NORSKE ABSTRAKTER PRESENTERT PÅ AHA 2017

Circulation. 2017;136:A

Abstract 19852: PDE3A Binds Directly to and Inhibits SERCA2 Activity Independently of its Catalytic Activity

Jonas Skogestad, Jan Magnus Aronsen, Karina Hougen, Marianne Lunde, Gustav B Lothe, Ingrid Albert, Mira Børstad, Serena Marshall, Ana Isabel Costa Calejo, Per Kristian Lunde, Jens Preben Morth, Kjetil Tasken, Cathrine R Carlson, Ivar Sjaastad

Introduction: SERCA2 controls cardiac contractility, and its activity is negatively regulated by the cAMP phosphodiesterase PDE3A through an unknown mechanism. Several preclinical trials have shown upregulation of SERCA2 gene therapy as beneficial in heart failure, but no specific SERCA2 activating agents have been reported.

Hypothesis: We propose that PDE3A is physically associated with SERCA, and that this interaction regulates SERCA2 activity independent of the cAMP-degrading properties of PDE3A.We also wanted to evaluate whether this protein-protein interaction represent a novel drug target to increase SERCA2 activity in heart failure.

Methods and Results: SERCA2 activity in PDE3A-transefected HEK293 vesicles was reduced compared to control. PDE3A also reduced SERCA2 activity in the presence of the PDE3A inhibitor Cilostamide, showing that PDE3A inhibits SERCA2 independently of its catalytic effect. A combination of immunoprecipitation and peptide interaction experiments revealed interaction between specific cytosolic regions on PDE3A and SERCA2. Active PDE3A co-purified and precipitated with SERCA2 from left ventricular myocardium, and proximity ligation assay demonstrated co-localization of PDE3A and SERCA2 in intact cardiomyocytes. SERCA2 activity assays in adult cardiomyocytes revealed increased SERCA2 activity by intracellular and extracellular administration of disruptor peptides of the SERCA2-PDE3A interaction, independent of protein kinas A and phospholamban. PDE3A-SERCA2 disruptor peptides were able to increase SERCA2 activity and prevent spontaneous contractions in ventricular myocytes from mice with chronic heart failure.

Conclusion: PDE3A is physically associated to SERCA2, and this direct interaction inhibits its SERCA2 activity. Cell permeable disruptor peptides of the PDE3A-SERCA2 protein-protein interaction are able to increase SERCA2 activity in both normal and failing adult cardiomyocytes. Specific disruption of PDE3A from SERCA2 may potentially offer a new therapeutic approach against arrhythmias and in chronic heart disease.

Abstract 16883: Liquid Chromatography-tandem Mass Spectrometry (lc-ms/ms) Demonstrates That Palmitate Can Ameliorate Cardiac Redox State Under Oxidized Conditions

Neoma T Boardman, Roy Andre Lysså, Ole-Martin Fuskevåg, Ellen Aasum

Introduction: Changes in the ratio of reduced (GSH) to oxidized (GSSG) glutathione is commonly used to indicate redox status in the heart. However, previously reported values of myocardial GSH, GSSG and redox state (GSH:GSSG) are conflicting, possibly due to a lack of sensitive, accurate quantification of GSH and GSSG, as well as blood contamination and auto-oxidation

during sample preparation. LC-MS/MS is a gold standard technique for the quantification of low molecular compounds but not commonly used for redox state assessment in heart tissue. Fatty acids (palmitate) are an important fuel for the heart and are suggested to influence cardiac glutathione homeostasis.

Hypothesis: Elevated palmitate levels will influence cardiac redox state (GSH:GSSG) following oxidative stress induced by diamide exposure or ischemia/reperfusion (I/R).

Methods: Isolated mouse hearts (n=6-8 per group) were exposed to normal (NF) or high palmitate (HF) concentration (0.4 and 1.6 mM). These hearts were exposed to diamide (200 uM, thiol-oxidizing agent) or global ischemia (25') and reperfusion (5'). At the end of reperfusion, left ventricular tissue was immediately placed in phosphate buffer with *N*-ethylmaleimide (NEM) to prevent oxidation of GSH. ^{13}C labeled internal standards were added to correct for loss of GSH and GSSG during sample preparation; GSH and GSSG were then quantified by LC-MS/MS.

Results: In normoxic NF perfused hearts, GSH was 1.4 µmol/gwwt, while GSSG levels were undetectable (<100 pmol/gwwt). Diamide exposure reduced GSH by ~50% and dramatically increased GSSG (~50-fold). Under these conditions, HF markedly decreased GSSG, while GSH was unchanged. I/R did not alter GSH and surprisingly, GSSG was not detectable. The presence of HF did not alter either GSH or GSSG following I/R.

Conclusions: This study indicates that pre-analytic strategies to limit auto-oxidation and contamination from blood may be important for avoiding overestimation of GSSG in the heart. While a potent oxidizing agent altered cardiac redox sate, we did not find any changes in glutathione following I/R. Finally, our findings suggest that palmitate can play a role in glutathione homeostasis under highly oxidized conditions.

Abstract 18611: Sex Differences in the Influence of Body Mass Index on Incidence of Atrial Fibrillation: The Tromsø Study 1979-2013

Jocasta Ball, Maja-Lisa Løchen, Tom Wilsgaard, Henrik Schirmer, Laila A Hopstock, Bente Morseth, Ellisiv B Mathiesen, Inger Njølstad, Sweta Tiwari, Simon Stewart, Ekaterina Sharashova

Introduction: Atrial fibrillation (AF) is the most common cardiac arrhythmia and imparts substantial burden. Prevalence is increasing in parallel with aging, improved survival and emerging epidemics of antecedent risk factors. Body mass index (BMI) is a validated risk factor for incident AF. However, the impact of BMI (including change over time) on the risk of AF in the different sexes has not been fully elucidated.

Methods: The Tromsø Study (Norway) is a longitudinal population study consisting of seven surveys conducted from 1974 to 2016. We used data collected at the second (1979-1980), third (1986-1987) and fourth (1994-1995) surveys. AF diagnosis (collected to 2013) was derived from hospital record linkage. Cox regression analysis was conducted using fractional polynomials of BMI, BMI change and age with all models adjusted for CVD risk factors, co-morbidities and antihypertensive drug use.

Results: Data were available for 24,843 individuals from the fourth Tromsø survey (mean age 45.5 ± 14.2 years, 52.9% female). Over a mean follow-up of 15.9 ± 5.4 years, n = 581 (4.4%) women and n = 595 (5.1%) men developed AF. In men, lower BMI was associated with a decreased risk of AF and higher BMI was associated with an increased risk (HR, 95% CI for BMI 18 kg/m^2 was 0.83, 0.78-0.89; for BMI 40 kg/m^2 was 4.49, 2.63-7.68, when BMI 23 kg/m^2 used as a reference). The same pattern was identified in women although associations were not as strong. Of the three surveys, 17,367 individuals attended at least two. In men, a decrease in BMI over 10 years was associated with a decreased risk of AF and an increase in BMI increased the risk of AF development (HR, 95% CI for 2 kg/m^2 decrease in BMI was 0.86, 0.75-0.99; for 4 kg/m^2 increase in BMI was 1.26, 1.02-1.55, when 1 kg/m^2 increase in BMI used as a reference). No associations between change in BMI and risk of AF were identified in women.

Conclusions: Within a population cohort, higher BMI was significantly and independently associated with an increased risk of future AF although this was stronger for men compared to women. Changes in BMI over time influenced the risk of AF in men but not women. Weight maintenance/reduction strategies should potentially be different for women and men but should form part of a lifetime approach to the primary prevention of AF.

Abstract 20215: Bedside Transcranial Dopplersonography for Prognostication After Cardiac Arrest

Antje Reichenbach, Lars Alteheld, Julia Henriksen, Espen R Nakstad, Geir Ø Andersen, Kjetil Sunde, Christofer Lundqvist

Background: Early prediction of outcome in comatose patients after out-of-hospital cardiac arrest (OHCA) is challenging. So far, recommended prognostication tools consist of clinical examination, biomarkers and neurophysiological tests. The aim of the present study was to explore whether the use of bedside transcranial doppler (TCD) could give additional information.

Methods: This was a substudy of the prospective observational Norwegian Cardiorespiratory Arrest Study (NORCAST), where 261 adult comatose OHCA patients were included between 2010 and 2014. All patients underwent standardised post resuscitation care including target temperature management to 33°C for 24 hours. Bedside TCD, blinded to the treating physician, was performed at day seven to measure peak systolic velocity (PSV), resistance index (RI) and pulsatility index (PI) in middle cerebral arteries. Primary endpoint was Cerebral Performance Category (CPC) at six months, which was dichotomized into good (CPC 1-2) and poor (CPC 3-5) outcome. The predictive value of the TCD results was determined by logistic regression analysis.

Results: In total, 140 patients (54%) survived to 6 months, 95% with good outcome. TCD-data was used in 111 of 201 alive at day seven. PSV in the left middle cerebral artery was 1.0 m/sek (95%CI 0.95-1.08) in patients with good outcome vs. 1.3 m/sek (95%CI 1.15-1.48) in patients with bad outcome (p=0.001, OR 8.9). There was no significant difference between right and left side data. PI and RI were not associated with clinical outcome at six months.

Conclusion: Early bedside TCD is a simple and low-cost examination that offers useful information for prognostication after cardiac arrest. PSV was lower in patients with good outcome. Its role in multimodal prognostication models should be further explored.

Abstract 20017: Cerebral Perfusion With Mean Arterial Pressure 90 vs. 60 mmHg in a Normothermic Porcine Post Cardiac Arrest Model

Christiane Skaare, Runar J Strand-Amundsen, Morten Eriksen, Vidar M Skulberg, Kjetil Sunde, Tor Inge Tønnessen, Theresa M Olasveengen

Background: Current guidelines for post resuscitation care recommend targeting mean arterial pressure (MAP) above 65 mmHg, but there is limited science to support these recommendations. Some registry- and observational data indicate better outcome with higher blood pressures. However, initial resuscitation during post resuscitation care needs to balance the brains need for perfusion with the hearts need for restitution. We hypothesized that maintaining a MAP of 90 mmHg would yield improved cerebral blood flow and metabolism compared to 60 mmHg.

Methods: Swine (35 kg) were anesthetized and instrumented prior to electrical induction of ventricular fibrillation. After 10 minutes of cardiac arrest, animals were resuscitated using a heart-lung machine at 100 ml/kg/min for two minutes before defibrillation. After ROSC, animals were randomized to MAP 90 or MAP 60, and blood pressure targets were managed with vasopressin, norepinephrine or nitroprusside. After a 30 minute stabilization period, animals were observed for an additional two hours. Brain tissue pCO_2, brain microdialysis (results to be analysed), carotid and intracerebral flow, intracerebral pressure, aortic pressure, right and left ventricular pressures were measured continuously. Values were extracted and analyzed for 15 minute epochs. All values listed are means ± standard deviation.

Results: Preliminary results were available for 8 and 6 planned animals in MAP 90 and 60 groups, respectively (total of 20 animals to be included). Absolute values indicate improved cerebral flow (146±44% vs. 94±24% of baseline), carotid flow (226±18 vs. 191±22 ml/min),and and lower brain tissue pCO2 (8.6±0.7 vs. 10.3±1.9 kPa) in the MAP 90 group 150 min after ROSC. There was improved cardiac function with higher cardiac output (4.4±0.3 vs. 4.0±0.2 l/min), left ventricular dp/dt max (1252±98 vs. 920±86 mmHg/sec), and mixed central venous saturation (58±4% vs. 49±6%), and lower left ventricular dp/dt min (-1243±108 vs. -830±98 mmHg/sec) and left ventricle end-diastolic pressure (6±2 vs. 10±1 mmHg) with MAP 90.

Conclusion: Preliminary results suggest targeting MAP to 90 mmHg after cardiac attest might provide better cerebral perfusion compared to 60 mmHg in a normothermic porcine model.

Abstract 20752: In-Hospital Telemetry Monitoring in Patients With Acute Coronary Syndrome - Arrhythmias and Long Term Survival

Nina Fålun, Jørund Langørgen, Per Ivar Hoff, Roy M Nilsen, Jan Erik Nordrehaug, Trond R Pettersen, Tone M Norekval

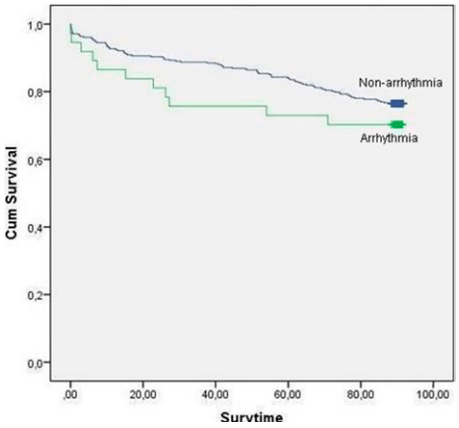
Introduction: In-hospital telemetry monitoring is recommended in all patients with ACS to reveal severe arrhythmias and sudden cardiac death. According to the Practice Standards for Electrographic Monitoring by AHA all patients with preliminary ACS diagnoses have Class I indication for telemetry monitoring. The aims of the study were to investigate the number of in-hospital arrhythmias, and whether arrhythmias versus non-arrhythmias predict long-term survival in ACS patients.

Methods: A prospective observational design was applied. All adult patients assigned to in-hospital telemetry monitoring at one university hospital during a three month period in 2009-2010 were consecutively enrolled (N=1194). A registration data sheet with sixty-four variables was developed, completed by monitor watchers at the central monitor station, and reviewed by the investigator. Data were collected 24/7. Medical records were reviewed in all

patients and re-reviewed in the ACS population (n=422) seven years after hospital discharge.

Results: Of the 422 ACS patients, 69% were men and mean age was 65 years. Only 23% of the patients experienced arrhythmic events, of which 1.4% was serious adverse events like third degree AV-block, sustained ventricular tachycardia and asystole. Of the entire ACS population, 24% died within seven years after hospital discharge. There were no significant differences in survival rates in patients with and without arrhythmic events during hospital stay (OR 1.6, 95% CI 0.79-3.25, p=0.189).

Conclusion: ACS patients under in-hospital telemetry monitoring had low rates of adverse arrhythmia events. No significant differences in patients with and without in-hospital arrhythmias in long-term survival challenge the AHA's Practice Standard as cardiac monitoring is recommended in all ACS patients. Further investigations in a larger population of ACS patients are required.



Abstract 13900: Secretoneurin is an Endogenous CaMKII Inhibitor That Attenuates Ca^{2+}-Dependent Arrhythmogenesis

Anett Hellebo Ottesen, Cathrine R. Carlson, Derek R. Laver, Peder L. Myhre, Bjørn Dalhus, Per Kristian Lunde, Marianne Lunde, Jon Erik Hoff, Kristin Godang, Mats Stridsberg, Torbjørn Omland, Geir Christensen, Helge Røsjø, William E. Louch

Introduction: Circulating secretoneurin (SN) levels are reported to predict mortality in patients with myocardial dysfunction. SN has also been observed to inhibit Ca^{2+}/calmodulin-dependent protein kinase II δ (CaMKIIδ) activity.

Objectives: To investigate the mechanism by which SN inhibits CaMKIIδ activity, and whether elevation of SN protects against Ca^{2+}-dependent arrhythmia.

Methods and Results: Using pull down experiments and structural homology modeling, SN binding was mapped to the substrate binding site in the catalytic region of CaMKIIδ. SN attenuated isoproterenol (ISO)-induced autophosphorylation of Thr287-CaMKIIδ in Langendorff hearts, and inhibited CaMKIIδ-dependent ryanodine receptor 2 (RyR2) phosphorylation. SN was also observed to decrease RyR2 open probability in lipid bilayer experiments. In line with CaMKIIδ and RyR2 inhibition, SN treatment decreased Ca^{2+} spark frequency and dimensions in cardiomyocytes during ISO challenge. Ca^{2+} wave frequency was reduced, which corresponded with lower incidence of delayed after-depolarizations and fewer spontaneous action potentials. SN treatment also reduced the incidence of early after-depolarizations during ISO; an effect paralleled by reduced magnitude of L-type Ca^{2+} current. Based on these protective actions of SN, we investigated SN levels in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) who are prone to Ca^{2+}-dependent arrhythmia. Circulating SN levels were increased in CPVT patients, while levels of established biomarkers were unchanged.

Conclusions: SN interacts with the substrate binding site of CaMKIIδ, thereby inhibiting its activity. A consequent reduction in RyR2 and L-type Ca^{2+} channel opening reduces incidence of early and late after-depolarizations. Production of SN may be an endogenous protective mechanism in patients with pathological cardiomyocyte Ca^{2+} handling, supporting its role as an emerging biomarker.

Abstract 17781: Single Measurement of Cardiac Troponin T With a High-Sensitivity Assay Provides Valuable Information in Unselected Chest Pain Patients

Sjur H Tveit, Peder L Myhre, Nils Jacob Hoff, Tri M Le, Tor-Arne Hagve, Torbjørn Omland, Helge Røsjø

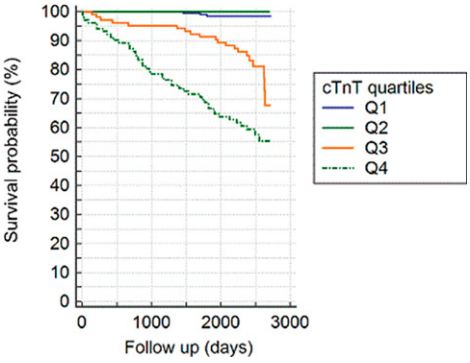
Introduction: Whether high-sensitivity cardiac troponin T (hs-cTnT) levels provide valuable diagnostic and prognostic information across the spectrum of patients with acute coronary syndrome (ACS) is not known.

Methods: We included 411 unselected patients with chest pain in a Norwegian teaching hospital, and the physicians in the Emergency Department annotated the probability of ACS from 0-100%. Blood samples were collected during admission. The index diagnosis of ACS vs. non-cardiac chest pain was adjudicated by two physicians.

Results: One-hundred-sixty-eight patients (40%) were classified as hospitalized with ACS, including 88 patients with unstable angina

in unadjusted (B, -0.010; 95% CI, -0.110 to 0.90, p=0.85) or adjusted (B, -0.041; 95% CI -0.128 to 0.045, p=0.35) models.

Conclusion: Smoking but not snus tobacco use was associated with circulating concentrations of cTnI. Different pathophysiological processes may be responsible for troponin release in users of smokeless and smoking tobacco.



Abstract 16343: Cardiac Troponin I Provides Superior Prognostic Information to C-Reactive Protein in the General Population: Data From The Nord-Trøndelag Health Study

Fjola D Sigurdardottir, Magnus N Lyngbakken, Oddgeir L Holmen, Håvard Dalen, Kristian Hveem, Helge Røsjø, Torbjørn Omland

Background: Both C-reactive protein (CRP) and cardiac troponin I (cTnI) measured with high-sensitivity assays have been associated with risk of fatal and nonfatal cardiovascular events in the general population, but their relative prognostic value remains unclear.

Methods: CRP and cTnI were measured in 9005 participants from the prospective observational Nord-Trøndelag Health Study. All study subjects were free from known cardiovascular disease at baseline.

Results: During a median follow up period of 13.9 years, 733 participants reached the composite endpoint of hospitalization for acute myocardial infarction or heart failure, or cardiovascular death. In adjusted models, cTnI concentrations >10 ng/L for women and >12 ng/L for men were associated with the incidence of the composite endpoint (hazard ratio [HR] 3.23 [95% confidence interval (CI) 2.58-4.04]), while the risk associated with increased CRP concentrations (>3 mg/L for both sexes) was weaker (HR 1.61 [1.32-1.96]). The addition of cTnI to established cardiovascular risk prediction models led to a net reclassification improvement (NRI) of 0.35 pectoris. The receiver operating characteristics area under the curve (AUC) of hs-cTnT to diagnose ACS was 0.83 (95%CI 0.78-0.87), the AUC of physicians was 0.80 (0.76-0.85), and the combination of hs-cTnT levels and physician yielded an AUC of 0.88 (0.85-0.91). All-cause mortality during median 6.6 years follow-up was 50 patients in the ACS-population (30%) and 16 patients in the non-ACS-population (7%). hs-cTnT measurements levels in the total population separated patients with a favorable and a poor prognosis (Figure). Adjusting for demographics, comorbidities and clinical status, hs-cTnT levels were still associated with time to death: HR 1.34 (95%CI 1.19-1.52), p<0.001.

Conclusions: hs-cTnT measurements provide valuable diagnostic and prognostic information across the spectrum of ACS.

Abstract 16340: Association Between Smokeless Tobacco Use and Circulating Concentrations of Cardiac Troponin I in the General Population: The Hunt Study (Nord-Trøndelag Health Study)

Julia B Skranes, Magnus N Lyngbakken, Ståle Nygård, Håvard Dalen, Oddgeir L Holmen, Kristian Hveem, Helge Røsjø, Torbjørn Omland

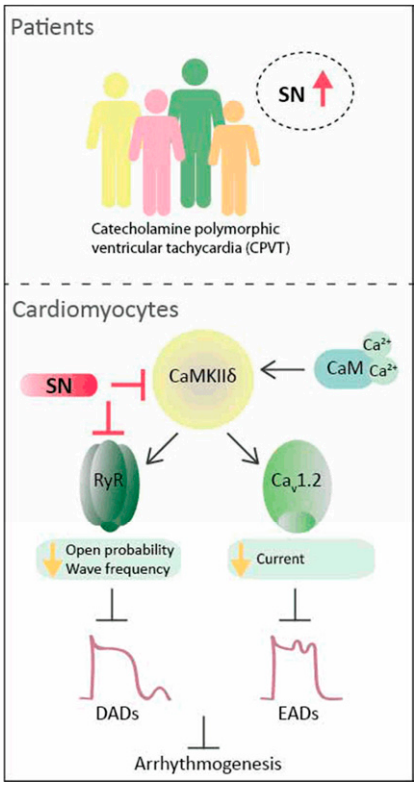
Background: Consumption of moist oral tobacco (snus) has increased in Scandinavia during the last decades, and in recent years snus has been aggressively marketed in the United States. While smoking is a well-established cardiovascular risk factor, the association between snus and cardiovascular risk is unclear. Current smoking is associated with lower concentrations of cardiac troponin I (cTnI). We examined the association between snus and smoking tobacco, respectively, and circulating concentrations of cTnI in the general population.

Methods: We used a high-sensitivity assay to detect cTnI in 5483 subjects enrolled in the prospective, population-based HUNT Study (Nord-Trøndelag Health Study). Self-reported tobacco habits (snus user/smoker) were reported as: never (n=4662/2193), former (n=229/1937) and current (n=390/1230). The association between self-reported tobacco use and cTnI was assessed by linear regression, and adjusted for traditional cardiac risk factors, C-reactive protein and estimated glomerular filtration rate.

Results: Current smoking was associated with lower cTnI concentrations in both unadjusted (B, -0.172; 95% confidence interval [CI], -0.239 to -0.104, p<0.001) and fully adjusted (B, -0.103; 95% CI, 0.159 to -0.048, p<0.001) linear regression models. In contrast, no association between cTnI and current snus use was observed

(95% CI 0.27-0.42), superior to that of CRP (0.21 [0.13-0.28]). The prognostic accuracy expressed as the area under the ROC curve of cTnI was 0.75 (0.74-0.76) and significantly greater to that of CRP, AUC 0.64 (0.63-0.65).

Conclusion: In subjects from the general population without a history of cardiovascular disease, cTnI provides prognostic information superior to that provided by CRP measurements. This suggests that cTnI measurement may be a better tool for identifying individuals at high cardiovascular risk compared to CRP and therefore also a better marker for targeted prevention.



Abstract 11699: Presence of Inconsistently Graded Severe Aortic Valve Stenosis Despite Pressure Recovery Adjustment Predicts Impaired Outcome

Edda B Bahlmann, Dana Cramariuc, Sahrai Saeed, Terje Pedersen, Nikolaus Jander, Jan Minners, John B Chambers, Karl Heinz Kuck, Eva Gerdts

Introduction: Conflicting evidence exists on the prognostic impact of inconsistently graded aortic valve stenosis (AS) in asymptomatic patients. Pressure recovery adjustment of aortic valve area (energy loss, EL) is recommended for more accurate grading, but the outcome in asymptomatic patients with inconsistently graded severe AS defined from combined EL ≤1cm² and mean aortic gradient ≤40mmHg has not been reported.

Hypothesis: Inconsistently graded severe AS identified by EL and mean gradient is associated with impaired outcome.

Methods: Data from 1497 patients with initially asymptomatic mild-moderate AS and normal ejection fraction enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study was used. Median follow-up was 4.3 years. 25 patients with consistently graded severe AS at baseline were excluded, and included patients were grouped according to presence of consistently graded non-severe AS or inconsistently graded severe AS. Outcome was assessed in Cox regression analysis and reported as hazard ratio (HR) and 95% confidence interval (CI).

Results: Inconsistently graded severe AS by EL was found in 213 patients (14.2%) at baseline and associated with older age, female sex, smaller aortic annulus diameter, more extensive valve calcification and lower stroke volume independent of more severe AS in multivariable logistic regression analysis (all $p<0.05$). In Cox regression analysis, inconsistently graded severe AS by EL was associated with a 3-fold increase in HR (95% CI 1.56-4.66) for hospitalization for heart failure and a 2-fold increase in HR (95% CI 1.10-3.09) for cardiovascular death also after adjusting for confounders (both $p<0.05$).

Conclusions: Presence of inconsistently graded severe AS despite adjustment for pressure recovery is associated with increased risk for heart failure and cardiovascular death in asymptomatic AS patients.

Abstract 17368: Influence of Left Ventricular Ejection Fraction on Fatal Outcomes After Myocardial Infarction Complicated by Heart Failure or Left Ventricular Dysfunction

Trygve S Hall, Thomas G von Lueder, Faiez Zannad, Patrick Rossignol, Kevin Duarte, Tahar Chouihed, Kenneth Dickstein, Dan Atar, Stefan Agewall, Nicolas Girerd

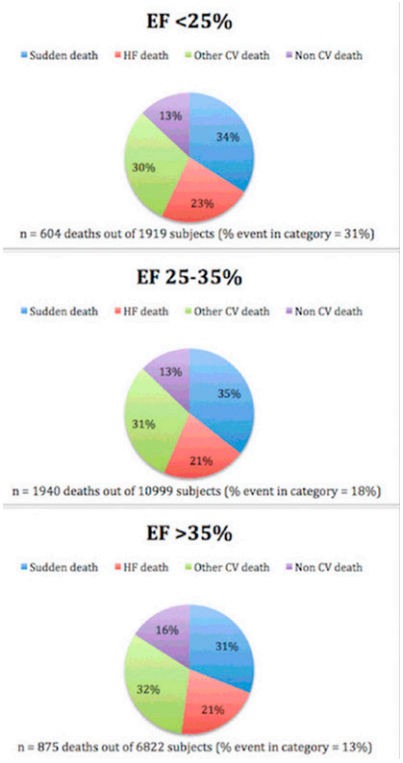
Introduction: Identifying risk factors for specific types of death in patients with HF or LV dysfunction after AMI may potentially reduce events. Low EF is associated with increased rates of death, but its ability to forecast specific causes of death remains unclear.

Hypothesis: Lower LVEF categories are associated with increases in sudden death, HF death, other CV death, and non CV death.

Methods: In an individual patient data meta-analysis of four merged large randomized trials (CAPRICORN, EPHESUS, OPTIMAAL, and VALIANT), Cox proportional hazards modeling was performed to study the association between LVEF at baseline and modes of death during follow-up. All the cause-specific deaths were adjudicated by independent committees.

Results: Three trials sampled LVEF as part of study protocol resulting in 19740 eligible patients (OPTIMAAL excluded). Over a median follow-up of 707 days, a total of 3419 deaths occurred. The distribution pattern of specific death causes (figure 1) was similar across LVEF categories (<25%, 25-35%, >35%). In multivariable models adjusted for age, sex, Killip class, systolic BP, diabetes, hypertension, renal failure, COPD, peripheral artery disease, medication use (beta-blockers, ACE inhibitors/ARB, diuretics), eGFR, Hb and sodium, the risk of all types of death increased with decreasing LVEF. Each 5% decrease in LVEF was associated with a 23% increased risk of sudden death (HR 1.23, 95% CI 1.14-1.33), a 26% increased risk of HF death (HR 1.26, 95% CI 1.15-1.39), a 13% increased risk of other CV death (HR 1.13, 95% CI 1.04-1.24), and a 14% increased risk of non CV death (HR 1.14, 95% CI 1.00-1.29).

Conclusions: In patients with HF or LV dysfunction after MI, low LVEF is an ubiquitous risk marker associated with death regardless of type. It consequently deserves great attention beyond the risk of sudden death and may be a marker not just specific to sudden death. Mode of death is equally represented throughout the categories of increasingly compromised LVEF.



Abstract 14527: Temporal Changes in Cardiac Troponin I and Risk of Cardiovascular Events in the General Population: The Nord-Trøndelag Health Study

Magnus N Lyngbakken, Helge Røsjø, Oddgeir L Holmen, Håvard Dalen, Kristian Hveem, Torbjørn Omland

Introduction: Concentrations of cardiac troponin are strongly associated with risk of heart failure (HF), myocardial infarction (MI), and cardiovascular death (CVD) in the general population. Temporal changes in cardiac troponin T have also been associated with increased cardiovascular risk, but the corresponding association for cardiac troponin I (cTnI) remains unclear.

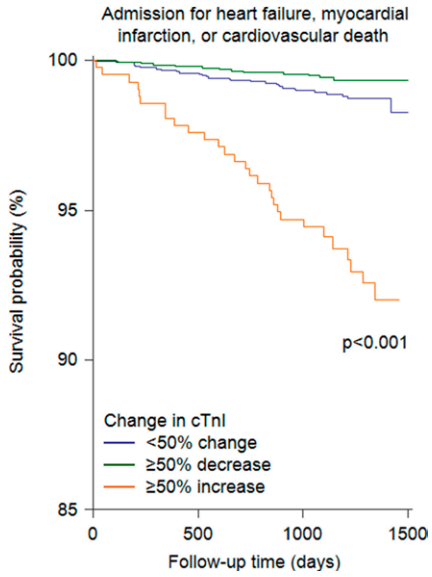
Hypothesis: Temporal changes in cTnI are associated with risk of HF, MI, and CVD in the general population.

Methods: We measured cTnI with a high-sensitivity assay in 4803 participants of the prospective observational HUNT Study, at study visit 2 (1995-97) and visit 3 (2006-2008). All subjects were free from known cardiovascular disease at baseline. Change in cTnI was modeled as change of <50%, increase of ≥50%, or decrease of ≥50% from concentrations at visit 2. A composite endpoint of first admission for MI or HF, or CVD was generated.

Results: Participants with relative decrease in cTnI were more frequently younger and female, and had lower blood pressure, body mass index, blood lipids and glucose. Participant with relative increase in cTnI were more frequently older and male, with higher systolic blood pressure and blood lipids. After a median follow-up time of 1326 days, 70 events for the composite endpoint were registered. The incidence rate was 21.0/1000 patient-years for study participants with relative increase in cTnI, and 1.8/1000 patient-years for participants with relative decrease in cTnI (p<0.001). This finding was reflected in Kaplan-Meier survival curves according to relative changes in cTnI (Figure). The adjusted hazard ratio (HR) associated with relative decrease in cTnI was 1.60 (0.78-3.25). The corresponding adjusted HR for relative increase in cTnI was 2.43 (1.28-4.58).

Conclusions: Relative increase in cTnI is independently associated with risk of HF, MI, and CVD. Serial measurements of cardiac tropo-

nin could provide guidance in individual risk prediction.



Abstract 15787: Impact of Hypertension and Diabetes on Prevalence of Subclinical Arterial Damage in Subjects With Increased Body Mass Index (the FATCOR Project)

Mai T Lønnebakken, Ingeborg Eskerud, Helga Midtbø, Hilde Halland, Marina Kokorina, Eva Gerdts

Introduction: Increased body mass index (BMI) is associated with a high prevalence of hypertension (HT) and diabetes (DM), and an increased risk of clinical cardiovascular (CV) disease. Whether increased BMI is associated with higher prevalence of subclinical arterial damage independent of concomitant HT and DM is still unclear.

Hypothesis: The increased prevalence of subclinical arterial damage observed in subjects with increased BMI is related to co-presence of HT and DM.

Methods: In 523 healthy subjects (mean age 48±9 years, 61% women) with BMI >27 kg/m^2 participating in the FAT associated CardiOvasculaR dysfunction (FATCOR) project, subclinical arterial damage was assessed by ultrasound and carotid-femoral pulse wave velocity (PWV). Arterial damage was defined as maximum carotid or femoral intima-media thickness >0.9 mm or as increased arterial stiffness with PWV>10 msec. The population was grouped according to presence or absence of coexisting HT and/or DM.

Results: Increased BMI without coexisting HT and DM (HTDMneg) was present in 219 (44%) subjects and associated with younger age, female sex, lower waist circumference, blood pressure, heart rate and serum triglycerides (all p<0.05) compared to subjects with increased BMI and HT and/or DM (HTDMpos). There was no difference in BMI, serum cholesterol or smoking habit between the groups. Prevalence of subclinical arterial damage was lower in HTDMneg (27% vs. 57%, p<0.001) compared to HTDMpos subjects with increased BMI. In logistic regression analysis, being HTDMpos was associated with incident subclinical arterial damage independent of significant associations with age, male sex and smoking, even after adjusting for obesity (Table).

Conclusion: In subjects with increased BMI, the prevalence of subclinical arterial damage was higher and strongly associated with coexisting HT and DM, emphasizing the impact of CV risk factor clustering on arterial health in subjects with increased BMI.

Abstract 17668: Heart Failure Epidemiology, Risk Factors and Mortality Risk by Gender in Community Cohorts Across Europe

Christina Magnussen, Teemu Niiranen, Francisco M Ojeda, Francesco Gianfagna, Stefan Blankenberg, Inger Njølstad, Erkki Vartiainen, Susana Sans, Gerard Pasterkamp, Simona Costanzo, Maria Benedetta Donati, Pekka Jousilahti, Allan Linneberg, Tarja Palosaari, Giovanni de Gaetano, Martin Bobak, Hester M den Ruijter, Ellisiv Mathiesen, Torben Jørgensen, Stefan Söderberg, Kari Kuulasmaa, Tanja Zeller, Veikko Salomaa, Licia Iacoviello, Renate B Schnabel

Introduction: Heart failure (HF) is a global epidemic that is common in aging populations.

Hypothesis: There are gender differences in HF epidemiology and risk.

Methods: In N=78,877 individuals without prevalent HF at baseline (median age 49.5 years, age range 39.6 to 59.4 years, 51.7% women) from 4 community-based European studies (FINRISK, DanMONICA, Moli-Sani, Northern Sweden), we examined gender differences in the association of incident HF with mortality, and the relation and attributable risks of classical risk factors, prevalent cardiovascular disease and biomarkers (C-reactive protein (CRP), N-terminal pro B-type natriuretic peptide (Nt-proBNP)) with HF incidence in women vs. men.

Results: Over a median follow-up of 12.7 years, fewer HF cases were observed in women (N=2,410, 5.9%) than in men (N=2,789, 7.3%).

Men had a worse cardiovascular risk factor profile and more prevalent cardiovascular disease. After HF onset, men had a higher mortality than women (P<0.001; multivariable-adjusted hazard ratio, 95% confidence interval: women: 6.34, 5.83-6.90; men: 6.74, 6.30-7.21). Multivariable-adjusted Cox models showed significant gender differences for the association of systolic blood pressure (P=0.0049), CRP (P=0.0014), Nt-proBNP (P=0.012), heart rate (P<0.001) and previous myocardial infarction or stroke (P=0.016) with incident HF. The population attributable risk of all risk factors combined was 58.3% in women and 63.7% in men. Overweight and obesity accounted for about 37% of women's risk.

Conclusions: HF risk was higher in men. HF onset dramatically increased mortality risk in both genders. Of the classical risk factors, BMI explained the largest proportion of HF risk. Prospective studies are needed to evaluate the observed gender differences for their role in gender-specific prevention approaches.

Figure: Cox regressions for mortality and HF as time-dependent covariate (model 1); additional adjustment for classical risk factors (model 2).

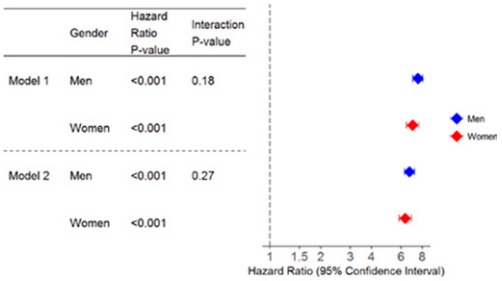


Table. CV death and HF outcomes by degree of change from baseline in vascular markers at week 12 with empagliflozin (pooled 10 mg and 25 mg) and placebo.*

		< median change (least reduction from baseline)		≥ median change (greatest reduction from baseline)	
		Placebo	Empa	Placebo	Empa
CV death					
By change in PP at week 12 < or ≥ 1.50 mmHg	n (patients)	1302	2193	1016	2480
	n (%) with event	74 (5.7)	81 (3.7)	53 (5.2)	85 (3.4)
	HR (95% CI)	*0.66 (0.48, 0.90)*		*0.64 (0.45, 0.90)*	
	P for interaction	*0.9075*			
By change in MAP at week 12 < or ≥ 2.00 mmHg	N	1334	2161	984	2512
	n (%) with event	79 (5.9)	90 (4.2)	48 (4.9)	76 (3.0)
	HR (95% CI)	*0.70 (0.52, 0.95)*		*0.64 (0.44, 0.91)*	
	P for interaction	*0.6914*			
By change in DP at week 12 < or ≥ 196.33 mmHgxHR	N	1307	2188	1011	2485
	n (%) with event	67 (5.1)	84 (3.8)	60 (5.9)	82 (3.3)
	HR (95% CI)	*0.76 (0.55, 1.04)*		*0.57 (0.41, 0.79)*	
	P for interaction	*0.2272*			
HF hospitalization or HF death					
By change in PP at week 12 < or ≥ 1.50 mmHg	n (patients)	1305	2186	998	2470
	n (%) with event	52 (4.0)	57 (2.6)	43 (4.3)	70 (2.8)
	HR (95% CI)	*0.68 (0.47, 0.99)*		*0.64 (0.43, 0.93)*	
	P for interaction	*0.8005*			
By change in MAP at week 12 < or ≥ 2.00 mmHg	N	1312	2177	991	2479
	n (%) with event	52 (4.0)	60 (2.8)	43 (4.3)	67 (2.7)
	HR (95% CI)	*0.71 (0.49, 1.03)*		*0.59 (0.41, 0.87)*	
	P for interaction	*0.5143*			
By change in DP at week 12 < or ≥ 196.33 mmHg xHR	N	1295	2194	1008	2462
	n (%) with event	54 (4.2)	59 (2.7)	41 (4.1)	68 (2.8)
	HR (95% CI)	*0.66 (0.45, 0.95)*		*0.67 (0.45, 0.99)*	
	P for interaction	*0.9525*			

*: Outcomes considering events onwards from day 84 (planday of week 12 measurement), adjusted for change from baseline to day 84 for the marker analysed, pooled empa vs placebo – TS

Abstract 16626: Empagliflozin Improves Cardiovascular (CV) Outcomes Regardless of Improvement in Cardiac and Vascular Hemodynamic Markers in Type 2 Diabetes Patients at High CV Risk in EMPA-REG OUTCOME

Robert J Chilton, Lars Gullestad, Sung-Ha Park, David Fitchett, Silvio E, Uwe Hehnke, Hans Juergen Woerle, Odd Erik Johansen

Introduction: In EMPA-REG OUTCOME, empagliflozin (empa) significantly reduced CV death by 38% (HR 0.62; 95% CI: 0.49, 0.77) and hospitalization for heart failure and HF death by 39% (0.61 (0.47, 0.79). As empa can rapidly reduce arterial stiffness and improve vascular compliance, these could be mechanisms involved in the drug's cardioprotective effects. We tested the hypothesis that reducing indices of vascular markers with empa could be related to the effects on HF outcomes and CV death.

Methods: 7020 patients with type 2 diabetes at high CV risk were randomized to receive placebo, empa 10 mg, or empa 25 mg in addition to standard of care. The short-term (12 week) changes in indices of arterial stiffness, vascular resistance and cardiac workload were calculated in the placebo and the pooled empa groups: pulse pressure (PP = SBP - DBP), mean arterial pressure (MAP = ([2 x diastolic BP] + systolic BP)/3) and the double product (DP = heart rate x SBP). Then the treatment group effects on CV death and the composite of HF hospitalization or HF death were assessed by the magnitude of changes in the above indices at week 12 (> vs. ≤ the median).

Results: 2333 patients were randomized to placebo and 4687 to empa. At baseline, median PP in the placebo group was 57.33 mmHg and in the pooled empa group 57.00. Median MAP and DP were also similar across the treatment groups at baseline (median MAP placebo: 96.22 mmHg; pooled empa: 96.11; median DP placebo: 9372 mmHg x HR; pooled empa: 9338). At week 12, significantly greater reductions in all parameters were observed with empa. The modulation of CV death and HF hospitalization/HF death by empa was consistent, however, between the subgroups of changes in PP, MAP and DP (Table).

Conclusions: It is known that indices of arterial stiffness, vascular resistance and cardiac workload carry prognostic information, empa reduced CV death and HF outcomes regardless of the

magnitude of improvement in these markers in patients with type 2 diabetes at high CV risk.

Abstract 18301: The Prognostic Utility of Dihomo-gamma-linolenic Acid (dgla) in Patients With Acute Coronary Heart Disease

Dennis W Nilsen, Hildegunn Aarsetoey, Volker Pønitz, Trygve Brugger-Andersen, Harry Staines, William S Harris, Heidi Grundt

Introduction: We previously investigated the prognostic utility of red blood cell (RBC) n-3 fatty acids (FAs) in survivors of an acute myocardial syndrome (ACS) but found no relationship with all-cause mortality and cardiac death or MI after two years. Here we extend our follow-up to 7 years, focusing on the potential predictive power of RBC n-6 FAs.

Hypothesis: We hypothesize that dihomo-gamma-linolenic acid (DGLA) may be a useful predictor of future cardiovascular events following an acute coronary syndrome.

Methods: We included 398 ACS patients presenting with increased troponin-T (TnT) levels for whom baseline RBC FA data were available. Cox regression analysis was used to relate the risk of future events to RBC n-6 FA levels, both continuously and by quartile.

Results: At 7-year follow-up 183 (46.0%) had died, 128 (32.2%) had experienced another MI and 24 (6.0%) had had a stroke. Death or MI occurred in 227 patients (57.0%); and death, MI or stroke in 235 patients (59.0%). In a multivariable Cox regression model for total death, the hazard ratio (HR) in the highest as compared to the lowest quartile of dihomo-γ-linolenic acid (DGLA) was 0.55 [95% confidence interval (CI), 0.35-0.88, p= 0.012, for death or MI [HR 0.62 (95% CI, 0.41-0.94), p= 0.025], and for the fully combined endpoint [HR 0.57 (95% CI, 0.38-0.86), p= 0.006]. Similar results were found in the per 1-SD analysis. No other RBC n-6 FAs significantly predicted these outcomes in multivariable models.

Conclusions: RBC DGLA levels had significant independent prognostic value in post-ACS patients. These findings need confirmation, and the possible biochemical pathways by which higher DGLA membrane levels may be cardioprotective should be explored.

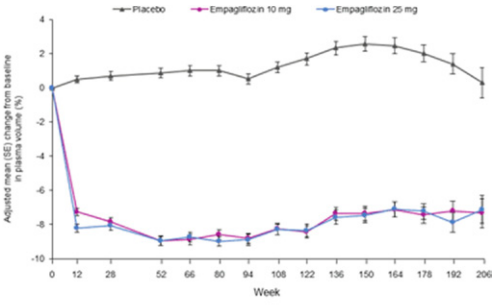
Abstract 15997: Empagliflozin Exerts Short- and Long-term Effects on Plasma Volume in Patients With Type 2 Diabetes: Insight From EMPA-REG OUTCOME

Morten Schou, Lars Gullestad, David Fitchett, Bernard Zinman, Silvio E Inzucchi, Uwe Hehnke, Max von Eynatten, Jyothis George, Odd Erik Johansen, Christoph Wanner

Introduction: In EMPA-REG OUTCOME®, empagliflozin (empa) significantly reduced CV death by 38% and hospitalization for heart failure by 35% relative to placebo. Haemodynamic changes and improvement in subclinical congestion mediated by the osmotic diuresis and natriuresis have been proposed as mechanism responsible for these outcomes. We hypothesized that short- and long-term treatment with empa reduced estimated plasma volume (ePV), and further explored whether responses in ePV were influenced by estimated glomerular filtration rate (eGFR) at baseline.

Methods: Patients with type 2 diabetes at high CV risk were randomized to receive placebo, empa 10 mg, or empa 25 mg in addition to standard of care. We analyzed short (12 week) - and long-term (up to 206 week) %-changes in ePV from baseline using a validated formula (Strauss formula) that incorporates hematocrit and hemoglobin concentrations (% ePV change = ((100 x [hemoglobin (before)/hemoglobin (after)]) x ([l- hematocrit (after)]/[l- hematocrit (before)]) - 100)). Changes in ePV were further analyzed in subgroups according to eGFR (MDRD formula) at baseline: < 45, 45-60, 60-90 and >= 90 ml/min/1.73 m^2.

Results: In total, 2333, 2345 and 2342 patients received placebo, empa 10 mg and empa 25 mg, respectively and followed for median 3.1 years. At week 12, the placebo-adjusted mean (SE) ePV %-change from baseline with empa 10 mg and 25 mg where -7.78 (0.30)% and -8.73 (0.30)% (both p<0.0001), respectively. Empa had a sustainable effect in reducing ePV (Figure 1). At



week 206, the corresponding placebo-adjusted ePV %-change were -7.65 (1.22)% and -7.44 (1.19)% (both p<0.0001). The magnitude ePV reduction was consistent across subgroups of eGFR (interaction p-value 0.209 and 0.9879 at week 12 and 206, respectively).

Conclusions: Empa, presumably through its glucuretic and natriuretic properties, induced a 7-8% reduction in ePV independent of eGFR. The effect occurred early and was sustained during long-term treatment.

Abstract 14626: Circulating Secretoneurin Levels Provide Additional Prognostic Information in Patients With Acute Coronary Syndrome

Peder L Myhre, Sjur H Tveit, Nils Jakob Hoff, Geir Christensen, Stridsberg Mats, Torbjorn Omland, Helge Rosjo

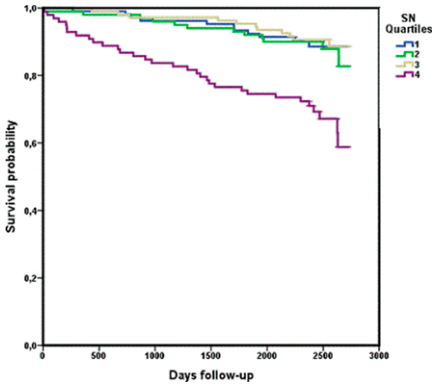
Introduction: Secretoneurin (SN) is associated with both myocardial ischemia and cardiomyocyte Ca^{2+} handling, and circulating SN levels provide incremental prognostic information to established risk indices in patients with acute heart failure, acute respiratory failure, and after cardiac arrest.

Hypothesis: We hypothesize that SN would provide prognostic information in unselected patients with acute coronary syndrome (ACS).

Methods: We included 411 patients hospitalized with chest pain at a teaching hospital and adjudicated all hospitalizations as ACS or non-ACS by two physicians working independently. Blood samples were drawn within 24 h from maximum chest pain symptoms and the average follow-up time was 6 y and 3 m.

Results: In total, 168 patients (40%) were classified as hospitalized with ACS, including 80 patients with acute myocardial infarction. Circulating SN levels were higher in patients with ACS compared to patients with non-cardiac chest pain: (134 [Q1-3 115-155] vs. 123 [106-143] pmol/L, p=0.001), but receiver operating-statistics area under the curve (ROC AUC) was 0.59 [95% CI 0.54-0.65] for SN and 0.83 (0.78-0.87) for high-sensitivity troponin T (hs-TnT) to diagnose ACS. Fifty patients hospitalized with ACS died (30%) and admission SN levels stratified patients with a favorable and poor prognosis (Figure). Adjusting also for demographic variables, previous diseases, and vital parameters, SN was associated with mortality in patients with ACS (hazard ratio 3.41 [1.08-10.77], p=0.02), but not in patients with non-ACS (16 deaths [7%]). In a separate model, adjusting for creatinine and hs-TnT levels, SN was still associated with mortality in patients with ACS: HR 4.22 (1.27-14.03). The ROC AUC for SN to predict mortality in patients with ACS was 0.66 (95% CI 0.57-0.76) and 0.56 (0.37-0.76) in non-ACS.

Conclusions: SN levels provide prognostic information in patients with ACS, but not in patients hospitalized with non-cardiac chest pain.



Abstract 16367: Treatment With Insulin is Associated With Worse Outcome in Patients With Chronic Heart Failure and Diabetes

Franco Cosmi, Li Shen, Michela Magnoli, William T Abraham, Inder S Anand, John G Cleland, Jay N Cohn, Deborah Cosmi, Giorgia De Berardis, Kenneth Dickstein, Maria Grazia Franzosi, Lars Gullestad, Pardeep S Jhund, John Kjekshus, Lars Køber, Vito Lepore, Giuseppe Lucisano, Aldo P Maggioni, Serge Masson, John J McMurray, Antonio Nicolucci, Vito Petrarolo, Fabio Robusto, Lidia Staszewsky, Luigi Tavazzi, Roberto Teli, Gianni Tognoni, John Wikstrand, Roberto Latini

Introduction: Up to a third of patients with type-2 diabetes mellitus (T2DM) and heart failure (HF) are treated with insulin.

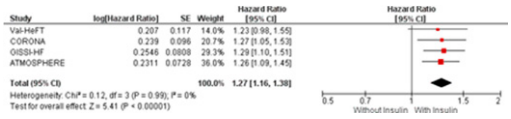
Hypothesis: As insulin causes sodium retention and hypoglycemia, its use might be associated with worse outcomes.

Methods: We investigated survival and hospitalization for HF in two datasets: (1) 24,012 patients with heart failure from 4 large randomized trials and (2) an administrative database of 4 million individuals. In the former, survival was examined using Cox proportional hazards models adjusted for baseline variables and separately for propensity scores. Fine-Gray competing risk regression models were used to assess the risk of hospitalization for HF, with death as a competing risk. For the latter, a case-control study nested within the cohort with propensity score was conducted.

Results: Prevalence of diabetes at study enrollment ranged from 25.5% to 29.5% across trials. Insulin was prescribed at randomization to 24.4% to 34.5% of those with T2DM. All-cause

mortality and hospitalizations for HF were higher in patients with T2DM, particularly in patients prescribed insulin (Figure: propensity score pooled HR for all-cause mortality). In the administrative registry, insulin prescription was associated with a higher risk of all-cause death (OR 2.02 95% CI [1.87-2.19]) and re-hospitalization for heart failure (1.42 [1.32-1.53]).

Conclusions: The reasons why use of insulin is associated with poor outcomes in patients with HF and T2DM needs further investigation. If the association represents an adverse effect of insulin, then consideration should be given to alternative drugs for blood sugar control.



Abstract 16305: A Comparison of Patients Implanted With Cardiac Resynchronization Therapy Pacemaker versus Cardiac Resynchronization Therapy Defibrillator -Results From the European Society of Cardiology Survey II With 11,088 Patients

Camilla Normand

Introduction: Cardiac Resynchronization Therapy (CRT) reduces morbidity and mortality in selected patients with heart failure and electrical dyssynchrony and therefore receives strong recommendations with high levels of evidence in current guidelines. These guidelines are regularly updated based on evidence from Randomized Control Trials. However, there is limited trial evidence available to assess which patients should be implanted with a CRT-P or a CRT-D device. Therefore, the guidelines do not provide clear recommendation regarding choice of device type.

Methods: In 2016, two ESC organisations, HFA and EHRA conducted CRT Survey II, a Survey of CRT implantations in 11,088 patients in 42 ESC member states. We have analysed the results of CRT Survey II to assess similarities and difference between patients implanted with CRT-P and CRT-D.

Results: Patients selected for a CRT-P had generally more co-morbidities including hypertension (67% vs 62% p<0.00001), atrial fibrillation (50% vs 37 % p<0.00001), valvular heart disease (30% vs 26 % p<0.00001), anaemia (18% vs 14% p<0.00001) and chronic kidney disease (35% vs 29% p<0.00001). They were significantly older (median, IQR 75, 67-80 vs 68, 61-74 p <0.00001), had more symptomatic heart failure (NYHA Class III & IV, 64% v 57% p <0.00001) and greater LVEF (%, median, IQR 30 , 25-37 vs 27, 21-31 p<0.00001).

Conclusions: Patients selected for implantation of a CRT-P device have more co-morbidities and more severe heart failure than patients implanted with a CRT-D.

Table 1 CRT Survey II - CRT-D vs CRT-P

	CRT-D	CRT-P	P-value
n	7449	3220	
Age (year, median, IQR)	68 (61-74)	75 (67-80)	<0.00001
Female (%)	21	31	<0.00001
Ischaemic heart failure aetiology (%)	50	33	<0.00001
Past Medical History: (%)			
Myocardial Infarction	41	25	<0.00001
Hypertension	62	67	<0.00001
Atrial fibrillation	37	50	<0.00001
Valvular heart disease	26	30	<0.00001
Obstructive airways disease	12	12	0.83
Diabetes Mellitus	32	30	0.05
Anaemia	14	18	<0.00001
Chronic kidney disease	29	35	<0.00001
Pre-implant clinical evaluation			
NYHA Class III & IV (%)	57	64	<0.00001
LVEF (% median, IQR)	27(21-31)	30 (25-37)	<0.00001
Pre-Implant ECG			
LBBB (%)	75	68	<0.00001
QRS (ms, median, IQR)	160 (142-174)	160 (140-173)	0.00012

Abstract 18119: Mechanical Active Compression-Decompression With LUCAS2AD Provide Equivocal $p_{Et}CO_2$ Values to the Standard LUCAS2 During Out-of-Hospital Cardiopulmonary Resuscitation

Per-Olav Berve, Tore Skålhegg, Bjarne Madsen Hardig, Jonas Carlson, Jo Kramer-Johansen, Lars Wik

Introduction: Studies comparing manual active compression-decompression CPR (ACD-CPR) to manual CPR have shown similar survival rates. Recently a new mechanical ACD-CPR device (LUCAS2AD, Jolife AB/Physio-Control, Lund, Sweden) was compared to the standard LUCAS2 device in pigs, documenting improved hemodynamics. In this first clinical study on mechanical ACD-CPR we hypothesized that it would produce better hemodynamic variables than the standard LUCAS2 device (ClinicalTrials.gov NCT02479152).

Methods: The trial is a prospective block-randomized unblinded study of out-of-hospital cardiac arrest patients >18 years old with anterior-posterior (AP) chest diameter 185-280mm, treated by the physician manned vehicle in Oslo. Inclusion criteria: simultaneous minimum 5 minutes of LUCAS2/LUCAS2AD chest compressions, intubated and side stream pCO_2 measurements. Exclusion criteria: traumatic arrest, pregnancy, imprisonment and previous chest surgery. LIFEPAK 15 data was exported via CodeStat 10 (both PhysioControl, Redmond, WA, USA) to Excel and analyzed by automatic algorithms in MatLab. The primary end-point $p_{ET}CO_2$was collected as the averaged top readings from two consecutive 3-12 seconds long ventilations every 30-second period. Generalized linear mixed model (GLMM) was used.

Results: Of 221 patients enrolled, 211 were analyzed (excluded n=10, (denied consent n=6, various n=4)). Eligible patients for per protocol final inclusion were 133 (LUCAS2 n=64, LUCAS2AD n=69). Intention-to-treat group had AP-diameter (<185mm n=53, >280mm n=2), too short observation period and technical issues (n=23). So far 90% of patient data is analyzed. Averaged $p_{ET}CO_2$: LUCAS2 32.5mmHg (n=61) and LUCAS2AD 31.0mmHg (n=65). GLMM did not reveal significant differences between the devices at any time-point (difference for LUCAS2AD: -1.2mmHg, standard error 2.40, CI -5.94 to 3.54, p=0.62). Calculation with ITT group did not change the result (difference for LUCAS2AD -1.05mmHg, standard error 2.57, CI -6.1 to 4.0, p=0.68). Overall survival was 6.3% (14) patients, all CPC 1 and 44.7% (99) patients had ROSC on arrival to hospital.

Conclusion: Preliminary analysis of $p_{ET}CO_2$ data in the LUCAS2AD trial did not find statistical differences between the two groups.

Abstract 20183: Atherothrombotic Risk Stratification and Magnitude of Benefit of Evolocumab in FOURIER

Erin A Bohula, David A Morrow, Terje R Pedersen, Estella Kanevsky, Sabina A Murphy, Robert P Giugliano, Peter S Sever, Anthony C Keech, Marc S Sabatine

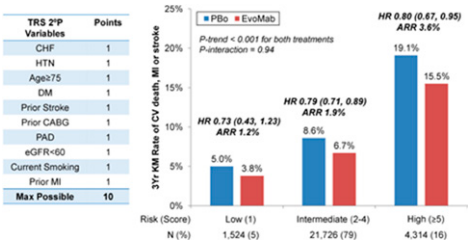
Introduction: Evolocumab (EvoMab) significantly reduced the relative risk of cardiovascular (CV) death, MI or stroke by 20% (absolute risk reduction 2% at 3 years) in patients with atherosclerotic CV disease. However, such patients vary in their risk for CV events.

Hypothesis: Risk stratification with the TIMI Risk Score for Secondary Prevention (TRS 2°P) will identify patients who have the greatest potential for benefit from EvoMab.

Methods: We applied the TRS 2°P prospectively to 27,564 pts with atherosclerotic CV disease and an LDL-C ≥70mg/dL randomized to EvoMab or placebo (Pbo) in FOURIER. The baseline risk as well as the relative and absolute risk reductions in CV death, MI or stroke with EvoMab were calculated by TRS 2°P strata.

Results: The 10-point integer-based scheme showed a strong graded relationship with the rate of CV death, MI or stroke and the individual components (p-trend<0.0001 for all). Intermediate-risk patients (TRS 2°P Score=2-4; 79% of population) had a 1.9% absolute risk reduction (ARR) in CV death, MI or stroke at 3 yrs with EvoMab compared to Pbo alone and high-risk patients (Score≥5; 16%) had a 3.6% ARR, translating to a number-needed-to-treat for 3 years of 53 and 28, respectively (Fig).

Conclusion: The TRS 2°P identifies high-risk patients with atherosclerotic CV disease who demonstrate a pattern of greater absolute risk reduction in major CV events with EvoMab.



Abstract 18347: Prognostic Significance of Activation Delay by Cross Correlation Analysis Using Tissue Doppler Imaging in Patients With Heart Failure and Narrow QRS Duration; an Echocardiography Guided Cardiac Resynchronization Therapy (Echo-CRT) Trial Substudy of Patients Not Randomized to CRT

Bhupendar Tayal, John Gorcsan 3rd, Jeroen Bax, Niels Risum, Niels Thue Olsen, Jagmeet P Singh, William T Abraham, Jeffrey S Borer, Kenneth Dickstein, Daniel Gras, Henry Krum, Josep Brugada, Michele Robertson, Ian Ford, Johannes Holzmeister, Frank Ruschitzka, Peter Sogaard

Introduction: Regional myocardial contraction heterogeneity with activation delay (AD) is observed by echocardiography among patients with heart failure (HF). It is never been investigated whether there is an association of regional AD among HF patients having narrow QRS and long-term outcomes in a prospectively followed population.

Hypothesis: AD by tissue-Doppler cross correlation analysis (CCA) is related to long-term outcome in Echocardiography Guided Cardiac Resynchronization Therapy (Echo-CRT) trial patients not receiving CRT.

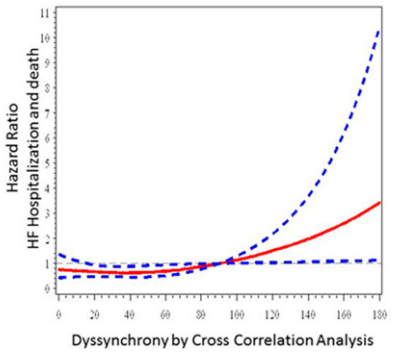
Methods: In Echo-CRT trial HF patients with narrow QRS (<130ms) having moderate to severe symptoms despite optimized medical therapy were included and randomized to CRT-On or CRT-Off in 1:1 fashion. At baseline, CCA could be performed on 404 of the 405 patients originally included randomized to CRT-Off. The primary composite outcome of the study was death or hospitalization due to HF and secondary outcome was hospitalization due to HF.

Results: Restricted cubic spline curve (figure) showed that patients with increased dyssyn-

chrony by CCA had poorer primary outcome. A cut-off of 90ms was determined from the figure. Among the 404 patients, 293 (73%) had lesser AD (< 90ms) by CCA and 111 (27%) had longer AD (≥ 90ms) by CCA. There were no significant difference of baseline characteristics among the two groups. For the primary composite outcome, presence of longer AD (≥ 90ms) by CCA at baseline was associated with poorer prognosis with borderline significance (adjusted HR 1.52, 95% CI 0.99-2.34, p=0.054). However, for the secondary outcome, presence of longer AD (≥ 90ms) by CCA was significantly associated with increased risk of HF hospitalization (adjusted HR 1.60, 95% CI 1.01-2.53, p=0.04).

Conclusions: Assessment of AD by CCA in HF patients with narrow QRS duration can be of prognostic significance.

Restricted Cubic Spline Curve Demonstrating the Association of Dyssynchrony by Cross Correlation Analysis to Study Outcome



Abstract 14975: Thyroid and Glucocorticoid Hormones Promote Functional T-tubule Development in Human Induced Pluripotent Stem Cell Derived Cardiomyocytes

Shan S Parikh, Daniel J Blackwell, Nieves Gomez-Hurtado, Michael Frisk, Lili Wang, Kyungsoo Kim, Christen P Dahl, Theis Tønnessen, Dmytro O Kryshtal, William E Louch, Bjorn C Knollmann

Introduction: Human induced pluripotent stem cells (hiPSCs) are increasingly used for modeling heart disease and are under development for regeneration of the injured heart. Incomplete structural and functional maturation such as a lack of t-tubules, relatively immature excitation-contraction (EC) coupling, and inefficient Ca-induced Ca release (CICR) remains a major limitation.

Hypothesis: Thyroid and glucocorticoid hormones are critical for fetal heart maturation. We *hypothesize* that their addition to standard protocols promotes t-tubule development and EC coupling maturation in hiPSC-cardiomyocytes (CM).

Methods: HiPSC-CMs were generated using a standard chemical differentiation method that was supplemented with triiodo-L-thyronine (T3) and/or dexamethasone (Dex) during days 16-30. Cells were then matured for 5 days on matrigel mattress and studied using confocal microscopy and whole cell patch clamp.

Results: HiPSC-CMs treated with T3+Dex, but not with either T3 or Dex alone, developed an extensive t-tubule network (**Fig 1**). T-tubule density was greater than that found in adult human atrial-CM but below that of adult human ventricular-CM (**Fig 1**). Notably, matrigel mattress was necessary for t-tubule formation (**Fig 1**). Consistent with ventricular-like EC coupling, transverse line scans demonstrated uniform Ca release in T3+Dex cells compared to U-shaped Ca release in control cells. Simultaneous measurement of L-type Ca current and intracellular Ca release confirmed enhanced functional coupling between L-type Ca channels and RyR2 in T3+Dex cells (EC coupling gain 0.15 ± 0.11 vs 0.057 ± 0.05 $\Delta F/F_0/I_{Ca}$, $p < 0.01$).

Conclusions: Our results suggest a permissive role of combined thyroid and glucocorticoid hormones during the cardiac differentiation process which, when coupled with further maturation on matrigel, is sufficient for robust t-tubule development, more ventricular-like EC coupling, and enhanced CICR.

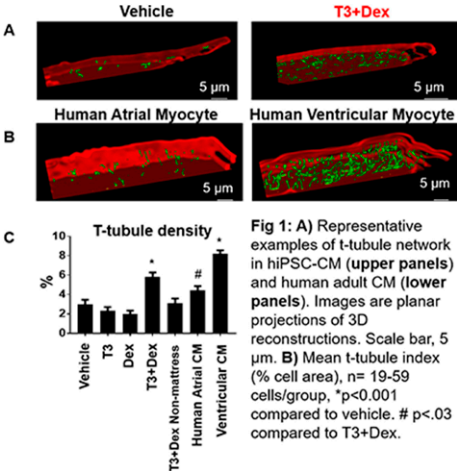


Fig 1: A) Representative examples of t-tubule network in hiPSC-CM (**upper panels**) and human adult CM (**lower panels**). Images are planar projections of 3D reconstructions. Scale bar, 5 µm. **B)** Mean t-tubule index (% cell area), n= 19-59 cells/group, *p<0.001 compared to vehicle. # p<.03 compared to T3+Dex.

Abstract 16714: Characterization of Types and Sizes of Myocardial Infarction Reduced With Evolocumab in FOURIER

Stephen D Wiviott, Robert P Giugliano, David A Morrow, Gaetano M De Ferrari, Basil S Lewis, Kurt Huber, Julia F Kuder, Sabina A Murphy, Danielle M Forni, Christopher Kurtz, Narimon Honarpour, Anthony C Keech, Peter S Sever, Terje R Pedersen, Marc S Sabatine

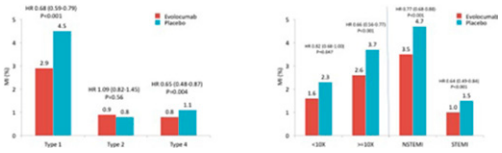
Introduction: The FOURIER trial recently showed that the PCSK9i evolocumab reduced major vascular events compared to placebo in patients with stable atherosclerotic CV disease, including reducing myocardial infarction (MI) by 27%. We investigated the types and sizes of MI in FOURIER.

Hypothesis: Evolocumab reduces spontaneous MI, regardless of size and type (NSTEMI or STEMI).

Methods: 27,564 patients were randomized to evolocumab or placebo and followed for a median of 26 months. Clinical endpoints were evaluated by the TIMI clinical events committee which was not aware of treatment assignment. MI was defined based on the Third Universal MI Definition, and further classified according to MI type (Universal MI subclass, STEMI vs NSTEMI) and by MI size (peak biomarker). Rates presented are 3-year KM estimates.

Results: A total of 1107 subjects had a total of 1288 MIs. The majority (68%) of the MIs were atherothrombotic (Type 1), with 15% supply/demand mismatch MI (Type 2) and 15% PCI-related (Type 4). Sudden death MI (Type 3) and CABG-related MI (Type 5) accounted for a total of 21 MIs (<2%). Evolocumab significantly reduced the risk of first MI by 27% (4.4 vs 6.3%, P<0.001), Type 1 MI by 32% and Type 4 MI by 35%, with no effect on Type 2 MI (Figure, left). Troponin values were available for 1151 MIs. Using fold elevation of Tn, the majority of MIs (689, 60%) were large with Tn ≥10x ULN. One fifth of MIs (238, 18%) were STEMI. The benefit of evolocumab was highly significant and consistent regardless of the size of MI with a 34% reduction in MIs with Tn ≥10x ULN and a 36% reduction in STEMI (Figure, right)

Conclusion: LDL-C lowering with evolocumab was highly effective in reducing the risk of myocardial infarction. This reduction included a robust benefit across multiple subtypes of MI related to plaque rupture, smaller and larger MIs, and both STEMI and NSTEMI. These data are consistent with known the benefit of LDL-C lowering and underscore the reduction in clinically meaningful events.



Abstract 18020: Competitive Athletes With Implantable Cardioverter Defibrillators - How to Program? Data From the ICD Sports Registry

Brian Olshansky, Gourg Atteya, David Cannom, Hein Heidbuchel, Elizabeth Saarel, Ole-Gunnar Anfinsen, Alan Cheng, Michael R Gold, Andreas Müssigbrodt, Kristen Patton, Leslie Saxon, Bruce Wilkoff, Rik Willems, Rachel Lampert

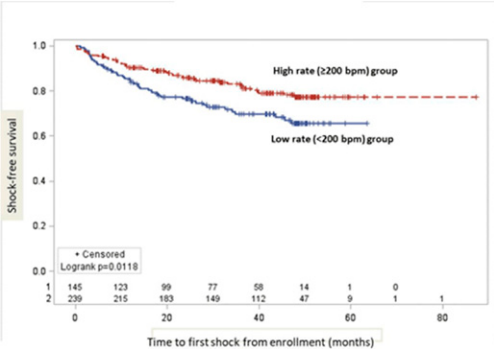
Introduction: Athletes, at risk for sudden cardiac death and who have implantable cardioverter defibrillators (ICDs), represent a unique group, for whom, optimal ICD programming remains uncertain. **Purpose:** To assess the association of ICD programming characteristics with occurrence and outcomes of ICD shocks, syncope, and death in athletes with ICDs.

Methods: A subanalysis of a prospective, observational, international registry of 440 athletes with ICDs followed over a median of 44 months was performed in 384 subjects, in whom, programming was documented (detection duration documented in 178). Programming including high (≥200) vs low (<200) rate cutoff and long (>nominal) vs nominal detection duration were analyzed separately. Endpoints included total, appropriate and inappropriate shocks, syncope and mortality.

Results: 62% were programmed with high-rate cutoff (38% low). 30% were programmed with long detection times (70% nominal). No athlete died from an arrhythmia related to sports (one arrhythmic death occurred at rest). Three subjects had sustained ventricular tachycardia below programmed detection rates (all in the high rate group), and presented with palpitations and/or dizziness. 98 athletes received ICD shocks, of which, 64 received appropriate, 32 received inappropriate and 2 received both. High rate cutoff was associated with fewer total (30% vs 19%, p=0.01) and inappropriate (11% vs 5%, p=0.04) shocks, with similar findings during competition or practice. Long detection duration was associated with fewer total shocks (32% vs 15%, p =0.02). Single vs dual chamber devices and number of tachycardia zones were not related to risk of shocks. Syncope, which occurred with 27 appropriate shocks, was not related to programming characteristics.

Conclusion: High-rate cut off and long detection duration programming of ICDs in athletes can

reduce total and inappropriate ICD shocks without impacting survival or incidence of syncope.



Abstract 18096: Interrelationship Between Reduction in Weight and Adiposity Indices and Improvement in Cardiovascular Death and Heart Failure Outcomes With Empagliflozin in Patients With Type 2 Diabetes in EMPA-REG OUTCOME

Ian J Neeland, Darren K McGuire, Uwe Hehnke, Hans-Juergen Woerle, David Fitchett, Odd Erik Johansen

Introduction: In EMPA-REG OUTCOME®, empagliflozin significantly reduced CV death by 38% and hospitalization for heart failure and HF death by 39%. Whether empagliflozin-mediated reduction in weight and visceral adiposity may partially explain the CV benefits is unknown. We tested the hypothesis that reducing weight and indices of adiposity with empagliflozin could be related to its beneficial effects on CV outcomes.

Methods: 7020 patients with type 2 diabetes at high CV risk were randomized to receive placebo or empagliflozin (10 mg or 25 mg) in addition to standard of care. The relationships between short-term (12 week) changes in weight (kg), waist circumference (WC [cm]), and estimated total body fat (eTBF [%]) and CV death and HF hospitalization/HF death outcomes at study-end were assessed in the placebo and pooled empagliflozin groups by ≥ and < median magnitude of change at 12 weeks.

Results: At baseline, median weight, WC, and eTBF were similar in the placebo and empagliflozin groups (85.0 kg vs 85.1 kg, 104.0 cm vs. 104.0 cm, 31.9% vs 32.0%, respectively). At week 12, greater reductions in all parameters were observed with empagliflozin. The reduction in CV death appeared to be greater with more weight reduction (Table, p-interaction=0.0114), whereas the magnitude of effect on CV death was similar by degree of WC or eTBF reduction.

Table. CV death and HF outcomes by degree of change from baseline in adiposity indices at week 12 with empagliflozin (pooled 10 mg and 25 mg) and placebo.*

		< median change (least reduction from baseline)		≥ median change (greatest reduction from baseline)	
		Placebo	Pooled empagliflozin	Placebo	Pooled empagliflozin
CV death					
By change in weight at week 12 < or ≥ 0.69 kg	n (patients)	1568	1926	750	2747
	n (%) with event	78 (5.0)	83 (4.3)	49 (6.5)	83 (3.0)
	HR (95% CI)	*0.84 (0.62, 1.14)*		*0.46 (0.32, 0.65)*	
	P for interaction	*0.0114*			
By change in WC at week 12 < or ≥ 0.00 cm	N	871	1249	1423	3392
	n (%) with event	47 (5.4)	42 (3.4)	80 (5.6)	123 (3.6)
	HR (95% CI)	*0.62 (0.41, 0.94)*		*0.64 (0.48, 0.85)*	
	P for interaction	*0.9207*			
By change in eTBF at week 12 < or ≥ 0.00%	N	1086	2124	1208	2517
	n (%) with event	56 (5.2)	73 (3.4)	71 (5.9)	92 (3.7)
	HR (95% CI)	*0.68 (0.48, 0.96)*		*0.61 (0.45, 0.83)*	
	P for interaction	*0.6198*			
HF hospitalization or HF death					
By change in weight at week 12 < or ≥ 0.69 kg	n (patients)	1623	2052	680	2604
	n (%) with event	62 (3.8)	57 (2.8)	33 (4.9)	70 (2.7)
	HR (95% CI)	*0.72 (0.50, 1.03)*		*0.54 (0.36, 0.82)*	
	P for interaction	*0.2984*			
By change in WC at week 12 < or ≥ 0.00 cm	N	865	1242	1415	3382
	n (%) with event	38 (4.4)	44 (3.5)	57 (4.0)	80 (2.4)
	HR (95% CI)	*0.81 (0.53, 1.25)*		*0.59 (0.42, 0.82)*	
	P for interaction	*0.2465*			
By change in eTBF at week 12 < or ≥ 0.00%	N	1079	2118	1201	2506
	n (%) with event	46 (4.3)	63 (3.0)	49 (4.1)	61 (2.4)
	HR (95% CI)	*0.70 (0.48, 1.02)*		*0.69 (0.41, 0.87)*	
	P for interaction	*0.5664*			

*Outcomes considering events onwards from day 84 (week 12 measurement), adjusted for change from baseline to day 84 for the marker analysed, pooled empa vs placebo – TS

There was a numerical trend towards a lower hazard for HF hospitalization and HF death with greater reduction in all adiposity indices.

Conclusions: Empagliflozin have a consistent effect on reducing CV death and hospitalization for HF and HF death by degree of weight and visceral adiposity reduction. However, the significant interaction p-value for CV death raises the hypothesis that weight reduction (potentially related to volume loss), rather than fat reduction per se, may contribute to the CV benefit seen with empagliflozin in patients with type 2 diabetes.

Abstract 20483: Characterization of Type B Acute Aortic Dissection Patients With Presenting Spinal Cord Ischemia

Jonathan Silverberg, Thomas G Gleason, Maral Ouzounian, Reed E Pyeritz, Marek P Ehrlich, Takeyoshi Ota, Eduardo Bossone, Stuart Hutchison, Truls Myrmel, Mark D Peterson, Gilbert R Upchurch, Daniel G Montgomery, Eric M Isselbacher, Christoph A Nienaber, Kim A Eagle, Himanshu J Patel

Introduction: Spinal cord ischemia (SCI) is a devastating complication of type B acute aortic dissection (TBAAD). Several studies have focused on TBAAD patients who develop post-procedure SCI, but there is minimal data on TBAAD patients who develop SCI as a consequence of dissection, either pre-procedure or with medical management alone. This study aims to better characterize these patients.

Methods: This study looked at TBAAD patients enrolled in the International Registry of Acute Aortic Dissection (IRAD) with presenting SCI (n=52), defined as those who were either diagnosed with SCI at admission (n=41), were medically managed and developed SCI in-hospital (n=3), or were procedural patients

who developed SCI in-hospital prior to surgery or endovascular therapy (n=8). Clinical factors and in-hospital and post-discharge outcomes associated with SCI were evaluated.

Results: Presenting clinical factors associated with presenting SCI included pulse deficits (46.5% v. 24.8%, p=0.001), ischemic peripheral neuropathy (36.7% v. 2.4%, p<0.001), and ischemic lower extremity (37.5% v. 6.3%, p<0.001). On imaging, abnormal cardiac contour on chest X-ray (36.4% v. 15.4%, p=0.001) and complete abdominal vessel involvement on CT (16.7% v. 6.9%, p=0.010) were also associated with SCI. Stroke (10.6% v. 1.4%, p<0.001), acute renal failure (24.5% v. 13.6%, p=0.031), and limb ischemia (33.3% v. 7.3%, p<0.001) occurred more often in SCI patients. For patients who received surgery or endovascular repair, post-procedure complications were acute renal failure (23.3% v. 5.6%, p<0.001), hypotension (8.7% v. 2.5%, p=0.032), and limb ischemia (8.9% v. 1.8%, p=0.010). Patients with presenting SCI also had significantly increased mortality both in-hospital (19.2% v. 8.4%, p=0.007) and post-discharge (Kaplan-Meier estimates of 5-year survival 47.7% with SCI v. 76.3% without, p=0.020).

Conclusions: We have identified multiple clinical factors that are associated with presenting SCI in TBAAD patients. Furthermore, it was determined that these patients have dramatically worse outcomes than patients who do not develop SCI under these criteria. These findings may help improve clinicians' ability to detect this complication early and intervene when warranted.

Abstract 15975: Multimorbidity is Associated With Greater Risk of Thromboembolism and Bleeding in Patients With Atrial Fibrillation but a Constant Benefit of Apixaban: Results From ARISTOTLE

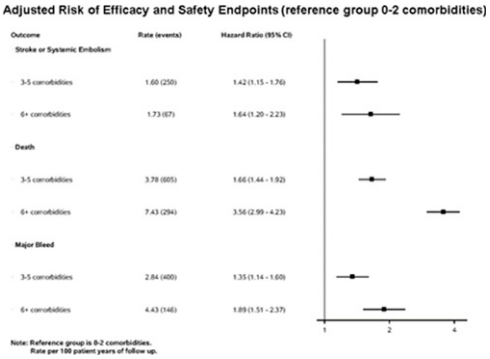
Karen P Alexander, Marc Brouwer, Hillary Mulder, Dragos Vinereanu, Renato D Lopes, Sana M Al-Khatib, Ziad Hijazi, Sigrun Halvorsen, Elaine M Hylek, Freek W Verheugt, John H Alexander, Lars Wallentin, Christopher B Granger

Background: Multimorbidity (MM), defined as ≥3 chronic conditions, is a marker of frailty, polypharmacy, and adverse events. For patients with atrial fibrillation (AF), anticoagulation may pose increased risks with greater MM burden. We assessed prevalence of MM, its association with clinical outcomes, and the efficacy and safety of apixaban and warfarin in the setting of MM.

Methods: ARISTOTLE randomized patients with AF to apixaban or warfarin. Baseline information on 17 different comorbid conditions including endocrine, GI, musculoskeletal, renal, hematologic, pulmonary, cognitive, vascular, and cardiac systems was collected. Enrolled patients age ≥55 years (N=16,800) were divided into groups based on number of conditions; few 0-2 (n=6087, 36.2%), moderate 3-5 (n=8491, 50.6%), and greatest 6+ (n=2222, 13.2%). Median follow-up was 1.8 years.

Results: MM was present in 63%. Compared with those with few comorbidities, the greatest comorbidity group was older (74 vs. 69 yrs), took twice as many medications (10 vs. 5), and had higher predicted stroke risk (CHA_2DS_2-VASc score 4.9 vs. 2.7); all p <0.001. Rates per 100 patient-years of stroke/systemic embolism, death, and major bleeding increased with MM, which was significant even after adjustment for age, sex, race and region (Fig). The benefits of apixaban over warfarin were consistent across range of MM, with less bleeding with apixaban than warfarin in all groups. ICH did not increase across MM groups (data not shown).

Conclusion: Multimorbidty is present in 63% of a contemporary trial population with AF. Although associated with greater risk of stroke/SE, death, and major bleeding, the efficacy and safety of apixaban versus warfarin was consistent even among patients with the greatest number of coexisting conditions. This supports the extension of trial results to community-treated patients with AF who often have greater MM than seen in clinical trials.



Abstract 16738: International Variation in Management and Clinical Outcome of Patients With Type 2 Diabetes and Heart Failure: Insights From TECOS

Ankeet S Bhatt, Nancy Luo, Nicole Solomon, Neha J Pagidipati, Giuseppe Ambrosio, Jennifer B Green, Darren K McGuire, Eberhard Standl, Jan H Cornel, Sigrun Halvorsen, Renato D Lopes, Harvey White, Rury R Holman, Eric D Peterson, Robert J Mentz

Introduction: We evaluated international variations in management and clinical outcome for

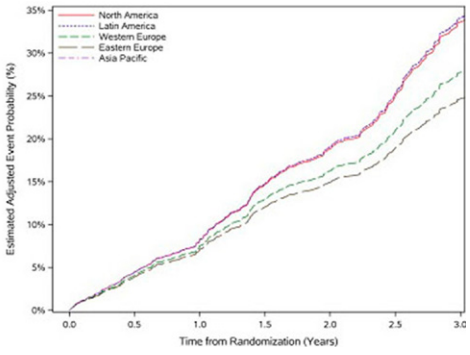
patients with type 2 diabetes and heart failure (HF) by region in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS).

Methods: Among 14,671 TECOS patients, those with a baseline history of HF for whom documented baseline ejection fraction (EF) was available (N=1591) were categorized by geographic region. We examined regional variation in baseline characteristics and clinical outcome (death/HF hospitalization) using adjusted Cox models with North America as the reference cohort.

Results: Of 1591 (10.8%) patients with HF and documented EF, the majority originated from Eastern Europe (Eastern Europe [N=847; 21% of enrolled in region], North America [N=237; 9% of enrolled in region], Western Europe [N=191; 9% of enrolled in region], Asia Pacific [N=162; 4% of enrolled in region], and Latin America [N=154; 10% of enrolled in region]). Most patients had EF≥40% (N=1267, 79.6%). Patients with EF<40% overall had highly prevalent use of beta-blocker (82%) and ACEI/ARB (87%), similar across geographic regions; mineralocorticoid antagonist use ranged from 19% to 37%. A joint test of whether any regions differed from North America in rates of death/HF hospitalization was statistically significant (p=0.004). However, during a median follow-up of 3.0 years, only Eastern European patients had significantly lower event rates (adjusted hazard ratio: 0.47; 95% CI: 0.31-0.72; Figure), largely driven by this region having the lowest HF hospitalization event rate among all regions. No significant difference was found in all-cause death rates.

Conclusions: In patients with type 2 diabetes and HF enrolled in an international clinical trial, variation exists with respect to the prevalence of HF and in the adjusted composite outcome of death/HF hospitalization across regions. These data may inform the design of future global trials that enroll patients with diabetes and HF.

Figure. Adjusted Kaplan-Meier curve of all-cause death or heart failure hospitalization by geographic region (n = 1591)



Abstract 15057: High Level of Adherence to Alirocumab and Concomitant Background Treatments for Patients With Heterozygous Familial Hypercholesterolemia in the ODYSSEY Open-Label Extension Study

Michel A Farnier, G. Kees Hovingh, Gisle Langslet, Robert Dufour, Marie T Baccara-Dinet, Chantal Din-Bell, Garen Manvelian, John R Guyton

Introduction: Non-adherence to lipid-lowering therapies (LLTs) is associated with adverse outcomes in patients with cardiovascular disease. The ongoing ODYSSEY open-label extension (OLE) study (NCT01954394) of four Phase 3 placebo-controlled studies (FH I, FH II, LONG TERM, and HIGH FH) in patients with heterozygous familial hypercholesterolemia (HeFH) is assessing the long-term (up to 40 months) efficacy and safety of alirocumab, a PCSK9 inhibitor.

Objective: To assess the long-term adherence to alirocumab and background LLTs during OLE.

Methods: Patients with HeFH from the four studies entered OLE and received alirocumab 75 mg (FH I, FH II, and LONG TERM patients) or 150 mg (HIGH FH patients) once every 2 weeks regardless of the study treatment received during the parent study. Alirocumab dose adjustment was allowed from Week 12 as per investigators' clinical judgment and patients' LDL-C level. Safety parameters were assessed. Adherence (based on patients' diary data) was defined as 100 - (days [%] with below-planned dosing + days [%] with above-planned dosing). The current analysis focuses on patients who had completed at least 1 year of OLE.

Results: A total of 985 patients (mean age 54.4 years; 44.2% female) were enrolled into OLE and received treatment. At time of analysis, 883 patients (89.6%) were on treatment, 46 (4.7%) had completed OLE treatment, and 56 (5.7%) had prematurely discontinued treatment. Mean exposure to alirocumab was 73.4 weeks. Mean overall adherence to alirocumab was high (98.3%) and most patients (99.6%; n=977/981) were ≥80% adherent. Statin interruptions and discontinuations at any visit were reported in 43/985 (4.4%) and 30/985 (3.0%) patients, respectively. A total of 70/985 patients (7.1%) had statin dose decrease; 43 (4.4%) were due to too low LDL-C levels as per investigators' judgment. Discontinuation of other LLTs was reported in 79/985 patients (8.0%) with 34 (3.5%) discontinuing ezetimibe. A total of 43/985 patients (4.4%) discontinued non-statin LLTs due to too low LDL-C levels as per investigators' judgment. The overall rate of adverse events was 77.4%.

Conclusions: In this ongoing OLE study, mean adherence to alirocumab was high (98.3%). Dose adjustments or discontinuations of statins and other LLTs were low.

Abstract 14465: Obesity Paradox on Outcome in Atrial Fibrillation Maintained Even Considering the Prognostic Influence of Biomarkers: Insights From the ARISTOTLE Trial

Roopinder K Sandhu, Justin Ezekowitz, Ziad Hijazi, Johan Westerbergh, John H Alexander, Christopher B Granger, Sigrun Halvorsen, Michael S Hanna, Renato D Lopes, Lars Wallentin

Background: Studies have shown that obese patients with atrial fibrillation (AF) have a favorable prognosis compared to those with a lower body mass index (BMI); however, the underlying cause for this 'obesity paradox' is unclear. Inflammation is a postulated link between obesity, AF and survival, yet data exploring this relationship remains sparse.

Methods: The ARISTOTLE trial randomized 18,201 patients with AF to apixaban or warfarin. High sensitive C reactive protein (hs-CRP), interleukin 6 (IL-6), growth differentiation factor-15 (GDF-15), troponin T, and N terminal B-type natriuretic peptide (NT-pro-BNP) were analyzed from 14,954 patients. Based on BMI (kg/m^2), 4052 patients were categorized normal (≥ 18.5-25), 6702 overweight (>25-30) and 7159 obese (≥ 30). Outcomes were stroke/systemic embolism (SSE), myocardial infarction (MI), composite (SSE, MI or all-cause mortality), all-cause and cardiac mortality, and major bleeding. Multivariable models were used to estimate hazard ratios (HR) within BMI categories adjusting for established risk factors, study treatment, inflammatory and cardiovascular biomarkers.

Results: Compared to normal BMI, obese patients had higher levels of hs-CRP [median 2.9 mg/L (interquartile range, 1.4-5.8) versus 1.5 mg/L (0.7-3.6)], IL-6 [2.5 ng/L (1.7-4.1) versus 2.2 ng/L (1.3-3.9)] and lower levels of GDF-15 [1328.0 ng/L (946-1981) versus 1491 ng/L (1058-2219)], troponin T [10.7 ng/l (7.4-16.2) versus 11.3 ng/L (7.7-317.1)] and NT-pro-BNP [623 ng/L (324-1070) versus 880 ng/L (443-1545)]. In multivariable analyses, elevated BMI was associated with lower mortality, cardiac death, and composite outcome but not SSE, MI or major bleeding. This relationship remained consistent even after adjustment (Figure 1).

Conclusions: Elevated BMI is associated with reduced mortality regardless of clinical factors or biomarkers indicating inflammation, and myocardial function. The obesity paradox in AF remains unexplained.

Figure 1. Multivariable-adjusted Hazard Ratio (HR) and 95% CI of Outcomes According to Categories of Body Mass Index (BMI).