# NORSKE ABSTRACTS PRESENTERT I LONDON

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## P6555 Growth differentiation factor 15 (GDF-15) is a strong predictor of outcome in heart failure patients with anaemia-results from the RED-HF study

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**Background:** Growth differentiation factor 15 (GDF-15), a stress-responsive cardiokine, was recently identified as a hepcidin-suppression factor that is expressed at high levels in patients with ineffective erythropoiesis.

**Purpose:** We investigated the predictive value of circulating GDF-15, and interactions with darbepoetin alfa treatment, on clinical outcomes in patients with heart failure (HF) and anaemia.

**Methods:** Serum levels of GDF-15 were analysed by enzyme immunoassays in 1588 patients with HF, reduced ejection fraction, and mild to moderate anaemia, followed for median 28 months in the Reduction of Events by Darbepoetin alfa in Heart Failure (RED-HF) trial. Association between baseline and change in GDF-15 (≥15 % increase, ≥15 % decrease or no change) and the primary composite outcome of all-cause death and HF hospitalization was evaluated with in multivariable Cox proportional hazard models. Modifying effects and interaction with darbepoetin alfa (to achieve a hemoglobin target of 13 g/dL) on GDF-15 were also assessed.

**Results:** Lower GDF-15 levels were negatively correlated with higher haemoglobin levels (r=0.20, p<0.001) at baseline. In univariate analyses, the risk for the primary composite outcomes steadily increased with successive tertiles of baseline GDF-15 [2nd tertile HR 2.10 [1.72–2.57], 3rd tertile HR 4.05 [3.25–4.90] relative to the lowest tertile (p<0.001). The association was attenuated, but persisted after multivariable adjustment: tertile 3 HR 1.56 [1.23–1.98] p<0.001. No interaction between baseline GDF-15 levels and darbepoetin alfa treatment was observed with regard to the primary composite outcome, despite a relatively greater decrease in GDF-15 within the treatment group (p=0.032) than in non-treated patients (p=0.039). An increase in serum GDF-15 of >15 % during 6 months follow-up was associated with a higher incidence of the primary outcome in univariate (HR 1.39 [1.15–1.69] p<0.002) and multivariable (HR 1.68 [1.38–2.06] p<0.001) analysis. No interaction between treatment and change in GDF-15 on outcome was observed.

**Conclusions:** In patients with HF, reduced ejection fraction, and anaemia, both higher serum levels GDF-15 and an increase during follow-up, were associated with adverse outcome. Baseline GDF-15 did not identify subgroups of patients who might benefit from correction of anaemia.

## P4566 Change in frailty status in octogenarians with severe symptomatic aortic stenosis after aortic valve replacement

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**Background:** Frailty has emerged as a measure of physiological reserves and as a predictor of mortality, prolonged hospitalization and readmissions after cardiac intervention.

**Purpose:** The aim of the study was therefore to observe change in frailty status six months after aortic valve replacement (AVR).

**Methods:** In this observational prospective cohort study including patients at 80+ with severe symptomatic aortic stenosis (AS) accepted for transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR), frailty status was assessed one day prior to and six months after AVR using the Study of Osteoporotic Fracture (SOF) Frailty Index. Patients were categorized as robust, pre-frail or frail accordingly. EuroScore was used to determine operative risk and Charlson Comorbidity Index to measure comorbidity. The

McNemar-Bowkers Test of Symmetry was used to investigate whether AVR could change frailty status in the total study population.

**Results:** In all, 143 patients were included, mean age 83 years (SD 2.7). Thirty-four percent were robust, 27 % pre-frail and 39 % frail. There was no significant difference in frailty status between treatment groups (p<0.11) or between sexes (p<0.88). Frail patients were in a higher New York Heart Association (NYHA) function class (p<0.03) and had higher S-ProBNP (p<0.04). No significant differences were detected in EuroScore (p<0.07), Charlson Comorbidity Index (p<0.12) or in aortic valve area (p<0.78). The proportion of patients who improved their frailty status was 34 % whereas 18 % changed for the worse. However, no significant overall change was observed (p<0.16).

**Conclusion:** No significant change was observed in overall frailty status after six months, but our findings show that frailty is a dynamic syndrom; an important finding from a clinical perspective which must be further studied.

## P6307 Differentiation of early arrhythmogenic right ventricular cardiomyopathy from right ventricular outflow tract ventricular tachycardia

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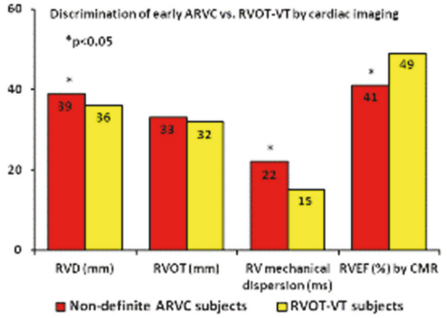
**Introduction:** Electrical disease precedes structural disease in arrhythmogenic right ventricular cardiomyopathy (ARVC) and ventricular tachycardia (VT) is often the first symptom. Differentiation of life threatening early ARVC from relatively benign right ventricular (RV) outflow tract VT (RVOT-VT) is challenging. Prognosis and treatment strategies differ substantially and correct diagnosis is important.

**Purpose:** We investigated if cardiac imaging can help to discriminate early ARVC from RVOT-VT.

**Methods:** We included 44 consecutive RVOT-VT patients (age 47±14 years) and 44 ARVC mutation carriers (age 39±17 years) with early ARVC disease, fulfilling non-definite diagnosis by Task Force criteria 2010. By echocardiography, we assessed RVOT and RV basal diameter (RVD), fractional area change (RVFAC) and LV ejection fraction (EF). By 2D speckle tracking strain echocardiography we assessed RV mechanical dispersion as standard deviation of time to peak longitudinal strain in 3 RV wall segments. By cardiac magnetic resonance imaging (CMR), we assessed RV ejection fraction (RVEF).

**Results:** RVD was larger (39±5mm vs. 36±4mm, p=0.02) and RV mechanical dispersion was more pronounced (22±15ms vs. 15±13ms, p=0.03) in ARVC compared to RVOT-VT subjects, but RVOT diameters did not differ (33±5mm vs. 32±4mm, p=0.36). RVEF by CMR was decreased in ARVC vs. RVOT-VT subjects (41±8 % vs. 49±4 %, p<0.001), while RV and LV function by echocardiography did not differ (RVFAC; 47±7 % vs. 46±5 %, p=0.96, LVEF; 58±4 % vs. 57±5 %, p=0.85, respectively).

**Conclusions:** Increased RVD, pronounced RV mechanical dispersion by echocardiography and reduced RV function by CMR discriminated early ARVC from RVOT-VT patients and may help correct diagnosis and treatment decisions.




## P3674 Obesity is associated with subclinical myocardial injury independently of a dysmetabolic state

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**Background:** Obesity is an independent risk factor of cardiovascular disease and is commonly associated with a dysmetabolic state. Circulating high sensitivity cardiac troponin I (hs-TnI) concentrations reflect cardiac mass and subclinical myocardial injury and are strongly predictive of subsequent risk of heart failure and premature death. It remains unclear whether obesity is associated with subclinical myocardial injury independently of a dysmetabolic state.

**Purpose:** Assess the association between obesity and subclinical myocardial injury in subjects with and without a dysmetabolic state.

**Methods:** hs-TnI was measured in 4431 men and 5281 women aged >20 years participating in the

*Levels of troponin I*

| BMI | | Median hs-TnI (IQR) | | |
|---|---|---|---|---|
| | n | Eumetabolic (p<0.001†) | Dysmetabolic (p=0.058†) | p |
| 18.5–24.9 | 3748 | 2.70 (1.90–4.00) ng/L | 4.80 (3.40–8.35) ng/L | <0.001* |
| 25.0–29.9 | 4149 | 3.40 (2.40–4.90) ng/L | 4.60 (3.10–6.90) ng/L | <0.001* |
| 30.0–34.9 | 1239 | 3.30 (2.50–4.80) ng/L | 4.30 (3.20–6.50) ng/L | <0.001* |
| 35.0–39.9 | 254 | 3.50 (2.50–4.90) ng/L | 4.30 (3.10–6.30) ng/L | 0.001* |
| ≥40.0 | 56 | 4.14 (2.00–7.10) ng/L | 4.00 (2.75–5.15) ng/L | 0.38* |

**Comparing levels of hs-TnI in eumetabolic and dysmetabolic subjects across BMI strata (Mann-Whitney U test); †Spearman rank correlation between BMI and levels of hs-TnI within groups.*

prospective observational Nord-Trøndelag Health Study (HUNT) using the ARCHITECT STAT High-Sensitive Troponin assay. All patients were classified according to body mass index (BMI) and metabolic status.

**Results:** 7879 and 1627 subjects were classified as eumetabolic and dysmetabolic respectively and were included in the analyses. Median hs-TnI levels (IQR) were 3.10 (2.10–4.50) ng/L in the eumetabolic and 4.40 (3.10–6.60) ng/L in the dysmetabolic (p<0.001). The dysmetabolic subjects exhibited significantly higher levels of hs-TnI through all BMI strata, except in those with BMI ≥40 (see Table.). In subsequent univariate analyses, hs-TnI levels were significantly associated with increasing body mass index in the eumetabolic group (p<0.001). No significant association was observed across BMI strata in the dysmetabolic group (p=0.058).

**Conclusion:** Obesity is associated with subclinical myocardial injury in the eumetabolic, but not in the dysmetabolic state.

*See table*

## P6477 Aerobic high-intensity exercise training improves coronary flow reserve velocity and endothelial function in individuals with chest pain and normal coronary angiogram

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**Purpose:** Patients with impaired coronary flow reserve and chest pain despite normal coronary angiogram constitute a therapeutic problem with considerable residual morbidity associated with functional limitation and reduced quality of life. Exercise training has been shown to improve endothelial function and symptoms in coronary artery disease. The aim of the current study was to assess the effect of high intensity aerobic exercise training on coronary flow reserve, endothelial function and functional capacity in this population

**Methods:** Sixteen patients with typical exercise induced chest pain and normal coronary arteries assessed by coronary angiography at our university hospital were included. Twelve patients underwent a 3 months high intensity aerobic exercise-training program with 1 to 1 monitored exercise session on treadmill in a 4 min x 4 manner 3 times a week. Four patients served as controls. Coronary flow velocity reserve (CFVR) was measured using adenosine-induced hyperemia in the mid to distal segments of the left anterior descending coronary artery and the posterior descending coronary artery with transthoracic color Doppler mapping. Adenosine was administered by intravenous infusion (0.14 mg/kg/min over 2 min) to record spectral Doppler signals during hyperemia. Peak diastolic flow velocities were measured, and coronary flow reserve calculated as the ratio of hyperemic to basal peak coronary flow velocities. Flow mediated endothelial function, measured as relative changes in brachial artery diameter (FMD), was measured with 2D brachial artery imaging using a 12 MHz linear-array transducer connected to a VIVID 7 ultrasound machine. Peak VO2 was measured with a maximal treadmill test and breath by breath ergo spirometry.

**Results:** After 3 months of exercise training CFVR increased from 2.45±0.53 to 2.85±0.43 (p=0.004) whereas FMD increased from 4.0±2.0 % to 7.8±2.7 % (p<0.001). This was associated with an increase in Peak VO2 which increased from 27.4±5.7 ml/kg/min to 31.2±6.6 ml/kg/min (p=0.003). There were no statistical significant changes for peak VO2, CFVR or flow mediated vasodilation in the control group: CFVR 2.6±0.4 vs 2.7±0.5, Peak VO2 (ml/kg/min) 26.5±4.1 vs 27.2±3.5, FMD % 4.3±2.1 vs 4.6±2.1

**Conclusion:** A 3 month program of high intensity aerobic exercise training improved coronary flow reserve, peak VO2 and flow mediated vasodilatation in patients with chest pain and normal coronary angiogram.

## P3497 Left ventricular mechanical dispersion predicts clinical outcome in patients with moderate to severe aortic stenosis

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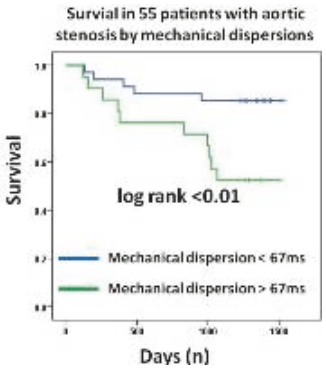
**Background:** New parameters to improve risk stratification and predict outcome in patients with aortic stenosis (AS) are needed. Left ventricular (LV) mechanical dispersion by strain echocardiography reflects heterogeneous myocardial contraction and is a novel marker of sudden cardiac death.

**Purpose:** We aimed to explore the prognostic value of mechanical dispersion in AS patients, and hypothesized that mechanical dispersion can be an additional clinical tool in risk assessment of these patients.

**Methods:** We included 55 patients (56 % women, 75±9 years) with moderate to severe AS. Global longitudinal strain (GLS) was assessed by speckle tracking echocardiography from a 16 LV segments model. Mechanical dispersion was calculated as standard deviation of time from Q/R on ECG to peak strain in 16 LV segments.

**Results:** Average aortic stenosis area was 0.7±0.2 $cm^2$. Most patients had LV septal hypertrophy (12±2 mm) and preserved LV ejection fraction (EF) (57±10 %). Aortic valve replacement (AVR) was performed in 37 (67 %). During 38±14 months follow-up, 15 (27 %) patients died (no 30-day mortality after AVR). LVEF and GLS did not differ between survivors and non-survivors (58±9 % vs 54±13 %, p=0.16, and −17.0±3.4 % vs. −16.7±4.0 %, p=0.78, respectively). Mechanical dispersion was the only echocardiographic parameter that differed between survivors and non-survivors (56±18ms vs. 69±19ms, p=0.02).C-statistics for mechanical dispersion showed an AUC of 0.70 (0.55–0.86) and a value of >67 ms indicated worse survival (log rank <0.01) (Fig.1)




**Conclusion:** LV mechanical dispersion was significantly higher in the AS non-survivors. Increased mechanical dispersion may be an additional risk marker and could give valuable prognostic information in patients with AS and preserved LVEF.

## P1404 Improvement in ventricular function and low incidence of ventricular arrhythmias in dilated cardiomyopathy

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**Background:** Current guidelines assign a IB indication for implanting a cardioverter defibrillator (ICD) in patients with non-ischaemic dilated cardiomyopathy (DCM) who have an left ventricular (LV) ejection fraction (LVEF) ≤35 % and who are in NYHA functional class II or III. However, studies have shown that LV function often improves in patients recently diagnosed with idiopathic DCM, and that the incidence of appropriate shocks in this population is low. Thus, the optimal timing of assessment for ICD implantation is uncertain.

**Purpose:** We aimed to assess whether the indication for ICD implantation changed over time in patients with recent-onset DCM, and the prevalence of serious arrhythmic events in this population.

**Methods:** 102 consecutive patients referred to our tertiary care hospital with idiopathic DCM, an LVEF <40 % and no implantable devices were included in a prospective cohort study. Pharmacological treatment was adjusted according to current guidelines, and follow-up was performed after one year. Vital status, heart transplantations, device implantations and arrhythmic events were subsequently recorded.

**Results:** At baseline, 3.0 (0.6–6.4) months after the diagnosis had first been made, pharmacological treatment had been initiated in 101 (99 %) of the patients. Over the first year of follow-up, three patients received cardiac allografts. In transplant free survivors, LVEF increased from 26±10 % to 41±11 % (p<0.001), and NYHA class improved by 0.6±0.8 units (p<0.001). The number of patients with an indication for ICD implantation according to current guidelines fell from 71 (70 %) to 26 (27 %).

After a median follow-up of 3.6 years, four patients were dead, and heart transplantations had been performed in nine patients. Only one patient, whose LVEF improved to 62 %, died a sudden, unexplained death more than three years after inclusion. Two patients had been admitted due to syncope. All together 31 patients had received ICDs, but only five of these patients received appropriate shocks during follow-up. Overall survival at 5 years was 93 %, and transplant-free survival was 84 %.

**Conclusion:** In patients with recent-onset DCM treated according to current guidelines, we observed a substantial improvement in LVEF and functional status within the first year of follow-up. The proportion of patients with an indication for ICD implantation fell from 70 % to 27 % during follow-up. The number of serious arrhythmic events was low. Our results suggest that in stable patients with recent-onset DCM, one can safely await improvement before considering ICD implantations.

## P3470 Mortality and the effect of target temperature management (33 vs. 36) in comatose patients resuscitated from cardiac arrest does not differ between males and females

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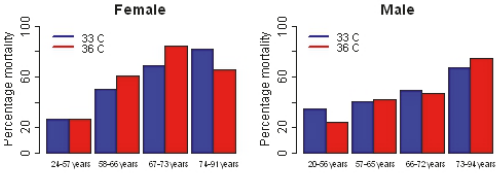
**Background and introduction:** Men and women who suffer an out-of-hospital cardiac arrest (OHCA) differ in characteristics such as location of arrest, bystanders performing cardiopulmonary resuscitation or probability of defibrillation. Women are also reported to receive fewer interventions in hospital and it is unknown whether the effect of target temperature management (TTM) is the same as in men.

**Purpose:** We aimed to determine mortality in comatose female vs. male survivors after OHCA and whether gender modifies the effect of TTM.

**Methods:** This study is a post-hoc study of the TTM trial, which randomized 939 patients to 24 hours of TTM of 33 oC or 36 oC. Nineteen percent were female and these were compared to the male patients regarding demographic characteristics, pre-hospital factors, in-hospital treatment and mortality.

**Results:** Compared to men, women more often had OHCA at home, p=0.04, and less often received defibrillation by bystanders, p=0.01. Within the first 24 hours, women received fewer coronary angiographies (CAG) and percutaneous interventions (PCI), both: p=0.02, but not significant after adjusting for confounders. Females had higher mortality than males in univariate analysis, hazard ratio (HR): 1.29, CI: 1.04–1.61, p=0.02. After adjusting for confounders, this difference was no longer significant. There was no interaction between sex and TTM allocation group, p=0.10, fig. 1.

**Conclusion(s):** Female gender is associated with a higher risk of adverse outcome, but this seems to be largely explained by less favourable resuscitation circumstances. There is no difference in mortality and we found no evidence of favoring one level of TTM over the other in females compared to males.




## P1397 Nadolol is superior to metoprolol SR in protection from exercise induced arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT)

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**Introduction:** Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable arrhythmogenic disease, predisposing to ventricular arrhythmias at exercise. Beta blockers are standard treatment, however not all beta blockers are equally effective.

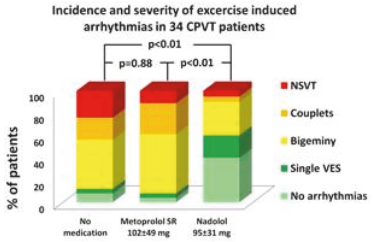
**Purpose:** We aimed to serially investigate the incidence and severity of exercise induced arrhythmias in CPVT patients without medication, on metoprolol SR and on nadolol.

**Methods:** We included 34 CPVT patients (crossover study, 34±19 years, 56 % male, 88 % RYR2 mutations). In each patient, we performed 3 exercise stress tests to exhaustion: prior to beta blocker treatment, and after >6 weeks on maximum tolerated doses of metoprolol SR and

nadolol, respectively. We recorded resting and maximum heart rate (HR) and the most severe arrhythmia during exercise. Severity of arrhythmias was scored as: no arrhythmias:0, single ventricular extra systoles:1, bigemini:2, couplets:3 and non-sustained VT:4. We performed 24 hour Holter recordings and scored arrhythmias similarly.

**Results:** HR at rest was similar on nadolol and metoprolol SR (53±10bpm vs. 56±14bpm, p=0.29), while maximum HR was lower on nadolol (120±20 bpm vs. 139±24 bpm, p<0.001). At exercise, incidence of arrhythmias was lower on nadolol (60 %) than on metoprolol SR (96 %) and no medication (92 %) (both p≤0.01). Also severity of arrhythmias was lower on nadolol than metoprolol SR (score 1.2±1.3 vs. 2.4±0.9, p<0.01) and no medication (1.2±1.3 vs. 2.5±1.2, p<0.01) (Figure). Arrhythmic score from Holter was lower on nadolol than no medication (0.8±1.0 vs. 1.2±1.0, p=0.03).

**Conclusion:** Incidence and severity of arrhythmias decreased on nadolol compared to metoprolol SR in patients with CPVT. Nadolol could be superior to metoprolol SR in arrhythmia control in CPVT patients.




## P602 Heart neuronal function assessed with I-123 MIBG after 3 months of exercise training in heart failure patients

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**Introduction:** Sympathetic overactivity is a generalised phenomenon in heart failure. In addition reduced presynaptic uptake of noradrenaline and down regulated postsynaptic beta adrenoseptor density is documented. I-123 MIBG (iodine-123 metaiodobenzylguanidine) examinations in the heart failure population is showing a lower heart to mediastinum ratio (H/M) and raised wash out ratio (WR) compared to healthy controls. We hypothesised that after a 3 months training period we would see higher I-123 MIBG uptake and reduced WR and that the degree of these parameters would correlate with the intensity of the training. To our knowledge this is the first study to examine high intensity interval training in relation to cardiac I-123 MIBG uptake in heart failure patients.

**Methods:** We included 23 patients which were randomised to regular exercise, continuos training and interval training. All patients were examined with I-123-MIBG before and after the training period and the difference in I-123 MIBG uptake after 15 min, 4 hours and wash out ratio (WR) was calculated. We used one way anova to calculate the difference of means between the three groups.

**Results:** After the training we did not see any significant difference between the three groups in either heart to mediastinum ratio, nor in wash out ratio. I-123 MIBG 15 min: F(2,20)=0.294, p=0.748, 123-I MIBG 4 hours: F(2,20)=0.425, p=0.660 and WR: F(2,20)=2.080, p=0.151.

**Conclusions:** A three months exercise program did not restore the abnormal sympathetic innervation measured with I-123-MIBG scintigraphy in this heart failure population.

## P711 Association between fetal congenital heart defects and maternal risk of hypertensive disorders of pregnancy

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**Background:** Pregnant women carrying fetuses with heart defects and women with hypertensive disorders of pregnancy (HDP) both often exhibit angiogenic imbalances, suggesting that the same underlying processes may play a role in the etiology of heart defects and the pathology associated with HDP.

**Purpose:** To determine whether fetal heart defects are associated with an increased risk of maternal HDP, and whether the mechanisms driving the association are primarily maternal or fetal.

**Methods:** Using Danish national registers, we constructed a cohort comprising all singleton pregnancies without chromosomal abnormalities continuing to ≥20 completed weeks gestation in Denmark, 1977–2011, and identified both pregnancies complicated by offspring congenital heart defects and those complicated by HDP (severe preeclampsia [PE]/eclampsia, moderate PE, gestational hypertension [GH]). Using polytomous logistic regression, we estimated odds ratios (ORs) for the association between carrying

a fetus with a congenital heart defect and maternal risk of an HDP in the second half of pregnancy, overall and for specific heart defects. We also estimated ORs for the association between 1) an HDP in a previous pregnancy and the risk of carrying a child with a heart defect in subsequent pregnancies, and 2) fetal congenital heart defects in a previous pregnancy and the risk of HDP in subsequent pregnancies.

**Results:** Carrying a child with a heart defect was associated with a 3-fold increase in the risk of severe PE later in the pregnancy (OR 3.02, 95 % confidence interval [CI] 2.71–3.37) and a modest increase in the risk of moderate PE (OR 1.29, 95 % CI 1.18–1.41), but not with the risk of GH (OR 1.08, 95 % CI 0.93–1.25). This association did not appear to depend on the type of offspring heart defect. Having a child with a heart defect in a previous pregnancy was also associated with PE (severe PE: OR 1.57, 95 % CI 1.24–1.97; moderate PE: OR 1.32, 95 % CI 1.16–1.51) but not with GH (OR 1.00, 95 % CI 0.82–1.22) in subsequent pregnancies. Similarly, a history of PE in a previous pregnancy, but not of GH alone, was associated with an increased risk of offspring heart defects in later pregnancies (severe PE: OR 1.46, OR 1.21–1.77; moderate PE: OR 1.13, 95 % CI 1.01–1.27; GH: OR 1.12, 95 % CI 0.91–1.37).

**Conclusion:** Our findings suggest that the same pathophysiological mechanisms may be involved in both congenital heart defects and severe PE (but are less important in less severe forms of HDP), and that these processes are most likely maternal, rather than fetal.

## P4531 NADPH oxidase 4 promotes adaptive cardiac remodelling through enhancing fatty acid oxidation in the murine heart

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**Background:** Hearts under chronic pressure-overload stress undergo an initial remodelling that is adaptive however they eventually succumb to failure. The underlying mechanisms that drive and maintain adaptive responses are not understood. Our recent studies indicate that NADPH oxidase (Nox) proteins, specialised enzymes that generate reactive oxygen species (ROS) involved in redox signalling, have distinct roles in the response to pressure-overload. Nox4 augments the adaptive response whilst Nox2 promotes a maladaptive response.

**Purpose:** The aim was to identify Nox4-driven mechanisms that enhance adaptive cardiac remodelling processes.

**Methods:** To identify pathways that might be driving Nox4-dependent effects a proteomic comparison of heart tissue from cardiac-targeted Nox4-overexpressing mice, Nox2-overexpressing mice and controls was undertaken using 2D-DIGE. This was complemented by 1H-NMR metabolomic analyses of heart tissue. Further studies were undertaken to explore the Nox4-dependent effects on substrate metabolism and bioenergetics in murine hearts using isolated working hearts and 31P-NMR. Finally endogenous Nox4-dependent effects on substrate handling were determined in cultured cardiomyocytes by perturbing the levels of Nox4 and examining extracellular flux with Seahorse XFe24.

**Results:** Proteomics identified glycolysis and fatty acid oxidation as the most enriched pathways altered by Nox4. Metabolomics also indicated significant differences in metabolites related to these pathways (e.g. 2.2 fold increase in acetylcarnitine concentration, p=0.002). Nox4 hearts demonstrated a significantly increased capacity for FAO compared to wild-type hearts (3.6 fold increase, p=0.01), which was sustained under pressure-overload. Cardiac energetics under basal or pressure-overload indicated that a reliance on FAO was not detrimental to cardiac function. Extracellular flux analyses confirmed the Nox4-dependent effects in augmenting FAO in isolated cardiomyocytes.

**Conclusion:** Nox4 is important in modulating metabolism, specifically enhancing FAO in the murine heart. This may help to explain the cardioprotective effects of Nox4 but also provides insight into novel ROS-mediated mechanisms that can regulate metabolism.

## P4307 Normal range of LV global longitudinal strain in asymptomatic lymphoma survivors

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**Background:** LV global longitudinal strain (GLS) has emerged as a sensitive marker of LV systolic function and is included in the latest guidelines for detecting cardiotoxicity during administration of chemotherapy. However, little is known about the normal range of LV GLS in asymptomatic cancer survivors years after cardiotoxic therapy.

**Purpose:** To determine the normal range of LV GLS after cardiotoxic treatment including anthracyclines (AC) and radiotherapy involving the heart (RT), assessed in asymptomatic lymphoma survivors (LS).

**Methods:** All LS treated with autologous hematopoietic stem cell transplantation (auto-HCT)

*LV GLS according to age and treatment*

| Age | AC | | AC+RT | | Controls | | P-value | P-value | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | (n=163) | | (n=82) | | (n=245) | | AC vs AC+RT | AC vs Ctr | AC+RT vs Ctr |
| | n | GLS (- %) | n | GLS (- %) | n | GLS (- %) | | | |
| 25–39 | 19 | 19.4 (1.7) | 13 | 19.0 (1.7) | 32 | 20.9 (1.8) | ns | 0.006 | 0.003 |
| 40–49 | 20 | 19.8 (2.1) | 30 | 17.2 (1.4) | 50 | 20.9 (2.0) | <0.001 | 0.03 | <0.001 |
| 50–59 | 42 | 19.1 (2.1) | 19 | 18.0 (1.7) | 61 | 20.6 (1.9) | 0.07 | <0.001 | <0.001 |
| 60–69 | 58 | 18.4 (2.6) | 13 | 17.7 (2.3) | 71 | 20.2 (1.9) | ns | <0.001 | 0.001 |
| 70–77 | 24 | 19.1 (2.8) | 7 | 17.2 (1.5) | 31 | 20.3 (2.1) | 0.03 | ns | 0.004 |

*P-values by one-way ANOVA.*

in Norway from 1987–2008 and aged ≥18 years at auto-HCT were eligible, but only asymptomatic LS are included in this report. LV GLS was estimated by two-dimensional speckle tracking echocardiography (Vivid 7 or E9, GE Vingmed Norway) in a 16-segment model, and stratified according to age and lymphoma treatment (AC alone vs AC+RT). Results in the LS were compared with those found in a healthy control group, matched in a 1:1 fashion based on age, gender, systolic blood pressure and body mass index.

**Results:** In total, 274 LS (69 % of all eligible) participated, of whom 245 were asymptomatic. The feasibility of LV GLS was 85 %. Median observation time since lymphoma diagnosis was 12 years (range 4–34) and 61 % were males. Mean doxorubicin exposure in LS treated with AC and AC+RT was 298±104 vs 325±147mg/m$^2$ (p=0.10), respectively. LV GLS was reduced in LS after AC+RT compared with AC alone (−17.8±1.8 vs −19.0±2.4 %, p<0.001). Furthermore, both treatment groups had reduced LV GLS compared with controls (LV GLS=−20.6±1.9 %, p<0.001 for both). LV GLS according to age in the two treatment groups and controls are presented in the table.

**Conclusions:** We present normal values for LV GLS in asymptomatic LS, stratified according to age and cardiotoxic treatment.

*See table*

## 336 The interleukin-6 receptor antagonist tocilizumab reduces inflammation and myocardial damage in non-ST elevation myocardial infarction - a randomized, double-blind, placebo controlled study

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**Background:** Inflammation plays a pivotal role in coronary artery disease and acute coronary syndromes (ACS). Interleukin-6 (IL-6) has been shown to contribute to both atherosclerotic plaque development and destabilization as well as myocardial injury during ischemia-reperfusion. IL-6 has also emerged as a marker of poor outcome in ACS. Thus, IL-6 appears as an attractive therapeutic target in ACS.

**Purpose:** We investigated the effect of a single dose of the anti-IL-6-receptor antibody, tocilizumab, in patients with acute non-ST elevation myocardial infarction (NSTEMI). We hypothesized that tocilizumab would have beneficial effects on systemic and plaque inflammation, resulting in increased plaque stability and attenuation of myocardial damage.

**Methods:** 117 eligible patients with NSTEMI were included at a median of 2 (0–12) days after symptom onset (placebo n=59, tocilizumab n=58). On the day of inclusion, baseline blood samples were obtained and study drug or placebo was infused with a double-blind design prior to coronary angiography. Blood samples were obtained at 6 consecutive timepoints between day 1 and 3. High-sensitive CRP (CRP) and high-sensitive Troponin T (TnT) were measured at all timepoints with area under the curve (AUC) for CRP being the primary endpoint.

**Main results:** AUC for CRP was 55 % lower in the tocilizumab group (p=0.009). Absolute changes in CRP and TnT from baseline (Δ) were consistently lower in tocilizumab- versus placebo-treated patients throughout all measurements. A statistical significant difference in Δ between treatment groups was reached for both CRP (p<0.001) and TnT (p<0.05) at 5 out of 6 timepoints. There was a significant correlation between CRP and TnT through all timepoints (r>0.5, p<0.001) in both treatment groups. The differences between the two groups were driven by PCI-treated and early included (≤2 days from symptom onset) patients. 6 months of follow-up did not uncover safety issues in tocilizumab-treated patients.

**Conclusions:** Tocilizumab exerts a potentially favorable effect in patients with NSTEMI in terms of attenuated inflammatory response and troponin release. This effect is most pronounced in patients with early administration of the drug and in patients undergoing PCI following drug administration. No safety issues were uncovered. Larger scale studies are warranted to evaluate the clinical implications of these findings.

## 4156 Global longitudinal strain to detect cardiotoxicity in adult survivors of childhood leukemia

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**Background:** Global longitudinal strain has been recommended for screening of cardiotoxicity in cancer survivors. However, there are limited study data supporting this recommendation, in particular in adult survivors of childhood cancer.

**Purpose:** To compare global longitudinal strain (GLS) in adult survivors of childhood leukemia with apparently normal left ventricular (LV) function, to a matched control group.

**Methods:** From a cross-sectional study of survivors of childhood acute lymphoblastic leukemia, we identified 62 survivors without known heart disease or hypertension, and with both normal LV ejection fraction and fractional shortening. We used a healthy control group matched for age, gender, systolic blood pressure and body surface area, for comparison. A single investigator (J.C.) blinded to the participants' status, measured GLS off-line in all participants with semi-automatic software (EchoPAC v. 112, GE Healthcare).

**Results:** The survivors were examined mean 18.5±5.3 years after diagnosis. Previous cancer treatment included anthracyclines in 57 (92 %). The survivors and controls were well matched (Table). Survivors had lower mean GLS (Table). In all, 13 survivors (21 %) had a GLS value lower than −17.4 %, which was the mean value - 2 SDs in the control group.

*Comparison of survivors and controls*

| Variable | Patients (n=62) | **Controls (n=46)** | **P value** |
|---|---|---|---|
| Age at exam (years) | 24.4±3.5 | 23.2±2.3 | 0.054 |
| Female gender ( %) | 52 | 52 | 0.954 |
| Systolic blood pressure (mmHg) | 126±14 | 124±11 | 0.527 |
| Body surface area ($m^2$) | 1.89±0.25 | 1.86±0.18 | 0.443 |
| Heart rate (bpm) | 66±9 | 65±12 | 0.438 |
| Global longitudinal strain ( %) | −19.0±2.1 | −21.0±1.8 | <0.001 |

**Conclusions:** We detected subclinical LV dysfunction assessed by GLS. This supports the use of GLS in follow-up after treatment for childhood cancer.

## P416 Mechanisms for the frequency-dependence of triggered activity in catecholaminergic polymorphic ventricular tachycardia

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**Background:** Patients with catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1) are prone to triggered ventricular tachyarrhythmias during physical or emotional stress. CPVT1 is caused by mutations in the cardiac ryanodine receptor (RyR2), which result in SR Ca2+ leak in diastole, propagating Ca2+ waves and delayed afterdepolarizations. It is not known how this chain of events is affected in situations with increased heart rate to cause the high risk of arrhythmias associated with such situations in CPVT1.

**Purpose:** To untangle factors contributing to the frequency-dependence of triggered arrhythmias in CPVT1.

**Methods:** ECGs were recorded during a bicycle test performed by 17 patients with CPVT1. Cardiomyocytes from mice with RyR2 R2474S-mutations (RyR2-RS) were employed for whole-cell Ca2+imaging at increasing stimulation frequencies (0.5, 4 and 8 Hz), in absence and presence of β-receptor activation with isoprenaline (200nM, ISO).

**Results:** ECG data confirmed the frequency-dependence of ventricular arrhythmias in CPVT1: The RR-interval at rest was 1101±50 ms and decreased to 457±19 ms before the first occurrence of premature ventricular complexes (PVC) and to 434±15 ms before PVCs in bigemini ($p<0.05$ vs. at rest). The RR-interval further decreased to 380±15 ms before coupled PVCs or VT ($p=0.05$ vs. PVC/bigemini).

RyR2-RS cardiomyocytes showed no difference in Ca2+ wave frequency compared to wild type (WT) at any stimulation frequencies in the absence of ISO. However, during ISO-exposure, Ca2+ wave frequency was higher in RYR2-RS both at 0.5 and 4 Hz compared to WT ($p<0.05$). Time to first Ca2+ wave was

shorter in RyR2-RS compared to WT at 8 Hz, and at 0.5, 4 and 8 Hz during ISO-exposure ($p<0.05$). Ca2+ transient amplitude was higher in cardiomyocytes from RYR2-RS at 4 and 8 Hz ($p<0.05$), but no differences were observed during ISO-exposure. Ca2+ removal rate did not differ between RyR2-RS and WT at any frequency.

**Conclusion:** Patient data confirmed the frequency-dependence of ventricular arrhythmias in patients with CPVT1. In cardiomyocytes from RyR-RS and WT, Ca2+ wave frequency was not different in absence of β-receptor activation. In RyR-RS cardiomyocytes, the occurrence of Ca2+ waves increased with increasing stimulation frequency. Ca2+ wave frequency was higher in RyR-RS cardiomyocytes compared to WT during ISO-exposure. These results indicate that β-receptor activation contributes decisively to the increased risk of ventricular arrhythmias in situations with increased heart rate in CPVT1.

## 966 Do risk factors explain the sex/gender gap in mortality from coronary heart disease?

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**Background:** In Europe, per year, approximately 253,000 men, but only 77,000 women die prematurely from coronary heart disease (CHD) before the age of 65, while, when considering all ages, slightly more women do so than men. CHD rates increase with age, however to a varying extent between men and women. At younger ages, incidence and mortality are markedly lower in women, whereas with increasing age this gap narrows. However, little is known regarding the contribution of cardiovascular risk factors to this sex/gender effect.

**Purpose:** While there have been studies investigating the possible different role of cardiovascular risk factors in men and women, there have not yet been, to our knowledge, any attempts to explore how much of the sex/gender effect is mediated through risk factors. Presumably, since no appropriate statistical modelling approach for survival data was available. Recently, a new approach for mediation analysis was developed that allows to assess the specific contribution of risk factors explaining the difference between men and women regarding CHD outcomes.

**Methods:** The sex-specific CHD mortality was examined in prospective cohort data from Austria, consisting of 117,264 individuals younger than 50 years (as a proxy for menopausal status) and 54,998 older ones, with 3,892 deaths from CHD during a median follow-up of 14.6 years. Mediation analysis was used to decompose the sex/gender effect into a direct and an indirect component that is mediated by the four major cardiovascular risk factors systolic blood pressure, total cholesterol, fasting blood glucose, and smoking status.

**Results:** The total effect of sex/gender on CHD mortality decreased with age. While the age-adjusted hazard ratio (men versus women) was 4.7 (95 % CI: 3.5 to 6.1) in individuals younger than 50 years, it was only 1.9 (95 % CI: 1.7 to 2.1) in the ≥50 years age group.

In the <50 years age group, the four major cardiovascular risk factors were able to explain 40.9 % of this difference. The strongest factor was systolic blood pressure explaining 21.7 % of the total sex/gender effect.

In the ≥50 years age group, the contribution of the risk factors was small amounting to only 8.2 %. Single risk factors contributed less than 5 %, with total cholesterol even showing a significant "negative" effect, i.e. mediation in favour of men.

**Conclusions:** The extent to which risk factors contribute to the gap between men and women regarding CHD mortality decreases strongly with age. Over the ages of 50 years, the persisting survival advantage of women can be explained only in small part through the pathways of major risk factors.

## P5024 Change in characteristics of the population receiving angiography in an era with decreasing cardiovascular incidence and mortality

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**Background:** Over the past 40 years, cardiovascular mortality in Northern Norway has decreased from 8‰, among the highest in Europe, to 1.7‰ - among the lowest. This is due to a large decrease in incidence, but lately also to >50 % reduction in case fatality.

**Purpose:** Our aim is to describe how decreasing incidence and case fatality is reflected in the population receiving angiography in the last decade.

**Methods:** From 2005–2012, a total of 27,218 angiographies were performed by a sole provider of angiography for 479,000 people. Patient characteristics were entered into a clinical registry. Changes in trends were analysed by age-adjusted logistic regression analyses. Gender differences

were tested with interaction terms. All the reported differences below had p<0.05.

**Results:** 19,923 patients (66 % men and 34 % women) had 25,232 admissions for angiography. Men were 64 years old and women were 67 at admission, of whom 62 % vs 75 % did not have former revascularisation. 25 % of men were admitted more than once vs only 20 % of women. 51 % of men and 45 % of women were admitted as acute coronary syndrome (ACS). In both genders, the total number of acute admissions increased by 1.5 % per year vs 3.8 % per year for elective admissions. Age of the admitted population increased 1 year from 2005 to 2012. ST-elevation myocardial infarction (STEMI) decreased from 24 % to 18 %, and prevalence of obstruction in either left main stem, proximal LAD or 3 vessels decreased from 22 % to 20 %. The number of ACS angiographies resulting in revascularisation decreased from 77 % to 65 % among those without former revascularisation vs from 63 % to 51 % among those with revascularisation. In the elective population, proportion with stable angina as referral cause decreased from 91 % to 85 %.The proportion resulting in revascularisation decreased from 62 % to 36 % among those without former revascularisation vs from 49 % to 40 % among those with either former percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). 63 % of first diagnosis of obstructive coronary heart disease occurred during acute admission in both genders.

**Conclusions:** The dramatic drop in cardiovascular mortality in Norway was reflected in less obstructive pathology detected both in emergency and elective settings and with less severe pathology. Despite a high and increasing rate of elective angiography, most obstructive disease in need of revascularisation were diagnosed during acute admissions. This possibly reflects the difference in underlying pathology in stable angina and ACS with more vulnerable plaques in the latter.

## P5257 Plasma levels of tumor necrosis factor in relation to intramuscular gene expression of TNF, metabolic related enzymes and skeletal muscle pathology in heart failure

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**Background:** In the syndrome of heart failure (HF) plasma levels of TNF are elevated, but the relationship between skeletal muscle abnormalities, skeletal muscle biosynthesis and the increased secretion of TNF has not been clarified. The purpose of the current study was to assess the interactions between expression of TNF mRNA in skeletal muscle, plasma levels of TNF, changes in skeletal muscle pathology and intramuscular gene expression of enzymes related to skeletal muscle biosynthesis

**Methods:** Twenty patients with HF and left bundle branch block who were offered cardiac resynchronization therapy (CRT) were studied. Blood samples and skeletal muscle biopsies were harvested at baseline and after 6 months of CRT. Plasma levels of TNF were measured using a multiplex cytokine immunoassay. Measurements of fibre diameter, interstitial fibrosis, vascular density and inflammation were performed with light microscopy. Point-counting stereology on electron micrographs was used for morphometric registration. Total RNA was extracted from skeletal muscle and quantification of skeletal muscle gene expression of TNF, mitochondrial transcription factor A (TFAM) and nicotinamide phosphoribosyltransferase (NAMPT) was performed.

**Results:** Alterations in plasma levels of TNF correlated statistically significant with alterations in intramuscular gene expression of TNF (R=0.56, p<0.05) and were negatively correlated to mRNA levels of TFAM (r=−0.81, p=0.001) and NAMPT (r=−0.81, p<0.001) within the skeletal muscle. Alterations in skeletal muscle expression of mRNA levels of TNF were statistically significant correlated with changes in mitochondrial density (r=−0.561, p=0.037) and borderline statistical significant correlated with changes in capillary density (r=0.564, p=0.036 Pearson's, r=0.475, p=0.086 Spearman'rho)

**Conclusions:** Alterations in plasma levels of TNF co-varies with alterations in intramuscular gene expression of both TNF and skeletal muscle mitochondrial protein synthesizing enzymes. The alterations in intra muscular gene expression of TNF correlate with alterations in skeletal muscle ultrastructure.

## 6043 The novel cardiovascular biomarker secretoneurin predicts mortality and shock in critical ill patients with infections

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**On behalf:** *FINNSEPSIS and FINNALI Study Groups*

**Background:** Secretoneurin (SN) has a direct effect on cardiomyocyte Ca2+ handling and provides independent prognostic information in patients with cardiovascular disease, but whether SN may predict mortality and shock in critically ill patients with infections is not known.

**Methods:** We measured circulating SN levels in 232 patients with severe sepsis (FINNSEPSIS Study) and validated the results in 94 patients with acute respiratory failure and infections (FINNALI substudy). SN was compared to established risk factors and biomarkers, including high-sensitivity troponin T (hs-TnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).

**Results:** SN levels measured on intensive care unit (ICU) admission in both cohorts were correlated with established risk indices in patients with critical illness, including SOFA and SAPS II scores, and with hospital mortality (Fig). In patients with severe sepsis, admission SN levels (logarithmically transformed) were associated with hospital mortality (OR 3.17 [95 % CI 1.12–9.00], p=0.030) and shock during the hospitalization (OR 2.17 [1.06–4.46], p=0.034) in analyses that adjusted for the other risk factors, including cardiovascular biomarkers. SN levels were also associated with hospital mortality after adjusting for other risk factors in the validation cohort, while neither hs-TnT nor NT-proBNP were associated with mortality or shock in multivariate analyses in the two cohorts. In both cohorts the optimal cutoff for SN levels on ICU admission to predict hospital mortality was ~175 pmol/L and higher levels were associated with mortality also when adjusting for SAPS II and SOFA scores.

**Conclusion:** SN levels provide incremental information to established risk indices for the prediction of mortality and shock in critically ill patients with severe infections.

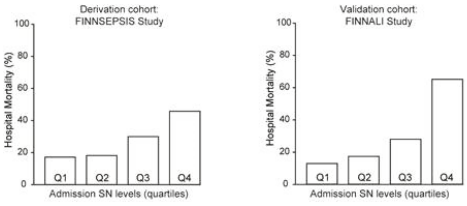


*Figure 1. Mortality according to SN levels*

## P1656 The association between serum apolipoprotein B and acute myocardial infarction is modified by plasma glycine

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**Background:** Hepatic cholesterol uptake and VLDL excretion depend on the availability of the amino acid glycine.

**Purpose:** We investigated whether plasma glycine levels modified the relationship between serum apoB and risk of acute myocardial infarction (AMI) among 4154 patients with suspected stable angina pectoris, of whom 80.1 % received statins.

**Methods:** Survival analyses were carried out by Cox regression models adjusted for age, gender and fasting status, and additionally adjusted for smoking, hypertension, diabetes, hs-cTnT, BMI, statin therapy and folate status. Interactions were tested according to low (< median) and high (≥ median) plasma glycine.

**Results:** Median (IQR) serum apoB was 87 (73–104) mg/dL, and slightly higher among patients with low glycine levels. After median 4.6 years, 344 patients (8.3 %) experienced an AMI, with equal incidence rates in strata of glycine levels. In analyses adjusted for age, gender and fasting status, the hazard ratio (HR) (95 % confidence interval (CI)) per 1 SD serum apoB in the whole cohort was 1.19 (1.07–1.31). However, the relationship between apoB and AMI was confined to patients with low glycine levels (Figure 1; P for interaction = 0.003). A similar effect modification was seen in multivariate analyses.

**Conclusion:** Serum apoB was a particularly strong predictor of incident AMI among patients with low plasma glycine. This suggests that the relationship between circulating apoB and cardiovascular risk might be influenced by decreased hepatic clearance, rather than increased secretion, of circulating apoB containing lipoproteins. Impaired turnover of VLDL remnant particles between the systemic and hepatic compartments may increase the life-span of circulating athero-

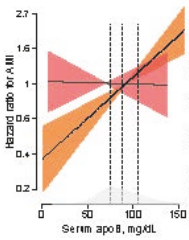


Figure 1. The associations between serum apolipoprotein B and incident acute myocardial infarction in strata of low (orange) and high (pink) plasma glycine. Solid lines depict the smoothed splines from a generalized additive Cox model adjusted for age, gender and fasting status, and the shaded areas 90 % confidence intervals. The horisontal dotted lines depict the 25th, 50th and 75th percentiles of the densityplot superimposed on the X-axis. AMI, acute myocardial infarction; apoB, apolipoprotein B.

genic lipoproteins, and making them more prone to oxidative damage.

## P4404 Evolving antithrombotic treatment patterns in patients with newly diagnosed atrial fibrillation in GARFIELD-AF

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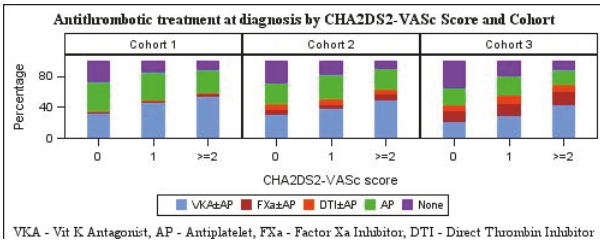
**On behalf:** GARFIELD-AF Investigators

**Purpose:** To study the evolving pattern of antithrombotic therapy in newly diagnosed non-valvular atrial fibrillation (AF) patients with ≥1 investigator-defined stroke risk factor.

**Methods:** 27,106 prospective patients were enrolled in three sequential cohorts in 2010–14 in the global GARFIELD-AF registry: C1 (2010–11), n=5516, mean CHA2DS2-VASc 3.2; C2 (2011–13), n=11,652, mean CHA2DS2-VASc 3.3; C3 (2013–14), n=9938, mean CHA2DS2-VASc 3.2. Baseline characteristics and antithrombotic therapy initiated at diagnosis were analysed by cohort.

**Results:** Baseline characteristics were similar in all three cohorts. From C1 to C3, the proportion of patients on anticoagulant (AC) therapy increased (C1 57.5 %; C2 62.3 %; C3 67.5 %). Use of vitamin K antagonist (VKA) ±antiplatelet (AP) decreased (C1 53.3 %; C2 48.5 %; C3 41.1 %), while use of non-VKA oral ACs (NOACs) ±AP increased (C1 4.2 %; C2 13.8 %; C3 26.4 %). The increase in use of AC was mainly in patients with CHA2DS2-VASc ≥2, with a smaller increase in patients with a score of 1. Use of AC in patients with a score of 0 (but with an investigator-defined stroke risk factor) varied from 35.3–45.0 %.

**Conclusion:** Since the introduction of NOACs, newly diagnosed at-risk AF patients are more often receiving guideline recommended therapy driven by increased use of NOACs and less treatment with VKA±AP or AP alone. However, patients with a score of 0 are also using more AC, with a greater proportion receiving NOACs.



VKA - Vit K Antagonist, AP - Antiplatelet, FXa - Factor Xa Inhibitor, DTI - Direct Thrombin Inhibitor

## 6039 Circulating microRNAs in experimental model of heart failure with preserved ejection fraction: effects of high-intensity exercise training

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**On behalf:** the OptimEx study group

**Background:** Although the incidence of heart failure with preserved ejection fraction (HFpEF) is increasing, current diagnostic methods are not precise and treatment remains a major challenge. Therefore, the need for better predictive methods and therapies is obvious.

**Purpose:** To investigate the diagnostic utility of plasma circulating miRNAs and the effects of high intensity interval training (HIT) on miRNA profile in an animal model of HFpEF.

**Methods:** Female Dahl salt-sensitive rats were randomized in three groups: sedentary low-salt diet (LS, N=15: 0.3 % NaCl), sedentary high-salt diet (HS, N=11: 8 % NaCl) or high-salt diet submitted to HIT (N=10: 8 % NaCl + HIT, 3×38 min/wk; 4 intervals of 4 min at 90 % peakVO2). Cardiac function was evaluated by echocardiography, while circulating miRNA profile was assessed in the plasma by qPCR, followed by construction of ROC curve analysis.

**Results:** We found two miRNAs (rno-miR-21-5p and rno-let-7b-5p) differently expressed in the plasma of HS compared to LS rats. Both miRNAs correlated modestly with most of the echocardiographic parameters for HFpEF (miR-21: R2=0.3913 and p=0.0016 for E/e' ratio; R2=0.5746 and p=0.0040 for E/A ratio; let-7b: R2=0.3807 and p=0.0019 for E/e' ratio; R2=0.3487 and p=0.0031 for E/A ratio). ROC curve analyses revealed that both miRNAs presented superior sensitivity and specificity as compared to NT-proBNP (AUC: 0.9273 vs. 0.8667

vs. 0.7879) for distinguishing HS from LS rats. MiR-21 was 1.5 fold reduced and let-7b level was 1.7 fold increased in HS when compared to LS rats. In addition, HIT prevented deregulation of both miR levels in HFpEF rats.

**Conclusion:** Taken together, our data suggest miRNA plasma profiling is a useful diagnostic tool for HFpEF. We also show that HIT prevented miRNA deregulation in an animal model of HFpEF, and therefore might serve as a potential new therapeutic strategy.

## 4960 Heterogeneous myocardial contraction is related to cardiac fibrosis and predict ventricular arrhythmias in patients with hypertrophic cardiomyopathy

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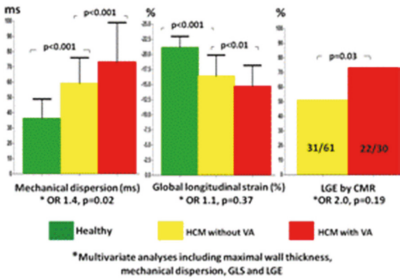
**Background:** Hypertrophic cardiomyopathy (HCM) patients are at risk of ventricular arrhythmias (VAs). Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) is a marker of fibrosis and is related to VAs.

**Purpose:** We aimed to explore if left ventricular (LV) systolic function by strain echocardiography is related to VAs and to the extent of LGE.

**Methods:** We included 150 HCM patients (54±14 years, 39 % female) and 50 age and sex matched healthy individuals. VAs were defined as suspected arrhythmic syncope, ventricular tachycardia or aborted cardiac arrest. Global longitudinal strain (GLS) was assessed by speckle tracking echocardiography. Mechanical dispersion (MD), reflecting heterogeneous contraction, was calculated as standard deviation of time from Q on ECG to peak strain in 16 LV segments. In 85 (57 %) patients, any LGE by CMR was defined as signal intensity 5 SD ≥ normal myocardium, and percentage LGE ( %LGE) was determined.

**Results:** HCM patients had similar ejection fraction (61±5 % vs.61±8 %, p=0.77), but worse GLS (−15.7±3.6 % vs. −21.1±1.9 %, p<0.001) and more pronounced MD (64±22 ms vs. 36±13 ms, p<0.001) than healthy (Figure). Patients with VAs (n=54) had worse GLS (−14.7±3.5 % vs. −16.4±3.5 %, p<0.01) more pronounced MD (73±26 ms vs. 59±16 ms, p<0.001), and higher %LGE (4.3±6.9 % vs. 0.5±1.0 %, p<0.001) than patients without VAs (n=96). MD was correlated to %LGE (R=0.52, p<0.001), and was the only parameter that predicted VAs independently of maximal wall thickness, GLS and the presence of LGE (Figure).

**Conclusion:** HCM patients had reduced LV function by GLS, despite normal function by ejection fraction. MD was a strong and the only independent predictor of VAs and was related to fibrosis and may help risk stratification of VAs in HCM.




## P1574 Increased endothelial activation is associated with impaired improvement of exercise capacity after exercise training in patients with type 2 diabetes and coronary artery disease

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**Background:** Endothelial dysfunction plays an important role in atherosclerotic disease and is also present in patients with type 2 diabetes. There are also studies showing association between presence of endothelial dysfunction and reduced exercise capacity. We investigated associations between biomarkers of endothelial activation measured at baseline and changes in VO2peak during a 12 months exercise trial in patients with type 2 diabetes and coronary artery disease (CAD).

**Methods:** Fifty-two patients in the exercise group completed the study. VO2peak before and after the exercise intervention was measured by cardiopulmonary exercise testing on a treadmill. Endothelial activation was assessed by circulating levels of ICAM-1, VCAM-1, E-selectin, ADMA, L-arginine and L-arginine/ADMA-ratio. Correlations were assessed by Pearsons correlation or Spearman rho as appropriate. Differences in changes of VO2peak within the exercise group were analyzed by independent Student t-test. Odds ratio was calculated by logistic regression.

**Results:** Correlations between biomarkers of endothelial activation at baseline and changes in VO2peak in the exercise group (mean 0.8 ml/kg/min (95 % CI -0.2 to 1.8)) are shown in the Table 1.

A clear cut-off point between second and third tertile was identified for both L-arginine/ADMA-ratio (120) and ICAM-1 (259 ng/ml). Patients with high L-arginine/ADMA-ratio (>120) and patients with low ICAM-1 (<259 ng/ml) had significantly more pronounced increase in VO2peak compared to patients with low L-arginine/ADMA-ratio (p=0.004) and high ICAM-1 (p=0.007), respectively. The odds ratio for no improvement of VO2peak during the intervention was 4.6 (95 % CI 1.2 to 17.2) (p=0.024) for patients with low compared to high L-arginine/ADMA-ratio, and 6.3 (95 % CI 1.4 to 27.0) (p=0.015) for patients with high compared to low ICAM-1.

**Conclusion:** In our population of patients with type 2 diabetes and CAD, patients with increased endothelial activation, indicated by low L-arginine/ADMA-ratio or high ICAM-1, experienced significantly poorer improvement of exercise capacity after exercise training compared with patients with less endothelial activation.

*Table 1. Coefficient of correlation*

| | ICAM-1 | VCAM-1 | E-selectin | ADMA | L-arginine/ ADMA-ratio |
|---|---|---|---|---|---|
| $\Delta VO_{2peak}$ | r=−0.229† | r=−0.101† | r=−0.181† | r=−0.070 | r=0.294 |
| | p=0.11 | p=0.49 | p=0.21 | p=0.64 | p=0.043 |

*Pearson correlation. †Spearman rho.*

## P460 Predictors of appropriate therapy from implantable cardioverter-defibrillators in Scandinavian arrhythmogenic right ventricular cardiomyopathy patients

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**Purpose:** Implantable cardioverter-defibrillator (ICD) therapy remains a corner stone of sudden death (SCD) prevention in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). However risk stratification and predictors of ICD interventions are not fully clarified. We aimed to assess predictors of adequate ICD interventions in ICD-treated ARVC patients enrolled in the Nordic ARVC registry.

**Methods:** Patients with definite ARVC by 2010 Task Force (TF2010) criteria who received ICD for primary or secondary prevention of SCD recruited at 8 sites in Denmark, Norway and Sweden were included in the analysis. The presence of major and minor diagnostic criteria for ARVC by TF2010, age at diagnosis, gender, history of syncope, history of SCD in a first-degree relative, genotype-positivity and detection of fibrosis in ventricular walls by delayed gadolinium enhancement magnetic resonance imaging (DE-MRI) were assessed as possible predictors of appropriate ICD intervention using the time from ICD implantation to the first antitachycardia pacing or shock as the main outcome measure.

**Results:** The population consisted of 170 ARVC patients with ICD (139 probands, 113 men, mean age at diagnosis: 40±15 years). In 21 patients ICD was implanted after aborted cardiac arrest. Genotyping was performed in 76 % of probands (n=105) and disease-causing genetic variants were found in 67 (64 %), of which plakophillin-2 genetic variants were the most frequent (n=42). Median follow-up was 8 (IQR 4–12) years. During that time 4 patients died (2 of these from non-cardiac causes and without prior ICD therapy). Appropriate ICD interventions were documented in 106 patients as either ATP (n=69, 41 %) or shocks (n=70, 41 %). Of the tested factors, young age at diagnosis (≤40 years), genotype-positivity, positive DE-MRI and ventricular tachycardia fulfilling the major arrhythmia criterion by TF2010 were found to be univariately associated to the outcome using Cox regression analysis. Genotype-positivity (HR=1.7; 95 % CI 1.04–2.83, p=0.017) and major arrhythmia criterion (HR=1.85; 95 % CI 1.16–3.06, p=0.034) remained significant predictors of the outcome in the multivariable model. Neither the history of aborted cardiac arrest nor the family history of SCD in the first-degree relative predicted ICD therapy.

**Conclusions:** In this registry study representing Scandinavian patients with ARVC, presence of a disease-causing genetic variant and the history of left bundle branch morphology ventricular tachycardia with superior axis independently predicted appropriate ICD interventions.

## P2621 Controlled release metoprolol for aortic regurgitation: a double blind, randomised controlled trial of efficacy and safety

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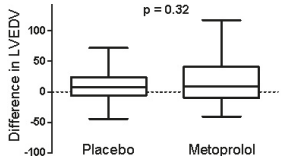
Background: Chronic aortic regurgitation creates a volume load on the left ventricle, which induces adaptive responses. With time, excessive left ventricular dilatation may precipitate heart failure unless aortic valve surgery is performed. Treatment with β-adrenergic receptor antagonists (β-blockers) is beneficial in patients with heart failure, but the effect of β-blocker therapy in aortic regurgitation is unclear. This trial was designed to evaluate the effect of controlled release metoprolol on left ventricular remodelling in patients with chronic aortic regurgitation.

Methods: In this randomised, double blind, placebo-controlled trial, 75 asymptomatic patients with moderate to severe chronic aortic regurgitation were randomised to receive metoprolol CR/XL up-titrated to 200 mg/day, or matching placebo. The primary end point was left ventricular end diastolic volume, measured by magnetic resonance imaging after 6 months of treatment.

Results: After 6 months of treatment, there was no difference in the baseline adjusted left ventricular end diastolic volume between patients allocated to metoprolol and those allocated to placebo (Figure). At follow-up, the mean adjusted left ventricular ejection fraction was 2.7 percentage points (0.1–5.3 percentage points; p=0.04) higher in the metoprolol group than in the placebo group. The exercise capacity and peak oxygen consumption did not differ between treatment arms; whereas, serum levels of N-terminal pro-B-type natriuretic peptide were higher in the metoprolol group. There were no serious adverse events in either treatment arm.

Conclusions: Treatment with controlled release metoprolol for 6 months did not reverse, nor exacerbate left ventricular remodelling in patients with moderate to severe aortic regurgitation.




*Change in LVEDV over six months*

## 2943 Clinical predictors of exercise-induced regression of coronary atherosclerosis: a serial intravascular ultrasonography study

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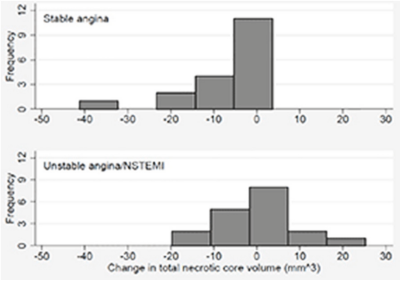
**Background:** Aerobic exercise induces beneficial changes in coronary atherosclerosis via reduced necrotic core (NC) and plaque burden (PB). The purpose of the study was to identify potential clinical predictors of regression of coronary atherosclerosis following aerobic exercise.

**Methods:** Post-hoc analysis of associations between baseline clinical variables and reductions in coronary NC and PB following aerobic exercise intervention. Plaque characteristics were measured with grayscale and radiofrequency intravascular ultrasound in 36 patients (median age 58.5 years, 7 women) with stable coronary artery disease (SCAD) or non-ST-elevation acute coronary syndrome (NSTE-ACS). Screening of variables was performed with random forest analysis followed by multivariate linear regression.

**Results:** The only significant variable for NC reduction was clinical presentation of disease (SCAD vs. NSTE-ACS, p=0.011). The change in NC was −4.94 (−10.33; −1.33) mm$^3$ in patients with SCAD, and 1.03 (−4.29;3.71) mm$^3$ in patients with NSTE-ACS (p=0.01). NC was reduced in 17 patients (94 %) with SCAD and 8 patients (44 %) with NSTE-ACS (p=0.01, Figure). R-squared for the model including baseline clinical presentation and baseline NC volume was 0.90. There were no significant explanatory variables for PB reduction.

**Conclusions:** Exercise-induced plaque stabilization via reduced NC may be strongly dependent




*Change in NC volume following exercise*

on clinical presentation of disease. We hypothesize that an increased pro-inflammatory load renders patients with NSTE-ACS more resistant to exercise-induced plaque stabilization than patients with SCAD. Furthermore, aerobic exercise may have a paricular potential for inducing beneficial effects on coronary atherosclerosis in patients with SCAD compared to patients in the early phase following an acute coronary syndrome.

## P3462 Early detection of low-grade myocardial ischemia by miniaturized 3-axis accelerometer

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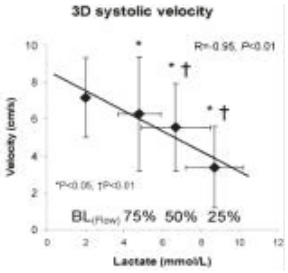
**On behalf:** ***The Research Group on Advance Cardiovascular Monitoring***

**Background:** Myocardial ischemia is a leading cause of death after heart surgery and sensitive methods for early detection are still needed. We tested a miniaturized 3-axis (3D) accelerometer for detection of myocardial ischemia and hypothesized the method could quantify the degree of myocardial ischemia during coronary artery flow reductions.

**Methods:** In 8 pigs, 3D accelerometers and intramyocardial microdialysis catheters were positioned in the left anterior descending (LAD) and circumflex (CX) coronary artery areas. During beating heart surgery with intracoronar shunt the left internal mammary artery (LIMA) was grafted to the LAD, which was occluded proximal to the anastomosis. Flow in LIMA was stepwise reduced by 25 % from 100 % (BL) to 75 %, 50 %, and 25 % for 18 min each. From the 3D accelerometer signals 3D peak systolic velocity was obtained by time integration of the acceleration signals. The reference method to detect myocardial ischemia was tissue lactate by microdialysis.

**Results:** Reduced systolic velocity by the 3D accelerometer was observed at all steps of coronary flow reduction and the decreases in velocity correlated closely to the degree of myocardial ischemia as measured by tissue lactate ($R=-0.95$, $P<0.01$) (Figure). There were no significant changes in 3D accelerometer systolic velocity and tissue lactate in CX area during the reductions in coronary artery flow.

**Conclusions:** The epicardially attached miniaturized 3D accelerometer enabled quantifying different levels of myocardial ischemia during stepwise reductions in coronary artery flow. A linear relationship among coronary blood flow, myocardial ischemia and function was found. These results demonstrate that 3D accelerometers can be used to detect graft failure during and after heart surgery.




*3D accelerometer vs tissue lactate*

## P451 The novel cardiovascular biomarker secretoneurin provides valuable prognostic information in patients with acute respiratory failure

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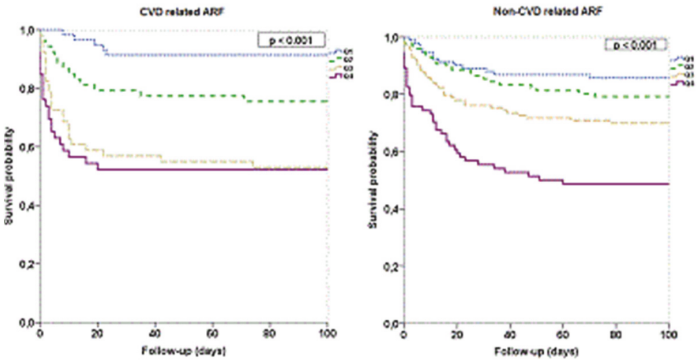
**Background:** Secretoneurin (SN) regulates cardiomyocyte Ca2+ handling and provides prognostic information in patients with cardiovascular (CV) disease, but whether SN provides prognostic information in patients with acute respiratory failure (ARF) is unknown.

**Methods:** We included those ARF patients in the FINNALI study whose blood samples were available at Intensive Care Unit (ICU) admission (n=584). ARF was defined as ventilatory support >6 h and the patients were categorized as CV vs. non-CV related ARF.

**Results:** In total, 209 patients (41 %) were hospitalized with CV related ARF. Circulating SN levels did not differ between patients with CV and non-CV related ARF: 120 (95–167) vs. 123 (98–160) pmol/L, p=0.60. Mortality rates during 90 day follow-up were 31 % for CV related and 28 % for non-CV related ARF (p=0.50 between groups). SN levels on ICU admission discriminated between patients with a poor and favorable outcome during 90 day follow-up (Fig; p<0.001 by the log-rank test in both groups). Admission SN levels were also associated with




*Survival according to SN quartiles*

mortality in both CV related ARF (HR 2.00 [95 % CI 1.03–3.91], p=0.04) and non-CV related ARF (HR 2.24 [95 % CI 1.10–4.56], p=0.03). These analyses were adjusted for other risk variables, including N-terminal pro-B-type natriuretic peptide (NT-proBNP). The area under the curve (AUC) of SN to predict mortality in CV related ARF was 0.72 (95 % CI 0.65–0.78) compared to 0.68 (0.63–0.72) for SN in non-CV related ARF. SN improved risk assessment of patients with CV related ARF as assessed by the category-free net reclassification index (0.32 [95 % CI 0.037–0.59], p=0.026), while NT-proBNP levels did not add to the basic risk model.

**Conclusions:** SN levels measured on ICU admission improve risk assessment in CV related ARF.

## P4093 New-onset midwall dysfunction predicts impaired prognosis in aortic valve stenosis with normal ejection fraction (the SEAS study)

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**Background:** In hypertension, low left ventricular (LV) midwall function is associated with impaired prognosis independent of normal ejection fraction (EF).

**Purpose:** To test the prognostic value of new-onset low LV midwall shortening (MWS) during follow-up of patients with asymptomatic aortic stenosis (AS) and normal EF.

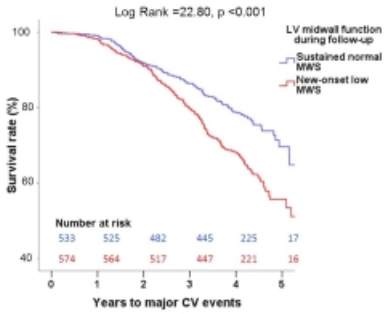
**Methods:** 1107 patients with AS, normal EF and MWS at baseline in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study were followed for a median of 4.0 years. LV systolic function was assessed by biplane EF (low if <50 %) and MWS (low if <14 %/16 % in men/women) at baseline and annual echocardiograms. New-onset low MWS was identified at follow-up visits before any clinical event.

**Results:** 574 patients (52 %) developed low MWS during follow-up. They included a higher proportion of elderly women with higher blood pressure and abnormal LV geometry (all p<0.05). In time-varying Cox analyses new-onset low MWS predicted 45 % increase in major CV events and a 2-fold increase in heart failure and CV death (Table, Figure).

**Conclusions:** In asymptomatic patients with AS and normal EF at baseline, new-onset low MWS was associated with increased CV morbidity and mortality during 4-year follow-up.

*Time-varying Cox analyses*

| | **Hazard ratio [95 % CI], p for new-onset low MWS** |
|---|---|
| Major CV events | 1.45 [1.15–1.83], p=0.002 |
| Aortic valve events | 1.49 [1.17–1.90], p=0.001 |
| Heart failure or CV death | 2.07 [1.17–3.67], p=0.013 |




*Adjustment for age, gender, study treatment, hypertension, and time-varying EF, severity of AS by energy loss index, and abnormal LV geometry. Kaplan-Meier hazard of major CV events*

## P1513 Patterns of uptake of non-vitamin K antagonist oral anticoagulants in Europe: an analysis from the GARFIELD-AF registry

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*On behalf: GARFIELD-AF Investigators*

**Purpose:** To compare non-vitamin K antagonist oral anticoagulant (NOAC) uptake in different European populations of atrial fibrillation (AF) patients.

**Methods:** 27,106 patients with newly diagnosed non-valvular AF and ≥1 additional stroke risk factor were enrolled in GARFIELD-AF in 2010–14; 16,805 in Europe. NOAC uptake was evaluated by country at 2-y follow-up. The date the first patient on a NOAC was enrolled in the registry was taken as the start of NOAC therapy in each country. The proportion of patients on NOACs is the number on NOACs at enrolment over the total number enrolled after the start date. Countries with a late start date did not have 2-y data.

**Results:** 2819 (16.8 %) European patients used NOACs at enrolment. Their mean age was 71.0 y; 46.6 % were female. The date of first NOAC use was from Mar 2010 (Austria) to Oct 2012 (the Netherlands and Russia). At 6 mo from first NOAC use, the proportion of patients on NOACs varied from 1.4 % (UK) to 50.0 % (Belgium). At 12 mo, it ranged from 1.5 % (France, Italy) to 52.8 % (Belgium). At 24 mo, it varied from 1.1 % (Italy) to 56.9 % (Belgium). The greatest increase was seen in France and Sweden. At the end of the enrolment period there were still marked differences in NOAC uptake, ranging from 3.0 % (Finland) to 57.0 % (Belgium).

**Conclusion:** Large variations in NOAC uptake were observed between European countries, which may be due to differences in availability and reimbursement.

## P5598 Stroke, major bleeding and mortality in newly diagnosed atrial fibrillation with moderate-to-severe chronic kidney disease: results from GARFIELD-AF

*S. Goto[1], D. Atar[2], J.-P. Bassand[3], K.A.A. Fox[4], S.Z. Goldhaber[5], F. Misselwitz[6], S. Oh[7], A.G.G. Turpie[8], F. Verheugt[9], A.K. Kakkar[10], [1]Tokai University - Kanagawa - Japan, [2]Oslo University Hospital Ullevål and University of Oslo - Oslo - Norway, [3]University of Franche-Comté - Besançon - France, [4]University of Edinburgh - Edinburgh - United Kingdom, [5]Harvard Medical School - Boston*

*Table 1*

| | | Austria | Poland | Germany | Spain | France | Italy | Norway | Finland | Denmark |
|---|---|---|---|---|---|---|---|---|---|---|
| | **First patient on a NOAC** | **Mar 2010** | **Jul 2010** | **Aug 2010** | **Nov 2010** | **Jan 2011** | **Mar 2011** | **May 2011** | **Jun 2011** | **Sep 2011** |
| Patients on NOACs, % (n/N) | After 6 months | 18.8 (3/16) | 3.0 (4/133) | 4.3 (19/438) | 2.7 (8/301) | 1.9 (3/162) | 2.3 (7/301) | 5.9 (1/17) | 3.1 (2/65) | 25.0 (20/80) |
| | After 12 months | 7.1 (6/84) | 4.9 (22/448) | 5.6 (47/833) | 2.3 (10/436) | 1.5 (4/259) | 1.5 (7/467) | 7.5 (4/53) | 1.8 (2/114) | 26.7 (36/135) |
| | After 24 months | 4.6 (9/195) | 3.4 (26/754) | 9.7 (136/1403) | 4.5 (40/888) | 15.6 (84/537) | 1.1 (8/748) | 16.5 (13/79) | 1.8 (3/165) | 27.2 (49/180) |
| | End of enrolment period | 18.5 (58/314) | 18.2 (284/1558) | 24.8 (591/2386) | 8.2 (126/1536) | 27.7 (260/940) | 4.9 (55/1116) | 42.4 (72/170) | 3.0 (8/269) | 27.7 (59/213) |
| | | **UK** | **Sweden** | **Belgium** | **Ukraine** | **Hungary** | **Czech Republic** | **Netherlands** | **Russia** | |
| | **First patient on a NOAC** | **Feb 2012** | **Apr 2012** | **Jun 2012** | **Jul 2012** | **Aug 2012** | **Sep 2012** | **Oct 2012** | **Oct 2012** | |
| Patients on NOACs, % (n/N) | After 6 months | 1.4 (4/276) | 4.0 (4/99) | 50.0 (108/216) | 8.4 (34/404) | 7.5 (13/174) | 9.6 (33/344) | 5.2 (10/192) | 13.9 (57/411) | |
| | After 12 months | 1.9 (10/532) | 15.7 (44/281) | 52.8 (214/405) | 9.9 (53/534) | 16.2 (71/438) | 11.2 (60/535) | 5.8 (21/359) | 13.9 (102/732) | |
| | After 24 months | 4.7 (56/1203) | 26.1 (147/564) | 56.9 (497/873) | 13.0 (127/977) | – | – | – | – | |
| | End of enrolment period | 5.1 (76/1476) | 26.5 (157/592) | 57.0 (500/877) | 13.0 (127/977) | 15.1 (103/681) | 12.3 (98/800) | 10.5 (57/545) | 15.8 (167/1058) | |

*NOAC, non-vitamin K antagonist oral anticoagulant; a dash indicates missing data.*

*- United States of America, [6]Bayer HealthCare Pharmaceuticals - Berlin - Germany, [7]Seoul National University Hospital - Seoul - Korea, Republic of, [8]McMaster University - Hamilton - Canada, [9]University Medical Centre - Nijmegen - Netherlands, [10]Thrombosis Research Institute - London - United Kingdom,*

**On behalf:** GARFIELD-AF Investigators

**Purpose:** To study outcomes in atrial fibrillation (AF) patients with moderate-to-severe chronic kidney disease (CKD; NKF-KDOQI stage≥3) vs mild/no CKD (stage<3).

**Methods:** GARFIELD-AF enrolled 17,168 patients with newly diagnosed non-valvular AF and ≥1 additional investigator-defined stroke risk factor in 2010–13. Hazard ratios (HR) were adjusted for CHA2DS2-VASc, ethnicity, antithrombotic therapy, smoking and AF type.

**Results:** 17,165 patients had data on renal function and 1-y outcomes. Stage ≥3 patients (n=1757) were older than stage <3 patients (n=15,408) and more often female. They had more comorbidities and higher CHA2DS2-VASc and HAS-BLED. Despite more frequent use of anticoagulant ± antiplatelet in stage ≥3 patients (66.4 % vs 60.1 %), the risk of stroke/systemic embolism (SE), all-cause death and cardiovascular death was higher than in stage <3 patients (HR [95 % confidence interval], 1.68 [1.15–2.46], 1.94 [1.59–2.37], 1.78 [1.34–2.35]). The HR for major bleeding was 2.19 (1.39–3.45).

**Conclusion:** Moderate-to-severe CKD is linked to a higher rate of stroke/SE, major bleeding and death, including cardiovascular death in AF patients.

See table

*Table 1*

| | Stage ≥3 CKD (n=1757) | Stage <3 CKD (n=15,408) |
|---|---|---|
| Women, n ( %) | 870 (49.5) | 6649 (43.2) |
| Age, mean (SD), y | 76.5 (9.1) | 69.0 (11.4) |
| Medical history, n ( %) | | |
| Congestive heart failure | 519 (29.5) | 3020 (19.6) |
| Coronary artery disease | 487 (27.7) | 2933 (19.0) |
| Acute coronary syndromes | 270 (15.4) | 1352 (8.8) |
| Hypertension | 1483 (84.4) | 11922 (77.4) |
| Diabetes | 522 (29.7) | 3237 (21.0) |
| $CHA_2 DS_2$ -VASc score, mean (SD) | 4.2 (1.5) | 3.1 (1.6) |
| HAS-BLED score, mean (SD) | 2.6 (0.8) | 1.3 (0.8) |
| 1-year outcomes, events/100 person-years (95 % CI) | | |
| All-cause death | 10.20 (8.74, 11.89) | 3.39 (3.10, 3.70) |
| Cardiovascular death | 5.29 (4.27, 6.55) | 1.74 (1.54, 1.97) |
| Stroke/systemic embolism | 2.49 (1.82, 3.40) | 1.24 (1.07, 1.44) |
| Major bleeding | 1.91 (1.33, 2.72) | 0.72 (0.60, 0.88) |

*CKD, chronic kidney disease; SD, standard deviation; CI, confidence interval.*

## P528 Current use of evidence-based recommendations for the biochemical diagnosis of acute myocardial infarction in routine clinical practice

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**On behalf:** European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group Cardiac Markers

**Objective:** To assess current use of evidence-based guidelines for the use of cardiac biomarkers for the diagnosis of acute myocardial infarction in Europe.

**Methods:** In 2013/14 a web-based questionnaire was distributed to European biochemical societies for circulation to their membership. Questions covered cardiac biomarkers measured, analytical methods used, decision thresholds and their derivations, sampling strategies, repeat sample interval, use of rate of change and use of decision-making protocols. Results were collated using a central database and analysed using comparative and descriptive nonparametric statistics.

**Results:** Returns were obtained from 442 hospitals, 50 % central or University hospitals and 39 % from local hospitals from 35 countries. 395/442 (89 %) provided an acute service and were analysed further. Cardiac troponin was the preferred cardiac biomarker in 99.5 % and the first line marker in 97.7 %. Creatine kinase or creatine kinase MB isoenzyme continue to be offered as supplementary markers either as part of cardiac marker panel or on request in 72 % of hospitals.

The decision limit for diagnosis was based on 10 % assay imprecision in 18.9 %, the 99th percentile in 52.1 %, an optimised decision thresholds from receiver operating characteristic curve analysis in 1.3 % and a local decision in 27.7 %. The choice of value for the decision limit was derived from the manufacturers package insert in 62.2 %, from peer-reviewed

literature in 12.5 % and from locally-based consensus review in 19.4 %.

A detailed analysis of the decision limits used was performed for troponin T (Roche diagnostics hs assay) and the largest single troponin I group (Abbott diagnostics). The decision limit used varied from 2 ng/L to 700 ng/L with peaks of utilisation at 30 ng/L, 50 ng/L and 100 ng/L. Only 50 % of hospitals used the 99th percentile (14 ng/L). A similar pattern was seen for cardiac troponin I. Only 23.8 % used the recommended decision limit of the 99th percentile, with a reported decision limit ranging from 25 ng/L to 500 ng/L with peaks of utilisation at 40 ng/L and 300 ng/L.

Serial testing was only performed in 70.2 % of hospitals with the use of rate of change only in 35.8 % of those 240/342 who report regularly using a serial testing.

**Conclusion:** There is currently a lack of understanding of the decision thresholds and testing strategies which should be in routine clinical use for the diagnosis of acute myocardial infarction using cardiac troponin measurement. Recent publications show that this lack of understanding will result in under diagnosis of preventable disease.

## P4657 Plasma hydroxyanthranilic acid and incident type 2 diabetes in patients with stable angina pectoris

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**Background:** The tryptophan metabolite hydroxyanthranilic acid (HAA) has been related to insulin resistance and atherosclerosis. Moreover, HAA was recently identified as a potent regulator of lipid metabolism and inflammation.

**Purpose:** We evaluated the associations of plasma HAA levels to incident type 2 diabetes (T2D) in patients with suspected stable angina pectoris (SAP).

**Methods:** A total of 4122 patients underwent elective coronary angiography at two Norwegian university hospitals in 2000–2004. Patients with self-reported diabetes mellitus and/or glycated haemoglobin >6.5 % (n=1603) were excluded leaving 2519 patients eligible for the analyses. The participants were followed for incident T2D throughout 2009. Odds ratios (OR) and 95 % confidence intervals (CI) for were calculated using logistic regression and are reported per standard deviation increment of plasma HAA (log-transformed). We assessed risk classification by calculating the continuous net reclassification improvement (NRI >0).

**Results:** Median age at inclusion was 62 years and 73 % were males. During follow-up, a new diagnosis of T2D was recorded in 114 (4.5 %) of the participants. Median plasma HAA values were substantially higher in those who subsequently developed T2D than in those who did not (40.0 vs. 33.8 nmol/L, P<0.001). In age and gender adjusted analyses, HAA provided an OR (95 % CI) for incident T2D of 1.57 (1.28–1.91), P<0.001. Adding body mass index, serum creatinine, study centre and fasting status to the multivariable model somewhat attenuated the association, which, however, remained statistically significant (OR [95 % CI]: 1.34 [1.08–1.67], P=0.009). Further adjustment including serum apolipoprotein A1, apolipoprtein B, triglycerides, C-reactive protein, glycated haemoglobin, and use of thiazides, statins and beta-blockers did not affect the risk estimate of HAA (OR [95 % CI]: 1.34 [1.07–1.67], P=0.01). Moreover, HAA significantly improved risk classification for T2D (NRI [95 % CI]: 0.19 [0.07–0.38], P=0.04).

**Conclusion:** In a large cohort of patients with SAP, we identified plasma HAA as a strong predictor of incident T2D. Underlying pathomechanisms should be further elucidated.

## P3589 Increased levels of NT-proBNP are associated with reduced exercise capacity and peak oxygen consumption in asymptomatic patients with chronic aortic regurgitation

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**Background:** In patients with chronic, haemodynamically significant aortic regurgitation (AR), a long period of remodelling usually precedes the development of symptoms or left ventricular dysfunction. The value of ergospirometric testing in patients with asymptomatic AR is not established.

**Purpose:** We aimed to investigate if peak oxygen consumption (VO2peak) were reduced in patients with AR, and whether exercise test parameters were associated with the size of the valvular regurgitation and indices of left ventricular (LV) dimension and function, including N-terminal pro-B-type natriuretic peptide (NT-proBNP).

**Methods:** 66 asymptomatic patients aged 44±14 years with moderate or severe, chronic AR and no indication for aortic valve replacement were evaluated by cardiac magnetic resonance

imaging and exercise testing with measurement of VO2peak. Determinants of VO2peak were assessed by uni- and multivariate analysis.

**Results:** The average LV end diastolic volume was 244±62 ml and the aortic regurgitant fraction 34±13 %. VO2peak was 35.8±8.9 ml/kg/min, corresponding to 107±26 % of the age, gender and weight adjusted expected value. As in healthy individuals, a relatively large LV end diastolic volume and a low resting heart rate were associated with a high exercise capacity and a high VO2peak. The aortic regurgitant fraction was not predictive of VO2peak. Higher levels of NT-proBNP were independently associated with poorer exercise capacity and VO2peak (Figure).

**Conclusion:** Our results indicate that in asymptomatic patients with moderate or severe AR and moderately dilated left ventricles, exercise capacity is preserved and remodelling is primarily adaptive. An increased level of NT-proBNP is associated with a reduced VO2peak, possibly heralding the onset of adverse remodelling.

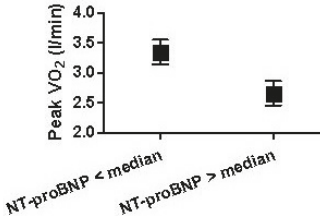


*Fig. Peak VO2 stratified by NT-proBNP*

## 6643 Soluble ST2 is associated with outcome in patients with heart failure and anaemia: results from the RED-HF study

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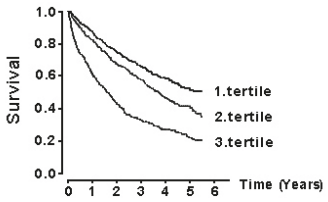
**On behalf:** On behalf of the RED-HF Committees and Investigators

**Background:** The soluble ST2 receptor (sST2) is associated with outcome in patients with HF, but the value of repeated measurements of sST2 is not established.

**Methods:** We measured sST2 in plasma at baseline and after 6 months in 1582 patients enrolled in the Reduction of Events by Darbepoetin Alfa (RED-HF) trial. We explored the association between baseline tertiles of sST2 and the primary composite outcome of time to death from any cause or first hospital admission for worsening HF as well as time to all-cause death in multivariable Cox proportional hazard models. We also assessed the prognostic value of a change in sST2 levels with time.

**Results:** At baseline, the median sST2 plasma concentration was 38 (IQR 28–52) ng/ml. In univariate analyses, sST2 was a strong predictor of the primary outcome (hazard ratio [HR] for third tertile as opposed to first tertile: 2.67; p<0.001) (Figure) and all-cause death (HR 2.59; p<0.001). Its predictive value was attenuated, but remained significant for the primary endpoint (HR 1.46; p<0.001) and all cause death (HR 1.42; p<0.001) after adjusting for clinical variables, CRP, TnT, and NT-proBNP. There was no interaction between darbepoetin treatment and sST2 levels with regard to these endpoints. A stable sST2 level was associated with a significantly lower risk of reaching the primary endpoint and all-cause death compared with an increase in ST2 levels ≥15 % (HR 1.54 and 1.51, respectively) or a decrease in ST2 levels ≥15 % (HR 1.44 and 1.31, respectively). These results remained significant after adjustment for clinical variables and CRP, TnT and NT-proBNP (all p-values <0.001).

**Conclusion:** sST2 is a strong, independent predictor of outcome in patients with HF and anaemia. A stable level of sST2 seems to be associated with a favourable outcome.




*Primary endpoint by tertiles of ST2*

## P3489 Peak systolic velocity by tissue Doppler detects changes in myocardial contraction related to inotropic effects of levosimendan in patients with acute heart failure complicating myocardial infarction

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**Purpose:** Peak systolic velocity (PSV) by tissue Doppler imaging (TDI) has been proposed for serial non-invasive assessment of myocardial contraction in patients receiving inotropic therapy due to its relative load- and heart rate-independent properties. However, this hypothesis has so far not been tested in a clinical setting. We therefore examined the ability of PSV by TDI to detect changes in contraction in a substudy of the LEvosimendan in Acute heart Failure following myocardial infarction (LEAF) trial (NCT00324766).

**Methods:** A total of 61 patients developing clinical signs of heart failure within 48 hours after a primary percutaneous coronary intervention-treated ST-elevation myocardial infarction (including cardiogenic shock), were randomized double-blind to a 25 hours infusion of levosimendan or placebo. Levosimendan is an inodilator where the effects, due to active metabolites with very long half-lives, last for several days after end of the infusion. Echocardiography was performed before infusion (baseline), on day 1, on day 5 and after 6 weeks. PSV (mean of septal, lateral, anterior and posterior mitral annular peak systolic velocity) measured by tissue velocity imaging, and global longitudinal strain (GLS) of the left ventricle measured by speckle tracking were analyzed at all time-points.

**Results:** There was significantly larger improvement in PSV from baseline to day 1 (P=0.007) and day 5 (P<0.001) in the levosimendan group compared to placebo (levosimendan 4.70 cm/s ± 1.34 to 5.74 cm/s ± 1.47 (day 1) and 6.07 cm/s ± 1.47 (day 5) vs. placebo 4.77 cm/s ± 1.02 to 5.08 cm/s ± 1.35 (day 1) and 4.90 cm/s ± 1.26 (day 5)). No significant differences were found in PSV after 6 weeks or in GLS at any time-point between the treatment groups. We have previously shown that levosimendan improved left ventricular function measured as changes in wall motion score index (WMSI) from baseline to day 5 compared to placebo (p=0.031, primary endpoint of the LEAF trial), however no significant changes in WMSI were found on day 1 or after 6 weeks between the treatment groups.

**Conclusion:** PSV by TDI seems to be a more sensitive echocardiographic method to detect changes in myocardial contraction during inotropic stimulation with levosimendan than WMSI and GLS. These results suggest that PSV by TDI can be used for assessment of changes in contraction in patients hospitalized for acute heart failure receiving inotropic therapy.

## P1791 Diastolic but not systolic dysfunction is prevalent in long term breast cancer survivors

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**Background:** Multimodal adjuvant treatment of loco-regionally advanced (stage II and III) breast cancer (BC) may lead to cardiotoxicity due to irradiation and chemotherapy. However, the magnitude of cardiac dysfunction and its risk factors in long term BC survivors are unknown.

**Purpose:** To evaluate the prevalence and the risk factors for left ventricular (LV) dysfunction in long term BC survivors by echocardiography compared to healthy controls.

**Methods:** 216 female patients were evaluated with healthy controls 1:1 matched for age, gender, weight and systolic blood pressure. Systolic dysfunction was defined by ejection fraction <55 % (Simpson's biplane) or fractional shortening <27 %. Subclinical systolic dysfunction was identified by peak systolic mitral annular velocity in septal and lateral position (<6.0 and 6.7 cm/s respectively) using pulsed wave tissue Doppler (TDI) and by global longitudinal strain <18 % using 2 dimensional speckle tracking echocardiography (2D STE). Diastolic dysfunction (DD) was defined by early diastolic velocity (e') of the septal <8 cm/s or the lateral mitral annulus <10 cm/s by pulsed wave TDI. Estimation of LV filling pressures was performed from parameters of pulsed wave Doppler measures of mitral inflow (E, Edt, E/A ratio) and pulmonary venous flow (S/D ratio, Ar-A duration), left atrial volume and E/e' ratio.

**Results:** Mean age was 62.0±7.8 years with mean follow-up time since diagnosis of 12.0±1.4 years. 112 (52 %) was treated for left sided BC. 129 (60 %) received anthracyclines with the same cumulative dose of 360 mg/m$^2$ epirubicin. None were treated with trastuzumab. Irradiation was performed after manual dose planning in 115 (53 %) and CT based dose planning in 101 (47 %). There was no difference in prevalence of systolic dysfunction between patients and controls even using TDI peak systolic velocities or 2D STE. However DD occurred in 142 (66 %) compared to 78 (36 %) in controls (odds ratio (OR) 3.5 (2.9–5.0), p<0.001). 8 % of patients with DD had elevated filling pressure compared to 3 % in controls. Age and manual dose planning of irradiation were significantly associated with DD (OR 1.2 (1.1–1.3), p<0.001 and 2.5 (1.1–5.6), p=0.03 respectively) while anthracycline therapy showed association of borderline significance

(OR 2.4 (1.1–5.8), p=0.06) in multivariate logistic modelling.

**Conclusion:** LV DD is markedly more frequent in long term BC survivors than in controls particularly after manually planned radiotherapy and anthracycline containing chemotherapy. Parameters of systolic function did not discriminate between patients and controls.

## P1147 Renal sympathetic denervation in patients with treatment resistant hypertension: a meta-analysis of randomized controlled trials

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**On behalf:** ***European Network COordinating research on Renal Denervation (ENCOReD)***

**Purpose:** Renal sympathetic denervation (RDN) is proposed as a new treatment modality in patients with resistant hypertension (TRH). However, the evidence that RDN effectively lowers BP is contradictory. This meta-analysis investigated the current effectiveness of RDN for TRH.

**Methods:** We performed a systematic review and meta-analysis of the randomized controlled trials (RCT) that reported office and ambulatory systolic BP in RDN and control (maintenance or reinforcement of medical therapy) groups at 6 months of follow-up in patients with TRH by searching medical literature databases. Pooled effect sizes were derived, using a random-effects model.

**Results:** Five RCTs were identified that randomized 867 patients and used the single-electrode Symplicity catheter. In the pooled analysis, RDN was associated with a non-significant decrease in office systolic BP (weighted mean difference (WMD): - 4.21 mmHg, 95 % CI: −17.12 to 8.69, p=0.52), or in 24-h ambulatory systolic BP (WMD: −1.94 mmHg, 95 % CI: −6.05 to 2.17 mmHg, p=0.36) compared to control at 6 months. The proportion of patients who normalized their 24-h ambulatory systolic BP in RDN group (reported in 3 RCTs) was 27.5 % compared to 26.5 % in control group at 6 months. There was significant heterogeneity among included studies with large between-patients variability in the BP response to RDN.

**Conclusions:** The overall BP lowering effect of RDN with the Symplicity catheter does not significantly differ from that of medical treatment in patients with TRH. Future research should identify the characteristics of patients who may respond to RDN, optimal catheter, effective ablation dose and biological measures that could confirm that RDN does occur. Accordingly, RDN should not be considered as a routine treatment modality of TRH.

See table

| Characteristic | SYMPLICITY HTN-2 | OSLO RDN | SYMPLICITY HTN-3 | PRAGUE 15 | DENER HTN |
|---|---|---|---|---|---|
| No. of patients, Control / RDN | 54 / 52 | 10 / 9 | 171 / 364 | 54 / 52 | 53 / 48 |
| No. of drugs, baseline | 5.3 / 5.2 | 5.0 / 5.1 | 5.2 / 5.1 | 5.4 / 5.1 | 3.0 / 3.0 |
| No. of drugs, at 6 months | - / - | 5.2 / 4.9 | 5.2 / 5.0 | 5.6 / 5.0 | 5.4 / 5.3 |
| Office SBP, baseline | 178 / 178 | 160 / 156 | 180 / 180 | 155 / 159 | 156 / 160 |
| Office SBP, Δ at 6 months | +1 / −32 | −18 / −8 | −11.7 / −14.1 | −14.3 / −12.4 | −9.5 / −15.1 |
| 24-h SBP, baseline | - / - | 149 / 151 | 160 / 159 | 147 / 149 | 147 / 152 |
| 24-h SBP, Δ at 6 months | −3 / −11 | −21 / −10 | −4.8 / −6.7 | −8.1 / −8.6 | −9.5 / −15.4 |

## 1325 Epileptic seizures are frequent in patients with long QT syndrome type 2

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**Background:** The long QT-syndrome (LQTS) is caused by cardiac ion channel dysfunction predisposing to ventricular arrhythmias. Cerebral ion channel dysfunction may lead to idiopathic epilepsies. Essential ion channels are co-expressed in the heart and in the brain. Accordingly, current theories suggest that some cases of syncopes in patients with LQTS may in fact be caused by a coexisting cerebral channelopathy (i.e. epilepsy). Case reports and small-scale studies have indicated that LQTS patients with LQTS type 2 (LQT2) have an increased prevalence of cerebral affection compared to other LQTS subclasses.

**Purpose:** We aimed to describe the semiology of loss of consciousness in LQT2 patients. In addition, we evaluated for alterations in the electroencephalograms (EEG) of these patients.

**Methods:** We studied 15 patients (age: 43 (21–72), 12 women) with a genotyped diagnosis of LQT2. We performed a

standardized medical history with emphasis on the semiology of previous syncopes and a clinical neurological examination. A 1hr 64-channel awake EEG has so far been analysed in 9 patients. The EEGs were assessed visually and the frequency of abnormalities was recorded.

**Results:** Of the 15 patients, 11 (73 %) had experienced syncopes, of which 6 (55 %) had experienced tonic-clonic activity or spells and urine incontinence. One of the 11 (9 %) had experienced urine incontinence in absence of tonic-clonic activity or spells. Two patients (13 %) had been diagnosed with epilepsy and received anti-epileptic medication prior to their LQTS diagnosis.

EEGs showed an increased frequency of theta activity fronto-centrally in 7 of the 9 examined patients, including one patient with confirmed epileptic activity.

**Conclusion:** Syncopes in LQT2 patients were frequently associated with tonic-clonic activity, spells and urine incontinence, which could also be consistent with epilepsy. In addition, 2/15 had co-existing diagnoses of epilepsy and LQT2. The majority of the EEGs showed minor to moderate changes with intermittent theta activity. Our study underlines the difficulties in differentiating between cardiac syncopes and epileptic seizures clinically. However, our results may also indicate overlapping causative mechanisms in the two conditions.

## P5592 Prevalence of abnormal glucose regulation 7 years after a ST-elevation myocardial infarction in patients without known diabetes at baseline: results of repeated oral glucose tolerance testing

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**Background:** Screening for undetected type-2 diabetes (DM) in patients with myocardial infarction, including an oral glucose tolerance test (OGTT), has been recommended in current guidelines.

**Purpose:** The aims of the present study were: 1) to study the long-term progression of glucometabolic abnormalities in ST-elevation myocardial infarction (STEMI) patients without known DM and 2) to evaluate the use of OGTT in STEMI patients in order to identify patients at risk of developing DM.

**Methods:** Stable patients with a primary PCI treated STEMI without known DM, age <85 years or s-creatinine <200 umol/l, were included. A standardised OGTT was performed in 140 STEMI patients during the acute phase (baseline, 17 h after PCI) and repeated after 3 months and 7 years follow-up and patients were classified according to the OGTT results.

**Results:** OGTT 7 years after STEMI: 16 (11.5 %), 25 (18 %) and 11 (8 %) of the patients had criteria for DM, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), respectively. The prevalence of abnormal glucose regulation (DM + IGT+ IFG) was 37, 22 and 37 % at baseline, 3 months and 7 years, respectively, however, about 50 % of the patients were reclassified during follow-up. Four patients fulfilled the DM criteria at all time-points, additionally, 12 patients were classified with DM at 7 years.

OGTT at baseline vs. 7 years: Of the 13 patients diagnosed with DM at baseline, only 4 had criteria for DM after 7 years and only 6 of the 34 patients classified with IGT at baseline fulfilled criteria for DM.

OGTT at 3 months vs. 7 years: All 5 patients classified with DM after 3 months remained in this category after 7 years. Of the 17 patients classified with IGT at 3 months only 2 patients fulfilled criteria for DM 7 years later and 5 of these patients were reclassified as having normal glucose tolerance. Five of the 109 patients with normal glucose tolerance at 3 months were classified with DM after 7 years.

**Conclusions:** Results of a very early OGTT during the acute STEMI do not provide reliable information about long-term glucometabolic abnormalities and should not be recommended. A DM diagnosis 3 month after index STEMI, was confirmed in all patients 7 years later. On the contrary, only 2 of 17 patients diagnosed with IGT at 3 months developed DM during 7 years follow-up. Follow up of STEMI patients without known diabetes revealed that relatively few patients developed DM during 7 years follow-up. Results from early testing of STEMI patients with OGTT should be interpreted with caution.

## P418 Lamin A/C mutation prevalence and cardiac penetrance in Norway

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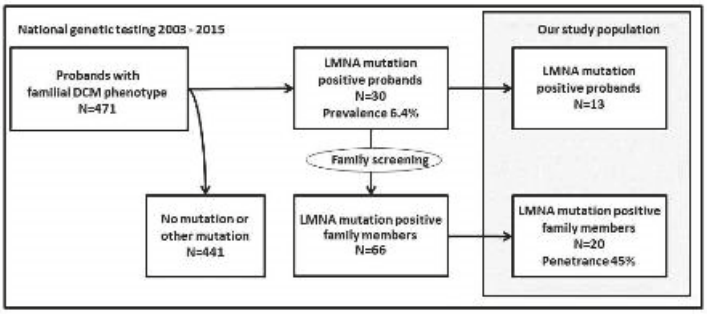
**Background:** Lamin A/C gene (LMNA) mutations are a cause of familial dilated cardiomyopathy (DCM) with higher incidence of ventricular




tachycardia (VT) compared to DCM of other etiology. Onset of cardiac symptoms is generally reported to about age 40 years.

**Purpose:** We explored the prevalence and penetrance of LMNA mutations among patients with familial DCM in Norway.

**Methods:** From 2003–2015, molecular testing of genes encoding LMNA, MYH7, MYBPC3, TNNT2, TNNI3, MYL2 and MYL3 has been a part of the diagnostic service in patients referred for familial DCM. The cardiac phenotype of LMNA mutation positive subjects was assessed by ECG, Holter and echocardiography and defined as atrioventricular (AV) block, atrial fibrillation/flutter (AF), ventricular arrhythmias or DCM.

**Results:** Of 471 unrelated DCM probands, 30 (6.4 %) had a LMNA mutation (Figure). Family screening diagnosed further 66 LMNA mutation positive family members. We followed 33 of the LMNA positive subjects at our center; age 35±16 years, 13 (40 %) probands, ejection fraction (EF) 51±11 %, 11 (33 %) with VT. All subjects >35 years (n=15) had a cardiac phenotype. In 20 asymptomatic LMNA mutation positive family members (age 29±17 years), examination revealed a cardiac phenotype in 9/20, giving a penetrance of 45 %. Four (20 %) family members had AF, 5 (25 %) had AV block, 3 (15 %) had non-sustained VT and 4 (20 %) had reduced EF <50 %.

**Conclusions:** Prevalence of LMNA mutations was 6.4 % of familial DCM in Norway. Cardiac penetrance was higher than expected in young asymptomatic LMNA mutation positive family members below 40 years of age, with frequent AV block, arrhythmias and reduced ventricular function, highlighting the importance of early family genetic screening and cardiologic follow-up.

## P5601 Atrial fibrillation is associated with stroke in veteran endurance athletes

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**Background:** Atrial fibrillation (AF) is associated with a five-fold increased risk of stroke in the general population, but AF in absence of co-morbid conditions (lone AF) has been suggested to have a favourable prognosis. Prolonged endurance exercise seems to increase the risk of AF, but stroke risk has previously not been investigated in veteran endurance athletes with AF.

**Purpose:** To study the associations between AF, lone AF and stroke among Norwegian veteran cross-country skiers.

**Methods:** All 3114 male veteran cross-country skiers aged ≥40 years who completed the 54-kilometre Birkebeiner race in 1999 were invited to this cohort study. During 2012, cross-sectional data on AF, stroke, co-morbid conditions, medication use, history of exercise, socioeconomic status and other possible confounding factors were collected by questionnaires. AF diagnoses were confirmed during a review of medical records in individuals with self-reported AF, and if no evidence for relevant co-morbid conditions was found, AF was classified as lone.

**Results:** In total, 2081 male veteran skiers aged 53–74 years were included in this analysis (mean age 62.8 years). The prevalence of self-reported AF was 13 %. The prevalence of stroke was 11 % in skiers with confirmed AF (n=112), compared to 4 % in skiers without AF (p<0.01). After adjustment for age, body mass index, socioeconomic status, concomitant heart disease, hypertension, diabetes mellitus, lipid-lowering treatment, smoking and exercise, AF was associated with an adjusted odds ratio (aOR) for stroke of 2.21 (95 % confidence interval (CI) 1.00–4.93). Also among skiers with lone AF (n=70), the prevalence of stroke was 11 % and lone AF was associated with an aOR for stroke of 2.89 (CI 1.15–7.25). Out of 71 veteran skiers with AF and at least one additional risk factor (corresponding to a CHA2DS2-VASc Score ≥1), 70 % used oral anticoagulation (OAC) treatment, while 13 % were treated with acetylsalisylic acid.

**Conclusions:** This study demonstrates a high prevalence of stroke among veteran endurance athletes with AF. AF was associated with a two to three-fold increased risk of stroke, also in

skiers without co-morbid conditions. Our results challenge the favourable prognosis suggested for lone AF and support that veteran athletes with AF should be treated with OAC in line with general guidelines.

## P6297 Wasted myocardial work in left ventricular dyssynchrony: a preliminary report of a novel principle to predict response to cardiac resynchronization therapy

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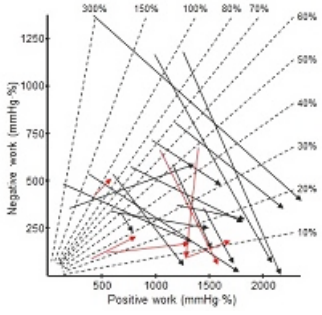
**Background and aim:** Cardiac resynchronisation therapy (CRT) in heart failure is limited by a large fraction of non-responders. We explore if degree of wasted left ventricular (LV) work identifies responders to CRT.

**Methods:** Twenty one patients who received CRT according to current guidelines were studied before and after an average of 8±2 months. By definition, segments which shorten in systole perform positive work, whereas segments which lengthen do negative work. Work was calculated from non-invasive LV pressure and strain by speckle tracking echocardiography. For each myocardial segment and for the entire LV wasted work fraction (WWF) was calculated as negative work in percentage of positive work. LV wall motion score index (WMSI) was assessed by echocardiography. Response to CRT was defined as ≥15 % reduction in LV end-systolic volume (ESV).

**Results:** Responder rate to CRT was 71 %. In responders WWF for septum was 117±102 %, indicating more negative than positive work, and decreased to 14±12 % (p<0.01) with CRT. In the LV free wall WWF was 19±16 % and showed no significant change. Global WWF decreased from 36±21 to 19±10 % (p<0.01) with CRT. In multiple linear regression analysis septal WWF and WMSI were the only significant predictors of ESV reduction (septal WWF: β=0.14, p=0.01; WMSI: β=1.25, p=0.03). Septal WWF together with WMSI showed AUC=0.86 (CI 0.71–1.0) for CRT response prediction.




*Fig, 1 Individual data – percentage of wasted work is indicated in dashed lines. CRT responders (black arrows) showed a shift to more positive work with drop in the WWF. The non-responders (red arrows) showed no consistent shift.*

**Conclusions:** In this pilot study septal WWF together with WMSI was a strong predictor of response to CRT. This novel principle should be studied in future larger studies.

## 4048 Preserved exercise capacity in lymphoma survivors with asymptomatic left ventricular systolic dysfunction

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**Background:** Lymphoma survivors (LS) have increased cardiovascular disease burden because of cardiotoxic treatment, and overt heart failure (HF) is well recognised and thoroughly studied. However, little is known about asymptomatic left ventricular systolic dysfunction (ALVSD).

**Purpose:** To estimate the prevalence of ALVSD in LS and to assess if ALVSD involves a limitation in exercise capacity compared with LS without ALVSD.

**Methods:** All LS aged ≥18 years at treatment with autologous hematopoietic stem cell transplantation (auto-HCT) in Norway from 1987–2008 were eligible. Participants underwent a medical examination including echocardiography (Vivid 7 or E9, GE Vingmed Norway) and cardiopulmonary exercise testing (CPET). LS with HF were excluded. We defined LVSD as global longitudinal strain (GLS) >-17 %. Bicycle-CPET was performed as recommended, and the peak results expressed as a percentage of the age-, gender- and weight-adjusted reference values (Hansen-Wasserman).

**Results:** In total, 274 LS (69 % of all eligible) participated and 29 (10.6 %) were excluded due to HF. The feasibility of GLS was 85 % and consequently 207 asymptomatic LS are included in this report. We observed ALVSD in 23.7 % (95 % CI, 17.9–29.5) and patient demographics are shown in the table. The peak oxygen uptake (peak VO2) in LS with and without ALVSD was 26.6±7.7 and 28.0±7.5 ml/kg/min (p=0.30), respectively, corresponding to an age-, gender- and weight-adjusted peak VO2 reference value of 102±20 and 106±21 % (p=0.25), respectively.

**Conclusions:** ALVSD was prevalent in LS after auto-HCT. However, exercise capacity was preserved and comparable to LS without ALVSD.

*Patient demographics*

| Variables | LS with ALVSD | LS without ALVSD | p-value |
|---|---|---|---|
| | (n=49) | (n=158) | |
| Age at survey (yrs) | 57 (11) | 54 (12) | ns |
| Observation time since lymphoma diagnosis (yrs) | 14 (7) | 12 (6) | ns |
| Male gender (%) | 71 | 59 | ns |
| Heart rate (beats pr min) | 69 (8) | 64 (10) | <0.01 |
| Systolic blood pressure (mmHg) | 136 (19) | 130 (19) | 0.03 |
| LV ejection fraction (%) | 52 (5) | 57 (4) | <0.01 |
| LV inner dimension (mm) | 51.3 (5.1) | 49.7 (4.6) | 0.05 |
| Doxorubicin (mg/m$^2$) | 330 (132) | 300 (120) | ns |
| Radiotherapy involving the heart (%) | 30 | 21 | ns |

*P-values by independant Student's t-test.*

## P6341 The heparan sulphate proteoglycan glypican-6 is increased in experimental and clinical heart failure and might play a role in cardiac fibrosis through PDGF-BB signalling

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**Purpose:** Cardiac remodelling due to chronic pressure overload is one of the leading causes of heart failure. Understanding the underlying molecular mechanisms is important for development of new therapies. Proteoglycans are glycosylated proteins that, despite playing important roles in connective tissues and wound healing, have received little attention in cardiac remodelling.We have investigated regulation of the six-membered glypican (GPC1–6) family, evolutionary ancient heparan sulphate proteoglycans anchored to the extracellular part of cell membrane, in murine pressure overload in vivo, in biopsies from patients and in cardiac fibroblasts.

**Results:** Mice subjected to aortic banding (AB; n=88) showed elevated left ventricular (LV) mRNA of GPC6 during concentric hypertrophic remodelling (1 and 3 weeks of AB; 2.8- and 1.9-fold) and during dilated, end-stage heart failure (16 and 18 weeks of AB; 2.0- and 2.4-fold). Immunoblotting confirmed GPC6 protein upregulation. There were minor alterations in GPC1–4 mRNA, while GPC5 was not expressed in the LV. LV GPC6 mRNA was 1.8-fold higher in LV tissue from explanted hearts of patients with end-stage, dilated heart failure (NYHAIII-IV, n=18) than in controls (n=7), correlating negatively with LV ejection fraction. Interestingly, in the AB mouse model, GPC6 mRNA correlated positively to mRNA of the fibrosis markers collagen I and III. In neonatal rat cardiac cells in vitro, GPC6 mRNA was 3.8-fold higher in fibroblasts than in myocytes, indicating fibroblasts to be the main source of cardiac GPC6. Adult mouse cardiac fibroblasts in vitro showed increased GPC6 mRNA during myofibroblast differentiation, correlating positively with the signature myofibroblast gene, α-smooth muscle actin (α-SMA). In HEK293 cells, GPC6 overexpression enhanced ERK1/2 and AKT phosphorylation, i.e. activation, induced by the platelet-derived growth factor B (PDGF-BB), suggesting that GPC6 acts as a co-receptor for PDGF-BB-mediated signalling. Supporting this, overexpression of GPC6 in NIH3T3 fibroblasts elevated α-SMA mRNA upon PDGF-BB stimulation.

**Conclusion:** Our data suggest that the cell membrane-localized proteoglycan GPC6 is involved in experimental and clinical heart failure progression, likely working as a co-receptor modulating pro-fibrotic PDGF-BB signalling in cardiac fibroblasts.

## 4900 Probability of echocardiographic left ventricular hypertrophy regression during antihypertensive treatment in a real-word context: The Campania Salute Network

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**Background:** Regression of hypertensive left ventricular (LV) hypertrophy (LVH) is a successful goal in clinical trials, but less in known of LVH regression in a real-world context.

**Methods:** We identified 2234 hypertensive patients (mean age 57±10 years, 48 % women) free of prevalent cardiovascular (CV) disease, with baseline LVH (LV mass index (LVMi) ≥47 g/m$^{2.7}$ in women and ≥50 g/m$^{2.7}$ in men) and at least 24 months follow-up (80±49 months) from the Campania Salute Registry. The characteristics associated with LVH regression was assessed,

also considering number and type of antihypertensive medications.

**Results:** 299 patients (13 %) exhibited regression of LVH during follow-up (reduction in LVMi was 13±8 % vs. 2±10 % in patients with stable LVH, p<0.001). Patients with LVH regression were younger, more likely to be males, less likely to have diabetes or obesity and with a shorter history of hypertension (all p≤0.001). Average systolic and diastolic blood pressure (BP) during follow-up, baseline BMI, carotid IMT and LVMi were lower (all p<0.01), while lipid profile, renal function and type of antihypertensive medication did not differ. In multivariate analysis, significant independent predictors of LVH regression were: younger age, male gender, lower systolic BP during follow-up and lower baseline LVMi and BMI (all p≤0.004) (Table), after adjustment for duration of hypertension, diastolic BP during follow-up, fasting plasma glucose, renal function, carotid IMT, number of antihypertensive drugs and follow-up time (all p>0.1).

**Conclusion:** In a real-world context, LVH regression occurs in 13 % of treated hypertensive patients, and is more likely in younger and male subjects, with better BP control during follow-up and more favorable CV risk profile. In particularly, obesity and more severe LVH at baseline reduce the chance of hypertensive LVH regression independent of BP control.

*Table 1. Significant predictors of LVH regression in treated hypertensive subjects*

| Variables | OR | 95 %CI | p-value |
|---|---|---|---|
| Age (years) | 0.97 | 0.96–0.99 | 0.001 |
| Male gender | 2.79 | 2.08–3.75 | <0.001 |
| Average systolic BP during follow-up (mmHg) | 0.98 | 0.97–0.99 | 0.004 |
| LVMi (g/m$^{2.7}$) | 0.85 | 0.82–0.88 | <0.001 |
| BMI (kg/m$^2$) | 0.91 | 0.88–0.95 | <0.001 |

## P6551 YKL-40 In chronic heart failure: Analysis from the controlled rosuvastatin multinational trial in heart failure (CORONA)

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**Background:** The inflammatory biomarker YKL-40 is associated with the presence and severity of coronary artery disease and may predict adverse outcome. We hypothesized that circulating YKL-40 can give prognostic information in patients with ischemic heart failure (HF) and identify a subgroup of patients who may benefit from statin therapy.

**Methods:** The association between serum levels of YKL-40 and the primary end point (cardiovascular [CV] death, nonfatal myocardial infarction, nonfatal stroke), all-cause mortality, CV death, the composite of all-cause mortality/hospitalization for worsening of HF or the coronary end point was evaluated in 1344 patients aged >60 years with ischemic systolic HF in a subset of patients from the Controlled Rosuvastatin Multinational Trial in HF (CORONA) population (n=5011), randomly assigned to rosuvastatin 10 mg or placebo.

**Results:** Serum levels of YKL-40 were associated with outcome in univariate analysis, but added no predictive information after full multivariable adjustment including hs-CRP and NT-proBNP. Statin treatment moderately reduced YKL-40 levels, whereas an increase was observed with placebo (difference in change between the groups p=0.002). A significant interaction between baseline YKL-40 and rosuvastatin on the primary endpoint (p=0.008) and CV death (P=0.027) was observed. Thus, whereas rosuvastatin had no effect in those with intermediate or high YKL-40 levels, primary endpoint and CV death were significantly reduced by rosuvastatin in tertile 1 also after full adjustment (primary outcome, HR 0.50 [0.30–0.82] p=0.006; CV death, HR 0.54 [0.30–0.97] p=0.040).

**Conclusions:** Circulating levels of YKL-40 were of limited predictive value in patients with chronic ischemic systolic HF. However, a beneficial modification of outcome was observed with statin therapy in patients with low YKL-40 levels.

## P4754 Left bundle branch block and resynchronisation therapy have major effects on right ventricular work load

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**Background:** Left bundle branch block (LBBB) results in abnormal motion of the septum and reduces left ventricular (LV) stroke work. Little is known about the effect of LBBB on right ventricular (RV) work and how this is modified by cardiac resynchronisation therapy (CRT).

**Purpose:** To determine how LBBB and CRT modifies RV work.

**Methods:** In 8 anaesthetised dogs, LBBB was induced by radiofrequency ablation, and CRT was applied by pacing the septum and the LV lateral wall. Pressures were measured by micromanometers. LV and RV short-axis diameters and septal and free wall longitudinal segment lengths were measured by sonomicrometry enabling estimation of work as the area of pressure-dimension loops.

**Results:** LBBB caused marked septal preejection shortening with subsequent rebound stretch (Arrow,Fig.A). Therefore, septal longitudinal work was reduced from 97±49 to 7±60 mmHg*mm (p<0.01). This was accompanied by an increase of work in the LV lateral wall from 126±97 to 198±113 mmHg*mm, p<0.01, but LV short-axis work decreased (Fig.B). In the RV, LBBB caused opposite changes with preejection lengthening of the RV short-axis diameter, and an increase in RV short-axis work. However, in the RV free wall LBBB caused a decrease in longitudinal work from 34±16 to 25±16 mmHg*mm, (p<0.05). CRT essentially normalized the abnormal septal contraction patterns and restored work in both ventricles (Fig.B). LV and RV dP/dtmax were increased by CRT (p<0.05).

**Conclusions:** Induction of LBBB caused opposite effects on RV and LV short-axis work due to altered septal motion. There were compensatory changes in work in the free wall of both ventricles. CRT restored LV work, but reduced RV short-axis work. It should be explored if the marked changes in RV work have impact on the effect of CRT in patients with RV failure.

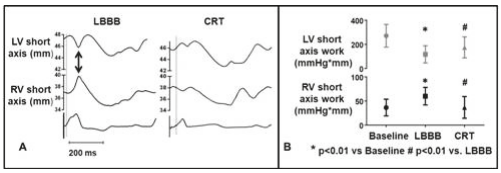


*Figure 1. A. Short-axis diameters; B. Short axis work*

## P422 Circulating levels of soluble IL-6 receptor in patients with ST-elevation myocardial infarction are associated with later major adverse cardiac events

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**Purpose:** The novel biomarkers soluble interleukin-6 receptor (sIL-6R) and soluble glycoprotein 130 (sgp130), known to be important in the IL-6 transsignalling pathway, are sparsely studied in patients with ST-elevation myocardial infarction (STEMI). The aim of the present study was to investigate the association between sIL-6R and sgp130 measured during the acute phase of STEMI and later first major adverse cardiovascular events (MACE).

**Methods:** Circulating levels of IL-6, sgp130, sIL-6R and CRP were measured in serum from 991 STEMI patients treated with primary PCI. Blood was collected the morning after admission at a median of 18 hours after PCI. MACE, defined as death, myocardial infarction, stroke, unscheduled revascularisation or rehospitalisation for heart failure were recorded at a median follow-up time of 4 years by telephone and cross checked with hospital records. Cox regression analysis were used to estimate hazards ratios (HR) with 95 % confidence intervals for 4th quartile vs. 1st quartile of each biomarker.

**Results:** The number of MACE was 201 (20.3 %). The highest levels defined as 4th quartile of sgp130, sIL-6R, IL-6 and CRP, were >260 ng/mL, >47.8 ng/mL, >30.1 pg/ml and >31.5 mg/L, respectively. The 4th quartile of sIL-6R was significantly related to MACE with a HR of 1.73 (1.08, 2.76), after adjustment for age, gender, hypertension, previous cardiovascular disease, diabetes, peak troponin T, proNT-BNP, admission glucose and ejection fraction. The 4th quartile of sgp130 was related to MACE in univariate analysis (HR 1.88 (1.26,2.80), p=0.002), but not after relevant adjustments. IL-6 and CRP were not associated with MACE in multi-variate analyses.

**Conclusion:** The results show that high levels of sIL-6R measured in the acute phase of STEMI are associated with later major adverse cardiovascular events.

## P512 Maximal left ventricular pressure change analyzed in a time domain might reveal the missing link between electrical dyssynchrony and left ventricular contractility in resynchronization therapy

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**Introduction:** In heart failure patients with left bundle branch block, biventricular pacing (BIVP) decreases electrical dyssynchrony of the left ventricle to a larger extent than left ventricular pacing (LVP) only. However, this decrease has not been shown to translate into improved ventricular performance compared to LVP.

**Purpose:** In this study we explored the acute differences between LVP and BIVP with regards to the preload dependent peak positive time derivate of left ventricular pressure (dP/dtmax), and the preload independent measurement of time dependent cardiac contractility; time to dP/dtmax (Td).

**Methods:** Twenty four patients underwent CRT implant during continuous LV pressure registration. Sequential dual chamber right ventricular pacing (RVP), LVP and BIVP were performed at a paced cycle length of 813±20ms, 10 % above the intrinsic heart rate, for one minute before dP/dtmax measurements were encountered. The paced AV-delay was set (126±4ms) lower than intrinsic AV delay (283±10ms) to avoid fusion with conduction through the right bundle. Td during RVP, LVP and BIVP was defined as the time from pacemaker stimuli to dP/dtmax. All data were pooled for linear regression and mixed models analyses (mean±SEM).

**Results:** DP/dtmax during RVP was significantly lower ($p<0.01$) than with both LVP and BIVP, but with no difference between the latter (833±42 mmHg/s vs 961±45 mmHg/s vs 952±48 mmHg/s). Td was negatively correlated with dP/dtmax ($R=0.50$, $p<0.01$) and positively correlated with paced cardiac cycle length ($R=0.25$, $P=0.03$). Td with BIVP was shorter than with LVP and RVP (159±4ms vs 177±5ms vs 184±5ms), ($p=0.01$). This finding was independent of correction for both paced cycle length and dP/dtmax.

**Conclusion:** There was no difference in dP/dtmax between LVP and BIVP. However, the time to dP/dtmax, Td, was significantly shorter with BIVP than with LVP. This suggests that less electrical dyssynchrony translates into a shorter Td, and hence improved contractility despite similar dP/dtmax. Td might be a key factor that links the electrical dyssynchrony to contractility.

## 4959 Clinical profile and predictors of arrhythmia-related symptoms in scandinavian arrhythmogenic right ventricular cardiomyopathy patients

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**Purpose:** Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically heterogeneous disease with largely unpredictable course. Prediction of prognosis and risk stratification in regard to sudden cardiac death (SCD) in patients with ARVC remains a challenging task. We aimed to assess clinical predictors of arrhythmia-related symptoms in ARVC patients enrolled in the Nordic ARVC registry.

**Methods:** Patients with definite ARVC by 2010 Task Force (TF2010) criteria recruited at 8 sites in Denmark, Norway and Sweden were included in the cross-sectional analysis. Patients were defined as symptomatic based on the occurrence of syncope, documented ventricular tachycardia (VT/VF), appropriate implantable cardioverter-defibrillator (ICD) therapy or aborted cardiac arrest (ACA). Demographical data and clinical characteristics, reflected in the TF2010 ARVC diagnostic criteria, as well as gender, genotyping results and extended repolarization abnormality defined as T-wave inversion in inferior limb leads were assessed for prediction of symptoms using multivariable logistic regression analysis. Patients were followed-up for a median of 8 (IQR 4–12) years.

**Results:** The study population included 243 subjects from 181 families (age 48±17 years, 64 % men). Genetic cascade screening was initiated in 130, and revealed disease-causing variant in 61 % of probands and PKP2 was the most commonly affected gene (66 %) followed by DSG2 (23 %). No arrhythmia-related symptoms were observed in 66 patients while 22 survived cardiac arrest, 35 had syncope and 120 had documented VT/VF. Median age at first symptom was 38 (IQR 27–49) years. ICD was implanted in 170 patients, of whom 106 had appropriate ICD therapies for VT/VF. ACA was the first symptom in 11 % of symptomatic patients. In the multivariate analysis, arrhythmia-related

symptoms were associated with male gender (OR 3.6, 95 % CI 1.56–8.24, p=0.003), the presence of disease-causing PKP2 variant (OR 2.46 95 % CI 1.07–5.64, p=0.034), the presence of epsilon-wave (OR 8.26 95 % CI 1.76–38.70, p=0.007) and T-wave inversion in lead aVF (OR 6.20 95 % CI 2.07–18.49, p=0.001).

**Conclusions:** In the Scandinavian cohort of patients with ARVC, male gender, presence of PKP2 mutations and advanced depolarisation and repolarization abnormalities independently predicted arrhythmia-related symptoms. T-wave inversions in inferior limb leads are not covered by current risk stratification schemes in ARVC and should be considered as an additional arrhythmia marker.

## 2032 Stroke and bleeding outcomes with apixaban versus warfarin in patients with high creatinine, low body weight or high age receiving standard dose apixaban for stroke prevention in atrial fibrillation

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**Background:** In the ARISTOTLE trial comparing apixaban with warfarin in pts with AF, apixaban 2.5 mg was used in pts with 2 or more dose reduction (DR) criteria: age ≥80 years, creatinine ≥1.5 mg/dL, weight ≤60 kg. Pts assigned 2.5 mg of apixaban vs. warfarin (n=831) had similar reductions in stroke/SE and major bleeding to pts assigned 5.0 mg of apixaban vs. warfarin (n=17,370).

**Methods:** We compared pts assigned to apixaban 5.0 mg or warfarin, with 1 of 3 DR criteria with pts with 0 of 3 criteria. Stroke/SE and major bleeding rates, hazard ratios and 95 % CIs were evaluated, and interactions between treatment and the presence of 1 vs. 0 DR criteria were determined.

**Results:** Among pts assigned 5.0 mg of apixaban or warfarin, 4046 (23 %) had one DR criteria. These pts were older (77 vs. 68 years), lighter weight (86 vs. 70 kg), and had worse renal function (creatinine 1.00 vs. 1.07 mL/min) than pts with no DR criteria. Pts with one DR criteria had more stroke/SE and major bleeding but had similar benefits of apixaban vs. warfarin on stroke/SE (p=0.41) and major bleeding (p=0.65). Similar patterns were seen for individual DR criteria.

**Conclusion:** Pts with isolated advanced age (≥80 years), low body weight ≤60 kg), or renal dysfunction (Cr≥1.5 mg/dL) had slightly more stroke/SE and significantly more major bleeding but similar benefits with apixaban 5.0 mg BID compared with warfarin to pts with none of these characteristics. Apixaban 5.0 mg BID is a safe and efficacious dose for these pts.

See table

## 3065 Proximal titin A-band truncation causes dilated cardiomyopathy in response to increased afterload in mice

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*Table 1. Stroke/SE and major bleeding by DR criteria and apixaban vs. warfarin*

| Outcome | Subgroup | Apixaban | | Warfarin | | HR (95 % CI) |
|---|---|---|---|---|---|---|
| | | n | Events ( %/yr) | n | Events ( %/yr) | |
| Stroke/SE | 5.0 mg BID with 0 DR criteria | 6675 | 137 (1.10) | 6681 | 176 (1.42) | 0.77 (0.62–0.97) |
| | 5.0 mg BID with 1 DR criteria | 2032 | 64 (1.79) | 2014 | 69 (1.95) | 0.92 (0.65–1.29) |
| | 5.0 mg BID with age DR criteria | 452 | 14 (1.73) | 453 | 13 (1.60) | 1.08 (0.51–2.30) |
| | 5.0 mg BID with weight DR criteria | 733 | 27 (2.20) | 706 | 32 (2.65) | 0.82 (0.49–1.37) |
| | 5.0 mg BID with creatinine DR criteria | 847 | 23 (1.50) | 855 | 24 (1.58) | 0.95 (0.54–1.69) |
| Major bleeding | 5.0 mg BID with 0 DR criteria | 6658 | 204 (1.77) | 6658 | 279 (2.46) | 0.72 (0.60–0.86) |
| | 5.0 mg BID with 1 DR criteria | 2020 | 106 (3.31) | 2009 | 152 (4.94) | 0.67 (0.52–0.86) |
| | 5.0 mg BID with age DR criteria | 448 | 30 (4.18) | 451 | 40 (5.75) | 0.73 (0.46–1.18) |
| | 5.0 mg BID with weight DR criteria | 731 | 26 (2.28) | 704 | 44 (4.00) | 0.57 (0.35–0.93) |
| | 5.0 mg BID with creatinine DR criteria | 841 | 50 (3.70) | 854 | 68 (5.29) | 0.70 (0.49–1.01) |

**Purpose:** Approximately 20 % of dilated cardiomyopathy (DCM) patients carry heterozygous truncating mutations in the giant protein titin (TTNΔ). Titin spans the cardiomyocyte sarcomere from Z-disc to M-line and is important for assembly, contraction, relaxation and signaling. Truncating mutations are overrepresented in A-band. To understand disease mechanisms, we generated a mouse with titin A-band truncation (TTNΔA) and assessed cardiac morphology, function, and transcriptional profile.

**Results:** To generate TTNΔA mice we introduced lox-P sites flanking exons 276–277 and crossed with EIIa-Cre mice, causing frameshift and a premature stop codon in the proximal A-band. 28 heterozygous intercrosses produced 120 pups: none were homozygous TTNΔA (p=6*10-10). Genotyping (n=125) revealed homozygous embryos at E8.5-E10.5, with fetal demise at E10.5. Heterozygous male and female mice (age 6–60 weeks) were viable, fertile and not different from wildtype (WT) in appearance, activity, or echocardiographic phenotype. Digital PCR of RNA from TTNΔA hearts (n=3) showed mutant transcripts levels 0.4-fold that of WT allele, and gels and immunoblots detected no mutant titin protein. TTNΔA and WT mice (n=5–6 per study) were stressed for ten weeks by voluntary cage-wheel running and two weeks of isoproterenol infusion, evoking no difference in echocardiographic phenotypes. Compound TTNΔA/LMNA mutation mice showed no exacerbation of DCM compared to LMNA mice (LVIDd 4.02mm vs. 3.97mm, both p<0.05 vs. WT). By contrast, TTNΔA mice treated for two weeks of ANGII infusion showed hypertrophy with exacerbated diastolic dysfunction (longitudinal strain rate 12.3$s^{-1}$ vs. WT: 9.6$s^{-1}$, p<0.05) and 3.8-fold higher BNP mRNA. Thoracic aortic constriction (TAC) exacerbated DCM in TTNΔA: LVIDd at 1 week 3.75mm vs. 3.38mm in WT (p<0.05) and at 4 weeks 4.36mm vs. 3.77mm (p<0.05). TAC increased left atrial diameter, lung weight and BNP in TTNΔA vs. WT. RNAseq (n=3) analyses of TAC and ANGII treated TTNΔA vs. WT confirmed reduced TTN transcripts and showed differential expression (fold change >1.5/<0.67, p<0.001) of 1465 and 1434 transcripts. Pathway analyses implicated TGFβ as upstream regulator and identified the cardiotoxic categories hypertrophy, cell death, infarction, dilation and damage.

**Conclusions:** Transcripts encoding a titin A-band truncation are expressed but do not yield detectable mutant protein. Homozygous mice are embryonic lethal, while heterozygous mice show no overt cardiac phenotype without stress. Increased afterload induces DCM in titin A-band truncation mice and promotes expression of cardiotoxic pathways.