lesion. We compared baseline characteristics, ECG findings, in-hospital treatment, and long-term outcomes between patients with and without occluded culprit arteries.

Results: In baseline characteristics, initial creatine level, peak troponin be-
fore PCI, initial ejection fraction in echocardiography, total stent length, follow-
up hsCRP showed significant difference between two groups. Also former as-
pin, statin, metformin use was different between two groups. Total occlusion in NSTEMI was frequent in left circumflex artery. Using multivariate cox-regression analysis, the hazard ratio for occluded infarct artery was 1.67 (95% confidence interval 1.30-2.70, p=0.03). Kaplan-Meier curve for median follow-up of 6 months showed a significant difference between occluded and non-occluded lesion group.

Conclusion: In NSTEMI, occluded lesion showed poor outcome than non-
occluded. Whether this remains a true hypothesis in STEMI is still a ques-
tion to solve, and the comparison between totally occluded NSTEMI and STEMI will be studied soon.

NEW INSIGHTS IN POST-MYOCARDIAL INFARCTION FOLLOW-UP

P5074 One-year risk of stroke following acute myocardial infarction

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Background: Ischaemic stroke following acute myocardial infarction (AMI) is an important complication. It is unknown whether the risk has changed as the treatment of AMI has improved during the last decade, particularly in terms of antithrombotic, lipid lowering and reperfusion treatment. There is also conflicting data about predictors of stroke risk.

Methods: To obtain the one-year incidence of stroke following AMI, the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) database for the years 1998 to 2008 was merged with the Swedish National Patient Registry (PAMR). The study was divided by dividing the entire time period into five separate periods. Independent predictors were identified using a multivariable Cox proportional hazards regression model.

Results: Between 1998 and 2008, 7108 out of 173233 patients with AMI suffered an ischaemic stroke within one year (4.1%). The years 2007/2008 were associated with a 21% relative risk reduction, com-
pared to the years 1998-2000, RR 0.86 (95% CI 0.80-0.93), p<0.001. A reduced risk of stroke was also found for the years 2003/2004 and 2005/2006, compared to 1998-2000, RR 0.86 (95% CI 0.80-0.93), p<0.001, and 0.81 (95% CI 0.75-0.88), p<0.001, respectively.

Independent predictors of stroke were age, female sex, STEMI, prior stroke, diabetes mellitus, heart failure at admission and atrial fibrillation. Reperfusion treatment with fibrinolysis and PCI and treatment with aspirin, P2Y12-inhibitors and statins predicted a reduced risk of stroke.

Conclusions: The risk of ischaemic stroke within a year following myocardial in-
farction is substantial but has clearly been reduced during the studied time period. The predictive factors found correlate well with previous investigations. Reperfu-
sion treatment, thrombocyte aggregation inhibition and lipid lowering are the main contributors to the observed risk reduction.


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Purpose: Recent evidence suggests improvements in provider care for acute my-
ocardial infarction (AMI) and significant reductions in in-hospital mortality across
High 3-year-mortality rates in females with newly diagnosed diabetes after acute STEMI and NSTEMI in clinical practice in Germany: results of the Sweetheart-registry


Background: Many patients with coronary artery disease suffer from diabetes and its pre-states. Joint guidelines by the ESC and the EASD recommend testing for diabetes using OGTT in patients with established CAD and without previously known diabetes.

Methods: Since 2007, 2,767 consecutive patients with STEMI or NSTEMI were enrolled into the MI-registry SWEETHEART to identify abnormal glucose metabolism and to document acute treatment and outcome. In patients with previously unknown diabetes, oral glucose tolerance test (OGTT) was performed at day 4 after acute MI. We examined gender differences in the prevalence of abnormal glucose metabolism and the impact of newly diagnosed diabetes on 3-year-mortality of MI.

Results: Female patients with MI were older, less often had prior MI and prior PCI as compared to males. Female patients had a higher rate of known diabetes as well as a longer duration of diabetes at the time of MI. The prevalence of newly diagnosed impaired glucose metabolism was much higher in females than in males. In females, OGTT identified another 19.8% with manifest diabetes and 18.1% with impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) as compared to 15.3% and 23.3% in males respectively. After 3 years of follow-up, female patients with newly diagnosed diabetes had a 30.5% mortality similar to that of females with already known diabetes (30.0%).

Conclusion: Although the prevalence of known diabetes was already much higher in females, the rate of newly diagnosed diabetes was significantly increased in females as compared to males. Females with newly diagnosed diabetes had the same 3-year mortality as those high risk patients with MI and already known diabetes.

References:

The rs12526453 polymorphism in intron of the PHACTR1 gene is associated with 5-year mortality of patients with STEMI

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Purpose: The rs12526453 (C/G) is a single nucleotide polymorphism in intron of PHACTR1 (5’ UTR). The purpose of this study was to investigate the association of the polymorphism with 5-year mortality risk in STEMI patients.

Methods: We included in our registry consecutive patients with STEMI treated with primary PCI who survived ≥48 hours from hospital admission. Genotyping was performed with a TaqMan SNP Genotyping Assay using the ABI 7500 Real Time PCR System (Applied Biosystems). The analyzed end-point was all-cause mortality with a mean follow-up of 3 years.

Results: The study group comprised 629 patients (mean age 62.2 ± 15.0 years, 72.9% males, 27.1% females). The proportion of patients with AMI achieving an OBCS for aspirin, ACE-inhibitor, statin, β-blocker, and referral for cardiac rehabilitation were 479/629 (76.7%) in 2004 and 2005, respectively. The proportion of patients achieving an OBCS > 80% was lower in females than males (P < 0.001), and decreased with increasing age group for STEMI (P < 0.001) and NSTEMI (P < 0.001). Of patients >80 years, only females with STEMI did not show a significant reduction in 30-day mortality risk. Male STEM1 and NSTEM1 demonstrated significant reductions in 30-day mortality risk, except STEMI aged > 80 years. For females, the only group to demonstrate a significant reduction in 30-day mortality risk were those aged > 80 years with NSTEMI.

Conclusions: In England and Wales, for patients hospitalized with AMI there are sex- and age-dependent differences in temporal improvements in 30-day mortality risk. The proportion of patients with an OBCS > 80% increased over time, 2004/5: 84.0%, 2006/7: 90.0%, 2008/9: 93.2%, P < 0.001. Compared with in-hospital mortality, equivalent temporal improvements in mortality do not appear to extend beyond the hospital stay for all groups of patients.

Conclusion:

The rs12526453 polymorphism in intron of the PHACTR1 gene is associated with increased 5-year mortality in patients with STEMI treated invasively.


The clinical significance of right ventricular dysfunction with or without pulmonary hypertension after acute myocardial infarction

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Background: Right ventricular (RV) dysfunction may accompany inferior wall infarction and is not uncommon in patients with acute anterior infarction. Pulmonary hypertension (PH) may exacerbate RV dysfunction (RVD). However, with severe RVD, pulmonary arterial pressure may decrease as a consequence of low RV output. We sought to determine the prognostic implications of RVD in relation to PH in acute myocardial infarction (AMI).

Methods: Echocardiography was performed in 1054 patients with AMI. RV function was assessed both visually and by measuring the RV fractional area change (RV-FAC). Patients were classified into 4 groups according to the presence or absence of pulmonary hypertension (estimated pulmonary artery systolic pressure > 35 mmHg by echocardiography) and RV (RV-FAC < 35%). The primary end-point was all-cause mortality with a mean follow-up of 3 years.

Results: RV was present in 141 patients, with 91 (6.8%) and 50 (4.7%) patients with and without PH, respectively. Compared with patients with RVD without PH, patients with RVD and PH presented with higher Killip class (Killip class II or higher: 48% vs. 14%, P = 0.01) and were more likely to have reduced left ventricular (LV) systolic function (LV ejection fraction ≤ 45%: 71% vs. 44%, P = 0.01).
The results of a multivariable Cox regression model are shown in the Figure. Patients with RVD and normal pulmonary pressures had the highest adjusted risk for mortality.

Conclusion: Patients with RVD without PH are at a particularly high risk for mortality despite better LV systolic function. These results emphasize the importance of interpreting RV function in combination with pulmonary pressures data.

**Background:** Risk of myocardial infarction (MI) in HIV infected patients is increased and short term prognosis is good. One year outcome remain to be determined in large scale study.

**Methods:** From the French nationwide hospital medical information database, all the consecutive patients hospitalized in the 1546 French hospital/clinics for myocardial infarction from 1st January 2005 to 31st December 2009 were included. We compared one year outcome between patients infected or not by HIV.

**Results:** Among the 628454 patients included, 1286 (0.2%) was infected by HIV. At one year of follow-up, we observed an increased rate of recurrent MI in HIV-infected patients than non-infected patients (14.9% vs 12.9%; p=0.02) and respectively 14.9% vs 11.3% (p<0.01) in a sub-group of patients matched for age, sex and type of MI (ratio 1:2).

**Conclusion:** From our large scale nationwide study, HIV patients have an increased risk of recurrent MI during follow-up, thus emphasizing the benefit of secondary prevention in such patients.

**P5079 One year outcome in HIV-infected patients with myocardial infarction**

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**Background:** Several high-sensitive cardiac troponins (hs-cTn) have recently been introduced. It is unknown which hs-cTn is most accurate for long-term prognosis and whether early changes improve prognostic accuracy.

**Methods:** In a prospective, international multicenter study, hs-cTn was measured with three assays (hs-cTnT, Roche Diagnostics; hs-cTnI, Beckman-Coulter; hs-cTnI, Siemens) in a blinded fashion at presentation and 1 hour later in 849 unselected patients with acute chest pain. Patients were followed-up 2 years regarding mortality.

**Results:** Acute myocardial infarction was the adjudicated final diagnosis in 150 (17.7%) patients. 62 (7.3%) patients died during the first 2 years. The prognostic accuracy of hs-cTnT (Roche Diagnostics) at presentation for mortality in the first 2 years as quantified by the ROC curve (AUC) was 0.756 (95% CI 0.726-0.785) and outperformed both hs-cTnI (Beckmann-Coulter) 0.704 (95% CI 0.672-0.734; p=0.029 for comparison) and hs-cTnI (Siemens) 0.687 (95% CI 0.653-0.718; p=0.010 for comparison) (Figure 1). Absolute changes in the first hour of hs-cTnT were more accurate than relative changes (AUC 0.660; 95% CI 0.627-0.692 vs. 0.512; 95% CI 0.477-0.548; p=0.035 for comparison) (Figure 2). Combining presentation values of hs-cTnT with the first hour did not further improve their prognostic accuracy (AUC 0.747; 95% CI 0.717 to 0.776; p=0.064 for comparison). Similar results were obtained for both hs-cTnI assays regarding the incremental value of changes.

**Conclusion:** Hs-cTnT seems to be more accurate than hs-cTnI in the prediction of long-term mortality. Absolute changes outperformed relative changes in the first hour as to long-term mortality in all three hs-cTn assays but were inferior to respective presentation values.

**P5081 Large differences between patients with acute myocardial infarction included in two Swedish health registers**

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**Background:** Acute myocardial infarction (MI) is a leading cause for morbidity and mortality in Sweden. We aimed to compare patients with an acute MI included in the Register of information and knowledge about Swedish heart intensive care admissions (RIKS-HIA, now included in the register Swedeheart), and the Swedish statistics of acute myocardial infarctions (S-AMI).

**Methods:** Population based register study including RIKS-HIA, S-AMI, the National patient register and the Cause of death register. Odds ratios were determined by logistic regression analysis.

**Results:** From 2001 to 2007, 114 311 cases in RIKS-HIA and 198 693 cases in S-AMI were included with a discharge diagnosis of an acute MI. Linkage was possible for 110 958 cases. These cases were younger, more often males, had less concomitant diseases and were more often treated with invasive coronary artery procedures than patients included in S-AMI only. There were substantial regional differences in proportions of patients reported to RIKS-HIA.

**Conclusion:** Approximately half of all patients with an acute MI are included in RIKS-HIA. They represent a relatively more healthy population than patients included in S-AMI only. These limitations are important to know about since the register has become increasingly important in international research. S-AMI covers almost all patients with an acute MI but has limited information about the patients. Used in combination these two registers can give better prerequisites for improved quality of care of all patients with acute coronary syndromes.
Non-ST-segment elevation acute coronary syndrome caused by the left main stem stenosis - impact of multivessel diseases on treatment strategy and 12-month. Analysis from the PL-ACS Registry

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The aim was to improve the management of multivessel disease on 12-month mortality in patients with NSTE-ACS caused by LM stenosis.

Methods: All patients with NSTE-ACS caused by LM stenosis registered in the PL-ACS between 10.2003 and 11.2009 were included. Patients were divided into 4 groups according to the number of significantly stenosed vessels.

Results (table): In PL-ACS Registry 1654 (2.5%) pts from 65767 had NSTE-ACS caused by LM stenosis. As the number of stenosed vessels increased the percentage of pts treated by PCI decreased and by CABG raised. In-hospital and 12-month mortalities increased together with the number of stenosed vessels. After adjustment the number of significantly stenosed vessels remains significantly associated with higher 12-month mortality (relative risk = 1.14, 95%CI = 1.01-1.29, P<0.038).

<table>
<thead>
<tr>
<th>Isolated LM stenosis</th>
<th>LM + PCI 1 v</th>
<th>LM + PCI 2 v</th>
<th>LM + PCI 3 v</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>352 (21.3%)</td>
<td>341 (20.6%)</td>
<td>312 (19.0%)</td>
<td>449 (27.1%)</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>63±11.3</td>
<td>60±11.5</td>
<td>66±13.5</td>
<td>64±15.8</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>19.9</td>
<td>21.7</td>
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<td>27.2</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>14.5</td>
<td>25.2</td>
<td>26.9</td>
<td>33.0</td>
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<tr>
<td>Prior PCI, %</td>
<td>5.1</td>
<td>10.8</td>
<td>4.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Cardiac arrest before admission, %</td>
<td>2.7</td>
<td>3.1</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Killip 3 or 4 on admission, %</td>
<td>4.5</td>
<td>4.7</td>
<td>8.4</td>
<td>8.7</td>
</tr>
<tr>
<td>NSTEMI, %</td>
<td>45.2</td>
<td>43.7</td>
<td>50.4</td>
<td>54.3</td>
</tr>
<tr>
<td>Coronary angioplasty (PCI), %</td>
<td>45.7</td>
<td>39.3</td>
<td>30.5</td>
<td>27.4</td>
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<tr>
<td>In-hospital bypass surgery (CABG), %</td>
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<td>9.1</td>
<td>11.1</td>
<td>10.5</td>
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<tr>
<td>CABG after discharge, %</td>
<td>44.9</td>
<td>48.4</td>
<td>57.8</td>
<td>63.7</td>
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<td>Left ventricular ejection fraction, %</td>
<td>51.8±9.9</td>
<td>48.8±12.2</td>
<td>47.2±11.6</td>
<td>47.0±12.1</td>
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<tr>
<td>In-hospital stroke, %</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>In-hospital major bleeding, %</td>
<td>1.7</td>
<td>1.2</td>
<td>1.2</td>
<td>2.2</td>
</tr>
<tr>
<td>In-hospital re-infarction, %</td>
<td>1.4</td>
<td>1.2</td>
<td>1.2</td>
<td>2.9</td>
</tr>
<tr>
<td>In-hospital mortality, %</td>
<td>4.3</td>
<td>2.6</td>
<td>5.9</td>
<td>8.4</td>
</tr>
<tr>
<td>12-month mortality, %</td>
<td>10.5</td>
<td>14.9</td>
<td>16.0</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Conclusions: The rates of revascularization by PCI in NSTE-ACS caused by LM stenosis decline as the extend of atherosclerosis rise, while the rates of CABG increase. Patients with more significantly stenosed arteries had higher 12-month mortality.
Persistence of high events rate following STE vs NSTE acute coronary syndrome in the contemporary era: 5-years outcome in a large real world registry

F. Vagnozzi, G. Norsini, N. Taglieri, L. Cinti, F. Sampini, S. Nanni, P. Ortolani, C. Rapezzi, A. Branzi, G. Melandri. University of Bologna, Institute of Cardiology, Bologna, Italy

Early mortality of acute coronary syndromes (ACS) has vastly declined thanks to interventional and pharmacological therapy. However there is growing evidence of high events in the long run, but data are mainly derived from large clinical trials. Studies addressing long term follow up of unselected patients with ACS are few and led to conflicting results.

Purpose: To compare 5-year outcome of unselected patients with STE versus NSTE ACS in a real-world context of contemporary acute treatment and secondary prevention.

Methods: All consecutive patients with ACS admitted in 2004-2005 were enrolled. The main study endpoint was 5-year mortality. The Kaplan-Meyer method was used to analyze the occurrence of death. A landmark analysis was performed: 0-30 days, 30 days-1 year and from 1 year to 5 years.

Results: 2046 patients were enrolled (896 STE, 1150 NSTE). Patients in the former group were younger, had fewer comorbidities and more often received antithrombotic drugs/PCI. Of note, almost 70% of NSTE patients were managed invasively and given dual antiplatelet therapy at discharge. In the whole population 5-year all-cause mortality rate increased from 5.7% (in-H) to 9.6% (30d), reaching 21.1% at 1 year and 43.2% at 5 years. Figure 1 shows the Kaplan-Meyer curves up to 5 years. In the first 30 days the mortality is higher for STE but curves intersect at 1 year and 5-year mortality tends to be higher for NSTE without statistical significance. Landmark analysis displays a greater risk for NSTE after the first year (STE vs NSTE HR=0.67 95%CI 0.51-0.84, p<0.001).

Conclusion: Despite the extensive use of antithrombotic therapies and PCI, the rates of in-hospital MB are acceptably low in the real world and similar to those reported for trials of ACS. On the contrary occurrence of MB is still high in the long run and greater than shown in trials.

High rate of bleeding complications in a real-life Swedish population with ACS

J. Alfredsson, S. Zolfagharian, A.C. Holm, E. Swahn. Division of Cardiovascular Medicine, Department of Medicine and Health Sciences, Linköping, Sweden

Purpose: Early revascularization and aggressive antiplatelet therapy in patients with acute coronary syndromes (ACS) has significantly reduced death and ischemic complications. However, bleeding complications has recently been shown to increase both mortality and ischemic complications during long-term follow-up. Incidence of bleeding complications in a Swedish cohort of patients with ACS is not known. The aim of this study was to determine the incidence, severity and type of bleeding after ACS. Secondary endpoints were death, myocardial infarction or stroke associated with bleeding complications.

Methods: A review of medical records for 402 consecutive patients treated for ACS in the county of Östergötland, Sweden during 2010 was performed. Incidences of in-hospital bleedings and bleedings within 1 year after discharge were determined. Differences in bleeding complications between men and women were assessed.

Results: In total 107 individuals developed non-surgery or surgery related bleeding (26.6%; n=402). Forty two (10.4%) developed in-hospital non-surgery related bleeding and forty two (10.4%) developed non-surgery related bleeding within 1 year after discharge. There were 7 (2.2%) TIMI major bleedings, 38 (9.5%) TIMI minor and 61 (15.2%) TIMI minimal non-surgery related bleedings. Most bleedings were due to gastrointestinal (GI) bleeding, 45.2% of the in-hospital bleedings and 54.8% of the follow up bleedings. Significantly more women developed GI bleedings (9.8% vs. 3.7%; P=0.013) during follow-up. Otherwise no gender differences in bleeding incidence were found. No increased risk of mortality or ischemic events during follow-up was found in patients who developed bleeding complications.

Conclusion: In a Swedish real life ACS population we found a substantial amount of bleeding complications during one year follow up. The majority of the non-surgery related bleedings were gastrointestinal and potentially preventable. In this relatively small cohort we could not verify earlier reported mortality risk associated with bleeding complications.

Impact of contrast-induced nephropathy on long-term cardiovascular events in acute coronary syndrome patients with Chronic Kidney Disease: results from icas registry

H. Watabe1, A. Sato2, T. Hoshii3, D. Abe4, E. Ojima2, Y. Kakefuda2, T. Harunari1, D. Hiyara2, Y. Noguchi1, K. Aonuma1. 1Tsukuba Medical Center Hospital, Tsukuba, Japan; 2University of Tsukuba, Graduate School of Comprehensive Human Sciences, Division of Cardiovascular, Tsukuba, Japan; 3Ibaraki Prefectural central Hospital, Tomobe, Japan

Background: Chronic kidney disease (CKD) is associated with the increase of the risk of the cardiovascular event. However, the association of contrast-induced nephropathy (CIN) and chronic kidney disease (CKD) in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI) has not been fully reported. We evaluated the impact of CIN on cardiovascular events in ACS patients with CKD.

Methods: A total of 1059 ACS patients who underwent emergent PCI in Ibaraki Cardiovascular Assessment Study (ICAS) multi-center registry were enrolled (69±12 yrs, 804 men, STEMI 604 patients). CIN was defined as an increase of ≥0.5mg/dl or ≥25% in pre-PCI serum creatinine in the week after the procedure. CKD was defined as estimated glomerular filtration rate <60mL/min/1.73m². Primary endpoints were defined as cardiovascular death, myocardial infarction, and cerebrovascular disorders.

Result: In our study, 368 (34.7%) patients had CKD. During follow-up periods (343±330 days), CIN was occurred in 164 patients (15.5%) and primary endpoints were occurred in 106 patients (10.0%). Multivariate Cox proportional-hazards model revealed that CIN and CKD were independent predictor of primary endpoints (hazard ratio 2.759; 95% confidential interval, 1.823 to 4.175; p<0.0001), (hazard ratio 1.689; 95% confidence interval, 1.101 to 2.591; p=0.0164). Kaplan-Meier analysis showed that primary endpoints were significantly increased with an increasing CKD stages and presence of CIN (p<0.0001) (figure).

Conclusion: Our long-term follow up study revealed that CIN was incremental significant predictor of cardiovascular events in ACS patients with CKD.

Impact of contrast-induced nephropathy on long-term cardiovascular events in acute coronary syndrome patients with Chronic Kidney Disease: results from icas registry

H. Watabe1, A. Sato2, T. Hoshii3, D. Abe4, E. Ojima2, Y. Kakefuda2, T. Harunari1, D. Hiyara2, Y. Noguchi1, K. Aonuma1. 1Tsukuba Medical Center Hospital, Tsukuba, Japan; 2University of Tsukuba, Graduate School of Comprehensive Human Sciences, Division of Cardiovascular, Tsukuba, Japan; 3Ibaraki Prefectural central Hospital, Tomobe, Japan

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Conclusion: Our long-term follow up study revealed that CIN was incremental significant predictor of cardiovascular events in ACS patients with CKD.
Pathological Q-wave development in myocardial infarction in patients treated by primary percutaneous coronary intervention

1Academic Medical Center, University of Amsterdam, Department of Cardiology, Amsterdam, Netherlands; 2VU University Medical Center, Amsterdam, Netherlands; 3Erasmus Medical Center, Department of Cardiology, Rotterdam, Netherlands

Background: The criteria for pathological Q-waves after acute myocardial infarction (MI) have changed in recent years. Also, there is limited data regarding correlation of Q-wave regression and preservation of left ventricular fraction (LVEF) in patients with an initial Q-wave MI.

Methods: Standard 12 lead electrocardiogram (ECG) was recorded in 200 STE-elevated myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention. ECGs were recorded before and following PCI, as well as at 1, 4, 12 and 24 months of follow-up. Cardiac magnetic resonance imaging (CMR) examination was performed at 4±2 days after reperfusion and repeated after 4 and 24 months.

Results: The incidence of Q-wave MI according to the 2007 criteria was 58%, 1 hour after PCI. At 24 months of follow-up, 22% of patients with initial Q-wave MI displayed Q-wave regression. The "classic" ECG criteria showed strongest correlation with infarct size as measured by CMR. Patients with Q-wave MI had larger infarct size and lower LVEF on baseline CMR respectively (24±10% LV mass and 37±8% vs 17±9% LV mass, p<0.01 and 45±8%, p<0.001). Patients with Q-wave regression displayed significantly larger LVEF improvement in 24 months (9±11%) as compared to both Q-wave MI (2±8%) as well as non-Q-wave MI (3±8%, p<0.04 for both comparisons).

Conclusion: Association of Q-waves with infarct size and LVEF is strongest when using the "classic" Q-wave criteria. Q-wave regression is associated with the largest improvement of LVEF over a 2 year follow-up.

Long-term prognosis estimation after acute coronary syndrome: is there a role for angiographic scores?

H. Dores, J. Ferreira, F.M. Costa, C. Aguilar, M. Trabolo, M.S. Carvalho, P.U. Sousa, P.A. Goncalves, M.S. Almeida, M. Mendes. Hospital West Lisbon, Hospital Santa Cruz, Department of Cardiology, Lisbon, Portugal

Background: Angiographic scores are useful tools to assess the severity of coronary lesions and can provide prognostic information. We aimed to explore the association of Leaman Score (LS) and Duke Jeopardy Score (DJS) with 10-year all-cause mortality in patients (Pts) with acute coronary syndrome (ACS).

Methods: Retrospective analysis of consecutive Pts with ACS submitted to coronary angiography. Extension of coronary disease was calculated using LS and DJS. ROC-curves were performed to test sensitivity and specificity of the scores for the prediction of 10-year mortality. The area under the curve (AUC) and the significance level of p-values were shown for both scores, and Kaplan-Meier analysis was used to compare Pts with LS and DJS under and above the cut-off. A multivariable Cox regression analysis was performed to test the independent association of scores with mortality.

Results: Of the 662 Pts included (mean age 62±11 years, 80% male), 151 (22.8%) died. The mean values were 3.9±1.0 for LS and 2.6±2.0 for DJS. The AUC was significant for both the Leaman Score (AUC 0.61), and Duke Jeopardy Score (AUC 0.58). The cut-off points of 2.0 and 4.0, respectively. Pts with LS and DJS over the cut-off presented significant increase in 10-year mortality, compared with Pts under the cut-off (Figure). Multivariable analysis revealed an independent association of Leaman Score with 10-year mortality (HR 1.06, 95%CI 1.01-1.12; p=0.018), not shown by the DJS (HR 1.03, 95%CI 0.92-1.14; p=0.65).

Conclusions: In this population of patients with ACS submitted to coronary angiography, both scores were associated with 10-year mortality in univariate analysis but only the Leaman score was an independent predictor of long-term mortality.

Bleeding complications in patients with acute myocardial infarction. A gender perspective

A.C. Holm, E. Swahn, J. Alfredsson. Division of Cardiovascular Medicine, Department of Medicine and Health Sciences, Linköping, Sweden

Purpose: During latest years bleeding complications associated with acute myocardial infarction (AMI) has gained increased attention. Many, but not all, studies have shown a higher incidence in women. Furthermore bleedings has been shown to have a large impact on outcome. Whether there are gender differences in consequence of a bleeding complication is not well known.

Methods: From the Swedish national quality register, SWEDEHEART, we included 97862 cases diagnosed with AMI (35747 women and 62115 men). Between the year 2003 and 2009 with one year follow up. Major bleeding was defined as fatal, intracranial or Hemoglobin decrease with ≥50 g/L. Non-major bleeding was defined as a bleeding requiring transfusion or surgical intervention. We used chi square test and students t-test for statistical analyses with a significance level of p<0.05.

Results: Women were older (75 vs 69 y) and had more diabetes and hypertension, while men wore more likely to be smokers or to have previous kidney disease. Men had more AMI in the history and also significantly more revascularization with either PCI or CABG.

Rates of severe bleedings were low, but higher in women (Table 1).

Table 1. Incidence of severe bleeding during hospital stay

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bleeding</td>
<td>98.3%</td>
<td>97.2%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.3%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Non-major bleed</td>
<td>1.4%</td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>

Non-bleeding women had significantly higher mortality than non-bleeding men, both short- and long-term mortality. 7.7 vs 5.2% (p<0.001) in 14 d and 19.9 vs 13.9% (p<0.001) in one y. Major bleeding had a high impact on outcome in both women and men regarding mortality at 14d (36.6% vs 42.9%, p=0.211) and 1y (46.2 vs 53.5%, p=0.021) but without difference between the genders. In patients with a bleeding complication requiring transfusion or surgery there was an indication of higher mortality in men at 14 d (11.4 vs 8.2, p=0.03) and at 1y (28.5 vs 24.6 p=0.08).
**Conclusion:** The major finding of this study is that women with AMI have a higher rate of bleeding complications than men. Even though women have an overall higher short-and long-term mortality, among bleeding patients there is no difference between the genders or even higher mortality in men. Consequently, the prognostic impact of a bleeding complication appears higher in men.

**P5094**

Copeptin predicts long-term mortality in patients with non-st-elevation myocardial infarction

C. Liebetrau1, O. Dörr2, S. Szardien1, C. Trodd1, C. Horstmann1, J. Rixe2, D. Sedding2, H. Moellmann1, C. Hamm1, H. Neufang1, Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany; 2Justus-Liebig University Giessen, Medical Clinic I, Cardiology, Giessen, Germany; 3Fritz-Groedel Institute of the Kerckhoff Clinic Heart & Thorax Center, Bad Nauheim, Germany

**Purpose:** Copeptin has been shown to improve diagnostic sensitivity when used in combination with conventional measured cardiac troponin T (cTnT) in patients with suspected acute coronary syndrome (ACS). However, less is known about the predictive value of differences in patients with and without acute myocardial infarction. Therefore, in the present study we aimed to analyse the possible predictive value of copeptin in patients with Non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA).

**Methods:** 321 patients with suspected Non-ST-elevation ACS (NSTEMI) were included in the study. Final diagnosis of NSTEMI was made in 201 patients (64%), 77 patients (24%) had unstable angina pectoris (UA). The remaining 33 patients (10.3%) were without coronary artery disease (CAD) documented by coronary angiography. Copeptin was measured on admission. Blood was taken immediately after admission and was sent to the laboratory for centrifugation and frozen stored at –80°C until assayed.

**Results:** Copeptin plasma levels were higher in patients with NSTEMI compared to patients without documented CAD (17.2 pmol/ml [10.7–34.1] vs. 13.2 pmol/ml [7.8–30.6]; P<0.019). There was no difference in copeptin plasma concentrations in patients with UA compared to patients without documented CAD (17.2 pmol/ml [10.7–34.1] vs. 13.7 pmol/ml [8.4–31.7]; P=0.08). During 5-year follow-up 29 (14.4%) patients with NSTEMI and 6 (8.9%) patients with UA and 3 (9.0%) patients without CAD died. The mortality rate among patients with NSTEMI and copeptin plasma concentration ≥ 14.0 pmol/ml was higher during 5-year follow-up (LogRank 12.1; P<0.01, multivariate Cox-Retrospective hazard ratio: 95% CI 1.003–1.023; P<0.01). Excluding patients with NSTEMI from the analyses mortality did not differ in patients with copeptin plasma concentration ≥ 14.0 pmol/ml compared to patients with copeptin levels ≤ 14.0 pmol/ml.

**Conclusion:** Copeptin has a predictive value for long-term mortality in patients with NSTEMI. However, this difference is restricted to patients with NSTEMI.
were significantly predictive of future MACE. Only Mon 2 counts were an independent predictor of MACE after adjusting for age and sex (Table 1).

Table 1. Predictive value of monocytes in MACE

<table>
<thead>
<tr>
<th>Monocyte</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Monocytes (cells/μL)</td>
<td>1.002 (1.001 - 1.003)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mon 1</td>
<td>1.001 (0.998 - 1.003)</td>
<td>0.111</td>
</tr>
<tr>
<td>Mon 2</td>
<td>1.008 (1.003 - 1.013)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mon 3</td>
<td>1.01 (0.999 - 1.02)</td>
<td>0.388</td>
</tr>
</tbody>
</table>

Conclusion: Increased total monocyte and Mon 2 counts in the first 24 hours post infarction are predictive of MACE in STEMI patients. Mon 3, despite an assumed role in reparation and fibroblast deposition, was not predictive of MACE in post-STEMI patients. This suggests a specific role for Mon2 monocyte subset in post-infarction recovery in STEMI, and a potential role of this subset as a future therapeutic target. Remodelling data from cardiac magnetic resonance is awaited.

**P5096 Prediction of late mortality after myocardial infarction by means of the GRACE Score in contemporary treated patients**

P. Barthal1, A. Mueller1, K. Ulm1, M. Malik2, G. Schmidt3, M. Beijk1, J. Kloek1, A. Vis1, M. Grundeken1, T. Wijns1, J. J. Koolen1, 1Cardiological University, Muenchen, Germany; 2St. Georges University, London, United Kingdom

Background: The GRACE Score (GS) was proposed for prediction of early and late mortality risk in acute coronary syndrome (ACS) patients. The GS includes age, history of congestive heart failure and previous myocardial infarction. These factors, systolic blood pressure and presence of ST-segment depression at admission, and serum creatinine, cardiac enzymes and percutaneous coronary intervention (PCI) during hospitalization, GS was developed and validated in patient with ACS collected in a multinational registry between 1999 and 2003. Less than one third of the registry patients were treated with PCI. Aim of this study was to investigate the predictive power of the GS in contemporary treated post-infarction patients.

Methods: 941 consecutive AMI patients aged ≥81 yrs were included. 93% underwent a PCI, 95% received beta-blockers, 94% ACE inhibitors and 95% statins. The GS was calculated according to the published protocol. Uni- and multivariable analyses were performed with traditional risk stratifiers like LVEF <35%, and diabetes mellitus. Follow-up was up to 5 years. Primary endpoint was total mortality. Follow-up was 5 years. Primary endpoint was total mortality.

Results: During follow-up, 72 patients (7.7%) died. The GS shows the strongest association with mortality in the univariable and multivariable analysis followed by reduced LVEF and Diabetes mellitus (see table). By analyzing the different components of the GS in a multivariable analysis, only age, serum creatinine and history of previous myocardial infarction were independent and significantly associated with mortality (HR CI 1.09 (1.06 – 1.12); 1.82 (1.42 – 2.34); 2.01 (1.12 – 3.63)).

Table 1. Predictive value of monocytes in MACE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE score (per point)</td>
<td>1.044 (1.03-1.05)</td>
<td>65.0 (0.001)</td>
</tr>
<tr>
<td>LVEF (&lt;35%)</td>
<td>4.39 (2.56-7.19)</td>
<td>36.0 (0.001)</td>
</tr>
<tr>
<td>Diabetes mellitus (y/n)</td>
<td>2.78 (1.74-4.47)</td>
<td>17.9 (0.001)</td>
</tr>
</tbody>
</table>

Conclusion: The GS is a strong risk predictor of 5-year mortality after acute myocardial infarction. Only components of the GS in a multivariable analysis, only age, serum creatinine and history of previous myocardial infarction carried the most predictive information of the GRACE score.

**P5097 Impact of gender on clinical profile and long-term outcomes in patients with early-onset myocardial infarction**

F. Notarangelo1, L. Foco1, F. Bontardelli1, M. Tubaro2, N. Marziliano3, P.M. Mannucci1, L. Bernardinelli1, C. Caminiti1, P.A. Mertini1, D. Ardissoni1 on behalf of Associazione per il Studio della Trombosi in Cardiologia, 1Hospital of Parma, Department of Cardiology, Parma, Italy; 2University of Pavia, Department of Applied Health Sciences, Pavia, Italy; 3San Filippo Neri Hospital. Department of Cardiology, Rome, Italy; 4Niguarda Ca’ Granda Hospital, Department of Cardiology, Milan, Italy; 5Foundation IRCCS Hospital Maggiore Polyclinic, Mangiagalli & Regina Elena, Milan, Italy; 6Hospital of Parma, Research and Innovation Unit, Parma, Italy

Purpose: Epidemiological and clinical data suggest that women with premature coronary artery disease have different risk factor profiles and angiographic characteristics from those of young men. Aim of this study was to assess gender-related differences in risk factors, clinical profiles, angiographic characteristics and long-term clinical outcomes in young patients with early-onset myocardial infarction.

Methods: This is the first study to report ULMCA related AMI data including in-hospital PCI and CABG treated patients. Clinical follow-up was obtained from STEMI and non-STEMI patients, most likely due to selection bias. This is demonstrated by TIMI 0 flow and distal LM lesion predicted performing PCI.

Results: This is the first study to report ULMCA related AMI data including in-hospital PCI and CABG treated patients. Clinical follow-up was obtained from STEMI and non-STEMI patients, most likely due to selection bias. This is demonstrated by TIMI 0 flow and distal LM lesion predicted performing PCI.

Conclusions: We evaluated 30-day and long-term mortality rates in contemporary treated post-infarction patients. Cardiothoracic Surgery, Amsterdam, Netherlands

Between January 1998 and December 2008, 87 patients with ULMCA related AMI have undergone revascularization treatment in our institution (57 with PCI, 30 with CABG). Clinical follow-up was obtained retrospectively by means of in- and outpatients medical charts. Patient’s vital status was verified with the national population registry. Cumulative event rates were estimated using the Kaplan–Meier method. Multivariate regression analyses were performed to identify predictors for 30-day mortality and PCI as revascularization treatment.

Clinical outcomes from those of young men. Aim of this study was to assess gender-related differences in risk factors, clinical profiles, angiographic characteristics and long-term clinical outcomes in young patients with early-onset myocardial infarction.

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Conclusions: There are significant differences in the risk factor profiles and angiographic features of male and female patients with early-onset myocardial infarction. Long-term mortality is similarly low in both genders, but women are less likely to experience the reoccurrence of myocardial infarction and to undergo coronary revascularisation.

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Figure 1

Results: 30-day mortality rate was 51%: 64% in the PCI group and 24% in the CABG group. One-year mortality rate was 54% (69% PCI; 24% CABG, figure 1). Major adverse cardiac and cerebrovascular event (MACE) rates were 58% (30-day) and 84% (1-year). Diabetes mellitus (HR 2.9, 95% CI 1.3-6.3, p=0.009) and TIMI 0 flow (HR 3.1, 95% CI 1.2-8.3, p=0.017) were independent predictors for 30-day mortality. Angiographic characteristics were independent predictors for revascularization treatment: TIMI 0 flow strongly predicted performing PCI, and distal (bifurcation) LM lesion predicted performing CABG.

Conclusions: There are significant differences in the risk factor profiles and angiographic features of male and female patients with early-onset myocardial infarction. Long-term mortality is similarly low in both genders, but women are less likely to experience the reoccurrence of myocardial infarction and to undergo coronary revascularisation.
Probable effects of obstructive sleep apnea on plaque vulnerability and progression of coronary atherosclerosis in patients with acute myocardial infarction

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Aims: Impact of OSA on the clinical and angiographic follow-up outcomes in patients undergoing primary percutaneous coronary intervention (PPCI). Polysomnography at first admission determined 124 patients with OSA defined as apnea-hypopnea index ≥ 15 events/h. Clinical outcomes measured were cardiac death, recurrence of acute coronary syndrome (ACS), and re-admission for heart failure. Major adverse cardiac events (MACE) were defined as composite end points of individual clinical outcomes. Follow-up angiography was performed in 222 patients. Interventional measures were target lesion revascularization (TLR) and newly necessitated PCI (new PCI) owing to disease progression.

Results: Mean follow-up duration was 4.0±1.7 years. Patients with OSA had more experienced the recurrence of ACS and MACE than control patients (17.6% vs. 6.6%, p=0.010; 21.8% vs. 10.3%, p=0.014). TLR was not different between the groups. In contrast, new PCI was significantly higher in OSA patients than in controls (28.4% vs. 14.8%, p=0.012). Cox regression hazard model showed that the OSA was an independent predictor for recurrence of ACS and MACE (hazard ratio=2.36, p=0.027; hazard ratio=1.98, p=0.027). Logistic regression analysis adjusted for OSA and other known risk factors indicated that only OSA was positively correlated with new PCI (odds ratio=2.23, p=0.021). Treatment with continuous positive airway pressure could not improve the outcomes.

Conclusions: OSA may be related to plaque vulnerability and a risk factor for progression of coronary atherosclerosis.

Background: The introduction in clinical practice of high sensitivity troponin (hs-cTn) assays has led to an increased diagnostic accuracy for Acute Coronary Syndrome (ACS) characterized by a higher sensitivity at the cost of a lower specificity leading to more false positive (FP) cases. The prognostic value of hs-cTn in false positive subjects has not been reported yet.

Methods: Four hundred and fifty-two (452) pts, admitted to ED because of chest pain, were enrolled. Serum levels of Roche hs-cTn were measured from baseline samples. All pts received a telephonic follow up (FU) contact at 30 and 360 days. The endpoint was the composite of MACE. Prognostic accuracy was evaluated by Kaplan-Meier curves.

Results: 60 pts were discharged with a diagnosis of ACS (13% of overall population) according to current guidelines. At follow up 412 patients were in good health, 8 had died (5 for cardiac causes and 3 of cancer) and 16 had experienced an episode of ACS (12 pts were lost to follow up). Among patients with negative hs-cTn at ED admission MACE were 3%, but were 8.5% in the group of FP and 12% in the true positive. Kaplan-Meier curves showed a significant difference in event-free survival between pts negative to hs-cTn versus FP pts (p=0.03) and versus true positive pts (p=0.004). However the last two group had a similar event free survival (p=0.5).

Conclusions: In pts admitted to ED for chest pain, a positive value beyond the hs-cTn cut-off (14 pg/ml) is associated with a similar prognostic value in true and false positive patients, suggesting that the latter group should receive an accurate work-out-in ED and a careful follow-up after discharge.

Chest pain patients with false positive hs-cTn in emergency department have the same one year risk of MACE as those who were hospitalized for acute coronary syndromes

M.T. Cardillo,¹ L.M. Biasucci¹, M. Zaninotto², N. Gentiloni Silveri¹, G. Biasiolo¹, M. Monri², G. Nicolli², M. Gustapane¹, M. Plebani², F. Crea¹,¹ Catholic University of the Sacred Heart, Rome, Italy;¹ University Hospital of Padua, Department of Laboratory Medicine, Padua, Italy

Background: The introduction in clinical practice of high sensitivity troponin (hs-cTn) assays has led to an increased diagnostic accuracy for Acute Coronary Syndrome (ACS) characterized by a higher sensitivity at the cost of a lower specificity leading to more false positive (FP) cases. The prognostic value of hs-cTn in false positive subjects has not been reported yet.

Methods: Four hundred and fifty-two (452) pts, admitted to ED because of chest pain, were enrolled. Serum levels of Roche hs-cTn were measured from baseline samples. All pts received a telephonic follow up (FU) contact at 30 and 360 days. The endpoint was the composite of MACE. Prognostic accuracy was evaluated by Kaplan-Meier curves.

Results: 60 pts were discharged with a diagnosis of ACS (13% of overall population) according to current guidelines. At follow up 412 patients were in good health, 8 had died (5 for cardiac causes and 3 of cancer) and 16 had experienced an episode of ACS (12 pts were lost to follow up). Among patients with negative hs-cTn at ED admission MACE were 3%, but were 8.5% in the group of FP and 12% in the true positive. Kaplan-Meier curves showed a significant difference in event-free survival between pts negative to hs-cTn versus FP pts (p=0.03) and versus true positive pts (p=0.004). However the last two group had a similar event free survival (p=0.5).

Conclusions: In pts admitted to ED for chest pain, a positive value beyond the hs-cTn cut-off (14 pg/ml) is associated with a similar prognostic value in true and false positive patients, suggesting that the latter group should receive an accurate work-out-in ED and a careful follow-up after discharge.
Hypercalcaemia is an independent predictor of long-term adverse outcomes. Thus, serum calcium concentration may constitute a cost-effective and useful tool for risk stratification.

Methods:
Serum calcium was measured at admission in 365 patients with ACS. Data on sociodemographic and clinical characteristics were evaluated. The occurrence of a composite outcome (all-cause mortality and hospitalization for congestive heart failure [CHF] or ACS) was assessed at 60 month follow-up.

Results:
Among all, 71% patients were male and the mean age was 64±13 years. Mean serum calcium was 2.38±0.33 mM/L and 20% of patients had hypercalcaemia (>2.60 mM/L). Patients with hypercalcaemia were more frequently women (45% vs 25%; p=0.001), diabetic (43% vs 24%; p=0.001), hypertensive (74% vs 60%; p=0.021) and presented more kidney disease (KD) (49% vs 21%; p<0.001) as well as left ventricular (LV) systolic dysfunction (45% vs 28%; p=0.010). At 5-year follow-up, composite outcome occurred in 92 (25%) patients and occurred more frequently in patients with hypercalcaemia (41% vs 22%; p=0.001). Furthermore, this patient group presented a significant preponderance of adverse events: ACS (25% vs 12%; p=0.005), CHF requiring hospitalization (16% vs 7%; p=0.003) and the same was observed by Kaplan-Meier analysis indicated that hypercalcaemia was a predictor of the composite adverse outcome (HR 2.2; CI 1.4-3.4). Multivariate survival analysis using Cox’s regression model, including hypercalcaemia, LV systolic function and KD confirmed the independent association of hypercalcaemia with adverse outcome (HR 1.7; CI 1.1-2.8).

Conclusions: Hypercalcaemia is an independent predictor of long-term adverse outcomes and serum calcium concentration may constitute a cost-effective and important prognostic indicator for ACS patients.

Table 1. Outcomes by age

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>≤65 yrs</th>
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<td>(95% CI)</td>
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<tr>
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<td>1.8</td>
<td>2.0</td>
<td>1.8</td>
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<tr>
<td>IH MACE</td>
<td>2.8</td>
<td>4.2</td>
<td>3.0</td>
<td>1.8</td>
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<tr>
<td>Major bleeding</td>
<td>0.6</td>
<td>1.4</td>
<td>2.4</td>
<td>1.5</td>
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</table>
| IH, inhospital OR, odds ratio; CI, confidence interval; MACE, major adverse cardiac event; All P trend < 0.001.

Figure 1

Conclusion: Endothelial function is markedly impaired in the acute phase of NSTE-ACS patients, but achieves values comparable to those of stable CAD patients over 3 months of follow-up. Both FMD on admission and at 3 months from the acute event independently predicted cardiac outcome in NSTE-ACS patients.

Figure 2

Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>≤65 yrs</th>
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association between glyemic parameters and the development of post-infarction HF. Finally, we identified the variables with an independent predictor value by a multivariate analysis of Hazard ratio by Cox regression.

**Results:** Of 194 included patients, 11 (5.6%) developed HF during follow-up (median: 1.0 years [0.8 to 1.5 years]). Glucose, fructosamine, glycated haemoglobin and AGE were predictors of post-infarction HF in the univariate analysis. After adjustment for clinical variables only AGE (Hazard ratio 1.016; IC 95%: 1.005-1.026; p<0.001), together with NT-proBNP and the infarction extension (measured by the troponin I peak), were predictors of the development of post-infarction HF. AGE levels over the median multiplied by 5 the risk of developing HF during the follow-up.

**Conclusions:** High levels of advanced glycation end products (AGE) are an independent predictor for the development of post-infarction HF.

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**P5109 Early effects of ivabradine in combination with beta-blockers compared to beta-blockers up titration on systolic and diastolic function, serum NT-proANP, and exercise capacity in pts after Q-MI with EF<45%**

K. Amosova, I.U. Rudenko, I. Prudky, Y. Xu, A. Bezrodnyi. National O.O. Bohomolets Medical University, Kiev, Ukraine

**Purpose:** To compare the early impact of heart rate (HR) control with ivabradine plus metoprolol and metoprolol up titration on left ventricular (LV) systolic and diastolic function, serum NT-proANP and exercise capacity in anterior Q-MI pts with EF<45%.

**Methods:** In single-blind parallel-group study 62 pts with a first Q-MI, EF 30-45%, sinus rhythm > 80 bpm, Killip class I-II were randomized 1:1 into ivabradine plus beta-blockers (BB) and BB up titration groups. Pts with anterior MI (24 and 18 respectively) were included in this analysis. Pts in Group 1 from day (D) 1 onward metoprolol (150 mg bid) and D 4-6 ivabradine (2.5 mg bid). In Group 2, beta-blockers (BB) were up titrated with metoprolol (100 mg) until D 5 and from D 6, ivabradine 2.5 mg bid, respectively (116.7 ±1.0 mg kg). The association between mitral regurgitation (MR) and systolic dysfunction was not studied. The 12-month mortality was 2.0% in group 1, 7.3% in group 2, 10.6% in group 3 and 13.6% in group 4.

**Results:** At D 2 and D 25, resting HR were higher in patients with MR (5.5±1.2 vs. 5.2±1.3 mmol/l, and 2.0±1.2 vs 1.7±1.0 mmol/l, respectively, all p<0.001). The rates of three or more affected coronary arteries (27.5 vs 18.3%, p=0.001), lesions of left main coronary artery (7.2 vs 1.1%, all p<0.001), circumflex artery (36.2 vs 26.7) and right coronary artery (57.3 vs 44.9%, all p<0.001) were higher in patients with MR as well as reduced LV systolic function (LV ejection fraction <50% - 63.7% and 25.6%) and LV dilatation (E/e>15 mm = 45.1 vs 30.3%). The levels of total cholesterol and triglycerides were higher in patients without MR (5.5±1.2 vs 5.2±1.3 mmol/l, and 2.0±1.2 vs 1.7±1.0 mmol/l, respectively, all p<0.001). The rates of three or more affected coronary arteries (27.5 vs 18.3%, p=0.001), lesions of left main coronary artery (7.2 vs 1.1%, all p<0.001), circumflex artery (36.2 vs 26.7) and right coronary artery (57.3 vs 44.9%, all p<0.001) were higher in patients with MR. According to results of multivariate analysis, MR was independently associated with LV dilatation, NYHA class of congestive heart failure, index of the left atrial size, and extent of LV wall motion abnormalities. The groups did not differ in localization of previous MI.

**Conclusions:** LV dilatation, NYHA class of congestive heart failure, index of the left atrial size, and extent of LV wall motion abnormalities were associated with moderate or severe MR in postinfarction myocardial infarction patients.

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**P5108 Risk stratification by Killip class and left ventricular systolic function in patients with acute myocardial infarction in modern era from Korean acute myocardial infarction registry**

J.H. Lee1, J.K. Kang1, S.Y. Jang1, W.S. Choi1, D.H. Yang1, H.S. Park1, Y. Cho1, S.C. Chae1, M.H. Jeong1, Y.J. Kim2. on behalf of Korean Acute Myocardial Infarction Registry Group, Kyungpook National University Hospital, Daegu, Korea, Republic of; 2Chonnam National University Hospital, Gwangju, Korea, Republic of; 3Yeonnam University Hospital, Daegu, Korea, Republic of

**Purpose:** The aims of this study were to determine the interactive effect of Killip class and left ventricular systolic function on 12-month mortality in patients with acute myocardial infarction (AMI) in modern era.

**Methods:** Between November 2005 and January 2008, 8,418 eligible patients (5,942 men; mean age = 62.7±12.5 years-old) were analyzed from the Korean AMI Registry. Patients were stratified into 4 groups based on Killip class (1 vs >2) and left ventricular ejection fraction (LVEF; <50% vs ≥50%); group 1 (Killip class 1 and LVEF >50%, n=4,003), group 2 (Killip class 1 and LVEF <50%, n=851), group 3 (Killip class >2 and LVEF >50%, n=1,344), and group 4 (Killip class >2 and LVEF <50%, n=1,144). The LVEF were measured by two-D echocardiography.

**Results:** The 12-month mortality was 2.0% in group 1, 7.3% in group 2, 10.6% in group 3, and 22.5% in group 4, respectively. Kaplan-Meier survival showed there was significant difference in 12-month mortality among 4 groups (log-rank p <0.001). Patients in group 2 had significantly higher 12-month mortality compared with patients in group 1 (hazard ratio [HR] 3.991, 95% confidence interval [CI] 2.728 to 5.610, p<0.001), as did patients in group 3 (HR 3.991, 95% CI 2.592 to 6.215, p<0.001) after adjustment for clinical and angiographic variables in Cox proportional hazards model. In fully adjusted model including medications during hospitalization and discharge, patients in group 2 had significantly lower 12-month mortality compared with patients in group 1 (HR 4.341, 95% CI 2.798 to 6.672, p<0.001), as did patients in group 3 (HR 3.395, 95% CI 2.125 to 5.310, p<0.001). The patients in group 4 had the highest 12-month mortality compared to patients in group 1 after adjustment for clinical and angiographic variables (HR 8.262, 95% CI 5.821 to 11.784, p<0.001), and after adjustment for clinical, angiographic, and discharge medications (HR 7.745, 95% CI 5.372 to 11.176, p<0.001).

**Conclusions:** Despite technical improvement and new medical treatment in modern era, conventional risk stratification by Killip class and LVEF still provide prognostic implication on 12-month mortality in post-MI patients.
end of observation; cut-point of 105 points displayed 58.5% sensitivity and 70.7% specificity). Multivariate analysis identified additional independent risk factors for long-term mortality (Table).

**Conclusion:** There are some risk factors obtained both from the medical history and during the hospitalization that could increase the power of the risk stratification model. This suggests need for particular risk stratification performed at discharge in context of long-term period.

**P5111** Prognosis importance of absence of angina in non-ST elevation myocardial infarction

J.Y. Tada, R.B. Ramos, S.D. Avakian, J.A.F. Ramires, A.P. Mansur. Heart Institute (InCor) - University of Sao Paulo Faculty of Medicine Clinics Hospital (HC-FMUSP), Sao Paulo, Brazil

**Purpose:** Cardiac troponins increased myocardial infarction diagnosis in patients without specific electrocardiographic changes. Absence of angina has become common and prognostic significance remains unclear.

**Methods:** We followed 204 consecutive patients after myocardial infarction non-ST elevation (NSTEMI) at emergency department. Outcomes were in-hospital death and follow-up death or cardiac readmission.

**Results:** No-angina (NAG) group (n = 27, 13.2%) had more women (p = 0.001), higher blood glucose (p = 0.011) and B-type natriuretic factor (p = 0.001). In-hospital (14.8% vs 4.5%, p = 0.035) and 20-month follow-up mortality (43.5% vs 12.9%, p < 0.001) were higher in NAG. Combination of death and cardiac readmission was similar (70.4% vs 53.1%, p = 0.093). Age (HR = 1.198, 95% CI 1.006 to 1.071), absence of angina at admission (HR 2.554, 95% CI 1.037 to 6.289), male gender (HR 2.706, 95% CI 1.099 to 6.667) and dyspnea (HR 3.113, 95% CI 1.147 to 6.842) were independent predictors of long-term mortality.

**Figure 1.** Kaplan-Meier curve

**Conclusion:** The absence of chest pain in NSTEMI implies in higher in-hospital and long-term mortality.

**P5112** Is female gender a real independent predictor of mortality after acute coronary syndrome?

A.T. Timoteo, J. Labandeiro, J.A. Oliveira, M.L. Ferreira, R. Cruz Ferreira, Hospital Santa Marta, CHUL, Lisbon, Portugal

**Background:** Female gender has been described as an important predictor of outcome after elective coronary interventions. Is this ominous impact of female gender also present in the context of acute coronary syndromes (ACS)?

**Methods:** Study of consecutive patients admitted for an ACS at a single-centre coronary care unit. Kaplan-Meier analysis and Cox regression analysis regarding the primary end-point of all-cause mortality at 30-day and one-year follow-up were performed to investigate the influence of gender on outcome.

**Results:** The study included 1423 patients, with a mean age of 64±13 years, 31% females. Thirty-day and one-year mortality were 6.7% and 8.5% respectively. ST-segment elevation acute myocardial infarction (STEMI) was present in 60.2% of the patients. Females were more elderly (70±12 vs 61±12 years, p<0.001), had more hypertension and diabetes and were less smokers. Heart rate and GRACE risk score were higher in females and estimated glomerular filtration rate lower.

**Methods:** Study of consecutive patients admitted for an ACS at a single-centre coronary care unit. Kaplan-Meier analysis and Cox regression analysis regarding the primary end-point of all-cause mortality at 30-day and one-year follow-up were performed to investigate the influence of gender on outcome. Females were more elderly (70±12 vs 61±12 years, p<0.001), had more hypertension and diabetes and were less smokers. Heart rate and GRACE risk score were higher in females and estimated glomerular filtration rate lower. Age (HR = 1.198, 95% CI 1.006 to 1.071), absence of angina at admission (HR 2.554, 95% CI 1.037 to 6.289), male gender (HR 2.706, 95% CI 1.099 to 6.667) and dyspnea (HR 3.113, 95% CI 1.147 to 6.842) were independent predictors of long-term mortality.

**Table 1.** All-cause mortality by age strata

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<td>263</td>
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<tr>
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<td>541</td>
<td>403</td>
<td>73</td>
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<tr>
<td>30-day</td>
<td>6.1%</td>
<td>7.9%</td>
<td>3.3%</td>
<td>2.0%</td>
<td>7.4%</td>
<td>6.7%</td>
<td>14.5%</td>
<td>13.7%</td>
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<tr>
<td>One-year</td>
<td>7.4%</td>
<td>10.9%</td>
<td>3.6%</td>
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<td>8.2%</td>
<td>6.0%</td>
<td>19.1%</td>
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</table>

**Conclusion:** Female gender is not a predictor of all-cause mortality after ACS. In fact, age is a major confounder in the influence of gender on outcome and must be taken into account, since women admitted with an ACS are significantly older than men.

**P5113** Peak Systolic Velocity (PSV) using colour-coded Tissue Doppler Imaging (TDI) is a strong and independent predictor of outcome in acute coronary syndrome patients

C. Westholm1, J. Johnson1, T. Jerberg1, R. Winter2,1 Karolinska Institute, Department of Medicine, Stockholm, Sweden;2Royal Institute of Technology, School of Technology and Health, Stockholm, Sweden

**Background:** Traditional echocardiographic methods like left ventricular ejection fraction (EF) and wall motion scoring (WMS) and new methods like speckle tracking (ST) based 2D strain and strain rate carry important prognostic information in acute coronary syndrome (ACS) patients. Parameters from tissue Doppler imaging (TDI), with its high time resolution, may further increase the prognostic value.

**Purpose:** Cardiac troponins increased myocardial infarction diagnosis in patients without specific electrocardiographic changes. Absence of angina has become common and prognostic significance remains unclear.

**Methods:** We followed 204 consecutive patients after myocardial infarction non-ST elevation (NSTEMI) at emergency department. Outcomes were in-hospital death and follow-up death or cardiac readmission.

**Results:** No-angina (NAG) group (n = 27, 13.2%) had more women (p = 0.001), higher blood glucose (p = 0.011) and B-type natriuretic factor (p = 0.001). In-hospital (14.8% vs 4.5%, p = 0.035) and 20-month follow-up mortality (43.5% vs 12.9%, p < 0.001) were higher in NAG. Combination of death and cardiac readmission was similar (70.4% vs 53.1%, p = 0.093). Age (HR = 1.198, 95% CI 1.006 to 1.071), absence of angina at admission (HR 2.554, 95% CI 1.037 to 6.289), male gender (HR 2.706, 95% CI 1.099 to 6.667) and dyspnea (HR 3.113, 95% CI 1.147 to 6.842) were independent predictors of long-term mortality.

**Conclusion:** Female gender is not a predictor of all-cause mortality after ACS. In fact, age is a major confounder in the influence of gender on outcome and must be taken into account, since women admitted with an ACS are significantly older than men.

**P5114** Left atrial volume and dynamics in chronic kidney disease

K. Kadappu1, L. Hee2, A. Aravindan2, S.T. Spicer1, G. Suryanarayanan3, J.K. French1, L. Thomas1, Liverpool Hospital and University of New South Wales, Liverpool, Sydney, Australia;4Liverpool Hospital, Liverpool, Sydney, Australia

**Background:** Left ventricular changes in end stage renal failure are well recognized, however; little is known about the same in early stages of chronic kidney disease (CKD) and associated changes in atrial function in the setting of CKD.

**Methods:** 50 CKD patients (eGFR 30-60 ml/min/1.73m2), underwent a transthoracic echocardiogram and were compared with 49 normal subjects as well as 30 hypertensive subjects. LV ejection fraction and LV mass indexed to body surface area (LVM) were measured. Biplane LA volume indexed to body surface area (LAVI); LA global and segmental function was measured using 2-dimensional strain imaging in the apical four and two chamber views from the septal and lateral walls using 2D speckle tracking. Systolic (S-GR), early (E-GR) and late (A-...
SR) diastolic strain rate were also measured. One-way ANOVA with Bonferroni correction used to examine the differences between the groups.

**Results:** LVMi was increased significantly in the hypertensive group compared with both the normal and hypertensive group (Table 1). There was an associated reduction in global strain compared to normal and hypertensives (Table 1). LA reservoir function (S-SR), and conduit function (E-SR) were significantly reduced in the CKD group compared with normals and hypertensive group. However, there was no significant difference in atrial contractile function with AS-SR was similar in all 3 groups.

**Conclusion:** LV diastolic dysfunction starts in early stages of CKD with consequent atrial changes as demonstrated by LA enlargement and reduced global as well as phasic functions. The severity of LA changes in CKD appears to exceed that due to the presence of LV hypertrophy as LAVi was significantly greater and LA function parameters significantly lower even compared to a cohort with hypertension with preserved kidney function.

### Table 1. Differences in LA volume, strain and strain rate in CKD group vs HT group vs controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=35)</th>
<th>Narrow QRS (n=35)</th>
<th>Wide QRS (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAVi (mL/m²/m²)</td>
<td>24.7±6.5</td>
<td>23.9±6.0</td>
<td>25.7±7.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global strain (%)</td>
<td>35.2±8.2</td>
<td>35.9±10.0</td>
<td>34.6±8.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S-SR (1)</td>
<td>1.7±0.4</td>
<td>1.1±0.3**</td>
<td>1.5±0.4*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E-SR (1)</td>
<td>1.6±0.5</td>
<td>1.3±0.3</td>
<td>1.4±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A-SR (1)</td>
<td>1.7±0.6</td>
<td>1.5±0.4</td>
<td>1.7±0.5</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*p<0.05 compared to normal; †p<0.05 compared to HT group.

### Figure 1

**Abstract P5116** – Figure 1. Atrial dyssynchrony

**Abstract P5116** – Table 1. Patient characteristics, atrial conduction times and atrial dyssynchrony

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Control (n=35)</th>
<th>Narrow QRS (n=35)</th>
<th>Wide QRS (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>27 (77.1%)</td>
<td>26 (74.3%)</td>
<td>28 (80%)</td>
<td>0.604</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>64.9±3</td>
<td>64.8±3</td>
<td>65.2±3</td>
<td>0.012</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>22 (62.9%)</td>
<td>22 (62.9%)</td>
<td>22 (62.9%)</td>
<td>0.765</td>
</tr>
<tr>
<td>Non ischemic heart disease, n (%)</td>
<td>13 (37.1%)</td>
<td>14 (40%)</td>
<td>14 (40%)</td>
<td>0.748</td>
</tr>
<tr>
<td>LA dyssynchrony (ms)</td>
<td>14.1±3</td>
<td>17.2±3</td>
<td>21.1±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RA dyssynchrony (ms)</td>
<td>14.6±3</td>
<td>22.8±4</td>
<td>37.1±7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** The combination of ALP and 6MW would improve the prediction of the AF development in CHF patients.
Noricandil improved electrical and structural remodeling and prevented ventricular tachyarrhythmias in a mouse model of desmin-related cardiomyopathy

M. Hirose, A. Sanbe, N. Matsushita, E. Taira. Iwate Medical University, Shiwa-gun Ybahachoh, Japan

Introduction: It is well known that cardiac arrhythmias were observed in patients with desmin-related cardiomyopathy. Transgenic (HSBP5 R120G-TG) mice with expression of an argl2 (R120G) missense mutation in HSBP5 display desmin-related cardiomyopathy. Recently, cardioprotective effect of noricandil, an ATP-sensitive potassium channel opener and NO donor, prolongs survival in HSBP5 R120G-TG mice. However, whether the TG mice induce ventricular arrhythmias and noricandil can inhibit the arrhythmias remains unknown. Therefore, we examined the effects of chronic administration of noricandil on ventricular electrical and structural remodeling and arrhythmias in HSBP5 R120G-TG mice.

Method and Results: Nicorandil (15mg/kg/day) was orally administered in HSBP5 R120G-TG mice from 5 weeks to 30 weeks of age. Ventricular function was investigated at the age of 30 weeks using two-dimensionally-directed M-mode echocardiography. Electrocardiogram (ECG) lead II and optical action potentials were recorded from HSBP5 R120G-TG mice and the epicardial surface of the Langendorff-perfused TG mouse hearts, respectively, at the age of 30 weeks. We also examined the expression of ventricular gap junction proteins (connexin43) in the TG mice using western blots. Nicorandil improved ventricular dysfunction, determined by reduction of LV fractional shortening in HSBP5 R120G-TG mice. Nicorandil also improved the prolonged P, PQ, and QT intervals in HSBP5 R120G-TG mice. Interestingly,nicorandil improved ventricular impulse conduction slowing and the increased protein expression levels of connexin43 in HSBP5 R120G-TG mouse hearts. The electrical slow pacing at the ventricle induced tachyarrhythmias (VT) in 6 of 8 vehicle-treated HSBP5 R120G-TG mouse hearts but in none of 8 nicorandil-treated HSBP5 R120G-TG mouse hearts (p < 0.05).

Conclusion: These findings suggest that nicorandil can inhibit ventricular electrical and structural remodeling and prevent VT induction in a mouse model of desmin-related cardiomyopathy.

Right atrial stretching does not inhibit fluid intake with myocardial infarction

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Purpose: Low-pressure cardiopulmonary receptors are important in maintaining body fluid balance. One set of these receptors is located in the superior vena cava-right atrium junction (SV-JA). Heart failure following myocardium infarction (MI) presents increased body fluid and may have an impairment of the mechanoreceptors receptors at SV-JA-RAJ. The function of this aim was to study the effect of SV-JA-RAJ stretching on water and sodium intake in rats after MI.

Methods: Male Wistar rats (BW: 280-300g) underwent surgical left coronary artery ligation (n=9) or sham operation (n=5). Four weeks later an echocardiogram was performed followed by the introduction of a balloon close to the atrioventriculare corner. Two days later, the balloon was stretched and the rats received furosamide (10mg/kg) plus captopril (5 mg/kg), in accordance to the FUROCAP protocol, to induce increased fluid intake. Both MI and sham rats were further divided into control (vehicle) and norticandil (10mg/kg) plus captopril (5 mg/kg), in accordance to the FUROCAP protocol, to induce decreased fluid intake. Both MI and sham rats were further divided into control (vehicle) and norticandil (10mg/kg) plus captopril (5 mg/kg), in accordance to the FUROCAP protocol, to induce decreased fluid intake. Both MI and sham rats were further divided into control (vehicle) and norticandil (10mg/kg) plus captopril (5 mg/kg), in accordance to the FUROCAP protocol, to induce decreased fluid intake.

Results: MI decreased ventricular systolic (0.86 ± 0.03 vs. 0.64 ± 0.03, P < 0.01) and systolic dimension (0.87 ± 0.09 vs. 0.62 ± 0.03 cm2, P < 0.001). MI rats and controls presented similar ingestion of NaCl 0.3M or water. SV-JA-RAJ stretching induced decreased intake of NaCl 0.3M only in the controls at 60 min monitoring (7.6 ± 2.0 vs 2.9 ± 1.1 ml/60 min).

Conclusion: Left ventricular dilation after MI is associated with lack of reduced salt intake following SV-JA-RAJ stretching. This suggests an impairment of cardiac low-pressure receptors.

Characterization of cyclophilin A in coxsackievirus B3-induced myocarditis

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Background: The Extracellular Matrix Metalloproteinase Inducer (EMMPRIN, CD147) and its ligand Cyclophilin A (CyPA) modulate MMP activity and appear to modulate inflammatory processes. To our knowledge the functional role of this receptor/ligand pair has not been characterized in inflammatory cardiomyopathy. Therefore we investigated the role of CD147 and CyPA in cytos in mouse models of acute and chronic coxsackievirus CB3-mycarditis.

Methods and Results: CyPA+/+ (SV129) and CyPA-/- mice were infected with CB3. EMMPRIN and CyPA were upregulated at 8 days (western blot, immunochemistry). Myocardial tissue of CyPA+/+ mice showed a significantly reduced number of infiltrated T-cells and macrophages at day 8 (macrophages: 7.5 ± 0.1 vs 10±0.1, p < 0.05; T cells: 5.8 ± 0.4 vs 10±0.3, p < 0.01). Consistently, in A7r5/SV129 mice, which are susceptible to chronic CBV3-myocarditis, treatment with the CyPA-inhibitor NIM811 starting at the day of infection significantly reduced macrophage and T-cell recruitment at day 8 (p < 0.05), which was associated by improved virus elimination. Interestingly, NIM811-treatment of CBV3-infected A.BY/SvJ mice starting at day 12 p.i. significantly reduced the myocardial amount of collagen in myocardial lesions.

Conclusion: In summary, our data suggest that CyPA is critically involved in the pathophysiology of virus-induced myocarditis. CyPA may represent a target to modulate myocardial remodeling in myocarditis.

Left ventricular diastolic and systolic and atrial dysfunction in patients with hypertension might be related to increased oxidative stress and inflammation-final results

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Purpose: To study the presence of oxidative stress, inflammation, hypercoagula-

Ventricular diastolic and systolic and atrial dysfunction in patients with hypertension might be related to increased oxidative stress and inflammation-final results

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Background: The pathophysiology of left ventricular (LV) heart failure with preserved ejection fraction (HFPEF) is poorly understood, in part due to the lack of appropriate animal models. We aimed to model HFPEF in pigs by induced hypertension and western diet.

Methods/Results: Eight landrace pigs were implanted with subcutaneous 90 day release DOCA pellets (an aldosterone analog) and subsequently fed a high salt diet (30% NaCl) for 12 weeks. This resulted in a high systolic blood pressure (11mmHg in DOCA vs 95±5mmHg in control, p < 0.05). Electrocardiography demonstrated pronounced concentric hypertrophy in both groups (LV mass index 155±10 vs 108±5 g/m2, p < 0.001 for both groups). CRP levels were elevated in both groups. No between groups difference was found in other laboratory parameters. The absolute values of the mean of maximal longitudinal systolic LV strain (S) (p < 0.05 for both groups) and systolic (p < 0.001 for both groups) and early diastolic (p < 0.05 for both groups; p < 0.001 for both groups) atrial reservoir period (p < 0.001 for both groups) and atrial reservoir period (p < 0.001 for both groups) SRs in both patient groups were reduced compared with controls. Numerous significant correlations between biochemical and echocardiographic parameters were found. Typically the degree of oxidative stress and inflammation, BNP and PAI-I levels correlated inversely with LV systolic and diastolic and atrial function.

Conclusion: In conclusion, oxidative stress [measure of total scavenger capacity (TSC), protein carbonylation (PK), tetrahydrobiopterin (BH4) levels], (2) inflammatory (measurement of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a) levels), (3) coagulation [measurement of fibrinogen levels, plasminogen activator inhibitor (PAI)-1 and von Willebrand factor] and (4) neuroendocrine parameters [chromogranin A (cGA) and B-type natriuretic peptide (BNP) levels] was carried out from plasma or serum samples. Results: 36/94 (40%) patients with HT had no diastolic dysfunction (HTDD- group), and 56/64 (69%) patients had diastolic dysfunction (HTDD+ group). TSC decreased and BH4 increased in both patient groups (p < 0.001 and p < 0.01 for both groups respectively), PK increased (p < 0.05) in the HTDD- group, CRP in-

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Olmesartan inhibits ventricular remodeling and anti-arrhythmias in a mouse model of chronic heart failure

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Introduction: While beneficial effects of olmesartan, an angiotensin type 1 receptor blocker, on chronic heart failure (CHF) have been demonstrated, whether it has inhibitory effects on ventricular arrhythmias induced by CHF is still unclear. Recently, we demonstrated that a transgenic mouse with transient cardiac expression of activated G protein α1 (Gaq-TG) develops CHF and frequent ventricular arrhythmias. We examined the effects of chronic administration of olmesartan on ventricular function, the number of premature ventricular contractions (PVC), and ventricular remodeling in Gaq-TG mice.

Method and Results: A lower dose of olmesartan (LDQ, 1mg/kg/day), higher dose of olmesartan (HDO, 3 mg/kg/day) or vehicle was orally administered to 30 Gaq-TG mice from 6 weeks to 32 weeks of age. At the age of 32 weeks, systemic blood pressure (SBP) and electrocardiogram (ECG) were measured and ventricular function was investigated using echocardiography. The degree of fibrosis was elucidated from left ventricular sections stained with Masson’s trichrome. Mean SBP was significantly decreased in HDO-treated Gaq-TG mice compared with those in LDO and vehicle-treated Gaq-TG mice (45±3.3 vs. 77±1.4 and 72±4.8 mmHg p<0.001). Both LDO and HDO-treated mice showed improved ventricular dysfunction, determined by reduction of LV fractional shortening (p<0.01) in Gaq-TG mice. During 10 min of ECG recording, PVC was frequently (more than 20 beats/min) observed in 9 of 10 vehicle-treated Gaq-TG mice but in none of 10 LDO-treated Gaq-TG mice (p<0.01 by Fisher’s exact test). Interestingly, the number of PVC was not decreased in HDO-treated Gaq-TG mice. Collected QT interval was significantly shorter in LDO-treated Gaq-TG mice than in HDO and vehicle-treated Gaq-TG mice (p<0.05). The degree of extensive interstitial fibrosis in the left ventricle was significantly less in both LDO and HDO-treated Gaq-TG mice than in vehicle-treated Gaq-TG mice (p<0.05).

Conclusions: These findings demonstrated that lower but not higher doses of olmesartan inhibited ventricular electrical remodeling and decreased the number of PVC in a mouse model of CHF, suggesting that relatively low dose of olmesartan is enough to treat CHF-induced ventricular arrhythmias.
The mitochondrial translocator protein ligands, 4'-chlorodiazepam and TRO40303 protect cardiomyocytes against doxorubicin toxicity

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Purpose: Doxorubicin is widely used as a chemotherapeutic agent for the treat- ment of a large spectrum of human neoplastic diseases but its administration in humans is limited by severe cardiotoxicity. Reactive oxygen species (ROS) production and mitochondrial permeability transition pore opening (mPTP) have been identified as major events in doxorubicin-induced damage. As the mitochondrial Translocator Protein (TSPO) ligands 4'-chlorodiazepam (CDZ) and TRO40303 have been shown to protect mitochondria and to reduce left ventricular dysfunction during myocardial ischemia-reperfusion through the inhibition of the opening of the mPTP, we examined their potential protective effect on doxorubicin-induced loss of contractility and ultimately on cell death in isolated adult rat cardiomyocytes.

Methods: The effects of doxorubicin (0.25-20 μM) on contractile function were evaluated in isolated adult rat cardiomyocytes paced at 1 Hz by electric field stimulation. Cell viability and ROS were determined with the fluorescent probes propidium iodide and dichlorofluorescin, respectively. Direct mPTP opening was assessed using fractions of the calcium loading CoCl2 and exposure to doxorubicin and the cardiomyocytes were pretreated by the TSPO ligands at concentrations previously shown as cardioprotective against ischemia-reperfusion injury by time PCR using specific sequences.

Results: At higher concentrations than 5 μM doxorubicin significantly reduced the velocities of contraction and relaxation of the cardiomyocytes and caused cell death. The deleterious effects of doxorubicin were associated with an increase in ROS production and involved mPTP opening as demonstrated using the calcium CoCl2 staining method and confirmed by the preventive effect of cyclosporin A. CDZ and TRO40303 improved cell viability, prevented the alterations of contractility of the cells and attenuated the collapse of maximal velocities of contractions and relaxation induced by doxorubicin. The cytoprotective effect of TSPO ligands involved a high reduction of doxorubicin-induced ROS production associated with inhibition of mPTP opening as attested by the maintenance of the mitochondrial calcium fluorescence observed in the presence of CDZ or TRO40303.

Conclusion: These data demonstrate that the TSPO ligands, CDZ and TRO40303 protect cardiac cells against doxorubicin toxicity and that this protection is at least in part mediated by prevention of ROS production and mPTP opening. Thus TSPO may represent a relevant pharmacological target for protection of the heart against doxorubicin-induced toxicity.
Matrix metalloproteinase level can predict left ventricular remodeling and systolic dysfunction after myocardial infarction

M. Abdelhamid, A. El Faramawy, H. Gabr, W. Ammar, F. Al Enezi

Purpose: Assessment of serum biomarker evidence of the early course of the cardiac type I collagen degradation (matrix metalloproteinase, MMP type -2) after myocardial infarction (MI) and relationship to left ventricular (LV) remodelling.

Methods: Our study included 28 patients (14 males & 14 females with a mean age of 57.8 yrs) with acute anterior STEMI (group) and 12 healthy volunteers (7 males & 5 females with a mean age of 59 yrs) as a control group (group). All patients were submitted to clinical evaluation, 12-lead ECG, echo-doppler study and laboratory work-up which included estimation of plasma activity level of MMP-2 within 24 h and 2 months post infarction. Echocardiography was performed within 48 h and 2 months after MI for assessment of LV volumes and ejection fraction (EF) by Simpson’s method.

Results: The mean level of MMP was higher in group I than group II (20.74 ± 1.27 mg/mL, p < 0.001). The mean EF in group I was 47.8 ± 37.0 within 48 hr and 2 months post MI respectively (p < 0.01). ANOVA test was conducted to evaluate the relationship between LV systolic function and MMP level both at baseline and 2 months after MI. The mean baseline MMP was 3.19, 18.6, 24.4 mg/mL in patients with normal (EF>55%), mild (EF=45-54%), moderate (EF=30-44%) LV systolic dysfunction. The mean MMP 2 months post MI was 2.74, 6.21, 23.7 and 35.3 mg/mL in patients with normal, mild, moderate and severe LV systolic dysfunction. ROC analysis revealed a cut off level of MMP > 3 mg/mL can predict the development of LV systolic dysfunction with a sensitivity and specificity of 89% and 84% respectively.

Conclusions: MMP increase after MI. The increase of MMP is associated with deterioration of LV systolic function both at baseline and 2 months later. A level ≥ 3 mg/mL can predict the development of LV systolic dysfunction with a sensitivity and specificity of 89% and 84% respectively.

Oxidative stress, inflammation and low levels of adiponectin as risk factors of left ventricular hypertrophy in type 2 diabetics with renal disease


Introduction: The pathophysiology of left ventricular hypertrophy is multifactorial and not completely understood. Recent studies have demonstrated the role of oxidative stress, inflammation and adiponectin in cardiovascular morbidity and mortality.

Purpose: The aim of this study was to evaluate factors associated with the left ventricular hypertrophy (LHV) in a population of type 2 diabetics with mild and moderate kidney disease.

Methods: In this cross-sectional study we included 78 type 2 diabetic patients (female: 30, male: 48), with a mean age of 61 years and a mean estimated glomerular filtration rate (MDRD) of 43.5 ml/min, followed in our outpatient nephrology clinic. We analyzed several laboratory parameters, such as: interleukin 6 (IL6), adiponectins (visfatin, resistin, adiponectin-36), oxidative stress (oxLDL), as well as the left ventricular mass index (LVMI) in our patients.

Results: In a simple regression model, the LVMI was positively correlated with age (r=0.322, p=0.004), IL6 (r=0.722, p<0.001), resistin (r=0.705, p=0.001), visfatin (r=0.76, p=0.001), oxLDL (r=0.752, p=0.001) and inversely with adipin-36 (r = -0.901 p<0.0001) and the glomerular filtration rate (r = -0.381 p<0.001). In a multiple regression model, only IL6 (r=0.148, p=0.049), oxLDL (r=-0.267 p=0.024) and adipin-36 (r = -0.736 p<0.0001), independently influenced the LVMI. ROC curve analysis showed that oxLDL (AUC= 0.852 p< 0.001) and IL6 (AUC= 0.931 p<0.0001) are predictors of left ventricular hypertrophy.

Conclusion: Our study showed that in type 2 diabetic patients with nephropathy, the oxidative stress, the inflammation and the adiponectins are determinants of left ventricular hypertrophy. Surely they also contribute to the complexity of CKD associated cardiovascular risk.

Cardiomyocyte structural deterioration and metabolic response in human DCM hearts

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Dilated cardiomyopathy (DCM) is associated with cardiac dysfunction and various histopathological characteristics and poorly known metabolic deterioration during structural and functional remodeling. The aim of this study was the expression pattern of structural deterioration and metabolic responses in human DCM hearts. The archived tissue samples of left ventricle originating from DCM hearts divided in respect to %EF on three groups: (1) 45-55% (n=13), (2) 30-40% (n=8) and (3) <30% (n=10) were investigated histopathologically, ultrastructurally by PAS staining and immunohistochemically with antibodies against desmin, PPARalpha, SMAalpha and caspase-3, then quantified by morphometric methods. Controls (ctr) were tissue samples from hearts with myocarditis (n=8) and recovered from myocarditis (n=8), all with EF=50%. Correlation coefficients between each set of data were determined by Spearman rang regression analysis. Analysis of histopathological data in relation to decreased EF have shown predominance of desmin appearance with increased expression and normal pattern in group 1 and declined with abnormal pattern and/or lack expression in some cardiomyocytes in group 2 and 3, and cumulating ultrastructural pathology as loss of contractile fibrils, increased size and number of mitochondria or mitochondria matrix and cristae deterioration. Increased cardiomyocytes diameter and fibrosis were significant only in 3 vs 1 and 2 group and both ctr. The decrease of PAS(+) material, and type expression of fetal phenotype in about 1% cardiomyocytes and PPARalpha in predominant number of nuclei was observed in group 1. Contrarily, in group 2 further advanced cellular pathology followed by minor number of nuclei PPARalpha(+) material, and type expression of fetal phenotype in about 5% cardiomyocytes and PPARalpha(+) characteristic features. Either glycogen nor SMAalpha and apoptosis were not detected in tissue sections in group 3. In this group PPARalpha expression was present in various number of nuclei (from 0 to 5%). The PPARalpha(+) material, increased size and number of mitochondria or mitochondria matrix, and cristae deterioration were characteristic features of ctr. There was a significant correlation between PPARalpha and %EF (R=0.684, p<0.001) and %EF (R=0.768, p<0.001) and %PPARalpha(+) cardiomyocytes (R=0.544, p<0.001).

The collective findings reveal a close relationship between functional, structural and metabolic remodeling of cardiomyocytes and PPARalpha expression. Disturbance in glycogen presence and PPARalpha expression in biopsies of DCM hearts seem to be markers of cardiomyocytes metabolic shift.

Abrogation of S100B expression in S100A1 deficient mice improves survival post myocardial infarction

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Post-myocardial infarction (MI) ventricular remodeling involves ventricular dilatation, hyper trophy of non-infarcted myocardium, myocyte apoptosis, the induction of S100B and the downregulation of S100A1. Whereas S100A1 deficiency results in cardiac functional impairment and high early mortality post-MI, abrogation of S100B preserves cardiac function in the setting of augmented hypertrophy post-MI. To assess the consequences of S100B expression in S100A1 knock-out (KO) mice, wild-type (WT), S100A1 KO, S100B KO and S100A1-B KO mice were subjected to LAD coronary artery ligation with age-matched sham-operated controls. S100A1-B KO mice demonstrated better survival as compared to S100A1 KO and WT mice.
The bone morphogenetic protein-antagonist Gremlin-1 serves as a new biomarker for structural heart disease and predicts clinical outcome


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Background: Gremlin-1 is involved in inflammatory and fibrotic processes. Aim of the present study was to assess the diagnostic and prognostic value of Gremlin-1 expression in endomyocardial tissue of patients with structural myocardial disease.

Methods: 214 unselected patients undergoing endomyocardial biopsy were enrolled. Endomyocardial tissue sections were evaluated according to standard histological and immunohistological criteria (CD68, H&E, CD3, virus genome detection) along with Gremlin-1 staining. The primary combined endpoint was death, heart failure, and rehospitalization due to heart failure again within this time frame.

Results: From the analyzed cytokines in the ICM group, only serum levels of IL-6 were significantly elevated (1.8 fold, p = 0.005) compared to controls. No significant changes regarding inflammatory cytokines were found for the DCM group. Circulating mDCs were significantly reduced in patients with DCM (0.14% vs 0.20%, p = 0.001) as well as in ICM (0.175% vs 0.20%, p = 0.039) compared to healthy controls. There was a significant inverse correlation between IL-6 levels and circulating mDCs in DCM (r = -0.25, p = 0.001) and ICM (r = -0.25, p = 0.05) was observed. In univariate analysis, we found mDCs, male gender, hypertension, diabetes, and dyslipidaemia to be predictive for HF for the DCM group, while mDCs, male gender and hypertension remained as independent predictors for HF. In contrast, for ICM, independent predictors were IL-6, male gender and dyslipidaemia.

Conclusions: We show different results in plasma levels of IL-6 and circulating mDCs in our patient collective with respect to their etiology of HF (ischemic vs. dilated cardiomyopathy). Circulating mDCs and IL-6 could therefore be useful as differentiation markers in the diagnosis of cardiomyopathies and they appear to be independent predictors of HF in DCM and ICM respectively.
linded as death of all causes, heart transplantation, rhythm events, and heart failure-related rehospitalization.

**Results:** Gremlin-1 expression was significantly enhanced in patients with structural myocardial disease. The left ventricular function in patients with positive Gremlin-1 staining was significantly reduced compared to patients with negative Gremlin-1 staining (39.4% ± 13.8 vs. 48.0% ± 14.5, p = 0.001). Furthermore, they showed a significantly enlarged left ventricle (53.1mm ± 10.2 vs. 49.6mm ± 9.0, p = 0.030) and higher serum levels of C-reactive protein (1.8 mg/dL ± 3.7 vs. 1.0 mg/dL ± 1.7, p = 0.015).

During a median follow-up of 11.4 months (29.9%) patients reached the combined endpoint. Independent predictors for the composite endpoint were Gremlin-1 expression, elevated levels of troponin I (Tnl), and NYHA class ≥ III (hazard ratio (HR); 95% confidence interval (CI): Gremlin-1: HR 6.0; CI (2.2 – 16.8), p=0.001; Tnl >0.03 μg/L: HR 2.0; CI (1.2 – 3.3); p=0.007; NYHA ≥ II: HR 1.7 (1.0 – 2.7), p=0.049).

**Conclusions:** Expression of Gremlin-1 is significantly enhanced in patients with structural myocardial disease. Besides Tnl and NYHA class ≥ III, Gremlin-1 is an independent predictor of clinical outcome.

**PREDICTORS FOR OUTCOME**

**P5140**

**Lung ultrasound for the evaluation of pulmonary congestion in a pre-transplantation heart failure outpatient clinic: comparison with natriuretic peptides**

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**Purpose:** Evaluation of pulmonary congestion is a frequent diagnostic challenge even by highly skilled clinicians. Recently, lung ultrasound (LUS) has been proposed for a reliable, easy evaluation of pulmonary congestion, by assessment of B-lines (also called ultrasound lungcomets). Our aim was to define the relationship between B-lines and natriuretic peptides (NT-proBNP) as part of the evaluation of pre-transplant heart failure (HF) patient in an outpatient clinic.

**Methods:** Fifty-eight patients admitted to a pre-transplantation clinic due to advanced systolic HF (65.5% men, mean age 49 ± 11 yrs, 47.2% with idiopathic and 29.3% with post-ischaemic cardiomyopathy) were enrolled. Clinical assessment, NT-proBNP determination at diagnosis, patients with ejection fraction below 50% (n=28) were excluded. Prognosis was assessed after a median follow-up of 561 days.

**Results:** When compared with AL patients without myocardial involvement, cardiac AL was characterized by increased wall thickness (p<0.001) and reduced end-diastolic LV volumes (p<0.001). As expected, diastolic dysfunction was evident in all cardiac AL patients, as evident by increased E/E' ratio (p<0.001). Midwall fractional shortening was markedly depressed (11.2±4.3 vs 22.1±4.4%, p<0.001), despite preserved ejection fraction. At multivariable analysis, midwall fractional shortening (p=0.003) and NT-proBNP determination at diagnosis. Patients with ejection fraction below 50% (n=28) were excluded. Prognosis was assessed after a median follow-up of 561 days.

**Conclusions:** In cardiac AL amyloidosis with normal ejection fraction, depressed midwall fractional shortening, a marker of myocardial contractile dysfunction, is a powerful predictor of survival.

**P5142**

**The electrocardiographic/echocardiographic mass ratio in the diagnosis of cardiac amyloidosis**

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**Background:** Systemic amyloidoses are characterized by extracellular deposition of insoluble fibrils in various tissues. Clinical presentation is variable, depending on the extension of deposits and on the extent of organ dysfunction. In AL amyloidosis, the amyloidogenic protein is an immunoglobulin light chain or a fragment of an Ig light chain that is synthesized by clonal plasma cells in bone marrow. Cardiac involvement is not only frequent, but it is also the most common cause of death. Cardiac amyloidosis represents an archetypal form of restrictive heart disease, characterized by profound diastolic dysfunction. Since ejection fraction is preserved until the late stage of the disease, the majority of patients with cardiac AL amyloidosis do fulfill the definition of diastolic heart failure, i.e. heart failure with preserved ejection fraction. In another clinical model of diastolic heart failure, i.e. pressure-overload left ventricular hypertrophy, depressed midwall fractional shortening (i.e. a marker of myocardial contractile dysfunction) has been shown to be a powerful prognostic factor.

**Methods:** To assess a potential prognostic role of midwall fractional shortening in cardiac AL amyloidosis patients, we enrolled 221 consecutive echocardiographic evaluation as well as NT-proBNP determination at diagnosis. Patients with ejection fraction below 50% (n=28) were excluded. Prognosis was assessed after a median follow-up of 561 days.

**Results:** When compared with AL patients without myocardial involvement, cardiac AL was characterized by increased wall thickness (p<0.001) and reduced end-diastolic LV volumes (p<0.001). As expected, diastolic dysfunction was evident in all cardiac AL patients, as evident by increased E/E' ratio (p<0.001). Midwall fractional shortening was markedly depressed (11.2±4.3 vs 22.1±4.4%, p<0.001), despite preserved ejection fraction. At multivariable analysis, midwall fractional shortening (p=0.003) and NT-proBNP determination at diagnosis. Patients with ejection fraction below 50% (n=28) were excluded. Prognosis was assessed after a median follow-up of 561 days.

**Conclusions:** In cardiac AL amyloidosis with normal ejection fraction, depressed midwall fractional shortening, a marker of myocardial contractile dysfunction, is a powerful predictor of survival.

**Figure 1. ROC Curve - B-lines number**

**Conclusion:** In a pre-transplantation heart failure outpatient clinic, B-lines evaluated by LUS are significantly correlated to NT-proBNP values. Given its accuracy, low cost and portability, LUS may be considered as a reliable tool for a quick and easy evaluation of pulmonary congestion in decompensated HF patients.
Evidence of subclinical perimyocardial involvement in patients with systemic lupus erythematosus: late gadolinium enhancement study

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Purpose: Increased inflammation has been linked to myocardial dysfunction and heart failure. We investigated whether patients with systemic inflammatory diseases, such as systemic lupus erythematosus (SLE), free of cardiac symptoms, have evidence of subclinical inflammatory myocardial involvement.

Methods and results: A total of 27 SLE patients (male=0, mean age 41±11 years) with no previous cardiac history underwent cardiovascular magnetic resonance imaging for assessment of function and late gadolinium enhancement on a 3 Tesla scanner. In these patients, the presence of significant coronary artery disease was excluded by virtue of negative adenosine myocardial perfusion or normal high-resolution magnetic resonance coronary angiography. Fifteen age-matched subjects with a low pretest probability acted as a control group. In SLE group, there was deceased global systolic function (SLE vs. controls: 47±2% vs. 60±5%, p<0.05) and increased LV mass index (68.2±43 g/m2 vs. 43.4±43 g/m2, p<0.01). Late gadolinium enhancement was detected in 20 SLE subjects: 14 patchy areas of intramyocardial enhancement and 6 subjects showed intramyocardial stria. Myocardial enhancement was invariably affecting the basal segments of inferior septum, inferior and inferolateral walls and right ventricular insertion points. None of the subjects showed regional myocardial fibrosis. Pericardial effusion was present in 4 patients. Pericardial enhancement was present in 17 patients (5 of these had no myocardial enhancement), enveloping globally right and left ventricles, with mean thickness of the pericardial space along the free LV wall of 3.1±7mm.

Conclusions: We demonstrate that in SLE patients free of significant coronary artery disease there is evidence of subclinical perimyocardial involvement.

Cardiac myosin binding protein C gene polymorphisms and diastolic heart failure

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Objective: Myosin binding protein C (MYBPC) plays a role in ventricular relaxation. The aim of the study was to investigate the association between cardiac myosin binding protein C (MYBPC) gene polymorphisms and diastolic heart failure (DHF) in a human case-control study.

Methods: A total of 352 participants of 1752 consecutive patients from the National University Hospital and its affiliated hospital were enrolled. 176 patients diagnosed with DHF confirmed by echocardiography were recruited. Controls were matched 1:1 by age, sex, hypertension, diabetes, renal function and medication use. We genotyped 12 single nucleotide polymorphisms (SNPs) according to hapMap Han Chinese Beijing databank across a 40 kb genetic region containing the MYBPC3 gene and the neighboring DNA sequences to capture 100% of haplotype variance in all SNPs with minor allele frequencies ≥5%. We also analyzed associations of SNPs and haplotypes with DHF and linkage disequilibrium (LD) structure of the MYBPC3 gene.

Results: In a single locus analysis, SNP rs2290149 was associated with DHF (allele-specific p = 0.004; permuted p = 0.031). The SNP with a minor allele frequency of 9.4%, had an odds ratio 2.14 (95% CI 1.25-3.66; p = 0.004) for the additive model and 2.06 for the autosomal dominant model (GG+GA: AA, 95% CI 1.17-3.63; p = 0.013), corresponding to a population attributable risk fraction of 12.02%. The haplotypes in a LD block of rs2290149 (C-C-G-G) was also significantly associated with DHF (odds ratio 2.10 (1.53 – 2.89); permuted p = 0.029).

Conclusions: We identified risk-conferring genetic variants of MYBPC3 gene for DHF in a Chinese population.

Subclinical abnormalities of the arterial tree and left ventricular myocardial deformation, relaxation and twist in chronic kidney disease

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Purpose: Chronic kidney disease (CKD) associates with adverse cardiovascular outcomes. However, the disadvantageous effects of renal dysfunction on left ventricular systolic and diastolic function remain unclear. The objective of this study was to look at the effect of CKD on (i) left ventricular (LV) systolic and diastolic strain patterns and LV twist with the use of conventional and 2D speckle tracking echocardiography, and (ii) arterial stiffness as measured by pulse wave velocity (PWV).

Methods: Seventy four consecutive CKD patients were assessed using conventional, 2D speckle tracking echocardiography (EchoPAC-GE) and applanation tonometry (Sphygmocor). Patients with (i) LV systolic dysfunction or regional wall motion abnormalities, (ii) moderate to severe valvular disease or (iii) heart rhythm other than sinus were excluded (N=5). Global systolic strain (GS) and strain rate (GSRs), early (GSRe) and late (GSRd) diastolic longitudinal strain rate, LV twist and twist rate, mitral inflow, tissue PW Doppler velocities and PWV were recorded.

Results: The mean age of CKD patients was 54±15.4 years and 34 (49.3%) were male. The female mean baseline LV ejection fraction (EF) was 62±5.4%. Six (8.7%) patients were stage 1 CKD, 17 (24.6%) stage 2, 29 (42%) stage 3, 12 (17.4%) stage 4 and 5 (7.2%) stage 5. Estimated Glomerular Filtration Rate (eGFR) correlated significantly with PWV (r=0.275, p=0.026) and E/E' ratio (r=0.370, p=0.002). There was no correlation between gEFr and GS, GSRe or GSRd. Including the echocardiographic parameters in a linear regression model with dependent variable eGFR, E/E' (beta -1.75, p=0.007) and LV twist rate (beta -0.27, p<0.01) were independent significant predictors. Amongst CKD stages 1-2 patients there were 6 (33.3%) with diastolic dysfunction, in stage 3 the figure increased to 17 (75%) and in stages 4 and 5 increased further to 14 (82.4%)

Conclusions: Arterial stiffness and LV relaxation demonstrate progressive deterioration with worsening eGFR whereas LV filling pressure and twist rate appear to increase, compensating for the impaired diastolic filling. Outcome studies may be required to identify the association of these early markers of cardiovascular disease in CKD patients.

Peak cardiac power output: a new hemodynamic tool to aid the diagnosis of heart failure with preserved ejection fraction? A pilot study

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Purpose: By coupling both the pressure and flow generating capacities of the heart, the peak cardiac power output peak (CPO) is a direct measure of cardiac function during exercise and a major determinant of exercise capacity. Furthermore, in patients with systolic heart failure (SHF), peak CPO < 1.5 W is an independent and powerful predictor of prognosis that can be measured non invasively using cardio-pulmonary exercise testing. This is the first study to investigate the diagnostic value of the CPO in patients with heart failure with preserved ejection fraction (HFpEF).

Methods: Among the 45 patients (age 66 [53-73] years) included into the study, 10 subjects were classified as HFpEF. 24 patients had SHF (EF < 35%) and 11 subjects served as a control group. All subjects underwent symptom limited exercise testing. This is the first study to investigate the diagnostic value of the CPO in patients with heart failure with preserved ejection fraction (HFpEF).

Results: The peak CPO was significantly different among the groups: 2.42 (1.88-3.82) W in controls, 1.67 (1.17-2.09) W in SHF vs. 1.44 (1.22-1.69) W in HFpEF (p=0.018). There was a significant correlation between the peak CPO and the peak oxygen uptake (VO2peak; n=45, p=0.002) and NT-proBNP levels (n=45, p=0.001).

Conclusions: The present study is the first to evaluate peak CPO as a direct measurement of hemodynamic response to exercise in patients with HFpEF. The peak CPO of patients with HFpEF and SHF was similar reduced. Therefore, peak CPO can identify abnormalities in cardiovascular function consistent with those

Predicators for outcome
predicting mortality in SHF. CPO has the potential to be a key diagnostic marker in HFrEF and may enhance the ability to accurately identify patients at greatest risk for heart failure related complications.

**P5147**

**Relationship of pro-collagen biomarkers of myocardial fibrosis with myocardial dysfunction and metabolic derangement in type 2 diabetes**

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**Purpose:** Myocardial fibrosis is a potential contributor to non-ischemic diabetic dysfunction (DD) in type 2 diabetes (T2DM). We sought the relationship between fibrosis markers, myocardial dysfunction and metabolic derangement.

**Methods:** Clinical, imaging and biochemical data were measured in 390 asymptomatic subjects (216 men, 58±10 yrs) with T2DM. Myocardial function was examined with standard 2D echo, early diastolic (em) and systolic velocity, strain, strain rate, and backscatter (ciB). Amino-terminal propeptides of pro-collagen type I (PINP) and type III (PIIINP) were measured by radio-immunoassay, and the carboxy-terminal propeptide of pro-collagen type I (PICP) was measured by enzyme immunoassay.

**Results:** Patients were stratified by metabolic derangement; 53 (14%) had isolated T2DM, 67 (17%) had T2DM with isolated hypertension, 178 (45%) had T2DM with both metabolic syndrome and 92 (24%) had T2DM with both metabolic syndrome and end-organ involvement (microalbuminuria). Progressive metabolic derangement was mirrored by worse DD (em p=0.001), increased ciB (p=0.016), greater insulin resistance (log HOMA-IR p=0.001) and worse exercise capacity (VO2 max p<0.001) but only a trend towards proportionally higher PIIINP levels (3.9±1.9 vs. 1.7 μg/l) was associated with insulin resistance (log HOMA-IR p=0.008) independent of age (p=0.017) and renal function (creatinine 0.227 vs. 0.004). PINP (42.2±26.4 μg/l) and PICP (275±90.4 ng/ml) were not associated with metabolic parameters or myocardial properties.

**Conclusions:** Metabolic derangement in T2DM is proportionally associated with worsening DD and increased myocardial signal intensity (ciB). The association with PIIINP levels is weak, suggesting a limited role of type III collagen turnover in subclinical, non-ischemic diabetic heart disease.

**P5148**

**Acute improvement of left atrial mechanics and left ventricular diastolic function after Transcatheter Aortic Valve Implantation**

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**Purpose:** Aortic stenosis leads to remodelling of the left ventricle and atrium that causes systolic and diastolic dysfunction. Transcatheter aortic valve implantation (TAVI) is a rapidly evolving therapy for severe aortic stenosis in high-risk patients. Two-dimensional speckle tracking echocardiography (STE)-derived strain measurements enable the regional assessment of left atrial (LA) mechanics. The goal of this study was to describe the acute effects on myocardial deformation of the LA and left ventricular (LV) diastolic function after TAVI.

**Methods:** 32 consecutive patients (17 female, mean age 76 years, mean Euroscore 18.7%, mean LVEF 52±5.17%) with severe aortic stenosis (0.73±0.19 cm²) were enrolled into our study. We performed transhорacic echocardiography including STE of the basal septal segment of the left atrium to determine peak positive strain (LASp), strain during early diastole (eLASD) and, if feasible, strain during atrial contraction (LAAC) representing LA reservoir, conduit, and contractile function, respectively. In addition, the corresponding strain rate values such as systolic atrial strain rate (SSR), early diastolic atrial strain rate (eSSR), and late diastolic strain rate (ASR) were analysed. Diastolic assessment of the left ventricle included standard indices and the atrial fraction. LA volumes throughout the cardiac cycle were also assessed.

**Results:** At baseline, 24 (75%) of our patients were in sinus rhythm. Heparin was administered before TAVI and after one week did not differ significantly. The atrial reservoir (LASp) and conduit function (LASp - eLASD) improved significantly (19.2±12.0% vs. 24.9±16.2%, P = 0.02 and 9.8±6.9%, 14.7±8.3%, P = 0.009, respectively). There was a significant reduction of the deceleration time (DT) (257±88 vs. 188±71 ms, P < 0.001) and an improvement of pw-tissue Doppler derived E (5.7±1.9 vs. 7.3±2.3 cm/s, P < 0.001). In contrast, there was no improvement in atrial contraction: contractile function (eLASD - LAA, 12.1±8.8% vs. 14.6±11.8% P = 0.4), A (6.3±6.1 cm/s vs. 6.3±5.6 cm/s, P = 0.25) and atrial fraction (0.37±0.14 vs. 0.34±0.13 P = 0.78). In addition, eE/’ and the LA diastolic volume (42.3±15.1 ml/m² vs. 39.0±15.1 ml/m², P = n.s.) did not differ significantly.

**Conclusion:** One week after TAVI only the reservoir and conduit function of the left atrium improved, whereas the late diastolic LA contraction and the LA volume were unchanged. This was accompanied by improvement of the early LV diastolic function indicating acute recovery of LV relaxation and LA function.

**P5149**

**Diagnostic value of pulsatile hemodynamics for heart failure with normal ejection fraction**

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**Purpose:** Increased arterial stiffness and wave reflections are present in most patients with heart failure with normal ejection fraction (HFrEF). We tested whether measures of pulsatile arterial function are useful for diagnosing HFrEF, in comparison with and in addition to Tissue Doppler Echocardiography (TDI).

**Methods:** Patients with dyspnea as leading symptom were categorized as having HFrEF or no HFrEF, based on invasively derived filling pressures and atrial natriuretic peptide levels. Pulse wave velocity was measured invasively (aPWV), arterial pulse pressure (aPP) and its components (incident pressure wave height – P1, forward wave amplitude – P2, augmented pressure – AP, backward wave amplitude – Pb) were quantified non-invasively from radial tonometry, using pulse waveform analysis and wave separation analysis.

**Results:** 71 patients were classified as having HFrEF, and 65 as no HFrEF (in 223 patients, intermediate results were present). Patients with HFrEF were older, more often had hypertension and diabetes, and had more advanced coronary artery disease, larger left atria and higher left ventricular mass. Blood pressures and all measures of arterial stiffness and wave reflections were higher in HFrEF group. Receiver operating curve analysis derived area under the curve values were 0.823 for EEC (medial annulus), the best TDE parameter, and 0.867, 0.851, 0.812, 0.813, 0.854, and 0.825 for aPWV, aPP, P1, AP and Pb, respectively (Figure). Multivariable logistic regression models proved that measures of pulsatile arterial function provided independent and additive diagnostic information.

**Conclusion:** Measures of arterial stiffness, central pressures and wave reflections complement TDE for the diagnosis of DHF.

**P5150**

**Perhexiline corrects energy deficiency and improves symptoms in chronic heart failure**

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**Background:** We hypothesized that the metabolic modulator perhexiline would ameliorate myocardial energy deficiency and improve symptoms in dilated cardiomyopathy.

**Methods and Results:** 50 patients with heart failure (NYHA II - IV, LVEF < 40%) were randomised to 100mg bid (n=25) or placebo (n=25) for 1 month in a double blind fashion. Myocardial ratio of phosphocreatine to adenine triphosphate, an established marker of cardiac energetic status, as measured by 31P magnetic resonance spectroscopy, echocardiography, symptoms and quality of life scores were assessed at baseline and at study end. Perhexiline improved the primary

**Parameter** | **Perhexine Group** | **Placebo Group** | **P**
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PCr/ATP ratio | 1.16±0.08 | 1.51±0.11 | 1.38±0.07 | 1.34±0.07 | 0.005
NYHA class | 1 (8); 2 (18) | 2 (10); 18 (8) | 14 (4); 10 (9) | 15 (6); 9 (11) | 0.02
MWHFQ | 25 (17-51) | 20 (9-46) | 36 (11-90) | 27 (9-59) | 0.26
NTPro-BNP pg/ml | 1325 (763-1890) | 454 (246-659) | 1237 (653-1821) | 451 (202-700) | 0.99
Predictors for outcome

We hypothesised that levosimendan will improve myocardial regional contractility without harmful side effects in acute PCI treated STEMI patients complicated by decompensated heart failure.

**Method:** Patients developing clinical signs of heart failure (including cardiogenic shock) within 48 hours after a primary PCI treated STEMI, with decreased wall-motion in ≥3 of 16 segments evaluated by echocardiography, were randomised to a 24-hour levosimendan infusion or matching placebo in a double-blind design. Primary endpoint was change in wall-motion score index (WMSI) from baseline to day 5. Infarct size was measured by single photon emission computed tomography (gated SPECT) at 6 weeks.

**Results:** (mean ±SD): A total of 61 patients were included. Age (64±13 years), peak cardiac troponin T (3083±6996 ng/l), BP (104/66 mmHg) and left ventricular EF (42±9%) at inclusion, were not significantly different between groups. Infarct size at 6 weeks (42±16%) was similar in both groups. There was significantly larger improvement in WMSI from baseline to day 5 in the levosimendan group compared to placebo (from 1.94±0.20 to 1.66±0.31 vs 2.02±0.26 to 1.83±0.26 respectively, p=0.03). There were no significant between-group-differences from baseline to day 5 in changes in NT-proBNP levels, a clinical composite score, frequency of atrial fibrillation or ventricular arrhythmia, new ischemic episodes or use of inotropy as rescue therapy. There were significantly more episodes of hypotension during study drug infusion in the levosimendan group (63% vs 36%, p=0.03), but no difference in blood pressure at the end of infusion or in use of vasopressors. One patient died in the levosimendan group and 4 patients in the placebo group during 6 months follow-up. No significant between-group-differences at 6 months in MACE (death, nonfatal myocardial infarction or revasculatization of the infarct related artery) or in rehospitalisation for heart failure, were present.

**Conclusion:** Levosimendan treatment improved regional contractility measured by WMSI in patients with acute PCI treated STEMI complicated by heart failure, but did not affect NT-proBNP levels or clinical symptom score. The treatment was well tolerated without any increase in atrial fibrillation or ventricular arrhythmias.

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**P5151**

**Index of lectin-like oxidized low-density-lipoprotein receptor is independently associated with left ventricular systolic dysfunction**

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**Background:** Lectin-like oxidized low-density-lipoprotein receptor-1 (LOX-1) is a multiple ligand receptor induced by oxidative stress. The LOX-index represents levels of soluble LOX-1 (sLOX-1) multiplied by levels of LOX-1 ligands containing apolipoprotein B (LAB), and serves as a marker of cardiovascular risk in a general population. Recently, we reported that left ventricular (LV) expression of LOX-1 is markedly increased in a rat model of heart failure (HF). However, the significance of LOX-index in patients with HF in the clinical situation is unknown.

**Methods and Results:** We carried out a cross-sectional study involving 335 out-patients whose NYHA classes were stable for at least 3 months. They were divided into 3 groups: 22 patients with systolic dysfunction (HF+), LV ejection fraction (LVEF) < 50%, 35 patients with LV hypertrophy (LHV: LV mass index (LVMI) ≥ 116 in male, >104 in female) but without systolic dysfuncion (LHV+HF-), and 278 patients without LHV or systolic dysfunction (LHV-HF-).

We examined serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), leptin, and adiponectin and the LOX-index. The body mass index, blood pressures, low-density-lipoprotein cholesterol (LDL-C), hsCRP, leptin, and adiponectin were similar among the 3 groups. However, both NT-proBNP and LOX-index were significantly increased in HF+ compared to LHV+HF- and LHV-HF-.

**Conclusions:** In comparison to NT-proBNP, a marker of both LHV and HF, LOX-index is independently associated with decreased EF but not with LHV. These findings suggest that a role of LOX-1 pathway in the development of systolic dysfunction.

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**P5152**

**Levosimendan improves contractility in post ischemic myocardium in patients with acutely revascularised infarction complicated by decompensated heart failure**

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**Background:** Reduced calcium sensitivity of the myofilaments is believed to be part of the injury seen after reperfusion of ischemic myocardium. The role of the calcium sensitizer levosimendan in patients with acute STElevation myocardial infarction (STEMI) is unresolved.

**Figure 1.** Average change in PCI/A TP ratio

**P5153**

**The effect of aldosterone-antagonist therapy on aortic elastic properties in patients with moderate heart failure**

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**Methods:** Many studies proved the prognostic importance of aortic stiffness as an independent predictor of cardiovascular death and mortality. Aldosterone-antagonist therapy could decrease aortic stiffness and fibrinolytic risk in experimental models. Nevertheless, there are few studies that describe the effects of aldosterone – antagonist on aortic stiffness in patient with dilatatated cardiomyopathy.

**Aims of study:** To evaluate the effect of a therapy with aldosterone – antagonist Spirolactone on aortic stiffness in patients with idiopathic dilated cardiomyopathy.

**Results:** We randomized (1:1) 102 patients with idiopathic dilated cardiomyopathy and New York Heart Association class I – II to receive Spironolactone 25 mg/die or placebo, in addition to recommended therapy. The end points were aortic stiffness index, aortic strain and aortic distensibility. All the measures were obtained with echocardiography M – mode at 3 cm above the aortic valve on parasternal long axis view and simultaneous brachial arterial pressure with sphygmomanometer.

**Results:** Ascending aorta measures, aortic stiffness index, aortic distensibility and aortic strain were similar at randomization in the two groups. After 6 month of therapy in the treated group we found a statistically significant reduction of aortic strain index (7.2±3.5 mm² cm⁻² 10⁻⁶ vs 9.6±4.8 mm² cm⁻² 10⁻⁶; p=0.03) and a significant increase of aortic distensibility (3.77±1.0 mm² cm⁻¹ 10⁻⁶ vs 2.92±0.55 mm² cm⁻¹ 10⁻⁶; p=0.01) and systolic aortic strain (10.0% ± 5.0% vs 8.0% ± 2.1%; p= 0.01). The therapy with Spironaolactone has not significantly modified systolic arterial pressure, diastolic arterial pressure and diastolic pressure in the two groups.

**Conclusions:** The therapy with aldosterone – antagonist Spirolactone reduced aortic stiffness in patients with idiopathic dilated cardiomyopathy. This effect could improve haemodynamics suggesting the use of aldosterone – antagonist in patients with low NYHA class (III).

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**P5154**

**The treatment in patients with chronic heart failure with erythropoietin failure**


**Purpose:** Anaemia although common in chronic heart failure (CHF) patients, reduces functional status quality of life and is an independent risk factor for hospital admission and mortality. Erythropoiesis stimulating agents (ESA) are frequently used for its treatment. The effects of ESA treatment in patients CHF with anaemia remain largely unknown.

Therefore, our aim was to perform the study to determine the effect of continuous erythropoietin receptor activating C.E.R.A.-
Acute heart failure patients with high initial blood pressure show paradoxical hemococoncentration on admission

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Introduction: As volume overload is a major profile of acute heart failure syndrome (AHFS), diuretics, as well as oxygen, nitrates, and morphine, are a mainstay of therapeutic strategy for these patients. Though decongestion/diuretic therapy are started immediately after admission in most of patients, changes in concentration of blood components in this period remain to be investigated.

Method: We studied 135 patients admitted to our hospital with symptoms of AHFS between January and December 2010. Changes in hemoglobin levels between on admission and 24-12 hours postadmission were evaluated. Patients with cardiogenic shock, hemodialysis, blood transfusion, and/or urgent coronary angiography were excluded.

Results: In spite of decongestion/diuretic therapy started immediately after admission, hemoglobin level on admission was paradoxically higher than the level of 24±12 hours postadmission in 95 patients (70%). Patients in the top tertile of baseline-to-24h decrease of hemoglobin (ΔHb) were defined to have an evidence of admission hemococoncentration. The ΔHb in patients with admission hemococoncentration was 1.8±0.7 g/dL (12.9±2.5 on admission and 11.1±2.4 at 24h, p<0.001) whereas 0.0±0.7 g/dL (11.6±2.1 on admission and 11.5±2.1 at 24h, p=0.71) in those without admission hemococoncentration, and it showed significant difference between two groups (p<0.001). Admission hemococoncentration was significantly more prevalent in patients with higher initial systolic blood pressure (SBP; > 140 mmHg) than lower SBP (45% vs. 16%, p<0.001). Furthermore, ΔHb was positively and significantly correlated not only with initial SBP (r=0.43, p<0.001) but also initial heart rate (r=0.28, p=0.001) suggesting sympathetic effect on the pathophysiology of admission hemococoncentration. Patients with admission hemococoncentration had significantly lower ejection fraction (31±12 vs. 39±14%, p=0.003), higher presence of New York Heart Association class 4 (45% vs. 17%, p=0.002), and night time admission (52% vs. 36%, p=0.002) than those without admission hemococoncentration. Age, sex, renal function, history of hypertension, diabetes, and dyslipidemia, presence of ischemic heart disease are comparable between two groups.

Conclusion: AHFS with high initial SBP shows paradoxical hemococoncentration on admission. Sympathetically mediated fluid shifts between extracellular and circulating volume may underlie the development of AHFS.

Myocardial and vascular dysfunction in young subjects, are related to dyslipidemia and abdominal obesity but not to glycaemia

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Purpose: To investigate the relationships between cardiovascular risk factors and subclinical myocardial and vascular dysfunction in young adults.

Methods: We recruited 53 young subjects under 30 years of age including 34 healthy volunteers (mean age 24.6±2.9 years) and 19 subjects with type 1 diabetes mellitus (mean age of 21.1±3.6 years, mean duration of diabetes 9.0±7.5 years; mean HbA1c 8.8±1.6%). All subjects had detailed echocardiography; all type 1 diabetics and 21 controls had myocardial velocity measurements of LV long-axis function (at the mitral anulus). Applanation tonometry was used to measure augmentation index and carotid-femoral pulse wave velocity. Local arterial stiffness parameters (beta and epsilon) and carotid intima media thickness (cIMT) were assessed using high-resolution B-mode ultrasound of the common carotid artery. Fasting blood samples were taken for glucose, HbA1c, lipid profiles and hsCRP.

Results: Conduit arterial stiffness was related to body weight (beta, r=0.32, p=0.023; and epsilon r=0.41, p=0.003). Pearson correlations). The stiffness parameter epsilon correlated with the waist-hip ratio (r=0.37, p=0.008). Early diastolic myocardial function was inversely related to waist-hip ratio (lateral mitral annular velocity e', r=-0.45, p=0.004) and, in those subjects who had detailed myocardial velocity imaging (n=40), also to fasting serum triglycerides (lateral e', r=0.41, p=0.009; and medial e', r=0.34, p=0.034). It was positively correlated with serum HDL cholesterol (lateral and medial myocardial annular velocities r=0.38, p=0.02 and r=0.37, p=0.02, respectively).

All measurements of vascular and myocardial function were unrelated to blood glucose, glycaemic control, and hsCRP.

Conclusions: In young adults, abdominal obesity and dyslipidaemia may be more important risk factors for early myocardial and vascular dysfunction than is glycaemia.
Sonographic pulmonary comet sign in diagnosis and monitoring of pulmonary congestion in HF

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Background and Aim: Pulmonary congestion is useful marker of decompensated HF. The aim was to study the importance of Lung “Comet tail” artefact in diagnosis and monitoring of Pulmonary Congestion in patients with different types Heart Failure.

Methods: We studied 430 patients with II-IV NYHA class HF. 338 Patients have Systolic HF (SHF), 92 patient – HF with preserved systolic function (DHF), and 155 patients with heart diseases but without HF (control). Sonographic evaluation of a lung was done in horizontal or vertical positions of patient, from 10 points of thoracic wall which corresponded to the projection lung lobes.

Results: In patients with CHF we significantly often found the “Comet Tail” artefact (CTa) There was good correlation between the count of CTa registration points from the thoracic wall and the heart failure NYHA class (r=0.57), left ventricular systolic (r=0.43) and diastolic (r=0.34) diameters and negative correlation with EF% (r=0.44). In the HF gr. CTa was registered from 3 or more points of thoracic wall in 89.6%, in SHF -91.4%, in DHF -82.6%, in COPD -9.1% and in control -7.1% of patients. If we take 4 points and more as a reference value the sensitivity of sign in diagnosis of pulmonary congestion was 83.5% an specify – 97.6%. In CHF group CTPh was prominent, protracted and multiple while in the II group it was single and short lasting. After use of diuretics CTa disappear or was less prominent then before treatment.

Conclusion: Thoracic US is accurate method for evaluation and monitoring of pulmonary congestion in patients with systolic and diastolic HF. The US sign of pulmonary congestion is a CTa, which is multiple and registered from larger area of thoracic wall (3 points or more). The intensity of CTPh is reduced if the dehydration is successful.

Circadian variation of the occurrence of acute heart failure syndromes contributes to long-term prognosis in patients with non-ischemic cardiomyopathy

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Background: Although previous studies reported that the occurrence of acute myocardial infarction peaked in the morning, little is known for the clinical significance of circadian variation in the occurrence of acute heart failure syndromes (AHFS) in patients with non-ischemic cardiomyopathy (NICM). We aimed to investigate the clinical significance of the occurrence of AHFS during the morning in NICM patients.

Methods: We have retrospectively studied consecutive 201 NICM patients admitted for AHFS. We defined the patients of AHFS, who developed their symptoms from the midnight until 8 a.m. as the morning-AHFS group, and the others as the control-AHFS group.

Results: Twenty seven patients with the occurrence of AHFS during the morning were recognized in the present study, whose characteristics were significantly higher age, increased systolic blood pressure (BP) than in the control-AHF group (72±13 vs 66±16 y.o., 156±56 vs 125$^{2}$.28 mmHg p<0.05). Although in- and out-of hospital mortality did not differ between the morning-AHF and control-AHF groups, the rate of re-hospitalization for heart failure in the morning-AHF group was significantly high contrary to the control-AHF group. Sub-analysis using polyomorphometry revealed that the prevalence of sleep apnea was significantly higher in the morning-AHF group compared with in the control-AHF group (100% vs. 74%, p<0.001).

Conclusion: The occurrence of acute heart failure syndromes in the morning itself predicts poor clinical prognosis in association with higher age and sleep apnea, suggesting that increased sympathetic nerve activity (SNA) in the morning may play a significant role in deteriorating HF. Management to control SNA by treating sleep apnea or BP control in chronic phase would be the key to reduce the re-hospitalization for the worsening heart failure.

Correlations between hemodynamic parameters and serum high sensitive troponin-T


Serum troponin is widely accepted as a prognostic biomarker of heart failure. However the correlation and cause of elevation of serum troponin has not been studied well.

Method: Heart rate, blood pressure, serum high sensitive troponin-T (Roche diagnostics) were detected in all patients (median 0.012 inter quartile range 0.007-0.021ng/ml). Stepwise regression analysis revealed age (coefficient 0.012, 95% confidence interval 0.006-0.018; p<0.001), serum hemoglobin concentration(-0.069, [-0.116;-0.022], p<0.005), estimated glomerular filtration rate(0.045, [-0.005;0.010]), left ventricular diastolic dimension(0.016, [0.004;0.029], p=0.009) were associated with serum high sensitive troponin-T.

New Radiological Score for the verification of evolving pulmonary congestion-edema in the course of Acute Myocardial Infarction

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Background: Twenty five percent of patients sustaining acute myocardial infarction (AMI) develop pulmonary congestion-edema (PEA) as a result of increased lung fluid content (LFC). There is no method to monitor a changes in LFC. Lung impedance (LI) that decreases with increasing LFC may be indicator of LFC, but needs verification.

Periodic chest radiographs are the most commonly used means, of assessing LFC. Disadvantages of this modality are relatively high inter- and intra-observer variability. The latter is possibly due to the fact that currently x-rays are analyzed qualitatively and there is no simple and reproducible radiological score (RS) to be used.

We designed radiological score (RS) based on numerical summation lung edema signs. LI reflects LFC and was measured by new 50 times more sensitive surfaces device based on transverse distribution of electromagnetic energy through the chest.

Aim: To evaluate, in AMI patients developing PEA, the dynamics of a proposed RS with the status of LFC as assessed by changes in the clinical score (CS) and in LI measurements.
Results: Study population included patients admitted for AMI, with no radiological and clinical signs of PE at admission. RS of 0-2 characterized patients with no lung edema, 3-4 with interstitial edema, a 5-6 alveolar lung edema, and 7-8 and 9-10 signified moderate and severe alveolar edema. Patients were undergone to 96 hrs of monitoring. 2327 x-rays were done.

480 of 636 patients did not develop PE (CS0). Their RS was 0.3±0.5 at the beginning. Maximal decrease of LI from initial during monitoring in this group was 6.3±6.1% (p<0.001). At this time RS was 1.3±1.2 (p<0.01).

156 patients developed PE. At CS1 (rates at lung bases) RS was 5.2±0.9 (p<0.001) and LI decreased by 21.9±5.5% (p<0.001). At CS2 (rates at low half lung) and 3(rates over all lung), RS were 6.9±1.1 and 9.8±0.5 (p<0.001). LI decreased by 30.1±8.3% and 39.3±7.7%, respectively (p<0.001). PE'd CS correlated with RS (r=0.6, p<0.001) and with LI (r=-0.6, p<0.001). RS correlated with LI (r=-0.9, p<0.001). Changes in RS and LI strikingly preceded the detection of lung rales.

Conclusions: RS was shown to be a simple and reliable method to assess changes in LFC in patients developing AHF and well correlated with the degree of lung congestion.

Predictors of augmented peripheral chemosensitivity in patients with systolic heart failure

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Background: Augmented peripheral chemosensitivity is a typical feature of chronic heart failure (CHF), associated with poor prognosis, however its clinical predictors remain poorly understood.

Purpose: We investigated clinical predictors of peripheral chemosensitivity in contemporary CHF patients receiving optimal medical treatment.

Methods: Thirty CHF patients were studied (NYHA class II, mean LVEF 27±1.7±1%), who were treated with beta-blocker (100%), angiotensin convert- ing enzyme inhibitor and/or angiotensin receptor blocker (98%) and aldosterone antagonist (87%). Peripheral chemosensitivity was assessed with the transient hyperventilation technique using nitrogen gas administration and expressed by the linear regression slope between SaO2 (%) and minute ventilation (l/min). Based on previous experience, high peripheral chemosensitivity was defined as a response ≥ 0.7 l/min\%.

Results: Thirty (43%) CHF patients showed high chemosensitivity. The following clinical parameters differentiated those with high vs normal chemosensitivity: elevated NTproBNP (453±210 vs 205±122 pg/ml), lower peakVO2 (14.1±1.8 vs 18.6±6.3 ml/kg/min), shorter pulmonary acceleration time (84.2±18.8 vs 103.6±17.7 ms), greater right venicle end-diastolic diameter (37.1±10.8 vs 27.0±7.5±16.8 mm) and more frequent incidence of atrial fibrillation (69% vs 24%) (high vs normal chemosensitivity, respectively, p<0.05 in all comparisons). Controlling for all these factors, NTproBNP alone significantly predicts chemosensitivity.

Conclusions: High peripheral chemosensitivity is common in contemporary CHF patients despite optimal neurohumoral blockade. Correlation of NTproBNP: peakVO2, pulmonary acceleration time and AF with chemosensitivity suggests 1) an association between peripheral chemosensitivity and 2) that common clinical measurements might be used to screen patients for peripheral chemosensitivity. Assessment of these parameters may therefore be useful for selection of patients for novel therapies targeting peripheral chemoreceptors.

BNP is higher in OptiVol alert with intraintrachoracic impedance than at baseline: from MOMOTARO study

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Background: Heart failure (HF) is one of the most common causes for hospitalizations. A major cause of HF related hospitalizations is fluid accumulation. Recent studies have suggested that intrathoracic impedance (ITI) may be a useful parameter to track daily changes in pulmonary fluid status. OptiVol alert, which is an association between peripheral chemosensitivity and 2) that common clinical measurements might be used to screen patients for peripheral chemosensitivity. Assessment of these parameters may therefore be useful for selection of patients for novel therapies targeting peripheral chemoreceptors.

Various examinations, including body weight, chest X-ray, electrocardiogram, a blood sample such as BNP concentration and echocardiography, at enrolment and following an OptiVol alert. We examined difference in various values between OptiVol alert and baseline. All patients were followed by a wireless remote monitoring system. We defined that primary endpoint was the difference of log BNP between OptiVol alert and baseline, and secondary endpoint was the difference of other parameters between OptiVol alert and baseline.

Results: From April 2010 to December 2011, 200 patients in 12 institutes were enrolled in the present study. Mean age was 65.3±12.2 years, mean ejection fraction was 44.2±14.3% and mean NTproBNP was 5.6±5.9. During a mean follow-up period of 15.3±4.2 months, we had 255 OptiVol alert events in the OptiVol threshold of 60. In primary endpoint, log BNP was higher in OptiVol alert than at baseline, but not significantly (5.2±1.1 vs 5.1±1.1, p<0.06). However, the rate of change in ITI was negatively correlated with the rate of change in log BNP (r=-0.35, p<0.01). In OptiVol alert events with ITI equal to or less than 96% of mean ITI, log BNP was significantly higher in OptiVol alert than at baseline (5.5±1.2 vs 5.2±1.0, p<0.01). In OptiVol alert events with ITI more than 96% of mean ITI, there was no significant difference in log BNP between OptiVol alert and baseline. In secondary endpoint, red blood cell, hemoglobin, hematocrit, total protein and albumin were significantly lower in OptiVol alert than at baseline.

Conclusion: OptiVol alert with decreased ITI, rather than OptiVol alert only, seems to represent fluid retention.

Predictors for outcome

Artificial neural network in early identification of heart failure progression in OptiVol alert: telemonitoring management of chronic heart failure

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Daily acquisition and analysis of vital sign data and clinical symptoms in chronic heart failure patients allow for early recognition of an emerging decompensation. Artificial Neural Networks (ANN) are a statistical model, which is able to learn probability distributions of a dataset by inductive example training. Here, the capability of a personalized ANN was tested to predict the progression of chronic heart failure in the individual patient.

Methods: In 169 patients hospitalized due to chronic heart failure decompensation, a multiparameter telemonitoring was performed after discharge for up to 3.5 years with 150,000 patient days in total. Daily recording of vital signs (ECG, body temperature, blood pressure, BP), oxygen saturation, transthoracic impedance, jugular vein distension, oedema, urine volume, request of contact) generated 1.5 million telemonitoring datapoints, which were used to predict the primary endpoint "new heart failure hospitalization" by ANN.

An ANN to predict the probability of a health state change was trained based on recent vital measurements. Therefore, 80% randomly chosen datapoints of all patients were used to train the ANN (group1). The remaining 20% were used to test the predictive value of the trained model (group2). Doing that, the last 7 measure...
ments of weight, systolic and diastolic BP and heart rate as well as time intervals were used as input parameters. Target output values were based on the study endpoint, e.g. 0 for a “stable health state” and 1 for the primary endpoint “new heart failure hospitalization”. An ANN with 255 hidden neurons within 3 hidden layers, backpropagation training and squared error function was used. The network topology has been determined experimentally. Network training lasted 4000 iterations and has been stopped as training root mean squared error (RMSE) converged towards 1.6%, indicating a good adaption to the training set.

**Results:** RMSE on the group 2 data was 9.5%, indicating a reasonable generalization of the training data onto this group. Mean value measurement data by the ANN classified for the primary endpoint “new heart failure hospitalization” were 0.80(±0.17), classified as “stable health state” were 0.20(±0.25). Measurement data hinting towards “unstable health state” have been assessed with mean of 0.44(±0.24) allowing for good group separation.

**Summary:** Out of the data of daily multiparameter telemonitoring recordings in patients with chronic heart failure an ANN was trained to predict the most probable healthstate of the monitored patient. This model analyzing telemonitoring data for heart failure deterioration may be used for decision support and alerting.

**Patients and Methods:** The ongoing multi-center SchlaHF registry documents demographic and clinical data on stable CHF patients. We analyzed the data of 3504 CHF prospectively enrolled patients from cardiology outpatient clinics and practices. Induction criteria are New York Heart Association class – II and left-ventricular ejection fraction (LVEF) ≥45%. SDB was determined by a two-channel screening (nasal airflow, pulse oximetry) using ApeanaLink (ResMed, Sydney, Australia).

**Results:** The symptoms analyzed were naptime, nocturnal dysnea and nocturia. The median naptime was 30 min. In an univariate analysis AH1 ≥15 (OR 1.217; CI 1.057-1.400) and ODI ≥5 (OR 1.365; CI 1.155-1.613) were statistically significant (p < 0.05) predictors for a naptime > 30 min while in a logistic regression it wasn’t. There was an increase in nocturia (>3 times a night) in patients with sdb being in NYHA functional class III and IV depending on severity of sdb, while this could not be seen in patients in NYHA functional class II. A logistical regression analysis for nocturia (>3 times a night) were AH1≥15 (OR = 1.261; 95% CI 1.048-1.517), NYHA III/IV (OR = 1.467; 95% CI 1.202-1.791); and age (per 10 years increment: OR = 1.328; 95% CI 1.217-1.450). Nocturnal dysnea increased with severity of sdb in NYHA functional class III and IV in patients in NYHA functional class II, although being more often seen in the patients with worse functional class. The logistical regression analysis for the presence of nocturnal dysnea revealed sdb with an AH1≥15 as a significant predictor (OR = 1.583; 95% CI 1.338-1.872). Other significant variables were NYHA III/IV (OR = 1.548; 95% CI 1.291-1.855), age (per 10 years increment: OR = 1.128; 95% CI 1.042-1.216), BMI - 30/m² (OR = 1.442; 95% CI 1.208-1.721) and LVEF -25% (OR = 1.624; 95% CI 1.289-2.045).

**Conclusions:** The multi-center SchlaHF registry shows that HF symptoms are linked to the presence and the severity of SDB. Age and the severity of CHF were other important clinical predictors.

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**Heart rate control is important even in heart failure patients - an interim analysis of the CHART-2 study**

**Purpose:** Elevated heart rate (HR) is an independent risk factor for mortality in heart failure (HF) patients. However, the medications for the management of HR often lower systolic blood pressure (SBP) that may worsen the prognosis of HF patients. We examined the importance of HR control in terms of SBP in patients of our Chronic Heart Failure Analysis and Registry in the Tohoku district 2 (CHART-2) Study.

**Methods:** The CHART-2 Study (N=10,216) is a multicenter prospective cohort study enrolling Stage B/C/D patients. The study subjects were 2,761 overt HF patients with sinus rhythm and divided them into 6 groups based on the tertiles of SBP and the median HR as follows; G1 (SBP ≥135 and HR ≥70, N=430), G2 (SBP ≥135 and HR ≥70, N=469), G3 (SBP ≥120, <135 and HR ≥70, N=444), G4 (SBP ≥120, <135 and HR ≥70, N=410), G5 (SBP ≥120, <120 and HR ≥70, N=490), G6 (SBP ≥120, <120 and HR ≥70, N=518).

**Results:** G3 had the lowest NYHA class and brain natriuretic peptide (BNP) level. On the other hand, G6 were characterized by lower beta-blocker use, lower left ventricular ejection fraction, and the highest BNP level. During a mean follow-up of 5.1 years, non-adjusted Kaplan-Meier curves for all-cause death and cardiovascular death showed that G3 had better prognosis and G6 had poorer prognosis (Figure). In multivariable Cox model including covariates that might influence HR and SBP, Groups with elevated HR showed ~16% increased hazard ratios for all-cause death as compared to G3 (reference). Furthermore, G4 and G6 had significant higher cardiovascular mortality.

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**Heart failure symptoms and sleep-disordered breathing in patients with chronic heart failure - results from the SchlaHF registry**

**Objective:** In patients with stable chronic heart failure (CHF) we investigated the clinical value of different heart failure symptoms and its relationship to the presence of sleep-disordered breathing (sdb).

**Methods:** The SCHLAHF Registry is a prospective observational cohort study that included 2,761 overt HF patients with sinus rhythm and divided them into 6 groups based on the tertiles of SBP and the median HR as follows: G1 (SBP ≥135 and HR ≥70, N=430), G2 (SBP ≥135 and HR ≥70, N=469), G3 (SBP ≥120, <135 and HR ≥70, N=444), G4 (SBP ≥120, <135 and HR ≥70, N=410), G5 (SBP ≥120, <120 and HR ≥70, N=490), G6 (SBP ≥120, <120 and HR ≥70, N=518).

**Results:** G3 had the lowest NYHA class and brain natriuretic peptide (BNP) level. On the other hand, G6 were characterized by lower beta-blocker use, lower left ventricular ejection fraction, and the highest BNP level. During a mean follow-up of 5.1 years, non-adjusted Kaplan-Meier curves for all-cause death and cardiovascular death showed that G3 had better prognosis and G6 had poorer prognosis (Figure). In multivariable Cox model including covariates that might influence HR and SBP, Groups with elevated HR showed ~16% increased hazard ratios for all-cause death as compared to G3 (reference). Furthermore, G4 and G6 had significant higher cardiovascular mortality.

**Conclusions:** Regardless of SBP, elevated HR was associated with higher mortality. In view these results and well-known importance of increased HR for mortality, HR control (<70/min) should be given higher priority even in the HF patients with relatively low SBP.
Incident heart failure with preserved ejection fraction in the general population

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Purpose: The incidence of heart failure (HF) with preserved ejection fraction (HF-PEF) is increasing, compared to HF with reduced ejection fraction (HF-REF). Data on distinctive epidemiology and prediction of incident HF-PEF and HF-REF in a general population have not been described.

Methods: In 8569 HF-free subjects of a general population based cohort study (PREVEND), we studied the performance of established cardiovascular risk factors on incident HF, their hazard ratios given per 1-SD increment and 95% confidence interval (CI), and the additive value of N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and high-sensitive troponin T (hs-TnT) by c-statistics and net reclassification improvement (NRI). Incident HF was diagnosed by record linkage with databases of regional hospitals. All cases were reviewed and scored as HF-PEF or HF-REF by an independent adjudication committee.

Results: During median follow-up for 10 years, 135 individuals were diagnosed with HF-PEF and 239 with HF-REF. When adjusted for age, sex and body mass index, development of HF-PEF showed strongest associations with hypertension (HR: 2.08, 95% CI: 1.02-4.27, p=0.045), cystatin-C (HR: 1.49, 95% CI: 1.05-2.11, p=0.024) and urinary albumin excretion (HR: 1.37, 95% CI: 1.14-1.65, p=0.001). In similar analyses, development of HF-REF showed strongest associations with history of myocardial infarction (HR: 2.45, 95% CI: 1.53-3.93, p=0.001), smoking (HR: 1.69, 95% CI: 1.07-2.68, p=0.025) and hypercholesterolemia (HR: 1.55, 95% CI: 1.03-2.34, p=0.037). NT-proBNP was independently associated with both incident HF-REF and incident HF-PEF (HR: 1.55, 95% CI: 1.21-1.97, p=0.001 and HR: 1.36, 95% CI: 1.03-1.80, p=0.030, respectively). Hs-TnT was independently associated with incident HF-REF (HR: 1.39, 95% CI: 1.22-1.60, p=0.001), but not with HF-PEF. CRP was not associated with either type of incident HF. For HF-PEF, NT-proBNP, hs-TnT and CRP significantly improved the model c-statistic from 0.85 to 0.86 (p<0.015) and enhanced risk reclassification (NRI=0.06, p=0.048). For HF-REF, the model c-statistic improved from 0.84 to 0.88 (p<0.001) and also enhanced risk reclassification (NRI=0.26, p<0.001).

Conclusions: HF-PEF shows a clear distinctive baseline profile compared to HF-REF, with a blood pressure and renal function pressure-load driven profile for the former and an ischemic driven profile for the latter. The incremental value of biomarkers seems to be less strong for predicting HF-PEF than for HF-REF.