# NORSKE ABSTRACTS I CHICAGO

*Circulation 2010; 122, Issue 21 Supplement; November 23,*
*From Scientific Sessions 2010*

## 8814: Onset of Systolic Shortening as a Marker of Electrical Dyssynchrony is Modified by Mechanical Function

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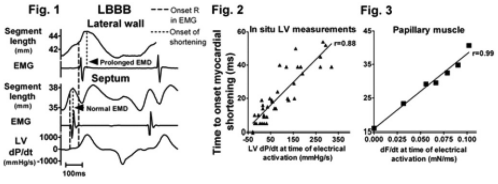
**Background:** In a left bundle branch block (LBBB) dog model we have observed increased delay from regional electrical activation to onset of regional shortening in the late activated lateral wall compared to the early activated septum. We investigated if the apparent increase in electromechanical delay (EMD) is due to a higher load (LVP) or due to a higher rate of rise in LV (dP/dt) at the time of electrical activation.

**Methods:** In 7 anesthetized dogs with LBBB and LV micromanometers we measured electromechanical delay from onset R in intramyocardial electromyograms (EMG) to onset shortening in the septum and LV lateral wall (Fig.1). LVP and LV dP/dt were measured at time of electrical activation. In an in vitro experiment with 5 rabbit papillary muscles, we measured time from activation to onset shortening: at different isotonic loads (F) and at different load rates (dF/dt), simulating the pressure and rate of LVP rise (dP/dt)at the time of activation, respectively.

**Results:** In the dog model there was no significant correlation between EMD and LVP at time of electrical activation (p=0.68), while there was a strong correlation between EMD and LV dP/dt (r=0.88, Fig 2). Similarly, in the papillary muscles, EMD was unaffected by isotonic load, but exhibited a close relationship to dF/dt, with r values ranging between 0.85 and 0.99 in the 5 muscles (Fig 3).

**Conclusions:** The delay from electrical activation to onset shortening depended on the rate of LV pressure rise (dP/dt). These findings suggest that a segment does not shorten until it generates active stress at a rate which is faster than the rate at which the load increases. In late activated segments that start contraction at a higher LV dP/dt, this mechanism causes a further delay in onset of shortening, aggravating mechanical dyssynchrony. This implies that time to onset shortening is modified by LV mechanical function and limits its ability to serve as a measure of electrical delay.



## 16243: Beta-Blocker Therapy Reduce Threshold for Exercise Induced Ventricular Arrhythmias in Patients with CPVT

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**Introduction:** Catecolaminergic polymorphic ventricular tachycardia (CPVT) is an inherited cardiac disease which predisposes to exercise-induced life-threatening arrhythmias. The current therapeutic recommendations are beta-blocker therapy and ICD implantation. We aimed to determine the effect of beta-blocker treatment on exercise-induced arrhythmias in CPVT patients.

**Methods:** A total of 38 CPVT patients were followed for 24 (8–288) months. Of these, 8 were index patients and 30 were mutation positive family members diagnosed by cascade genetic screening. Clinical evaluation including exercise test was performed at inclusion and repeated 3 months after initiation of beta-blocker therapy in maximum tolerable doses. Heart rate and workload at occurrence of ventricular premature beats (VPB), couplets and non-sustained VT (nsVT) were recorded.

**Results:** Exercise-induced arrhythmias were observed in 28 (79 %) patients before treatment. Resting and maximum heart rate during exercise test were reduced by beta-blocker treatment ($p<0.001$) (Table). VPBs and most severe arrhythmias on beta-blocker therapy appeared at 14% and 15% lower heart rate, respectively (both $p=0.01$), but at a similar workload as without beta-blocker therapy (Table). Beta-blocker therapy suppressed nsVT in 4 of 6 mutation carriers ($p=0.02$). Less serious arrhythmias were not affected.

**Conclusion:** Exercise-induced arrhythmias in CPVT patients occurred at lower heart rates on beta-blocker treatment. Beta-blocker therapy suppressed nsVT, while less severe arrhythmias were unchanged. Treatment effect of beta-blocker therapy in CPVT should therefore not be evaluated by occurrence of VPBs at exercise test. These findings suggest that the protective effects of beta-blocker therapy in CPVT patients are not only due to negative chronotrophy.

Results from exercise test before and after start of beta-blocker therapy in 38 CPVT patients

| | Before beta-blocker | On beta-blocker | p-value |
|---|---|---|---|
| Heart rate at rest (bpm) | 69±17 | 55±13 | <0.001 |
| Maximum heart rate during exercise test (bpm) | 174±22 | 140±23 | <0.001 |
| Heart rate for debut of VPB (bpm) | 131±36 | 113±22 | 0.01 |
| Workload for debut of VPB (Watt) | 121±43 | 123±44 | 0.78 |
| Heart rate at most severe arrhythmia (bpm) | 144±30 | 123±20 | 0.01 |
| Non-sustained VT (n) | 6 | 2 | 0.05 |

Mean ± standard deviation. P-value from paired student t-test and Fisher Exact test
Bpm: beats per minute, VPB: ventricular premature beat

## 15062: Aortic Stiffness and ProBNP Are Increased at Term and 6 Months After Pre-Eclamptic Pregnancy

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**Introduction:** Pre-eclampsia (PE) is defined by hypertension and proteinuria and occurs in 3–10% of all pregnancies. The hemodynamic patophysiology of the heart and systemic arteries in these patients have not been well described. Thus, we compared systemic arterial properties to cardiac hormonal status (proBNP) at term and 6 months post-partum in women with PE and in women with normal pregnancy (NP).

**Methods:** 40 women (32 ± 6 years) with PE and 65 (33 ±1 years) with NP were studied. Non-invasive estimates of aortic root flow pressure and pressure were obtained by Doppler and calibrated right subclavian artery pulse trace. Total arterial compliance (C), arterial elastance (end systolic pressure/ stroke volume, Ea), characteristic impedance ($Z_0$), and peripheral arterial resistance (R) were estimated both by use of a 4-element Windkessel model (WK) and by Fourier analysis of pressure and flow data. ProBNP was determined by an electrochemiluminescence immunoassay on a modular platform (Roche Diagnostics, Basel, Switzerland).

**Results:** (Table) At term, in PE pregnancy, $Z_0$, Ea and R were higher and C was lower than in NP, indicating a higher resistance in the entire systemic arterial tree. Furthermore, $Z_0$, Ea and R were maintained elevated at 6 months follow-up in PE underscoring the chronic nature of this disease. Also, in PE pregnancy proBNP was almost three-fold increased at term compared with 6 months follow-up. ProBNP in PE pregnancy at term correlated with the systemic arterial resistance parameters R ($r = -0.442$, $p = 0.007$) and Ea ($r = -0.515$, $p = 0.001$).

**Conclusion:** PE is characterized by an increased systemic arterial proximal and peripheral resistance at term and 6 months post partum, with significantly elevated proBNP levels, also when compared to NP. These results indicate that the

| | At term NP | 6 mo PP NP | At term PE | 6 mo PP PE | P Δ (ΔNP vs ΔPE) |
|---|---|---|---|---|---|
| MAP (mmHg) | 85 ± 7 | 86 ± 7 | 115 ± 9*# | 98 ± 11# | 0.001 |
| HR ($min^{-1}$) | 77 ± 10* | 66 ± 7 | 75 ± 10# | 70 ± 10# | 0.001 |
| CO ($l\ min^{-1}$) | 5.8± 1.1* | 4.9± 0.9 | 6.3 ± 1.2*# | 5.5 ± 1.33 | 0.920 |
| R (mmHg $ml^{-1}$ $s^{-1}$) | 0.92 ± 0.23* | 1.10 ± 0.29 | 1.13 ± 0.23# | 1.13 ± 0.27# | 0.008 |
| $Z_0$ WK ($10^{-3}$mmHg $ml^{-1}$ $s^{-1}$) | 65 ± 24 | 68 ± 22 | 88 ± 24# | 80 ± 30# | 0.039 |
| $Z_0$FD ($10^{-3}$mmHg $ml^{-1}$ $s^{-1}$) | 45 ± 23* | 50 ± 21 | 66 ± 34# | 58 ± 27# | 0.002 |
| C WK (ml $mmHg^{-1}$) | 1.55 ±0.46* | 1.40 ± 0.45 | 1.34 ± 0.43# | 1.40 ± 0.48 | 0.037 |
| C PPM (ml $mmHg^{-1}$) | 1.21 ± 0.33 | 1.14 ± 0.30 | 0.95 ± 0.26*# | 1.06 ± 0.31# | 0.017 |
| Ea (mmHg $ml^{-1}$) | 1.19 ± 0.28 | 1.27 ± 0.28 | 1.49 ± 0.32# | 1.41 ± 0.37# | 0.104 |
| ProBNP (pmol $l^{-1}$) | 5.2±3.6* | 6.8±3.9 | 26.9±30.9*# | 8.7±12.2# | 0.001 |

*p<0.05 vs 6 months, #p<0.05 vs normal pregnancy, FD=frequency domain. PPM= pulse pressure method.

pathophysiological cardiovascular disturbances in PE prevail after pregnancy.

## 19211: Myocardial Connective Tissue Growth Factor (CCN2/CTGF) Improves Infarct Healing and Attenuates Left Ventricular Remodeling after Myocardial Infarction

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**Purpose:** Myocardial CCN2/CTGF is induced in both experimental and human heart failure. However, its pathophysiological role in ischemic heart failure remains unresolved.

**Methods:** Transgenic mice with cardiac-restricted overexpression of CTGF (Tg-CTGF) were compared with nontransgenic littermate control mice (NLC). Myocardial infarction (MI) was induced by ligation of the left coronary artery in Tg-CTGF (n=22) and NLC mice (n=21). Left ventricular (LV) remodeling and cardiac function was assessed after 4 weeks. Area at risk was estimated in separate groups of animals after perfusion with Evans blue dye, and was similar among Tg-CTGF and NLC mice. In addition, serum levels of CTGF (s-CTGF) were measured in 42 patients admitted to hospital for ST-elevation MI, 2 days, 1 week, 2 months and 1 year after percutaneous coronary intervention (PCI). Cardiac MRI was performed at the same time points to determine infarct size and LV ejection fraction (EF).

**Results:** During the 4 weeks follow-up, survival was significantly higher in Tg-CTGF than in NLC mice; 64% vs. 38%, p<0.05. In vivo pressure-volume analysis after 4 weeks revealed preserved cardiac performance in Tg-CTGF mice, as measured by dp/dt max, LV end-diastolic and end-systolic pressures, and cardiac output. End-point analysis after excision of the hearts revealed attenuation of cardiac hypertrophy in Tg-CTGF vs NLC mice (Heart weight/body weight ratio; 5.3±0.2mg/g, n=14 vs 8.0±0.9mg/g, n=9, p<0.05). Also, markers of myocardial remodeling, i.e. myocardial BNP and beta-myosin heavy chain mRNA levels were significantly lower in Tg-CTGF than in NLC hearts. Interestingly, in patients in which s-CTGF levels increased from day 2 after PCI until 2 months after PCI (n=21), infarct healing was significantly improved and LV remodeling attenuated one year after the ischemic event. Consistently, EF was also significantly higher in these patients after one year, as compared to patients with unaltered or decreased s-CTGF levels (n=21).

**Conclusion:** CTGF prevents development of ischemic heart failure in mice, and increase in s-CTGF levels in patients after MI is associated with attenuated LV remodeling and improved cardiac function. These results indicate cardioprotective effects of CTGF in ischemic heart failure.

## 9272: Energy Loss Index as Predictor Of Aortic Valve Events in Asymptomatic Aortic Stenosis Patients - (a Seas Substudy)

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**Background:** Aortic valve area index (AVAI) is routinely used for assessment of aortic stenosis (AS) severity. Pressure recovery adjusted AVAI [energy loss index (ELI)] has been suggested as a superior measure of AS severity. However, its prognostic value has not been assessed in a large, prospective study of initial asymptomatic AS patients.

**Methods:** Cox regression and receiver operating curve (ROC) analysis were used to assess the relation between baseline ELI and rate of aortic valve events (AVE) in 1563 patients with asymptomatic AS (mean age 67±10 years, 39% women) receiving randomized placebo controlled combined simvastatin-ezetimibe treatment in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. AVE was a prespecified secondary end—point (combined cardiovascular death,

aortic valve replacement and hospitalisation for heart failure due to AS progression). Severe AS was identified as ELI and AVAI <0.6 $cm^2/m^2$, respectively.

**Results:** A total of 498 AVE occurred during 4.3 years of treatment. Severe AS by ELI was present in 374 patients. In univariate Cox regression analyses, lower baseline ELI (HR=5.3, CI=3.9–7.4) and AVAI (HR=17.0, CI=10.3–27.8) both predicted higher rates of AVE (p<0.001). In ROC analysis, the area under the curve (AUC) was similar for ELI and AVAI (both AUC=0.32, p<0.001). In multivariate Cox regression analysis, lower ELI predicted higher rate of AVE independent of having severe AS by AVAI (Table).

**Conclusion:** In initial asymptomatic AS patients both AVAI and ELI predict rates of AVE. However, independent of having severe AS by AVAI, ELI gives additional prognostic information.

Table: Multivariate Cox regression analysis of independent predictors of outcome.

| | HR | 95% CI | p-value |
|---|---|---|---|
| AVAI severe | 1.5 | 1.1-1.9 | 0.005 |
| ELI | 3.2 | 2.0-5.1 | <0.001 |
| Treatment | 0.9 | 0.8-1.10 | 0.199 |

## 16289: Global Strain by Strain Echocardiography May Help Risk Stratification of Ventricular Arrhythmias in Patients With Non Ischemic Dilated Cardiomyopathy

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**Background:** Risk prediction of ventricular arrhythmias in patients with non ischemic dilated cardiomyopathy (DCM) is challenging. Guidelines for ICD and CRT-D indications are based on LV ejection fraction (EF) and QRS duration although they are insufficient in arrhythmic risk prediction. Myocardial strain by echocardiography can accurately quantify ventricular function. We therefore hypothesized that global strain may be a marker of ventricular arrhythmias in patients with DCM.

**Methods:** In all, 58 patients with non ischemic DCM were investigated with strain echocardiography. Of these, 11 had arrhythmic events defined as sustained VT or cardiac arrest. QRS duration was recorded from ECG. By speckle tracking echocardiography, global strain was calculated as average peak negative strain from a 16 LV segments model. LVEF and body surface corrected LV mass were assessed from standard echocardiography.

**Results:** Global strain was reduced in DCM patients with arrhythmic events compared to those without (–7.2±5.9% vs. –12.2±5.9%, p=0.02). DCM patients with arrhythmias had higher LV mass and prolonged QRS compared to those without (184±55 $g/m^2$ vs. 149±43$g/m^2$, p=0.03 and 134±39ms vs. 96±31ms, p=0.002). EF did not differentiate between those with and without arrhythmic events (35±16% vs. 41±16%, p=0.28).

**Conclusions:** Global strain, LV mass and QRS duration were markers of arrhythmias in patients with DCM, while EF was not. Global strain by echocardiography may provide added value in risk assessment of ventricular arrhythmias in DCM patients.

## 20066: Reduced Left Ventricular Function in Hodgkin's Lymphoma Long-Term Survivors After Anthracycline Chemotherapy - A Two-Dimensional Speckle Tracking Echocardiographic Study

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**Introduction:** Anthracycline therapy is well known for its cardiac adverse effects. There are, however, few studies for long-term follow-up of left ventricular (LV) function in adult Hodgkin's lymphoma survivors receiving anthracycline. Two-dimensional speckle tracking echocardiography (2D-STE) is an accurate angle-independent modality for quantification of LV function. We hypothesized that anthracycline administered 20 years ago may Results in reduced LV function that could be detected by 2D-STE.

**Methods:** Echocardiography was performed in 47 Hodgkin's lymphoma survivors 22±2 years following successful mediastinal radiotherapy with (n=27) or without (n=20) anthracycline treatment, and in 20 healthy controls. LV function was assessed by LV ejection fraction (EF) and global longitudinal strain, calculated as the average of peak systolic strain by 2D-STE in a 16-segment LV model.

**Results:** The two patient groups received similar dosage of radiation (41±3Gy vs. 41±1Gy, ns). Patients with anthracycline (doxorubicin) treatment received a total dose of 309±92 mg. Global longitudinal strain was reduced in patients receiving anthracycline with mediastinal radiotherapy compared to those receiving mediastinal radiotherapy alone or combined radiotherapy and regimens without anthracycline (–16.1±1.9%

vs. –17.5±1.7%, p<0.05). Both patient groups had reduced strain compared to healthy controls (–20.4±1.7%, both p<0.05). LVEF could not differ between the two patient groups (55±8% vs. 56±6%, ns), but both groups had reduced function compared to controls (62±5%, both p<0.05).

**Conclusions:** Myocardial function was reduced in Hodgkin's lymphoma survivors two decades after successful treatment consisting of mediastinal radiotherapy with or without additional chemotherapy, indicating irreversible myocardial impairment. Despite so-called safe doses of anthracycline administered 20 years ago, patients receiving anthracycline had additional negative long-term effect on LV function.

## 9424: Low In -Treatment HDL Cholesterol Levels Strongly Predict the Development of New Diabetes Mellitus: The LIFE Study

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**Background:** Hypertensive patients are at increased risk of developing diabetes mellitus (DM). Although low baseline HDL levels predict a higher incidence of DM, whether changing levels of HDL over time are more strongly related to the risk of new DM has not been examined..

**Methods:** Incident DM was examined in relation to baseline and in-treatment HDL levels prior to development of DM in 7445 hypertensive patients with no history of DM who were randomly assigned to losartan- or atenolol-based treatment. HDL levels at baseline and each year of testing were categorized into quartiles according to baseline HDL levels.

**Results:** During 4.6±1.2 years follow-up, new DM developed in 520 patients (6.9%). In univariate analyses, compared with HDL >1.78 mMol/L, baseline and in-treatment HDL <1.21 entered as a time-varying covariate identified patients with >5 and >9-fold higher risk of new DM respectively; patients with baseline or in-treatment HDL in the 2nd or 3rd quartiles had intermediate increased risk of DM. In multivariate Cox analyses adjusting for randomized treatment, baseline age, sex, race, prior antihypertensive therapy, body mass index (BMI), serum glucose (and baseline HDL for in-treatment HDL) treated as standard covariates, and in-treatment Cornell product LVH, diastolic and systolic pressure, BMI, hydrochlorothiazide and statin use treated as time-varying covariates, the lowest quartile of in-treatment HDL remained associated with a >9-fold increased risk of new DM whereas the risk of new DM was significantly attenuated for baseline HDL <1.21.

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

## 19856: No Impact of Weight Gain on Blood Pressure and Left Ventricular Mass Variation in Hypertensive Patients with Left Ventricular Hypertrophy: the LIFE Study

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**Background:** Although decrease in body weight (BW) substantially influences blood pressure (BP) reduction, it is unclear whether changes in BW affect BP control and cardiovascular (CV) phenotype in hypertensive subjects with LV hypertrophy (LVH) during systematic treatment to pre-specified BP targets. Thus, we evaluated the relations between changes in BW (ΔBW) and changes in BP and CV phenotype (evaluated as percent changes from baseline values), over 4.8 years of follow-up in participants in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, according to intention-to-treat analysis.

**Methods:** We analyzed data from 8599 treated hypertensive patients with ECG LVH (by Cornell voltage duration product or Sokolow-Lyon voltage) and available follow-up BW measurements (53% women; mean age 67±7 yrs), 788 of whom also underwent echocardiographic exam. The population was divided into tertiles of ΔBW. The highest tertile of increase in BW was compared to the others, by ANCOVA adjusting for age,

gender, diabetes (DM), randomized treatment and prevalent CV disease.

**Results:** The 2847 participants (33%) exhibiting BW gain during follow-up, had slightly lower baseline BW than those maintaining or reducing BW (77±15 vs. 78±15 Kg, p<0.0001), with no significant differences for age, sex, randomized treatment or prevalent DM, obesity or CV disease. Percent decrease in BP (systolic, diastolic and pulse) were nearly identical in the two groups. Similarly, reductions of both Cornell and Sokolow-Lyon were similar, without differences in the prevalence of LVH at the end of the follow-up. In the echo-substudy, no significant differences were found in reduction in arterial stiffness (estimated as pulse pressure/stroke index ratio: –19% in participants who gained BW vs –16% in those who maintained or reduced BW) and LV mass index (–15% vs. –17%). However, increase in stroke index was significantly higher in participants who gained BW (6.2 vs 3.3%, p=0.04).

**Conclusions:** In aggressively-treated hypertensive patients with LVH, in-treatment BW gain is not related to modifications of BP, LV mass or arterial stiffness, whereas it is associated with increase in volume load.

## 10837: Brain Natriuretic Peptide, but Not Calprotectin or the Long Pentraxin 3 Independently Predicts Stroke in Long-Term Follow-up of Patients With Acute Coronary Syndrome.

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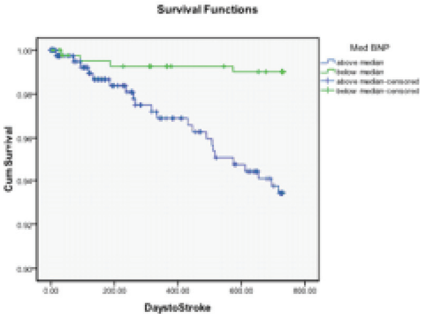
**Background:** Besides its predictive utility for mortality, Brain Natriuretic Peptide (BNP) also predicts stroke in a general population, patients with heart failure and in patients undergoing haemodialysis. Less evidence exists whether BNP or the novel cardiac biomarkers Calprotectin and The Long Pentraxin 3 (PTX3) may predict stroke in patients admitted with acute coronary syndrome (ACS).

**Methods:** Admission BNP, PTX3 and Calprotectin were measured in 795 patients admitted with symptoms suspective of an ACS. Multivariate analysis was performed using a Cox Proportional Hazard Ratio model. Variables included in the model were BNP, Calprotectin, PTX3 and 18 conventional risk factors for cardiovascular disease including heart failure, hypertension and hs-CRP.

**Results:** 27 out of 795 patients had an incident of stroke during the follow-up time of two years. Admission level of BNP above the median (median 95pg/mL) significantly predicted stroke (HR 6.7; 95% CI 2.3–19.6, p<0.001, KM survival plot displayed in figure). Following adjustment in the multivariate analysis, BNP remained an independent predictor for stroke (HR 3.2; 95% CI 1.0–9.7, p<0.05). In contrast, neither Calprotectin nor PTX3 provided independent prognostic information for stroke.

**Conclusions:** Admission level of BNP but not of Calprotectin or PTX3 independently predicts stroke in long term follow-up of patients admitted with chest pain suspective of an ACS.




## 16790: Hematopoietic Nampt Overexpression Impairs Monocytic Differentiation and Polarization Towards Ccr2high Phenotype, pPeventing Atherosclerosis Progression

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Visfatin is a ubiquitously expressed enzyme originally viewed as a proinflammatory adipokine, the recent notion that it is identical to NAMPT, a key molecule in the salvage pathway of the $NAD^+$/NADH biosynthesis, has considerably widened its physiological impact. As NAMPT serum levels were recently shown to be elevated in patients with unstable angina pectoris. Herein, we have examined the potential pathogenic role of NAMPT in atherosclerosis *in vivo* and *in vitro*. LDLr–/– chimeras were generated with lentiviral NAMPT overexpression in the hematopoietic lineage and effects were determined on leukocyte differentiation and activation as well as on plaque development. In keeping with its presumed anti-

apoptotic effect, neutrophils and macrophages from mice with superphysiological NAMPT expression (+43%; P<0.01) were less apoptotic compared to the control group (–40 % and –15% respectively; p<0.05). Moreover NAMPT overexpression appeared to sensitize myeloid precursors not only to G-CSF (+52%; p= 0.009), but also to GM-CSF (+34%; p= 0.03). Remarkably, the number of circulating granulocytes LY6G$^{high}$ was unchanged by NAMPT overexpression, while CD11b+ monocyte numbers were even reduced (–51%; p=0,036). Monocytes of mice with NAMPT overexpression were polarized towards a Ly6C$^{low}$ phenotype and showed decreased CCR2 expression (–39.8%; p=0.02). Despite these profound effects, total intima area and plaque cellularity were unchanged upon NAMPT overexpression, while plaque collagen content did not differ between groups as well. However, reconstitution with NAMPT overexpressing bone marrow resulted in a sharp reduction in necrotic core size (–46%; P=0.0001, n=10) and in plaque apoptosis (–56%; P<0.001) compared to the control, while plaque macrophage content was also significantly reduced (–60%, p= 0.0002, n=10), consistent with the aforementioned anti-apoptotic and monocytopenic activity of NAMPT.

In conclusion, we are the first to demonstrate profound phenotypic effects of hematopoietic NAMPT overexpression on monocytic differentiation, survival and atherosclerosis, identifying this longevity gene as a promising target for therapeutic intervention in inflammation related disorders such as atherosclerosis

## 12990: Dephosphorylation of the Z-Disc Protein Syndecan-4 Activates Pro-Hypertrophic Calcineurin-NFAT Signaling in the Myocardium

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The signaling mechanisms involved in myocardial hypertrophy are poorly understood. We have previously linked syndecan-4, a transmembrane proteoglycan localized to the Z-discs and focal adhesions in cardiomyocytes, to myocardial hypertrophy. Mice lacking syndecan-4 do not develop concentric hypertrophy after aortic banding (AB). Here we demonstrate that syndecan-4 anchors and activates the pro-hypertrophic calcineurin A-Nuclear Factor of Activated T-cells (CnA-NFAT) signaling pathway. In syndecan-4 KO AB, NFATc4 activation and expression of NFAT-target genes BNP and RCAN1–4 were significantly lower than in WT AB. Conversely, overexpression of syndecan-4 in HEK293 cells and treatment of cardiomyocytes with a cell-permeable syndecan-4- derived peptide activated NFATc4. Immunoprecipitations showed increased association between CnA, its co-activator calmodulin and syndecan-4 in AB hearts compared to sham-operated controls. Peptide array experiments showed that CnA binds to the cytoplasmic V-C2 region of syndecan-4 through its autoinhibitory domain. Cell permeable V- or C2-region peptides inactivated or activated NFATc4, respectively, while a C1-derived peptide had no effect, suggesting that syndecan-4 both anchors (V-region) and activates (C2-region) CnA. Moreover, we show that phosphorylation of serine 179 (pS179) is reduced in aortic stenosis patients and in AB murine hearts compared to controls. More CnA was pulled down with non-phosphorylated syndecan-4 than with the phosphorylated form, indicating that reduced pS179 in syndecan-4 is involved in the hypertrophic response. Accordingly, pull-down with pS179 resulted in reduced binding of CnA. Activation of NFATc4 occurred in HEK293 cells transfected with a mutant mimicking minimally phosphorylated S179 (S179A), whereas a mutant mimicking constitutive phosphorylation (S179E) did not. Finally, overexpression of CnA in HEK293 reduces pS179, indicating that CnA regulates its own binding and activation by syndecan-4. Our data indicate that in a pressure-overloaded heart, syndecan-4 activates pro-hypertrophic CnA-NFATc4 signaling, and suggest a crucial role for phosphorylation of syndecan-4 and the syndecan-4-CnA interaction in development of myocardial hypertrophy.

## 88: Changes in Chest Compression Force Required to Achieve Adequate Compression Depth Throughout a Cardiac Arrest Resuscitation Event

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**Background:** A recent study demonstrated decreases in compression depth over time suggesting rescuer performance decay, but remodeling of the chest secondary to compressions has not been excluded as a potential explanation. CPR is known to induce trauma, including broken ribs and pulmonary hemorrhage. Yet, the effects of these changes on chest wall compliance, and therefore the force required to achieve the same depth of chest compressions, is unknown.

**Objective:** To measure differences in the elastic force required to generate the same compression depth over time during actual in-hospital CPR.

**Methods:** Consecutive index adult in-hospital cardiac arrests from a single academic medical center were enrolled between June 2007 and May 2010, which were recorded using a CPR-sensing defibrillator (MRX with QCPR, Philips Healthcare). Cases were included if they had concurrently available accelerometer and force data, lasted more than 10 minutes, and had an average accelerometer displacement of at least 50 mm (to offset the expected mattress compression component of displacement). Data from each case were analyzed in 5 minute blocks, comparing elastic force required to reach 50 mm depths throughout the resuscitation.

**Results:** Fifty patients met inclusion criteria. The average age was 60±17 and 16(32%) were men. 27(54%) occurred in the ICU and the average BMI was 27.4±7.9 kg/m$^2$. The average elastic force required to achieve an accelerometer displacement of 50 mm was 23.1±4.8 kg, and did not vary significantly over time in unadjusted analysis (see Figure). Paired analyses and cluster-adjusted multivariable logistic regression accounting for patient characteristics confirmed these results.

**Conclusions:** The elastic force required to achieve adequate chest compression depth does not significantly change over time. This supports the notion that measured decreases in compression depth over time are a product of rescuer performance decay and not changes in chest wall dynamics.

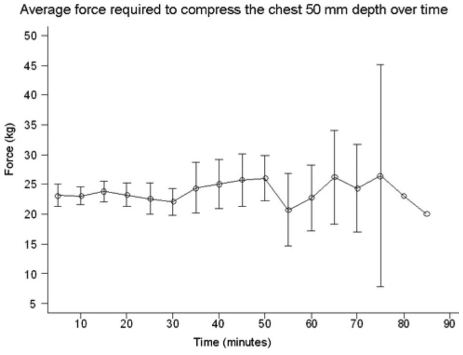


Table 1

| | Prediction of improvement of EF (> 10%) | | | |
|---|---|---|---|---|
| Parameters | Area under the ROC-curve | Cutt-off value | Sensitivity | Specifity |
| EF (%) | AUC = 0.64; p = n.s. | - | - | - |
| LVEDd (mm) | AUC = 0.77; p = 0.01 | < 69 | 73 % | 71 % |
| LV volume (ml) | AUC = 0.79 ; p = 0.013 | < 208 | 81 % | 64 % |
| QRS-Duration (ms) | AUC = 0.73; p = 0.029 | < 110 | 70 % | 60 % |
| S (%) | AUC = 0.33; p = n.s. | - | - | - |
| SRs (1/s) | AUC = 0.40; p = n.s. | - | - | - |
| SRe (1/s) | AUC = 0.85; p = 0.009 | > 0.62 | 88 % | 70 % |

## 8921: Prediction of Response to Heart Failure Therapy in Patients With Dilated Cardiomyopathy: A Two-Dimensional Ultrasound Speckle Tracking Study.

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**Backround:** The aim of the study was to assess the value of newer echocardiographic parameters of regional myocardial function for prediction of response to heart failure therapy in patients with dilated cardiomyopathy (DCM).

**Methods:** Fourty-five patients (mean age 48 ± 14 years) with DCM, defined as ejection fraction (EF) < 45 %, left ventricular (LV) enddiastolic diameter (LVEDd) > 27 mm/m$^2$BSA and normal coronary angiogram, underwent echocardiograpic examination. EF, LVEDd and endiastolic LV volume were measured. Greyscale cine-loops were obtained from three apical views (4-chamber, 2-chamber and apical long axis). Based on two-dimensional ultrasound speckle tracking echocardiography following parameters were extracted: strain (S), systolic (SRs) and diastolic strain rate (SRe). The parameters were expressed as mean values between all views. In all patients an acute or chronic active myocarditis was excluded by ECG, troponin I and myocardial biopsy. After receiving heart failure therapy for more than 6 months (mean 15 , range 6 — 31) an improvement of EF (> 10 %) was observed in 15 patients. In 26 patients optimal medical treatment did not lead to an increase in EF. Four patients, who received a CRT pacemaker, were excluded.

**Results:** The area under the ROC-curves of different parameters are displayed in table 1.

**Conclusions:** In this small, prospective study, SRe, which measures regional diastolic relaxation, was the best predictor of response to heart failure therapy in patients with DCM, being superior to LV dimensions and QRS duration. Parameters of systolic deformation (S and SRs) failed to predict improvement of LV function.

## 19027: Influence of Intravenous Ferric Carboxymaltose on Health-Related Quality of Life Measures in Patients with Chronic Heart Failure and Iron Deficiency: an Analysis from the FAIR-HF Study

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**Background:** Patients with chronic heart failure (CHF) show impaired health-related quality of life (HRQoL), which is an important target for therapeutic intervention. Impaired iron homeostasis may be one mechanism underlying the poor physical condition of CHF patients. This analysis of the FAIR-HF trial evaluated baseline HRQoL of iron-deficient CHF patients, and the effect of iron repletion using intravenous ferric carboxymaltose (FCM) on HRQoL.

**Methods:** The FAIR-HF trial randomized 459 CHF patients with impaired left ventricular ejection fraction and iron deficiency with or without anemia, to FCM or placebo (2:1). A total of 449 patients had evaluable HRQoL data at baseline. HRQoL was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the generic EQ-5D questionnaire (Visual Analogue Scale) at baseline and after 4, 12, and 24 weeks of therapy. In both, higher scores mean better HRQoL.

**Results:** HRQoL was poor at baseline (mean VAS 54.3±16.4; KCCQ overall summary score: 55.9±18.7) compared to previously published, age-matched reference population data (mean VAS: 79.8±17.5). FCM significantly improved HRQoL measures at all time points (mean differences from baseline in KCCQ overall, clinical and total symptom scores: all p<0.001 vs placebo). FCM improved all KCCQ domain mean scores from week 4 (p=0.05), except for the self-efficacy domain. EQ-5D scores also revealed the positive impact of FCM vs placebo on HRQoL. The VAS general health score was improved at weeks 4, 12 and 24 in response to FCM (all p<0.001 vs placebo). FCM resulted in significant improvements in 4 of the 5 EQ-5D dimensions (mobility: p=0.006, self-care: p<0.001, pain/discomfort: p=0.010, anxiety/depression: p=0.016, usual activity: p=0.09, all vs placebo). FCM improved HRQoL in CHF patients both with and without anemia (p-values for interaction: 0.93 [VAS] and 0.66 [KCCQ overall score]).

**Conclusions:** Health-related quality of life in iron-deficient patients with chronic heart failure is impaired, making it an important therapeutic target. Intravenous ferric carboxymaltose resulted in significant improvements of quality of life during 24 weeks of therapy. The positive effects were seen already after 4 weeks of treatment and were independent of anaemia status.

## 9064: Lower Achieved Systolic Pressure (≤130 mm Hg) is Not Associated With Improved Outcomes in Hypertensive Patients With Electrocardiographic Left Ventricular Hypertrophy: The LIFE Study

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**Background:** Hypertensive patients with ECG left ventricular hypertrophy (LVH) are at increased risk of cardiovascular (CV) morbidity and mortality. Although regression of ECG LVH is associated with improved CV outcomes in these patients, whether more aggressive reduction of systolic blood pressure (SBP) is associated with greater reduction of CV risk is unclear.

**Methods:** Risk of stroke, myocardial infarction, CV death, the composite endpoint of these events and all-cause mortality was examined in relation to in-treatment SBP just prior to event in 9193 hypertensive patients with ECG LVH randomly assigned to losartan- or atenolol-based treatment. Patients with in-treatment SBP ≤130 mm Hg (lowest quintile at last measurement) and SBP between 131 and 141, were compared with patients with in-treatment SBP ≥142 (median SBP at last measurement).

**Results:** In univariate analyses, compared with in-treatment SBP ≥ 142, in-treatment SBP between 131 and 141 entered as a time-varying covariate identified patients with significantly lower risk of all events. In contrast, patients with SBP ≤130 had less reduction in MI, stroke and composite endpoint and no significant decrease in CV or all-cause mortality. In multivariate Cox analyses adjusting for treatment, Framingham risk score and in-treatment diastolic BP and Cornell product LVH, SBP of 131 to 141 remained

associated with a decreased risk of all endpoints. In contrast, patients who achieved a SBP ≤130 had no significant reduction in risk of MI, stroke or composite endpoint, had a trend to increased CV mortality and a statistically significant 29% increased risk of death.

**Conclusions:** Achieved SBP ≤130 is not associated with lower CV risk than SBP of 131 to 141 and is associated with a significantly increased risk of death and trend towards increased CV mortality. These findings suggest that treating hypertensive patients with ECG LVH to lower SBP goal may not improve outcome and may be associated with an increased risk of death.

## 9199: Racial Differences in Incident Atrial Fibrillation Among Hypertensive Patients During Antihypertensive Therapy: The LIFE Study

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**Background:** Blacks have a higher prevalence of risk factors for atrial fibrillation (AF) than non-blacks, such as hypertension, obesity and heart failure. Although a recent study found a significantly lower AF incidence in blacks during 17 year follow-up of a population cohort, the relationship of new AF to race in hypertensive patients during aggressive blood pressure lowering has not been examined.

**Methods:** Incident AF was examined in 518 black and 8313 non-black hypertensive patients with no AF by history or on a baseline ECG who were randomly assigned to losartan- or atenolol-based treatment.

**Results:** Compared with non-blacks, blacks were younger, more obese, more likely to be male, smoke, have diabetes, a history of ischemic heart disease and stroke, had higher baseline serum creatinine and albuminuria, less severe baseline left ventricular hypertrophy (LVH) by Cornell product criteria and more severe LVH by Sokolow-Lyon voltage. During 4.7±1.1 years mean follow-up, new AF occurred in 701 patients (7.9%); 5-year AF incidence was significantly lower in black than non-black patients (6.1 vs 8.3%, p=0.027). In univariate Cox analyses, black race was associated with a 37% lower risk of new AF (HR 0.63, 95% CI 0.45.1.00, p=0.05). In multivariate Cox analyses adjusting for randomized treatment, age, sex, body mass index, diabetes, history of heart failure, MI, ischemic heart disease, stroke, peripheral vascular disease, smoking status, baseline serum total and HDL cholesterol, creatinine, glucose, urine albumin/creatinine ratio and for incident MI, in-treatment heart rate, diastolic and systolic pressure, Cornell product and Sokolow-Lyon voltage criteria for LVH treated as time-varying covariates, black race remained associated with a 45% decreased risk of developing new AF (HR 0.55, 95% CI 0.35–0.87, p=0.011).

**Conclusions:** Incident AF is substantially less common among black than non-black hypertensive patients. The lower risk of developing AF in black patients persists after adjusting for the higher prevalence of AF risk factors in blacks, treatment effects, in-treatment blood pressure and the known predictive value of in-treatment ECG LVH and heart rate for incident AF in this population.

## 10255: Resting Heart Rate as Predictor for Development of Heart Failure and Left Ventricular Dysfunction: The Multi-Ethnic Study of Atherosclerosis

***Anders Opdahl; Veronica R Fernandes; Colin O Wu; Khurram Nasir; Eui-Young Choi; Andre L Almeida; Boaz Rosen; Thor Edvardsen; Benilton S Carvalho; David A Bluemke Joao A Lima. Johns Hopkins Univ, Baltimore, MD; Harvard Med Sch, Boston, MA; National Heart, Lung and Blood Institute, Bethesda, MD; Johns Hopkins Univ, Baltimore, MD; Univ of Utah Sch of Medicine, Salt Lake City, UT; Oslo Univ Hosp, Rikshospitalet, Oslo, Norway; Univ of Cambridge, Cambridge, United Kingdom; National Institute for Biomedical Imaging and Bioengineering, Bethesda, MD; Johns Hopkins Univ, Baltimore,MD;***

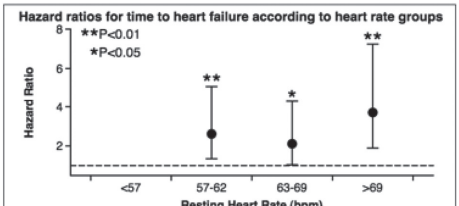
**Background:** Resting heart rate (RHR) has been introduced as a predictor for heart failure (HF) in patients with cardiovascular (CV) disease. However, this association is not well described in an asymptomatic multi-ethnic population of both genders. This study investigates the relationship between baseline RHR and to development of HF and left ventricular (LV) dysfunction.

**Methods:** Participants in the Multi-Ethnic Study of Atherosclerosis (MESA, n=6814) had RHR measured at inclusion. Incident HF was registered (n=139) during follow-up (median 5.8 years). Changes in ejection fraction (EF) and peak circumferential strain (Ecc) were measured as markers of developing global and regional LV function in 1056 participants imaged at baseline and 5 years later. Time to HF (Cox model) and changes in Ecc and EF (multiple linear regression

models) were adjusted for age, gender, ethnicity, exercise- and education level, alcohol- and cigarette use, body mass index, height, blood pressure, diabetes, cholesterol, calcium score, LV end-diastolic volume and mass, and medication (incl. beta-blockers) in addition to RHR.

**Results:** The Cox analysis demonstrated that for 1 bpm increase in RHR there was a 4% increase in adjusted relative risk for incident HF (Hazard Ratio, 1.04; 95% CI, 1.02 to 1.07; P<0.001). Importantly, for the highest quartile in RHR we observed a threefold increase in adjusted relative risk for incident HF (Figure), when compared to the lowest quartile. Adjusted multiple regression models demonstrated that RHR was positively associated with deteriorating Ecc and EF, even when all CV events were excluded from the model.

**Conclusions:** Elevated resting heart rate is associated with increased risk for incident heart failure in asymptomatic participants in MESA. Furthermore, higher heart rate is related to development of regional and global LV dysfunction independent of subclinical atherosclerosis and clinical cardiovascular events.




Hazard ratios (95% CI, adjusted model) relative to heart rate <57 bpm. Horizontal line indicates hazard ratio=1.

**Multivariate analysis for heart rate vs. change in LV function**

| | Change in Regional LV Function (Ecc): | | | Change in Global LV Function (EF): | | |
|---|---|---|---|---|---|---|
| | B* (95% CI) | P | $R^2$ | B* (95% CI) | P | $R^2$ |
| Entire MRI Cohort | 0.04 (0.02, 0.06) | 0.001 | 0.42 | -0.09 (-0.14, -0.04) | 0.001 | 0.27 |
| MRI Cohort Excluding CV Events | 0.04 (0.02, 0.07) | <0.001 | 0.43 | -0.09 (-0.14, -0.04) | 0.001 | 0.29 |

*Regression coefficients (adjusted models) are the corresponding change in Ecc or EF per 1-bpm changes in resting heart rate.
Baseline Ecc and EF were added in models for changes in Ecc and EF, respectively.
LV-Left Ventricular, MRI-Magnetic Resonance Imaging, CV-Cardiovascular.

## 10412: Calpain-10 Genetic Variants Interact with Plasma Saturated Fatty Acid Levels to Influence Insulin Resistance in Patients with Metabolic Syndrome

***Pablo Perez-Martinez; Javier Delgado-Lista; Antonio Garcia-Rios; Hanne L Gulseth; Olfa Helal; Audrey C Tierney; Ulf Riserus; Ellen E Blaak; Beata Kie Ć-Wilk; Julie A Lovegrove; Helen Roche Jose Lopez-Miranda. Reina Sofia Univ Hosp, Maimonides Institute for Biomedical Rsch at Cordoba (IMIBIC), Univ of Cordoba, Ciber Phyisiopatology of Obesity and Nutrition, Cordoba, Spain; Institute of Basic Med Sciences, Faculty of Medicine, Univ of Oslo, Oslo, Norway; Univ Méditerranée Aix-Marseille 2, Faculty of Medicine, Marseille, France; UCD Sch of Public Health and Population Science, UCD Conway Institute, Univ College Dublin, Dublin, Ireland; Dept of Public Health and Caring Sciences, Uppsala Univ, Uppsala, Sweden; Nutrition and Toxicology Rsch Institute Maastricht (NUTRIM), Maastricht, Netherlands; Jagiellonian Univ Med College, Krakow, Poland; Hugh Sinclair Unit of Human Nutrition, Univ of Reading, Reading, United Kingdom; UCD Sch of Public Health and Population Science, UCD Conway Institute, Univ College Dublin, Dublin, Ireland; Reina Sofia Univ Hosp, Maimonides Institute for Biomedical Rsch at Cordoba (IMIBIC), Univ of Cordoba, Ciber Phyisiopatology of Obesity and Nutrition, Cordoba, Spain***

**Introduction:** Calpain-10 protein may play a role in glucose metabolism, pancreatic beta-cell insulin secretion and regulating thermogenesis. Several CAPN10 polymorphic sites have been studied for their potential use as markers for type 2 diabetes mellitus and metabolic syndrome (MetS). Dietary fat is a key environmental factor, which may interact with genetic factors to affect glucose metabolism. Hypothesis: We hypothesized that genetic variations affecting the activity and/or expression of calpain-10 in humans could be associated with variability in insulin response to dietary fat. Thus, our aim was to examine whether the genetic variability at the CAPN10 gene locus is associated with the degree of insulin resistance to dietary plasma fatty acid in MetS patients.

**Methods:** Insulin sensitivity (HOMA-IR, glucose sensitivity, insulin sensitivity index), insulin secretion (disposition index, acute insulin response, HOMA-B), plasma fatty acid composition and five CALPN10 SNPs were determined in a cross-sectional analysis of 430 patients with MetS participating in the LIPGENE dietary intervention cohort (NCT00429195).

**Results:** Gene-nutrient interactions were detected. In the whole cohort, the rs2953171 SNP interacted with plasma saturated fatty acids (SFA) to significantly associate with insulin resistance. Among subjects with low SFA consumption (below the median), the minor A allele was associated with higher fasting insulin concentration (P<0.031) and HOMA-IR (P<0.028), and lower glucose sensitivity (P<0.013) compared with the GG genotype. In contrast, subjects carrying the A allele with the highest consumption of SFA (above the median) showed lower fasting insulin and HOMA-IR, and higher glucose sensitivity compared with the GG genotype. There were no significant interactions between other

plasma fatty acid variables and CAPN10 SNPs on glucose metabolism.

**Conclusions:** This study supports that certain polymorphism at the CAPN10 gene locus may influence insulin resistance by interacting with plasma fatty acid composition in MetS patients. Further investigation of these novel associations and gene-nutrient interactions may help to improve therapeutic efficacy of dietary recommendations with a 'personalised nutrition' approach.

## 15262: Preserved Sublingual Microcirculation and Compensatory Up-regulated Liver and Kidney Mitochondrial Respiration in Pigs with Myocardial Ischemia and Cardiogenic Shock

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**Objectives:** Microcirculatory and cellular derangements leading to organ failure following cardiogenic shock (CS) are poorly understood. We aimed to elucidate the metabolic, microcirculatory and mitochondrial responses following 14 ± 1 hours of global hypoperfusion from severe myocardial ischemia. Model: Cardiogenic shock was induced in pigs (n=8–10, mean ± SEM) by left coronary microembolization. Hemodynamics and organ-specific metabolism were assessed by intravascular catheters, sublingual microcirculation by sidestream dark field imaging, in vitro mitochondrial respiration by oxygraph and mitochondrial free radicals production (ROS) by confocal microscopy.

**Results:** Hemodynamic shock was evident by an alteration in MAP (mmHg), MPAP (mmHg), HR (bpm), CO (L/min) and SVO2 (%) from pre-ischemic values of 87 ± 6, 22 ± 1, 75 ± 4, 5.0 ± 0.3 and 57 ± 2 compared to 54 ± 5, 35 ± 2, 148 ± 15, 3.3 ± 0.3 and 29 ± 3 approximately fourteen hours after ischemia. Sham operated animals (n= 6) had stable hemodynamics. Despite acute heart failure, microcirculation was unaltered at 24 ± 1 mm/mm2 (perfused capillary density), concomitant with an excessive metabolic oxygen extraction exemplified by a hepatic vein oxygen saturation fall from 37 ± 2 (pre-ischemia) % to 13± 4 % (post-ischemia; $P < 0.01$). ADP stimulated (state III) mitochondrial respiration from kidney and liver was increased in CS (92 ± 9 and 81 ± 4) compared to sham animals (61 ± 8 and 55 ± 4; nmol O2/min/mg; $P < 0.05$). Mitochondrial viability (RCR) and efficiency (ATP/O-ratio) in the liver and kidney was unaffected. In mitochondria harvested from the ischemic left ventricle however, state III, RCR and ATP/O were all impaired (150 ± 41, 4.0 ± 1.0 and 2.2 ± 0.3) compared to sham animals (213 ± 16, 7.1 ± 0.8 and 2.9 ± 0.1; $P < 0.05$). ROS production in mitochondria from liver, kidney and heart was elevated in CS animals (59 ± 19, 28 ± 5 and 99 ± 26) compared to sham (40 ± 8, 18 ± 3 and 37 ± 10).

**Conclusion:** A preserved microcirculation and a compensatory enhanced respiration in both liver and kidney mitochondria were evident in our pig model of CS, without vasoactive drug support. This suggests that the intrinsic organ and cellular regulatory responses are compensatory and protective even after several hours of global hypoperfusion.

## 15392: Not Lost in Translation - An International Multicenter Study of Concordance of Diastolic Function Evaluation After the Publication of Guidelines

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**Background:** Echocardiographic assessment of diastolic function is prognostically important but also complex. Recent guidelines have sought to standardize this assessment but the impact of guidelines on observer concordance is undefined. We sought the interpretation of diastolic class and assessment of filling pressure.

**Methods:** 20 consecutive pts were identified with complete diastolic evaluation (transmitral flow, LA volume, tissue Doppler, pulmonary venous flow, mitral flow propagation, LV images), and interpreted by 11 experts in 7 countries (220 case reads). Each investigator was asked to interpret diastolic class and LV filling pressure. Concordance was assessed as kappa and accuracy was compared to specific application of the ASE guidelines by one investigator.

**Results:** For recognition of raised filling pressure, complete agreement between all readers was obtained in 10 of 20 cases, and the sensitivity and specificity were similar (Table). Diagnosis of normal and categories of abnormal filling were cor-

rect in from 71–95%, with similar results for US and non-US readers (Table). Variations appeared to be attributable to differences in weighting of conflicting observations. Overall, kappa values for filling pressure was 0.71 (range 0.60–0.80) and for class was 0.68 (range 0.54–0.86)

**Conclusions:** Correct results for estimation of filling pressure are obtained in a high proportion of readers, irrespective of location. Classification of diastolic stage continues to be variable and might be addressed by provision of a uniform hierarchy of observations.

## 19874: CCN2/CTGF as a Novel Stimulator of Proliferation and Survival of Cardiac Progenitor Cells/ Stem Cells.

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**Background:** Stem cell therapy is a novel tentative treatment option for myocardial infarction. Current challenges are more effective means of proliferation and survival of cardiac stem cells, as well as development of procedures for transplantation and engraftment of cardiac stem cells in the heart. In this study we investigate the function of the matricellular protein CCN2 on stem cell proliferation and survival.

**Methods:** Cardiospheres were isolated from mouse myocardial tissue, propagated and maintained in IMDM/CEM media designed to stimulate formation of cardiospheres and proliferation of cardiac progenitor cells/stem cells.(Messina et al.*CircRes. 2004;95:911–921.*) Immunocytochemical analysis confirmed the phenotypic characteristic of cardiac stem cells positive for Sca-1, C-kit, Gata4, Nkx–2.5 and Isl–1. Cell proliferation was analyzed by EdU Flow Cytometry. In addition, cardiac progenitor cells exposed to $H_2O_2$ damage (100 μmol/L) was compared in the presence or absence of CCN2 (300nmol/L). Recombinant human CCN2 was purified from the cell culture media of HEK293 cells and purified by sequential affinity chromatography (heparin-Sepharose) and ion-exchange chromatography (S-Sepharose) to more than 95% purity.

**Results:** Recombinant human CCN2 stimulated cardiosphere formation and cardiosphere growth. CCN2 stimulated proliferation of cardiac stem cell by stimulating progression through S and G2 phase of the cell cycle. CCN2 stimulated cell cycle progression was concentration dependent and correlated with AKT/GSK-3β phosphorylation (EC50 ~250 nmol/L). Cell cycle progression was shown to be dependent on AKT/GSK-3β signaling (abrogated by PI3 kinase inhibitor LY294002 and AKT inhibitor API-2) and was associated with robust upregulation of cyclin D2 mRNA expression in cardiac stem cells. The survival of cardiac progenitor cells was significantly increased in the presence of CCN2 as assayed by activity of cellular reductases (MTT Survival Assay).

**Conclusion:** In the current study we demonstrate that CCN2 stimulate proliferation and survival of cardiac stem cells by activation of AKT/GSK-3β signaling and upregulation of cyclin D2. CCN2 may become an important factor for amplification and survival of cardiac stem cells in stem cell therapy

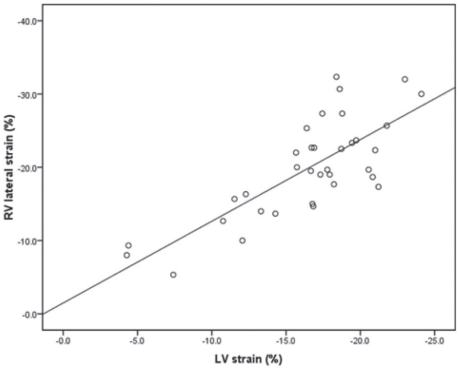
## 16201: Frequent Left Ventricular Dysfunction In Patients With Arrhythmogenic Right Ventricular Cardiomyopathy

***Kristina H Haugaa; Sebastian I Sarvari; Ole-Gunnar Anfinsen; Otto A Smiseth; Jan P Amlie Thor Edvardsen. Oslo Univ Hosp, Rikshospitalet, Oslo, Norway***

**Background:** Recent reports indicate that left ventricular (LV) impairment is more frequent in ARVC patients than earlier suggested. Myocardial strain by echocardiography is a sensitive tool for assessing cardiac function. The purpose of this study was to investigate how frequently LV function is reduced in patients with established ARVC.

**Methods:** We included 36 patients with an ARVC diagnosis according to current guidelines. 27 healthy individuals served as control group. Strain measurements were assessed by speckle tracking echocardiography. RV strain was calculated in the 3 lateral RV segment and LV strain in a 16 LV segment model.

**Results:** Ventricular arrhythmias were documented in all ARVC patients. ARVC patients had significantly reduced strain in RV (-19.3±6.8% vs. -29.1±6.7%, p<0.001) and LV (-16.5±4.7% vs. -22.4±2.6%, p<0.001) compared to healthy individuals. ARVC patients had lower LV ejection fraction (57±14% vs. 64±5%, p=0.01). LV strain was significantly correlated to RV lateral strain



in ARVC patients (R=0.77, p<0.001) indicating a close relationship in ventricular function (Figure). Reduced LV strain (<-20%) was found in 27 patients (75%), and 28 patients (78%) had reduced RV strain (<-25%). Reduced LV strain was present in 5 patients (14%) despite normal RV strain and 4 patients (11%) had reduced RV strain with normal LV strain.

**Conclusion:** Systolic function was concomitantly reduced in both ventricles, confirming that ARVC is a biventricular disease. Isolated reduction in LV function did occur in a few cases. ARVC diagnosis should be considered even in patients with merely LV dysfunction and ventricular arrhythmias. Myocardial strain may be a useful tool in quantifying RV and LV function in patients with ARVC.

## 16271: Transmural Dispersion of Myocardial Contraction in Patients With Long QT Syndrome 2 and Jervell and Lange-Nielsen Syndrome

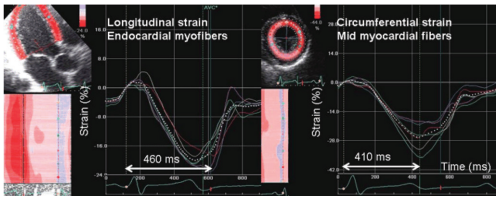
***Kristina H Haugaa; Jan P Amlie; Knut-Erik Berge; Trond P Leren; Otto A Smiseth Thor Edvardsen. Oslo Univ Hosp, Rikshospitalet, Oslo, Norway***

**Introduction:** LQTS is characterized by prolonged myocardial action potential duration (APD). The longest APD is reported in the endo- and mid-myocardium. Prolonged APD in LQTS may cause prolonged cardiac contraction which can be assessed by strain echocardiography. We hypothesized that myocardial contraction is most prolonged in subendocardial myofibers in LQTS patients and that inhomogeneous transmural contraction is related to risk of spontaneous arrhythmia.

**Methods:** We included 99 genotyped LQTS mutation carriers (64 LQT1, 26 LQT2 and 9 with Jervell and Lange-Nielsen syndrome) and 35 healthy individuals. A history of cardiac arrhythmias (syncope or documented ventricular arrhythmia) was present in 47 mutations carriers and 52 were asymptomatic. Myocardial contraction duration was assessed by strain echocardiography as time from ECG Q to peak strain in 16 LV segments. Strain was assessed along the longitudinal axis, representing subendocardial fibers and along the circumferential axis, representing mid-myocardial fibers.

**Results:** Contraction duration by longitudinal strain was longer than by circumferential strain in symptomatic LQTS patients (460±45ms vs. 440±45ms, p<0.05) (Figure) indicating transmural mechanical dispersion. This difference was not present in asymptomatic patients and healthy. The most prominent time differences were found in septal and anterior segments in LQT2 and patients with Jervell and Lange-Nielsen syndrome (445±65ms vs. 400±45ms, p=0.01and 500±60ms vs. 410±55, p=0.01).

**Conclusions:** Contraction duration in symptomatic LQTS mutation carriers was longer in the subendocardium than in the mid-myocardium, indicating transmural mechanical dispersion which was not present in asymptomatic and healthy individuals. Transmural mechanical dispersion was particularly pronounced in patients with LQT2 and Jervell and Lange-Nielsen syndrome.




## 17103: Cdc42 Controls Vascular Network Assembly Through Protein Kinase Ciota

***Yanmei Qi; Jie Liu; Xunwei Wu; Cord Brakebusch; Michael Leitges; Alan M Graham Shaohua Li. Robert Wood Johnson Med Sch, New Brunswick, NJ; Harvard Med Sch, Charlestown, MA; Univ of Copenhagen, Copenhagen, Denmark; Univ of Oslo, Oslo, Norway; Robert Wood Johnson Med Sch, New Brunswick, NJ***

Vasculogenesis is the process in which endothelial precursor cells differentiate into endothelial cells and subsequently form the primitive vascular network. The signaling pathways that mediate this fundamental biological process are largely unknown. Here we demonstrate that Cdc42 ablation in embryonic stem cells blocks vascular network assembly but not endothelial lineage differentiation during embryoid body (EB) vasculogenesis. Stable expression of Cdc42 in mutant EBs largely rescues the vascular network, indicating that Cdc42 is essential for vascular network assembly. To explore the underlying mechanisms, we isolate endothelial cells from wild type and Cdc42-null EBs. The Cdc42-null endothelial cells are defective in directional migration and in network formation on Matrigel. In addition, PKCiota activation is abolished in the absence of Cdc42, and GSK3-β phosphorylation at Ser9 is significantly reduced by both Cdc42 ablation and inhibition of atypical PKCs. Targeted deletion of PKCiota blocks vascular network assembly, while expression of kinase-dead GSK3-β in Cdc42-null EBs promotes the formation of cord-like endothelial segments. These results suggest that PKCiota and GSK3-β are downstream of Cdc42 in mediating directional migration and/or endothelial network formation. Furthermore,

we found that endothelial cell aggregates formed at the early step of vasculogenesis are associated with a nascent basement membrane. This basement membrane and VEGF synergistically activate Cdc42, and integrin β1 is required for the synergistic effect to occur. Altogether, our results suggest a model in which VEGF and basement membrane synergistically activate Cdc42, and the latter controls vascular network assembly through activating protein kinase Ciota.

## 17341: The Impact of Intravenous Ferric Carboxymaltose on Renal Function: An Analysis of the FAIR-HF Study

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**Background:** Renal dysfunction commonly complicates the natural course of chronic heart failure (CHF) and predicts poor outcome. Currently applied CHF therapies have either no effect on, or even worsen renal function. The FAIR-HF study demonstrated that treatment with intravenous ferric carboxymaltose (FCM) in iron deficient CHF patients is well tolerated and improves symptoms and quality of life. We report here the results of the FAIR-HF analysis designed to assess the effects of FCM on renal function.

**Methods:** We enrolled 459 CHF patients (NYHA class II-III, LVEF 32%) with iron deficiency (ferritin <100 μg/L, or 300 μg/L if transferrin saturation <20%); 304 patients were randomly assigned to FCM and 155 to placebo; treatment was continued for 24 weeks. Renal function was assessed at baseline and at Week 4, 12 and 24 visits, either by measurement of serum creatinine, or as estimated glomerular filtration rate (eGFR) using the MDRD formula.

**Results:** At baseline, renal function did not differ between groups (63.8±21.2 vs 64.8±25.3 ml/min/1.73m$^2$, FCM vs placebo). Treatment with FCM was associated with an improvement in renal function (table) across the whole spectrum of CHF patients (p>0.2 for interaction with baseline renal function, age, sex, CHF severity, underlying CHF etiology, presence of anemia). Additionally, more patients in the FCM group demonstrated an eGFR improvement of 5ml/min/1.73m2 (week 4: 38% vs 34%, week 12: 33% vs 26%, week 24: 35% vs 25%, FCM vs placebo respectively).

**Conclusions:** Correction of iron deficiency with intravenous FCM in CHF patients was associated with an improvement in renal function.

| Variable | Anemic | | Non-Anemic | |
|---|---|---|---|---|
| | FMC | Placebo | FMC | Placebo |
| Age [yr(SD)] | 68.2 (10.7) | 67.9 (11.2) | 67.5 (9.9) | 67.0 (11.2) |
| Female sex [n(%)] | 92 (59.4) | 45 (58.4) | 67 (45.0) | 40 (51.3) |
| NYHA [n(%)] | | | | |
| II | 22 (14.2) | 13 (16.9) | 31 (20.8) | 16 (20.5) |
| III | 133 (85.8) | 64 (83.1) | 118 (79.2) | 62 (79.5) |
| LVEF [%(SD)] | 31.8 (5.8) | 32.6 (6.5) | 32.1 (5.2) | 32.1 (5.2) |
| 6MWT [m(SD)] | 251 (96) | 251 (117) | 297 (108) | 287 (98) |
| KCCQ (SD) | 48.1 (18.5) | 51.6 (16.6) | 56.9 (19.7) | 53.4 (17.8) |
| EQ-5D VAS score (SD) | 52.0 (17.2) | 54.8 (13.8) | 56.7 (16.7) | 53.4 (16.6) |
| Hb [g/L(SD)] | 109 (8) | 108 (8) | 130 (7) | 130 (9) |
| Serum ferritin [ug/L(SD)] | 51.3 (62.9) | 59.2 (68.4) | 53.7 (44.4) | 60.9 (65.0) |
| TSAT [%(SD)] | 16.6 (15.6) | 13.5 (7.4) | 18.8 (8.4) | 19.8 (8.1) |
| CRP [mg/L(SD)] | 7.62 (4.55) | 9.71 (4.56) | 7.30 (6.07) | 8.47 (6.35) |
| eGFR [mL/min/1.73m$^2$ (SD)] | 61.9 (22.6) | 61.7 (26.5) | 65.8 (19.6) | 67.9 (23.9) |

## 17546: Effect of Intravenous Ferric Carboxymaltose on Symptoms and Quality of Life in Iron-Deficient Patients With Chronic Heart Failure With and Without Anemia: A Sub-Analysis of the FAIR-HF Trial

***Gerasimos Filippatos; Josep Comin Colet; Kenneth Dickstein; Thomas Lüscher; Ronnie Willenheimer; Claudio Mori; John Norrie; Ian Ford; Piotr Ponikowski Stefan D Anker. Athens Univ Hosp Attikon, Athens, Greece; Hosp del Mar (IMAS), Barcelona, Spain; Stavanger Univ Hosp, Stavanger, Norway; Univ Hosp Zürich, Zürich, Switzerland; Lund Univ, Malmö, Sweden; Vifor Pharma, Glattbrugg, Switzerland; Univ of Glasgow, Glasgow, United Kingdom; Univ of Glasgow, Glasgow, United Kingdom; Med Univ, Wroclaw, Poland; Charité, Campus Virchow-Klinikum, Berlin, Germany***

**Background:** Therapy with intravenous iron in patients with chronic heart failure (CHF) and iron deficiency improves symptoms, functional capacity and quality of life. We sought to investigate whether the presence of anemia at treatment onset affects these beneficial outcomes.

**Methods:** FAIR-HF randomized 459 patients with chronic heart failure (New York Heart Association [NYHA] class II or III, left ventricular ejection fraction ≤40% [for NYHA II] or ≤45% [for NYHA III]) and iron deficiency to intravenous iron as ferric carboxymaltose (FCM) or placebo in a 2:1 ratio. We analyzed the study's primary and secondary efficacy end-points according to the presence or absence of anemia (hemoglobin concentration ≤120g/L) at baseline.

**Results:** Of 459 patients, 232 had anemia at baseline (51%).

| Variable | Anemic | | Non-Anemic | |
|---|---|---|---|---|
| | FMC | Placebo | FMC | Placebo |
| **Age** [yr(SD)] | 68.2 (10.7) | 67.9 (11.2) | 67.5 (9.9) | 67.0 (11.2) |
| **Female sex** [n(%)] | 92 (59.4) | 45 (58.4) | 67 (45.0) | 40 (51.3) |
| **NYHA** [n(%)] | | | | |
| II | 22 (14.2) | 13 (16.9) | 31 (20.8) | 16 (20.5) |
| III | 133 (85.8) | 64 (83.1) | 118 (79.2) | 62 (79.5) |
| **LVEF** [%(SD)] | 31.8 (5.8) | 32.6 (6.5) | 32.1 (5.2) | 32.1 (5.2) |
| **6MWT** [m(SD)] | 251 (96) | 251 (117) | 297 (108) | 287 (98) |
| **KCCQ** (SD) | 48.1 (18.5) | 51.6 (16.6) | 56.9 (19.7) | 53.4 (17.8) |
| **EQ-5D VAS score** (SD) | 52.0 (17.2) | 54.8 (13.8) | 56.7 (16.7) | 53.4 (16.6) |
| **Hb** [g/L(SD)] | 109 (8) | 108 (8) | 130 (7) | 130 (9) |
| **Serum ferritin** [ug/L(SD)] | 51.3 (62.9) | 59.2 (68.4) | 53.7 (44.4) | 60.9 (65.0) |
| **TSAT** [%(SD)] | 16.6 (15.6) | 13.5 (7.4) | 18.8 (8.4) | 19.8 (8.1) |
| **CRP** [mg/L(SD)] | 7.62 (4.55) | 9.71 (4.56) | 7.30 (5.07) | 8.47 (6.35) |
| **eGFR** [mL/min/1.73m$^2$(SD)] | 61.9 (22.6) | 61.7 (26.5) | 65.8 (19.6) | 67.9 (23.9) |

At week 24, the effect of FCM on the primary end points of self-reported Patient Global Assessment (PGA) and NYHA class (adjusted for baseline class was similar in patients with and without anemia; for PGA, the odd ratios (OR) and 95% confidence intervals (CI) were 2.48 (1.49, 4.14) for anemic and 2.60 (1.55, 4.35) for non-anemic patients, respectively, (p=0.98 for interaction). For NYHA class, OR and 95% CI were 1.90 (1.06, 3.40) for anemic and 3.39 (1.70, 6.75) for non-anemic patients (p=0.51). The effect of FCM on the secondary end points was the same in patients with or without anemia.

**Conclusions:** Treatment of iron deficiency with intravenous ferric carboxymaltose in patients with CHF is symptomatically effective irrespective of anemia suggesting that mechanisms other than erythropoesis are affected. Therefore, iron status should be assessed in all CHF patients regardless of the presence of anemia.

## 17579: Pericellular Fibrosis is Associated With Cardiac Events and Reduced Septal Contraction in Patients With Obstructive Hypertrophic Cardiomyopathy.

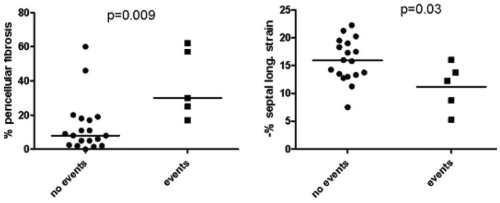
*Vibeke M. Almaas; Kristina Hermann Haugaa; Erik H. Strøm; Helge Scott; Christen P. Dahl; Odd R. Geiran; Svend Aakhus; Thor Edvardsen Jan P. Amlie. Oslo Univ Hosp, Rikshospitalet, Oslo, Norway*

**Purpose:** Myocardial fibrosis is associated with increased risk of malignant arrhythmias in patients with hypertrophic cardiomyopathy (HCM) and is frequently located in the hypertrophied inter ventricular septum. The aim of this study was to explore the impact of regional septal contraction by strain echocardiography and extent of septal fibrosis (pericellular and/or replacement-type fibrosis) on serious events in obstructive HCM-patients undergoing basal septal reduction with surgical myectomy.

**Methods:** Of 24 HCM-patients included (54% men; mean age 58±10 years), 5 experienced a serious event (cardiac arrest, non sustained VT, unexplained syncope), while 19 had no events. Myocardial strains by speckle tracking technique were averaged from 4 septal segments (basal and mid septal segments from apical long axis and 4-chamber views) as a measure of septal contraction. Degree of pericellular and replacement type fibrosis was determined in percentage of total specimen, by histopathology of surgical specimen.

**Results:** Maximal septal thickness was 1.9±0.3 cm, left ventricular outflow peak gradient by Doppler was 65±21 mmHg and NYHA classification was 2.9±0.4. In patients with events the median percentage area of pericellular fibrosis was higher (30%, range 17–62) than in patients without events (8%, range 0–60), p=0.009 (Figure). Mean septal strain was reduced in patients with events (–11.2 ±4.2%) vs. no events (–15.9 ±3.8%), p=0.03 (Figure). There was a weak but significant correlation between area of pericellular fibrosis and septal strain (R=0.27, p=0.01). Replacement type fibrosis was not associated with events.

**Conclusion:** Increased area of pericellular fibrosis and reduced septal contraction were interrelated and associated with serious events in patients with obstructive HCM. These findings indicate that septal pericellular fibrosis may serve as an arrhythmic substrate and cause reduced septal contraction.




## 13829: The Effects of Exercise Training on Systemic Brain Natriuretic Peptide (BNP) and N-terminal BNP Expression in Heart Failure Patients: An Individual Patient Meta-analysis

*Neil A Smart; Tim Meyer; John Butterfield; Claudio Passino; Malfatto Gabriella; Filipo Sarullo; Solrun Jonsdottir; Ulrik Wisloff Francesco Giallauria. Bond Univ, Gold Coast, Australia; Universität des Saarlandes, Saarbrücken, Germany; Alere, Brisbane, Australia; Fondazione G. Monasterio and Scuola Superiore Sant'Anna, Pisa, Italy; Ospedale San Luca, Milano, Australia; Buccheri La Ferla Fatebenefratelli Hosp, Palermo, Italy; Landspitali, Reykjavik, Iceland; Norwegian Univ of Science and Technology, Trondheim, Norway; Univ of Naples "Federico II", Naples, Italy*

**Background:** BNP and the N-terminal portion (NT-pro-BNP) have emerged as powerful tools in the diagnosis and prognosis of heart failure. Exercise training has been shown to reduce BNP/NT-pro-BNP levels - in either non-randomized and/

or small randomized studies, which limit the generalizability of the results. We therefore obtained individual patient data from several studies and examined the hypothesis that changes in BNP, NT-pro-BNP, peak $VO_2$ were related to the different training regimen applied. Additionally we aimed to identify patient characteristics that increase the likelihood of exercise-induced reduction in BNP, NT-pro-BNP and peak $VO_2$.

**Methods:** A systematic search of Medline (Ovid), Embase.com, Cochrane Central Register of Controlled Trials and CINAHL (up until July 2008) identified randomized controlled trials of aerobic and/or resistance exercise training in systolic heart failure patients measuring BNP and/or Pro-BNP. Primary outcome measures were change in BNP, NT-pro-BNP and peak $VO_2$. Other independent variables were exercise energy expenditure, exercise program intensity, duration and number of sessions. Sub-analyses were conducted to identify (1) patient groups that may benefit the most, (2) exercise program parameters that may enhance favourable changes in primary outcome measures.

**Results:** Ten randomized controlled studies met our eligibility criteria, authors providing individual patient data for a total of 565 patients (313 exercise and 252 controls). Exercise training had a favorable effect on BNP (–28.3%, p<.0001), NT-pro-BNP (–37.4%, p=<.0001) and peak $VO_2$ (17.8%, p<.0001). We observed a low but significant correlation between change in peak $VO_2$ and change in BNP (r=–.31, p<.0001) and change in NT-pro-BNP (r=–.22, p<.0001). Patients with LVEF<34% and peak $VO_2$<14ml·$kg^{-1}$·$min^{-1}$ showed largest reductions in BNP and NT-pro-BNP. Mena weekly exercise energy expenditure >457 Kcal·$week^{-1}$ was correlated with improved BNP (r=.19, p=.04), and peak $VO_2$ (r=.45, p<.0001).

**Conclusion:** Individual patient meta-analysis suggests exercise training has a favorable effect on BNP, NT-pro-BNP and peak $VO_2$ in heart failure patients. Patients with lower LVEF and peak $VO_2$ appear to benefit the most.

## 20999: Determinants of Reaching Guideline-Recommended LDL-Cholesterol Targets in Secondary Prevention in Europe and Canada: Results of the Dyslipidemia International Study

***Anselm K Gitt; Heinz Drexel; Lawrence Leiter; Kristian K Thomsen; Jean Ferrieres; Giuseppe Di Pasquale; Pedro Marques da Silva; Terje Pedersen; Jose-Ramon Gonzalez-Juanetey; Pia Lundman; David Wood John F Kastelein. Klinikum Ludwigshafen, Ludwigshafen, Germany; Landeskrankenhaus Feldkirch, Feldkirch, Austria; St. Michael's Hosp, Toronto, Canada; Sydvetjysk Sygehus Esbjerg, Esbjerg, Denmark; Unité de Prévention de l'Athérosclérose, Toulouse, France; Ospedale Maggiore, Bologna, Italy; Hosp de Santa Marta, Lisbon, Portugal; Ullevål Univ Hosp, Oslo, Norway; Hosp Clínico Universitario Santiago de Compostela, Santiago de Compostela, Spain; Danderyds sjukhus, Hjärt kliniken, Stockholm, Sweden; National Heart and Lung Institute, London, United Kingdom; Academic Med Cntr, Amsterdam, Netherlands; DYSIS Study Group***

**Background:** The majority of patients with dyslipidemia are currently treated with a statin. However, many patients do not achieve recommended lipid targets, and persistent lipid abnormalities will continue to contribute to cardiovascular risk in statin-treated patients.

**Methods:** Between June 2008 and February 2009, 2,987 primary care physicians, cardiologists, endocrinologists and internists in 11 European countries and Canada enrolled 22,063 consecutive statin-treated outpatients into DYSIS (Dyslipidemia International Study) to assess the prevalence of dyslipidemia (lipid values were recorded when on chronic statin treatment). ESC recommendations were used to classify patient's risk and define the LDL-C goal. We examined predictors of LDL-C goal achievement in clinical practice.

**Results:** Overall nearly half of all patients had LDL-cholesterol not at goal (48.5%).

**Conclusion:** Patients with already known ischemic heart disease, cerebrovascular disease or diabetes were more likely to achieve the recommended LDL-C goal. Treatment with higher statin dosages, with ezetemibe and treatment by specialists (internists, cardiologists, diabetologists) were independent predictors of better LDL-C goal achievement in clinical practice.

| Covariates | OR (95% CI) | Pr > ChiSquare |
|---|---|---|
| **More likely to achieve LDL-C goal** | | |
| Statin dose: ≥80 mg/day Simvastatin equivalent | 2.84 (2.50-3.24) | <0.0001 |
| Statin dose: 20-40 mg/day Simvastatin equivalent | 1.86 (1.69-2.05) | <0.0001 |
| Ischemic heart disease | 1.54 (1.44-1.65) | <0.0001 |
| Diabetes mellitus | 1.51 (1.41-1.61) | <0.0001 |
| Specialists (Internist/Diabetologist/Cardiologist) | 1.35 (1.26-1.44) | <0.0001 |
| Ezetimibe | 1.25 (1.13-1.39) | <0.0001 |
| BMI >=30 $kg/m^2$ (obesity) | 1.24 (1.16-1.33) | <0.0001 |
| Hypertension | 1.23 (1.14-1.32) | <0.0001 |
| Age >=70 years | 1.22 (1.15-1.31) | <0.0001 |
| Cerebrovascular disease | 1.22 (1.10-1.36) | =0.0002 |
| **Less likely to achieve LDL-C goal** | | |
| 1st grade fam. hist. of premature CVD | 0.91 (0.85-0.97) | 0.0046 |
| Current smoker | 0.87 (0.80-0.95) | 0.0013 |
| Peripheral artery disease | 0.87 (0.79-0.96) | 0.0079 |
| Sedentary lifestyle | 0.86 (0.81-0.91) | <0.0001 |
| Alcohol consumpt. >2 units/week | 0.84 (0.78-0.89) | <0.0001 |
| Heart failure | 0.80 (0.71-0.89) | <0.0001 |
| Female | 0.76 (0.71-0.81) | <0.0001 |
| BP >=140/90 mmHg (sys/dia) | 0.66 (0.62-0.70) | <0.0001 |

## 93: "Push Hard" Prompts Transiently Increase Depth of Chest Compressions on Manikins by Nurses

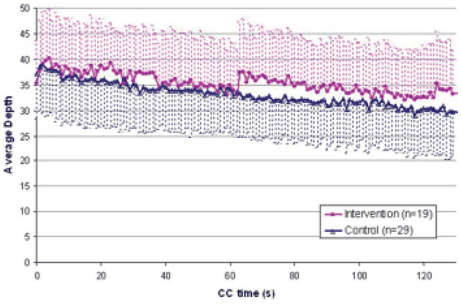
*Isabelle L Banville; Ronald E Stickney; Fred W Chapman Lars Wik. Physio-Control, Redmond, WA; Institute for Experimental Med Rsch and National Competence Cntr for EmergencyMedicine, Oslo, Norway*

Studies that have evaluated CPR quality show that most trained rescuers do not perform at the chest compression depth and rate recommended by international guidelines. Recent work has shown that CPR coaching such as a CPR metronome was effective for compression and ventilation rates. In an effort to improve chest compression depth, we evaluated the effectiveness and usability of a vocal prompt to "Remember to push hard."

**Methods:** Critical care nurses were randomized to perform CPR on an intubated, instrumented manikin using an AED with metronome guidance alone (control), or with the metronome plus a prompt to "remember to push hard" every 60 seconds (intervention). Each participant performed chest compressions for 4 minutes, rested for 2 minutes, then completed another 2 minutes of compressions.

**Results:** Mean weight and height did not differ for 29 control and 18 intervention participants. The compression rate (99±6/min control vs 103±8/min intervention, mean ± standard deviation) and total number of compressions (595±37 vs 616±46) did not differ between groups. Mean compression depth over all six minutes of CPR was 31±9 mm control vs 33±10 mm intervention (NS). For intervention participants the greatest difference in depth occurred around the time of the prompt with a mean depth for the 3 seconds before (33.9±9.1 mm, n=99) vs 3 seconds after (36.8±9.6 mm, n=96) the prompt given at minute 1 (p=0.03). The number of participants that performed any compressions with either excessive depth or incomplete release was not different between groups.

**Conclusion:** A periodic "push hard" prompt may be effective at improving chest compression depth among trained rescuers and does not result in a decrease in CPR performance. Further work is needed to identify the optimal prompting frequency.




## 19047: The Six-Transmembrane Protein STAMP2 Regulates Macrophage Inflammatory Responses and Protects From Atherosclerosis

*Henrik Ten Freyhaus; Ediz S Calay; Sara N Vallerie; Abdullah Yalcin; Ling Yang; Fahri Saatcioglu Gokhan S Hotamisligil. Harvard Sch of Public Health, Boston, MA; Univ of Oslo, Oslo, Norway; Harvard Sch of Public Health, Boston, MA*

The six-transmembrane protein STAMP2 plays a critical role in metabolic homeostasis and STAMP2-deficiency recapitulates most features of the metabolic syndrome in mice. As metabolic syndrome is associated with inflammation and accelerated atherosclerosis, we evaluated the role of STAMP2 in this context. We found that STAMP2 expression in macrophages was regulated strongly upon differentiation or by stimulation with inflammatory mediators. In the atherogenic ApoE−/− genetic background, STAMP2-deficiency significantly accelerated atherosclerosis both in the whole aorta and in the aortic root. This effect was independent of changes in systemic metabolism. To elucidate the mechanisms, we studied inflammatory and metabolic responses in macrophages. STAMP2-deficient primary macrophages showed an aggravated inflammatory response to lipopolysaccharide. Furthermore, STAMP2-deficiency led to increased macrophage foam cell formation and decreased cholesterol efflux of cells. Bone marrow transplantation studies showed that deficiency of STAMP2 in bone marrow-derived cells is sufficient to promote atherogenesis in ApoE−/− mice. These data suggest that STAMP2 has an important role in the control of metabolic and inflammatory responses in macrophages and a significant role in atherosclerosis.

## 19085: Prevalence and Correlates of Aortic Root Dilatation in Hypertensive Patients with Left Ventricular Hypertrophy (The LIFE Study) - Application of New Multivariate Predictive Models.

*Alexander Lilja; Björn Dahlöf; Eva Gerdts; Kurt Boman; Markku S Nieminenen; Richard B Devereux Kristian Wachtell. Rigshospitalet, Copenhagen, Denmark; Sahlgrenska Univ Hosp-Östra, Gothenburg, Sweden; Hauke-*

*land Univ Hosp, Bergen, Norway; Skellefaa Laseratt, Skellefaa, Sweden; Helsinki Univ Central Hosp, Helsinki, Finland; The Weill Med College of Cornell Univ, New York, NY; Rigshospitalet, Copenhagen, Denmark*

**Background:** Based on echocardiographic measurements of 1207 healthy individuals, Devereux et al. have recently derived multivariate predictive models for Sinus of Valsalva (SoV) diameter for height.

**Methods:** 774 patients with hypertension and left ventricular (LV) hypertrophy had the necessary baseline characteristics and echocardiographic 2D measurements of aortic root size to be included. These variables were used to identify patients with aortic root dilatation at the SoV (defined as a measured diameter greater than the predicted diameter plus 1.96·SEE). Predicted SoV diameter for height was calculated by 1.519+(age[years] ·0.010)+(height[cm] ·0.010)-(sex[1=M, 2=F] ·0.247). Clinical and echocardiographic characteristics were compared between patients with and without aortic root dilatation. Multivariate analysis was used to identify correlates of aortic root dilatation.

**Results:** The prevalence of aortic root dilatation was 13.3%. There were no difference in the prevalence of aortic dilatation between diabetics and non-diabetics and no difference between genders. Obese patients had a higher prevalence of aortic root dilatation (22.4% vs. 11.8%, p=0.001). Aortic root dilatation was associated with higher prevalence of aortic regurgitation (28.3% vs. 14.0%, p<0.001), lower systolic pressure (170±21 vs. 174±20 mmHg, p=0.03), higher diastolic pressure (98±12 vs. 94±12 mmHg, p=0.03), higher LV mass (LVM, 253±61 vs. 231±55 g, p<0.001), higher stroke volume (SV, 85±19 vs. 77±17 ml, p<0.001), lower pulse pressure (PP, 72±15 vs. 76±16 mmHg, p=0.01) and lower total peripheral resistance (TPR, 1814±439 vs. 2010±578 dynes·s·cm−5). Multiple linear regression analysis is presented in table.

**Conclusions:** In hypertensive patients with LV hypertrophy SoV dilatation is common. The prevalence of dilatation was higher in obese patients, and multivariate analysis showed that PP, SV and LVM predicted measured over predicted SoV diameter ratio.

*Ratio of: measured over predicted Sinus of Valsalva diameter, multiple linear regression analysis, $R^2$=0.081, SEE=0.089*

| | Unstandardized Coefficients | | Standardized Coefficients | | Collinearity Statistics | |
|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | Sig. | Tol. | VIF |
| Pulse pressure | -0.001 | 0.000 | -0.168 | <0.001 | 0.991 | 1.009 |
| Stroke volume | 0.001 | 0.000 | 0.181 | <0.001 | 0.903 | 1.107 |
| Body mass index | 0.001 | 0.001 | 0.064 | 0.072 | 0.958 | 1.044 |
| Left ventricular mass | 0.000 | 0.000 | 0.073 | 0.046 | 0.900 | 1.111 |

## 19247: Biventricular and Left Ventricular Pacing Reduces Stroke Work in Ventricles With Preserved Function Due to Non-Uniform Work Distribution

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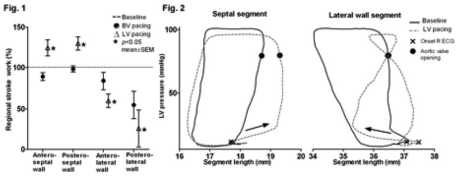
**Purpose:** Pacing therapy for heart failure (HF) patients with narrow QRS has gained increasing interest. We investigated the responses to biventricular (BV) and left ventricular lateral wall (LV) pacing in hearts with intact LV function and no electrical conduction delay.

**Methods:** In 6 anesthetized dogs with micromanometers we measured dimension changes with sonomicrometry in 4 circumferential segments. Peak intersegmental time delay (ITD) was measured between onset R in intramyocardial electromyograms. Stroke volume (SV) was calculated from an aortic flowmeter and stroke work (SW) from pressure-volume loops. Regional work was defined as the area of the pressure-segment length loops. Measurements were performed during baseline, BV pacing and LV pacing.

**Results:** LV pacing increased ITD from 11±4.8ms (mean±SD) to 30±7.6ms (p<.01), indicating electrical dyssynchrony. BV pacing increased ITD to 17±6.7ms, p<.05. LV- and BV pacing decreased SV by 10 ± 8% (p<.05) and 5±7 % (n.s.) and SW by 28±13% (p<.01) and 17±14% (p<.05), respectively. *LV pacing* caused a marked redistribution of segmental work (fig. 1) and pre-ejection deformation (fig. 2). LV pacing and to a lesser degree BV pacing caused marked pre-ejection shortening in the early-activated lateral wall and reduced segmental work. There was pre-systolic lengthening in the late activated septal myocardium, and during LV pacing this resulted in increased segmental work in the septum (Fig.2).

**Conclusion:** In hearts with intact LV function and normal electrical conduction, LV pacing reduced stroke work and stroke volume, and there were similar trends with BV pacing. These responses were attributed to non-uniform distribution of segmental work with reduced work in the early-activated lateral wall. Clinical studies should be done to determine if a similar mechanism may attenuate responses to pacing therapy in patients with LV failure and narrow QRS.



## 19264: Wnt Inhibitory Factor-1 is Elevated and Predicts Mortality in Symptomatic Aortic Stenosis

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**Purpose:** Calcific aortic stenosis (AS) shares histopathologic features with atherosclerosis, including active calcification and ossification. Wnt inhibitory factor-1 (WIF-1), a secreted Wnt-antagonist, regulates differentiation of bone and cartilage in vitro, but the clinical significance remains unresolved. We therefore sought to investigate a possible role for WIF-1 in AS.

**Methods:** One hundred and forty five patients with symptomatic AS, evaluated for aortic valve surgery, were enrolled in the study and compared to twenty age- and sex-matched controls. All participants underwent routine echocardiographic examinations upon study inclusion. Plasma WIF-1 levels were determined by enzyme immunoassay.

**Results:** AS patients had markedly elevated plasma WIF-1 levels compared to controls (median 114 pg/ml, interquartile range [86, 171] vs 58 [32, 71] pg/ml; $p<0.001$). Plasma WIF-1 correlated with NT-proBNP ($r=0.30$; $p<0.001$), left ventricular (LV) internal dimension in systole, LV posterior wall diameter and LV end systolic volume ($r=0.27$, 0.17 and 0.19; $p<0.05$ for all). An inverse relationship was found for LV fractional shortening and LV ejection fraction ($r=-0.30$ and -0.20; $p=0.001$ and 0.018). WIF-1 correlated with ultrasound backscatter ($r=0.26$; $p=0.003$). During a mean follow up of 42 months (range 35–47), 34 patients (23%) died. We observed a markedly reduced survival for patients with WIF-1 levels in the fourth quartile compared to the lower three quartiles ($p=0.002$). WIF-1 added no significant independent predictive information for risk estimation beyond established risk factors in multivariate analyses. However, combining the fourth quartiles of WIF-1 and NT-proBNP proved superior to either of the parameters alone in predicting all-cause mortality (Conditional Cox-adjusted HR 6.24, CI 2.59–14.99; $p<0.001$).

**Conclusion:** Plasma levels of WIF-1 are elevated in patients with symptomatic AS. WIF-1 correlates with ultrasound backscatter, possibly reflecting a relationship between WIF-1 and degree of valvular calcification. In multivariate analyses a model of combined WIF-1 and NT-proBNP proved superior to either of the parameters alone in predicting all-cause mortality in AS patients.