NORSKE ABSTRACTER PRESENTERT PÅ AHA

Summaries of the AHA Council Lectures 2011

Dickinson W. Richards Memorial Lecture

Improving Cardiac Arrest Outcomes: Fine-tuning or Paradigm Shift?

Petter Andreas Steen, MD, PhD, FERC. Oslo University Hospital, Oslo, Norway

In the 1970-80ies we studied barbiturates, moderately severe hypothermia, free radical scavengers and calcium blockers without impacting outcome after cerebral ischemia. In fact cardiac arrest outcome in general did not improve much until 2005. We underestimated the impact of CPR quality. Long pauses in inadequate depth chest compressions, particularly before, during and after series of defibrillation attempts were documented and found detrimental. We and others have shown that quality can be improved, but as with quality work also outside the health care industry, it requires continuous focus, local champions and continuous feedback both on performance and results. This is true both pre-and in-hospital, both during CPR and in the post-arrest period. The controversy of CPR or defibrillation first is solved, at least for the moment. The place of drugs during CPR is questionable, without solid clinical evidence for improved long term outcome for any drug. Although not universally achieved, significant improvements in cardiac arrest outcome have been reported by some pre- and in-hospital services over the last 5-6 years due to fine-tuning of the treatment process including much focus on the post-arrest period with temperature control/hypothermia and coronary interventions. There are more fine-tuning challenges ahead, and better implementation of known science is required, but what about paradigm shifts? We tend to forget that globally cardiac arrest of non-cardiac origin is a much larger challenge and opportunity that cardiac arrest of cardiac origin, both as potential lives saved, and even more as life-years saved.

Abstract 17087: Doubled Survival From Out-of-Hospital Cardiac Arrest in a Rural Community in North-Norway Following Implementation of an Aggressive Chest Pain Protocol with Early Prehospital Thrombolysis for STEMI

Janne M Lien Nilsen; Ida Bø; Jan R Rasmussen; Esten K Haanaes; Mads Gilbert. Clinic of Emergency Medicine, University Hosp of North Norway, Tromsoe, Norway

Introduction Survival from prehospital cardiac arrest (PCA) remains low. Tromsø municipality in rural North-Norway has a mixed urban-rural population of 60.000, good ground and air ambulance systems, short response times, and dispatch centres staffed with nurses and paramedics, all loyal to current guidelines.

Hypothesis By changing focus from the onset of '*collapse*' in PCA to the onset of *chest pain* in acute coronary syndrome, we hypothesized that more PCA-patients could survive by saving time to alarm, dispatch, diagnosis and first defibrillation. We started an aggressive criteria based prehospital chest pain protocol in 2000. Local GPs and ambulance paramedics were trained in symptoms and signs of STEMI, to access and transmit prehospital 12-leads ECG, give MONA as well as early prehospital thrombolysis (PHT) to patients with prehospital diagnosed acute STEMI. We applied defibrillation pads to all chest pain. The population was informed through media stunts.

Methods Retrospective study of survival from PCA during two 5-years periods in Tromsø (1999 -2004; 2004-2009). Each PCA patient's Utstein-chart, digital dispatch centre logs, hospital records and non-survivors autopsy reports were analysed.

Results Annual incidence of PCA with resuscitation attempts and ambulance dispatched was 45,3 pr. 100.000. During first 5-years, 10,5 % of all patients (18/172) with PCA were discharged alive. During second period, survival to discharge doubled to 22,3 % (31/139, $p<0,05$). Presence of an initial shockable rhythm (VF/VT) increased significantly. In patients with witnessed PCA of cardial etiology and a shockable first rhythm, survival to discharge was 21,4 % during the first 5-years period, but doubled to 44,2 % (19/43, $p<0,05$) in the second period. CPR was started by lay bystanders prior to ambulance arrival in

68,2 % of patients during first, increasing to 76,3 % during the second study period (NS). Prehospital ambulance response time was unchanged at 10 min in each period. By moving system attention 'to the left of cardiac arrest', survival to discharge doubled.

Abstract 10997: Apheresis in Homozygous Familial Hypercholesterolemia - Results of 35 Years of Follow-Up of All Norwegian Patients with Homozygous Familial Hypercholesterolemia

Martin P Bogsrud[1]; Asgeir Græsdal[1]; Kirsten B Holven[1]; Marit S Nenseter[1]; Ingunn Narverud[2]; Gisle Langslet[1]; Magne Brekke[3]; Kjetil Retterstøl[1]; Kjell-Erik Arnesen[1]; Leiv Ose[1]. [1] Lipidklinikken (Lipid Clinic), Oslo Univ Hosp Rikshospitalet, Oslo, Norway, [2] Dept of Nutrition, Institute for Basic Med Sciences, Univ of Oslo, Oslo, Norway, [3] Departement of Cardiology, Heart-, Lung- and Vascular Disease Clinic, Oslo Univ Hosp Ullevål, Oslo, Norway

Objective: Homozygous familial hypercholesterolemia (HFH) affects 1 per million, and leads to extreme cholesterol values and premature cardiovascular disease. Although removal of LDL-cholesterol by apheresis has significantly improved life expectancy for these patients, premature cardiovascular disease is still frequent. The aim of the present study was to obtain an overview of the seven HFH patients treated by LDL-apheresis in Norway.

Methods and results: Quality of life, clinical, laboratory, and cardiovascular status was assessed. Data are given as median (range). LDL-cholesterol at diagnosis (untreated) was 18.2 (15.3 - 32.8) mmol/L. Start of medication was at age 9 (2 - 35) years. Start of apheresis treatment was at age 10 (6 - 44) years. On regular weekly treatment with apheresis combined with maximum tolerable dose of statin and ezetimibe, LDL-cholesterol was reduced to 5.1 (4.5 - 7.3) mmol/L pre-apheresis, and 2.2 (1.3 - 2.8) mmol/L post-apheresis. Mean interval LDL-cholesterol was calculated being 4.2 (3.5 - 5.7) mmol/L. Two of the patients had untreated elevated levels of Lipoprotein (a) [2558 mg/L (reduced to 1390 mg/L pre- and 521 mg/L post-apheresis), and 1700 mg/L (reduced to 1630 mg/L pre- and 508 mg/L post-apheresis), respectively]. Time in apheresis treatment was 11 (1.5 - 24) years. Four patients had significant cardiovascular manifestations at the start of apheresis, and three of these experienced further progression despite treatment. Three patients did not have significant cardiovascular manifestations at start of apheresis, but two developed significant manifestations despite treatment. Thus, only one of the patients is totally free from cardiovascular findings. The patients scored high on both physical and mental health as measured by SF-36®, comparable to a healthy normal population in Norway.

Conclusion: LDL-apheresis is a well tolerated treatment. Five of seven patients had progression of cardiovascular manifestations despite mean interval LDL-cholesterol far below suggested treatment goals. It seems clear that treatment goal for these patients should be even lower, in line with patients having the much more frequent heterozygous form, orally treated (e.g. statins) to an LDL-cholesterol level of 1.8-2.6 mmol/L.

Abstract 183: Prevalence and Development of Clinical States During Resuscitation from In-Hospital Cardiac Arrest

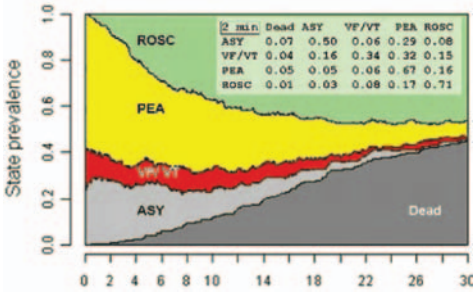
Trond Nordseth[1]; Dana P Edelson[2]; Daniel Bergum[1]; Theresa M Olasveengen[3]; Trygve Eftestøl[4]; Benjamin Abella[5]; Eirik Skogvoll[1]. [1] Norwegian Univ of Science and Technology, Trondheim, Norway, [2] Univ of Chicago, Chicago, IL, [3] Univ of Oslo, Oslo, Norway, [4] Univ of Stavanger, Stavanger, Norway, [5] Univ of Pennsylvania, Philadelphia, PA

Background During resuscitation of a patient in cardiac arrest the clinical state determines the management. The state will change either spontaneously (e.g. pulseless electrical activity [PEA] - asystole [ASY]), or due to intervention (e.g. ventricular fibrillation/-tachycardia [VF/VT] - return of spontaneous circulation [ROSC] following shock). The aim of this study was to describe and analyze the development of clinical states in patients receiving advanced life support (ALS).

Methods Defibrillator files from 261 in-hospital cardiac arrests at the University of Chicago Hospital (Il, USA) and St.Olav University Hospital (Trondheim, Norway) were analyzed. The clinical states ASY, PEA, VF/VT, ROSC and death were annotated along the time axis. The average transition probabilities over all 2-minute periods (recommended CPR "loop" duration), were estimated using a Markov model.

Results The figure shows the development of clinical states during the first 30 minutes of ALS. The inserted matrix shows the estimated probabilities of moving from one state (rows) to another (columns), during the next two minutes of ALS. E.g. a patient in PEA has a probability of 0.16 of gaining ROSC during (any) two minutes. Relapse to PEA from ROSC has a probability of 0.17. The prevalence of ROSC continues to increase until about 25 minutes of ALS, where about 45% of the patients have obtained ROSC and 35% have been declared dead.

Discussion We provide a basic description of the dynamics of resuscitation from in-hospital cardiac arrest. Understanding these dynamics enables the provider to focus on important transitions (e.g. relapse from ROSC), and may provide a basis for improved tailored therapy.



Abstract 49: Optimal CPR Loop Duration for Asystole and Pulseless Electrical Activity During In-Hospital Cardiac Arrest

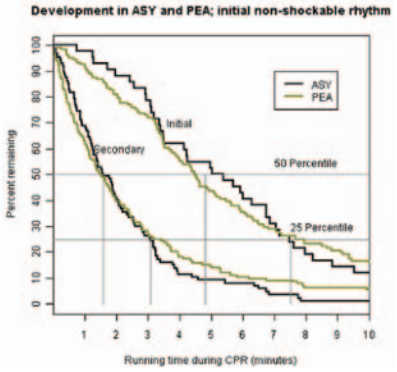
Trond Nordseth[1]; Dana P Edelson[2]; Daniel Bergum[1]; Theresa M Olasveengen[3]; Trygve Eftestøl[4]; Benjamin Abella[5]; Eirik Skogvoll[1]. [1] Norwegian Univ of Science and Technology, Trondheim, Norway, [2] Univ of Chicago, Chicago, IL, [3] Univ of Oslo, Oslo, Norway, [4] Univ of Stavanger, Stavanger, Norway, [5] Univ of Pennsylvania, Philadelphia, PA

Background Cardiopulmonary resuscitation (CPR) is a process where time-cycled "loops" of chest compressions form the basis of action. Optimal loop duration is a compromise between interrupting compressions and detecting a change in the clinical state. Current CPR guidelines recommend a two-minute loop duration. The aim of this study was to investigate optimal loop duration in asystole (ASY) and pulseless electrical activity (PEA).

Material and methods Detailed defibrillator recordings from 261 in-hospital cardiac arrests at the University of Chicago Hospital (Chicago, Ill., U.S) and St.Olav University Hospital (Trondheim, Norway) were analyzed. The clinical states ASY, PEA, ventricular fibrillation/-tachycardia (VF/VT), return of spontaneous circulation, and death were annotated along the time axis. We analyzed the development of clinical states ASY and PEA, both as initial and secondary states. As the development of initial VF/VT depended on heterogeneous shock strategies implemented by providers, these patients (n=46) were excluded from further analysis.

Results The figure shows the development of PEA and ASY as Kaplan-Meier plots.ASY and PEA behaves similarly. By 5 minutes 50% percent of the patients with initial ASY/PEA have progressed to a different clinical state; by 8 minutes 25 % remain. Secondary ASY/PEA progresses earlier to other clinical states.

Discussion To minimize pauses in chest compressions it is reasonable to aim between the 50th and 25th percentile, when a change of state most likely has occurred. Optimal loop in initial PEA and asystole appears to be between 5 and 8 minutes, and between 1 and 3 minutes in secondary PEA and ASY.



Abstract 14841: A Video-based Cardiopulmonary Resuscitation Analysis System "See-CPR"

Chih-Wei Yang[1]; Min-Chun Hu[2]; Ja-Ling Wu[2]; Joar Eilevstjønn[3]; Matthew Huei-Ming Ma[4]. [1] Dept of Emergency Medicine, Dept of Med Education, National Taiwan Univ Hosp, Taipei, Taiwan, [2] Communications and Multimedia Lab, National Taiwan Univ, Taipei, Taiwan, [3] Dept of Electrical and Computer Engineering, Laerdal Med AS, Stavanger, Norway, [4] Dept of Emergency Medicine, National Taiwan Univ Hosp, Taipei, Taiwan

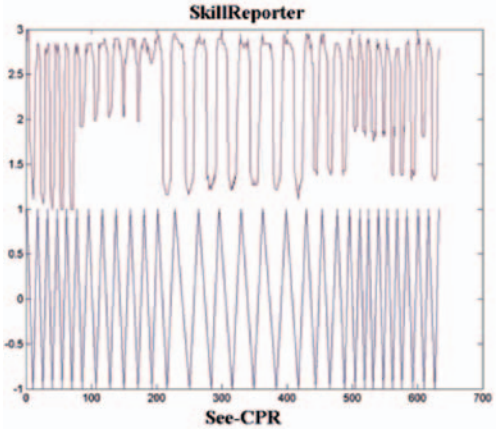
Objectives: Various devices, either expensive or inconvenient, were developed to monitor the quality of cardiopulmonary resuscitation (CPR), which is crucial to resuscitation performance and patient survival in cardiac arrest events. A video-based CPR analysis system, called "See-CPR", was designed to automatically detect and analyze CPR qualities.

Methods: To automatically detect chest compression (CC) movements in videos documenting CPR, we first estimated the motion of objects using the motion vectors of MPEG videos. We extracted representative features and used a hierarchical detecting scheme, including frame-level detection and group-level classification, to determine the location of CC occurrence in both time and spatial domains. Compression rate, chest compression duration, and hands-off time can then be shown on videos simultaneously. (Figure 1) To determine the precision and recall, the number of detected CC was compared with

real CC, which was detected by CPR reporting software (SkillReporter, Laerdal, Norway) connected to a mannequin (Resusci Anne, Laerdal, Norway). (Figure 2)

Results: Five video sequences, which recorded CC performance by different subjects, were used as test data for CC detection. The overall precision and recall achieved 99.7% and 100% respectively. The only one falsely detected CC was intentionally incorrect performance.

Conclusions: A reliable, video-based CPR detection and analysis system for automatically reporting real-time CPR qualities was proposed. It can be used for monitoring, real-time feedback and training of resuscitation.



Abstract 11793: Secretoneurin, a Peptide Associated with Mortality in Heart Failure, Modulates Cardiomyocyte Calcium Homeostasis

Anett H. Ottesen[1]; William E. Louch[2]; Cathrine Carlson[2]; Ole J. B. Landsverk[3]; Arne D. Høiseth[4]; Mats Stridsberg[5]; Erik Øie[6]; Torbjørn Omland[4]; Geir Christensen[2]; Helge Røsjø[7].
[1] Dept of Medicine, Akershus Univ Hosp, Lørenskog, Norway, [2] Institute for Experimental Med Rsch, Oslo Univ Hosp Ullevaal, Oslo, Norway, [3] Dept of Molecular Biosciences, Univ of Oslo, Oslo, Norway, [4] Dept of Internal Medicine, Akershus Univ Hosp, Lørenskog, Norway, [5] Dept of Clinical Chemistry and Pharmacology, Univ Hosp, Uppsala, Sweden, [6] Dept of Cardiology, Oslo Univ Hosp Rikshospitalet, Oslo, Norway, [7] Dept of Cardiology, Akershus Univ Hosp, Lørenskog, Norway

Background: In patients hospitalized with acute heart failure (HF), we have found a close association between plasma secretoneurin (SN) levels and the severity of HF, including a graded increase in mortality during follow-up according to admission SN level. We have recently also identified the cardiomyocytes of the left ventricle as important contributors to the elevated SN levels in HF, but currently no information is available about the influence of high SN levels on the pathophysiology of HF.

Aim: To assess the functional aspects of elevated SN levels in HF.

Methods: Functional aspects of SN were assessed in isolated cardiomyocytes and fibroblasts by immunoblotting, real-time PCR, confocal microscopy, and electrophysiology.

Results: SN perfusion (10 μg/mL) increased cardiomyocyte contraction by 53% vs. cells in standard buffer (p=0.01) and reduced the time to peak by 16% (p=0.01). SN stimulation also increased Ca^{2+} transient amplitude by 21% (p=0.002) and reduced the time to half decay by 14% (p=0.02). We observed a 21% increase in sarcoplasmic reticulum Ca^{2+} content (p<0.001) after SN stimulation, and a reduction in Ca^{2+} spark magnitude by 4% (p=0.05) with a corresponding reduction in width (12%, p<0.001) and duration (16%, p<0.001) of Ca^{2+} sparks. We observed that endogenous SN is distributed throughout the cytoplasm of cardiomyocytes, and found that AlexaFluor-labeled SN was taken up from the suspension to cardiomyocytes. No co-localization was observed with the non-specific uptake of dextran, indicating a distinct uptake mechanism for SN. Uptake of SN was verified by immunoblotting, where we found increased intracellular SN levels with higher concentration of SN applied to the cell culture. There was no effect of SN on cardiomyocyte hypertrophy or fibroblast function, as assessed by transcriptional alterations in genes involved in these processes.

Conclusion: We have found a direct effect of SN on cardiomyocyte Ca^{2+} homeostasis and specific uptake of SN in cardiomyocytes. The effect of SN on Ca^{2+} homeostasis could be clinically important as patients with HF and elevated SN levels have a poor prognosis.

Abstract 16253: The DNA Glycosylase Neil3 Regulates Stem Cell Recruitment, Cell Proliferation and DNA Repair Following Myocardial Infarction

Alexandra V Finsen[1]; Gunn Hildrestrand[2]; Ivar Sjaastad[3]; Leif Erik Vinge[1]; William Louch[4]; Øystein Sandanger[5]; Christine G Neurater[2]; Luisa Luna[2]; Lars Gullestad[1]; Geir Christensen[4]; Pål Aukrust[5]; Arne Yndestad[5]; Magnar

Bjørås[2]. [1] Dept of Cardiology, Rsch Institute for Internal Medicine, Oslo, Norway. [2] Univ of Oslo, Cntr for Molecular Biology and Neuroscience, Oslo, Norway, [3] Dept of Cardiology, Institute for Experimental Med Rsch, Oslo, Norway, [4] Univ of Oslo, Institute for Experimental Med Rsch, Oslo, Norway, [5] Univ of Oslo, Rsch Institute for Internal Medicine, Oslo, Norway

Background: Accumulation of DNA damage by impaired base excision repair (BER) could play a role in the pathogenesis of myocardial failure. The DNA glycosylase Neil3 is known to carry out BER during oxidative stress induced DNA damage. In addition we have previously demonstrated that Neil3 is localized to stem-cell rich areas in the neonatal murine brain and that Neil3$^{-/-}$ mice display only 50% DCX positive progenitor cells in the corpus striatum 3 days after induction of cerebral hypoxia/ischemia, as compared to wild type mice (WT). We therefore hypothesized that Neil3 plays an important role in myocardial remodeling and regeneration following myocardial infarction (MI), potentially involving BER mechanisms as well as stem cell physiology.

Methods and results: Myocardial gene expression of several DNA glycosylases were up-regulated in the murine post-MI heart failure (HF) model, with particularly enhanced expression of Neil3 (18-fold and 5.2-fold increase [3 days], 13-fold and 5.8-fold increase [7 days] and 2.6-fold and no increase [21 days] post-MI in infarcted and non-infarcted left ventricular (LV) tissue, respectively). Moreover, we found increased Neil3 expression (8.4-fold) in myocardial biopsies from HF patients, which significantly decreased following improvement of myocardial function during LV assist device treatment. Studying Neil3$^{-/-}$ mice, we found a significantly lower number of Sca-1 positive stem cells in the heart. Likewise, cardiospheres from adult Neil3$^{-/-}$ mice derived *in vitro* were significantly smaller than those from WT mice.

Conclusion: Our data suggest that the DNA glycosylase Neil3 has a role in regulating stem cells and cell differentiation and proliferation, in addition to its role in DNA repair, during development of post-MI HF.

Abstract 11803: Extracellular Mitochondrial DNA is a Putative Toll-Like Receptor 9 Agonist on Cardiac Fibroblasts During Myocardial Infarction

Ingrid Kristine Ohm[1]; Øystein Sandanger[1]; Ståle Haugset Nymo[1]; Alexandra Vanessa Finsen[1]; Marte Bliksøen[2]; Lars Henrik Mariero[2]; Guro Valen[3]; Ingebjørg Seljeflot[4]; Svein Solheim[5]; Pål Aukrust[1]; Arne Yndestad[1]; Leif Erik Vinge[1]. [1] Rsch Institute for Internal Medicine, Oslo Univ Hosp-Rikshospitalet, Oslo, Norway, [2] Institute for Experimental Med Rsch, Oslo Univ Hopsital-Ullevål, Oslo, Norway, [3] Institute of Basic Med Sciences, Univ of Oslo, Oslo, Norway, [4] Dept of Cardiovascular Medicine, Oslo Univ Hosp-Ullevål, Oslo, Norway, [5] Dept of Cardiology, Oslo Univ Hosp-Ullevål, Oslo, Norway

Background Toll-like receptor 9 (TLR9) recognizes CpG-motifs in bacterial DNA. Mitochondrial DNA (mtDNA) resembles bacterial DNA, and has been shown to be an endogenous ligand for TLR9. In such, there is a rationale for hypothesizing that mtDNA is released upon myocardial infarction (MI) with subsequent stimulation of cardiac TLR9. Therefore we investigated the expression and function of myocardial TLR9.

Methods and Results By PCR, we observed that plasma levels of mtDNA displayed a rapid, transient increase during human MI and PCI as compared to patients with stable angina pectoris undergoing the same procedure. We further analyzed TLR9 expression by RT-PCR in viable cardiac tissue at 3, 7 and 28 days after induction of MI in mice. An induction peaking at day 7 post-MI was seen. Furthermore, murine cardiac myocytes, fibroblasts and endothelial cells were isolated and analyzed for the presence of TLR9. Although present in all cellular entities, substantially higher TLR9 levels were observed in fibroblasts. Accordingly, further *in vitro* studies were performed in adult murine cardiac fibroblasts stimulated with different mtDNA mimicking molecules (i.e. CpG ODN) on activation of two canonical signaling pathways (NFκB and IRF/IFNβ by detection of TNFα and IL-8, *and* IFNβ, respectively). First, we demonstrated increases of TNFα, IL-8 and IFNβ upon stimulation with CpG A, B and C with varying potency. Using the most potent CpG (B), the dose-response relationship, as well as temporal profile was assessed. Peak expression levels were seen at 5 hours. Furthermore, a robust dose-response relationship was demonstrated with calculated EC_{50} values being equal for TNFα, IL-8 and IFNβ. We also demonstrated that induction of TNFα and IL-8 depends on internalization of CpG as chloroquine effectively attenuated activation. Finally, we demonstrated that CpG B exclusively signals through cardiac fibroblast TLR9 as a specific TLR9 antagonist (ODN 2088) completely inhibited activation within a narrow dose-inhibition window.

Conclusion TLR9 is both expressed and functional in cardiac tissue with cardiac fibroblasts being the putatively most important cellular source. This suggests that mtDNA released upon MI can function as a ligand mediating activation of cardiac TLR9.

Abstract 11007: Three Months Treatment with Adaptive Servo-Ventilation Improves Cardiac Function and Physical Activity in Patients with Chronic Heart Failure and Cheyne-Stokes Respiration in a Prospective Randomized Controlled Trial

Arild Hetland[1]; Kristina H Haugaa[2]; Margareth Olseng[1]; Ola Gjesdal[2]; Stian Ross[1]; Joerg Saberniak[1]; Morten B Jacobsen[4]; Thor Edvardsen[2]. [1] Dept of Medicine, Hosp of Oestfold, Fredrikstad, Norway, [2] Dept of Cardiology, Oslo Univ Hosp, Rikshospitalet, Oslo - Univ of Oslo, Oslo, Norway, [4] Dept of Rsch, Hosp of Oestfold, Fredrikstad, Norway

Background: Cheyne-Stokes respiration (CSR), is a sleep disordered breathing frequently occurring in patients with congestive heart failure (CHF). CSR causes repetitive episodes of hypoxia and arousal from sleep, leading to sympathetic activation, fatigue and excessive daytime sleepiness. Adaptive servo-ventilation (ASV) is a novel therapy shown to be more effective in reducing CSR than Continuous Positive Airway Pressure-machine and nasal oxygen in CHF patents with CSR. The aim of this study was to investigate the effects of ASV on CHF parameters in a prospective randomized controlled trial.

Methodes: 51 patients (age 57-81, 4 women), New York Heart Association(NYHA) functional class III or IV, despite optimal cardiac medication, and/or left ventricular ejection fraction (LVEF) ≤ 40% and CSR more than 25% of sleeping time were randomized to either treatment with ASV or as a control group. Thirty patients completed the study, 15 in each group. Primary end point was any changes in LVEF from baseline to 3 months. Secondary end points were alterations in physical capacity by six-minutes walk test and NYHA class.

Results: At baseline, there were no statistical differences between the 2 groups regarding LVEF, NYHA and six-minutes walk test. In the ASV treatment group LVEF significantly improved from baseline (32±11%) to study end at 3 months (36±13%, p=0.004). Six-minutes walk test improved from 377±115m to 430±123m (p=0.001) and NYHA class improved from 3.2±0.4 to 2.3±0.6 (p<0.001). In the control group there were no significant changes in any parameter after 3 months.

Conclusion: These results suggest that CHF patients with CSR might benefit from treatment with ASV supplemental to standard medication.

Abstract 9572: Post-Stenotic Dilatation in Asymptomatic Aortic Stenosis

Edda Bahlmann[1]; Richard B. Devereux[2]; Christoph A. Nienaber[3]; Dana Cramariuc[4]; Christa Gohlke-Baerwolf[5]; Simon Ray[6]; Kristian Wachtell[7]; Karl Heinz Kuck[1]; Eva Gerdts[8]. [1] Cardiology, Asklepios Clinic St. Georg, Hamburg, Germany, [2] Med college, Weill Med College of Cornell Univ, New Yok, NY, [3] Cardiology, Universitätsklinikum Rostock, Dept of Cardiology, Rostock, Germany, [4] Cardiology, Univ of Bergen, Bergen, Norway and Haukeland Univ Hosp, Bergen, Norway, Bergen, Norway, [5] Cardiology, Herz-Zentrum Bad Krozingen, Dept of Cardiology, Bad Krozingen, Germany, Bad Krozingen, Germany, [6] Cardiology, Manchester Academic Health Sciences Cntr, Univ Hosp of South Manchester, Manchester, United Kingdom, [7] Cardioloy, Rigshospitalet, The Heart Cntr, Dept of Cardiology , Copenhagen, Denmark, Copenhagen, Denmark, [8] Cardiology, Univ of Bergen and Haukeland Univ Hosp, Bergen, Norway

Background: Post-stenotic aortic root dilation is often observed in aortic stenosis (AS) patients, but the relation to AS severity has not been reported from a large population of asymptomatic AS patients.

Methods: Baseline data in 1223 patients with asymptomatic AS (mean age 67 years, 39% women) in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study was used. Annular diameter was measured from inner to inner edge in mid-systole. Inner and leading edge aortic root diameter was measured at the levels of sinus of Valsalva, sinotubular junction and supracoronary. Predicted aortic diameters were calculated from age and body size adjusted equations derived in normal adults.

Results: On average, mean aortic annulus diameter was 2% larger, sinus of Valsalva diameter 11% larger, sinotubular junction diameter 22% larger and supracoronary diameter 32% larger in SEAS participants than that predicted from body size. Enlarged aortic diameter was found in 42%, 78%, 96% and 98% of patients at these levels and associated with larger inner diameter and thicker aortic wall (both p<0.01). In multivariate regression analysis, larger sinus of Valsalva or sinotubular junction diameter was independently associated with more severe AS (Table).

Conclusions: Post-stenotic aortic root dilatation is common in asymptomatic AS with increasing prevalence from proximal to distal part. Aortic root dilation at the sinus of Valsalva and sinotubular junction level was associated with higher AS severity.

Abstract 11598: Impact of Valvuloarterial Impedance on Cardiovascular Outcome in Patients with Asymptomatic Aortic Stenosis (The SEAS Study)

Dana Cramariuc[1]; Åshild E Rieck[2]; Giovanni Cioffi[3]; Anne B Rossebø[4]; Christa Gohlke-Bärwolf[5]; Simon Ray[6]; Eva Gerdts[7]. [1] Heart Disease, Haukeland Univ Hosp, Bergen, Norway, [2] Institute of Medicine, Univ of Bergen, Bergen, Norway, [3] Heart Disease, Villa Bianca Hosp, Trento, Italy, [4] Div of Cardiology, Aker Univ Hosp, Oslo, Norway, [5] Heart Disease, Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany, [6] Cardiology, South Manchester Univ Hosp, Manchester, United Kingdom, [7] Heart Disease and Institute of Medicine, Haukeland Univ Hosp and Univ of Bergen, Bergen, Norway

Introduction: Valvuloarterial impedance (Zva) is a measure of the combined valvular and arterial load opposing left ventricular (LV) ejection in aortic stenosis (AS). We assessed the hypothesis that Zva had prognostic significance in patients with asymptomatic AS. This had not yet been studied prospectively.

Methods: 1473 patients with mild-moderate, asymptomatic AS in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study were followed-up during 4.3 years of randomized, placebo-controlled treatment with combined simvastatin 40 mg and ezetimibe 10 mg daily. The impact of baseline Zva on rate of major cardiovascular events (CV, primary endpoint), as well as aortic valve events and ischemic CV events (both secondary endpoints), was assessed in Cox proportional hazards models. Zva was calculated using Doppler-derived stroke volume and indexed for height$^{2.04}$, and LV ejection fraction by Simpson's biplane method.

Results: Baseline peak aortic velocity was 3.08±0.54m/s and Zva 6.17±1.93 mm Hg/ml · m$^{2.04}$. During follow-up, a total of 509 major CV events occurred. In Cox regression analyses, 1 standard deviation (1.93 mm Hg/ml · m$^{2.04}$) higher Zva predicted a 23% higher rate of major CV events, and 24% and 15% higher rates of aortic valve and ischemic CV events, respectively (all p<0.05), independent of study treatment, severity of AS, degree of aortic valve calcification, hypertension and LV ejection fraction (Table).

Conclusion: Assessment of valvuloarterial impedance adds valuable prognostic information in asymptomatic AS to that provided by established prognosticators like peak aortic jet velocity, degree of aortic valve calcification and LV ejection fraction.

Table. Multivariate Cox analyses of aortic valve events and ischemic CV events

	Aortic valve events (N=435)	Ischemic CV events (N=228)
	HR (95% CI)	HR (95% CI)
Active treatment	0.88 (0.72-1.05)	0.74 (0.57-0.96)*
Hypertension	0.90 (0.68-1.19)	2.22 (1.31-3.76) **
Peak aortic jet velocity (m/sec, per 1 SD higher)	1.86 (1.66-2.09)**	1.33 (1.14-1.56)**
Moderate/severe aortic valve calcification	1.66 (1.22-2.27)**	1.32 (0.90-1.93)
Lower LV ejection fraction (%, per 1 SD lower)	1.19 (1.08-1.30)**	1.01 (0.89-1.15)
Zva (mm Hg/ml · m$^{2.04}$, per 1 SD higher)	1.24 (1.14-1.36)**	1.15 (1.01-1.29)*

*p<0.05, **p<0.01

Abstract 14938: Exercise Improves Ventricular Function And Decreases Myocardial Oxygen Waste In Diet-induced Obese Mice

Anne D Hafstad[1]; Jim Lund[1]; Anje C Höper[1]; Elin Hadler-Olsen[2]; Martin Hagve[1]; Ulrik Wisløff[3]; Terje S Larsen[1]; Ellen Aasum[1]. [1] Cardiovascular Rsch Group, Univ of Tromsø, Tromsø, Norway, [2] Tumor Biology Group, Univ of Tromsø, Tromsø, Norway, [3] K.G. Jebsen Cntr of Exercise in Medicine, Dept of Circulation and Med Imaging, Univ of Science and Technology, Trondheim, Norway

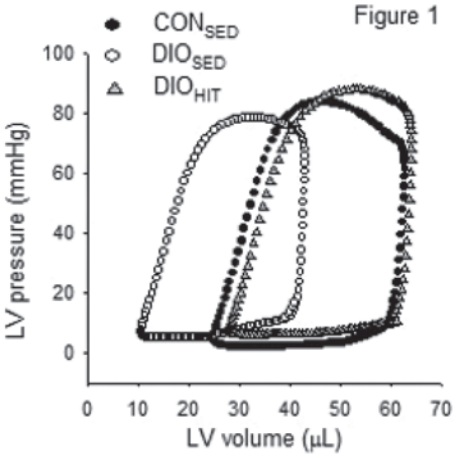
Background: Diabetes/obesity is associated with left ventricular (LV) dysfunction, altered myocardial metabolism, decreased cardiac efficiency and impaired LV energetics. Exercise has been shown to influence myocardial calcium handling, oxidative stress and mitochondrial uncoupling, processes which are known to influence the progression of cardiomyopathy associated with diabetes/obesity. The aim of the present study was therefore to examine the effect of high intensity interval training (HIT) on LV function and energetics, using diet-induced obese (DIO) mice as experimental model.

Methods and Results: DIO mice (given a Western diet) were subjected to 8 weeks of HIT (1 h, 5 days a week). Hearts from sedate DIO mice (DIO_{SED}) showed diastolic and systolic dysfunction (Fig. 1) and increased oxygen cost for basal metabolism (BM) and excitation-contraction (E-C) coupling (Fig. 2). DIO mice subjected to HIT (DIO_{HIT}) showed increased aerobic capacity, reduced obesity and improved glucose tolerance. In addition, LV function (Fig. 1) and cardiac efficiency were normalized. Analysis of the relation between MVO_2 and LV pressure-volume area revealed unaltered contractile efficiency, while unloaded MVO_2 was normalized, due to reduced oxygen cost for BM and E-C coupling (Fig. 2). These changes were accompanied by attenuation

of DIO-induced myocardial oxidative stress, and not by changes in energy substrate utilization.

Conclusion: Exercise-induced improvement of LV function and energetics are associated with attenuation of obesity-induced myocardial oxygen waste, most likely due to decreased ROS-induced impairments of mitochondrial function and Ca^{2+} handling.

Figure 1



Abstract 9070: Secretoneurin is Produced in the Ischemic Border Zone of Animals with Myocardial Infarction and Heart Failure, Attenuates Ischemic Injury, and is Associated with the Progression of Heart Failure in Patients

Helge Røsjø[1]; Mats Stridsberg[2]; Geir Florholmen[3]; Kåre-Olav Stensløkken[4]; Anett H Ottesen[1]; Ivar Sjaastad[3]; Cathrine Husberg[3]; Mai Britt Dahl[1]; Arne D Høiseth[1]; Erik Øie[5]; William E Louch[3]; Torbjørn Omland[1]; Geir Christensen[3]. [1] Medicine, Akershus Univ Hosp, Loerenskog, Norway, [2] Med Sciences, Uppsala Univ, Uppsala, Sweden, [3] Institute for Experimental Med Rsch, Oslo Univ Hosp, Ullevål, Oslo, Norway, [4] Molecular Biosciences, Univ of Oslo, Oslo, Norway, [5] Rsch Institute for Internal Medicine, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway

Background: Secretoneurin (SN) is a peptide belonging to the granin protein family. As two other granin proteins, chromogranin A and B, are increased in cardiac tissue in heart failure (HF), we hypothesized that SN could play a role in cardiovascular pathophysiology.

Methods: Production and functional aspects of SN were assessed in experimental models and circulating levels measured in two cohorts of HF patients.

Results: Pro-SN mRNA levels were 11.5 fold increased in viable left ventricular (LV) tissue of mice subjected to coronary artery ligation and with echocardiographical confirmed HF. Protein levels were also increased in the LV of HF animals vs. sham-operated animals, including in the ischemic border zone where we observed increased processing from pro-SN to shorter SN fragments (>100% increase, p=0.001). Immunohistochemistry localized myocardial SN production to cardiomyocytes. We did not observe increased SN production in other organs than the LV. Perfusing isolated cardiomyocytes with SN rapidly induced Stat3 and Erk1/2 phosphorylation, protected from hydrogen peroxide-induced cardiomyocyte apoptosis *in vitro*, and reduced ischemia-reperfusion injury by 30% (p<0.05) in the isolated perfused rat heart. Circulating levels of SN were increased in patients with stable and acute HF compared to control subjects and increased in proportion to HF severity as evaluated by NYHA functional class (p=0.04 for trend). In 68 patients hospitalized for acute HF, admission SN levels provided excellent discrimination for all-cause mortality (n=17) during a median follow-up of 373 days: Hazard ratio [per 0.05 nmol/L increase of SN] 2.34 (95% CI 1.63-3.38), p<0.001. Adjustment for established clinical risk factors including comorbidities, renal function, and LV ejection fraction in multivariate analysis did not attenuate the association between SN levels and mortality: HR 2.43 (95% CI 1.63-3.61), p<0.001.

Conclusion: SN production is increased in viable cardiomyocytes adjacent to the infarcted area in animals with myocardial infarction and HF, which could be beneficial as SN protects from myocardial ischemia. Based on our results, SN could represent a protective feedback response that is activated in proportion to the severity of HF.

Abstract 10377: Vitamin D Status is a 2-Year Predictor of All-Cause Mortality and Cardiac Death in Chest Pain Patients: A Prognostic Study from Salta, Northern-Argentina

Patrycja A Naesgaard[1]; Ricardo Leon de la Fuente[2]; Patricio Gallo[3]; Cato Brede[4]; Heidi Grundt[1]; Torbjoern Aarsland[5]; Leik Woie[5]; Stein Tore Nilsen[5]; Harry Staines[6]; Dennis W Nilsen[7]. [1] Dept of Internal Medicine, Stavanger Univ Hosp, Stavanger, Norway, [2] Dept of Cardiology, Cntr Cardiovascular Salta, Salta, Argentina, [3] Dept of Cardiology, Cntr Cardiovacular Salta, Salta, Argentina, [4] Dept of Clinical Chemistry, Stavanger Univ Hosp, Stavanger, Norway, [5] Dept of Rsch, Stavanger Univ Hosp, Stavanger, Norway, [6] Sigma Statistical

Services, Sigma Statistical Services, Balmullo, United Kingdom, [7] Dept of Cardiology, Stavanger Univ Hosp, Stavanger, Norway

Background: Several studies have shown a correlation between vitamin D deficiency and cardiovascular risk. We have assessed the prognostic impact of vitamin D status, serum 25-hydroxy-vitamin D (25(OH)D), in 982 chest-pain patients with suspected acute coronary syndrome (ACS) from Salta, Argentina.

Methods: Blood serum samples for determination of 25(OH)D were obtained at admission. Baseline data consisted of Troponin T (TnT), high sensitive C-reactive protein (hsCRP), B-type natriuretic peptide (BNP), creatinine and clinical parameters, including age, gender, assessment of previous MI, angina pectoris, previous revascularizations (percutaneous coronary intervention or coronary artery bypass graft, congestive heart failure, diabetes mellitus, smoking status, hypercholesterolemia (defined as total cholesterol concentrations above 250 mg/dl or statin treated hypercholesterolemia), beta-blocker, arterial hypertension, body mass index and months of the year.

Results: After a follow-up period of 2 years, 119 patients had died. The 25(OH)D levels were significantly lower among patients dying than in long-term survivors, both in the total population and in the TnT positive patients (TnT > 0.01 ng/mL). In a multivariable Cox regression model for all cause mortality and cardiac death within 2 years in the total patient population, the hazard ratio (HR) for 25(OH)D in the highest quartile (Q4) as compared to the lowest quartile (Q1) was 0.38 (95% confidence interval (CI), 0.20-0.75), p = 0.005 and 0.20 (95% CI, 0.07-0.59), p = 0.004, respectively. For all-cause mortality and cardiac death, the HR for 25(OH)D in TnT positive patients were 0.25 (95% CI, 0.11-0.58), p = 0.001 and 0.19 (95% CI, 0.05-0.64), p = 0.008, respectively. See Figure. This biomarker was not shown to have any prognostic impact in the TnT negative patients.

Conclusion: Vitamin D status may act as clinically useful biomarker when obtained at admission in chest pain patients with suspected ACS.

Abstract 16175: Effect of Dietary Intake of Kiwi Fruit on 24-Hour Ambulatory Blood Pressure

Mette Svendsen[1]; Tor O Klemsdal[1]; Eli Heggen[1]; Ingar Holme[1]; Terje R Pedersen[1]; Ingebjørg Seljeflot[2]; Rune Blomhoff[8]; Serena Tonstad[1]. [1] Preventive Cardiology, Oslo Univ Hosp, N-0424 OSLO, Norway, [2] Cntr for Clinical Heart Rsch, Oslo Univ Hosp, N-0424 OSLO, Norway, [3] Institute of Nutrition Rsch, Univ of Oslo, N-0316 OSLO, Norway

Objective Kiwi fruit contains lutein, an oxycarotenoid that has antioxidant properties. An increased antioxidant capacity may lower blood pressure (BP) through modulation of nitric oxide mediated vascular reactivity. In the present study we studied the effect of adding kiwi to the usual diet on 24-hour ambulatory BP in mildly hypertensive subjects.

Subjects and methods A total of 50 men and 68 women aged 55 ± 9 years with systolic/diastolic BP 128 ± 14 mmHg/ 85 ± 8 mmHg were randomized to intake of three kiwi fruits (intervention group) or one apple (control group) per day for eight weeks. No other dietary changes were made. Ambulatory BP was measured at randomization and at the end of the study. Results between groups were analyzed using a general linear model with change from baseline to eight weeks as the dependent variable, intervention group as a categorical variable, and with adjustment for the baseline value of the analyzed variable (model 1) or adjustment for BMI, gender, age and the baseline value of the analyzed variable (model 2).

Results After eight weeks, 24-hour ambulatory systolic BP was lower in the group randomized to kiwi versus apple (between group difference, 3.6 mmHg [95% CI 0.7, 6.5], P=0.017 in model 1 and 3.3 mmHg [95% CI 0.4, 6.2], P=0.029 in model 2). Ambulatory diastolic BP was lower in the kiwi group after adjusting for baseline values of the variable (between group difference, 1.9 mmHg [95% CI 0.3, 3.6], P=0.040; model 1), but not when adjusting for all covariates (1.6 mmHg [95% CI -0.2, 3.4], P=0.079; model 2).

Conclusion Three kiwi a day improved 24-hour BP more than an apple a day. Incorporating kiwi intake as part of DASH or other diets for treatment of hypertension should be studied.

Abstract 11732: The Z-Disc Proteoglycan Syndecan-4 Regulates Mechanical Stress-Induced Calcineurin-NFAT Signaling in Cardiomyocytes

Ida G Lunde[1]; Geir Florholmen[1]; Alexandra V Finsen[2]; Biljana Skrbic[1]; Heidi Kvaløy[1]; Ivar Sjaastad[1]; Theis Tønnessen[3]; Sarah A Wilcox-Adelman[4]; Cathrine R Carlson[1]; Geir Christensen[1]. [1] Dept of Surgery, Institute for Experimental Med Rsch, Oslo, Norway, [2] Dept of Cardiology, Rsch Institute for Internal Medicine, Oslo, Norway, [3] Dept of Surgery, Dept of Cardiothoracic Surgery, Oslo, Norway, [4] Boston Biomedical Rsch Institute, Boston Biomedical Rsch Institute, Boston, MA

Mechanical stress is regarded as an important stimulus for the hypertrophic response in cardiomyocytes, but the signaling systems involved

are still unknown. We have previously shown that syndecan-4, a transmembrane proteoglycan localized to the cardiomyocyte Z-discs, is essential for development of concentric hypertrophy following pressure overload. We here demonstrate that syndecan-4, which connects the extracellular matrix to the cardiomyocyte cytoskeleton, regulates mechanical stress-induced calcineurin-Nuclear Factor of Activated T-cell (CnA-NFAT) signaling in cardiomyocytes. Syndecan-4 protein levels were increased 1.7-fold in biopsies from hypertrophic human myocardium obtained peroperatively from aortic stenosis patients. When introduced as a gene or cell-permeable peptide (gain of function), syndecan-4 activated NFATc4 in cardiomyocytes in vitro. To examine whether mechanical stimuli activate CnA-NFAT through syndecan-4, cardiomyocytes from syndecan-4 KO-NFAT-luciferase reporter mice were subjected to cyclic mechanical stretch (10%, 1Hz). NFAT activation was increased 11.6-fold by 24 hrs of mechanical stretch in NFAT-luciferase cardiomyocytes. Importantly, NFAT activation was only 1.6-fold increased following stretch in syndecan-4 KO-NFAT luciferase cardiomyocytes, i.e. significantly lower than in the NFAT-luciferase cardiomyocytees subjected to the same stretch protocol. Similar data were obtained in stretched syndecan-4 KO and wild-type cardiomyocytes as assessed by NFATc4 phosphorylation. Hypertrophy, as measured by protein synthesis, as well as NFAT activation, assessed by NFAT-luciferase activity and phosphorylation, were reduced in syndecan-4 KO cardiomyocytes subjected to autonomous growth, compared to wild-type controls. In vivo, we showed that mechanical stress following aortic banding of syndecan-4 KO mice induced less activation of NFAT as assessed by NFATc4 phosphorylation and expression of the NFAT target gene RCAN1-4, compared to wild-type controls. Conclusively, our data indicate that in cardiomyocytes of a pressure-overloaded heart, mechanical stimuli are sensed by the Z-disc proteoglycan syndecan-4 which activates pro-hypertrophic CnA-NFAT signaling.

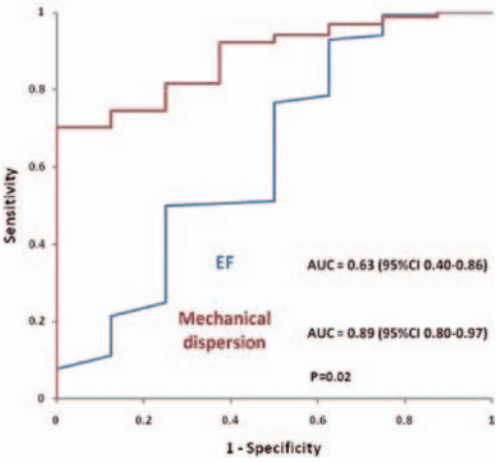
Abstract 11932: Mechanical Dispersion Predicts Ventricular Arrhythmias After Myocardial Infarction

Kristina H Haugaa[1]; Bjørnar L Grenne[2]; Jens-Uwe Voigt[3]; Anca Florian[3]; Benthe Sjøli[2]; Harald Brunvand[2]; Christian H Eek[4]; Walter Desmet[3]; Jesper H Svendsen[5]; Otto A Smiseth[1]; Thor Edvardsen[1]. [1] Cardiology and Institute for Surgical Rsch, Oslo Univ Hosp, Rikshospitalet, CCI and Univ of Oslo, Oslo, Norway, [2] Dept of Medicine, Sørlandet Hosp, Arendal, Norway, [3] Dept. of Cardiovascular Diseases, Univ Hosp Gasthuisberg Katholic Univ Leuven, Leuven, Belgium, [4] Cardiology, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway, [5] Kardiologisk Laboratorium, Rigshospitalet, Copenhagen, Denmark

Introduction Prediction of ventricular arrhythmias after myocardial infarction (MI) is still insufficient. LV ejection fraction (EF) <35% serves as the main criterion for selecting patients for ICD therapy. However, the majority of patients dying suddenly after MI have EF >35%. Mechanical dispersion by strain echocardiography reflects inhomogeneous timing in myocardial contraction and has been shown to predict ventricular arrhythmias. We hypothesized that mechanical dispersion may improve arrhythmic risk stratification in post MI patients.

Methods In this prospective multi center study we included 177 post MI patients (114 ST elevation and 63 non-ST elevation). Echocardiography was performed minimum 40 days post MI. Time from ECG R to peak negative strain was assessed in 16 longitudinal LV segments. Mechanical dispersion was assessed as the standard deviation from these 16 time intervals, reflecting contraction heterogeneity.

Results Ventricular arrhythmias defined as sustained VT, VF or sudden death during 33(14-76) months of follow up occurred in 8 (4.5%) patients. Mechanical dispersion was higher in patients with arrhythmic events (68±18ms vs. 38±18ms, p<0.001) and, as expected, EF was lower (47±15% vs. 55±9%, p=0.03). In those with EF>35% (n=172), mechanical dispersion was higher in those with arrhythmic events (63±19ms vs. 38±18ms, p=0.001) while EF did not differ (54±9% vs. 55±8%, p=0.76). By logistic regression, mechanical dispersion predicted arrhythmic events independently of EF (OR 2.1(95%CI 1.3-3.4) per 10ms increase (p=0.001). By ROC analyses, mechanical dispersion was superior to EF in identifying arrhythmic events (Figure).



Conclusions Mechanical dispersion by strain echocardiography predicted arrhythmic events independently of EF in post MI patients. Mechanical dispersion can identify patients for ICD therapy who do not fulfill current indications for primary ICD (EF>35%).

Abstract 14719: Wasted Work Fraction - A Novel Method For Assessing Dyssynchrony In Patients With Left Bundle Branch Block

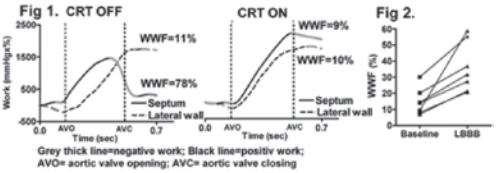
Kristoffer Russell[1]; Morten Eriksen[2]; Lars Aaberge[3]; Nils Wilhelmsen[3]; Espen W Remme[2]; Helge Skulstad[3]; Ola Gjesdahl[3]; Anders Opdahl[2]; Erik Kongsgaard[3]; Thor Edvardsen[3]; Otto A Smiseth[3]. [1] Cardiology and Institute for surgical research, Oslo university Hosp, Rikshospitalet, Oslo, Norway, [2] Cardiology, Institute for surgical research, Oslo, Norway, [3] Cardiology, Oslo university Hosp, Rikshospitalet, Oslo, Norway

Background: In patients with left bundle branch block (LBBB) left ventricular (LV) late activated segments are stretched initially by the contraction of early activated segments and early activated segments are stretched (after initial contraction) when late activated segments start to contract. The result of this dyssynchrony is that substantial amounts of LV work does not contribute to ejection and is "wasted". We therefore introduce "wasted work fraction" (WWF) which may be used to quantify LV wasted work.

Methods: In a dog model (n=7) and in patients (n=14) with LBBB we measured segmental strain by speckle tracking echocardiography (dogs and patients) and sonomicrometry (dogs) and LV pressure (LVP) by micromanometry. Regional work was calculated using strain to assess regional shorting and LVP as an analog for wall stress. Instantaneous strain rate and LVP were multiplied resulting in a measure of instantaneous power. Power was then integrated over time to give work displayed as a function of time. Work during segmental shortening was defined as positive (black line in fig 1) and work during segmental lengthening as negative (grey line in fig 1), the latter was considered as wasted work. WWF could then be calculated as percent negative work of total positive work for a specific segment and as a mean WWF incorporating all LV walls (global).

Results: In the dogs global WWF increased significantly from baseline to LBBB (mean ±SD, 15±8 vs. 36±15% and 16±5 vs. 34±9%) using sonomicrometry (Fig 2) and STE, respectively. Patients with LBBB also had a large degree of WWF (30±9%). Figure 1 shows regional work analysis for two segments in a patient with cardiac resynchronization therapy (CRT).

Conclusions: In a clinical setting WWF may be used to quantify the cardiac mechanical disadvantage of dyssynchrony and the WWF may indicate the potential for improvement in function by CRT. This analysis may serve as an important tool when evaluating patients for CRT and optimizing device settings.



Grey thick line=negative work; Black line=positiv work;
AVO= aortic valve opening; AVC= aortic valve closing

Abstract 213: Changing Hand Position During Manual Chest Compressions in Cardiac Arrest Affects the Hemodynamic Response: A Clinical Pilot Study

Eric Qvigstad[1]; Øystein Tømte[2]; Kjetil Sunde[2]; Tore Skålhegg[3]; Øyvard Sørensen[3]; Jo Kramer-Johansen[2]; Theresa Mariero Olasveengen[2]. [1] Oslo Univ Hosp, Institute for Experimental Med Rsch, Oslo, Norway, [2] Oslo Univ Hosp, Oslo, Norway, [3] Oslo Univ Hosp, EMS, Oslo, Norway

Introduction: Optimal hand position during manual chest compressions (MCC) in cardiac arrest is unknown, but current Guidelines recommend a hand position on the lower half of the sternum. Recent imaging studies suggest that significant inter-individual anatomical differences exist, which might cause altered hemodynamic responses during standard MCC. In this prospective pilot study we wanted to assess the feasibility of utilizing capnography to optimize MCC and identify the optimal hand position in out-of-hospital cardiac arrest (OCHA).

Materials and methods: Patients treated by the physician-manned ambulance for non-traumatic OCHA between February and May 2011 were included. Continuous $EtCO_2$ was measured by sidestream capnography (Lifepak 12, Physio Control, WA, USA). The three minute intervention period was initiated after endotracheal intubation. In the first minute chest compression rate and depth was optimized with hand-position at the recommended point (P0). A two-minute test phase followed; 50 compressions performed at three different sternal positions two cm below P0; P1 midline, P2 two cm to the left, P3 two cm to the right. The hand-position with the highest $EtCO_2$ value was used during the remaining resuscitation effort. $EtCO_2$ values are given as means (range), and presented in kPa (1 kPa = 7.5 mmHg).

Results: Variations in $EtCO_2$ values could be documented in 15 OHCA patients. Average

$EtCO_2$ values for 11 patients with cardiac etiology were 4.5 (1.9, 8.3), 5.3 (2.3, 9.6), 5.1 (2.4, 10.3), and 5.1 (2.5, 9.1) for P0 - P3, respectively, and for four non-cardiac etiology patients 4.8 (0.8, 9.7), 5.3 (0.8, 10.7), 5.8 (0.7, 10.3), and 5.1 (0.4, 8.4) for P0 - P3, respectively. The optimal $EtCO_2$ value was found in P0 in three patients, and in alternative hand positions in 12 patients, with the following distribution; P1: five patients, P2: five patients, P3: one patient, and in one patient P1, P2 and P3 was equally good.

Conclusions: Monitoring and optimizing CPR performance and interventions using capnography was feasible. We could demonstrate inter-individual differences affecting hemodynamics, and there were no indications that one specific hand position could be expected to give optimal cardiac output in all patients.

Abstract 15136: Global Strain by Echocardiography Is Superior to Ejection Fraction to Predict Ventricular Arrhythmias After Myocardial Infarction

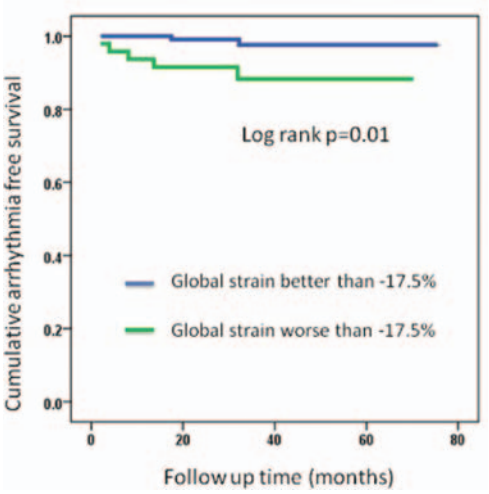
Kristina H Haugaa[1]; Bjørnar L Grenne[2]; Jens-Uwe Voigt[3]; Anca Florian[3]; Benthe Sjøli[2]; Harald Brunvand[2]; Christian H Eek[4]; Walter Desmet[3]; Jesper H Svendsen[5]; Otto A Smiseth[1]; Thor Edvardsen[1]. [1] of Cardiology and Institute for Surgical Rsch, Oslo Univ Hosp, Rikshospitalet, CCI and Univ of Oslo, Oslo, Norway, [2] Dept of Medicine, Sørlandet Hosp, Arendal, Norway, [3] Dept. of Cardiovascular Diseases, Univ Hosp Gasthuisberg Katholic Univ Leuven, Leuven, Belgium, [4] Cardiology, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway, [5] Kardiologisk Laboratorium, Rigshospitalet, Copenhagen, Denmark

Introduction LV function measured as ejection fraction (EF) is currently the main selection parameter when identifying ICD-candidates. Global strain by echocardiography is a more sensitive measure of myocardial function than EF. We recently reported that reduced global strain by echocardiography predicted arrhythmic events in patients after myocardial infarction (MI) with ICD. We hypothesize that strain echocardiography may improve arrhythmic risk stratification in prospectively included post MI patients.

Methods In this prospective multi center study 177 post MI patients were included (114 ST elevation and 63 non-ST elevation). Echocardiography was performed minimum 40 days post MI. From speckle tracking strain we assessed global strain as average peak systolic longitudinal strain from 16 LV segments.

Results Of 177 post MI patients, 8 (4.5%) experienced ventricular arrhythmias defined as sustained VT, VF or sudden cardiac death during 33(14-76) months of follow up. EF was reduced in patients with arrhythmic events (47±15% vs. 55±9%, p=0.03). Global strain was markedly lower in those with arrhythmic events (14.4±4.8% vs. -18.9±3.3%, p<0.001). By ROC analyses, global strain was superior to EF in prediction of arrhythmic events (AUC 0.79(95%CI(0.64-0.94) vs. 0.63(95%CI(0.39-0.88), p=0.05), with sensitivity = 74% and specificity = 75%. Optimal cut off for global strain was -17.5%. Survival analyses showed better arrhythmia free survival in those with global strain better than -17.5% (p=0.01) (Figure).

Conclusions Global strain by echocardiography was superior to EF to predict arrhythmic events in this prospective study of post MI patients. Strain echocardiography may refine selection of patients for ICD therapy after MI.



Abstract 12700: Novel Method For Noninvasive Myocardial Work Analysis in Patients With Left Bundle Branch Block

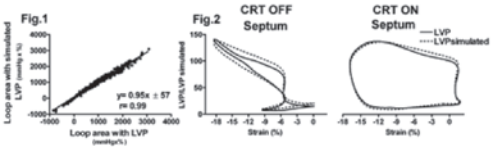
Kristoffer Russell[1]; Morten Eriksen[2]; Lars Aaberge[3]; Nils Wilhelmsen[3]; Espen W Remme[2]; Anders Opdahl[2]; Kristina H Haugaa[1]; Thor Edvardsen[1]; Otto A Smiseth[1]. [1] Cardiology and Institute for surgical research, Oslo university Hosp, Rikshospitalet, Oslo, Norway, [2] Cardiology, Institute for surgical research, Oslo, Norway, [3] Cardiology, Oslo university Hosp, Rikshospitalet, Oslo, Norway

Background: Left bundle branch block (LBBB) causes a heterogeneous work distribution in the left ventricle (LV). The aim of cardiac resynchronization therapy (CRT) is to synchronize LV contraction which in turn leads to improved pump function and reverse remodeling. Currently work analysis relies on invasive pressure measurements. In the present study we introduce

a new noninvasive LV pressure (LVP) analog and validate its ability to assess regional work in combination with strain measurements by echocardiography.

Methods and Results: In patients with LBBB (n=12) and ischemic cardiomyopathy (n=6) we measured segmental strain by speckle tracking echocardiography and LVP by micromanometry. LVP traces from all patients were pooled and synchronized by identifying timing of opening and closing of the mitral and aortic valves for each of the pressure traces and stretching/compressing the traces along the time axis making valvular events coincide for all recordings. The profile of the averaged waveform could then be fitted to the relevant cardiac cycle by adjusting the duration of time intervals to match the actual valvular timing as determined by ultrasound imaging from a specific subject. Brachial cuff pressure was used to scale peak systolic pressure. Segmental work was calculated using two approaches: 1. As the area of the LVP-strain loops. 2. As the area of the LVP analog-strain loops. Work analysis using the two methods showed a good correlation (r=0.99) and agreement (mean difference ± 2SD, 3.5 ± 194 mmHgx%) (Figure 1). Figure 2. shows work loops for a septal segment in a patient with CRT on and off using the two approaches.

Conclusions: The use of a pressure analog allows for noninvasive work analysis based on echocardiographic imaging, systolic blood pressure and valvular timing. In a clinical setting this can be used to assess regional myocardial function which may serve as an important clinical tool when evaluating patients for CRT and optimizing device settings.



Abstract 8594: Rapid ST-upslope on Exercise Electrocardiogram Predicts Reduced Long Term Mortality from Coronary Heart Disease.

Christian Hodnesdal[1]; Erik Prestgaard[1]; Gunnar Erikssen[2]; Knut Gjesdal[2]; Sverre Kjeldsen[2]; Knut Liestol[3]; Per Torger Skretteberg[2]; Jan Erikssen[1]; Johan Bodegard[2]. [1] Faculty of Medicine, Univ of Oslo, Oslo, Norway, [2] Dept of Cardiology, Oslo Univ Hosp, Oslo, Norway, [3] Faculty of Informatics, Univ of Oslo, Oslo, Norway

Aims The prognostic value of a rapid ST-upslope on exercise electrocardiogram (ECG) is unknown among healthy individuals, but it may be associated with a well-balanced control of the autonomic nervous system. We aim to test the hypothesis that rapid ST-upslope is associated with reduced risk of dying from coronary heart disease (CHD).

Methods and results A group of healthy middle-aged men (n=2014) participated in a cardiovascular survey examination. They underwent an examination program including a symptom limited ECG bicycle exercise test. Exercise induced ST- segments were categorized in three groups: normal ST-segment (n=1383), rapid ST-upslope (n=401) and ST-depression (n=230). Survival analyses were adjusted for smoking status, total cholesterol, systolic blood pressure, maximal heart rate, and physical fitness. The rapid ST-upslope group was associated with a 30% decreased risk of CHD-death (Hazard Ratio (HR) = 0.70 [95%CI 0.51-0.95]) compared to the normal ST-segment group (see image below). The risk of CVD-death was numerically lower in the rapid ST-upslope group (0.82 [95%CI 0.65-1.04]) compared to the normal ST-segment group. The ST-depression group was associated with a 1.45-fold (HR = 1.45 [95%CI 1.09-1.90]) increased risk of CHD-death compared to the normal ST-segment group.

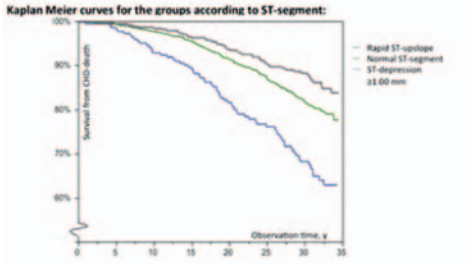
Conclusions The rapid ST-upslope on exercise ECG was a common finding (20%) among healthy middle aged men and was associated with a 30% reduced risk of dying from CHD compared to individuals with normal ST-segment. We suggest that rapid ST-upslope on exercise ECG is the true healthy state.

Cox model analyses showing the risk of death from coronary heart disease with different ST-segment compared to the group with normal ST-segment :

	Normal ST-segment (n = 1383)	Rapid ST-upslope (n = 401)	ST-depression ≥1.00 mm (n = 230)
Age-adjusted Hazard Ratio (95% CI)	1.00	**0.69** (0.50–0.94)	**1.47** (1.11–1.93)
Multiple-adjusted Hazard Ratio (95% CI)*	1.00	**0.70** (0.51–0.95)	**1.45** (1.09–1.90)

*Adjusted for smoking status, total cholesterol, systolic blood pressure, maximal heart rate, and physical fitness.

Kaplan Meier curves for the groups according to ST-segment:



Abstract 10250: The Association Between Neutrophil Gelatinase-Associated Lipocalin and Clinical Outcome in Chronic Heart Failure: Results From CORONA

Staale H Nymo[1]; Thor Ueland[1]; Erik T Askevold[1]; Trude H Flo[2]; John Kjekshus[3]; Johannes Hulthe[4]; John Wikstrand[4]; John McMurray[5];

Dirk J van Veldhuisen[6]; Lars Gullestad[3]; Paal Aukrust[1]; Arne Yndestad[1]. [1] Rsch Institute for Internal Medicine, Oslo Univ Hosp, Oslo, Norway, [2] Dept of Cancer Rsch and Molecular Medicine, Univ of Technology and Science, Oslo, Norway, [3] Dept of Cardiology, Oslo Univ Hosp, Oslo, Norway, [4] Wallenberg Laboratory for Cardiovascular Rsch, Gothenburg Univ, Gothenburg, Sweden, [5] BHF Glasgow Cardiovascular Rsch Cntr, Univ of Glasgow, Glasgow, United Kingdom, [6] Dept of Cardiology, Univ of Groningen, Groningen, Netherlands

Objective: To analyze (i) the relationships between Neutrophil gelatinase-associated lipocalin (NGAL) levels and clinical variables and biomarkers of heart failure (HF) in a large population of HF patients; (ii) the ability of NGAL to predict fatal and non-fatal outcomes in this population.

Background: NGAL is a marker of kidney injury as well as matrix degradation and inflammation, and has previously been shown to be increased in HF.

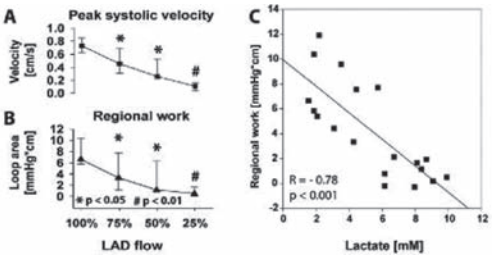
Methods and results: Plasma levels of NGAL and its relation to primary outcomes (cardiovascular death, non-fatal stroke and non-fatal myocardial infarction, n=398), and all cause mortality (n=414), cardiovascular mortality (n=338), hospitalizations (n=798) and number of hospitalizations (n=1934) was analyzed in 1415 patients with chronic HF (>60 years, NYHA class II-IV, ischemic systolic HF) in the CORONA population, randomly assigned to 10 mg rosuvastatin or placebo. NGAL levels were significantly correlated with impaired kidney function (eGFR), systemic inflammation (hsCRP) and the degree of HF (NT-proBNP). Multivariate analysis revealed that NGAL added significant information when adjusting for clinical variables, but was no longer significant when further adjusting for ApoB/ApoA-1, GFR and NT-proBNP. However, belonging to the highest NGAL tertile was associated with more frequent hospitalization, even after adjusting for clinical variables as well as GFR and ApoB/ApoA-1, but not after adjustment for NT-proBNP.

Conclusion: Although NGAL, as many other markers, is inferior to NT-proBNP as a predictive marker in HF, our findings may indicate an association between NGAL and the severity of HF, suggesting that NGAL could be added to the list of mediators that may be involved in the progression of this complex disorder.

Abstract 10254: Continuous Monitoring of Regional Function by a Miniaturized Ultrasound Sensor Allows Early Quantification of Low Grade Myocardial Ischemia

Stefan Hyler[1]; Soeren E Pischke[2]; Per S Halvorsen[1]; Andreas Espinoza[2]; Jacob Bergsland[1]; Tor I Tonnessen[2]; Erik Fosse[1]; Helge Skulstad[3]. [1] The Intervention Cntr, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway, [2] Dept of Anesthesiology, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway, [3] Dept of Cardiology, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway

Ischemia is a leading cause of decreased ventricular function during and after heart surgery. Continuous, sensitive methods for early detection are therefore crucial. We hypothesized that low grade ischemia could be detected quantitatively by a miniaturized epicardial ultrasound probe allowing continuous registrations. Myocardial lactate was used as reference method in a model of graded coronary flow reduction. In a porcine model (n=7) miniaturized epicardial ultrasonic transducers (Ø 5mm) were positioned in the LAD- and Cx-area. Left ventricular pressure (LVP) was obtained by a micromanometer. The left anterior mammary artery (LIMA) was grafted to the LAD, which was occluded proximal to the anastomosis. Coronary flow was regulated by intermittently reducing LIMA-flow from baseline to 75%, 50% and 25% for 18 min each. Subendocardial tissue velocity was displayed continuously. Peak systolic velocity (Vmax) was measured and a displacement trace was calculated by time integration. Regional work was assessed as pressure-displacement (LVP-D) loops. Tissue lactate from intramyocardial microdialysis was used to quantify ischemia. All steps of coronary flow reduction demonstrated myocardial ischemia by elevated tissue lactate concentrations. Vmax and LVP-D loops area were significantly reduced from baseline ($p<0.05$) during each intervention (Fig. 1A and B). The decreases in Vmax and LVP-D loop area were closely related to the degree of ischemia, and there were significant inverse correlations between tissue lactate and Vmax ($r=-0.86$, $p<0.001$) and regional work ($r=-0.78$, $p<0.001$) (Fig. 1C). No significant effects were seen in the Cx-area. In conclusion increasing loss of regional function and myocardial work, due to enhancing regional myocardial ischemia was quantified by a miniaturized epicardial ultrasound probe. This method is promising for sensitive and continuous real-time monitoring of myocardium at risk during and after cardiac surgery.



Abstract 13039: Prostaglandin E_1 Facilitates 5-HT_4 Serotonergic and Beta-adrenergic Receptor Mediated Inotropic Effects in Failing Human Heart

Jon Riise[1]; Øivind Ørstavik[1]; Eirik Qvigstad[1]; Christen P Dahl[2]; Jan-Bjørn Osnes[1]; Tor Skomedal[1]; Finn O Levy[1]; Kurt A Krobert[1]. [1] Pharmacology, Univ of Oslo, Oslo, Norway, [2] Cardiology, Oslo Univ Hosp Rikshospitalet, Oslo, Norway

Introduction and hypothesis: Prostaglandins have displayed both beneficial and detrimental effects in clinical studies in patients with severe heart failure. Prostaglandins are known to increase cardiac output, but the mechanism is not clarified. Here, we assessed the hypothesis that prostaglandins increase contractility in human heart by amplifying cAMP-dependent inotropic responses.

Methods: Contractility was measured *ex vivo* in isolated left ventricular strips from explanted human hearts. Phosphodiesterase (PDE) activity was measured through a two-step PDE activity assay on homogenates of the same failing human left ventricles.

Results: PGE_1 (1 μM) alone did not modify contractility, but given prior, amplified maximal serotonin (5-HT)-evoked (10 μM) contractile responses several-fold (24±7 with PGE_1, n=8 vs. 3±2, 5-HT alone, n=9, % above basal, $p<0.05$). The 5-HT-evoked inotropic response was amplified by the PDE3 inhibitor cilostamide and further amplified when PGE_1 was given simultaneously with cilostamide (26±6, n=9, vs. 56±12, n=9, % above basal, $p<0.05$). The maximal β–adrenergic inotropic response was unaffected by PGE_1 alone. However, in this situation, the time to reach 90% of maximal isoprenaline-evoked inotropic response was significantly shortened compared to isoprenaline alone (299±33s, n=14 vs. 406±46s, n=14, $p<0.05$). PGE_1 also facilitated the inotropic effect of isoprenaline above that with PDE3 inhibition alone (time to reach 90%: 111±39s, n=14 vs. 183±37s, n=14 respectively, $p<0.05$). PGE_1 did not modify PDE activity in the homogenate, neither alone nor when given simultaneously with PDE3 and/or PDE4 inhibitors.

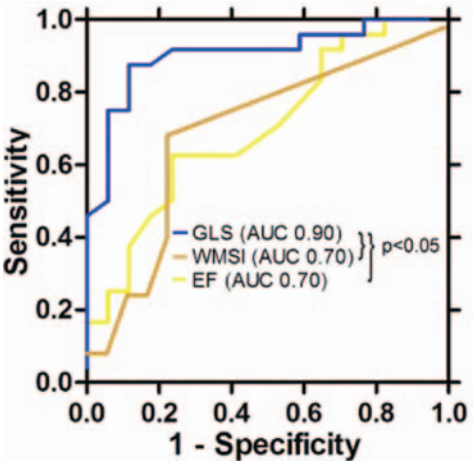
Conclusion: Our results show that PGE_1 can enhance cAMP-mediated responses in failing human ventricle, possibly explaining some of the hemodynamic effects of prostaglandins. The mechanism seems to be independent of PDE inhibition. Possibly, PGE_1 may facilitate 5-HT and β-adrenergic-mediated inotropic effects by synergistic effects upon adenylyl cyclase activation. Alternatively, PGE_1 contributes to a re-organization of factors regulating compartmentation, allowing more efficient transduction of cAMP signaling to activate the contractile apparatus.

Abstract 11678: Early Strain Echocardiography May Exclude Significant Coronary Artery Stenosis in Suspected Non-ST-Elevation Acute Coronary Syndrome

Thomas Dahlslett[1]; Bjørnar Grenne[1]; Christian Eek[2]; Benthe Sjøli[1]; Helge Skulstad[2]; Otto A Smiseth[2]; Thor Edvardsen[2]; Harald Brunvand[1]. [1] Dept of Medicine, Sørlandet Hosp, Arendal, Norway, [2] Dept of Cardiology, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway

Background: Many patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS) have no significant coronary artery disease. Current diagnostic approach with repeated ECG and cardiac biomarkers requires observation for at least 6-12 hours. The aim of this study was to investigate whether global strain by echocardiography measured at admission may exclude significant coronary artery stenosis in patients presenting with inconclusive ECG and normal cardiac biomarkers.

Methods: Patients without known coronary artery disease presenting with suspected NSTE-ACS were enrolled consecutively. 12-lead ECG, Troponin t assay and echocardiography was performed on admission and patients underwent coronary angiography after 27±18 hours. Conclusive ECG was defined as >1 mm ST-segment change in any lead. Troponin t >0.03 μg/L was considered abnormal and >50 % stenosis of any coronary artery was considered significant. Echocardiography was analyzed by a single observer blinded to patient data. Global peak systolic longitudinal strain was measured using speckle tracking echocardiography in the 3 apical image



planes and calculated by averaging all segments in a 16 segment model. Ejection fraction (EF) and wall motion score index (WMSI) were calculated.

Results: Out of 86 patients (age 60±13 years, 71 % male) 41 patients presented with inconclusive ECG and normal cardiac biomarkers. No significant stenosis in any coronary artery was found in 17 (41%) of these patients. A global peak systolic longitudinal strain value of <-21% excluded significant coronary artery stenosis with 77% sensitivity and 92 % specificity (AUC = 0.90) (figure).

Conclusions: Strain by echocardiography may become an accurate and easily available tool to exclude significant coronary artery stenosis among patients presenting with suspected non-ST-elevation acute coronary syndrome with inconclusive ECG and normal cardiac biomarkers.

Abstract 18079: Among CHD Patients in the IDEAL Study, Those with Elevated Levels of Alanine Aminotransferase at Baseline Had a Lower Rate of Major Coronary Events

Matti J Tikkanen[1]; Rana Fayyad[2]; Rachel Laskey[2]; Ingar Holme[3]; Ole Faergeman[4]; Anders G Olsson[5]; Christina Lindahl[6]; John J Kastelein[7]; Mogens Lytken Larsen[4]; Terje R Pedersen[8]; On Behalf of the IDEAL Investigators. [1] Dept of Medicine, Helsinki Univ Central Hosp, Helsinki, Finland, [2] Med, Pfizer Inc, New York, NY, [3] Cntr of Preventive Medicine, Oslo Univ Hosp, Oslo, Norway, [4] Dept of Medicine - Cardiology, Aarhus Univ Hosp, Aarhus, Denmark, [5] Dept of Internal Medicine, Univ Hosp, Linkoping, Sweden, [6] Med, Pfizer Sweden, Sollentuna, Sweden, [7] Dept of Vascular Medicine, Academic Hosp Amsterdam, Amsterdam, Netherlands, [8] Cntr of Prentive Medicine, Oslo Univ Hosp, Oslo, Norway

Background: Previous evidence suggests that statin therapy can reduce cardiovascular (CV) morbidity in patients with mild-to-moderately abnormal liver tests. In this post hoc analysis of the IDEAL study, we investigated the relationship of elevated baseline levels of the liver enzyme alanine aminotransferase (ALT) on CV events, and compared the effects of atorvastatin (ATV) 80 mg versus simvastatin (SIM) 20-40 mg in patients with normal and elevated baseline ALT levels.

Methods: IDEAL was a large randomized trial comparing ATV 80 mg with SIM 20-40 mg in 8888 patients with CHD over 4.8 years of follow-up. Cox regression analysis was performed to investigate the relationship of normal levels of ALT (defined as baseline ALT <ULN [upper limit of normal]; 87.8% of subjects) vs elevated ALT (baseline ALT ≥ULN; 11.5% of subjects had ALT ≥ULN-<2 ULN and 0.74% had ALT ≥2 ULN-<3 ULN) on the risk of major coronary events (MCE: CHD death, non-fatal MI or resuscitated cardiac arrest). In addition, treatment effect (ATV 80mg vs SIM 20-40 mg) was examined for subjects with normal and elevated ALT at baseline.

Results: Over the course of the study, mean ALT levels increased among patients with normal baseline ALT (n=7782) and decreased for those with ALT ≥ULN at baseline (n=1081). Overall, those patients with normal ALT levels at baseline experienced significantly more MCE than patients with higher baseline ALT levels (≥ULN) (HR=0.76; 95% CI 0.61, 0.96; p=0.02). This finding was consistent in patients treated with ATV (HR=0.60; 95% CI 0.42, 0.87; p=0.007) but not those receiving SIM (p=0.464). In patients with elevated ALT baseline levels, ATV significantly reduced the risk of MCE compared with SIM (HR=0.62; 95% CI 0.40, 0.96; p=0.03), but in patients with normal baseline ALT the difference between treatment groups did not reach statistical significance.

Conclusions: In the overall population of CHD patients treated with ATV or SIM, those with normal baseline ALT levels experienced significantly more MCE than those with baseline ALT ≥ULN. The clinical benefits of intensive lipid lowering with ATV compared with a more moderate regimen with SIM were generally greater in patients with abnormal liver tests than in patients with normal liver tests.

Abstract 9749: Impact of QRS Duration and Morphology on The Risk of Sudden Cardiac Death in Asymptomatic Patients with Aortic Stenosis: The Simvastatin and Ezetimibe in Aortic Stenosis Study

Anders M Greve[1]; Eva Gerdts[2]; Kurt Boman[3]; Christa Gohlke-Baerwolf[4]; Anne B Rossebø[5]; Richard B Devereux[6]; Lars Køber[1]; Simon Ray[7]; Ronnie Willenheimer[8]; Kristian Kristian Wachtell[9]. [1] Dept of medicine B-2142, Rigshospitalet, Copenhagen, Denmark, [2] Dept of Cardiology, Univ of Bergen and Haukeland Univ Hosp, Bergen, Norway, [3] Dept of Cardiology, Skelleftå Lasarett and Umeå Univ, Skelleftå, Sweden, [4] Dept of cardiology, Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany, [5] Dept of Cardiology, Oslo Univ Hosp, Ullevål, Oslo, Norway, [6] Dept of cardiology, Weill Cornell Med College, New York, NY, [7] Dept of cardiology, Manchester Academic Health Sciences Cntr, Manchester, United Kingdom, [8] Dept of cardiology, Heart Health Group and

Lund Univ Hosp, Malmö, Sweden, [9] Dept of cardiology, Rigshospitalet and Gentofte Univ Hosp, Copenhagen, Denmark

Background: QRS duration and morphology are associated with poor prognosis in many different populations, but the predictive value, particularly of the risk of sudden cardiac death (SCD), in asymptomatic patients with aortic stenosis (AS) has not been well studied.

Methods: Clinical examination, electrocardiography and echocardiography were obtained in 1,873 asymptomatic AS patients randomized to simvastatin/ezetimibe combination *vs.* placebo in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Association of QRS duration, evaluated as a categorical variable of <85 msec *vs.* 85-99 msec and ≥100 msec (excluding bundle branch block [BBB]) and QRS morphology in those with BBB, with the risk of cardiovascular morbidity and mortality was assessed by adjusting for biomarkers, clinical- and echocardiographic covariates as well as randomized treatment.

Results: QRS data were available in 1,542 patients; followed for a mean of 4.3±0.8 years (6,631 patients-years of follow-up). QRS duration was <85 msec in 900 patients (58.4%), 85-99 msec in 396 (25.7%), ≥100 msec without BBB in 144 (9.3%) and 102 (6.6%) had BBB. In multivariable analyses, those with QRS duration ≥100 msec had, compared to those with QRS duration <85 msec, a 4.9-fold higher risk of sudden cardiac death (95% confidence interval [CI], 1.4 to 16.9, p=0.01) and a 2.7-fold higher risk of cardiovascular death (CI, 1.3 to 5.8, p=0.01). In univariate analyses, left BBB (n=43) was, compared to QRS duration <85 msec, associated with a 3.8-fold higher risk heart failure and right BBB combined with left anterior fascicular block (n=20) with a 4.6-fold higher risk of myocardial infarction (both p<0.05).

Conclusion: QRS duration and morphology in asymptomatic patients with AS are independently associated with poor prognosis, particularly the risk of SCD.

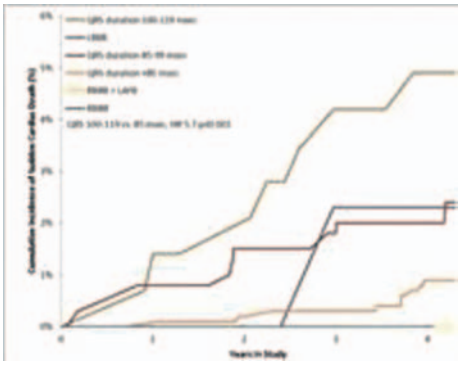


Figure: Incidence of Sudden Cardiac Death According to Baseline QRS Duration and Morphology: During 4.3 Years of Follow-Up.

Abstract 13262: High Sensitivity Troponin I in Acute Decompensated Heart Failure: Insights from the ASCEND-HF Study

G. Michael Felker[1]; W.H. Wilson Tang[2]; Adrian F Hernandez[1]; Vic Hasselblad[1]; Paul W Armstrong[3]; Gregg C Fonarow[4]; Adriaan A Voors[5]; Marco Metra[6]; Javed Butler[7]; Kenneth Dickstein[8]; Richard W Troughton[9]; Stefan D Anker[10]; Gretchen M Heizer[1]; Barry M Massie[11]; John J McMurray[12]; Robert M Califf[13]; Randall C Starling[2]; Christopher M O'Connor[1]. [1] Duke Univ Med Cntr, Duke Clinical Rsch Institute, Durham, NC, [2] Cleveland Clinic Main Campus, Cleveland Clinic, Cleveland, OH, [3] Univ of Alberta, Univ of Alberta, Edmonton, Canada, [4] Room 247, UCLA, Los Angeles, CA, [5] Hanzeplein 1, Univ Med Cntr Groningen, Groningen, Netherlands, [6] Cardiology, Univ of Brescia, Brescia, Italy, [7] Cardiology, Emory Univ, Atlanta, GA, [8] Institute of Internal Medicine, Univ of Bergen, Stavanger Univeristy Hosp, Bergen, Norway, [9] Cardiology, Univ of Otago, Christchurch, New Zealand, [10] Dept of Cardiology, Applied Cachexia Rsch, Berlin, Germany, [11] San Francisco VA Med Cntr, Univ of California, San Francisco, San Francisco, CA, [12] Cardiology, Univ of Glasgow, Glasgow, United Kingdom, [13] Duke Univ Med Cntr, Duke Translational Medicine Institute, Durham, NC

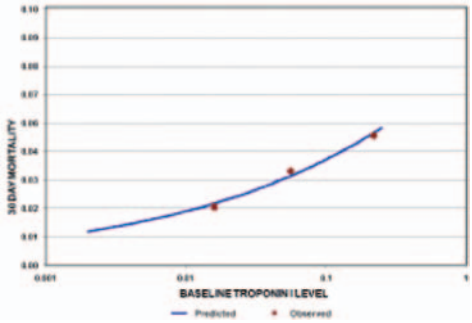
Background: Prior data suggest that circulating cardiac troponin (cTn) may be a useful prognostic marker in patients with acute decompensated heart failure (ADHF). Recent improvements in the sensitivity of troponin assays suggest the need for reassessment of the significance of troponin elevation in HF in order to define clinically relevant cut-points. We examined the prognostic importance of high sensitivity troponin I (cTnI) in a cohort of patients enrolled in the ASCEND-HF study, a randomized clinical trial of nesiritide in ADHF.

Methods: cTnI was measured at a central core laboratory in 808 ADHF patients enrolled in the ASCEND-HF study using a contemporary high sensitivity assay (VITROS Trop I ES, Ortho Clinical Diagnostics) with a lower limit of detection of 0.012 ng/mL and a 99% upper reference limit (URL) of 0.034 ng/mL. Logistic regression was used to assess the relationship between log (cTnI) and 30-day mortality.

Results: Baseline cTnI was undetectable in 22% and elevated above the 99% URL in 50%. Patients with cTnI >0.034 ng/mL were more often male, were older, and had higher NTproBNP and worse renal function (p<0.05 for all). Higher log (cTnI) was associated with a higher 30-day

mortality in logistic regression (odds ratio=1.23 per doubling of cTnI, p=0.035, c-index=0.60), and there was no evidence for a threshold effect at any level of cTnI (figure). After adjustment for other known predictors using the ASCEND-HF mortality model (age, blood pressure, urea nitrogen, sodium), cTnI was no longer associated with 30-day mortality (adjusted odds ratio=1.19 per doubling of cTnI, p=0.31).

Conclusions: cTnI was associated with 30-day mortality in ADHF, but this effect was no longer significant after multivariable adjustment. There was no evidence for a threshold effect at any level of troponin elevation, suggesting that the 99% URL utilized for the diagnosis of acute MI has no particular significance in patients with ADHF.



Abstract 15992: STAMP2 Controls Macrophage Inflammatory Responses by NADPH Regulation

Henrik ten Freyhaus[1]; Ediz S Calay[2]; Sara N Vallerie[2]; Abdullah Yalcin[2]; Ling Yang[2]; Fahri Saatcioglu[3]; Gokhan S Hotamisligil[4]. [1] Klinik 3 Fuer Innere Medizin, Univ of Cologne, Cologne, Germany, [2] Dept of Genetics and Comples Diseases, Harvard Sch of Public Health, Boston, MA, , [3] Molecular Biosciences, Univ of Oslo, Oslo, Norway, [4] Dept of Genetics and Comples Diseases and Nutrition, Harvard Sch of Public Health, Boston, MA

Regulatory mechanisms are important to control systemic metabolic homeostasis and to counteract visceral adipose tissue inflammation to metabolic challenges. The six-transmembrane protein of prostate (STAMP)-2 plays an important role in this context. STAMP2-deficiency recapitulates most features of the metabolic syndrome in mice including a pro-inflammatory phenotype of visceral adipose tissue. STAMP2 is expressed in macrophages, and macrophage inflammation is a hallmark of atherosclerosis. Consequently, we evaluated the role of STAMP2 in this context. STAMP2-deficiency of primary macrophages led to significantly increased expression (n=6-8, p<0,05) and secretion (n=9-12, p<0,05) of Interleukin- (IL)-6, IL-1β, TNF-α, and MCP-1 compared to WT. Furthermore, expression of inducible NO synthase (iNOS) (n=10 for mRNA, n=11 for protein, p<0,05) and NO production (n=11, p<0,05) were enhanced compared to WT. As (i) iNOS is an NADPH-dependent enzyme and (ii) STAMP2 possesses NADPH oxidoreductase activity, we measured NADPH levels in WT and STAMP2-deficient macrophages. We found that NADPH levels were significantly higher in STAMP2-deficient macrophages (n=3, p<0,01). Both pharmacological inhibition with dehydroandrosterone and RNA interference blocked increased inflammation of STAMP2-deficient macrophages (n=3, p<0,05), confirming an important role of NADPH for the observed phenotype. Adding back full-length STAMP2 to STAMP2-deficient macrophages decreased NADPH levels, whereas adding back STAMP2 lacking NADPH oxidoreductase activity did not (n=4-5, p<0,05). These data show that NADPH oxidoreductase activity of STAMP2 is involved in regulation of NADPH levels in macrophages. To assess, whether macrophage STAMP2 deficiency has in vivo relevance, we analyzed atherosclerotic lesion formation in the atherogenic ApoE-/- genetic background. STAMP2-deficiency led to accelerated atherosclerosis both in the en face aorta (n=10-12, p<0,01) and in the aortic root (n=8, p<0,01). Taken together, these data show that STAMP2 has an important role in atherosclerosis and in the control of macrophage inflammation that is partially attributable to control of NADPH levels of cells.

Abstract 16319: Physical Fitness Modifies the Predictive Impact of Weight Gain and Body Mass Index for Incident Atrial Fibrillation

Irene Grundvold; Per T Skretteberg; Sverre E Kjeldsen; Harald Arnesen; Johan Bodegard , Dept of Cardiology, Oslo Univ Hosp, Oslo, Norway

Introduction: The incidence of both atrial fibrillation (AF) and obesity is increasing in the general population, and lifestyle intervention is recommended. We tested the hypothesis that measured physical fitness modifies the long-term predictive impact of body mass index (BMI) and weight gain since 25 years of age for incident AF.

Methods: From 1972-1975, 2014 healthy middle-aged Norwegian men participating in a prospective cardiovascular survey, underwent a comprehensive clinical examination including a symptom-limited bicycle exercise ECG test. Physical fitness was defined as the total exercise work divided by body weight. During up to 35 years follow-up, 269 men were documented with

AF by scrutinizing all hospital discharges. Risk estimation for incident AF was analyzed using Cox proportional hazard models and tested for age-adjusted physical fitness above and below median. All analyses were adjusted for age, systolic blood pressure, current smoking, total cholesterol and blood glucose.

Results: Mean baseline BMI was 24.6 kg/m^2 (SD 2.8) and only 24 % of the men had weight gain of 10 kg or more from the age of 25 to midlife, defining this as a lean population. Men with physical fitness below median and BMI >= 28 kg/m^2 had a 1.60-fold (95 % CI 1.04-2.41) increased risk of AF compared with men with BMI < 28 kg/m^2. Correspondingly, men with physical fitness below median and weight gain >=10 kg had a 3.14-fold (95 % CI 1.14-12.95) risk of AF compared with men with weight loss since 25 years of age. However, among men with above median physical fitness neither weight change nor BMI predicted incident AF.

Conclusions: BMI >= 28 kg/m^2 and weight gain >=10 kg since 25 years of age are long-term predictors of incident AF in initially healthy middle-aged men with low physical fitness, but not in physically fit men. High physical fitness reduced the risk of AF associated with BMI and weight gain, and these results might be consistent with the obesity paradox phenomenon where overweight and obese persons have the same favorable outcome as normal weight persons for various cardiovascular events.

Abstract 9245: Incident Atrial Fibrillation is Associated with an Increased Risk of Sudden Cardiac Death in Hypertensive Patients During Antihypertensive Therapy: The LIFE Study

Peter M Okin[1]; Kristian Wachtell[2]; Darcy A Hille[3]; Sverre E Kjeldsen[4]; Björn Dahlöf[5]; Richard B Devereux[1]. [1] Cardiology, Cornell Med Cntr, New York, NY, Cardiology, The Heart Cntr, Rigshospitalet, Univ of Copenhagen, Copenhagen, Denmark [3] Late Development Statistics, Merck&Co., Inc., North Wales, PA, [4] Cardiology, Oslo Univ Hosp Ullevål, Oslo, Norway, [5] Internal Medicine, Sahlgrenska Univ Hosp/Östra, Gothenburg, Sweden

Background: Incident atrial fibrillation (AF) is associated with an increased risk of mortality in the general population and after myocardial infarction. Prevalent AF is associated with an increased risk of appropriate device therapies for ventricular arrhythmias in patients with ICDs and with a higher rate of sudden cardiac death (SCD) in advanced heart failure patients. However, whether hypertensive patients with incident AF are at higher risk of SCD has not been examined.

Methods and Results: The predictive value of incident AF for SCD was examined in 8831 hypertensive patients with ECG left ventricular hypertrophy (LVH) with no history of AF, in sinus rhythm on their baseline ECG, who were randomly assigned to losartan- or atenolol-based treatment. During 4.8±0.9 years mean follow-up, new-onset AF occurred in 701 patients (7.9%) and SCD in 151 (1.7%). SCD was significantly more frequent in patients with new AF than in those without (3.6 vs 1.5%, p<0.001). In univariate Cox analyses, new-onset AF, treated as a time-varying covariate, was associated with a subsequent 113% higher risk of SCD (HR 2.13, 95% CI 1.31-3.44, p=0.002). In multivariate Cox analyses adjusting for randomized treatment, age, sex, race, body mass index, diabetes, history of heart failure, myocardial infarction, ischemic heart disease, stroke, peripheral vascular disease, smoking, serum total and HDL cholesterol, creatinine, glucose, urine albumin/creatinine ratio and for incident MI, in-treatment heart rate, diastolic and systolic pressure, Cornell voltage-duration product and Sokolow-Lyon voltage LVH treated as time-varying covariates, incident AF remained associated with a 74% increased risk of SCD (HR 1.74, 95% CI 1.05-2.91, p=0.033).

Conclusions: The development of new-onset of AF identifies hypertensive patients at increased risk of SCD, independent of the higher prevalence of risk factors in patients with new AF, treatment effects, in-treatment blood pressure and the established predictive value of in-treatment ECG LVH and heart rate for SCD in this population.

Abstract 9493: Plasma Levels Of Soluble CD36 In Type 2 Diabetes - A Link Between Platelet Activation, Inflammation And Oxidative *Stress*

Giovanni Davì[1]; Rossella Liani[1]; Bente Halvorsen[2]; Simona Sestili[1]; Aase Handberg[3]; Francesca Santilli[1]; Gloria Formoso[4]; Pål Aukrust[2]. [1] Hemostasis and Thrombosis Unit, Univ of Chieti, Chieti, Italy, [2] Rsch Institute of Internal Medicine, Univ of Oslo, Oslo, Norway, [3] Dept of Clinical Biochemistry, Aarhus Univ Hosp, Aalborg, Denmark, [4] Diabetology and Metabolism Unit, Univ of Chieti, Chieti, Italy

Introduction Inflammation, oxidative stress and platelet activation are involved in the pathogenesis of type 2 diabetes (T2DM) and its complications. Soluble CD36 (sCD36) has been proposed to early identify diabetic subjects at risk of developing accelerated atherothrombosis.

Hypothesis We aimed at characterizing the platelet contribution to sCD36 in T2DM, to correlate its formation with the extent of *in vivo* lipid peroxidation and to investigate the effects of low-dose aspirin on these processes.

Methods A cross-sectional comparison of sCD36, soluble CD40L (sCD40L) as a marker of platelet-mediated inflammation, urinary 11-dehydro-TxB_2 and 8-iso-$PGF_2\alpha$, *in vivo* markers of platelet activation and lipid peroxidation, respectively,was performed between 200 T2DM patients (94 of them on low-dose aspirin) and 47 healthy controls.

Results sCD36 (median [IQR]: 0.72 [0.31-1.47] vs 0.26 [0.2-0.37], p=0.003) and urinary 11-dehydro-TxB_2 levels (666 [293-1336] vs 279 [160-396], p≤0.0001) were significantly higher in T2DM patients not on aspirin (n=106) than in healthy subjects. These variables were significantly lower in aspirin-treated diabetics than in untreated patients (p<0.0001). Among patients not on aspirin, those with long-standing diabetes had significantly higher sCD36 levels in comparison to patients with diabetes duration <1 year (1.01 [0.62-1.86] vs 0.44 [0.22-1.21], p=0.001). Consistently, in the same group of patients, a significant linear correlation was found between sCD36 and diabetes duration (rho=0.347; p=0.0001), fasting blood glucose (rho=0.378; p=0.002) and HbA_{1c} (rho=0.255; p=0.026). sCD36 linearly correlated with urinary 11-dehydro-TxB_2, 8-iso-$PGF_{2\alpha}$ and sCD40L in diabetics not on aspirin. On multiple regression analysis, 11-dehydro-TxB_2 (β=0.360; SEM=0.0001, p=0.001), 8-iso-$PGF_{2\alpha}$ (β=0.469; SEM=0.0001, p<0.0001) and diabetes duration (β=0.244; SEM=0.207, p=0.017) independently predicted sCD36 levels.

Conclusions sCD36 may be a link among hyperglycemia, inflammation, lipid peroxidation and platelet activation. Because it can only incompletely be down-regulated by low-dose aspirin, additional antiplatelet strategies in T2DM should be investigated to interrupt CD36-dependent platelet activation.

Abstract 9521: Obesity Increases the Prevalence of Cardiovascular Target Organ Damage in Hypertension

Eva Gerdts[1]; Giovanni de Simone[2]; Rafaelle Izzo[3]; Marina De Marco[2]; Giusy Casalnuovo[2]; Renata Giudice[3]; Bruno Trimarco[4]; Nicola De Luca[4]. [1] Institute of Medicine, Univ of Bergen, Bergen, Norway, [2] Dept of Clinical and Experimental Medicine, Federico II Univ Hosp, Napoli, Italy, [3] Dept of Clinical Medicine, Cardiovascular and Immunological Sciences, Federico II Univ Hosp, Napoli, Italy, [4] Dept of Clinical Medicine, Cardiovascular and Immunological Sciences,, Federico II Univ Hosp, Napoli, Italy

Background: Whether concomitant obesity in hypertension is associated with increased prevalence of vascular as well as cardiac target organ damage needs further clarification.

Methods: Data from carotid ultrasound and echocardiography in 10800 hypertensive patients free of prevalent CV disease, participating in the Campania Salute Network were used. The population was grouped into body mass index (BMI) classes: normal BMI 20-24.9 kg/m^2, overweight BMI 25-29.9 kg/m^2 and obese BMI>30 kg/m^2. Vascular and cardiac target organ damage was defined as plaque in >1 of the common or internal carotid arteries and left ventricular hypertrophy (LVH), respectively. LVH was defined as LV mass/$height^{2.7}$ >46.7 g/$m^{2.7}$ in women and >49.2 g/$m^{2.7}$ in men, respectively.

Results: A majority of the patients were either overweight or obese (Table 1). In spite of more use of combination therapy, the obese group had slightly higher blood pressure (BP) and included more patients with carotid plaques and LVH (Table 1). In multivariate logistic analyses, concomitant obesity was associated with a 21% (95% confidence interval [CI] 7-36%) increased prevalence of carotid plaques, a 3.7 times higher prevalence of LVH (95% CI 3.32-4.18) and a 2.4 times higher prevalence of combined vascular and cardiac target organ damage (95% CI 2.12-2.78, all p<0.01) independent of significant associations with gender, age, diabetes mellitus, clinic systolic BP and antihypertensive treatment.

Conclusion: In hypertensive patients participating in the Campania Salute Network, concomitant obesity is associated with a highly increased prevalence of LVH, and a modest increased prevalence of carotid plaques.

Table 1.

Variable	Normal BMI (n=2708)	Overweight (n=5252)	Obesity (n=2840)
Women (%)	53.1	36.7*	45.5
Diabetes mellitus (%)	3.7	5.3*	8.1*
Clinic systolic BP (mmHg)	144±19	144±18	146±19*
Clinic diastolic BP (mmHg)	88±12	89±11*	90±12*
Carotid plaque (%)	55.4	59.3*	61.6*
LVH (%)	22.6	40.1*	60.2*
Combined carotid plaque and LVH (%)	17.4	28.3*	42.6*
Combination therapy (%)	49.3	60.0*	65.3*

BP, blood pressure. *p<0.01 vs. Normal weight group

Abstract 10682: Is Acute Heart Failure Admission Linked to a Change in Temperature? Insights from ASCEND-HF

Justin A Ezekowitz[1]; Jeffrey A Bakal[1]; Cynthia A Westerhout[1]; Dan Atar[2]; John J McMurray[3]; Adrian F Hernandez[4]; Christopher M O'Connor[4]; Paul W Armstrong[1]. [1] Medicine, Univ of Alberta, Edmonton, Canada, [2]

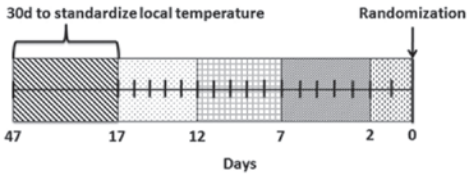
Medicine, Oslo Univ Hosp, Oslo, Norway, [3] *Medicine, Glasgow, Glasgow, United Kingdom,* [4] *Medicine, Duke Clinical Rsch Institute, Durham, NC*

Introductions: Weather has been suggested as a factor that precipitates an acute heart failure (AHF) episode but prior observations are limited by regional data and use of monthly temperatures. We sought to identify a vulnerable population susceptible to changes in weather conditions, and the relationship between weather and time intervals prior to an AHF episode.

Methods: ASCEND-HF enrolled 7007 pts with AHF between 2007 and 2010 (397 sites, 30 countries). A Google interface identified the weather stations reporting data to the National Climatic Data Center nearest to each site. Each station provides 4 daily measurements for each variable (temperature (TEMP), relative humidity, barometric pressure, wind speed, and precipitation). A TEMP change was defined as occurring <10% of the time against the local 30d TEMP history (to control for local seasonality and region).(FIGURE) "Vulnerable pts" were those with older age, increased Charlson index, a low EF and ischemic etiology.

Results: The mean age of pts was 65yrs (SD 14.2), 66% were male, 83% had EF<40%, and 60% had an ischemic etiology. Overall, there was no association globally between TEMP or other climate variables and HF presentation or comorbidity burden. In the analysis of "vulnerable pts" we observed that an AHF episode following a TEMP rise in the 48hrs preceding their randomization was more likely (aOR= 1.22; 95%CI 1.00-1.49) for those with a low EF. In the more distant time intervals, ischemic pts were more sensitive to temperature increases in the 3-7d prior to randomization (aOR = 1.13; 95%CI 1.00-1.28), whereas the non-ischemic pts were more sensitive to a drop in TEMP in the 3 distant time periods (aOR = 1.12; 95%CI 0.99-1.25).

Conclusion: Weather events did not herald AHF events in the overall ASCEND-HF population using daily pt-normalized meteorological data. However, pts with a low EF and those with an ischemic etiology were susceptible to changes in TEMP, independent of comorbidity burden.



Abstract 10698: Syndecan-4 Regulates Myofibroblast Differentiation Following Mechanical Stress

Kate M Herum; Ida G Lunde; Dina Behmen; Biljana Skrbic; Ivar Sjaastad; Geir Florholmen; Cathrine R Carlson; Geir Christensen. Institute for Experimental Med Rsch, Oslo Univ Hosp Ullevaal, Oslo, Norway

Mechanical stress caused by 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 likely to involve stress-sensing molecules located in focal adhesions, such as the transmembrane proteoglycan syndecan-4. We have previously shown that syndecan-4 activates the calcineurin-NFAT (nuclear factor of activated T-cells) signaling system in cardiomyocytes during development of cardiac hypertrophy. However, the role of this signaling pathway in cardiac fibroblasts is not clear. Here, we hypothesized that syndecan-4 activates NFAT in response to mechanical stress leading to myofibroblast differentiation. *In vivo*, aortic banding caused a 2.2-fold increase of the myofibroblast marker gene smooth muscle α-actin (SMα-actin) in wild type hearts. Strikingly, this effect was completely absent in the syndecan-4 knockout (KO) hearts, indicating an essential role for syndecan-4 in myofibroblast differentiation during pressure overload. Following cyclic stretch (10 %, 1 Hz) of cardiac fibroblasts *in vitro*, NFATc4 was found to become activated in a calcineurin-dependent manner. This activation was significantly reduced in syndecan-4 KO cardiac fibroblasts implying involvement of syndecan-4 in stretch-induced NFAT activation. Furthermore, syndecan-4 and calcineurin colocalized (proximity ligation assay) suggesting a possible interaction. Previously, we have found that phosphorylation of serine 179 (pS179) in the cytoplasmic part of syndecan-4 negatively regulates binding and activation of calcineurin in cardiomyocytes. Following cyclic stretch of cardiac fibroblasts, pS179 was reduced by 50%, favouring calcineurin-NFAT activation. Finally, overexpressing NFATc4 in fibroblasts caused a 2.3-fold increase in SMα-actin after stretch. In conclusion, we show that syndecan-4 activates calcineurin-NFAT signaling in mechanically stressed cardiac fibroblasts and that this signaling pathway could induce the differentiation into myofibroblasts.

Abstract 16892: Trends in the Presentation, Diagnosis and Outcomes of Acute Aortic Dissection Over 15 Years, From the International Registry of Acute Aortic Dissection (IRAD).

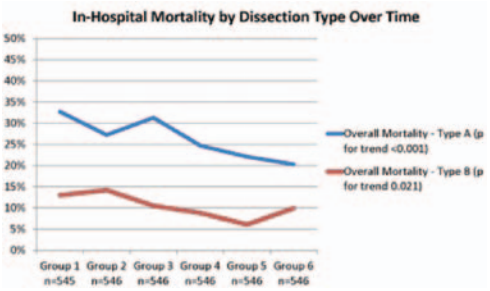
Linda Pape[1]; Mazen Awais[2]; Toru Suzuki[3]; Santi Trimarchi[4]; Arturo Evangelista[5]; Truls Myrmel[6]; Magnus Larsen[6]; Kevin M Harris[7]; Kevin Greason[8]; Marco Di Eusanio[9]; Daniel Montgomery[2]; Kim A Eagle[2]; Christoph A Nienaber[10]; Eric M Isselbacher[11]; Patrick O'Gara[12].
[1] Cardiovascular Medicine, Univ of Massachusetts Hosp, Worcester, MA, [2] Cardiology, Univ of Michigan, Ann Arbor, MI, [3] Cardiovascular Medicine, Univ of Tokyo, Tokyo, Japan, [4] Cardiovascular Medicine, IRCCS Policlinico San Donato, San Donato, Italy, [5] Cardiovascular Medicine, Hosp General Universitari Vall D'Hebron, Barcelona, Spain, [6] Thoracic and Cardiovascular Surgery, Tromso Univ Hosp, Tromso, Norway, [7] Cardiovascular Medicine, Univ of Minnesota - Minneapolis Heart Institute, Minneapolis, MN, [8] Cardiovascular Surgery, Mayo Clinic, Rochester, MN, [9] Cardiovascular Medicine, Univ Hosp S. Orsola, Bologna, Italy, [10] Internal Medicine, Univ Hosp Eppendorf-Rostock, Rostock, Germany [11] Thoracic Aortic Cntr, Massachusetts General Hosp, Boston, MA, [12] Cardiology, Brigham&Women's Hosp, Boston, MA

Introduction/Purpose: To examine trends in patient presentation, diagnosis and outcomes of acute aortic dissection over 15 years since the original report from the International Registry of Acute Aortic Dissection (IRAD).

Methods: Patient data were collected at 28 international referral centers from 1996 up to the present. Trends were analyzed among 3275 patients divided according to date of enrollment into 6 equal groups and by Type: A (n=2110) or B (n=1165).

Results: There was no change over time in the presenting complaints of severe or worst ever pain for Type A and Type B (90% and 96%, respectively), or in the incidence of chest pain (80% in Type A and 70% in Type B, respectively), with considerable overlap in chest vs. back pain between types. The report of pulse deficits did not change over time, present in 30% of Type A patients. Normal chest X-ray on presentation increased in Type A acute aortic dissection (AoD) from 13.7% to 31.3% over time (p-value for trend <0.001). In Type B the report of normal chest X-ray increased from 19.9% to 40.9% (p-value for trend <0.001). There were significant trends in initial imaging modalities for Type A: increased use of CT (from 49.4% to 71.6%, p-value for trend <0.001) and decreased use of TEE (from 45.3% to 25.4%, p-value for trend <0.001). For Type B, use of CT increased from 77.2% to 88.4% (p-value for trend .013). A decrease in overall mortality over time was significant for both Type A and Type B patients (see graph). Surgical mortality in Type A patients fell from 25.3% to 16.5% (p-value for trend 0 .003).

Conclusions: No significant difference was seen over time in pain severity, chest pain, and presence of pulse deficits. The incidences of a normal chest X-ray, originally thought to be uncommon in dissection cases, increased over time to 30% in Type A and 40% in Type B AoD. Use of CT as the initial imaging modality increased for both Type A and Type B. Lastly, a significant decrease in overall mortality was seen for both Type A and Type B patients.



Abstract 17170: Acute Aortic Intramural Hematoma: an Analysis from the International Registry of Acute Aortic Dissection

Kevin M Harris[1]; Alan C Braverman[2]; Reed Pyeritz[3]; Truls Myrmel[4]; Mark Peterson[5]; Matthias Voehringer[6]; Rossella Fattori[7]; James L Januzzi[8]; Dan Gilon[9]; Daniel Montgomery[10]; Kim A Eagle[10]; Christoph A Nienaber[11]; Eric M Isselbacher[12]; Arturo Evangelista[13].
[1] Minneapolis Heart Institute Foundation, Minneapolis, MN, [2] Marfan Syndrome Clinic, Washington Univ, St. Louis, MO, [3] Dept of Cardiology, Univ of Pennsylvania, philadelphia, PA, [4] Dept of Cardiology, Tromso Univ Hosp, Tromso, Norway, [5] Dept of Cardiology, St. Med Hosp, Toronto, Canada, [6] Minneapolis Heart Institute, Univ of Minnesota, Auerbachstrasse, Germany, [7] Dept of Cardiology, Univ Hosp S. Orsola, Policlinico, Italy, [8] Cardiology Div, Massachusetts General Hosp, Boston, MA, [9] Heart Institute, Hadassah Univ Hosp, Jerusalem, Israel, [10] Cardiology, Univ of Michigan, Ann Arbor, MI, [11] Internal Medicine, Univ Hosp Eppendorf-Rostock, Rostock, Germany, [12] Thoracic Aortic Cntr, Massachusetts General Hosp, Boston, MA, [13] Cardiology, Hosp General Universitari Vall D'Hebron, Barcelona, Spain

Background: Acute aortic intramural hematoma (IMH) represents an important subgroup of aortic dissection though controversy continues to surround the appropriate management.

Methods: We evaluated patients with acute aortic syndromes in the IRAD registry (between 1996 and 2011) and examined differences between patients (based on the initial imaging test) with IMH or classic dissection (AD).

Results: Of 2908 patients, 182 had IMH (72 type A (TA), 39.6%, 110 type B (TB), 60.4%). Patients with IMH were older in both TA (68.9 years vs. 61.4, p<0.001) and TB (69.3 vs 62.7, p<0.001), and more frequently female in TA (44.4% vs 32.3%, p=.031). Patients presented with similar symptoms such as severe pain in TA (98.4% vs 91.6%, p=NS) and TB (95.7% vs 93.0%, p=NS). Patients with TA IMH were less likely to present with aortic regurgitation (37.3% vs 54.8%, p=.008) or pulse deficits (16.7% vs31.5%, p=.015). Patients with TA IMH were more likely to have periaortic hematoma (47.5% vs 19.9%, p<0.001) and pericardial effusion (60.0% vs 41.2%, p=.002). Patients with IMH were more likely than classic AD to be managed medically (TA, 22.2% vs 12.6%, p=.017, type B 85.5% vs 62.9%, p<0.001). Overall in-hospital mortality was similar for type A IMH (26.4% vs 26.4%, p=NS); those with type A IMH managed medically had significant mortality (37.5%) though less than those with classic AD (58.5%, p=NS). Those with type B IMH had lower in hospital mortality (4.5% vs 10.9%, p=.043) than classic AD. One year mortality was similar for both groups.

Conclusion: The IRAD registry includes 182 cases of IMH and represents the largest series to date on this important variant of AD. Acute IMH has similar presentation to classic AD but is more frequently complicated with pericardial effusions and periaortic hematoma. Patients with IMH have similar mortality to those with classic AD. Although a substantial subgroup of type A patients with IMH are managed medically, they do have a significant hospital mortality.

Abstract 14923: Disruption of Ca^{2+} Homeostasis induces activation of Heat Shock Proteins and a Shift in Cytoskeleton Composition

Cathrine Husberg[1]; Giulio Agnetti[2]; Staale Nygaard[1]; Kristin Breivik Andersson[1]; Geir Christensen[1]; Jennifer E Van Eyk[3]. [1] Institute for Experimental Med Rsch, Oslo Univ Hosp, Oslo, Norway, [2] Dept Of Medicine, Johns Hopkins Univ, Baltimore, MD, [3] Dept. Of Medicine,, Johns Hopkins Univ, Baltimore, MD

Background: Alteration of Ca^{2+} homeostasis is known to be an important mechanism underlying the progression to heart failure. However, a conditional, cardiac specific SERCA2 knockout (SERCA2 KO) mouse has sustained *in vivo* cardiac function for several weeks despite dramatically altered cytosolic Ca^{2+} handling and SR function. So far, it is not clear which biological processes are altered in the SERCA2 KO myocardium in the compensatory phase.

Aim: To examine the molecular mechanism behind this intriguing compensation using a proteomic approach.

Methods and results: Nine days after tamoxifen-induced gene disruption in the SERCA KO mice, the abundance of SERCA2 protein was reduced to 30% of control levels (western blot) yet there were no differences in cardiac function (left atrial diameter, echocardiography, n= 6 for both KO and age matched controls). Using two dimensional gel electrophoresis (pH 4-7 and 6-11) and tandem mass spectrometry, we identified alterations in more than 60 cytosolic proteins. Fundamental changes were found in the cytoskeletal composition with alterations in vinculin, actin, gelsolin and coffilin-2. These were accompanied by regulation of a subset of heat shock proteins (HSPs), HSPB1, alpha-B-crystallin and HSPA5. Knowing that HSPB1 can stabilize proteins comprising the cytoskeleton and myofilament, we focused our experiments on the functional importance of HSPB1. The function of HSPB1 is depending on its phosphorylation status which was increased in the KO animal - including both known and novel sites (S13, S15, S86, T114). *In vitro* studies in a number of different cell types (HEK293, HL1 and neonatal rat cardiomyocytes), showed that PKC activation (1 μM PMA/1hr) can induce HSPB1 phosphorylation. Finally, we show how the phosphorylation status affects HSPB1 ability to interact with its binding partners.

Conclusions and perspectives: We have linked altered Ca^{2+} homeostasis to activation of heat shock proteins and a shift in cytoskeleton composition. Our results show that disruption of Ca^{2+} homeostasis can give phenotypical effects in the myocardium beyond the contractile apparatus, also involving the cardiomyocyte cellular architecture.

Abstract 15006: Transmural Infarct Distribution in Reperfused Myocardium after STEMI

Thomas M Helle-Valle; Hans-Jørgen Smith; Einar Hopp; Ketil Lunde; Vartdal Trond; Ola Gjesdal; Thor Edvardsen; Otto A Smiseth. Dept of Cardiology, Rikshospitalet, Oslo, Norway

Background: The conventional distinction between transmural and non-transmural infarcts has been challenged by reports of irregular morp-

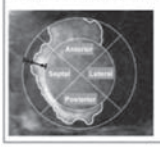
hology of reperfused myocardium. This study investigates the transmural infarct distribution of reperfused myocardium.

Methods: We studies 62 patients 6 months after revascularization by PCI due to acute LAD-occlusion (STEMI). Myocardial infarction was visualized by late enhancement MRI, and quantified according to a 17-segment LV model. In each segment infarct extent was both measured as infarct area in percentage of total segment area (IA%) and as maximal endo- to epicardial infarct transmurality (ITM%; Figure). By both methods, infarct extent >50% was defined as transmural.

Results: Mean LV ejection fraction was 56±11%. LV infarct size was 19±12% of the total LV mass. By ITM%, 94% of the patients had ≥1 segment with transmural infarction, and the distribution between segments of non-transmural and transmural infarction was 23 vs. 77% (Table). By IA%, 80% of the patients had ≥1 segment with >50% infarction and the distribution between segments of non-transmural and transmural infarction 71 vs. 29%. Importantly, in segments classified as non-transmural by IA%, 66% were transmural by ITM%. Correlation between EF and infarct extent by the 2 methods were identical (r= 0.50, P<0.0001).

Conclusion: Due to the irregular distribution of infarct transmurality in reperfused infarcts, the conventional distinction between infarcts of transmural or non-transmural extent is ambiguous.

Figure. Typical heterogenous transmural infarct distribution



Segments	$IA_{\%}$	$ITM_{\%}$
Anterior	72	100
Septal	38	67
Posterior	40	84
Lateral	0	0

Table. Number of segments of various infarct extent

		Segmental infarct extent (%)				
		0	1-25	26-50	51-75	76-100
$IA_{\%}$	(n=)	502	202	172	95	60
$ITM_{\%}$	(n=)	502	21	100	165	243

Abstract 186: Coronary Angiographic Findings in Patients with or Without ST-Segment Elevation Resuscitated After Out-of-Hospital Cardiac Arrest

Ziaullah Kamal; Geir Oystein Andersen; Jan Eritsland; Tomas Draegni; Kjetil Sunde; Arild Mangschau. Oslo Univ Hosp Ulleval, Oslo, Norway

Background: Long-term survival after out-of-hospital cardiac arrest (OHCA) has improved in the last decade with special focus on the post cardiac arrest syndrome. Therapeutic hypothermia and percutaneous coronary intervention (PCI) are the two most important in-hospital interventions. International guidelines recommend aggressive use of coronary angiography in patients with ST segment elevation myocardial infarction (STEMI), but it is not clear if also patients without ST elevation should undergo early coronary angiography (ECA). The aim of the study was to document outcome in all OHCA patients of cardiac etiology, with special focus on angiographic findings and survival among patients with or without ST segment elevation.

Methods: All patients admitted to our hospital after primary resuscitated OHCA are registered in our Post-resuscitation care registry. Electrocardiogram (ECG), coronary angiographic findings and overall survival of patients admitted in 2008 with cardiac etiology were investigated retrospectively by reviewing medical charts. Patients were classified according to the presence of ST segment elevation on post-resuscitation ECG or not.

Results: Altogether 62 patients were included. ST elevation was present in 33 (53%) patients in whom all underwent ECA, 24 (73%) had an acute coronary occlusion, 5 (15%) had old occlusions, 17 (51%) had multivessel disease, and 29 (88%) received PCI. Among the 29 (47%) patients without ST elevation, 24 (83%) underwent ECA, of whom 5 (17%) had an acute coronary occlusion, 12 (50%) had old occlusions, 18 (75%) had multivessel disease, and 12 (38%) received PCI. In total, 60% of the patients were treated with therapeutic hypothermia with no difference between the two groups. Overall survival was 64% and 59% in patients with and without ST elevation, respectively (ns).

Conclusion: Overall survival after OHCA of cardiac etiology was good, with no difference between patients with or without ST segment elevation. The presence of ST elevation on ECG was highly associated with the presence of an acute coronary occlusion, but a substantial proportion of patients without ST elevation also had coronary occlusions treated by PCI and more studies are warranted to determine whether all patients should undergo ECA.

Abstract 19: Targeted Education Can Change Paramedics' Attitudes to CPR

Andres Neset[1]; Eric Beairsto[2]; Edgar Goulette[2]; Susan Dugas[2]; Mathieu Hachée[2]; Jo Kramer-Johansen[1]. [1] Oslo Univ Hosp, Oslo, Norway, [2] Ambulance New Brunswick, Moncton, Canada

Objectives: One reason for sub-standard CPR quality may be linked to long-held beliefs and lack of knowledge. We wanted to study if tar-

geted education could change these attitudes among paramedics.

Methods: Ambulance New Brunswick introduced a continuous quality improvement system (CQI) for out-of-hospital cardiac arrest in 2008 based on CPR-performance recordings. Shortly after this, all paramedics were invited to answer a survey, to study the attitudes and knowledge towards CPR. Learning objectives were constructed from the survey to address attitudes and lack of knowledge, and were used in the following training sessions. The survey was repeated in 2011 to evaluate the effect training had on attitudes. Respondents graded statements on a five-point Likert scale from strongly agree to strongly disagree. Chi-square tests with continuity correction (SPSS v16) were used to test for changes in proportions between the combined agree and disagree answers.

Results: Of 761 invited paramedics, 288 answered in 2008; in 2011 233 of 967 answered. Learning objectives on three subjects were identified: importance of compression depth, confidence in the importance of pre-hospital cardiac arrest care and acceptance of CQI system. A positive change was seen for all three learning objectives, see table 1.

Conclusion: It is possible to change long-held beliefs and attitudes towards CPR trough targeted education.

Table 1- Neset et al.

	Statement	2008 Agree	2008 Disagree	2011 Agree	2011 Disagree
Compression depth	Too deep chest compressions may cause severe injury to the patient	83 %	17 %	66 %	35 %
	Compressing within Guidelines recommended depth may often result in severe patient injury	26 %	74 %	18 %	82 %
	I feel very uncomfortable when I sense I am breaking ribs	40 %	60 %	24 %	76 %
Confidence	The hospital has better equipment for treating cardiac arrest patients	76 %	24 %	55 %	45 %
	The doctors at the hospital know better what to do with cardiac arrest patients	65 %	35 %	44 %	56 %
	What I do to the patient before he/she gets to the hospital is of minor importance	3 %	97 %	2 %	98 %
	Most cardiac arrest patients die regardless of what I do	46 %	54 %	34 %	66 %
CQI system	I trust that collected quality data are not used in a disciplinary manner towards paramedics, but rather to improve the system	72 %	28 %	85 %	15 %

Abstract 74: Cardiopulmonary Resuscitation Quality Assessed by Electrocardiography Signal Processing Using Hilbert-Huang Transform Correlates Well with Accelerometer

Huang-Fu Yeh[1]; Chiao-Hao Lee[1]; Lian-Yu Lin[1]; Wen-Chu Chiang[1]; Patrick C Ko[1]; Eric H Chou[1]; Kah-Meng Chong[1]; Men Tzung Lo[2]; Joar Eilevstjønn[3]; Helge Mykelbust[3]; Matthew H Ma[1]. [1]

National Taiwan Univ Hosp, Taipei, Taiwan, [2] National Central Univ, Chungli, Taiwan, [3] Laerdal Med AS, Stavanger, Norway

Objectives High quality cardiopulmonary resuscitation (CPR) is paramount to patient outcomes in cardiac arrests (CA). Methods to assess CPR quality using widely available data should be explored. This study was aimed to compare CPR quality assessed by surface ECG signal processing vs. accelerometer.

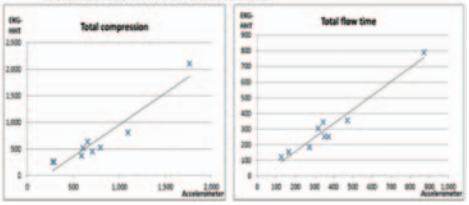
Methods Adult patients with CA receiving CPR in the emergency department of a tertiary university hospital, from Dec 2010 to March 2011 were included. CPR was monitored continuously by recording the surface ECG signals and sternal displacement via an accelerometer. CPR quality parameters including total compression numbers, no flow time (pause > 1.5 sec), total flow time (time with pause < 1.5 sec) and average compression rate for up to the first 10 min of CPR were obtained by 1) ECG signal processing algorithm using empirical mode decomposition via Hilbert-Huang Transform (ECG-HHT) and 2) sternal displacement recorded by an accelerometer (ACCEL).

Results CPR sessions of 9 CA (6 males, mean age 79.9 years) were analyzed. Compared to ACCEL, ECG-HHT showed lower total compressions, higher no flow time, and lower total flow time. There are good correlations between ECG-HHT vs. ACCEL in total compression numbers (R=0.95) and total flow time (R=0.97).

Conclusions ECG-HHT correlates well with ACCEL in certain CPR quality parameters and may be used to assess CPR quality through widely available ECG data.

	ECG-HHT (mean ± SD)	ACCEL (mean ± SD)
Total compression	660.2 ± 568.9	750.9 ± 452.2
No flow time (sec)	86.9 ± 56.6	31.5 ± 27.6
Total flow time (sec)	305.8 ± 199.1	366.0 ± 217.2
Compression rate (min^{-1})	121.9 ± 18.5	122.4 ± 10.3

Figure. Correlation of total compression (left) and total flow time (right) between ECG-HHT vs. Accelerometer



Abstract 12482: Differing Predictive Value of LDL Cholesterol and Systolic Blood Pressure on Components of CV Events in 21,727 High-Risk Patients With CHD and/or Diabetes: Pooled Analyses of TNT, IDEAL, and CARDS Trials

Prakash C Deedwania[1]; Helen M Colhoun[2]; Terje R Pedersen[3]; David A DeMicco[4]; Andrei Breazna[4]. [1] Cardiology Section, VA Med Cntr, Fresno, CA, [2] Wellcome Trust Cntr for Molecular Medicine, Univ of Dundee, Dundee, United Kingdom, [3] Cntr of Preventive Medicine, Section of Preventive Cardiology,, Oslo Univ Hosp, Oslo, Norway, [4] Med, Pfizer Inc, New York, NY

Background: We investigated the effect of baseline systolic blood pressure (SBP) and baseline LDL-C on the risk of various vascular outcomes in a large population of patients at high-risk of future cardiovascular (CV) events.

Methods: Data were pooled from the TNT (atorvastatin [ATV] 10 mg vs 80 mg in stable CHD patients), IDEAL (ATV 80 mg vs simvastatin 20-40 mg in post-MI patients) and CARDS (ATV 10 mg vs placebo in patients with type 2 diabetes and without established CHD) trials. A total of 21,727 patients (10,001 from TNT; 8888 from IDEAL; 2838 from CARDS) were included in this analysis. The effect of baseline SBP and baseline LDL-C on CV events, coronary events and stroke was evaluated. The pooled analysis was based on a bivariate Cox model, including baseline SBP and baseline LDL-C as the two predictor variables and stratifying by study.

Results: In the pooled dataset, risk of CV events was significantly higher for patients with higher baseline SBP or LDL-C (Table). Higher baseline SBP was a significant risk factor for stroke, but not for coronary events. Higher baseline LDL-C levels were significantly predictive of coronary events but not stroke. Results for a subgroup of individuals with type 2 diabetes (5408 patients; 1501 from TNT, 1069 from IDEAL, and 2838 from CARDS) were consistent with those of the overall cohort; baseline SBP and LDL-C were again significantly predictive for the risk of CV events, with the association to SBP predominantly related to effect on stroke and that of LDL-C to effect on coronary events.

Conclusions: In this cohort of high-risk patients, baseline SBP and LDL-C were significantly predictive of CV outcomes, but the effect of the studied factors appears to be different on the cerebrovascular and coronary systems. Understanding the effect of such traditional risk factors, should contribute to the planning of both clinical research and clinical care for patients at high-risk of CV disease.

	Hazard ratio (95% CI)	
	SBP*	LDL-C†
All CV events	1.04 (1.03-1.06); p<0.0001	1.04 (1.03-1.05); p<0.0001
All coronary events	1.01 (0.99-1.03); p=0.247	1.05 (1.03-1.06); p<0.0001
Fatal/nonfatal stroke	1.16 (1.12-1.21); p<0.0001	1.01 (0.98-1.04); p=0.583

*Risk associated with each 10 mm Hg increase in baseline SBP; †Risk associated with each 10 mg/dL increase in baseline LDL-C

Abstract 12578: Clinical Implications of Electrocardiographic Left Ventricular Strain and Hypertrophy in Asymptomatic Patients with Aortic Stenosis: The Simvastatin and Ezetimibe in Aortic Stenosis Study

Anders M Greve[1]; Kurt Boman[2]; Christa Gohlke-Baerwolf[3]; Antero Y Kesäniemi[4]; Christoph Nienaber[5]; Simon Ray[6]; Kenneth Egstrup[7]; Anne B Rossebø[8]; Richard B Devereux[9]; Lars Køber[1]; Ronnie Willenheimer[10]; Kristian Wachtell[11]. [1] Dept of medicine B-2142, Rigshospitalet, Copenhagen, Denmark, [2] Dept of Medicine, Inst of Public Health and Clinical Medicine, Skelleftå, Sweden, [3] Dept of cardiology, Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany, [4] Dept of Internal Medicine and Biocenter Oulu, Institute of Clinical Medicine, Helsinki, Finland, [5] Dept of Cardiology and Angiology, Univ Hosp Rostock, Rostock Sch of Medicine, Rostock, Germany, [6] Dept of Cardiology, North West Heart Cntr, Univ Hosps of South Manchester, Manchester, United Kingdom, [7] Medicinsk Afdeling, OUH Svendborg Sygehus, Odense, Denmark, [8] Dept of Cardiology, Oslo Univ Hosp, Ullevål, Oslo, Norway, [9] Dept of cardiology, Weill Cornell Med College, New York, NY, [10] Dept of cardiology, Heart Health Group and Lund Univ Hosp, Malmö, Sweden, [11] Dept of cardiology, Rigshospitalet and Gentofte Univ Hosp, Copenhagen, Denmark

Background: The impact of electrocardiographic left ventricular (LV) strain and hypertrophy (LVH) on cardiovascular morbidity and mortality in asymptomatic aortic stenosis (AS) has not been well described.

Methods: Clinical-, electro- and echocardiographic examinations were performed in 1,873 asymptomatic patients with mild to moderate AS randomized to simvastatin/ezetimibe combination *vs.* placebo in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Predictive value of electrocardiographic LV strain (defined as T-wave inversion in leads V_{4-6}) and LVH (assessed by the Sokolow-Lyon voltage criterion ($R_{V5-6}+S_{V1} \geq 35$ mV) and Cornell voltage-duration criteria ($(RaVL+S_{V3}+[6\text{ mV in women}]) \times \text{QRS-duration} \geq 2440$ mV·msec)), was evaluated in models adjusting for randomized treatment and other important prognostic covariates.

Results: A total of 1,533 patients were followed for 4.3±0.8 years (6,628 patient-years of follow-up). At baseline, electrocardiographic strain was present in 340 (23.6%) patients; LVH was detected by Sokolow-Lyon voltage in 260 (17.1%) and in 221 (14.6%) by Cornell voltage-duration product. In multivariable analyses, baseline electrocardiographic LV strain was associated with a 3.1-fold higher risk of myocardial infarction (95% confidence interval [CI], 1.4 to 6.8, p=0.004); LVH by Sokolow Lyon-voltage criterion with a 4.0 -fold higher risk of heart failure (CI, 1.8 to 9.3, p=0.001). Finally, presence of electrocardiographic LV strain or LVH by either electrocardiographic criterion was independently predictive of increased risk of AVR.

Conclusions: Electrocardiographic LV strain and LVH were, independent of echocardiographic and clinical covariates, predictive of poor prognosis during watchful waiting in asymptomatic AS.

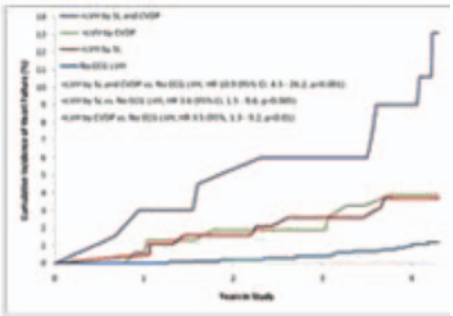


Figure: Incidence of Heart Failure in Patients with and without Baseline Electrocardiographic Left Ventricular Hypertrophy: During 4.3 years of Follow-Up.

Abstract 225: Hands-off Fraction Is Not Negatively Impacted by Deployment of the AutoPulse During Out-of-Hospital Cardiac Arrest

Lars Wik[1]; Jan-Aage Olsen[1]; David Persse[2]; Fritz Sterz[3]; Michael Lozano[4]; Marc A Brouwer[5]; Mark Westfall[6]; Chris M Souders[2]; Reinhard Malzer[7]; Pierre M van Grunsven[8]; David Travis[9]; Anne Whitehead[10]; Ulrich R Herken[11]; E Brooke Lerner[12]. [1] National Competence Cntr of Emergency Medicine, Oslo Univ Hosp, Oslo, Norway, [2] Houston Fire Dept and the Baylor College of Medicine, Houston, TX, [3] Med Univ of Vienna, Vienna, Austria, [4] Lake Erie College of Osteopathic Medicine, Bradenton, FL, [5] Heart Lung Cntr, Radboud Univ Med Cntr, Nijmegen, Netherlands, [6] Theda Clark Regional Med Cntr, Neenah, WI, [7] Vienna City Administration, Emergency Med Services, Vienna, Austria, [8] Regional Ambulance Service Gelderland-Zuid, Nijmegen, Netherlands, [9] Hillsborough County Fire Rescue, Tampa, FL, [10] Fylde College, Lancaster Univ, Lancaster, United Kingdom, [11] ZOLL Med Corp, Chelmsford, MA, [12] Med College of Wisconsin, Milwaukee, WI

Background: Deployment of mechanical chest compression devices is suspected to increase hands-off fraction. A potential benefit of mechanical devices is defibrillation during compressions, but it is unknown if this is utilized in the field. Our objectives were to compare hands-off fraction between manual CPR (M-CPR) and integrated AutoPulse CPR (iA-CPR), and to determine if providers will defibrillate during mechanical compressions.

Methods: An international randomized clinical trial of EMS treated adult cardiac arrests of cardiac origin was conducted at 5 sites from March 2009 to January 2011. All EMS providers received 4 hours of training in providing high quality CPR and AutoPulse deployment. After initial manual compressions, patients were randomized to iA-CPR or M-CPR. ECG and impedance or accelerometer data were analyzed to determine the number of compressions per minute, and hands-off fraction was calculated at 10 and 20 minutes. Descriptive statistics and 95% CI were calculated.

Results: A total of 4,232 subjects were enrolled. Electronic data were available for 4,135 (98%) cases (2,055 M-CPR, 2,080 iA-CPR). There were 117 (3%) cases with no compression data (69 M-CPR, 48 iA-CPR). There were more compressions per minute in the M-CPR arm (table). The mean hands-off fraction at 10 minutes was 20.4% M-CPR and 21.5% iA-CPR (difference 1.1%; 95% CI 0.5% to 1.7%) and at 20 minutes was 20.2% M-CPR and 19.6% iA-CPR (difference -0.6%; 95% CI -1.2% to 0.1%). Average time to AutoPulse start after defibrillator on was 172 seconds (±183). In 84% of the iA-CPR cases the device was not stopped during the first cycle of resuscitation. 74% of the defibrillated iA-CPR cases were shocked during compressions.

Conclusion: This is the first study to document operational deployment of the AutoPulse. There was no difference in hands-off fraction between M-CPR and iA-CPR. Providers without prior experience using the AutoPulse shocked through compressions in the majority of cases.

Comparison of Study Arms		
	M-CPR	iA-CPR
Average compressions per minute (first 10 minutes)	89.2±17.4	66.3±10.7
Percent of subjects defibrillated	41%	39%
Median number of shocks	3	2

Abstract 12877: Social Gradient of Cardiovascular Risk Factors in Poland: Baseline Profile of the Polish Norwegian Study (PONS)

Marta Manczuk[1]; Rajesh Vedanthan[2]; Lars Vatten[3]; Anna Polewczyk[4]; Paolo Boffetta[5]; Witold Zatonski[6]. [1] Cancer Epidemiology and Preventive Div, The Maria Sklodowska-Curie Memorial Cancer Cntr and Institute of Oncology, Warsaw, Poland, [2] Cardiology, Mount Sinai Sch of Medicine, New York, NY, [3] Public Health, Norwegian Univ of Science and Technology, Trondheim, Norway, [4] Cardiology, Voivodship Hosp, Kielce, Poland, [5] Translational Epidemiology, Mount Sinai Sch of Medicine, New York, NY, [6] Cancer Epidemiology and Preventive Div, Cancer Cntr and Institute of Oncology, Warsaw, Poland

Introduction: The burden of cardiovascular disease (CVD) is increasing in Central and Eastern Europe. The Polish Norwegian Study (PONS) is a prospective cohort study in South-Eastern Poland (Kielce District) which aims to investigate the incidence, case-fatality, and risk factors for CVD and other chronic diseases. Here we provide a preliminary analysis of the baseline prevalence and correlates of CVD risk in the PONS Cohort, highlighting the social gradient of CVD risk.

Methods: PONS is enrolling individuals aged 45-64. Structured lifestyle and food frequency questionnaires were administered. Diabetes and hypertension were defined by self-report. Anthropometric characteristics were measured and blood samples were drawn and analyzed. Multivariate logistic regression was used to determine adjusted odds ratios (OR) for associated factors, using Stata version 9.

Results: A total of 1005 adults have been enrolled in the PONS cohort and are included in the present analysis. The prevalence of diabetes, hypertension, obesity, and hypercholesterolemia was 6.9%, 39.0%, 27.4% and 15.5% respectively, and increased with age. Aside from hypercholesterolemia, these risk factors were more prevalent among individuals with lower education (Table). Obesity was associated with both diabetes (OR 2.70 (1.63, 4.49)) and hypertension (OR 3.17 (2.35, 4.28)). The prevalence of current tobacco smoking was 15.9%. Tobacco smoking was more prevalent in men than women but was not associated with age or CVD risk factors.

Conclusions: Our findings suggest that this region of Poland is experiencing significant burden of CVD risk factors such as diabetes, hypertension, obesity, hypercholesterolemia and tobacco smoking. There is a strong social gradient of cardiovascular risk, which will be investigated in detail in the prospective study. There is an urgent need to increase awareness about CVD and institute early aggressive risk factor control measures.

Table. Association between selected sociodemographic characteristics and prevalence of diabetes, hypertension, hypercholesterolemia, and obesity - Odds ratios and 95% confidence intervals adjusted for the variables in the table

Characteristics	Diabetes	Hypertension	Hypercholesterol.	Obesity
Age *	1.84 (1.02, 3.32)	2.26 (1.69, 3.01)	1.41 (0.96, 2.07)	1.73 (1.26, 2.37)
Sex**	0.64 (0.38, 1.07)	0.89 (0.67, 1.18)	1.39 (0.94, 2.06)	0.86 (0.63, 1.16)
Education - secondary***	0.58 (0.32, 1.07)	0.74 (0.51, 1.09)	0.97 (0.59, 1.59)	0.71 (0.49, 1.05)
Education - higher***	0.32 (0.16, 0.65)	0.46 (0.31, 0.68)	0.87 (0.52, 1.46)	0.38 (0.25, 0.58)
Urban residence****	1.84 (0.77, 4.39)	1.91 (1.27, 2.89)	0.91 (0.55, 1.44)	0.95 (0.63, 1.44)

* Age group 55-64 vs. age group 45-54 (reference group)
** Women vs. men (reference group)
*** Secondary or higher education vs. less than secondary (reference group)
**** Urban (Kielce) residence vs. rural residence (reference group)

Abstract 8551: Left Atrial Strain by Speckle Tracking Echocardiography In Patients with Heart Failure - An Independent and Incremental Predictor of Cardiac Death or Need of Heart Transplantation

Thomas Helle-Valle; Anders Opdahl; Kaspar Broch; Einar Gude; Arne Andreassen; Otto A Smiseth; Lars Gullestad. Dept of Cardiology, Oslo Univ Hosp, Rikshospitalet, Oslo, Norway

Background: We have recently shown that left atrial (LA) stretching during atrial filling, measured as peak LA strain by speckle tracking echocardiography (STE), is a strong and independent predictor of cardiac death or heart transplantation (HTx) in patients with heart failure (HF). Furthermore, our study demonstrated that while logNT-proBNP and left ventricular ejection fraction (LVEF) were independent predictors of these end points, age, LA area and E/e' were not. In the present study we investigate if LA strain adds predictive power to that provided by NT-proBNP and LVEF.

Methods: We included 143 patients (age 54±11 years), with ischemic or dilated cardiomyopathy (NYHA II-IV, LVEF= 31±13%). Peak LA strain by STE and LVEF were measured. Time to death or HTx (Cox model) was adjusted for age, logNT-proBNP and LVEF in addition to LA strain. We computed receiver-operating characteristic (ROC) curves and tested for equality of the areas under the curve (AUC) for models with and without LA strain.

Results: Median follow-up time was 3.0 years. There were 39 events and median time to event was 0.7 years (range 0.1 to 4.3). LVEF (P=0.008), logNT-proBNP (P=0.007) and LA strain (P=0.007) were independent predictors of cardiac events. When LA strain was added to age, LVEF and logNT-proBNP, AUC demonstrated significantly better predictive power (0.68±0.05 vs. 0.73±0.05, P=0.048; Figure 1).

Conclusion: LA strain by STE is an independent and incremental predictor of death or need of HTx in patients with moderate to severe HF. This finding suggests that LA strain by STE may serve as a marker in the risk stratification of patients with HF.

Figur

Abstract 8654: Low In-Treatment HDL Cholesterol Levels Strongly Predict New Heart Failure in Hypertensive Patients: The LIFE Study

Peter Okin[1]; Darcy A Hille[2]; Kristian Wachtell[3]; Sverre E Kjeldsen[4]; Lars H Lindholm[5]; Björn Dahlöf[6]; Richard B Devereux[1]. [1] Cardiology, Cornell Med Cntr, New York, NY, [2] Late Development Statistics, Merck & Co., Inc., North Wales, PA, [3] Cardiology, The Heart Cntr, Rigshospitalet, Univ of Copenhagen, Copenhagen, Denmark, [4] Cardiology, Ullevaal Univ Hosp, Oslo, Norway, [5] Dept of Public Health and Clinical Medicine, Umeå Univ, Umeå, Sweden, [6] Internal Medicine, Sahlgrenska Univ Hosp/Östra, Gothenburg, Sweden

Background: Although low HDL levels predict incident heart failure (HF) in a population-based study, whether low HDL is associated with increased risk of new HF in hypertensive patients is unclear.

Methods: Incident HF was examined in relation to in-treatment HDL levels in 8445 hypertensive patients with no history of HF with baseline HDL levels randomly assigned to losartan- or atenolol-based treatment. In-treatment HDL at each year of testing was categorized into the lowest quartile vs upper 3 quartiles according to baseline HDL levels or examined as a continuous variable with hazard ratios calculated for each SD of the baseline mean lower HDL (0.44 mmol/l).

Results: During 4.7±1.1 years follow-up, there were 264 new HF hospitalizations (3.1%). In univariate Cox analyses, compared with HDL ≥1.21 mmol/l, in-treatment HDL <1.21 was associated with a 117% greater risk of new HF. In parallel analyses which used in-treatment HDL as a continuos variable, each 1 SD lower HDL was associated with a 45% higher HF risk. In multivariate Cox analyses adjusting for randomized treatment, age, sex, body mass index, prevalent and history of atrial fibrillation and diabetes, history of MI, ischemic heart disease, stroke, peripheral vascular disease, smoking status, baseline serum creatinine, glucose, urine albumin/creatinine ratio as standard risk factors and for incident MI, in-treatment diastolic and systolic pressure, heart rate, QRS duration, Cornell product and Sokolow-Lyon voltage criteria for left ventricular hypertrophy and non-HDL cholesterol levels as time-varying covariates, the lowest quartile of in-treatment HDL remained associated with a 102% greater risk and, in alternative analyses, each 1 SD lower HDL treated as a continuous variable with a 38% higher risk of incident HF.

Conclusions: Lower in-treatment HDL is an independent predictor of new HF in hypertensive patients, even after adjusting for other potential risk factors and treatment effects.

Analysis	By In-Treatment HDL (lowest quartile vs upper 75%)		
	HR (Quartile 1 vs upper 75%)	95% CI	p value
Univariate	2.17	1.70-2.77	<0.001
Multivariate	2.02	1.53-2.66	<0.001
	By In-Treatment HDL as a Continuous Variable		
	HR (per 1SD lower HDL)	95% CI	p value
Univariate	1.45	1.24-1.69	<0.001
Multivariate	1.38	1.16-1.65	<0.001

Abstract 9146: Antithrombotic Use and Outcomes in Patients with Atrial Fibrillation Complicating Acute Coronary Syndromes

Renato D Lopes[1]; Jennifer A White[1]; Dan Atar[2]; Matyas Keltai[3]; Neal S Kleiman[4]; Harvey D White[5]; Petr Widimsky[6]; Uwe Zeymer[7]; Kevin Jackson[1]; Robert P Giugliano[8]; Pierluigi Tricoci[1]; Eugene Braunwald[9]; C. M Gibson[1]; Christoph Bode[10]; E. M Ohman[1]; Paul W Armstrong[11]; Frans Van de Werf[12]; Robert A Harrington[1]; L. K Newby[1]. [1] Duke Clinical Rsch Institute, Duke Univ Med Cntr, Durham, NC, [2] Aker Univ Hosp, Univ of Oslo, Oslo, Norway, [3] Dept of Cardiology, Semmelweis Univ, Budapest, Hungary
[4] The Methodist DeBakey Heart&Vascular Cntr, The Methodist Hosp, Houston, TX, [5] Green Lane Cardiovascular Service, Auckland City Hosp, Auckland, New Zealand, [6] Depts. of Cardiology&Cardiac Surgery, Univ Hosp Kralovske Vinohrady, Prague, Czech Republic, [7] Cardiology, Herzzentrum Ludwigshafen, Ludwigshafen, Germany, [8] TIMI Study Group, Brigham and Women's Hosp, Boston, MA, [9] TIMI Study Group, Brigham and Women's Hosp, Durham, MA, [10] Dept of Cardiology and Angiology, Univ Hosp of Freiburg, Freiburg, Germany, [11] Canadian VIGOUR Cntr, Univ of Alberta, Edmonton, Canada, [12] Dept of Cardiovascular Diseases, Gasthuisberg Univ Hosps Leuven, Leuven, Belgium

Background: Little is known about the use of oral anticoagulant and antiplatelet agents in patients with atrial fibrillation (AF) complicating non-ST-segment elevation (NSTE) ACS.

Methods: We examined the occurrence and timing of AF and use of antithrombotic therapy in 9242 high-risk NSTE ACS patients randomized in EARLY ACS to early eptifibatide vs. delayed provisional use at PCI for whom AF information was

available. Logistic regression with a landmark approach examined the association of AF within 7 days after ACS with death at 30 days. Adjusted models considered important clinical variables available prior to the 7-day landmark period.

Results: Overall, 550 patients (6.0%) had AF as an in-hospital complication. AF events occurred at a median of 4 (2, 8) days after ACS, and 395 (72%) AF events occurred within 7 days. AF patients were older (median age 72 vs. 67 years), had worse renal function (median eCrCl 66 vs. 74 ml/min), more frequently had elevated troponin at baseline (90 vs. 83%), and more often had diabetes (34 vs. 30%), HTN (74 vs. 71%), or history of heart failure (15 vs. 12%) compared with patients without AF. The table shows rates of discharge antiplatelet and antithrombotic therapy. Among AF patients, 87% received aspirin at discharge, 48% received clopidogrel, and 19% received warfarin. Triple therapy (combination of aspirin, clopidogrel, and warfarin) was used in only 5.7%. After adjusting for clinical variables, in-hospital AF within 7 days post ACS was associated with nearly 5-fold higher risk for death between 7 and 30 days (HR 4.83, 95% CI 3.06-7.62).

Conclusions: AF complicated 6% of post-ACS patients and was associated with substantially greater risk for death at 30 days. The majority of AF patients did not receive oral anticoagulation with antiplatelet agents at discharge, highlighting unmet needs to better optimize antithrombotic therapy at hospital discharge in these patients.

Table. Antithrombotic use at discharge according to the presence of atrial fibrillation

	No AF (N=8692)	AF (N=550)
Aspirin	95.3%	87.0%
Clopidogrel	77.5%	47.7%
Warfarin	2.7%	19.3%
Aspirin only	18.8%	32.9%
Clopidogrel only	1.7%	1.2%
Warfarin only	0.6%	4.1%
Warfarin plus aspirin	0.9%	8.1%
Warfarin plus clopidogrel	0.2%	1.4%
Aspirin plus clopidogrel	74.4%	39.0%
Aspirin plus clopidogrel plus warfarin	1.0%	5.7%

Abstract 9728: Arterial Stiffness is Associated with Carotid Atheromatosis in Hypertensive Patients (Campania Salute Network)

Giuseppina Casalnuovo[1]; Eva Gerdts[2]; Raffaele Izzo[3]; Marina De Marco[1]; Renata Giudice[3]; Giovanni De Simone[1]; Bruno Trimarco[3]; Nicola De Luca[3]. [1] Clinical & Experimental Medicine, Federico II Univ Hosp, Naples, Italy, [2] Institute of Medicine, Univ of Bergen, Bergen, Norway, [3] Internal Medicine and Cardiovascular Sciences, Federico II Univ Hosp, Naples, Italy

Background: Pulse pressure/stroke index (PP/SVi) is a validated measure of total arterial stiffness, but its relation to carotid atherosclerosis is unknown.

Methods: Data from 6209 hypertensive patients without prevalent cardiovascular disease (coronary heart disease, stroke, heart failure) in the Campania Salute Network underwent standard transthoracic echocardiography and carotid ultrasound. SVi was obtained by echocardiographic LV volumes computation; mean and maximal (max) carotid intima-media thickness (IMT) and the presence of plaques (≥1.3 mm) in the common and internal carotid arteries were assessed. The population was stratified into thirtiles of PP/SVi and analyzed using ANOVA.

Results: Increase from the lowest to the highest thirtiles of PP/SVi was associated with increasing age, progressively higher systolic and diastolic blood pressure (BP), higher total cholesterol and larger number of antihypertensive drugs (Table 1). The highest PP/SVi thirtile was also associated with higher max and mean IMT and higher prevalence of carotid plaques (Table1). In multivariate logistic regression analysis, compared to the lowest thirtiles, the prevalence of carotid plaque increased by 16% (95% confidence interval [CI] 1-34%, p<0.05) in the second PPSVi thirtile and by 33% (95% [CI] 15-55%, p<0.01) in the the highest PPSVi thirtile, independently of significant associations with diabetes mellitus, age, gender and total cholesterol.

Conclusion: In treated hypertensive patients included in the CampaniaSalute Network, higher PP/SVi is associated with carotid atherosclerosis independently of others confounders.

Variable	Tertile 1 PP/SVi (Range 0.77-2.08)	Tertile 2 PP/SVi (Range 2.09-2.65)	Tertile 3 PP/SVi (Range 2.66-6.15)
Women (%)	39.7	40.1	49.0
Age (years)	52±10	53±11	55±12*
Diabetes Mellitus (%)	8.0	8.2	12.3*
Clinic systolic BP (mmHg)	138±15	144±16	153 ±19*
Clinic diastolic BP (mmHg)	89±11*	90±11	90±12
Carotid plaque (%)	52.8	57.8	64.8*
Combination therapy (n)	1.8±1.1	1.9±1.1	2.0±1.1*
Total cholesterol (mg/dL)	206±37	206±39	210±40**
Max. IMT (mm)	1.50±0.64	1.58±0.70	1.74±0.81*
Mean carotid IMT (mm)	1.11±0.32	1.15±0.34	1.26±0.45*

IMT, intima-media thickness. *p<0.01 vs. other groups; **p<0.05 vs. other groups.

Abstract 9732: Mitral Annular Calcification and Incident Embolic Stroke in Treated Hypertensive Patients: The LIFE Echo-Substudy

Marina De Marco[1]; Giovanni De Simone[1]; Eva Gerdts[2]; Giuseppina Casalnuovo[1]; Teresa Migliore[1]; Kris Wachtell[3]; Kurt Boman[4]; Bjorn Dahlöf[5]; Richard B Deveraux[6]. [1] Clinical&Experimental Medicine, Federico II Univ Hosp, Naples, Italy, [2] Institute of Medi-

cine, Univ of Bergen, Bergen, Norway, [3] Dept of Medicine Copenhagen County, Univ Hosp Glostrup, Glostrup, Denmark, [4] Dept of Medicine, Hosp and Umea Univ Skelleftea, Skelleftea, Sweden, [5] Dept of Medicine, Sahlgrenska Univ HospÖstra, Gothenburg, Sweden, [6] Dept of medicine, Weill Med College of Cornell Univ, New York, NY

Background: Mitral anular calcification (MAC) is not considered as a substantial echocardiographic finding and is often neglected in routine reports. However, MAC has been associated with increased risk of embolic stroke in the general population. Whether MAC also predicts incident embolic stroke in treated hypertensive patients with LV hypertrophy is unclear.

Methods: Baseline clinical and echocardiographic parameters were assessed in 945 hypertensive patients with ECG left ventricular hypertrophy (LVH) participating in the LIFE echo-substudy (66 ±7 years, 42% women, 11% diabetes). Fifteen participants were excluded because of aortic stenosis and 1 because of mitral stenosis.

Results: At the baseline echocardiogram, MAC was found in 48% of the study population. Patients with MAC were older (67±7 versus 64±7 years), had higher systolic blood pressure (176±22 versus 171±20 mmHg), heart rate (69±12 versus 67±12 bpm) left atrial diameter (4.1±0.5 versus 3.8±0.5 cm) and LV mass index (58 ±13 versus 54±12 g/m 2.7) and included more women (47% versus 36%), and more patients with diabetes (13% versus 9%) and albuminuria (29% versus 22%, all p<0.01). Over a mean follow-up of 4.8 years, 56 participants (6%) had an embolic stroke. Risk of incident embolic stroke was significantly associated with presence of baseline MAC (log Rank=11, p=0.001). In multivariate Cox- regression analysis, baseline MAC was associated with 2 -fold increased risk of embolic stroke (HR=1.99, CI95%:1.08-3.67,p=0.03), independently of age, gender, baseline systolic BP, heart rate, presence of diabetes, baseline LV mass index, left atrial diameter, albuminuria, prevalent and/or incident atrial fibrillation and randomized antihypertensive treatment (atenolol/losartan).

Conclusions: In a population of treated hypertensive patients with ECG LVH, MAC was frequently present and was associated with increased risk for incident embolic stroke, independent of other established risk factors.

Abstract 9939: Insulin Receptor Substrate-2 Genetic Variants Interact with Plasma Monounsaturated and n-3 PUFA Fatty Acid Levels to Influence Insulin Resistance: From the LIPGENE Study

Pablo Perez-Martinez[1]; Javier Delgado-Lista[1]; Antonio Garcia-Rios[1]; Hanne L Gulseth[2]; Ellen E Blaak[3]; Beata Kiec-Wilk[4]; Olfa Helal[5]; Julie A Lovegrove[6]; Ulf Riserus[7]; Helen M Roche[8]; Jose Lopez-Miranda[1]. [1] Lipid and Atherosclerosis Unit, Reina Sofia Univ Hosp, Maimonides Institute for Biomedical Rsch at Cordoba (IMIBIC), Univ of Cordoba, Ciber Phyisiopatology of Obesity and Nutrition (CIBEROBN), Instituto de Salud Carlos III, Cordoba, Spain, [2] Dept of Endocrinology, Oslo Univ Hosp, Oslo, Norway, [3] Dept of Human Biology, NUTRIM, Sch for Nutrition, Toxicology and Metabolism, Maastricht, Netherlands, [4] Dept of Clinical Biochemistry, Jagiellonian Univ Med College, Krakow, Poland, [5] Lipid nutrients and prevention of metabolic diseases, INSERM 476, Université de la Méditerranée, Marseille, France, [6] Dept of Food and Nutritional Sciences, Institute for Cardiovascular and Metabolic Rsch, Univ of Reading, Reading, United Kingdom, [7] Clinical Nutrition and Metabolism, Dept of Public Health and Caring Sciences, Uppsala Univ, Uppsala, Sweden, [8] Nutrigenomics Rsch Group, UCD Sch of Public Health and Population Science, UCD Conway Institute, Univ College Dublin, Dublin, Ireland

Background: The insulin receptor substrate-2 (IRS-2) is a major insulin signalling molecule. IRS-2 regulates body weight control and glucose homeostasis. Several *IRS-2* polymorphic sites have been studied for their potential use as risk markers for obesity and type 2 diabetes mellitus. Fatty acids are key metabolic regulators which may interact with genetic factors and influence glucose metabolism.

Objective: To examine whether the genetic variability at the *IRS-2* gene locus was associated with the degree of insulin resistance and plasma fatty acid levels in subjects with metabolic syndrome (MetS).

Design: Intravenous glucose tolerance tests (IVGTT) and HOMA indices were used to estimate insulin sensitivity (insulin sensitivity index, HOMA-IR), insulin secretion (first phase insulin secretion (AIRg), disposition index, HOMA-B) and glucose effectiveness. Plasma fatty acid composition and three *IRS-2* single nucleotide polymorphisms (SNPs) were also determined in a cross-sectional analysis of 452 subjects with MetS participating in the LIPGENE dietary intervention cohort (NCT00429195).

Results: The rs2289046 SNP interacted with plasma monounsaturated (MUFA) and omega-3 polyunsaturated fatty acids (n-3 PUFA) levels which were significantly associated with insulin resistance. Among subjects with the lowest level of MUFA (below the median) the A/A genotype was associated with lower glucose effectiveness (P<0.03), higher fasting insulin concentrations (P<0.02) and higher HOMA-IR (P<0.03) compared to subjects carrying the minor G-allele (A/G and G/G). In contrast, among subjects with the highest level of MUFA (above the median), the A/A genotype was associated with lower fasting insulin concentrations and HOMA-IR. Whereas, individuals carrying the G allele and with the highest level of n-3 PUFA (above the median) showed lower fasting insulin (P<0.01) and HOMA-IR (P<0.02) compared with A/A subjects.

Conclusions: The rs2289046 polymorphism at the *IRS-2* gene locus may influence insulin resistance and glucose effectiveness by interacting with plasma fatty acid composition in subjects with the MetS. Further studies are needed to confirm whether targeted dietary recommendations can prevent MetS in genetically susceptible individuals.

Abstract 194: A Combination of Metabolic Strategies and Cardiopulmonary Bypass Allows Improved Short-Term Resuscitation from Prolonged Lethal Cardiac Arrest

Manuel Boller[1]; Sung K Jung[2]; Silje Odegaard[3]; Joseph M Katz[1]; Amy Muehlmatt[1]; Lance B Becker[1]. [1] Univ of Pennsylvania, Philadelphia, PA, [2] Seoul National Univ, Seoul, Korea, Republic of, [3] Univ of Oslo, Oslo, Norway

Background: The metabolic or late phase of cardiac arrest is highly lethal. Emergency cardiopulmonary bypass (ECPB) can resuscitate many patients even after prolonged cardiac arrest and provides immediate vascular access for correction of metabolic derangement during the reperfusion process. We developed a rodent model of ECPB resuscitation which showed the superiority of ECPB over conventional CPR, especially when combined with hypothermia. For this study we examined a metabolic strategy against ischemia/reperfusion (MS-I/R) injury that included: leukoreduction, low Ca2+, Mg, buffered pH, red blood cells and a colloid. We tested whether ECPB plus MS-I/R and/or hypothermia reduced reperfusion injury and showed better outcomes compared to our standard ECPB reperfusate.

Methods: Using a 2x2 factorial design we tested ECPB with (a) MS-I/R versus standard solution, and (b) hypothermia versus normothermia in our rat model (n=38). The four reperfusion strategies included: (1) MS-I/R reperfusate plus hypothermia, (2) MS-I/R with normothermia, (3) standard plasmalyte reperfusate plus hypothermia, or (4) plasmalyte plus normothermia. Animals underwent 12 min of untreated asphyxial arrest and were resuscitated with ECPB with one of the strategies for 30 min. Thereafter ECPB was stopped and ICU-like support was provided for 3 hours, while hemodynamic, perfusion and other metrics were serially measured.

Results: All rats achieved ROSC with ECPB. Significant differences emerged after 3 hrs, the best outcomes were in animals with MS-I/R perfusate plus hypothermia (lactate: 1.0±0.3 mmol/L; MAP: 84±12 mm Hg, seizures: 0/10), while the worst outcomes were with standard plasmalyte reperfusate and normothermia (lactate: 8.8±4.3 mmol/L, MAP: 36±13 mm Hg, seizures: 7/10, P<0.001). The outcomes of the other two groups (hypothermia only; MS-I/R reperfusate only) were intermediate. Both hypothermia and MS-I/R reperfusate independently improved outcome.

Conclusions: While most human ECPB is applied without a MS-I/R reperfusate, we observed that in rodents the addition of a MS-I/R reperfusate plus hypothermia to ECPB resuscitation resulted in short-term benefit after prolonged arrest. Future long-term and translational survival studies are warranted.