NORSKE ABSTRAKTER PRESENTERT I LOS ANGELES

18411 Dietary Intake of n-3 Long-Chain Polyunsaturated Fatty Acids, Diabetes Mellitus and Risk of Myocardial Infarction in Patients with Suspected Coronary Artery Disease

Ottar Nygård, Elin Strand, Eva R Pedersen, Univ of Bergen, Bergen, Norway; Marta Ebbing, Haukeland Univ Hosp, Bergen, Norway; Gard Svingen, Univ of Bergen, Bergen, Norway; Hall Schartum-Hansen, Haukeland Univ Hosp, Bergen, Norway; Bodil Bjørndal, Univ of Bergen, Bergen, Norway; Reinhard Seifert, Haukeland Univ Hosp, Bergen, Norway; Klaus Mayer, Univ of Bergen, Bergen, Norway; Dennis Wt Nilsen, Stavanger Univ Hosp, Stavanger, Norway; Jan E Nordrehaug, Univ of Bergen, Bergen, Norway

Background: A high intake of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) is usually recommended in secondary prevention of coronary heart disease, particularly in patients with high triglyceride levels. Furthermore, a beneficial effect has been observed in patients with heart failure, who are frequently insulin resistant. Objective: The aim was to study the influence of impaired glucose metabolism and diabetes mellitus on the relation between dietary intake of n-3 LCPUFAs and risk of acute myocardial infarction (AMI) in patients undergoing coronary angiography for suspected coronary artery disease in 2000-2004. Design: This study included 2378 participants of the Western Norway B-Vitamin Intervention Trial (WENBIT). Daily intakes of n-3 LCPUFAs were estimated based on average dietary intakes during the last year as reported in a food-frequency questionnaire at baseline. Hazard ratios (HRs (95% CI)) of AMI (fatal and non-fatal) according to n-3 LCPUFA intake were calculated using Cox-regression adjusted for cardiovascular risk factors by comparing upper vs. lowest tertile and as trend across tertiles. Patients were followed until 31 December 2006. Results: Mean age of the participants was 62 years and 80% were male. Patients were sub-grouped into nondiabetics (HbA1c <5.7%), pre-diabetics (HbA1c ≥5.7%), and diabetics (diagnosed), and were also stratified according to median triglyceride levels. Among patients with diabetes there was a significantly reduced risk of AMI in the upper vs. the lowest tertile of n-3 LCPUFA intake, multivariate HR (95% CIs) 0.34 (0.14, 0.82), P for trend=0.008. In non-diabetic patients with HbA1c <5.7% there was an increased risk of AMI in the upper tertile of n-3 LCPUFA intake, 1.97 (1.05, 3.67), P for trend=0.02. Risk estimates were strengthened in their respective directions in both diabetic and nondiabetic patients with triglyceride levels above median. No risk associations were seen in pre-diabetics. Conclusions: Among patients with established coronary artery disease, a high intake of n-3 LCPUFAs was associated with a reduced risk of AMI in diabetic patients and an increased risk of of AMI in non-diabetic patients. The effects were particularly pronounced in those with elevated triglyceride levels.

13277 Beneficial effects on Aerobic Capacity and Threshold Heart Rate for Arrhythmias from Exercise Training in Patients with Catecholaminergic Polymorphic Ventricular Tachycardia

Ravinea Manotheepan, Oslo Univ Hosp and Univ of Oslo, Oslo, Norway; Jörg Saberniak, Inst for Surgical Res, Oslo Univ Hosp, Rikshospitalet, Univ of Oslo, Oslo, Norway; Tore Kristian Danielsen, Oslo Univ Hosp and Univ of Oslo, Oslo, Norway; Thor Edvardsen, Inst for Surgical Res, Oslo Univ Hosp, Rikshospitalet, Univ of Oslo, Oslo, Norway; Ivar Sjaastad, Oslo Univ Hosp and Univ of Oslo, Oslo, Norway; Kristina Hermann Haugaa, Inst for Surgical Res, Oslo Univ Hosp, Rikshospitalet, Univ of Oslo, Oslo, Norway; Mathis Korseberg Stokke, Oslo Univ Hosp and Univ of Oslo, Oslo, Norway

Background Patients with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) have an increased risk of ventricular arrhythmias (VA) triggered by exercise. During exercise testing, these arrhythmias occur at an individual heart rate (HR). We hypothesized that this threshold HR for arrhythmias may be influenced by systematic exercise. Furthermore, we explored if the HR for arrhythmias could be employed to create an individualized exercise training program without risk of adverse events.

Methods We included 13 patients with confirmed CPVT-causing mutations in the ryanodine receptor 2 gene on optimal medical treatment. The threshold HR for VA was identified for each patient as the HR when bigeminal ventricular extrasystoles or more severe VAs occurred during exercise testing. Six patients were enrolled in an exercise program with ergometer bicycling

over 12 weeks (3 x 60 minutes / week). Each session consisted of 4 6-minute intervals at 80-90 % of HR 5 beats per minute (bpm) below threshold HR for arrhythmias, interspersed with three-minute rest periods at 60 %. Seven CPVT patients performed exercise testing at baseline and after 3-12 months with unaltered advice to avoid intense physical and emotional stress and served as control group.

Results: Baseline threshold for occurrence of VA was 100±6 bpm in the training group and 135±4 bpm in the control group. The training patients completed 28±3 sessions (78±8 % program completion) and obtained 12.4±3.2 % increase in VO2max (17.9±5 % vs. 20.2±5 %, P<0.05). No change in VO2max was observed for control patients (29.8±5 vs 30.8±5). No adverse events occurred during training sessions. The threshold HR for VA after the training period was 111±10 bpm in training patients and 123±6 bpm in sedentary controls. The threshold for occurrence of VA increased in training patients compared to controls (+11 vs -12 bpm, P<0.05).

Conclusion Patients with CPVT improved their aerobic capacity through an individualized exercise program without occurrence of adverse events. Threshold for occurrence of VA was increased in CPVT patients after a 12 weeks exercise program compared to sedentary CPVT patients. These findings may indicate a positive impact of training on occurrence of arrhythmias in patients with CPVT.

14212 Aortic Stenosis in Mice and Men; Myocardial Activation of Pro-Hypertrophic NFAT Transcription Factor Isoforms is Attenuated by Relief of Pressure Overload

Ida G Lunde, Biljana Skrbic, Inst for Experimental Medical Res, Oslo, Norway; Theis Tønnessen, Dept of Cardiothoracic Surgery, Oslo, Norway; Heidi Kvaløy, Ulla Enger, Inst for Experimental Medical Res, Oslo, Norway; Ivar Sjaastad, Dept of Cardiology, Oslo, Norway; Geir Christensen, Cathrine R Carlson, Inst for Experimental Medical Res, Oslo, Norway

Aortic stenosis (AS) is a major health problem causing hypertrophy and failure. Dephosphorylation of the four nuclear factor of activated T-cell (NFATc) transcription factors by Ca 2+ -dependent calcineurin is thought to be central, regulating pro-hypertrophic signaling and as much as 10% of human cardiac genes. NFATc1-c4 are believed to play specific roles, yet it is unknown whether all four are activated in human heart disease. Although calcineurin-NFAT is a promising therapeutic target, it remains uncertain whether NFAT signaling can be reversed, such as after aortic valve replacement (AVR) for aortic stenosis (AS). We investigated NFATc1-c4 isoform activation and reversibility in pressureoverloaded human and murine hearts. Using antibodies validated for NFATc1-c4 specificity, we investigated myocardial NFATc activation in biopsies sampled per-operatively from AS patients and controls (n=17), and in experimental AS/AVR, aortic banding (AB)/debanding (DB) and sham-operated controls, in wild-type (n=36) and NFAT-luciferase (n=51) reporter mice. NFATc1-c4 proteins were substantially up-regulated in AS/AB despite minor mRNA changes. Increased NFATc activation was confirmed by 1.5- /4.8-fold increase in a direct target gene of NFATc, the regulator of calcineurin 1-4 (RCAN1-4), in AS/AB, although considerable NFATc1-c4 fractions remained phosphorylated (inactive). mRNA of all four NFATc correlated positively to RCAN1-4 in the human heart. In mice, DB significantly reduced AB-induced hypertrophy (ventricular weight, wall thickness) and failure (lung weight, atrial diameter), and normalized fractional shortening and body weight. Importantly, DB caused complete reversal of RCAN1-4 (8.4- to 0.9-fold), reduced NFAT-luciferase activity (8.3- to 2.6-fold) and reduced NFATc1-c4 protein. NFATc-regulatory enzymes, i.e. calcineurin, GSK-3β, Akt and MAPKs (ERK/JNK/p38), and NFATc-activating transient receptor potential canonical (TRPC1/3/6) membrane channels, were elevated in AS/AB and reversed by DB.

Our data suggest that all four NFATc isoforms participate in the early human hypertrophic response. Attenuated NFAT signaling by relief of pressure overload in mice indicates reversal of NFAT activation in AS patients after AVR.

9556 Effect of High Intensity Interval Training in Heart Transplant Recipients - A Randomized Controlled Trial

Kari Nytrøen, Oslo Univ Hosp Rikshospitalet, Oslo, Norway; Lene Annette Rustad, Norwegian Univ of Science and Technology, Trondheim, Norway; Pål Aukrust, Thor Ueland, Oslo Univ Hosp Rikshospitalet, Oslo, Norway; Jostein Hallén, Norwegian Sch of Sport Sciences, Oslo, Norway; Inger Holm, Katrine Rolid, Tove Lekva, Arnt Fiane, Jan P Amlie, Svend Aakhus, Lars Gullestad, Oslo Univ Hosp Rikshospitalet, Oslo, Norway

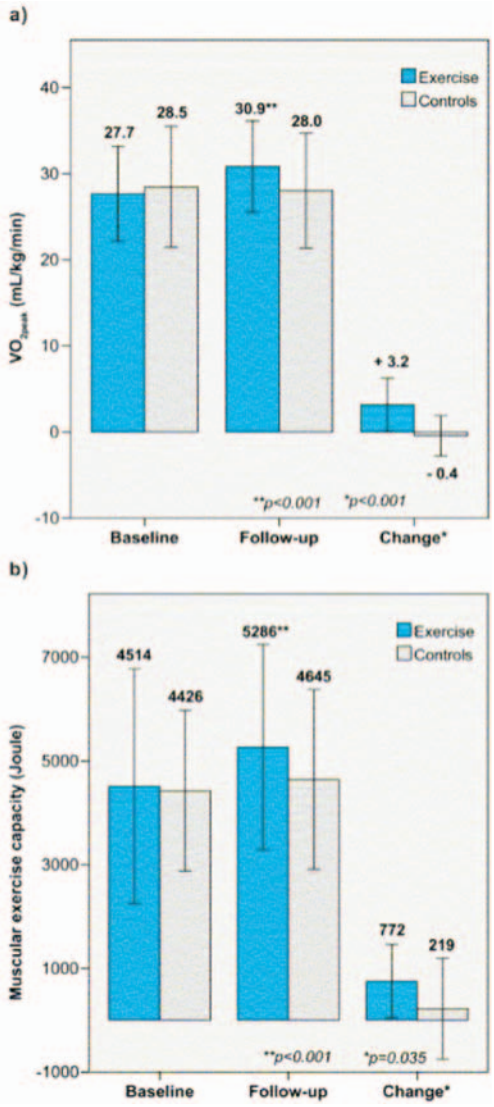
Background High intensity interval training (HIIT) is an efficient form of exercise training in patients with coronary heart disease and heart failure, while heart transplant (HTx) recipients, mainly because of denervation, traditionally have not been exposed to HIIT. Even if many studies have documented effect of exercise in HTx recipients, VO2peak remain below normal: 50 to 70% of predicted. Our hypothesis was that

HIIT is an applicable and safe form of exercise in heart transplant (HTx) recipients, and that it would markedly improve VO2peak. Secondarily, we wanted to evaluate central and peripheral mechanisms behind a potential VO2peak increase.

Methods Forty-eight clinically stable HTx recipients >18 years old and 1-8 years after HTx underwent maximal exercise testing on a treadmill, muscle strength testing, echocardiography and quality of life questionnaires. They were randomized to either exercise group (a one-year HIIT-program) or control group (usual care).

Results The mean±SD age was 51±16 years, 71% were male and time since HTx was 4.1±2.2 years. The mean VO2peak difference between groups at follow-up was 3.6 [2.0, 5.2] mL/kg/min (p<0.001). The exercise group had achieved 89.0±17.5% of predicted VO2peak vs. 82.5±20.0% in the control group (p<0.001). In addition, the exercise group improved their muscular exercise capacity significantly (p<0.001) and had subjectively significant better general health (p<0.001). There were no changes in cardiac function measured by echocardiography.

Conclusions The present study documents that a long-term, partly supervised and community-based HIIT-program is an applicable, effective and safe way to improve VO2peak , muscular exercise capacity and quality of life in HTx recipients. The results indicate that HIIT should be more frequently used among stable HTx recipients in the future.



16342 Non-invasive Analysis of Regional Myocardial Work Predicts Total Coronary Artery Occlusion in Non-ST-Elevation Myocardial Infarction Patients

Espen Boe, Russell Kristoffer, Inst for Surgical Res, Oslo, Norway; Christian Eek, Deparment of Cardiology, Oslo, Norway; Morten Eriksen, Inst for Surgical Res, Oslo, Norway; Bjornar Grenne, Harald Brunvand, Sorlandet Hosp Arendal, Arendal, Norway; Otto Smiseth, Helge Skulstad, Inst for Surgical Res, Oslo, Norway

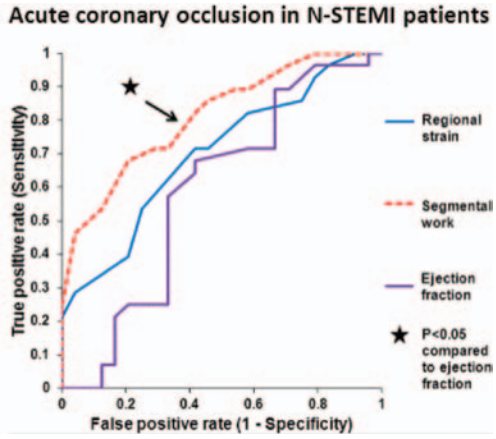
Introduction: Approximately 30% of patients with non-ST-elevation myocardial infarction (N-STEMI) have acute coronary artery occlusion (CAO), which may lead to reduced regional myocardial function. In the present study we investigated if a previously validated non-invasive method for assessing segmental myocardial work (SW) can identify patients with CAO.

Methods: Echocardiography was performed before coronary angiography (CA) in 52 patients with N-STEMI. Longitudinal strain (LS) curves were assessed by speckle tracking echocardiography for each myocardial segment in a 16-segment LV model. Left ventricular pressure (LVP) was estimated by utilizing a normalized reference curve which was adjusted according to LV isovolumic and ejection phases, as defined by timing of aortic and mitral valvular events. Systolic arterial cuff pressure was used to scale the LVP reference curve. SW was calculated as the area of the LVPLS loop. To evaluate the ischemic region affected by a CAO, the number of segments with systolic dysfunction judged by empirical cut-off values of <1700%·mmHg for SW and >-14% for segmental peak systolic strain (SPSS) were assessed. CAO was determined by CA. ROC analysis was performed by using the number of segments as the threshold variable. Area under the curve (AUC) (95%CI) for SW

and SPSS were compared to ejection fraction (EF).

Results: The AUCs were; SW 0.81(0.68-0.91); SPSS 0.70(0.56-0.82) and EF 0.59(0.44-0.72) (figure 1). 4 or more adjacent segments with reduced SW resulted in 67% sensitivity, 68% specificity, 70% negative predictive value and 64% positive predictive value for identifying CAO.

Conclusion: In the present study assessment of non-invasive myocardial segmental work could predict acute coronary artery occlusion in N-STEMI patients. SW was the only predictor significantly better than EF at identifying CAO, and may therefore be an important clinical tool for selecting N-STEMI patients in need of immediate invasive treatment



16425 Slow Ca 2+ Sparks Desynchronize Ca 2+ Release in Failing Cardiomyocytes: Evidence for Altered Ryanodine Receptor Distribution?

William Louch, Univ of Oslo, Oslo, Norway; Johan Hake, Simula Res Lab, Oslo, Norway; Halvor K Mørk, Karina Hougen, Biljana Skrbic, Univ of Oslo, Oslo, Norway; Glenn T Lines, Simula Res Lab, Oslo, Norway; Theis Tønnessen, Ivar Sjaastad, Ole M Sejersted, Univ of Oslo, Oslo, Norway

In heart failure, cardiomyocytes exhibit slowing of the rising phase of the Ca 2+ transient which contributes to the impaired contractility observed in this condition. We investigated the underlying mechanisms in a murine model of congestive heart failure (CHF). Myocardial infarction was induced by left coronary artery ligation, and at 10 weeks postinfarction, mice exhibited symptoms of CHF with reduced cardiac function and increased lung weight. Cardiomyocytes were isolated from viable regions of the septum, and septal myocytes from SHAM-operated mice served as controls. Ca 2+ transients (fluo-4 AM, 1Hz) rose markedly slower in CHF than SHAM myocytes with longer time to peak (CHF=172±13% of SHAM, P<0.05). The rise time of Ca 2+ sparks was also increased in CHF (SHAM=9.6±0.6 ms, CHF=13.1±0.6 ms, P<0.05), due to a sub-population of sparks (≈20%) with markedly slowed kinetics. Regions of the cell associated with these slow spontaneous sparks also exhibited slowed Ca 2+ release during the action potential. Thus, greater variability in spark kinetics in CHF promoted less uniform Ca 2+ release across the cell. Dyssynchronous Ca 2+ transients in CHF additionally resulted from T-tubule disorganization, as indicated by FFT analyses, but slow sparks were not associated with orphaned ryanodine receptors located at gaps between T-tubules. Rather, mathematical modeling predicted that slowed spark kinetics were caused by altered composition of Ca 2+ release units, including a reduction in ryanodine receptor density and/or distribution of ryanodine receptors into sub-clusters. Thus, our findings indicate that slow rise of the Ca 2+ transient in failing cardiomyocytes results from dyssynchronous Ca 2+ release due to T-tubule loss and altered ryanodine receptor configuration in Ca 2+ release units.

9778 Harmonizing Cutoff Values for Severe Aortic Valve Stenosis

Jan Minners, Univ Hosp Basel, Basel, Switzerland; Christa Gohlke-Baerwolf, Univ Heart Ctr, Bad Krozingen, Germany; Edda Bahlmann, Asklepios Klinik St. Georg, Hamburg, Germany; Simon Ray, Univ Hosp Manchester, Manchester, United Kingdom; John B Chambers, Guys - St Thomas Hosp, London, United Kingdom; Eva Gerdts, Univ of Bergen, Bergen, Norway; Kristian Wachtell, Rigshospitalet, Copenhagen, Denmark; Anne Rossebo, Oslo Univ, Aker Hosp, Oslo, Norway; Ronnie Willenheimer, Lund Univ, Malmö, Sweden; Kurt Boman, Umea Univ, Umea, Sweden; Kenneth Egstrup, Svendborg Hosp, Svendborg, Denmark; Terje Skjaerpe, St Olav`s Hosp, Trondheim, Norway; Antero Kesaniemi, Univ of Oulu, Oulu, Finland; Terje R Pedersen, Univ of Oslo, Oslo, Norway; Philippe Brudi, Merck, Whitehouse Station, NJ; Christoph A Nienaber, Univ Hosp Rostock, Rostock, Germany; Franz-Josef Neumann, Nikolaus Jander, Univ Heart Ctr, Bad Krozingen, Germany

Background: Decision making in patients with aortic valve stenosis (AS) and normal left ventricular function may be complicated by inconsistencies in cutoff values for severe AS. Particularly, the constellation of severe stenosis according to aortic valve area (AVA) <1cm2 and non-severe stenosis according to mean pressure

gradient (MPG) ≤40mmHg is a frequent finding which may, at least in part, be due to systematic discrepancies between cutoff values. Methods: We evaluated the effect of adjusting the cutoff value for severe AS from AVA 1.0cm2 to 0.8cm2 on discrepancies in classification of severity and event rates in 1525 asymptomatic patients with normal ejection fraction prospectively followed for a mean of 46 months from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study. Results: The diagnosis of a severe AS was made in 56 (4%) patients according to the MPG >40mmHg criterion, in 470 (31%) based on an AVA of <1.0cm2 and in 185 (12%) with an AVA of <0.8cm2 . After dividing the population into quintiles according to AVA and MPG an aortic valve related event rate of 0.40 was observed in patients with a mean AVA of 1.0±0.1cm2 which was similar to patients with a MPG of 27±2mmHg (0.40, p=ns). In turn, patients with a MPG of 37±5mm had an event rate of 0.65 and patients with an AVA of 0.74±0.1cm2 had an event rate of 0.53 (figure). Cardiovascular death rates followed a similar pattern.

Conclusion: Adjusting the cutoff value for severe stenosis in patients with normal left ventricular function from AVA 1.0cm2 to 0.8cm2 may harmonize parameters for the assessment of aortic stenosis both with respect to stenosis severity as well as clinical outcome.

16735 High Heart Rate Reserve Predicts Reduced Risk of Death from Cardiovascular Disease in Healthy Men with Low but Not with High Physical Fitness

Kristian Engeseth, Per T Skretteberg, Irene Grundvold, Oslo Univ Hosp, Ullevål, Oslo, Norway; Knut Liestøl, Oslo Univ, Oslo, Norway; Johan Bodegård, Sverre E Kjeldsen, Oslo Univ Hosp, Ullevål, Oslo, Norway; Jan E Erikssen, Oslo Univ, Oslo, Norway

Background: An impaired heart rate reserve (HRR) has previously been reported to predict mortality and cardiovascular disease (CVD). We tested if HRR predicts death from CVD independently of physical fitness in healthy men during long-term (35 years) follow up. Methods: HRR was measured among 2,014 apparently healthy, middle-aged men during a maximal bicycle exercise test in 1972. The men were divided into quartiles (Q1-Q4) by HRR. Death from CVD including coronary heart disease, stroke, pulmonary embolism and aortic disease was registered from the Norwegian death registry and a nationwide survey of all participants´ hospital charts through 2008. Relative risk of death from CVD in the quartiles was calculated using Cox proportional hazard regression adjusting for age, smoking, cholesterol, systolic blood pressure and resting heart rate. Results: A total of 528 deaths from CVD were registered. The incidence of CVD death was lowest among men with highest HRR (Q4) (Table). Q4 was associated with reduced CVD death-risk compared with Q1. After stratifying the men based on baseline exercise test by age-adjusted physical fitness (PF), above and below median, these results were statistically significant among the men with low PF (Table). Conclusions: A high heart rate reserve (≥ 112 BPM) proved independently associated with reduced risk of death from CVD over 35 years in apparently healthy, middle-aged men. However, the impact of high heart rate reserve on CVD was limited to men with PF below the median. Thus, assessment of heart rate reserve may be clinically useful when judging CVD death risk in apparently healthy middle-aged men with physical fitness below the average.

Quartiles (HRR)	Q1 (28 to 92) median = 85 n=494	Q2 (93 to 102) median = 98 n = 539	Q3 (103 to 111) median = 107 n = 483	Q4 (112 - 149) median = 118 n = 498
CVD deaths (n)	181	150	107	90
Multiple adjusted	1	0.75 (0.60-0.94)	0.63 (0.49-0.82)	0.58 (0.43-0.78)
-above median PF	1	1.15 (0.75-1.80)	0.93 (0.59-1.49)	0.96 (0.59-1.60)
-below median PF	1	0.72 (0.54-0.95)	0.68 (0.48-0.96)	0.50 (0.31- 0.78)

14286 Vascular Structure and Function in Healthy Obese Subjects

Mai Tone Lønnebakken, Univ of Bergen and Haukeland Univ Hosp, Bergen, Norway; Åshild E Rieck, Univ of Bergen, Bergen, Norway; Barbara Rogge, Marina V Kokorina, Haukeland Univ Hosp, Bergen, Norway; Eva Gerdts, Univ of Bergen and Haukeland Univ Hosp, Bergen, Norway

Objectives: Atherosclerotic plaques and increased arterial stiffness are recognized as predictors of cardiovascular events. However, the association between preclinical structural and functional vascular changes has been less studied in healthy overweight subjects. Methods: Ultrasound of the carotid and femoral arteries and applanation tonometry were performed in 126 subjects (age 51±10 years, 60% women and body mass index [BMI] 32.5±4.8 kg/m2) included in the FAT-associated CardiOvasculaR (FATCOR) project. Plaque was defined as an intima-media thickness (IMT) ≥1.50 mm. Vascular function was assessed by carotid femoral pulse wave velocity (PWV) and central blood pressure. Results: In the total study population, mean IMT was 0.71±0.02 mm and plaques were detected in 33%. Subjects with plaques were older (57±9 vs. 48±9 years), included more smokers (26% vs. 15%) and had higher central systolic blood pressure (127±19 vs.117±16 mmHg, all p<0.05) while prevalence of hypertension and diabetes did not differ. Smoking (β=0.20), higher age (β=0.38) and PWV (β=0.28) were independent predictors of increased IMT in multiple linear regression analysis

(Multiple R2= 0.34, all p<0.01). In multiple logistic regression analysis, age and smoking were the independent predictors of presence of atherosclerotic plaques (table). Conclusions: Higher IMT is associated with increased arterial stiffness in obesity. However, in healthy overweight subjects subclinical atherosclerotic plaques were primarily predicted by smoking.

11550 Calpain Mediated Proteolysis of The Cardiac Sodium-Calcium Exchanger 1 (NCX1) in Failing Hearts: Molecular Interactions

Pimthanya Wanichawan, Ida G Lunde, Jan M. Aronsen, Marianne Lunde, Inst for Experimental Medical Reseach, Oslo, Norway; Theis Tønnessen, Dept of Cardiothoracic Surgery, Oslo, Norway; Ivar Sjaastad, Ole M. Sejersted, Cathrine R. Carlson, Inst for Experimental Medical Reseach, Oslo, Norway

Introduction: In cardiac excitation-contraction coupling, the sarcolemmal Na+/Ca2+ exchanger 1 (NCX1) is a central component in maintaining intracellular Ca2+ homeostasis. Upregulation of NCX1 activity is associated with cardiac diseases such as heart failure, hypertrophy or ischemia reperfusion. Moreover, increased calpain activity, a ubiquitous intracellular Ca 2+ -activated protease, has been implicated in degradation of several cardiac proteins in failing hearts. Previous studies showed that calpain cleaves NCX1 and thereby increases conductance of NCX1, suggesting that calpain is an important regulator of NCX1 activity, but further insights into the underlying molecular mechanisms remain to be addressed. In the present study, we aim to identify NCX1-calpain protein interaction and their binding sites.

Methods and Results: Pull-down assays and peptide overlay assays have been employed and our preliminary results show that calpain binds directly to two distinct sites in the cytoplasmic loop of NCX1. In reciprocal experiments, we also found that NCX1 binds to catalytic region and domain III (membrane binding domain) in calpain. Further investigations on mapping of protein binding sites are ongoing to confirm their interaction sites. Consistent with these observations, NCX1 and calpain-1 are co-immunoprecipitated in the rat left ventricle suggesting NCX1 and calpain-1 physical interact. Interestingly, we also found that both full-length NCX1 and the 75 kDa proteolytic NCX1 fragment were upregulated in the failing left ventricle of rats after chronic pressure-overload induced by aortic banding for six weeks, indicating a role for NCX1 proteolysis during development of heart failure. In addition, we also observed an increased proteolysis of protein kinase Cα (PKCα), one of well-known calpain substrates, providing strong evidence that calpain activity was upregulated in our cardiac disease model.

Conclusion: Our present study shows a direct NCX1-calpain interaction and increased levels of the proteolytic fragment of NCX1 in the pressure-overloaded heart, providing further step to understand how calpain modulates NCX1 activity during development of heart failure.

15262 The Adhesion Site Transmembrane Proteoglycan Syndecan-4; an Integrator of ProHypertrophic and Pro-Inflammatory Signaling in the Heart?

Mari E Strand, Kate M Herum, Zaheer A Rana, Biljana Skrbic, Maria Vistnes, Oslo Univ Hosp Ullevaal and Univ of Oslo, Oslo, Norway; Ivar Sjaastad, Theis Tønnesen, Oslo Univ Hosp Ullevaal, Oslo, Norway; Cathrine R Carlson, Geir Christensen, Ida G Lunde, Oslo Univ Hosp Ullevaal and Univ of Oslo, Oslo, Norway

Cellular adhesion sites such as the cardiomyocyte Z-disc and fibroblast focal adhesion (FA) are emerging hot spots for cardiac disease. Particularly, transmembrane adhesion proteins are thought to be important for mechanical and inflammatory responses, critical stimuli for pathological cardiac remodeling. We have shown that mice lacking syndecan- 4, a transmembrane Z-disc and FA proteoglycan, develop premature failure with impaired mechanical load-induced prohypertrophic signaling. Syndecan-4 is up-regulated in human and murine hypertrophic myocardium, and we here investigated mechanisms regulating its cardiac expression and syndecan-4-mediated pro-inflammatory signaling in response to pressure overload. Cardiac syndecan-4 mRNA correlated to TNFα, IL-1β, IL-6 and TGFβ after aortic banding (AB) in mice, suggesting that pro-inflammatory cytokines induce syndecan-4 in vivo. Indeed, syndecan-4 mRNA was elevated in neonatal rat cardiomyocytes and fibroblasts by TNFα (~2-fold), IL-1β (~2-fold) and LPS (~2/~5- fold). ANGII, NE, CXCL16, IL-18, TGFβ and IL-6 had no effect. Interestingly, cyclic mechanical stretch induced syndecan-4 mRNA ~1.5-fold in cardiomyocytes, but not in fibroblasts. In fibroblasts, immunohistochemistry revealed that TNFα and IL-1β stimulated formation of syndecan-4-dependent mature FAs. Bioinformatical analyses identified pro-inflammatory and pro-hypertrophic NF-κB and NFAT transcription factor sites in the syndecan-4 promoter. Accordingly, blocking NF-κB inhibited TNFα-, IL-1β- and LPS-induced syndecan-4 expression. Moreover, the calcineurin-NFAT blocker CsA inhibited TNFα-induced syndecan-4 expres-

sion, and NFAT-luciferase and the NFAT target gene RCAN1-4 confirmed that TNFα activated NFAT. Importantly, syndecan-4 overexpression in HEK293-cells previously shown to activate NFAT also activated NFκB. In syndecan-4 knock-out hearts after AB, T-cell specific CD3/CD4/CD8 mRNA was reduced, suggesting impaired inflammation. Cardiac expression of the adhesion proteoglycan syndecan-4 is induced by mechanical and inflammatory signals, affecting immune cell infiltration and hypertrophic remodeling. We suggest syndecan-4 to integrate pro-hypertrophic and pro-inflammatory signaling.

16336 Calcium Channel Blockers Improve Exercise Capacity and Lower NT-proBNP Levels Compared to Beta Blockers in Patients with Permanent Atrial Fibrillation

Sara R Ulimoen, Steve Enger, Vestre Viken HF Baerum Hosp, Rud, Norway; Are H Pripp, Michael Abdelnoor, Harald Arnesen, Knut Gjesdal, Oslo Univ Hosp Ullevaal, Oslo, Norway; Arnljot Tveit, Vestre Viken HF Baerum Hosp, Rud, Norway

Introduction Rate control of atrial fibrillation (AF) is a main treatment modality, but there is still a lack of data regarding the effects of the different rate reducing drugs.

Hypothesis We hypothesized that calcium channel blockers may have more favourable effects than beta blockers on exercise capacity and NT-proBNP levels in patients with permanent AF.

Methods We included 60 patients (mean age 71±9 years, 18 women) with permanent AF and normal left ventricular function in a cross-over, investigator-blinded study. Diltiazem 360 mg, verapamil 240 mg, metoprolol 100 mg and carvedilol 25 mg were administered o.d. for three weeks, in a randomized sequence. At baseline and on the last day of each treatment period, the patients underwent a maximal cardiopulmonary exercise test on a bicycle ergometer. Blood samples for NTproBNP analyses were obtained at rest and at peak exercise.

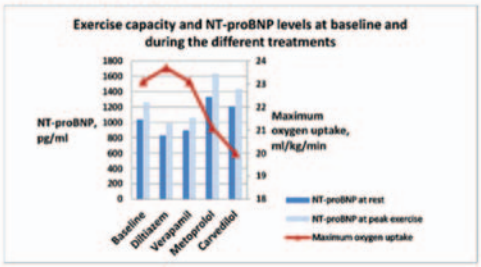
Results The VO2 peak was significantly lower during treatment with metoprolol and carvedilol compared to baseline or treatment with diltiazem and verapamil ($p<0.001$ for all). Compared to baseline, treatment with diltiazem and verapamil significantly reduced the NT-proBNP levels both at rest and at peak exercise, whereas treatment with metoprolol and carvedilol increased the levels ($p< 0.05$ for all). See table.

Conclusion In conclusion, rate reducing treatment with diltiazem and verapamil preserved exercise capacity and reduced levels of NT-proBNP compared to baseline whereas treatment with metoprolol and carvedilol had the opposite effect. Calcium channel blockers should hence be considered more often for rate control in AF patients without comorbidities that mandate the use of beta blockers.

Main Results

N=60	NT-proBNP at rest, pg/ml	NT-proBNP at peak exercise, pg/ml	Maximum oxygen uptake, ml/kg/min
Baseline	1039±636	1262±759	25.1±5.9
Diltiazem	831±528	985±597	23.7±6.4
Verapamil	897±517	1063±602	23.1±6.5
Metoprolol	1332±815	1634±962	21.1±6.5
Carvedilol	1205±742	1440±832	20.0±5.5

Data given as mean ± standard deviation



14069 A Three Dimensional Accelerometer Can Monitor Left Ventricular Function Independent of Sensor Alignment with the Cardiac Coordinate Axes

Ole-Johannes Grymyr, Espen W Remme, Andreas Espinoza, Stefan Hyler, Helge Skulstad, Ole Jakob Elle, Oslo Univ Hosp, Oslo, Norway; Lars Hoff, Vestfold Univ Coll, Tønsberg, Norway; Erik Fosse, Per Steinar Halvorsen, Oslo Univ Hosp, Oslo, Norway

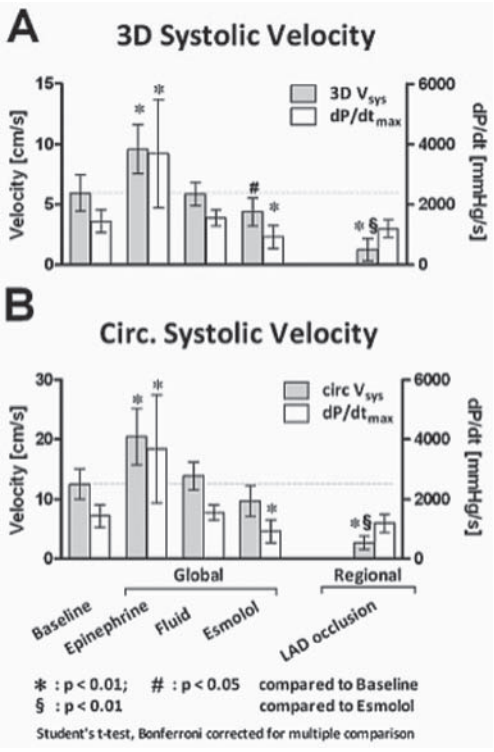
Introduction: Technological advances may allow development of multifunctional pacemakers with incorporated accelerometers aimed to provide continuous information on LV function. Circumferential motion by accelerometer is a sensitive parameter for LV function. However, a condition for this is alignment of the sensor to the cardiac coordinate system.

Hypothesis: Alignment of the sensor can be avoided by using a 3 axis (3D) accelerometer. Methods: In 20 open-chest pigs a miniaturized 3D accelerometer was fixed on LV in the left anterior apical region. Accelerations (sampling rate 500 Hz) in circumferential, longitudinal and radial directions were continuously measured. From these signals an epicardial 3D velocity vector was calculated. Peak 3D systolic velocity (3D Vsys) were compared to LV dP/dtmax and peak circumferential systolic velocity (Circ Vsys), also obtained by the accelerometer, during changes in global LV function (epinephrine, esmolol and

fluid loading) and regional LV function (LAD occlusion for 3 min).

Results: Significant and typical changes in accelerometer 3D Vsys and Circ Vsys were seen in global and regional interventions (Figure A-B). Both 3D Vsys and Circ Vsys reflected LV contractility by correlating significantly to LV dP/dtmax during global interventions, r 2 =0.98 and r 2 =0.97 respectively (both P<0.001). ROC analysis demonstrated excellent and similar sensitivity and specificity of accelerometer 3D and Circ Vsys to discriminate LAD occlusion from global interventions with sensitivity and specificity of 0.90 and 0.92 (cut-off value 3.3 cm/s) for 3D Vsys and 0.90 and 0.88 (cut-off value 7.0 cm/s) for Circ Vsys .

Conclusion: Accelerometer 3D Vsys and Circ Vsys were clinical relevant indices of global and regional LV function. Alignment of the sensor with the cardiac coordinate system was not needed by use of 3D data. Multifunctional pacemakers with incorporated 3D accelerometers may be a future method for monitoring LV function.



13464 Pentraxin 3 is Uninfluenced by High Doses of Concentrated Omega-3 Fatty Acids Administered for 12 Months Following an Acute Myocardial Infarction

Volker Poenitz, Heidi Grundt, Stavanger Univ Hosp, Stavanger, Norway; Barbara Bottazzi, Ivan Cuccovillo, Alberto Mantovani, Istituto Clinico Humanitas, Rozzano, Italy; Dennis WT Nilsen, Stavanger Univ Hosp, Stavanger, Norway

Background: Treatment with n-3 fatty acids has shown to improve outcome in patients with myocardial infarction (MI). However, the pathophysiological mechanisms of their beneficial effect are still being debated. Although anti-inflammatory mechanisms have been postulated, their influence on high sensitivity C-reactive protein (hs-CRP) is controversial. HsCRP belongs to the pentraxin family, so also does the recently identified long pentraxin 3 (PTX3) which has been found to reflect the inflammatory state of the vasculature and has been shown to predict outcome in MI patients. The aim of the present analysis was to assess the effect of long-term treatment with high doses of omega-3 fatty acids on circulating plasma levels of PTX3.

Methods: In the OFAMI study (ClinicalTrials.gov; NCT01422317), 300 MI patients were randomised to blindly receive 4 gelatine capsules of omega-3 in a concentrated ethylester form, each capsule containing 850-882 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Omacor, Pronova A/S, Oslo, Norway), or 4 g of corn oil, administered daily for a period of 12 months. Blood samples were collected 4-6 days following admission (just prior to intervention) and after a treatment period of 12 months. PTX3 was determined in citrated plasma by a specific enzyme-linked immunoabsorbent assay (ELISA) based on antibodies and reference protein developed in-house. Sensitivity is 100 pg/ml and no cross reaction with CRP is evident.

Results: A complete dataset for the analysis of PTX3 was available in 234 patients. PTX3 levels correlated well with hsCRP (r=0.40; p<0.01) and N-terminal Pro Brain Natriuretic Peptide (NTproBNP) (r=0.30; p<0.01) but not with troponin T (TnT), CD40L and serum lipids. During the intervention period, PTX3 decreased in both treatment groups; in the omega-3 group from median 3.60 to 3.15 ng/mL (p<0.01) and in controls from median 4.25 to 3.32 ng/mL (p<0.01). However, there was no statistical significant inter-group difference in PTX3 change.

Conclusion: PTX-3 levels were unaffected by high-dosed omega-3 fatty acids during an intervention period of 12 months in acute MI patients.

17365 Patients with Peripartum Cardiomyopathy Have Reduced Left Ventricular Reserve Capacity by Ergometric Stress Echocardiography 10 Months Postpartum

Mette-Elise Estensen, Kristina Hermann Haugaa, Eldrid Langesaeter, Knut Erik Berge, Trond Paul Leren, Lars Gullestad, Svend Aakhus, Helge Skulstad, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway

Background Peripartum cardiomyopathy (PPCM) is associated with high maternal mortality. Risk of recurrence of PPCM in a subsequent pregnancy is significant although risk prediction of recurrence is challenging. The aim of this study was to evaluate the left ventricular (LV) functional reserve capacity post partum by use of ergometric stress echocardiography (ESE) in patients PPCM.

Methods Patients with PPCM were investigated at delivery with echocardiography, including LV ejection fraction and strain analyses. Pro-BNP was collected. After 10±3 months, tests were repeated and an additional ESE was performed. All patients received optimal medical treatment. Genetic testing was performed, including 7 genes involved in dilated cardiomyopathy (MYH7, MYBPC3, TNNT2, MYL2, MYL3, LMNA, ACTC).

Results In all, 8 women (age 33±7 years) with PPCM were included. At follow up, all patients were asymptomatic. Pro-BNP almost normalized (541±628 to 18±13 pmol/l, p<0.05). LVEF and global strain at rest were improved (34±8% vs. 55 ±8%, p<0.05 and -10.6±3.2% vs. -16.7±2.3%, p<0.05). LV end-diastolic diameter was reduced (5.7±0.3 cm to 5.1±0.3 cm, p<0.01). During ESE, heart rate increased from 77±11 to 138±13 bpm (p<0.01) and blood pressure from 108±20/68±11 to 141±18/84±13 mmHg (p<0.01). Mean duration of ESE was 8±2 min and maximum work load was 78±20 Watt. ESE showed a slight improvement in global means of LV function (LVEF: 57±9% vs 55 ±8%, p<0.05 and global strain: -17.1±4.2% vs -16.7±2.3 %, p<0.05). No mutations were found in the 7 DCM related genes.Conclusion All patients had improved LV function at rest 10 months post partum. However, improvement of LV function during exercise testing was small. These findings may suggest that patients with PPCM have a reduced LV reserve capacity despite normalization of ventricular function at rest. This might be a potential reason for the high risk of recurrence of PPCM in a subsequent pregnancy.

18191 Secreted Frizzled Related Protein 3, an Inhibitor of Wnt-signaling, is Upregulated in Clinical and Experimental Heart Failure

Erik T Askevold, Pål Aukrust, Ståle Nymo, Svend Aakhus, Trine Ranheim, Arnt Fiane, Christen P Dahl, Alexandra V Finsen, Arne Yndestad, Lars Gullestad, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway; Roberto Latini, Serge Masson, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; Luigi Tavazzi, GVM Hosp of Care and Res, Cotignola, Italy; Thor Ueland, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway; GISSI-HF Investigators

Background: In response to pathological stress the heart reactivates fetal signaling pathways from a quiescent state in the adult myocardium. One of these pathways is the Wnt pathway, which has been linked to hypertrophic cardiac growth in experimental studies. We hypothesized that secreted frizzled related protein (sFRP) 3, a modulator of Wnt signaling, would be up-regulated in heart failure (HF) and investigated this by studies in experimental and clinical HF, including the ability of sFRP3 to prognosticate adverse advents in a predefined cohort of patients from the GISSI-HF trial.

Methods: sFRP3 gene expression was measured in myocardium from mice subjected to myocardial infarction (MI) or aortic banding (AB), and compared to sham-operated animals. Human left ventricle (LV) specimens harvested at time of LVAD implantation and/or from explanted hearts were analyzed for BNP and sFRP3 expression. Finally, plasma sFRP3 was measured by ELISA in 1202 stable HF patients (NYHA II-IV) enrolled in the GISSI-HF trial and association with outcomes evaluated.

Results: Our main findings were: (1) sFRP3 mRNA levels were elevated in infarcted mouse LV at 3, 7 (65-fold increase) and 21 days post-MI as well as in pressure overloaded (AB) murine hearts compared with sham-operated animals. (2) sFRP3 gene expression was increased in end-stage human LV compared to controls (n=28 vs 12, p<0.0001), correlated with BNP expression (r=0.6, p=0.001), and decreased during reverse LV remodeling in patients on LVAD therapy (n=18, p=0.037). (3) During a median follow-up of 47 (37-55) months, 315 (28%) patients died in the GISSI-HF substudy. Univariate Cox proportional hazard models showed significant associations between tertiles of baseline sFRP3 levels and all-cause and CV mortality. After multivariable adjustment (age, sex, BMI, NYHA, LVEF, eGFR, ischemic etiology, CRP and NT-proBNP) the associations were no longer significant, but a trend (p=0.053) was observed for the third tertile of sFRP3 in relation to CV mortality.

Conclusion: In this study we show myocardial up-regulation of sFRP3 in experimental and clinical HF and demonstrate for the first time an association of circulating sFRP3 with outcomes in a large, well characterized, representative HF population.

12862 Energy Loss Index as Prognosticator in Inconsistently Graded Asymptomatic Aortic Stenosis

Edda Bahlmann, Asklepios Clinic St. Georg, Hamburg, Germany; Eva Gerdts, Univ of Bergen and Haukeland Univ Hosp, Bergen, Norway; Dana Cramariuc, Haukeland Univ Hosp, Bergen, Norway; Christa GohlkeBaerwolf, Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany; Christoph Nienaber, Univsklinikum Rostock, Rostock, Germany; Kristian Wachtell, Rigshospitalet, The Heart Ctr, Copenhagen, Denmark; John Chambers, Cardiothoracic Ctr, Guys - St.Thomas Hosp Trust, London, United Kingdom; Karl Heinz Kuck, Asklepios Clinic St. Georg, Hamburg, Germany; Simon Ray, Univ of Manchester, Univ Hosp of South Manchester, Manchester, United Kingdom, Manchester, United Kingdom

Background: We tested pressure recovery adjusted aortic valve area index (ELI) in prediction of outcome in asymptomatic patients with inconsistently graded AS (mean gradient ≤40 mmHg and aortic valve area <1.0 cm^2).This is a pre-specified analysis. Methods and Results: The relation between ELI and rate of aortic valve events (AVE) was assessed by Receiver Operating Characteristic (ROC) analysis and Cox regression in 1563 patients with initial asymptomatic AS in the Simvastatin and Ezetimibe in Aortic Stenosis study. Inconsistently graded AS was present in 28.3% patients at baseline, and 48.6% of these patients experienced an AVE during 4.3 years of follow-up. In multivariate Cox regression, lower ELI predicted a 3-fold higher rate of AVE independent of conventional measures of AS (Table). However, when hazards from the final Cox regression model with and without ELI among the covariates were compared in ROC analysis , adding ELI to the model did not significantly increase the AUC (0.69 vs. 0.67, p= 0.579).

Conclusion: In asymptomatic patients with inconsistently graded severe AS, ELI predicted rates of AVE independent of but not superior to conventional measures of AS severity.

Table. Baseline ELI as predictor of AVE in patients with inconsistently graded severe AS. Multivariate Cox regression analyses. Variable included in all models: study treatment. na, not included in model *p<0.001, †p<0.05

Variables	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Lower ELI (cm^2/m^2)	8.93 (2.77-28.57)*	3.92 (1.16-13.16)†	3.41 (1.01-11.49)†
Peak aortic jet velocity (m/sec)	na	2.41 (1.75-3.31)*	na
Mean aortic gradient (mmHg)			1.06 (1.04-1.08)*

10904 The Seattle Post Myocardial Infarction Model (SPIM): Prediction of Mortality after Acute Myocardial Infarction

Eric S Ketchum, Univ of Washington, Seattle, WA; Kenneth Dickstein, Univ of Bergen, Bergen, Norway; John Kjekshus, Univ of Oslo, Oslo, Norway; Bertram Pitt, Univ of Michigan, Ann Arbor, MI; David T Linker, Wayne C Levy, Univ of Washington, Seattle, WA

Background: Ischemic heart disease is a leading worldwide cause of death. The Seattle Post Myocardial Infarction Model (SPIM) was developed to predict survival six months to two years after an acute myocardial infarction. Methods: 6,632 subjects from EPHESUS were used to derive the predictive model, while 5,477 subjects from OPTIMAAL were used to validate the model. After analysis of univariate predictors, Cox proportional hazards modeling was used to develop a multivariate risk score predictive of survival at six months, one year, and two years. Results: The SPIM risk score integrated lab and vital parameters (age, pulse, systolic blood pressure, Killip class, hemoglobin, sodium, white blood cell count, creatinine), features associated with the acute myocardial infarction (reperfusion therapy), the number of cardiac evidence-based medicines at baseline (aspirin, statin, beta-blocker, ACEI/ARB, aldosterone blocker), the region of the hospitalization, and the number of risk factors (current smoker and history of diabetes mellitus, cardiovascular disease, or heart failure). Each evidence based medicine improved survival by 15%, while each cardiac risk factor decreased survival by 38%. The model was predictive of all-cause mortality after myocardial infarction, with an AUC of 0.75 at six months and 0.75 at two years in the derivation cohort and 0.77 and 0.78 for the same time points in the validation cohort. This compared to 6-month AUCs of 0.69 and 0.73 for the GRACE discharge score in our derivation and validation cohorts (p<.0001 for the difference between SPIM and GRACE). Model predicted versus Kaplan-Meier observed survival was excellent in the derivation cohort and remained so in the validation cohort: 84.9% versus 85.0% at two years. Correlation between predicted and observed survival was high (r 2 =0.973, p<.0001). The 10% of subjects with the highest predicted risk had approximately 25 times higher mortality at two years than the 10% of subjects with the lowest predicted risk.

Conclusion: The SPIM score was a powerful predictor of outcomes after myocardial infarction. Its highly accurate predictions should improve

patient and physician understanding of survival and may prove a useful tool in post-infarct risk stratification.

13457 Electrocardiographic and Imaging Diagnostic Criteria are Predictive of Syncope, Ventricular Tachycardia or Aborted Cardiac Arrest in the Nordic Arrhythmogenic Right Ventricular Cardiomyopathy Registry

Pyotr G Platonov, Lund Univ, Lund, Sweden; Anders G Holst, Rigshospitalet - Copenhagen Univ Hosp, Copenhagen, Denmark; Kristina H Haugaa, Thor Edvardsen, Oslo Univ Hosp Rikshospitalet, Oslo, Norway; Thomas Gilljam, Sahlgrenska Univ Hosp, Gothenburg, Sweden; Catarina Lundin, Lund Univ, Lund, Sweden; Ole Eschen, Aalborg Univ Hosp, Aalborg, Denmark; Jim Hansen, Gentofte Univ Hosp, Copenhagen, Denmark; Henning Bundgaard, Jesper H Svendsen, Rigshospitalet - Copenhagen Univ Hosp, Copenhagen, Denmark

Background: Revision of arrhythmogenic right ventricular cardiomyopathy (ARVC) Task Force diagnostic criteria in 2010 (TF2010) increased the sensitivity for detection of patients at early stages of the disease. Whether this is associated with increased detection of patients at risk of severe manifestations of the disease, has not been fully clarified. Our aim was to assess the relation between baseline diagnostic criteria and severe debut of the disease in patients enrolled in the Nordic ARVC Registry.

Methods: Patients with definite ARVC by TF2010 enrolled in the registry in Denmark, Norway and Sweden were included in the analysis: n=139 (102 families), age 48±15 years, 57% male. Patients were defined as symptomatic based on the occurrence of syncope, documented ventricular tachycardia (VT) or aborted cardiac arrest (ACA) by enrolment. Using this definition, the performance of TF2010 criteria was tested for prediction of symptoms.

Results: The study population comprised 102 probands and 37 family members, of whom 24 were identified via family screening (17%). Initial disease manifestations were VT (n=43, 31%), syncope (n=16, 12%) or ACA (n=12, 9%), while 68 (49%) patients had not experienced any of these symptoms at baseline. Median age at first symptom was 40 [range 17-75] years. ACA occurred earlier (28 [range 18-50] years) than syncope (41[18-75] years) or VT (42[17-75] years) as the first symptom (p=0.013). Syncope, VT or ACA as an initial manifestation of ARVC were independently associated with the presence of major depolarisation (OR=2.54 95%CI 1.03-6.31, p=0.044), repolarisation (OR=2.34 95%CI 1.11- 4.93, p=0.025) or imaging (OR=5.45 95%CI 2.32-12.78, p<0.001) criteria. The family history of sudden death or ARVC in a 1st degree relative did not predict symptoms. The freedom from any imaging criteria was strongly associated with freedom from symptoms (OR=0.18 95%CI 0.08-0.43, p<0.001).

Conclusion: In patients with definite ARVC enrolled in the Nordic ARVC Registry the presence of major imaging, depolarisation or repolarisation diagnostic criteria were independently associated with syncope, VT or ACA as an initial manifestation of the disease. A family history of sudden death or ARVC, however, was not associated with a severe disease debut.

10632 Impact of Intracoronary Cell Therapy on Left Ventricular Function in the Setting of Acute Myocardial Infarction, A Collaborative Meta-analysis of Randomized Controlled Clinical Trials

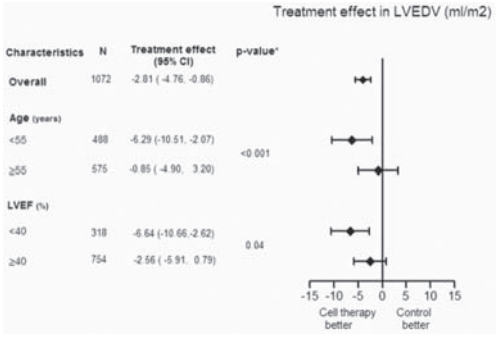
Ronak Delewi, Alexander Hirsch, Jan Tijssen, Academical Medical Ctr-Univ of Amsterdam, Amsterdam, Netherlands; Volker Schächinger, Goethe Univ, Frankfurt, Germany; Wojciech Wojakowski, Medical Univ of Silesia, Katowice, Poland; Jérôme Roncalli, Chu Rangueil, Toulouse, France; Svend Aakhus, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway; Sandra Erbs, Univ of Leipzig, Heart Ctr, Leipzig, Germany; Birgit Assmus, Goethe Univ, Frankfurt, Germany; Michal Tendera, Medical Univ of Silesia, Katowice, Poland; Patricia Lemarchand, Univ of Nantes, Nantes, France; Ketil Lunde, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway; Feng Cao, Xijing Hosp, Fourth Military Medical Univ, Xi'an, China; Heikki Huikuri, Univ of Oulu, Oulu, Finland; Stefan Janssens, Gasthuisberg Univ Hosp, Leuven, Belgium; Kai Wollert, Hannover Medical Sch, Hannover, Germany; Michal Plewka, Medical Univ of Lodz, Lodz, Poland; Stefan Grajek, Poznań Univ Sch of the Medical Sciences, Poznań, Poland; Jay Traverse, Abbott Northwestern Hosp, Univ of Minnesota, Minnesota, MN; Felix Zijlstra, Eramus Medical Ctr, Rotterdam, Netherlands; Jan Piek, Academical Medical Ctr-Univ of Amsterdam, Amsterdam, Netherlands

Background The objective of the present collaborative analysis was to systematically examine the effect of intracoronary bone marrow cell (BMC) therapy on left ventricular function after acute myocardial infarction in various subgroups of patients by performing a collaborative patient pooled meta-analysis of all large randomized controlled trials.

Methods We identified all randomized controlled trials comparing intracoronary BMC infusion as treatment for acute myocardial infarction. We contacted the principal investigator for each participating trial to provide summary data with regard to 10 different prespecified subgroups (age, diabetes mellitus, time from symptoms to percutaneous coronary intervention, infarct related artery, left ventricular (LV) end-diastolic volume (EDV), LV ejection fraction (EF), infarct size, presence of microvascular obstruction, timing of cell infusion, and injected cell number) and 3 different endpoints (change in LVEF, LVEDV and LV end-systolic volume (ESV)). Data from all 12 large BMC therapy studies were combined including 1177 patients (631 cell therapy, 446 controls).

Results The absolute improvement in LVEF was greater among BMC treated patients compared to controls: (1.7% increase, 95% Confidence Interval (CI) 0.8 to 2.5, p<0.001). Cell therapy significantly reduced LVEDV and LVESV (-2.8 mL/m², 95% CI -4.8 to -0.9, p<0.001; -3.2 mL/m², 95% CI -4.6 to -1.7, p<0.001, respectively). Treatment benefit in terms of LVEF, LVEDV and LVESV improvement was more pronounced in patients with baseline LVEF <40% and age <55 years (see Figure).

Conclusion For the first time, individual patient data from all large cell therapy studies were pooled and analyzed. We show that intracoronary BMC infusion is associated with improvement of LV function and remodeling in patients after acute myocardial infarction. Especially, younger patients and patients with depressed LVEF at baseline derived most benefit from this adjunctive therapy.



13985 In Patients with Intestinal Carcinoid Disease, Myocardial Function Deteriorates Progressively in Both Ventricles and Predicts Mortality

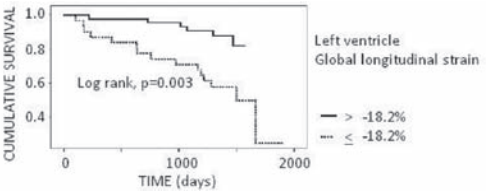
Wasim Zahid, Oslo Univ Hosp, Oslo, Norway; Kristina Haugaa, Deidi Bergestuen, Helge Skulstad, Espen Thiis-Evensen, Erik Fosse, Thor Edvardsen, Oslo Univ Hosp, 0424 OSLO, Norway

Background: Cardiac fibrosis is an important complication of intestinal carcinoid disease (CD). Evaluation of myocardial function in patients with CD has focused on the right ventricle (RV) function. It has recently been suggested that the left ventricle (LV) function is also affected. Impaired myocardial function increases mortality, and we hypothesized that function by LV and RV strain could predict death in patients with intestinal CD.

Methods: 89 patients (age 61±12 years) with verified intestinal CD were examined with 2-dimensional speckle tracking echocardiography (2D-STE) at baseline. LV global longitudinal strain was calculated from a 16 segments model, and RV longitudinal strain was calculated in a 3 segments model (free wall). The patients were followed up for a period of 1252 ± 374 days. Mortality data was obtained from hospital records. Survival was calculated by the Kaplan-Meier method, and log-rank test was used to compare the survival curves. Follow up 2D-STE was done among survivors.

Results: Twenty-one patients (24%) died during follow up. LV function by global strain at baseline was significantly reduced (-17.6 ± 2.0% vs. -19.3 ± 2.6%, p=0.001) in those who died during follow up. RV function was also significantly reduced (-23.9 ± 4.6% vs. -26.6 ± 4.0%, p=0.02). By Cox regression analysis, LV and RV baseline strain were independent predictors of mortality (LV: Hazard ratio (HR) 1.17 (95% CI 1.04-1.32) (p=0.011), RV: HR 1.26 (95% CI 1.04-1.53) (p=0.018)). At follow up of survivors, myocardial strain was significantly reduced from baseline in both LV (19.6 ± 2.6% to 17.9 ± 2.5%, p<0.001) and RV (-27.1 ± 4.0% to -24.8 ± 4.9%, p=0.01) supporting biventricular involvement of this disease.

Conclusion: LV and RV myocardial strain predicted mortality in patients with intestinal CD during 3.5 years of follow up. Our findings



indicate a biventricular progressive deterioration in patients with intestinal CD.

18355 Predictors of Fatigue in Heart Failure

Ana C Perez-Moreno, Pardeep S Jhund, Univ of Glasgow, Glasgow, United Kingdom; John G Cleland, Univ of Hull, Cottingham, United Kingdom; Dirk J van Veldhuisen, Univ Medical Ctr Groningen, Groningen, Netherlands; Lars Gullestad, Rikshospitalet Univ Hosp, Oslo, Norway; John Wikstrand, Sahlgrenska Univ Hosp, Göteborg, Göteborg, Sweden; John K Kjekshus, Univ of Oslo, Oslo, Norway; James D Lewsey, John J McMurray, Univ of Glasgow, Glasgow, United Kingdom

Introduction Although fatigue is regarded as a prototypical symptom of heart failure (HF), little is known about its prevalence, severity and predictors. We examined which baseline characteristics predicted fatigue at baseline in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA).

Methods CORONA enrolled 5011 patients aged ≥ 60 years with symptomatic (NYHA class II-IV), ischemic, systolic (LVEF ≤ 40%) heart failure. Fatigue "during the past few days" was measured using a five point scale: 0 none, 1 on heavy exertion, 2 moderate exertion, 3 slight exertion, 4 at rest. For the purposes of analysis, patients were grouped into 3 categories: fatigue score 0-1 (n= 588), 2 (n=1,898) and 3-4 (n= 2,525). The 3 category fatigue outcome was analyzed using ordered logistic regression, checking covariates for linearity and the proportional odds assumption. Only baseline variables that were significant (P< 0.05) predictors of fatigue in univariate analyses were included in the multivariable models.

Results Fatigue was reported by 96% of patients with half scoring 4 or 5 out of a possible score of 5. The baseline variables which were independent predictors of fatigue are shown in the table. NYHA class was the strongest predictor. Both atrial fibrillation/flutter and higher heart rate were predictors. Lower serum creatine kinase (CK) levels were associated with more fatigue. Adding drug therapy made little difference to the models although some treatments were additional predictors of fatigue (e.g. diuretics) whereas others (e.g. beta-blockers) were not. Notable by their absence as predictors were LVEF, blood pressure, body mass index, diabetes, renal dysfunction and NT proBNP.

Baseline variable	OR (95% CI)	Z score	P value
Female sex	1.41 (1.22, 1.63)	4.58	<0.001
NYHA* III/IV vs. II	5.84 (4.77, 7.15)	17.06	<0.001
Heart rate (per 10 bpm)	1.12 (1.06, 1.18)	4.04	<0.001
Myocardial infarction	1.26 (1.11, 1.42)	3.62	<0.001
Angina pectoris‡	1.78 (1.47, 2.15)	5.97	<0.001
Hypertension	1.44 (1.27, 1.63)	5.67	<0.001
Atrial fib/flutter	1.24 (1.07, 1.43)	2.83	0.005
Creatine kinase	0.74 (0.65, 084)	-4.65	<0.001

*NYHA did not fulfil proportional odds assumption, the OR (95% CI) presented in the table is for fatigue 1 vs. 2, for fatigue 1 vs. 3 the OR (95% CI) was 11.48 (9.89, 13.27) with a p value ≤0.001, z statistic of 32.52
‡History of angina did not fulfil proportional odds assumption, the OR (95% CI) presented in the table is for fatigue 1 vs. 2, the OR (95% CI) for fatigue 1 vs. 3 was 1.16 (1.00,1.35) with a p value of 0.044, z statistic of 2.01

Discussion Fatigue was an almost universal symptom and was pronounced in many patients. Fatigue was associated with NYHA class but not measures of cardiac function (LVEF, NT proBNP). Interestingly, fatigue was associated with lower CK, probably indicative of lower muscle mass.

11583 Syndecan-4 Regulates Cardiac Myofibroblast Differentiation and Extracellular Matrix Production in Response to Mechanical Stress by Signaling via NFAT

Kate M Herum, Ida G Lunde, Biljana Skrbic, Geir Florholmen, Dina Behmen, Ivar Sjaastad, Cathrine R Carlson, Oslo Univ Hosp Ullevaal, Oslo, Norway; Maria F Gomez, Lund Univ, Malmö, Sweden; Geir Christensen, Oslo Univ Hosp Ullevaal, Oslo, Norway

Pressure overload of the heart leads to differentiation of cardiac fibroblasts into myofibroblasts characterized by the ability to contract and an excessive production of extracellular matrix. This compromises heart function by increasing stiffness of the myocardium. The molecular mechanisms for stress-induced myofibroblast differentiation are poorly defined but are likely to involve stress-sensing molecules located in focal adhesions, such as the transmembrane proteoglycan syndecan-4. We hypothesized that syndecan-4 responds to mechanical stress by signaling via calcineurin/NFAT to induce myofibroblast differentiation and extracellular matrix production. Aortic banding increased smooth muscle α-actin (SMA; 2-fold), collagen I and III (6-fold) in the left ventricle of WT mice. Remarkably, this response was completely absent in syndecan-4 -/- mice, indicating an essential role for syndecan-4 in myofibroblast differentiation in the pressure-overloaded heart. Myofibroblast differentiation as well as NFAT activity was impaired in vitro in cardiac fibroblasts lacking syndecan-4 -/- , as assessed by expression of SMA, collagen I and III, and NFAT-luciferase reporter gene expression. Treatment with calcineurin/NFAT blockers inhibited all these responses in fibroblasts from WT mice. Following cyclic stretch, NFATc4 was activated in cardiac fibroblasts in a syndecan-4- and calcineurin-dependent manner and over-expression of syndecan-4 caused dephosphorylation (activation) of NFATc4. Syndecan-4, calcineurin and EGFP-NFATc4 all coincided at focal adhesions, substantiating formation of a mechanosensitive signaling complex. This complex is possibly activated by the 44% reduction in phosphorylated serine179 of syndecan-4 observed after

mechanical stress which has previously been found to favor calcineurin interaction. Finally, over-expression of NFATc4 up-regulated collagen III, MRTF-A (a transcriptional regulator of SMA) and the NFAT-target RCAN1.4.

In conclusion, we demonstrate that syndecan-4 regulates the production of collagen I and III, and differentiation of cardiac fibroblasts into myofibroblasts in response to mechanical stress in vivo and in vitro by engaging the calcineurin/NFAT signaling pathway.

18133 Severity of Obstructive Sleep Apnea is Independently Associated with Cardiac Troponin I Concentrations

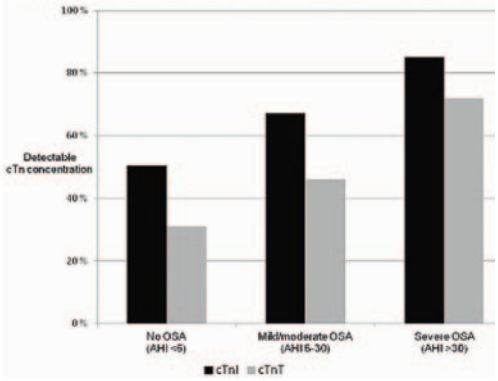
Gunnar Einvik, Helge Røsjø, Akershus Univ Hosp, Lørenskog, Norway; Virend K Somers, Mayo Clinic, Rochester, MN; Torbjørn Omland, Akershus Univ Hosp, Lørenskog, Norway

Objectives: Chronic, low-level cardiac troponin (cTn) elevation is associated with left ventricular (LV) dysfunction and hypertrophy. Obstructive sleep apnea (OSA) is associated with increased risk of several cardiovascular disorders, including LV hypertrophy and heart failure. Accordingly, in a community-based study we tested the hypothesis that severity of OSA, as measured by the apnea-hypopnea index (AHI), is associated with increasing concentrations of cTnI and cTnT.

Methods: In fasting morning venous samples from 531 persons (54% men, mean age 48 years) included in the Akershus Sleep Apnea Project, cTnI was analyzed with a prototype high-sensitivity (hs) assay (Abbott, limit of detection (LoD) 1.2 ng/L). cTnT was analyzed with a commercially available hs-assay (LoD 3.0 ng/l). AHI was assessed by inhospital polysomnography.

Results: hs-cTnI and hs-cTnT were detectable in 330 (62%) and 229 (44%) participants, respectively. Severity of OSA was associated with detectable cTnI and cTnT-levels (p for trend =0.001) (Figure 1). In multivariate linear regression analyses that adjusted for age, gender, creatinine levels, prior coronary artery disease (CAD), use of antihypertensives, current smoking, diabetes mellitus, systolic blood pressure (SBP), body mass index (BMI), and total/ high-density lipoprotein cholesterol ratio, higher AHI was independently associated with increasing hs-cTnI levels (standardized beta=0.13, p=0.004). Age, prior CAD, SBP and creatinine levels were other determinants of increasing hs-cTnI levels. In contrast, AHI was not independently associated with hs-cTnT levels. In participants with hs-cTnT levels below the LoD (n=292), an independent association between higher AHI and increasing hs-cTnI levels (p=0.005) was observed.

Conclusion: The severity of OSA is independently associated with circulating cTnI, but not cTnT concentrations.



10673 Early Diastolic Strain Rate Predicts Response to Heart Failure Therapy in Patients With Dilated Cardiomyopathy

Bjoern Goebel, Univ Hosp of Jena, Jena, Germany; Kristina Haugaa, Rikshospitalet Univ Hosp and Univ of Oslo, Oslo, Norway; Kathleen Meyer, Sylvia Otto, Christian Jung, Univ Hosp of Jena, Jena, Germany; Gerhard Mall, Klinikum Darmstadt, Darmstadt, Germany; Hans R Figulla, Univ Hosp of Jena, Jena, Germany; Thor Edvardsen, Rikshospitalet Univ Hosp and Univ of Oslo, Oslo, Norway; Tudor C Poerner, Univ Hosp of Jena, Jena, Germany

Objective: The aim of this prospective study was to assess the value of speckle tracking echocardiographic (2D-STE) parameters to predict response to heart failure therapy in patients with dilated cardiomyopathy (DCM).

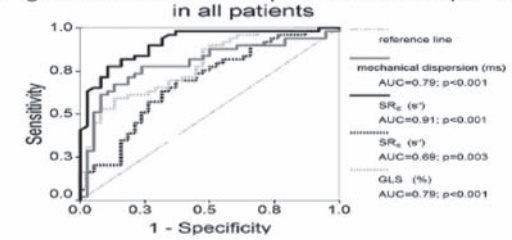
Methods: Eighty-seven patients (mean age 51±13 years) with DCM, defined as ejection fraction (EF) <45%, left ventricular (LV) end-diastolic diameter >112% of normal range derived from age and body surface area. Based on 2DSTE following parameters were extracted from three apical views of the LV: global longitudinal strain (GLS), systolic (SRS) and diastolic strain rate (SRE). Mechanical dispersion was calculated as standard deviation of time-to-peak strain values including all LV segments.

Results: After receiving heart failure therapy (mean 25 months, range 1.5-42) 50 patients reached combined endpoint defined as following: death, heart transplantation, rehospitalisation due to heart failure, and absence of improvement in EF. On stepwise multivariate regression analysis, SRE was independently of EF and LV volumes predictive for combined endpoint (OR 0.44, 95%CI 0.27-0.70, p=0.001) with an area under the ROC-curve (AUC) of 0.91 (Figure 1). In

patients with cQRS duration ≤120ms mechanical dispersion was predictive for combined endpoint with the highest AUC (OR 1.53, 95%CI 1.08-2.16, p=0.002; AUC=0.94)

Conclusions: In this study, SRE, a surrogate parameter of myocardial relaxation, was able to predict a response to heart failure therapy in patients with DCM. In patients with narrow QRS complex, mechanical dispersion yielded the highest predictive value. Parameters of 2D-STE may contribute to risk stratification in this patient population.

Figure 1 ROC curves for prediction of endpoint in all patients



11853 Coronary Artery Occlusions in Patients with Non-ST Elevation Acute Coronary Syndrome May Be Identified by Layer-Specific Strain Echocardiography

Sebastian I Sarvari, Kristina H Haugaa, Wazim Zahid, Bjørn Bendz, Svend Aakhus, Lars Aaberge, Thor Edvardsen, Oslo Univ Hosp, Oslo, Norway

Background: The left ventricular (LV) wall of the heart comprises 3 myocardial layers. The endocardial layer is most susceptible to ischemic injury. We hypothesised that patients with coronary occlusion have reduced endocardial function assessed by strain compared to patients without occlusion.

Methods and Results: We prospectively included 77 patients with suspected non-ST elevation (NSTE) acute coronary syndrome (ACS). Coronary angiography showed coronary occlusion in 28, significant stenosis in 21 and no stenosis in 28 patients. Echocardiography was performed before angiography. Layer-specific longitudinal and circumferential strains were assessed by 2D speckle-tracking echocardiography (2D-STE) from endo-, mid- and epicardium. Global longitudinal strain (GLS) was averaged from 16 and global circumferential strain (GCS) from 6 LV segments in all 3 layers. Patients with occlusion had worse function in all 3 myocardial layers assessed by GLS and GCS compared to patients without occlusion. Endocardial GLS and GCS were most affected, -14.8 ± 2.3% vs 17.9 ± 2.6%, and -18.5 ± 3.7% vs -22.5 ± 4.3% , p<0.001 respectively. The absolute difference between global longitudinal endo- and epicardial and circumferential endo- and epicardial strains were lower in patients with occlusion than in those without occlusion (Table). This reflects a relatively more pronounced decrease of endocardial function in patients with occlusion. Receiver operating characteristic curve analyses showed that endo- and mid-myocardial GLS were significantly better to identify occlusion than epicardial GLS (p=0.01 and p=0.01, respectively), and EF (p<0.001 and p=0.003, respectively).

Conclusions: NSTE-ACS patients with coronary occlusion might be identified by assessing layer-specific strain using 2D-STE. Endocardial function was more affected than epicardial function in patients with coronary occlusion.

Table: Absolute difference between epicardial and endocardial deformation

	No coronary occlusion (n=49)	Coronary occlusion (n=28)	p-value
Global Longitudinal Strain (%)	Δ4.7 ±2.0	Δ3.1 ±1.1	0.02
Global Circumferential Strain (%)	Δ8.8 ±3.8	Δ6.6 ±3.8	0.001

11623 Strain by Echocardiography is Superior to Ejection Fraction in Detection of Reduced Exercise Capacity

Nina E Hasselberg, Kristina H Haugaa, Sebastian Sarvari, Arne K Andreassen, Thor Edvardsen, Oslo Universtiy Hosp. Rikshospitalet, 0424 Oslo, Norway

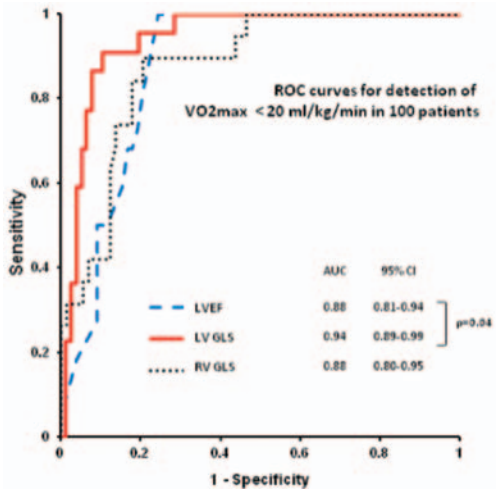
Background: Exercise capacity obtained by cardiopulmonary exercise testing (CPET) is considered a gold standard for estimating prognosis in patients with all grades of myocardial dysfunction. Global longitudinal strain (GLS) is shown to be more accurate than left ventricular (LV) ejection fraction (EF) for quantification of myocardial function. We explored the relationship between exercise capacity and myocardial function by LVEF and strain. We hypothesized that strain candetect reduced myocardial function in patients with reduced exercise capacity, with and without preserved LVEF.

Methods: CPET (by bicycle ergometry) detemined maximal oxygen uptake (VO2max) as a measure of exercise capacity. GLS was assessed by 2D speckle-tracking echocardiography in a 16 LV and 6 right ventricular (RV) segment model. LVEF was assessed by the Simpson biplane method.

Results: We included 100 patients with suspected or verified cardiovascular disease (mean age 56±12 years, 26% females, NYHA class 2.3±1.1 and LVEF 42±19%). In all patients LVEF, LV and RV GLS correlated to VO2max (R=0.64,

-0.65 and -0.60 respectively, p <0.001 for all). Importantly, in patients with preserved LVEF (≥55%, n=34), only LV and RV GLS correlated to VO2max, (R=-0.52, p=0.002 and -0.44, p=0.01, respectively) while LVEF did not (R=0.23, p=0.19). By ROC analyses (n=100), LV GLS was better to identify patients with VO2max < 20 ml/kg/min compared to LVEF (AUC: 0.94 vs. 0.88, p=0.04). (Figure).

Conclusion: In general, all measurements of LV and RV functions were correlated with exercise capacity. LV GLS analyses, however, were superior in identifying patients with decreased exercise capacity, including patients with normal LVEF. Considering the strong relationship between exercise capacity and cardiac prognosis, evaluation of myocardial strain may help detect patients with poor prognosis, including those with mildly decreased myocardial function.



12734 A New 4-group Classification of Left Ventricular Hypertrophy Based on left Ventricular Geometry Located a New High-risk Group within Eccentric Hypertrophy in Hypertensive Patients - A LIFE Study

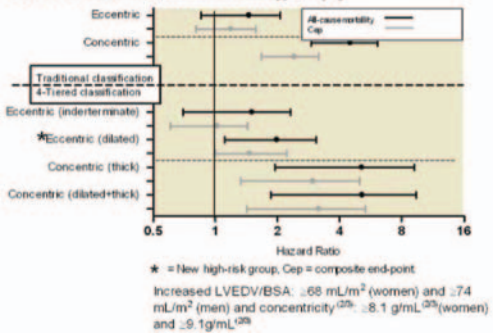
Casper N Bang, Weill Cornell Medical Coll, New York, NY; Eva Gerdts, Univ of Bergen, Bergen, Norway; Gerard P Aurigemma, Univ of Massachusetts Medical Sch, Worcester, MA; Kurt Boman, Umeå Univ, Umeå, Sweden; Markku S Nieminen, Helsinki Univ Hosp, Helsinki, Finland; Björn Dahlöf, Sahlgrenska Univ Hosp, Gothenburg, Sweden; Lars Køber, Rigshospitalet, Copenhagen, Denmark; Kristian Wachtell, Gentofte Hosp, Copenhagen, Denmark; Richard B Devereux, Weill Cornell Medical Coll, New York, NY

Background: Left ventricular hypertrophy (LVH) is traditionally classified as concentric or eccentric, based on LV relative wall thickness (RWT, wall thickness/chamber radius). We evaluated a 4-group LVH classification based on LV concentricity (mass/end-diastolic volume [M/EDV] (2/3)) and indexed LV EDV in hypertensive patients.

Methods: In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, hypertensive patients with LVH on a screening ECG were randomized to a mean of 4.8 years of losartan- or atenolol-based treatment. Echocardiography was performed in 939 at baseline and yearly thereafter. The patients with LVH (LVmass/height 2.7 ≥46.7 g/m2.7 in woman ≥49.2 g/m2.7 in men) were divided into 4 groups (Figure); "indeterminate" (normal M/EDV and EDV), "dilated" (increased EDV, normal M/EDV), "thick" (increased M/EDV with normal EDV), "thick and dilated" (increased M/EDV and EDV) and compared to non-LVH patients. The 4 LVH groups were considered as time-varying covariates in Cox models for all-cause mortality and a composite endpoint (CEP) of cardiovascular death, stroke, heart failure and myocardial infarction. Results: At baseline, the 939 patients were categorized as "indeterminate" in 13%, "dilated" in 25%, "thick" in 25%, "thick and dilated" in 19% and non-LVH in 17%. Treatment reduced prevalences of the 4 LVH groups to 10%, 35%, 5%, 5%, and 45% with no LVH after 4 years. In time-varying Cox analyses, the "indeterminate" LVH group had no increased risk of all-cause mortality, while "dilated", "thick" and "both think and dilated" did (Figure). With the traditional method the eccentric LVH was not associated with increased risk of all-cause mortality, however concentric LVH was (Figure).

Conclusions: The new 4-tiered classification method of hypertrophy located a subgroup of eccentric hypertrophy with increased risk of all-cause mortality, while the traditional classification method did not.

Figure. Hazard ratio and confidence interval for all-cause mortality and the composite end-point in the "traditional" and the new 4-tiered classification of left ventricular hypertrophy.



19302 Area Strain for the Assessment of Myocardial Infarction Scar Size by Ultrasound 3D Speckle Tracking: Validation with Late Gadolinium Enhancement Magnetic Resonance Imaging

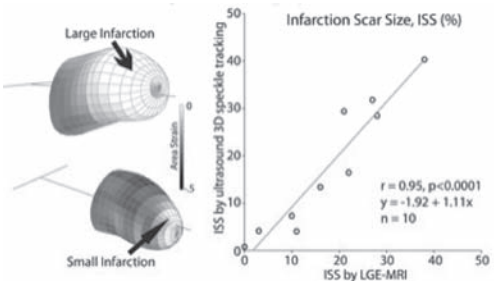
Stefano F de Marchi, Einar Hopp, Stig Urheim, Rolf Svendsmark, Anders Hervold, Klaus Murbræch, Richard J Massey, Espen W Remme, Per K Hol, Svend Aakhus, Oslo Univ Hosp, Oslo, Norway

Background: Myocardial infarction scar size (ISS) is an important predictor of mortality, but accurate quantitative echocardiographic methods to determine ISS are lacking. We developed a new functional imaging method based on geometric analysis of 3D meshgrid-representations of the left ventricle (LV) derived from ultrasound 3D speckle tracking. The study was performed to validate our method for the quantitative assessment of ISS.

Methods: 3D full volume echocardiographic clips and late gadolinium enhancement magnetic resonance images (LGEMRI) were acquired in 10 patients three months after acute myocardial infarction. ISS was determined from LGE-MRI images. 3D speckle tracking was performed on EchoPac (GE Vingmed), and LV meshgrids were analyzed offline using our novel software. Area strain, a parameter of regional wall thickening, was computed and displayed in 336 LV regions (figure). Infarction zone was delineated by a blinded observer as the region with reduced end-systolic area strain. The size of the delineated zone was calculated relative to the total LV surface.

Results: ISS in LGE-MRI ranged from 0 to 38% (median 18.5%). ISS closely correlated between echocardiography and LGE-MRI (figure). Bias and S.D. of bias of our method, as assessed from two different echocardiographic clips in all patient, was -1.94% and 5.01%, respectively.

Conclusions: The total size of reduced end-systolic area strain accurately reflects ISS as assessed by LGE-MRI. Thus, functional imaging based on 3D speckle tracking has great potential for the accurate determination of myocardial infarction scar size by echocardiography.



9463 Septal Myocardial Function is reduced in Carriers of Lamin A/C mutations and related to Atrioventricular Block, Ventricular Tachycardia and Septal Fibrosis

Nina E Hasselberg, Thor Edvardsen, Oslo Univ hospital. Rikshospitalet, Oslo, Norway; Helle Petri, Natl Univ Hosp, Rigshospitalet, Copenhagen, Denmark; Knut E Berge, Trond P Leren, Oslo Univ hospital. Rikshospitalet, Oslo, Norway; Henning Bundgaard, Natl Univ Hosp, Rigshospitalet, Copenhagen, Denmark; Kristina H Haugaa, OsloUniv hospital. Rikshospitalet, Oslo, Norway

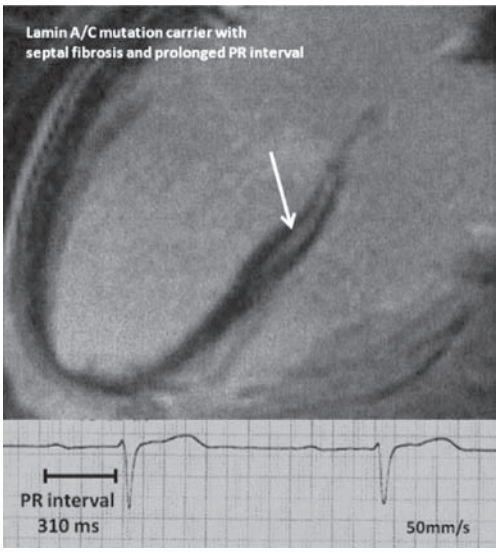
Background: Mutations in the Lamin A/C gene may cause dilated cardiomyopathy accompanied by atrioventricular (AV) block, atrial fibrillation and ventricular tachycardia (VT). VTs are frequent and commonly occur before development of dilated cardiomyopathy. Mechanisms of AV block and VT in these patients are not fully understood.

Methods: We included 41 Lamin A/C mutation carriers with LV (left ventricular) EF 55±13%. PR interval from resting ECG and occurrence of VT by Holter monitoring and ICDs were recorded. Global and LV septal myocardial function were assessed by echocardiographic speckle tracking strain analysis. Nine patients were eligible for magnetic resonance imaging (MRI) with late gadolinium enhancement (LGE) to assess presence and distribution of myocardial fibrosis.

Results: VT was documented in 21 patients (51%). Prolonged PR interval ($p<0.001$), presence of AV block ($p<0.001$) and reduced global longitudinal strain ($p=0.01$) were markers of VT, while LVEF was not ($p=0.55$). LV septal function was markedly reduced compared to function in the rest of the left ventricle (strain -16.7% vs. -18.7%, $p=0.001$). Prolonged PR interval correlated with reduced LV septal function ($R=0.41$, $p=0.03$). By LGE MRI, 4/5 patients (80%) with documented VT showed LV septal fibrosis while no fibrosis was detected in 4/4 (100%) patients without VT ($p=0.05$). Fibrosis by MRI was located exclusively in the LV septum. PR interval was longer in patients with LV septal fibrosis compared to those without (320±26 vs. 172±66ms, $p=0.002$).

Conclusion: In Lamin A/C mutation carriers, myocardial function was most decreased in the LV septum and correlated to prolonged PR interval. Prolonged PR interval was a marker of VT. Myocardial LV septal fibrosis was associated with prolonged PR interval and VT. Localized

fibrosis in the LV septum may be the mechanism behind AV block, VT and reduced LV septal function in Lamin A/C mutation carriers.



228 Neurological Outcomes of Cardiac Arrest Survivors with Myoclonus Following Resuscitation

David B Seder, Richard R Riker, Maine Medical Ctr, Portland, ME; Barbara Unger, Intl Cardiac Arrest Registry, Portland, ME; Kjetil Sunde, Oslo Univ Hosp, Ulleval, Norway; Sten Rupertsson, Uppsala Univ Hosp, Uppsala, Sweden; Michael Mooney, Minneapolis Heart Inst, Minneapolis, MN; Pascal Stammet, Ctr Hosp de Luxembourg, Luxembourg, Luxembourg; Hans Friberg, Lund Univ, Lund, Sweden; Niklas Nielsen, Helsingborg Hosp, Helsingborg, Sweden; International Cardiac Arrest Registry

Objectives: Historically, myoclonus was thought to portend a hopeless prognosis after cardiac arrest (CA). We evaluated the outcomes and characteristics of CA survivors with myoclonus in a large prospective registry.

Methods: Retrospective review of the International Cardiac Arrest Registry (INTCAR)

Findings: Of 2564 patients entered into INTCAR between 12/2008-12/2011, 466 (18%) had myoclonus, with an average age of 61.8 (SD 15.9) years, 84% OHCA, initial rhythm VT/VF in 47%, asystole in 28%, and PEA in 21%. Mean "no flow" interval was 8.6 (7.2) minutes, "low flow" interval 17 (15.2) minutes, and total time to return of circulation (TTROSC) 25.6 (15.5) minutes. Therapeutic hypothermia (TH) was applied in 444 (95%) patients, and 334 (72%) had EEG monitoring. Good Outcome (GO) with CPC1-2 occurred in 27 patients at ICU discharge, increasing to 43 (9.2%) at hospital discharge. For patients with GO, mean age was 53.6 (15.6), 79% VT/VF, and TTROSC was 18.6 (12.8) minutes. The EEG showed continuous activity with diffuse slowing in 61% of GO patients, and median hospital LOS was 14.5 days [IQR 9-22]. Of 423 myoclonus patients with poor outcome (PO = CPC3-5), life support was withdrawn in 330 (78%); due to neurological futility in 293 (89%), and the EEG (n=306) showed burst suppression in 152 (49.7%), status epilepticus in 102 (33.3%), severe background attenuation in 75 (24.5%) and continuous activity with diffuse slowing in 75 (24.5%). Among PO patients, 49 (11.6%) did not receive or complete TH. Median hospital LOS in this cohort was 5 [IQR3-7] days. Of 293 patients that died of "neurological futility", 131 (45%) died less than 5 days after CA.

Conclusions: Myoclonus after cardiac arrest should not be considered uniformly fatal. Despite early withdrawal or less than fully aggressive life supportive measures in many patients, 9.2% of myoclonus patients in a large registry population had good outcomes.

9371 Low In-Treatment HDL Cholesterol Strongly Predicts Incident Atrial Fibrillation: The LIFE Study

Peter M Okin, Weill Cornell Medical Coll, New York, NY; Darcy A Hille, Merck Res Labs, North Wales, PA; Kristian Wachtell, The Heart Ctr, Rigshospitalet, Copenhagen, Denmark; Sverre E Kjeldsen, Univ of Oslo, Ullevål Hosp, Oslo, Norway; Björn Dahlöf, Sahlgrenska Univ Hosp/Östra, Gothenburg, Sweden; Richard B Devereux, Weill Cornell Medical Coll, New York, NY

Background: Hypertensive patients are at increased risk of atrial fibrillation (AF). Although low baseline HDL levels have been associated with a higher risk of AF in some analyses, this has not been born out in recent population-based studies; whether changing levels of HDL over time are more strongly related to the risk of new AF has not been examined.

Methods: Incident AF was examined in relation to baseline and in-treatment HDL levels prior to development of AF in 8267 hypertensive patients with no history of AF, in sinus rhythm on their baseline ECG, randomly assigned to losartan- or atenolol-based treatment. HDL levels at baseline and each year of testing were categorized into quartiles according to baseline HDL levels.

Results: During 4.7±1.1 years follow-up, new AF developed in 645 patients (7.8%). In univariate analyses, compared with HDL >1.78 mMol/L, patients with in-treatment HDL <1.21 entered as

a time-varying covariate had a 53% greater risk of new AF; patients with in-treatment HDL in the 2 nd or 3 rd quartiles had intermediate increased risks of AF. Baseline HDL was only a weak predictor of new AF. In multivariate Cox analyses adjusting for multiple AF risk factors, including the previously demonstrated predictive value of in-treatment heart rate and Cornell product LVH, there was no attenuation of the risk of new AF associated with low in-treatment HDL. In-treatment non-HDL cholesterol (p=0.171) and statin use (p=0.626) were not significant predictors of new AF in the multivariate model including in-treatment HDL. Baseline HDL was not a significant predictor of AF in multivariate analysis.

Conclusions: Lower in-treatment HDL is strongly associated with risk of new AF, even after adjusting for other potential AF risk factors and treatment effects. These findings suggest that serial assessment of HDL can better estimate AF risk in hypertensive patients. Further study is indicated to determine whether therapies that increase HDL can lower risk of developing AF.

Analysis	Hazard Ratios (95% Confidence Interval)			
	Quartile 1 HDL <1.22	Quartile 2 HDL 1.22-1.47	Quartile 3 HDL 1.48-1.78	Quartile 4 HDL >1.78
Univariate Cox Model				
Baseline HDL	1.14 (0.90-1.43)	1.24 (0.99-1.56)	1.30 (1.04-1.63)	1
In-treatment HDL	1.53 (1.19-1.97)	1.35 (1.04-1.75)	1.27 (0.97-1.65)	1
Multivariate Cox Model*				
Baseline HDL	1.01 (0.78-1.31)	1.24 (0.97-1.58)	1.24 (0.97-1.57)	1
In-treatment HDL	1.54 (1.16-2.05)	1.41 (1.07-1.85)	1.34 (1.02-1.76)	1

*Adjusted for randomized treatment, baseline age, sex, race, history of MI, heart failure, diabetes, prior antihypertensive therapy, serum glucose and creatinine, urine albumin/creatinine ratio treated as standard covariates, and incident MI, incident heart failure and in-treatment nonHDL cholesterol, heart rate, Cornell product LVH, diastolic and systolic pressure, and statin use treated as time-varying covariates

9692 Lower Achieved Systolic Pressure (≤130 mm Hg) is Associated With a Decreased Risk of New Diabetes Mellitus in Hypertensive Patients With Electrocardiographic Left Ventricular Hypertrophy: The LIFE Study

Peter M Okin, Weill Cornell Medical Coll, New York, NY; Darcy A Hille, Merck Res Labs, North Wales, PA; Lars H Lindholm, Umeå Univ, Umeå, Sweden; Sverre E Kjeldsen, Univ of Oslo, Ullevål Hosp, Oslo, Norway; Björn Dahlöf, Sahlgrenska Univ Hosp/Östra, Gothenburg, Sweden; Richard B Devereux, Weill Cornell Medical Coll, New York, NY

Background: There is a well-established association between higher blood pressure (BP) and insulin resistance and hypertensive patients are at increased risk of developing diabetes mellitus (DM). Although lower achieved systolic BP (SBP) was not associated with reduced mortality or cardiovascular outcomes in diabetic hypertensives or in hypertensive patients with ECG left ventricular hypertrophy (LVH) in the LIFE study, whether more aggressive reduction of SBP is associated with a lower incidence of DM has not been examined.

Methods: Risk of new-onset DM was examined in relation to last in-treatment SBP prior to DM diagnosis or last instudy measurement in the absence of new DM in 7485 hypertensive patients with ECG LVH with no history of DM randomly assigned to losartan- or atenolol-based treatment. Patients with in-treatment SBP ≤130 mm Hg (lowest quintile at last measurement) and SBP between 131 and 141, were compared with patients with in-treatment SBP ≥142 (median SBP at last measurement).

Results: During 4.6±1.2 years follow-up, new-onset DM was diagnosed in 520 patients (6.9%). In univariate analyses, compared with in-treatment SBP ≥142, in-treatment SBP ≤130 entered as a time-varying covariate was associated with a 57% lower risk (95% CI 39-69%) of new DM and in-treatment SBP between 131 and 141 with a 30% lower risk (95% CI 14-42%) of developing DM. After adjusting for randomized treatment, age, sex, race, prior antihypertensive therapy, baseline body mass index (BMI), uric acid, serum glucose and baseline HDL cholesterol entered as standard covariates, and for in-treatment Cornell product LVH, diastolic BP, BMI, HDL, hydrochlorothiazide and statin use treated as time-varying covariates, achievement of a SBP ≤130 remained associated with a 38% lower incidence (95% CI 12- 57%) of new DM whereas an in-treatment SBP between 131 and 141 was no longer predictive of a reduced risk of new DM.

Conclusions: Achieved SBP ≤130 is associated with a significantly lower risk of developing new-onset DM in hypertensive patients with ECG LVH, independent of other known and possible risk factors for DM. Further study will be needed to determine whether targeting hypertensive patients without DM to lower SBP goals can reduce the burden of new DM in this high-risk population.

19144 New Ischemic Stroke and Outcomes with Vorapaxar vs. Placebo: Results from TRA 2°P-TIMI 50 Trial

Marc P Bonaca, Benjamin M Scirica, Eugene Braunwald, Stephen D. Wiviott, TIMI Study Group, Brigham and Womens Hosp, Boston, MA; Shinya Goto, Tokai Univ Sch of Med, Tokai, Japan; Dennis Nilsen, Vernon Bonarjee, Stavanger Univ Hosp, Stavanger, Norway; Sabina A. Murphy, David A Morrow, TIMI Study Group, Brigham and Womens Hosp, Boston, MA

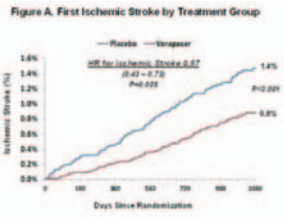
Vorapaxar is a potent platelet inhibitor that reduces thrombotic events in stable patients with a history of myocardial infarction (MI) or peripheral artery disease (PAD); however, this

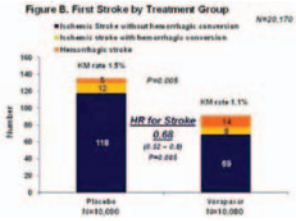
benefit is offset by increased bleeding including intracranial hemorrhage particularly in patients with established cerebrovascular disease (CVD). We investigated the outcomes in patients with MI or PAD experiencing a first ischemic stroke on vorapaxar.

Methods: The TRA2P-TIMI 50 trial was a randomized, double-blind, placebo controlled trial of vorapaxar 2.5 mg daily in 26,449 patients with established atherosclerotic vascular disease. Patients were stratified at randomization by their qualifying atherosclerotic condition (MI, PAD, or CVD). After two years, the Data and Safety Monitoring Board recommended discontinuation of study treatment in those with prior stroke or incident stroke. We evaluated the risk of new ischemic stroke outcomes with vorapaxar in 20,170 patients with MI or PAD but no history of CVD.

Results: In patients with MI or PAD and no history of CVD, vorapaxar significantly reduced ischemic stroke (HR 0.57, 95% CI 0.43 - 0.75, p<0.001)(Figure A). Overall there were numerically fewer hemorrhagic conversions in patients treated with vorapaxar who suffered a first ischemic stroke. The risk of hemorrhagic conversion (HR 1.19, 95% CI 0.49 - 2.91, p=0.70) or death (HR 1.09, 95% CI 0.57 - 2.07, p=0.79) during follow up was not significantly increased with vorapaxar. Although hemorrohagic stroke was increased (HR 2.78, 95% CI 1.00- 7.73, p=0.049) overall stroke was significantly reduced (HR 0.68, 95% CI 0.52 - 0.8, p=0.005) with vorapaxar (Figure B).

Conclusions: Vorapaxar reduces thrombotic events including ischemic stroke in stable patients with MI or PAD. There is no significant increase in the risk of hemorrhagic conversion or death in MI or PAD patients who experience a first ischemic stroke on vorapaxar. Hemorrhagic stroke is increased but all stroke is reduced.





159 The Impact of Hypothermia Treatment on Survival to Hospital Discharge for Patients with Out-of-Hospital Cardiac Arrest in the Circulation Improving Resuscitation Care (CIRC) Trial

Lars Wik, Jan-Aage Olsen, Natl Competence Ctr of Emergency Med, Oslo Univ Hosp, Oslo, Norway; David Persse, Houston Fire Dept and the Baylor Coll of Med, Houston, TX; Fritz Sterz, Medical Univ of Vienna, Vienna, Austria; Michael Lozano Jr, Lake Erie Coll of Osteopathic Med, Bradenton, FL; Marc A Brouwer, Heart Lung Ctr, Radboud Univ Medical Ctr, Nijmegen, Netherlands; Mark Westfall, Theda Clark Regional Medical Ctr, Neenah, WI; Chris M Souders, Houston Fire Dept and the Baylor Coll of Med, Houston, TX; Reinhard Malzer, Vienna City Admin, Emergency Medical Services, Vienna, Austria; Pierre M van Grunsven, Regional Ambulance Service Gelderland-Zuid, Nijmegen, Netherlands; David Travis, Hillsborough County Fire Rescue, Tampa, FL; Ulrich R Herken, ZOLL Medical Corp, Chelmsford, MA; E Brooke Lerner, Medical Coll of Wisconsin, Milwaukee, WI

Background: Therapeutic hypothermia (TH) has been associated with increased survival after out-of-hospital cardiac arrest (OHCA). There is ongoing debate over when TH should be applied to a patient after OHCA. For patients enrolled in the Circulation Improving Resuscitation Care (CIRC) trial, application of TH was captured for three distinct treatment periods: prehospital (PH), in the emergency department (ED), and in-hospital (IH). In a post hoc analysis of the CIRC database we evaluated the effect of TH during these three periods on survival to hospital discharge.

Methods: All study patients admitted to hospital were included in the analysis, regardless of treatment of arm. Because patients could have TH initiated in the PH, ED, or IH phase of their care and not all patients had hypothermia maintained between one phase of care and the next a TH score was created. The score awarded points for each location where TH was provided: 3 for PH, 2 for ED, and 1 for IH. Patients could receive a maximum score of 6 if they had TH in all three settings or a minimum score of 0 if no TH was provided. Logistic regression was used to determine the interaction between the TH score and survival to hospital discharge, adjusting for the same covariates used in the CIRC study survival analysis: shockable initial rhythm, witnessed arrest, age group, and study site.

Results: Of the 4231 subjects enrolled in CIRC, 1068 were admitted to hospital. Survival information could not be obtained for two subjects. Of the remaining 1066, 36% had a score of 0 (no TH), 8% score of 1 (IH - TH only), 3% score of 2 (ED - TH only), 26% score of 3, 6% score of 4, 3% score of 5, and 17% score of 6 (PH-, ED-, and IH-TH). The adjusted OR for survival to discharge was 1.105 (95% confidence interval 1.030 - 1.186, p < 0.01) for each one point increase in the TH score. For example, a subject that received PH-, ED-, and IH-TH (score of 6) had an OR of 1.8 for survival to hospital discharge.

Conclusion: Our analysis indicates that TH treatment in OHCA patients shows the most benefit when started in the field and continued into the hospital without interruptions in the emergency department.

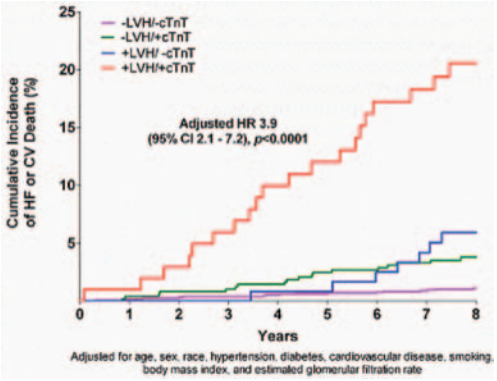
14833 Chronic Cardiac Injury Identifies a Malignant Left Ventricular Hypertrophy Phenotype in the General Population

Ian J Neeland, Mark H Drazner, Jarett D Berry, Univ of Texas Southwestern Medical Ctr, Dallas, TX; Christopher R deFilippi, Univ of Maryland Sch of Med, Baltimore, MD; Colby R Ayers, Sandeep R Das, Amit Khera, Darren K McGuire, Univ of Texas Southwestern Medical Ctr, Dallas, TX; Torbjørn Omland, Univ of Oslo, Oslo, Norway; James A de Lemos, Univ of Texas Southwestern Medical Ctr, Dallas, TX

Background: The interaction between left ventricular hypertrophy (LVH) and chronic cardiac injury, as reflected by very low but detectable circulating levels of cardiac troponin T (cTnT), on outcomes in the general population is unknown. Methods: Left ventricular (LV) mass was measured by MRI and cTnT by a highly sensitive assay (Roche Diagnostics) in individuals with LV ejection fraction ≥40%, eGFR ≥60 mL/min/1.73 m2 , and without clinical heart failure (HF) enrolled in the Dallas Heart Study, a multiethnic population-based cohort study. LVH was defined as LV mass/body surface area ≥89 g/m2 in women and ≥112 g/m2 in men. Participants were placed into 4 categories based on the presence of LVH and detectable cTnT (≥3 ng/L). The primary outcome of incident HF or cardiovascular (CV) death was determined through a median 8.1 years of follow-up.

Results: Of 2413 participants meeting study criteria (mean age 44; 56% women; 48% black), 223 (9.2%) had LVH and 590 (24.5%) had detectable cTnT. 102 (4.2%) participants had both LVH and detectable cTnT (+LVH/+cTnT) and were older; more likely to be male and black; with more hypertension, diabetes, and CV disease compared with those with neither or only 1 phenotype (p<0.0001 for each). The cumulative incidence of HF or CV death was 20.6% in the +LVH/+cTnT group compared with 1.1%, 3.9%, and 5.8% in the -LVH/-cTnT, -LVH/+cTnT, and +LVH/-cTnT groups, respectively (p<0.001 for each, Figure). In multivariable analysis, +LVH/+cTnT was associated with a marked increase in the risk for HF or CV death (HR 3.9, 95% CI 2.1 - 7.2 vs. neither or only 1 phenotype) and was the single strongest predictor in this population (X 2 =19 vs. X 2 <12 for other covariates). A highly significant interaction was observed between LVH and cTnT for the primary outcome (pinteraction=0.0005).

Conclusions: Circulating cTnT is a powerful marker of chronic cardiac injury in individuals with LVH and identifies a sub-phenotype at extremely high risk for HF and death.



9193 Variation in Quality of Care Among Patients Hospitalized With Acute Heart Failure in an International Trial: Findings From ASCEND-HF

Jonathan G Howlett, Foothills Hosp, Univ of Calgary, Edmonton, AB, Canada; Justin A Ezekowitz, Mohua Podder, Univ of Alberta, Edmonton, AB, Canada; Adrian F Hernandez, Duke Clinical Res Inst, Durham, NC; Rafael Diaz, Estudios Cardiologicos Latino America, Santa Fe, Argentina; Kenneth Dickstein, Univ of Bergen, Rogaland Bergen, Norway; Paul W Armstrong, Univ of Alberta, Edmonton, AB, Canada; Gregg C Fonarow, UCLA, Los Angeles, CA

Background: Translation of evidence-based heart failure (HF) therapies to clinical practice is incomplete and may be subject to international variation. We compared key HF quality indicators in acute HF (AHF) patients enrolled in the international Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial.

Methods: Patients were admitted to hospital for AHF and comprised 5 regions (North America

n=3149, Latin America n=658, AsiaPacific n=1744, Central Europe n=966 and Western Europe n=490). Quality indicators assessed at hospital discharge from the US-based Get With The Guidelines program were used, including: medications (ACEI/ARB, beta blockers, aldosterone inhibitors, hydralazine-nitrates, statin therapy and warfarin) for eligible patients, use (or planned use) of implantable intracardiac devices (ICD, CRT) for eligible patients and blood pressure control (<140/90 mmHg).

Results: 7007 intent-to-treat AHF patients in 398 centres were enrolled. There was significant variation in conformity between different quality indicators, ranging from 0% to 89% (See Table). Of all potential performance opportunities, 24,807 of 39874 (62%) were met, with Central Europe highest at 68%, followed by North America (65%), Western Europe (63%), Latin America (59%) and Asia-Pacific (56%), P<0.0001.

Conclusion: Quality of care for patients hospitalized with AHF remains suboptimal even within a randomized clinical trial. Moreover, significant unexplained inter-regional variability in quality of care exists. Further study is required to understand and overcome the global barriers to delivery of optimal evidence-based care.

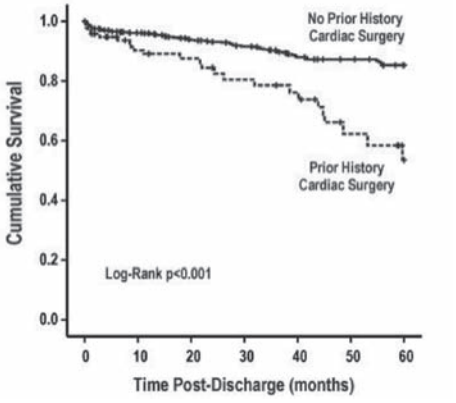
18683 Outcomes of Patients Presenting with Acute Type A Aortic Dissection in the Setting of Prior Cardiac Surgery: An Analysis from the International Registry of Acute Aortic Dissection

Nicholas Teman, The Univ of Michigan, Ann Arbor, MI; Mark D Peterson, St. Michael's Hosp, Toronto, ON, Canada; Mark J Russo, Univ of Chicago Medical Ctr, Chicago, IL; Marek P Ehrlich, Univ of Vienna, Vienna, Austria; Truls Myrmel, Tromso Univ Hosp, Tromso, Norway; Gilbert R Upchurch Jr, Univ of Virginia Health System, Charlottesville, VA; Kevin Greason, Mayo Clinic, Rochester, MN; Mark Fillinger, Dartmouth-Hitchcock Medical Ctr, Lebanon, NH; Alberto Forteza, Hosp Univrio "12 de Octubre", Madrid, Spain; Michael G Deeb, Daniel G Montgomery, Kim A Eagle, The Univ of Michigan, Ann Arbor, MI; Eric M Isselbacher, Massachusetts General Hosp, Boston, MA; Christoph A Nienaber, Univ Hosp Eppendorf-Rostock, Rostock, Germany; Himanshu J Patel, The Univ of Michigan, Ann Arbor, MI

Introduction: Prior cardiac surgery can complicate the clinical presentation, diagnosis, and management of patients with type A aortic dissection (TAAAD). This report from the International Registry of Acute Aortic Dissection (IRAD) examines this hypothesis. Methods: 352 of 2289 TAAAD patients (15.4%) enrolled in IRAD had cardiac surgery prior to dissection, including coronary artery bypass grafting (CABG, 34.6%), aortic or mitral valve surgery (38.4%), aortic surgery (44.7%), and other cardiac surgery (18.1%).

Results: Comparative differences in baseline demographics, clinical presentation, and management time are shown in Table 1. Patients with prior cardiac surgery were more likely to undergo CABG (p=0.006) or mitral valve replacement (p=0.001) at the time of dissection repair. Total cardiopulmonary bypass time was higher in patients with prior cardiac surgery (p<0.001); no difference was seen in cardiac arrest time (p=0.113) or cerebral ischemia time (p=0.286). Inhospital mortality was significantly higher for patients with prior cardiac surgery (33.5% vs.

Variable	Prior Cardiac Surgery	No Prior Cardiac Surgery	p-value
Demographic Factors			
Age (mean ± SD)	65.5±14.2	61.3±14.4	<0.001
Gender – male	264 (75.0%)	1286 (66.4%)	0.001
History of hypertension	271 (80.4%)	1365 (71.2%)	<0.001
History of diabetes	30 (9.1%)	107 (5.6%)	0.014
History of atherosclerosis	165 (50.0%)	326 (17.2%)	<0.001
Clinical Presentation			
Chest pain	242 (73.3%)	1552 (83.0%)	<0.001
Syncope	36 (11.4%)	342 (18.6%)	0.002
Presenting hypotensive	35 (11.5%)	312 (17.2%)	0.013
Timing of Management			
Time from symptom onset to initial hospital presentation (median ± SD), hours	3.8 (1.1-19.3)	2.0 (1.0-9.9)	0.004
Time from symptom onset to tertiary hospital presentation (median ± SD), hours	12.0 (4.3-48.0)	7.8 (4.0-24.0)	0.003
Time from symptom onset to diagnosis (median ± SD),	14.1 (4.0-45.0)	8.1 (3.5-24.0)	0.001



24.0%, p70 (RR1.58, 95% CI 1.25-1.99), and medical management of acute dissection (RR 4.79, 95% CI 3.62-6.34). Kaplan-Meier analysis is shown in Figure 1.

Conclusion: Prior cardiac surgery not only delays presentation and diagnosis of acute type A dissections, but is also an important adverse risk factor for early and late mortality.

11025 Ventricular Efficiency Depends Critically on Systolic Contraction Below Unloaded Equilibrium Volume

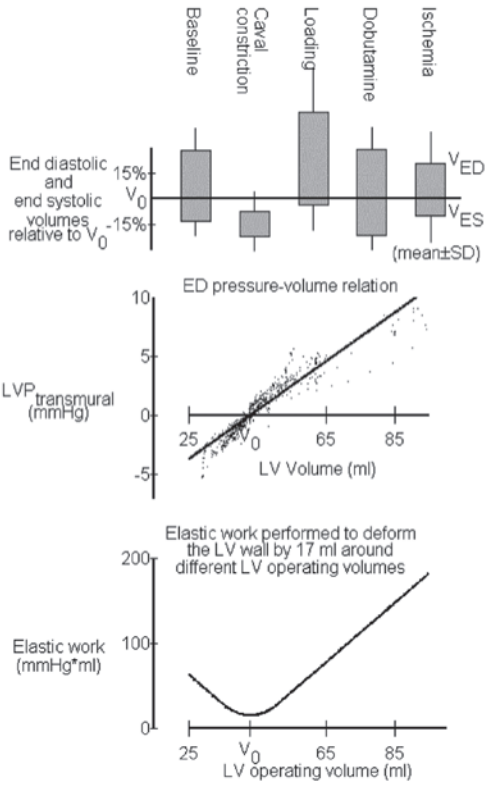
Espen W. Remme, Anders Opdahl, Morten Eriksen, Otto A. Smiseth, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway

Background: Systolic left ventricular (LV) contraction below unloaded LV equilibrium volume (V0) generates restoring forces which enhance early diastolic filling, equivalent to lengthening of a spring that has been compressed below slack length. It is debated whether the LV normally contracts below V0 or if it operates above V0 the entire ventricular cycle. We investigated this in dogs and further calculated the work the myocardium spends on pure elastic deformation of the myocardial wall at different operating volumes relative to V0. This elastic work must be generated in addition to the work that moves blood in and out of the ventricle and should be as low as possible to optimize efficiency.

Methods: In 10 anesthetized open chest dogs with resutured pericardium we measured LV volume by sonomicrometry and LV and pericardial pressures during baseline, caval constriction, volume loading, dobutamine infusion, and ischemia. We assessed end systolic (VES) and end diastolic (VED) volumes. V0 was found from gradual caval constriction as the zero LV transmural pressure crossover of ED volume points. The passive LV pressure-volume operating stiffness was assessed and used to calculate the elastic work required to deform the ventricle by the mean stroke volume. This work was calculated for operating volumes below, around, and above V0.

Results: In almost all cases the LV contracted below V0. Mean VES and VED are shown in the top panel of the figure relative to V0 for each intervention. Mean passive pressure-volume relation is shown in the middle panel. The elastic work required to deform the ventricle by mean stroke volume showed a minimum for contraction below and filling above V0 (lower panel).

Conclusions: The LV contracted below and filled above V0 in the open-chest anesthetized dogs with slightly depressed function. The findings therefore suggest that also the normal LV, with presumably better contractility, operates around V0, which seems to be the most energetically efficient.



16388 Efficacy and Safety of Early Dalcetrapib Treatment on Lipid Profile and Markers of HDL Functionality in Patients Hospitalized for an Acute Coronary Syndrome - The dal-ACUTE Study

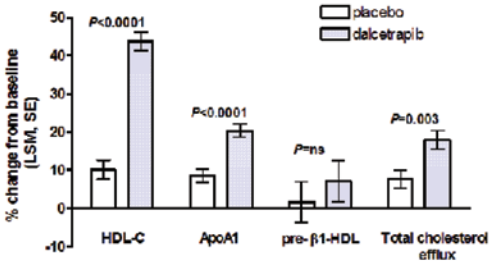
Kausik Ray, St George's Univ of London, London, United Kingdom; Marc Ditmarsch, David Kallend, Gabriela Suchankova, F. Hoffmann-La Roche Ltd, Basel, Switzerland; Judith Anzures-Cabrera, Ruchi Upmanyu, Roche Products Ltd, Welwyn Garden City, United Kingdom; Valerie Lehnert, Meike Pauly-Evers, Eric J Niesor, F. Hoffmann-La Roche Ltd, Basel, Switzerland; Ingar MK Holme, Oslo Univ Hosp, Oslo, Norway; Josef Stasek, Charles Univ Faculty Hosp, Hradec Králové, Czech Republic; Maarten WJ van Hessen, Groene Hart Zieckenhaus, Gouda, Netherlands; Peter H Jones, Baylor Coll of Med, Houston, TX

Introduction: The dal-ACUTE study assessed the efficacy and safety of the CETP modulator dalcetrapib in patients with a recent acute coronary

syndrome (ACS) event. Methods: In this Phase III, multi-center study, patients were randomized (1:1) to dalcetrapib 600 mg or placebo daily for 20 weeks within 1 week of hospitalization for an ACS event with 4-week safety follow up. The primary efficacy endpoint was percent change from baseline in HDL-C after 4 weeks. Secondary endpoints included blood lipid, lipoprotein and apolipoprotein levels and measures of HDL functionality (pre-β1-HDL and cholesterol efflux capacity). P<0.05 was considered statistically significant.

Results: 300 patients were randomized, within mean 3.9 days of the index ACS event. The majority of patients (75.2%) were statin naïve prior to the index event. By Week 4, dalcetrapib increased HDL-C by 33.7% vs placebo (P<0.0001), with a corresponding increase in ApoA1 of 11.8% (P<0.0001). LDL-C and ApoB levels declined post ACS but did not differ between placebo and dalcetrapib (both P>0.1). Pre-β1-HDL levels were unchanged vs placebo (P=0.42), however, total cholesterol efflux (% efflux over 4 hours) was significantly increased with dalcetrapib [LSM (95% CI) 9.5% (3.17, 16.18) P=0.003]. The change in cholesterol efflux correlated moderately with changes in HDL-C, pre-β1-HDL and ApoA1 (r = 0.42, 0.40 and 0.54 respectively, all P<0.0001). Dalcetrapib was generally well tolerated with a similar adverse event profile to placebo.

Conclusions: Dalcetrapib was well tolerated and significantly increased HDL-C and ApoA1 levels consistent with previous studies in stable patients. In the context of ACS, the variance (r 2) in cholesterol efflux with dalcetrapib was approximately twice as strong with change in ApoA1 than with change in HDL-C levels. The clinical relevance of these different parameters will be assessed in other datasets.



16312 Work Physiology Revisited

Henrik Loe, Øivind Rognmo, Ulrik Wisløff, NTNU, Trondheim, Norway

Background: Evidence supports a robust inverse association between cardiorespiratory fitness and all-cause mortality. Prior research assessing cardiorespiratory fitness data and the correlation between these variables tend to use peak oxygen uptake, indirect measuring methods and selected populations.

Purpose: The aim of this study was to provide a large reference material on exercise physiology data in a healthy mixed sex population age 20-90 years. Methods: Data in the HUNT 3 fitness study was obtained from a representative cross-section of volunteering Norwegians consisting of 1929 males and 1881 females, and was collected from June 2007 to June 2008. VO2max, maximal heart frequency, O2 pulse and workload was measured during treadmill running. O2 pulse was measured at 3 different work intensity levels including maximum work capacity, and subjective perception of fatigue (Borg scale: 6-20) was stated at each level. The physical activity index score (PAI) was calculated from the candidates response to a questionnaire.

Results: The highest VO2max and heart rate among males and females was found in the youngest age group and was 54.4 ± 8.4 mL•kg-1•min-1 and 43.0 ± 7.7 mL•kg-1•min-1 (gender differences, p<0.001) and 196 ± 10 beats•min-1 and 194 ± 9 beats•min-1 (gender differences, p<0.05), respectively, with a subsequent reduction of approximately 1 MET and 6 beats•min-1 per decade. The highest O2 pulses are displayed in the 3 youngest age groups among males and females, 22.3 mL•beat-1 ± 3.6 and 14.7 mL•beat-1 ± 2.7 (gender differences, p<0.001), respectively, with no significant difference between these age groups. Following age groups display an 8% reduction per decade among both genders. Reported Borg scores appear to give a good estimate of the relative exercise intensity. The youngest age group, both males and females, presented physical activity index score (PAI) considered to indicate a high level of physical activity, whereas all other groups displayed PAI scores indicating moderate physical activity.

Conclusion: The HUNT 3 fitness study provides reference values on a range of exercise physiological parameters in a large healthy population age 20-90 years. It also displays associations between physiological variables.

276 A Genetic Algorithm Prognostic Tool Nested Within a 2500-Patient Registry of Post-Cardiac Arrest Care

Niklas Nielsen, Helsingborg Hosp, Helsingborg, Sweden; David Seder, Maine Medical Ctr, Portland, ME; Hans Friberg, Lund Univ, Lund, Sweden; Michael Mooney, Minneapolis Heart Inst, Minneapolis, MN; Sten Rubertsson, Uppsala Univ Hosp, Uppsala, Sweden; Pascal Stammet, Ctr Hospier de Luxembourg, Luxembourg, Luxembourg; Kjetil Sunde, Oslo Univ

Hosp, Oslo, Norway; Barbara Unger, INTCAR, Portland, ME; Richard R Riker, Maine Medical Ctr, Portland, ME; INTCAR Study Group

Objectives: Predicting outcome after cardiac arrest (CA) is challenging. With data collected in the International Cardiac Arrest Registry (INTCAR), a novel prediction tool based on genetic algorithm (GA) was developed.

Methods: 2,564 adult, resuscitated, comatose CA patients were included from 35 sites in Europe and USA. Primary outcome was hospital discharge Cerebral Performance Category (CPC) dichotomized into good (GO=CPC1-2) and poor outcomes (PO=CPC 3-5). The GA-based models were constructed using Experlytics® software including all 180 candidate variables from the registry. A decision tree displaying the relation of the information carrying variables was evolved and pruned to a final model and optimized towards accuracy, sensitivity, specificity and Receiver-Operating Characteristic (ROC) value. .

Results: Median age was 64 (IQR 54-73) years, 30% were female, the CA was witnessed in 84%, and initial rhythm was VF/VT in 55%, asystole in 23%, PEA in 17%. Time to ROSC was 19 (10-30) min. 37% had a GO at hospital discharge. 35% had coronary disease, 14% insulin dependent diabetes mellitus (IDDM), 8 % non-IDDM and 14% pulmonary disease. The final tree (figure 1) had an accuracy of 85%, a sensitivity of 91% and a specificity of 72%. The area under the ROC curve was 87% (CI 83-90).

Conclusions: A novel tool based on GA predicted outcome comparable to previous models. The GA could visually display the important information carrying variables and their relation. This model requires external validation, but represents a promising tool to better predict outcome and define the relationship between important risk factors

Figure 1. Relation of variables in a decision tree displaying good and poor outcome. ACD, automatic compression decompression, CPC, cerebral performance category, CPR, cardiopulmonary resuscitation, GCS, Glasgow Coma Scale, IDDM, Insulin dependent diabetes mellitus, MRI, magnetic resonance imaging, ROSC, return of spontaneous circulation.

15052 Cardiovascular Event Reduction Versus New-Onset Diabetes During Atorvastatin Therapy: Effect of Baseline Risk Factors for Diabetes

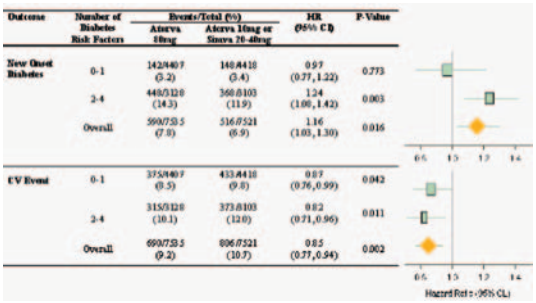
Jennifer E. Ho, Massachusetts General Hosp, Boston, MA; David D. Waters, San Francisco General Hosp, San Francisco, CA; David A. DeMicco, Pfizer, Inc, New York, NY; Benoit J. Arsenault, Univ Laval, Quebec, QC, Canada; S. Matthijs Boekholdt, Academic Medical Ctr, Amsterdam, Netherlands; Michael Messig, Pfizer, Inc, New York, NY; John J.P. Kastelein, Academic Medical Ctr, Amsterdam, Netherlands; Terje R. Pedersen, Oslo Univ Hosp, Oslo, Norway

Background: Statins reduce cardiovascular (CV) events but increase the incidence of new-onset diabetes (NOD). We previously reported that in each of 3 large randomized trials using atorvastatin 80 mg/day, 4 risk factors were independent predictors of NOD: baseline fasting glucose >100 mg/dl, fasting triglycerides >150 mg/dl, body-mass index >30 kg/m2 , and a history of hypertension. We sought to compare CV event reduction and NOD in 15,056 non-diabetic patients with coronary disease in the TNT (n=7,595) and IDEAL (n=7,461) trials.

Methods and Results: Patients were randomized to atorvastatin 80 vs 10 mg/day (TNT) or atorvastatin 80 vs simvastatin 20-40 mg/day (IDEAL) and followed for a median of 5 years in both trials. CV events included coronary heart disease death, myocardial infarction, stroke and resuscitated cardiac arrest. High-dose atorvastatin was associated with an increased odds of NOD among participants with 2-4 risk factors (OR 1.24, 95% CI 1.08-1.42, P=0.003), but not in those with 0-1 risk factors for NOD (OR 0.97, 95% CI 0.77-1.22, P=0.77), when compared with low-dose atorvastatin or simvastatin (Figure). In contrast, high-dose atorvastatin was associated with a decreased odds of CV events regardless of the number of NOD risk factors present (Figure). There was a suggestive interaction between

treatment and risk factor group in the prediction of NOD (P=0.07).

Conclusion: Compared to low-dose statin therapy, treatment with atorvastatin 80 mg/day was not associated with an increased risk of NOD in patients with 0-1 NOD risk factors. Among patients with 2-4 NOD risk factors, atorvastatin 80 mg was associated with a 24% increase in NOD. CV events were significantly reduced with atorvastatin 80 mg regardless of NOD risk factors.



14287 The Matricellular Protein CCN2/CTGF Alters Remodeling and Fibrotic Response Following Myocardial Infarction in Mice

Geir Florholmen, Ole J Kosbøll, Jørgen Gravning, Else M Hagelin, M Shakil Ahmed, Håvard Attramadal, Inst for Surgical Res, Oslo, Norway

Myocardial infarction (MI) causes remodeling of the myocardium where fibrosis is an important response. Several secreted factors, including transforming growth factor (TGF)β, are shown to participate in the development of fibrosis. We have previously shown increased myocardial expression of CCN2 in postschemic remodeling of the heart, but it is not known how this may regulate the fibrotic response. The objective of this study is to investigate the role of CCN2 in development of remodeling and fibrosis following MI. MI was induced by ligation of the left coronary artery in transgenic mice with cardiac-restricted overexpression of CCN2 (Tg-CCN2) and compared with non-transgenic littermate control (NLC) mice. Animals were harvested after 28 days. Fibroblasts were isolated from NLC mice, maintained in culture (passage 1) and stimulated with recombinant CCN2 (250 nmol/L) and TGFβ-1 (0.5 μg/ml) for 48 hours. Following MI we observed that the increase in myocardial collagen contents were smaller in Tg-CCN2 mice than in NLC mice (3.2±0.4-fold vs. 5.8±0.5-fold, n=6, p<0.01). Tg-CCN2 mice also maintained higher LV fractional shortening (20.2±1.5% vs. 14.3±2.3%, n=12, p<0.05) and ejection fraction (40.7±2.7% vs. 29.2±4.4, n=12, p<0.05) and revealed less dilatation of LV end-diastolic inner diameter (5.1±0.1mm vs. 5.7±0.3mm, n=12, p<0.05). Finally, more Tg-CCN2 animals survived the study period (67% vs. 38%, p<0.05). In isolated fibroblasts, CCN2 reduced protein expression of the myofibroblast marker α-smooth muscle actin (SMA) to 44±5%, p<0.01 (n=3) of control values. CCN2 reduced stress fiber formation (α-SMA) in fibroblasts maintained in culture. Interestingly, CCN2 inhibited a TGFβ-1-induced differentiation of fibroblasts by preventing upregulation of α-SMA protein levels. We also observed CCN2 to inhibit TGFβ-1 induced stress fiber formation.

We conclude that the remodeling process is attenuated and LV function improved in mice with cardiac-restricted overexpression of CCN2 following MI. These changes may be related to direct effects of CCN2 on fibroblasts in the myocardium. Our results also suggest that CCN2 diminishes effects of the pro-fibrotic responses of TGFβ-1.

12886 Rare Variants in GJA5 Associated with Early-Onset Atrial Fibrillation

Ingrid E Christophersen, Danish Arrhythmia Res Ctr, Copenhagen Ø, Denmark; Haya N Holmegard, Javad Jabbari, Stig Haunsø, Danish Arrhythmia Res Ctr, 2100 Copenhagen Ø, Denmark; Arnljot Tveit, Bærum Hosp, Vestre Viken Hosp Trust, NO-1309 Rud, Norway; Jesper H Svendsen, Morten S Olesen, Danish Arrhythmia Res Ctr, 2100 Copenhagen Ø, Denmark

Background: GJA5 encodes the atrial-specific gap-junction protein Cx40, which together with Cx43 is responsible for the electrical coupling of the atrial cardiomyocytes. Gollob et al. were the first to associate mutations in this gene with atrial fibrillation (AF) in a study published in NEJM in 2006. They also showed that genetic variants in GJA5 can lead to altered expression of the gene-product Cx40, and changes in the functional coupling of wild type Cx43. The regulatory single nucleotide polymorphism (SNP) rs10465885 in GJA5 was recently associated with early-onset lone AF (<60 y) and with the levels of Cx40 mRNA. We hypothesized that this gene would have strong impact in patients with onset of lone AF before the age of 50, and that the findings regarding rs10465885 could be replicated in this group.

Methods: The coding region and flanking intron sequences of GJA5 was resequenced in 342 patients with onset of lone AF before the age of 50 (mean age at onset 34 ± 9, 82% men, median age 44 y, IQR 38-48 y) and in 216 controls (52% men, median age 39 y, IQR 30-48 y). The SNP rs10465885 was genotyped in 342 patients and

534 controls (52% men, median age 65 y, IQR 60-70 y) and ORs were calculated for different genetic models.

Results: Genotyping of rs10465885 showed that the patients with early-onset lone AF were more likely to carry the A-allele compared to controls (OR=0.77, p=0.011). When resequencing GJA5, we identified the mutation A96S, which previously has been associated with lone AF. This was not present in our controls and has not been described in any publicly available database or in the NHLBI Exome Variant Server, holding data on 10.758 alleles.

Conclusions: To our knowledge, this is the largest reported cohort of patients with such a highly selected AF phenotype, and no other study has investigated the impact of both rare and common variants in GJA5 in these patients. We report a significant association of the A-allele of the promoter variant rs10465885 in GJA5, with early-onset lone AF. The biological link between this variant and the development of AF might be that increased levels of the atrial-specific gapjunction protein Cx40, could lead to disturbance of the natural connexin balance, resulting in decreased atrial conduction velocity and thus an increased risk of AF.

11917 Angiotensin-Converting Enzyme Inhibitors are not Associated With Increased Sudden Cardiac Death, Cardiovascular Mortality or All-cause Mortality In Patients With Mild to Moderate Aortic Stenosis - The SEAS Study

Casper N Bang, Anders M Greve, Lars Køber, Rigshospitalet, Copenhagen, Denmark; Anne B Rossebø, Oslo Univ Hosp, Oslo, Norway; Simon Ray, Manchester Academic Health Sciences Ctr, Manchester, United Kingdom; Kurt Boman, Umeå Univ, Med Skellefteå, Umeå, Sweden; Christoph A Nienaber, Univsklinikum Rostock, Rostock, Germany; Richard B Devereux, Weill Cornell Medical Coll, New York, NY; Kristian Wachtell, Gentofte Hosp, Copenhagen, Denmark

Objectives: Evaluate if angiotensin-converting enzyme inhibitors (ACEI) are well tolerated in patients with mild to moderate aortic stenosis (AS).

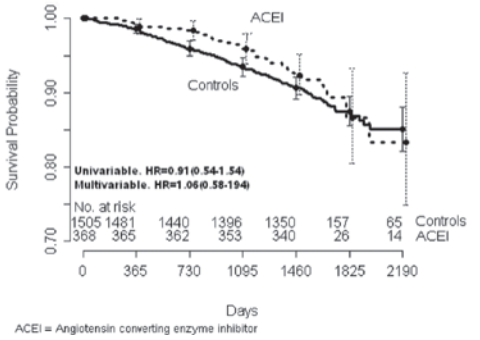
Background: ACEI are avoided in AS patients because of the risk of hypotension.

Methods: From the Simvastatin Ezetimibe in Aortic Stenosis study patients with asymptomatic mild to moderate AS (transaortic Doppler velocity 2.5 and 4.0 m/sec) and preserved LV ejection fraction (EF) were included. Risks of hypotension (systolic bloodpressure<90mmHg), sudden cardiac death, cardiovascular mortality and all-cause mortality and according to ACEI use were analyzed by time-varying Cox models adjusted for age, gender, other medication and comorbidity, and additionally in propensity score matched analysis.

Results: 1873 patients (mean age was 68±10years) were analyzed, including 368 (19.6%) patients receiving ACEI. At baseline treated patients had higher systolic blood pressure (148±20.2 vs. 144±19.8mmHg) and LV mass index (106±34.4 vs. 99±29.6g/m2) than the non-treated, but there was no difference in gender, age, aortic valve area or simvastatin/ezetimibe treatment. During a median follow-up of 52.2 months, there were 2.4% vs. 2.1% sudden cardiac deaths, 7.6% vs. 5.0% cardiovascular deaths and 9.5% vs. 11.3% all-cause deaths in the patients receiving vs. not receiving ACEI. Only 6 patients had in-study hypotension. The multivariable time-varying Cox analysis showed no increase in the risk of sudden cardiac death (HR: 1.47 [95%CI: 0.43-5.07], p=0.538), cardiovascular mortality (HR: 2.03 [95%CI: 0.78-3.28], p=0.203) or all-cause mortality (HR: 1.06 [95%CI: 0.58-1.94], p=0.857, Figure) among ACEI treated. These outcomes were supported in propensity matched analysis (All p>0.05).

Conclusions: Angiotensin-converting enzyme inhibitors were not associated with increased risk of sudden cardiac death, cardiovascular mortality or all-cause mortality in patients with asymptomatic mild to moderate AS.

K-M Estimate of All-cause Mortality According to Treatment



ACEI = Angiotensin converting enzyme inhibitor