ORAL PRESENTATIONS

Unexpected identification of Fabry disease among patients with the clinical diagnosis of hypertrophic cardiomyopathy in Iceland

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Purpose: The aim of this study was to investigate the prevalence of Fabry disease (FD) among all hypertrophic cardiomyopathy (HCM) patients in Iceland.

Methods: 137 patients with clinically diagnosed HCM were studied; 76 carried the *MYBPC3* c.927-2A>G founder mutation; the remaining 61 underwent targeted sequencing of 8 HCM genes and the α-galactosidase A gene (*GLA)*. If a *GLA* sequence variant was found, then the enzyme activity of plasma and leukocyte alpha-galactosidase A (α-Gal A) and the urine concentration of globotriaosyleramide (Gb3) were measured. In vitro protein expression was performed in cases of new mutations. Patients were evaluated clinically and kidney function tests made. Brain and cardiac MRI was performed on patients with *GLA* sequence variants.

Results: Eight of the 137 patients (5.8%) had pathogenic *GLA* mutations, 5 males and 3 females, all without sarcomeric gene mutations. Age at LVH diagnosis was 46 ± 10 years (34-59), left ventricular wall thickness was 24 ± 5 mm (19-36). Two pathogenic mutations were identified. The I232T mutation was found in 3 patients from two families. In vitro protein expression showed 32% α-Gal A activity compared to wild type (WT). I232T was related to late onset disease with cardiac and cerebral manifestations. The D322E mutation was found in 5 patients from two families. In vitro protein expression showed 3% α-Gal A activity compared to wild type (WT). D322E seems to cause almost the classical form of FD. Familial studies allowed the diagnosis of FD in 12 additional patients: 2 males with classical FD, 3 males with cardiomyopathy as the only manifestation of FD, 7 young females without Fabry manifestations.

Conclusions: In Iceland, the prevalence of FD is high (about 6%) among patients with a clinical HCM diagnosis. Our results underscore the importance of considering FD in the differential diagnosis of unexplained LVH and presumed HCM.

Expression of selected genes in aspirated coronary thrombi in patients with acute myocardial infarction

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Background: Reports on the content of aspirated coronary thrombi have until now mainly focused on structural and cellular components.

Objectives: Investigate the genetic expression of selected mediators and proteases actively involved in plaque rupture, platelet and neutrophil cell activation, coagulation, fibrinolysis and inflammation in aspirated coronary thrombi from patients with acute myocardial infarction.

Patients/Methods: In this cross-sectional study, RNA from coronary thrombi in 67 subjects with acute myocardial infarction was isolated. Gene expression arrays of selected markers were performed by RT-PCR with relative quantification.

Results: Twenty of 22 markers were expressed in > 50% of the samples. The relative quantification of P-selectin correlated negatively to total ischemic time (p = 0.01), while genes related to fibrinolysis (t-PA, u-PA, PAI-1), inflammation (PTX3, CXCL9, MCP-1, IL18, TNF-alfa) and plaque instability (MMP-2 and TIMP-1) correlated positively to total ischemic time (all < 0.05). Long ischemic time (>4.0 hours) associated with a relative reduction in the expression of P-selectin and a relative increase in the expression of t-PA, u-PA, PAI-1, PTX3, CXCL9, MCP-1, IL18, TNF-alfa, MMP-9 and TIMP-1. The presence of type 2 diabetes increased PAI-1 expression 3.2-fold (adjusted p=0.033), while the presence of hypertension reduced IL-8 and TIMP-1 to about half-fold. Smoking and overweight did not affect any markers.

Conclusions: The coronary thrombi were highly genetic active. The expression profile changed along with ischemic time and with the precence of type 2 diabetes mellitus and hypertension. These observations contribute to increased insight into the genetic aspects of coronary atherothrombosis, which may have implications for future management of acute MI.

Modest effects of exercise training on HbA_{1c} and VO_{2peak} in patients with type 2 diabetes and coronary artery disease: a randomised clinical trial

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Background: Few studies have investigated the effects of exercise training in patients with both type 2 diabetes and coronary artery disease (CAD). We investigated the effects of 12 months combined aerobic and resistance training on glycemic control and exercise capacity in these patients, hypothesising that exercise would improve HbA_{1c} and VO_{2peak}.

Methods: Patients with type 2 diabetes and CAD (n=137) were randomised to exercise or normal follow-up. The training program consisted of 150 minutes weekly group-based and individual exercises. HbA_{1c} was measured before and after the intervention. Changes in VO_{2peak}, ventilatory threshold (VT) and time to exhaustion (TTE) were assessed by cardiopulmonary exercise testing (CPET). Between group differences in changes were calculated by one-way ANCOVA. "Intention to treat" (ITT) *and* "per protocol" (PP) analyses were performed.

Results: One hundred and twenty-three patients completed the study (ITT), and nine patients were excluded from the PP analyses due to low exercise adherence (< 40%). No between group differences in changes were observed in HbA_{1c} or VO_{2peak}, whereas VT and TTE increased significantly (p=0.046 and p=0.034) (PP). The relative increase in VT and TTE was significantly larger than in VO_{2peak} (12.8% and 13.7% vs. 4.5%). Presence of *advanced vascular disease* (previous AMI and/ or diabetes microvascular complications) interacted with the treatment principle with respect to changes in HbA_{1c} and VO_{2peak} (p=0.036 and p=0.063), and in the strata of patients without *advanced vascular disease* (n=46) the exercise group did improve these parameters compared to controls (p=0.052 and p=0.035).

Conclusions: No significant effects of exercise training were observed on HbA_{1c} or VO_{2peak} levels, although VT and TTE increased significantly indicating improved exercise performance and capacity. Patients without *advanced vascular disease* did improve both HbA_{1c} and VO_{2peak}, implying that the *degree* of vascular disease influences exercise responses in patients with type 2 diabetes and CAD.

Clinical presentation predicts coronary atheroma necrotic core reduction in patients undergoing aerobic exercise intervention

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Background: Vulnerable coronary lesions are characterized by a large amount of necrotic core (NC). We have previously demonstrated a significant reduction in NC in patients on optimal medical treatment following moderate continuous exercise or aerobic interval training for 12 weeks (*in press,* clinicaltrials.gov, NCT01228201). In a post-hoc analysis we assessed clinical variables at baseline that could predict NC reduction.
Methods: NC was measured with radiofrequency intravascular ultrasound, and analyzed at an independent Core Laboratory. Baseline explanatory variables included age, sex, anthropometrics, medication, endothelial function, blood biomarkers and clinical presentation (stable angina pectoris or non-ST elevation acute coronary syndrome, NSTEACS).
Variable screening was performed using random forest analysis (bootstrap, n=2000) following dichotomization of the outcome (NC change) into reduction or no change/increase. Significant variables were further analyzed using multivariate linear regression with NC change as a continuous variable (mm^3).
Results: In the random forest analysis, significant variables at baseline for NC reduction were use of angiotensin enzyme inhibitors/angiotensin II receptor antagonist, and clinical presentation. In linear regression, only clinical presentation remained significant (p=0.011, Rsquared 0.90). The median change in NC was -4.94 (-10.33;-1.33) mm^3 in patients with stable angina pectoris, and 1.03 (-4.29;3.71) mm^3 in patients with NSTE-ACS (between-group difference p=0.01). Mean NC volume at follow-up was 7.19 (1.87;12.50) mm^3 higher in patients with NSTE-ACS compared to stable angina pectoris. NC volume was reduced in 17 patients (94%) in the stable angina group compared to 8 patients (44%) in the NSTE-ACS group (between-group difference p=0.01).
Conclusions: Reduction of coronary atheroma NC in patients undergoing aerobic exercise may be strongly dependent on clinical presentation, and was much more frequent in patients with stable angina pectoris in our cohort. Based on our data, it could be hypothesized that an increased pro-inflammatory load renders patients with NSTE-ACS more resistant to exercise-induced plaque stabilization.

Conflicts of interest: None.

Right ventricular diameter is superior to right ventricular outflow tract to predict ventricular arrhythmias in subjects with ARVC

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Purpose: Ventricular arrhythmias are frequent in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). The Task Force Criteria 2010 include right ventricular outflow tract (RVOT) measurements and improve ARVC diagnosis, but risk stratification of ventricular arrhythmias is still challenging. We investigated right ventricular (RV) echocardiographic parameter's relation to ventricular arrhythmias in ARVC subjects.

Methods: We studied 110 ARVC subjects (mean age at diagnosis 42±17 years, 58% male). RV basal diameter (RVD), proximal RVOT diameter and RV fractional area change (RV FAC) were assessed by echocardiography. RV strain was averaged from the 3 RV free wall segments. Ventricular arrhythmias were defined as documented ventricular tachycardia or fibrillation or aborted cardiac arrest.

Results: Of the 110 included, 65 (59%) were index patients and 45 (41%) were mutation-positive family members. Ventricular arrhythmias occurred in 66 (60%). RVOT and RVD were increased in ARVC subjects with ventricular arrhythmias compared to those without (RVOT: 38±9 mm vs. 32±6 mm, $p<0.01$; RVD: 47±8 mm vs. 39±7 mm, $p<0.001$) and RV function was reduced by RV FAC (34±10% vs. 45±9%, $p<0.001$) and RV strain (-20.8±8% vs. -26.0±5.5%, $p<0.001$). By ROC analyses, RVD, with an AUC of 0.81; 95% CI 0.73-0.90, had better ability than RVOT to detect subjects with arrhythmias ($p<0.01$) (Figure). RVD predicted arrhythmic events independently of RVOT, RV FAC and RV strain (OR 1.14; 95% CI 1.01-1.27, $p=0.02$).

Conclusions: ARVC subjects with ventricular arrhythmias had increased RV diameters and decreased RV function by echocardiography. RVD is currently not included in the Task Force Criteria, but was superior to RVOT in detecting ventricular arrhythmias. RVD should be included in echocardiographic assessment of ARVC subjects.

Heart rate during maximal exercise testing in patients with permanent atrial fibrillation

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Aims: To investigate the relation between heart rate (HR) response to exercise and exercise capacity (peak VO2) in patients with permanent atrial fibrillation (AF), with and without rate-reducing drug treatment.
Methods: Sixty patients (mean age 71±9 years, 18 women) with permanent AF and normal left ventricular function were included in the study. All received diltiazem 360 mg, verapamil 240 mg, metoprolol 100 mg and carvedilol 25 mg once daily for three weeks, in a randomized sequence. At baseline and on the last day of each treatment period, the patients underwent a maximal cardiopulmonary exercise test on a bicycle ergometer.
Results: Treatment with all four rate-reducing drugs lowered HR both at rest and during all stages of exercise and recovery, compared to baseline ($p<0.001$ for all)(Figure 1). In multivariate regression analysis, adjusting for age, gender, BMI, ejection fraction and FEV1, peak VO2 remained positively correlated to the heart rate reserve (difference between HR at peak exercise and resting HR, divided by the resting HR)($r=0.40$, $p<0.001$) and inversely correlated to the relative increase in HR during the four minutes warm-up phase ($r=-0.22$, $p<0.001$).
Conclusion: Preserved HRR was correlated to better exercise capacity while excessive HR response to minor exercise was predictive of reduced exercise capacity in patients with permanent AF.

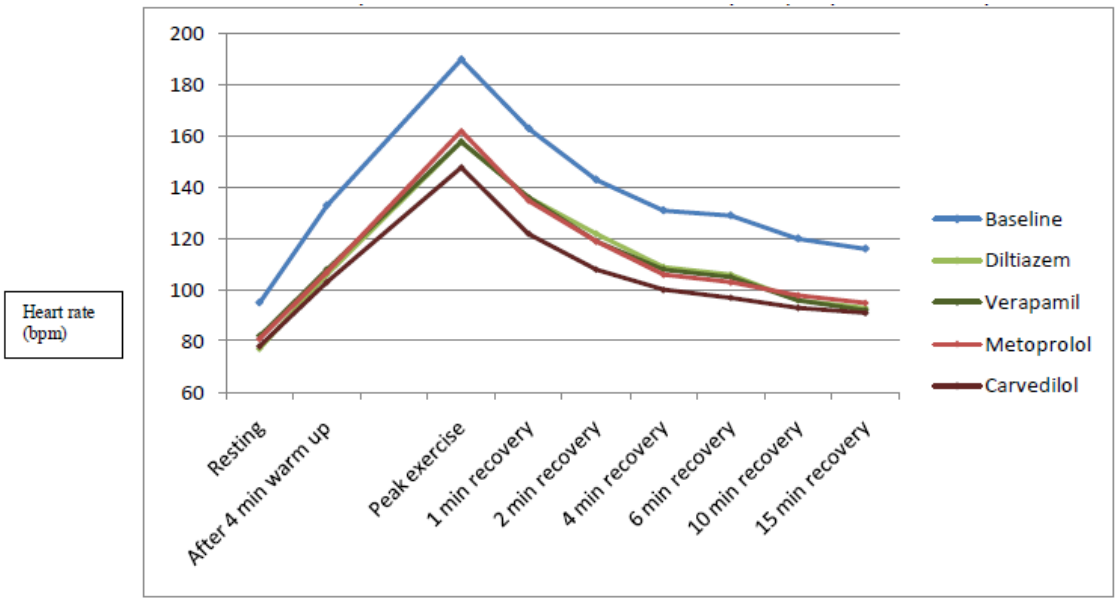

Figure 1. Heart rate during the exercise tests, at baseline and with the different drugs.

POSTER PRESENTATIONS

Non-Invasive Myocardial Work Index Identifies Acute Coronary Occlusion in Patients with Non-ST-Segment Elevation – Acute Coronary Syndrome

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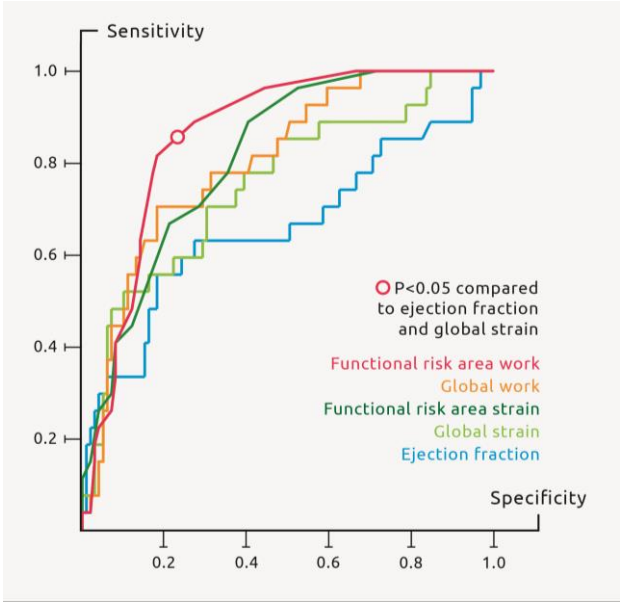
Introduction: Acute coronary artery occlusion (ACO) occurs in approximately 30% of patients with non-ST-segment elevation – acute coronary syndrome (NSTE-ACS). We investigated the ability of a regional non-invasive myocardial work index (MWI) to identify ACO.

Methods and Results: Segmental strain analysis was performed before coronary angiography in 126 patients with NSTE-ACS. Left ventricular (LV) pressure was estimated non-invasively using a standard waveform fitted to valvular events and scaled to systolic blood pressure. MWI was calculated as the area of the LV pressure-strain loop. Empirical cut-off values were set to identify segmental systolic dysfunction for MWI (<1700 mmHg•%) and strain (>-14%). The number of dysfunctional segments was used in ROC analysis to identify ACO. 27 patients suffered ACO. The presence of ≥ 4 adjacent dysfunctional segments assessed by MWI was significantly better than both global strain and ejection fraction at detecting the occurrence of ACO (P<0.05). Regional MWI had a higher sensitivity (81% vs. 78%) and especially specificity (82% vs. 65%) compared to regional strain. Logistic regression demonstrated that elevated systolic blood pressure significantly decreased the probability of actual ACO in a patient with an area of impaired regional strain.



Conclusions: The presence of a region of reduced myocardial work in patients with NSTE-ACS identified patients with ACO, and was superior to all other parameters. The regional MWI was able to account for the influence of systolic blood pressure on regional contraction. We therefore propose that MWI may serve as an important clinical tool for selecting patients in need of prompt invasive treatment.

Cardiac resynchronization therapy in left bundle branch block improves right ventricular function

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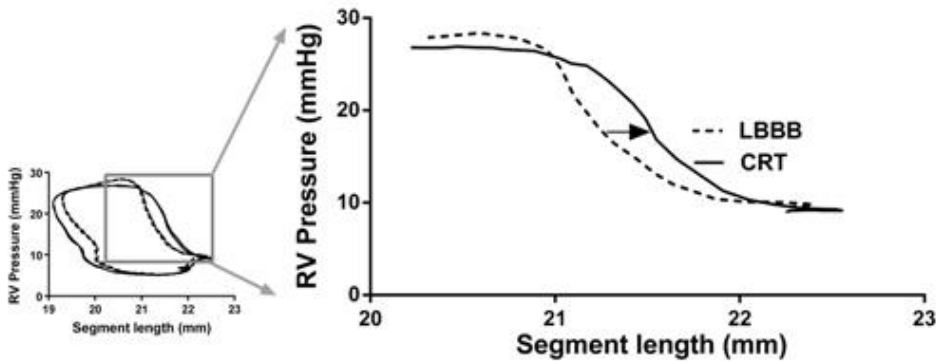
Purpose: Right ventricular (RV) function has been recognized as a predictor of clinical response to cardiac resynchronization therapy (CRT) during left bundle branch block (LBBB). In an experimental setting, we aimed to study the impact of CRT on RV function during LBBB.

Methods: In 6 anaesthetised dogs with LBBB induced by radio frequency ablation, we applied CRT with one electrode on the right side of the interventricular septum and one epicardially on the LV lateral wall. RV pressure was measured by a micromanometer in the RV cavity and segmental length (SL) by sonomicrometry in the RV free wall. The area of the RV pressure-SL loop was used as an index of regional work in the RV free wall. Pre-ejection RV shortening, measured at 50% increase of RV pressure, was calculated in percentage of peak systolic shortening.

Results: Induction of LBBB was associated with a reduction in RV free wall work from 41±13 to 29±16 mmHg*mm (P<0.05). This was in part due to distortion of the pressure-SL loop with marked pre-ejection shortening (33±14%) of total shortening. CRT increased segmental work to 41±15 mmHg*mm, P<0.05 and RV dP/dt max increased from 361±78 to 446±76mmHg/s (P<0.05). Neither maximum RV pressure (28±3 vs. 27±3mmHg, NS) nor total shortening (8±3 vs. 8±3%, NS) was changed by CRT. However, the RV pre-ejection shortening decreased substantially to 13±12% (P<0.05 vs. LBBB) of total shortening (figure).

Conclusions: During LBBB there is ineffective contraction in the RV free wall as approximately 1/3 of the contraction occurs during low pressure prior to ejection. The efficiency was improved by CRT, which markedly increased regional work in the RV free wall. The findings suggest that improvement in RV function may be important for success of CRT in LBBB.



Pro-arrhythmic consequences of hypokalemia in atrial cardiomyocytes

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Up to 20% of hospitalized patients exhibit hypokalemia, and mortality in these patients is 10 times higher than in those with normal potassium levels. Many studies have observed an association between hypokalemia and atrial fibrillation. We hypothesized that lowered extracellular K^+ levels promote ectopic beats in atrial myocytes by triggering early and delayed afterdepolarizations. Our previous work has shown that when [K^+] is reduced from 5.0 mM to 2.7 mM, rat ventricular cardiomyocytes briefly exhibit depressed Ca^{2+} transients followed by a recovery and overshoot of Ca^{2+} transient amplitude. In addition to larger Ca^{2+} transients at steady-state, we observed that ventricular cells exhibited spontaneous Ca^{2+} waves during hypokalemia, which generate delayed afterdepolarizations. In rat atrial cardiomyocytes exposed to the same protocol, the majority of cells exhibited early spontaneous release during the decline of the Ca^{2+} transient consistent with early afterdepolarizations. Approximately half of atrial cells exhibited a biphasic response of Ca^{2+} transient amplitude and spontaneous Ca^{2+} waves at steady state, which was reminiscent of observations made in ventricular cells. Remaining atrial cells exhibited a monophasic decrease in Ca^{2+} transient amplitude. Our work in ventricular cells has shown that the biphasic response is dependent on the presence of the alpha-2 isoform of the Na^+-K^+ ATPase in the t-tubules. Since we observed that t-tubules are present in about half of rat atrial myocytes, we believe that it is these tubulated cells which exhibit biphasic responses during hypokalemia. Importantly, increased occurrence of both Ca^{2+} waves and early spontaneous Ca^{2+} release events in atrial cells during hypokalemia was largely reversed upon return to normal extracellular K^+ levels. These results support the notion that increasing blood K^+ levels may have therapeutic value in patients with atrial fibrillation, and we are currently investigating this hypothesis in a parallel clinical study.

ROSUVASTATIN INDUCED CAROTID PLAQUE REGRESSION IN PATIENTS WITH INFLAMMATORY JOINT DISEASES: THE RORA-AS STUDY

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Background: Patients with rheumatoid arthritis (RA) and carotid artery plaques (CP) have increased risk of acute coronary syndromes. Statin treatment with low density lipoprotein cholesterol (LDL-c) goal $\leq$ 1.8 mmol/L is recommended for patients with CP in the general population. In the ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases (RORA-AS) study, the aim was to evaluate the effect of 18 months intensive rosuvastatin treatment on change in CP height.

Methods: Eighty-six patients (60.5% female) with CP and IJD [RA (n=55), ankylosing spondylitis (n=21) and psoriatic arthritis (n=10)] were treated with rosuvastatin to obtain LDL-c goal. CP height was evaluated by B–mode ultrasound.

Results: Age was 60.8±8.5 years (mean±SD). At baseline, median number and height of CP was 1.0 (range 1-6) and 1.80 mm (IQR 1.60, 2.10). Change in CP height after 18 months rosuvastatin treatment was -0.19±0.35 mm ($p<0.001$). Baseline and change in LDL-c was 4.0±0.9 mmol/L and -2.3±0.8 mmol/L ($p<0.001$). Mean LDL-c level during 18 months rosuvastatin treatment was 1.7±0.4 mmol/L. The degree of CP height reduction was independent of the LDL-c level exposure during the study period ($p=0.36$). Attainment of LDL-c $\leq$ 1.8 mmol/L or the change in LDL-c did not influence the degree of CP height reduction ($p=0.44$ and $p=0.46$, respectively). The higher the CP was at baseline - the larger height reduction after 18 months with rosuvastatin treatment ($p< 0.001$). Joint disease activity during the study period was inversely associated with change in CP height ($p=0.02$), so that patients with the highest disease activity had the smallest change in CP height and vice versa.

Conclusion: This is the first clinical study showing that intensive lipid lowering with statin induced regression of atherosclerosis in patients with IJD. Our results indicate that disease activity may influence the effect of anti-atherosclerotic treatment.

Hypertrophic cardiomyopathy in a large cohort of *MYBPC3* c.927-2A>G founder mutation carriers

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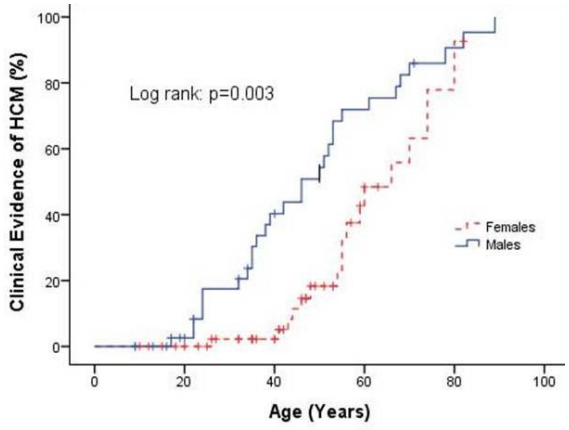
Purpose: Most hypertrophic cardiomyopathy (HCM) cohort studies are characterized by great heterogeneity of sarcomeric protein gene mutations. The aim of this study was to determine the penetrance and clinical disease expression in a large cohort of patients and relatives carrying the same *MYBPC3* c.927-2A>G founder mutation, arising more than 500 years ago.

Methods: The initial study population comprised 88 probands carrying the *MYBPC3* c.927-2A>G. Additionally, 223 first degree relatives accepted to undergo genetic testing and clinical evaluation, including echocardiography.

Results: Out of 223 family members, 95 c.927-2A>G mutation carriers were identified, of whom 47 (50%) were clinically affected with left ventricular hypertrophy (LVH) ≥13 mm. The penetrance was age related (34% <40 years versus 61% ≥ 40 years, *p*=0.009) and greater in males (67%) than females (35%, *p*=0.001). Gender specific, cumulative age related penetrance is shown in the figure below.



Neither males nor females were affected until age 17 and by age ≥80, more than 90% of individuals were affected. The degree of LVH among the relatives ranged from 13 mm to 28 mm, none had left ventricular outflow tract gradient ≥30 mmHg at rest. The pattern of septal hypertrophy was reverse curve in 67% of patients, neutral in 21%, apical in 5.8%, and 3.5% had sigmoid septum.

Conclusions: HCM related to the *MYBPC3* c.927-2A>G founder mutation is mainly late onset and shows gender specific penetrance. Other genetic or environmental factors must play an important role in disease phenotype.

C-reactive protein is associated with peak oxygen uptake, but not with endothelial function: The HUNT 3 Fitness Study

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Background: Biomarkers of inflammation, particularly C-reactive protein (CRP), have received attention as predictors of cardiovascular disease (CVD). Some studies suggest that CRP participates actively in atherogenesis. The aim of the present study was to investigate whether CRP (a marker of general inflammation), neopterin (a marker of activated macrophages), and lactoferrin (a marker of activated neutrophils) are associated with aerobic fitness, endothelial function, and the metabolic syndrome, in self-reported healthy respondents.
Methods: A cross-sectional association study included 1432 men and women from the HUNT 3 Fitness Study. 740 respondents identified as having the metabolic syndrome were age- and sex-matched with 692 controls from the same cohort. Associations between the biomarkers of inflammation and aerobic fitness (VO2peak = peak oxygen uptake during treadmill test), endothelial function (FMD = flow-mediated dilation), and the metabolic syndrome, were analyzed by linear and logistic regression.
Results: CRP was strongly associated with metabolic syndrome, male gender, and VO2peak (Figure 1, all $p<0.005$). In gender-stratified analyses, smoking was associated with CRP only in men ($p<0.005$). There was no association between FMD and CRP ($p=0.34$). Lactoferrin was associated with metabolic syndrome ($p<0.005$), but neither neopterin nor lactoferrin were associated with VO2peak or FMD. In logistic regression, the metabolic syndrome was strongly associated with male gender, lactoferrin and VO2peak ($p<0.005$). Each 1 ml*kg-1*min-1 increase in VO2peak corresponded to a ≈ 6 % risk reduction for the metabolic syndrome.
Conclusions: CRP was clearly associated with VO2peak and the metabolic syndrome, but not with FMD. Based on these findings, we hypothesize that aerobic fitness may have a significant effect on low-grade inflammation in a population without CVD. We hypothesize that a modest increase in aerobic fitness may protect against a detrimental clustering of CVD risk factors as in the metabolic syndrome.

Conflicts of interest: None.

OTHER SUBMITTED ABSTRACTS

Effects on length of stay and costs with same–day retransfer to the referring hospitals for patients with Acute Coronary Syndrome after angiography and/or percutaneous coronary intervention.

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Introduction: Fast track (FT) interventions may generate benefits for patients and hospitals, representing a potential for shorter hospital stays with less costs. The aim of this study was to investigate how same-day retransfers to the referring hospital after angiographic examination and/or percutaneous coronary intervention (PCI) at the PCI centre affected length of stay (LOS) and hospital treatment costs for patients with acute coronary syndrome (ACS).

Method: 399 consecutive admitted ACS patients from different referring hospitals were prospectively randomized to ordinary care (OC) with overnight stay or fast track (FT) with same-day retransfers. LOS at both the PCI-centre and the referring hospital after the stay at the PCI centre, were recorded. Costs at the PCI centre related to examinations and treatments were collected.

Results: The OC group included 206 patients and the FT group 193 patients. 46% underwent PCI and 10% CABG in the OC group. In the FT group 40% had PCI and 6% CABG. LOS was reduced at the PCI centre from median 1.25 days for the OC group to median 0.24 days for the FT group ($p<0.001$), with a significant reduction for patients performing selective coronary angiography (SCA) alone, or PCI - but not for patients undergoing CABG. No significant difference was identified in LOS at the referring hospitals. Median treatment costs were significant reduced from NOK 23657 for the OC group to NOK 15730 for the FT group ($p<0,001$). The main driver behind the reduction was the reduction in LOS with the corresponding decline in ward costs at the PCI centre.

Conclusion: Our findings confirmed that a same-day retransfer for patients with ACS to the referring hospital reduces LOS and hospital treatment costs for patients undergoing SCA and PCI.

Timing of intervention in NSTEMI/UAP is not according to current ESC guidelines. A retrospective study at Ringerike Hospital.

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Background: In high risk patients with NSTEMI/UAP, studies have shown superiority of early invasive therapy with regard to risk of recurrent ischemic events. Thus according to ESC guidelines, timing of intervention should be adjusted to patients risk profile.

Patients with high risk (GRACE > 140 or with one or more high risk criteria (rise and/or fall in troponins or dynamic ST/T changes), should undergo invasive therapy within 24 hours.

For referral to early invasive therapy, we send a PCI-FAX to our collaborative catheterization facility and patients are transferred at the earliest convenience.

We retrospectively studied time from admission to catheterization for this patient group.

Method: Records for all patients admitted in the period 01.12.12-30.06.13 with the ICD code I20-I21 and a confirmed referral through a PCI-FAX, were reviewed. Patient risk profile, time of admission, referral and invasive therapy was registered.

Results: 99 patients (65 males, 34 females), with a mean age of 67 (range 46-85), were included. There were 48 patients with NSTEMI and 51 patients with UAP (3 patients classified as high risk).

22% of the NSTEMI/UAP (high risk) group, underwent invasive therapy within the first day. Median time from admission to catheterization was 2 days (range 2-10)

Median referral time for patients with intermediate-low risk UAP were 5 days (range 1-12).

Median time from admission to PCI-FAX sent was 0(range 0-4) in the high risk group and 1(range 0-7) in the intermediate-low risk group.

Conclusion: Only 22 % of our high-risk patients, underwent angiography according to guidelines. The delay observed is partly due to diagnostic delay at our end. However, examining time from PCI-FAX sent to catheterization, only 45 % of the high-risk group received invasive therapy within 1 day.

We conclude that the PCI-FAX should be sent as soon as possible, clearly communicating patients risk profile. We also believe that a more dynamic 2-way communication system, would improve our adherence to guidelines.

The effect of autologeous bone marrow derived stem cells on leukocyte markers in acute myocardial infarction

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Background: The effect of intracoronary injection of autologeous bone marrow derived stem cells (mBMC) in STEMI on leukocyte avtivation is unknown.

Objectives: Explore pentraxin 3 (PTX3) and myeloperoxidase (MPO) levels in relation to mBMC and infarct size.

Methods: STEMI subjects undergoing PCI were randomised to mBMC (n = 50) or controls (n = 50). Blood samples were drawn the day before mBMC (baseline) and after one day, 3 days, 2-3 weeks and 3 months. ELISA and RT-PCR were used for biochemical analysis. Infarct size was assessed by SPECT and CKMB levels.

Results: PTX3 and MPO levels did not differ between the groups at any time point. Relative reduction of PTX3 from baseline to Day 1 was less in the mBMC group than in the control group (p=0.002). PTX3 levels decreased in the mBMC group from baseline to Day 3 and subsequenly, and in the control group from baseline to Day 1 and further during the study period (p all <0.05). Levels of MPO decreased in the mBMC group from baseline to Day 1 and subsequently, and in the control group from baseline to Day 3 and subsequently (p all <0.05). MPO correlated to baseline EF (SPECT) (r=-0.229, p=0.025) and peak CKMB (r=0.037, p=0.05). Gene expression of PTX3 from circulating leukocytes correlated to circulating PTX3 levels at all corresponding measure points (r=0.379-0.448, p all <0.01). PTX3 and MPO gene expression decreased in the range 16-39 % and 16-48 %, respectively, during the study period.

Conclusions: Administration of mBMCs after STEMI had limited effect on PTX3 and MPO levels. The initially high PTX3 and MPO levels, the correlation between MPO and myocardial injury and the regulation of PTX3 support the importance of leukocyte activation in STEMI.

Impact of Atrial Fibrillation on Levels of High-Sensitivity Troponin I in a 75-Year-Old Population

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Purpose: Atrial fibrillation (AF) has been associated with elevated levels of cardiac troponins, however it is not clear if this association is independent of underlying cardiovascular disease. The aim of this study was to investigate the impact of AF on cardiac troponin I (TnI) levels in a 75-year old cohort from the general population, using a recently introduced, highly sensitive assay.

Methods: All 75-year-old citizens in Asker and Baerum counties were invited to participate in a prevalence study of AF. High-sensitive troponin I (hs-TnI) levels were measured (Abbott Diagnostics) in serum samples collected from 62 subjects with AF and in a gender-matched control group of 126 subjects in sinus rhythm.

Results: TnI was detectable in all subjects (median 7.3 pg/mL (range 3.0-88.7)). Patients with AF had higher levels than subjects in sinus rhythm (8.3 pg/mL (3.7-88.7) vs. 6.8 pg/mL (3.0-77.5); p=0.011). Male gender (p=0.002), hypertension (p=0.001), coronary heart disease (p<0.001), heart failure (p<0.001), prior stroke or transient ischemic attack (p=0.013) and serum creatinine (p<0.001) were all associated with higher levels of hs-TnI in univariate analysis. After adjustment for heart failure and coronary heart disease, which were the significant confounders, the relation between AF and hs-TnI was no longer statistically significant.

Conclusion: All subjects aged 75 had detectable levels of hs-TnI. AF patients had higher hs-TnI levels than subjects in sinus rhythm; however, this difference was not statistically significant after adjustment for heart failure and coronary heart disease, which were the significant confounders.

Impact of severe aortic stenosis on health related quality of life (HRQoL)

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Background – HRQoL is assuming a greater role in decision making of surgery for severe aortic stenosis (AS). However, knowledge of how severe AS affects HRQoL is sparse. We aimed to explore how and to what degree severe AS affects HRQoL in patient referred for surgery compared to age and sex specific population norms.

Method and Results – In a prospectively design, 480 patients referred for consideration of AVR completed the SF-36 version 2. A majority of 272 (57%) were men, mean age 75 (11) years. The majority of the youngest patients were in NYHA class II, while most of the oldest were in NYHA class III. Patients scored significantly lower than population norms for PCS, MCS and physical functioning, role physical, general health, vitality, role-emotional and mental health of the SF-36 scales. The differences in HRQoL were inversely related to age, (p<0.05) for all scales except MCS, Bodily Pain, Vitality and Mental Health. The youngest patients had greater deviations in HRQoL than the oldest patients when compared to the general population norms. Analysis reveals that 55-58 % of the patients in the oldest two quartiles did not reach level of deviation defined as clinical important difference.

Conclusion

Severe AS has a substantial impact on HRQoL. Deviation from population norms shows an age wise decreasing trend with older age. This age wise reduction in deviation from general population strongly suggests watchful expectation, especially if quality of life is preferred over quantity of life in elderly, frail and comorbid population.

Rosuvastatin improves arterial stiffness in patients with inflammatory joint diseases: Results from the RORA-AS study

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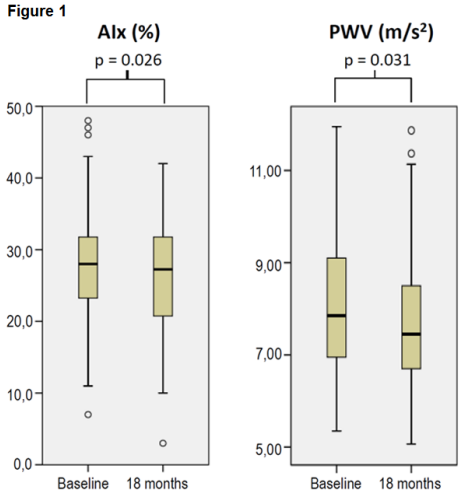
Background Arterial stiffness, as pulse wave velocity (PWV) and augmentation index (AIx), are early risk markers of cardiovascular disease (CVD). Intensive statin treatment induces carotid plaque (CP) regression in patients with inflammatory joint diseases (IJD). We evaluated the effect of rosuvastatin treatment on arterial stiffness in IJD patients with CP.

Methods The study population included 89 statin naïve IJD patients (rheumatoid arthritis: 55, ankylosing spondylitis: 23, psoriatic arthritis: 11). All patients had ultrasound verified CP and received rosuvastatin therapy over 18 months. PWV and AIx were measured at baseline and end of the study. Change in PWV and AIx from baseline was assessed with paired t-tests. Logistic regression analyses were performed with PWV and AIx as outcome variables, defined as decrease or no change/increase during the study, to assess for associations with other outcome measures.

Results From baseline to study end, mean (SD) AIx and PWV was significantly improved from 27.9 (7.7) % and 8.1 (1.6) m/s2, to 26.2 (8.2) % (p=0.03) and 7.8 (1.5) m/s2 (p=0.03), respectively. The logistic regression models revealed these associations: 1) Between PWV and change in systolic blood pressure (sBP) (p=0.008) and exposure of sBP (0.03). 2) Between AIx and change in CP height (p=0.03) and rosuvastatin dose (p=0.01). All associations were robust to adjustments for adverse lifestyle changes.

Conclusion Rosuvastatin therapy significantly improved arterial stiffness in IJD patients with CP. The improvement was associated with sBP change, rosuvastatin dose and atherosclerotic regression.

Figure 1



Participation in an Aerobic Interval Training Program Significantly Improves Measures of Depression and Quality of Life in ICD Patients with Heart Failure

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Abstract:

Introduction: Exercise training (ET) has several documented beneficial effects in patients with heart failure (HF). Only a few studies have evaluated the effects of ET in patients with an implantable cardioverter defibrillator (ICD), and even fewer have assessed effects on quality of life (QoL) and symptoms of anxiety and depression. This study is the first to evaluate short and-long term effects of Aerobic Interval Training (AIT) with respect to these issues among HF patients with an ICD.

Methods: This prospective, controlled study enrolled 38 patients with HF and an ICD. The AIT group performed a 12-week program composed of 3 weekly 60-minute sessions. All patients were evaluated at baseline, after 12-weeks and at 2-years, with a survey including the Short Form-36 (SF-36) and the Hospital Anxiety and Depression Scale (HADS). We assessed activity level at follow-up using the International Physical Activity Questionnaire (IPAQ).

Results: Following the AIT intervention a significant reduction in the HADS depression (HADS-D) score was seen. Further the AIT group also noted a significant improvement in several SF-36 sub scores indicating improved measures of QoL. At follow-up, results in the AIT group moved towards baseline or maintained stable whereas HADS-D score and several SF-36 sub scores deteriorated significantly in the sedentary control group. The hospitalization rate and risk of ICD shocks were similar in the two groups during the follow-up period. At follow-up, AIT patients reported significant less sedentary activities compared to the control group. There was also a trend towards more physical activity in the AIT group.

Conclusions: Participating in a 12-week AIT program significantly improved HADS-D score and several SF-36 sub scores related to measures of QoL in heart failure patients with an ICD. At follow-up, we noted a significant deterioration in HADS-D and measures of QoL in the control group.

CONFLICTING PATTERNS IN ECG IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Purpose: Patients with Chronic Obstructive Pulmonary Disease (COPD) often have abnormal ECG. We examined the prevalence of electrocardiographic abnormalities according to severity of COPD and investigated if there were distinct patterns in the ECG abnormalities.

Methods: 112 patients with COPD and 33 healthy controls were recruited in 2006. 12-lead resting ECGs were read by two investigators and ECG-findings categorized according to COPD severity. COPD was defined as mild/moderate (FEV1 > 50% of predicted) and severe COPD (≤50%).

Results:

Table 1: ECG signs in COPD

ECG variable		Healthy controls		Mild/moderate COPD		Severe COPD	
		mean (std)	prevalence	mean (std)	prevalence	mean (std)	prevalence
Abnormal ECG			16/33 (48%)*		40/48 (83%)		50/64 (78%)
P-wave axis < 0 or > 75°		52°(±21) *	1/33 (3%) *	65° (±28)	13/48 (27%)	68° (±30)	20/63 (32%)
QRS	**left axis deviation (-31° to -90°)**	34° (±42) *	3/33 (9%)	61° (±25)	0 §	51° (±55)	6/64 (9%)
	right axis deviation (> 90°)		0		0		3/64 (5%)
	duration < 70 or > 120 ms	92 (±15) *	2/33 (6%) *	88(±15)	12/48 (25%)	86(±15)	15/64 (23 %)
	R/S in V5 <1	10 (±11) *	2/29 (7%)	6 (±7) §	1/44 (2%) §	5 (±6)	11/59 (19%)
Heart rate >100 beats/min		66 (±12) *	0 *	80 (±16)	5/48 (10%)	85 (±17)	13/64 (20%)

* significant difference controls vs COPD
§ significant difference mild/moderate COPD vs severe COPD

Conclusion: In COPD, ECG is often abnormal, without distinct patterns. ECG abnormality did not increase from mild to severe disease. The most consistent changes were a more vertical P-axis, QRS axis deviation (in either direction) and clock-wise rotation of the QRS. The likely reason for this discrepancy is the diverse effects of COPD on ECG from the various pathological processes involved. This may indicate that there are distinct phenotypes of the disease.

The MMP-9-1562 C/T polymorphism increases the risk of cardiovascular events in patients with metabolic syndrome, partly mediated through circulating MMP-9 and EMMPRIN

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Background: Elevated levels of matrix metalloproteinase (MMP)-9 have been associated with the metabolic syndrome (MetS) and cardiovascular events. The MMP-9 -1562 C/T polymorphism has furthermore been shown as a risk factor for coronary artery disease (CAD). The non-favourable cardiometabolic state in MetS may increase the risk. We aimed to investigate the influence of the MMP-9 -1562 C/T polymorphism in subjects with CAD and MetS.

Methods: Patients (n = 1000) with angiographically verified CAD (78% men, men age 62 years) stratified in Mets+/- (n = 244/756), were analyzed for the MMP-9 -1562 C/T polymorphism and related to clinical events after 2 years follow-up. Serum levels of total MMP-9 and tissue inhibitor of metalloproteinase (TIMP)-1were analyzed in all, whereas MMP-9 activity, extracellular matrix metalloproteinase inducer (EMMPRIN), and expression of the two genes were analyzed in a subset of 240 randomly selected patients.

Results: Totally, 106 clinical endpoints were recorded (composite of nonfatal acute myocardial infarction, unstable angina pectoris, stroke and all-cause mortality).
In MetS subjects, the T-allele associated with 5.5 fold increase in event rate ($p<0.0001$, adjusted for age and gender), increased with number of MetS components and 117 % increase in total MMP-9 levels (TT homozygous, $p=0.05$). MetS subjects had significantly higher total- and endogenous active MMP-9 and TIMP-1 levels as compared to levels in non-MetS subjects ($p<0.01$ all, adjusted), and EMMPRIN was inversely correlated with pro- and endogenous active MMP-9 ($p<0.05$, both). In subjects without MetS, the T-allele was not associated with new events, nor higher MMP-9 levels. EMMPRIN was significantly correlated with total MMP-9 and TIMP-1 ($p<0.01$, both) and the two genes were inter-correlated ($p<0.001$).

Conclusion: In CAD patients with MetS, the MMP-9 T-allele increased the risk of clinical events, probably mediated through elevated MMP-9 levels and altered MMP-9 regulation.

ASYMTPTOMATIC CAROTID PLAQUES IN PATIENTS WITH RHEUMATOID ARTHRITIS ARE ASSOCIATED WITH INCREASED HDL FUNCTION

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Background: Reverse cholesterol transport (RCT) is a major anti-atherogenic function of high density lipoprotein cholesterol (HDL-c) and has been shown to be related to disease activity in patients with rheumatoid arthritis (RA).
Objectives: To evaluate if atherosclerosis affects the HDL-c function differently in RA patients compared to healthy controls.
Methods: RA patients from the Oslo RA register and the European Research on Incapacitating Disease and Social Support cohorts without cardiovascular disease (CVD) and not using lipid lowering agents or biologic medication were included. Healthy community controls were selected by Statistics Norway. RCT was measured as plasma induced 14C-cholesterol efflux from 14C-cholesterol loaded human THP1 macrophages as previously described.[1] Apolipoprotein A1 (ApoA1) and paraoxgenase-1 (PON-1) activity was measured in serum using commercial kits.
Results: 20 RA patients with (n=10) and without (n=10) asymptomatic carotid plaques (CP), and 10 controls were age and gender matched. Traditional CVD risk factors were comparable for all groups. None had diabetes. Untraditional biomarkers of CVD as CRP, ESR and proBNP were also comparable across the 3 groups; p=0.53, p=0.86 and p=0.45. RA disease factors were comparable between RA patients with and without CP. Efflux capacity was significantly increased in RA patients with CP compared both to controls without CP (p=0.03) and controls with CP (p=0.01). Likewise, both ApoA1 and PON-1 activity was increased in RA patients with CP compared to controls (p=0.02 and p=0.05, respectively). Further, APOA1 and PON-1 activity were comparable between RA patients without CP and controls (p=0.58 and p=0.69, respectively).
Conclusions: The cholesterol efflux capacity was increased in RA patients with early atherosclerosis compared to controls, independent of HDL-c level and CRP. Our findings indicate an association between atherosclerosis and upgraded HDL-c function in patients with RA when disease activity is low, possibly as a compensatory mechanism to the atherosclerotic process.

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RISK OF CARDIOVASCULAR DISEASE IN PATIENTS WITH OSTEOARTHRITIS: RESULTS FROM THE MUST-HEART STUDY

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Background: Controversies exist regarding whether patients with osteoarthritis (OA) have an increased risk of cardiovascular (CV) disease.
Objectives: Our aim was to evaluate the CV risk and presence of established CV disease in a population-based OA cohort.
Methods: The Musculoskeletal pain in Ullensaker STudy (MUST) is a cross-sectional investigation comprising a thorough clinical examination, recording of CV risk factors in addition to radiographic evaluation of hands, hips and knees of persons with self-reported OA. Of the 604 persons examined, 438 fulfilled the American College of Rheumatology classification criteria for OA in the hand, knee and/or hip joints. CV risk was calculated by the Systematic Coronary Risk Evaluation (SCORE) algorithm[1] for persons without CV disease, not using lipid lowering and/or antihypertensive medication (OA n=200 and non-OA n=87). An estimated CV risk <5% for experiencing a fatal myocardial infarction coming 10 years is defined as low to medium risk, while ≥5% is the cut off for initiation of CV preventive pharmacotherapy.
Results: The median CV risk for patients with OA [1.40 (IQR 0.65, 2.92)] was significantly higher compared to non-OA [0.99 (IQR 0.52, 1.92)] (p=0.02). The difference in the CV risk was related to higher age (p<0.001), but not to total cholesterol (p=0.07), systolic blood pressure (p=0.13) or to the OA diagnosis. Only 17/200 (8.5%) of the OA patients and 3/87 (3.4%) of the non-OA persons had a CV risk ≥5% (p=0.12). The presence of established CV disease was comparable for those with (n=72/438, 16.8%) and without OA (n=34/166, 21.1%) (p=0.23). Inflammatory biomarkers were in the normal range for the whole study population, with no difference between OA and non-OA (p=0.30 and 0.10).
Conclusions: Inhabitants with OA in a Norwegian municipality had an overall low risk of CV disease and did not have higher prevalence of established CV disease compared to non-OA.

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CARDIOVASCULAR PREVENTIVE MEDICATION AND TREATMENT TARGETS IN PATIENTS WITH OSTEOARTHRITIS: RESULTS FROM THE MUST-HEART STUDY

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Background: Guidelines recommend cardiovascular (CV) preventive pharmacotherapy when the CV risk evaluated by SCORE is ≥5%, and after diagnosed CV disease. Undertreatment and poor goal attainment of blood pressure (BP) and lipid goals have been reported in the general population.[1,2]

Objectives: Our aim was to evaluate CV primary and secondary preventive treatment and attainment of recommended goals in patients with OA in the Musculoskeletal pain in Ullensaker STudy (MUST).

Methods: The MUST is a population-based investigation comprising a comprehensive clinical examination of persons with self-reported osteoarthritis (OA)(n=630), of which 438 fulfilled the American College of Rheumatology criteria for OA. Usage of primary and secondary CV preventive medication as lipid lowering agents (LLA), anti-hypertensive medication (a-HT) and anti-thrombotic medication (AT) was recorded. Guideline recommended BP goal is ≤140/90 mmHg, and low density lipoprotein cholesterol (LDL-c) goals for primary/secondary prevention are ≤2.5/≤1.8 mmol/L, respectively. Attainments of these targets were evaluated.

Results: Primary or secondary CV prevention was indicated in 72 and 26 patients, respectively. Of the 72 patients with diagnosed CV disease, 38 (52.8%) were using LLA, 47 (65.3%) a-HT medication and 25 (34.7%) were on AT medication. Of the 125 patients (without CV disease) who had hypertension, 57 (45.6%) used a-HT medication. Of the 26 patients with a calculated CV risk by SCORE ≥5%, 2 (7.7%) used LLA.

Of the patient who were using a-HT medication, BP goal attainment was 20/47 (42.6%) and 0/57 (0%) for patients in the secondary and primary prevention groups. Of all patients using LLA, patients with CV disease achieved goals for TChol were 12/38 (31.6%) and LDL-c: 9/38 (23.7%).

Conclusions: There was a substantial underuse of cardio-protective drugs in patients with OA in the MUST-Heart study, resulting in poor BP and lipid goal attainment, with even lower numbers than what is reported for the general population.

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