

NORSKE ABSTRAKTER VED HEART FAILURE-KONGRESSEN

Sex differences in optimal doses of heart failure medication

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Background: Guideline-recommended doses of angiotensin-converting-enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) and beta-blockers are similar for men and women with heart failure with reduced ejection fraction (HFrEF), even though there are known sex differences in pharmacokinetics of these drugs. We hypothesized that there may be sex differences in the optimal dose of ACE-inhibitors/ARBs and beta-blockers in patients with HFrEF.

Methods: We performed a post-hoc-analysis of BIOSTAT-CHF, a prospective study of HF patients in whom initiation and up-titration of ACE-inhibitors/ARBs and beta-blockers was encouraged by protocol. Findings were validated in an independent cohort (ASIAN-HF) of 3,539 men and 961 women with HFrEF.

Results: Among 1,308 men and 402 women with HFrEF from BIOSTAT-CHF, women were older (74 vs. 70 years, $p < 0.001$), and had lower body weight (72 vs. 85 kg, $p < 0.001$) and height (162 vs. 174 cm, $p < 0.001$) than men. A similar

% of men and women reached guideline-recommended target doses of ACE-inhibitors/ARBs (25 vs. 23%; $p = 0.61$) and beta-blockers (14 vs. 13%; $p = 0.54$). The lowest hazards of death and/or HF-hospitalization occurred at 100% of the recommended dose of ACE-inhibitors/ARBs and beta-blockers in men, but at only 50% of the recommended doses in women. These sex differences were still present after adjusting for clinical covariates including body surface area. In ASIAN-HF, similar patterns were observed for both ACE-inhibitors/ARBs and beta-blockers, with women having a better clinical outcome at significantly lower doses as compared to men.

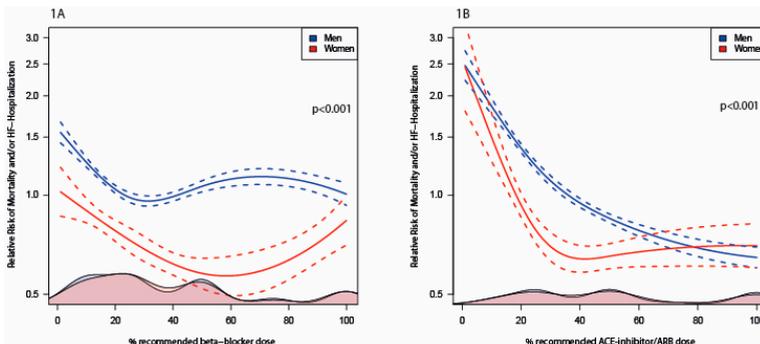
Conclusion: The optimal doses of ACE-inhibitors/ARBs and beta-blockers may be lower in women than in men with HFrEF.

Heart failure outcomes in patients with diabetes with and without atrial fibrillation - data from the EMPA-REG OUTCOME study

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Introduction: Atrial fibrillation (AF) is a frequent comorbidity in heart failure (HF), and it worsens the



outcome, reflecting a more advanced myocardial disease. AF confers an additional risk associated with HF, and HF treatments, such as beta blockers, have not demonstrated reductions in mortality in patients with AF. In the EMPA-REG OUTCOME study, empagliflozin led to a reduction in HF hospitalisations (HHF), cardiovascular (CV) death, CV death or HHF, and incident or worsening nephropathy in patients with type 2 diabetes (T2D) and established CV disease.

Purpose: This post-hoc analysis of the EMPA-REG OUTCOME study aimed to examine (1) classical and expanded HF outcomes in a T2D population with and without pre-existing AF, and (2) the effect of empagliflozin in patients with AF compared with those without AF.

Methods: In total 7020 patients with T2D and CV disease were treated with empagliflozin 10 mg, 25 mg or placebo, and followed for a median of 3.1 years. We explored the association between investigator-reported history of AF at baseline and time to first HHF, CV death, HHF or CV death, first introduction of loop diuretics, first occurrence of oedema and incident or worsening of nephropathy. We also assessed the consistency of the effect of empagliflozin treatment in patients with and without AF at baseline. Differences in the risks between treatment groups were assessed using a Cox proportional hazards model with factors for age, sex, baseline body mass index (BMI), baseline glycosylated haemoglobin (HbA1c), baseline estimated glomerular filtration rate (eGFR), region, treatment, AF and treatment by AF interaction. All analyses were performed on a nominal two-sided alpha of 0.05 without adjustment for multiplicity.

Results: A total of 389 patients had investigator-reported AF at baseline. Patients with AF were more often male (78.1 vs 71.1%), older

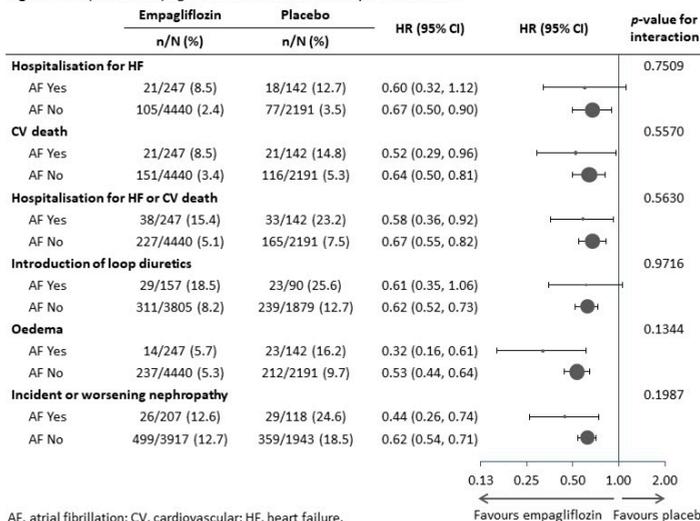
(mean age 68.4 vs 62.8 years), had higher BMI (mean 31.7 vs 30.6 kg/m²), and lower eGFR (mean 67.4 vs 74.4 ml/min/1.73 m²). Furthermore, patients with AF vs without AF at baseline had higher rates of HHF or CV death on placebo (Plac) and empagliflozin (Empa): (Plac/Empa 23.2%/15.4% vs Plac/Empa 7.5%/5.1%). Increased risks were also detected for HHF (Plac/Empa 12.7%/8.5% vs 3.5%/2.4%), introduction of loop diuretics (Plac/Empa 25.6%/18.5% vs 12.7%/8.2%), first occurrence of edema (16.2%/5.7% vs 9.7%/5.3%) as well as incident or worsening of nephropathy (24.6%/12.6% vs 18.5%/12.7%). Empagliflozin consistently reduced HHF, CV death, HHF or CV death, introduction of loop diuretics, occurrence of oedema and incident or worsening of nephropathy in patients with and without AF (figure).

Conclusion: In patients with T2D and CV disease, AF is associated with an increased risk of CV and HF outcomes and mortality. The treatment effects of empagliflozin are consistent in patients with and without AF.

Gender differences in plasma levels and prognostic value of NT-proBNP in chronic heart failure

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Figure 1: Impact of empagliflozin on HF outcomes by AF at baseline



AF, atrial fibrillation; CV, cardiovascular; HF, heart failure.

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Background: Natriuretic peptides are established biomarkers of heart failure (HF). The existence of gender-related differences in circulating levels and prognostic value are still controversial.

Methods: Individual patient data from studies assessing cardiac biomarkers (N-terminal fraction of pro-B-type natriuretic peptide - NT-proBNP - and high-sensitivity troponin T) for risk prediction in stable chronic HF were analysed.

Results: Women (n=1964, 23%) had higher median [interquartile interval] NT-proBNP concentrations than men (1678 [659-4215] vs. 1294 [522-2973] ng/L, p<0.001). Female gender predicted higher NT-proBNP independently from age, body mass index, glomerular filtration rate, left ventricular ejection fraction (LVEF), and atrial fibrillation.

Over a 2.4-year follow-up (1.6-3.2), 2351 patients (27%) died, and cardiovascular death occurred in 1558/8271 (19%). HF hospitalization was recorded in 2088/7944 (26%) over 2.0 years (1.3-2.6). Women and men had similar areas under the curve for the 3 endpoints, with higher cut-offs among women: all-cause death, 2328 ng/L vs. 1319 ng/L; cardiovascular death, 2328 ng/L vs. 1413 ng/L; HF hospitalization, 1265 ng/L vs. 907 ng/L. In the prognostic model above, the risk of the three endpoints increased by 32%, 35%, and 17%, respectively, per doubling of NT-proBNP in women, and by 41%, 45%, and 30% in men.

Conclusions: Women with chronic HF display higher NT-proBNP levels than men in the whole population as well as across many patient subgroups. This difference is not entirely explained by heterogeneity in age, BMI, or renal function. NT-proBNP holds independent prognostic signifi-

cance in both genders, although alternative prognostic cut-offs might be considered for women.

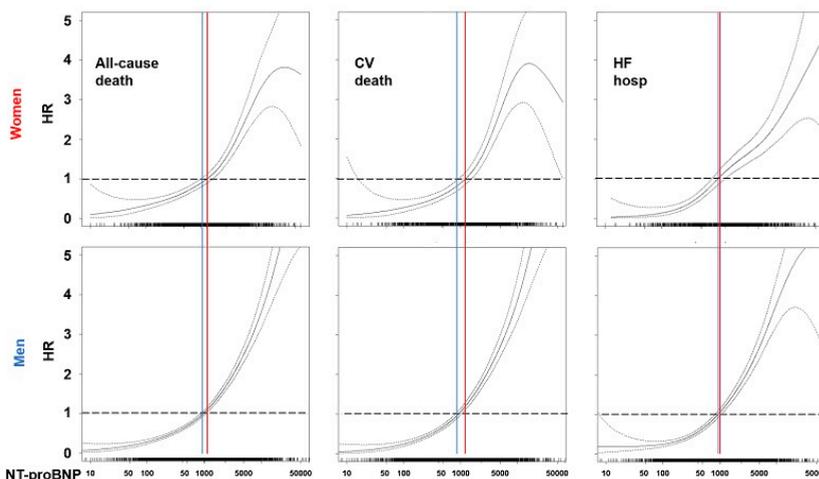
Young computer-literate health care professionals have the greatest expectations for heart failure telemonitoring

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Background: The attitude and expectations of health care professionals (HCPs) for using remote telemonitoring (TM) in patients with heart failure (HF) may be important for implementation of the remote care into clinical practice.

Objective: To identify the characteristics of HCPs who have high expectations for TM of HF patients.

Design and Methods: Data from a cross-sectional survey examining HCPs' expectations of non-invasive HF telemonitoring was performed nationwide in three Nordic Baltic countries. Participants were cardiologists and nurses working with HF patients in 41 hospitals in Lithuania (n=310), 57 hospitals in Norway (n=226) and 61 hospitals in Sweden (n=120).



quality of life with increasing HR irrespective of rhythm ($p < 0.001$).

Heart rate (beats/min)	Sinus rhythm (N=3036)	Atrial fibrillation (N=1488)	p-value for differences
< 70	1.65 ± 1.09	1.89 ± 1.09	<0.001
70-79	1.85 ± 1.09	2.05 ± 1.11	0.004
80-89	1.94 ± 1.17	2.15 ± 1.06	0.016
>90	1.94 ± 1.17	2.19 ± 1.07	0.9

Average Minnesota Living with Heart Failure Questionnaire scores ± standard deviation and type of heart rhythm and heart rate at the first visit to the hospital specialized outpatient units.

Characteristics of patients with advanced heart failure managed in a cardiomyopathy expert center

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Background: Cardiomyopathies are a heterogeneous group of intrinsic myocardial diseases most frequently genetic, whose evolution can lead to sudden cardiac death or heart failure (HF). Advanced HF (AHF) occurs when patients experience persistent severe symptoms that interfere with daily life despite maximum evidence-based medical therapy, as defined by severe persistent symptoms (NYHA class III-IV), severe cardiac dysfunction or high levels of BNP, pulmonary or systemic congestion requiring high-dose IV diuretics, episodes of low cardiac output requiring inotropes or malignant arrhythmias.

Purpose: to describe the particularities of the patients with genetic cardiomyopathies and AHF from the Expert Center for rare genetic cardiovascular diseases.

Methods: We evaluated cardiovascular parameters in all consecutive pts diagnosed with AHF in our center considering HFA-ESC criteria for defining AHF. All pts had a cardiomyopathy (dilated, DCM; hypertrophic, HCM; restrictive, RCM; arrhythmogenic, AC; specific diseases). Analyzed data on file included clinical, biologic (cardiac and renal markers), ECG, ECG holter and echocardiographic (conventional measurements and myocardial Doppler velocities and Speckle tracking based deformation study).

Results: The database included 22 pts consecutively diagnosed with AHF due to the evolution of a cardiomyopathy, with an average age of 46.2±13.9 years, 16 men (72.7%). The main diagnostics were: DCM (11, 50%), cardiac

amyloidosis (5, 22.7%), HCM (2, 9.1%), RCM (2, 9.1%), Fabry disease (1, 4.5%) and AC (1, 4.5%). All patients were in NYHA class III (14, 63.6%) and IV (8, 36.4%), with INTERMACS between stages 1 and 6. Permanent pacemakers were present in 11 pts (50%), and ICDs in 7 pts (31.8%). Lab work-up showed very high levels of BNP (1608.6±1037.1pg/ml) or NTproBNP (10038.4±6008.3pg/ml), positive Troponin I (0.076±0.05ng/ml) and GFR below 60 mL/min in 11 pts (50%) at baseline. Atrial fibrillation was present in 10 pts (45.5%). Holter ECG study showed nonsustained VT in 9 pts (40.1%). Cardiac ultrasonography findings included: HpEF in 5 pts (22.7%) and HFrEF in 17 pts (77.3%), with LVEF ranges from 14% to 60%, abnormal LV longitudinal function (mean septal S' wave 3.8±1.1 cm/s), all pts had diastolic dysfunction (E/E' 23.1±10, LAVi 65.1±25.8 mL/m²). Mitral regurgitation was present in all 22 pts (severe in 8, 36.4%) and 18 pts (81.8%) presented indirect criteria for pulmonary hypertension. All pts received diuretics as part of their treatment, 20 (90.9%) needed diuretics associations, 18 (81.2%) required IV diuretics during their evolution and 3 of them (13.6%) inotropic agents.

Conclusions: Although they are not the most frequent causes of HF, genetic cardiomyopathies can lead to AHF that represents the end stage in the evolution of the disease in absence of a pathogenic treatment, leading to persistent symptoms and decreased quality of life, increasing the number of hospitalizations and their costs.

Concentric versus eccentric remodeling in heart failure with reduced ejection fraction: clinical characteristics, pathophysiology and response to treatment

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Aims: Heart failure (HF) is traditionally classified by left ventricular (LV) ejection fraction (EF), rather than by LV geometry, with effective guideline-directed medical therapies in HF with reduced EF (HFrEF) but not HF with preserved

EF (HFpEF). Most patients with HFrEF have eccentric LV hypertrophy, but some have concentric LV hypertrophy. We aimed to compare the clinical characteristics, biomarkers patterns, and response to treatment of patients with HFrEF and eccentric versus concentric LV hypertrophy.

Methods: We included 1213 patients with HFrEF (LVEF<40%) from the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIO-STAT-CHF) study and classified LV geometry by standard echocardiographic methods. Network analysis of 92 biomarkers was used to investigate pathophysiologic pathways in geometry groups. The response to uptitration of ACE-inhibitors/angiotensin receptor blockers (ACEi/ARBs) and beta-blockers was adjusted for the likelihood of uptitration, based on a previously published model using inversely probability weighing.

Results: Concentric LV hypertrophy was present in 157 (13%) patients with HFrEF, who were on average older, more often female and more likely hypertensive compared to those with eccentric LV hypertrophy. Network analysis revealed that NT-proBNP was the most important hub in eccentric LV hypertrophy, whereas in concentric LV hypertrophy, tumor necrosis factor receptor 1 (TNF-R1), urokinase plasminogen activator surface receptor (U-PAR), paraoxonase (PON3) and P-selectin (SELP) were the most important hubs. Uptitration of ACEi/ARBs and beta-blockers was associated with a mortality benefit in HFrEF with eccentric but not concentric LV hypertrophy (p for interaction =0.02).

Conclusion: Patients with HFrEF with concentric LV hypertrophy were distinctly different from those with eccentric hypertrophy. Patients with HFrEF and concentric LV hypertrophy resembled patients with HFpEF in their clinical and biomarker profile, as well as (lack of) response to HFrEF therapy.

A novel rotary blood pump for HFpEF

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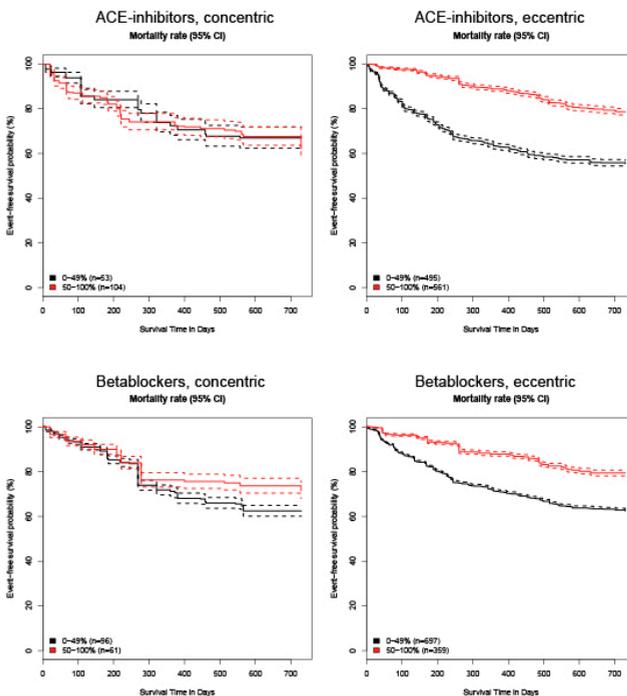
Heart Failure with preserved ejection fraction (HFpEF) has no treatment options to improve survival. We have developed a novel assist pulsed device for treatment of HFpEF.

The system consists of a small diagonal centrifugal rotary blood pump using hydrodynamic suspension of a four bladed impeller with partial unloading from the left atrium (LA) to the descending aorta. The pump is adaptive to patient physiological needs and is adjusted by feedback from the ECG and sensors. Pulsed rpm maintains pulse pressure. Implantation is by a small left side thoracotomy and minimally invasive procedure.

Animal studies in sheeps 50-80 kg have tested a spectrum of unloading and demonstrated adequate pulsed pump unloading between 1.5-3.0 l/min. ECG gated rpm increase in systole avoided LA suction and arrhythmia, interference with

mitral valve opening and ventricular underfilling. Blood pulsepressure was maintained at 95-70 mmHg, CVP 10 mmHg and native cardiac output of 3.0-5.0 l/m. Human whole blood without added anticoagulation for 8 hours and 6 consecutive days have demonstrated no hemolysis, increase in energy consumption, heat increase or clotting inside the pump. Long-term animal studies will be performed.

Partial systolic pulsed unloading of LA demonstrated adequate hemodynamics and maintained pulse pressure. This novel pump may be the first effective treatment for HFpEF.



The 6-min walk test in assessment for mortality in patients with heart failure

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Background Exercise testing is recommended in patients with heart failure (HF) to obtain an objective evaluation of functional capacity and to guide exercise prescription according to current ESC guidelines (IIA - evidence C). While peak oxygen consumption is a strong predictor of cardiovascular events and death, the value of the 6 min walk test (6MWT), which is easier to perform, is less clear.

Purpose: The aim of the present study was to examine the 6MWT in relation to mortality in our HF registry.

Method: All the patients were assessed at the first visit to the specialized outpatient HF clinics (N=5924) where a 6MWT is included in the protocol. Patients were divided into tertiles of distance walked (category 1-3 where 1 walked longest). Patients who did not perform the test was assigned category 4 (N=1990). Cox regression analysis of time to death using available demographic and measured variables was examined.

Results: 6MWT (mean meter \pm SD) were 549 \pm 60, 415 \pm 33, 237 \pm 91 for tertile 1-3, respectively. Patients in category 3 and in those that did not perform the test, category 4, were older, had poorer renal function, lower systolic blood pressure, used more diuretics, had more anemia and stroke and had a higher proportion of women than categories 1 and 2. The figure shows the Kaplan Meier plot of the differences in mor-

tality for the categories and these were highly significant ($p < 0.001$). In Cox regression analysis of time to death, the categories of the 6MWT were highly significant independent predictors for mortality adjusted for age, NYHA functional class, s-sodium, eGFR, systolic blood pressure, gender and daily dose of diuretic ($p < 0.001$). The 6MWT was also a highly significant independent predictor for mortality when used as a continuous variable ($p = 0.001$).

Conclusions: The 6MWT is easy to perform and is a powerful tool in assessing the risk for mortality in outpatients with HF. This suggests that it should be used on a regular basis in the work up of these patients.

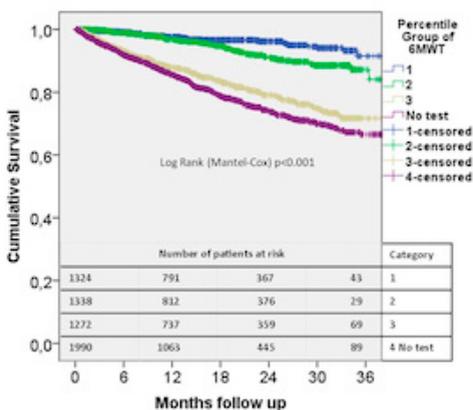
Comparative effectiveness of loop diuretics on mortality in the treatment of patients with chronic heart failure - A multicenter propensity score matched analysis

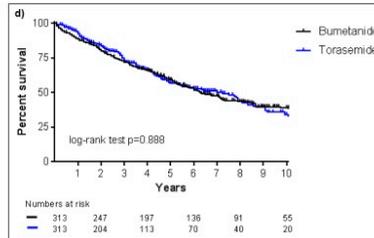
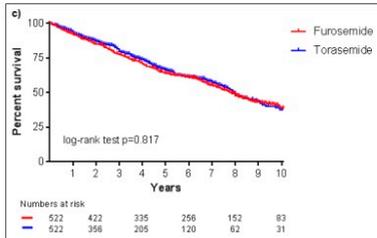
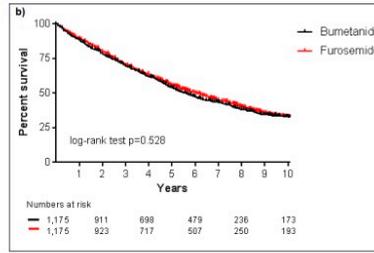
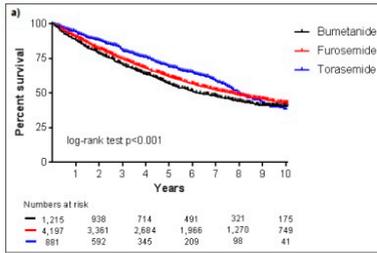
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Background: Loop diuretics are given to the majority of patients with chronic heart failure (HF). Whether the different pharmacological properties of the three guideline-recommended loop diuretics result in differential effects on survival is unknown.

Methods: 6,293 patients with chronic HF using either bumetanide, furosemide or torasemide were identified in three European HF registries. Patients were individually matched on both the respective propensity scores for receipt of either drug and dose-equivalents thereof.

Results: During a follow-up of 35,038 patient-years, 652 (53.7%), 2,179 (51.9%), and 268 (30.4%) patients died amongst those prescribed bumetanide, furosemide, and torasemide, respectively. In univariable analyses of the general sample, bumetanide and furosemide were both associated with higher mortality as compared with torasemide treatment (HR 1.50, 95% CI 1.31-1.73, $p < 0.001$, and HR 1.34, CI 1.18-1.52, $p < 0.001$, respectively). Mortality was higher in bumetanide users when compared to furosemide users (HR 1.11, 95% CI 1.02-1.20,





p=0.01). However, there was no significant association between loop diuretic choice and all-cause mortality in any of the matched samples (bumetanide vs. furosemide, HR 1.03, 95% CI 0.93-1.14, p=0.53; bumetanide vs. torasemide, HR 0.98, 95% CI 0.78-1.24, p=0.89; furosemide vs. torasemide, HR 1.02, 95% CI 0.84-1.24, p=0.82). The results were confirmed in subgroup analyses with respect to age, sex, left ventricular ejection fraction, NYHA functional class, cause of HF, rhythm, and systolic blood pressure.

Conclusions: In patients with HF, after adjustment for potential prescribing-biases, mortality does not appear to be affected by choice of loop diuretic in clinical practice. The results of randomised trials comparing diuretic agents are awaited.

Epidemiology and long-term outcome in outpatients with chronic heart failure in north-western Europe

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Objective: To describe the epidemiology, long-term outcomes and temporal trends in mortality in ambulatory patients with

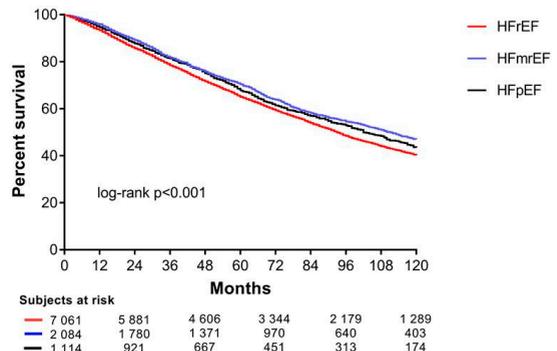
chronic heart failure (HF) with reduced (HFrEF), mid-range (HFmrEF) or preserved ejection fraction (HFpEF) from three European countries.

Methods: We identified 10,312 patients from three European HF registries. Patients were classified according to baseline left ventricular ejection fraction (LVEF) and time of enrolment (period 1: 1995-2005 vs. period 2: 2006-2015). Predictors of mortality were

analysed by use of univariable and multivariable Cox regression analyses.

Results: Among 10,312 patients with stable HF, 7,080 (68.7%), 2,086 (20.2%), and 1,146 (11.1%) were classified as having HFrEF, HFmrEF, or HFpEF, respectively. A total of 4,617 (44.8%) patients was included in period 1, and 5,695 (55.2%) patients were included in period 2. Baseline characteristics significantly differed with respect to type of HF and time of enrolment. During a median follow-up of 66 (33-105) months, 5,297 patients (51.4%) died. In multivariable analyses, survival was independent of LVEF category (p>0.05), while mortality was lower in period 2 as compared to period 1 (HR 0.81, 95% CI 0.72-0.91, p<0.001). Significant predictors of all-cause mortality regardless of HF category were increasing age, NYHA functional class, NT-proBNP, and use of loop diuretics.

Conclusion: Ambulatory HF patients stratified by LVEF represent different phenotypes. However, after adjusting for a wide range of covariates, long-term survival is independent of LVEF category. Outcome significantly improved during the last two decades irrespective from type of HF.



Gut microbiota composition and interactions with diet: dysbiosis in heart failure is partly related to lower fiber intake

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Objectives: To explore differences in the gut microbiota between patients with heart failure (HF) and healthy controls with a particular focus on associations with diet, etiology and disease severity. **Background:** Recent reports have suggested alterations in the gut microbiota of patients with HF. Associations with diet remain largely uninvestigated. **Methods:** The microbiota composition of two independent, cross-sectional cohorts (discovery, n=40 and validation, n=44) of patients with systolic HF and healthy controls (n=266) were characterized by sequencing of the bacterial 16S rRNA gene. Dietary and metabolite data were available for the valida-

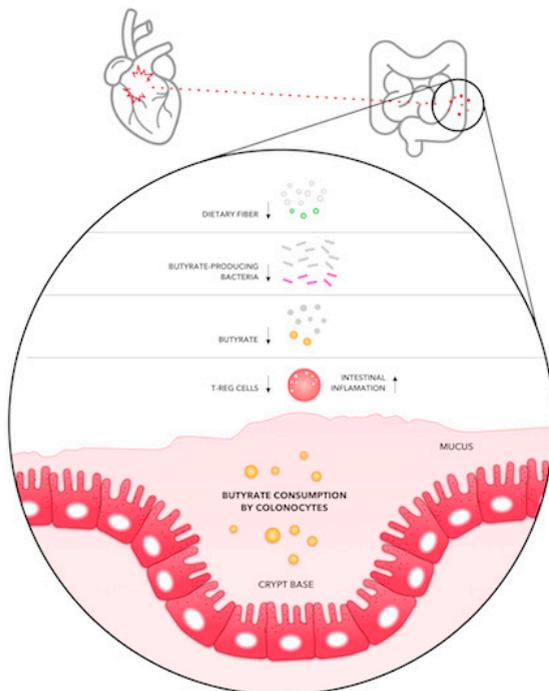
tion cohort and follow-up data were available for the discovery cohort. **Results:** The overall microbial community (beta diversity) differed between patients with HF and healthy controls in both cohorts (P<0.05). Patients with HF had a lower Firmicutes/Bacteroidetes (F/B)-ratio than controls (P=0.005), with a decreasing trend going from healthy controls via ischemic HF to non-ischemic HF (p for trend <0.05). Patients reaching a clinical endpoint (heart transplant or death) showed lower alpha diversity and lower F/B-ratio compared to healthy controls (P<0.01). Meat intake was associated with levels of trimethylamine-N-oxide (P=0.016). Finally, bacterial richness and abundance of several genera in the Firmicutes phylum were positively associated with fiber intake. **Conclusions:** The gut microbiota composition in chronic HF was characterized by a decreased F/B ratio, which was associated with etiology and clinical outcome. The dysbiosis in patients with HF was related to low fiber intake, thus dietary patterns should be included in future studies, both as covariates and potential treatment targets.

Risk willingness and survival in patients with severe aortic stenosis.

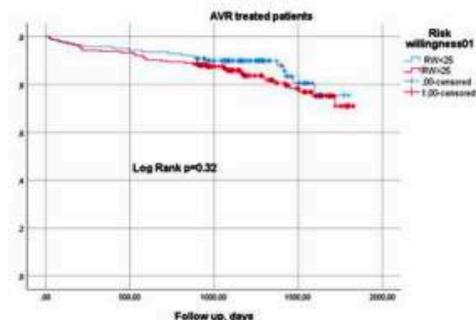
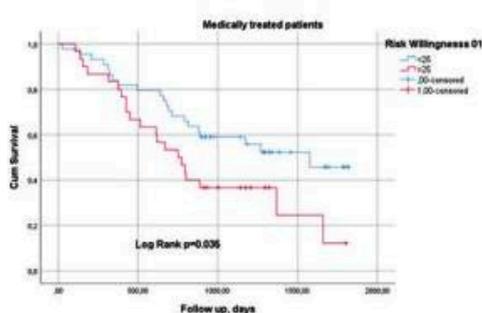
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Background: Standard Gamble (SG) is a validated tool for assessing patient preferences of treatment. SG derived risk willingness (RW) scores takes into account the notion of risk adhered to the intervention and uncertainty of the outcome, making it well suited to be used in patients with severe aortic stenosis (AS) referred for evaluation of aortic valve replacement (AVR). We anticipated an association between preoperatively assessed risk willingness and survival, but that the association would differ in strength depending on whether patients were operated or not.

Method: Consecutive patients > 18 years with severe AS were preoperatively examined with echocardiography, blood sampling, quality of life questionnaires, functional test, and SG. All patient assessment, including SG was done before and blinded to the treatment decision made by The Heart team. Patients with a Mini Mental Score less than 24 were excluded from this analysis. All-cause mortality data were collected at 5 years after the initial time of decision or intervention. We used the median RW score in the total sample



Risk willingness and survival



(25%) as a cut of to compare patients with high and low RW.

Results: Overall, 439 patients were included, 365 patients underwent AVR while 74 patients were medically treated (med-treated). Operated patients had a higher RW-score as compared to med-treated patients; 30% IQR (7-50%) vs. 12.5% IQR (1-40%), respectively, $p < 0,005$. There was no association between RW and 5-year survival in patients undergoing AVR (Fig. 1), while in the med-treated group; patients with low risk willingness had higher survival compared to those with high risk willingness, (1229 \pm 98) vs. (903 \pm 111), $p = 0.035$ respectively (days) (Fig. 2). A Cox regression analyses showed that higher RW was associated with increased mortality also when adjusted for gender, NYHA class and NT-proBNP at baseline in the medically treated group.

Conclusion: Patients with severe AS and higher risk willingness are more likely to undergo AVR. The risk willingness is associated with survival only in medically treated patients with severe AS. Patient's risk willingness adds to our knowledge of survival in medically treated patients additionally to established disease markers as NYHA class and NT-proBNP.

High prevalence of sleep apnea in patients with paroxysmal atrial fibrillation

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Background: Recent studies have suggested an association between sleep apnea (SA) and different cardiovascular disorders. The prevalence, severity and type of SA in patients with paroxysmal atrial fibrillation (AF) are less known.

Purpose: We aimed to examine the prevalence, severity and type of SA in patients with paroxysmal AF.

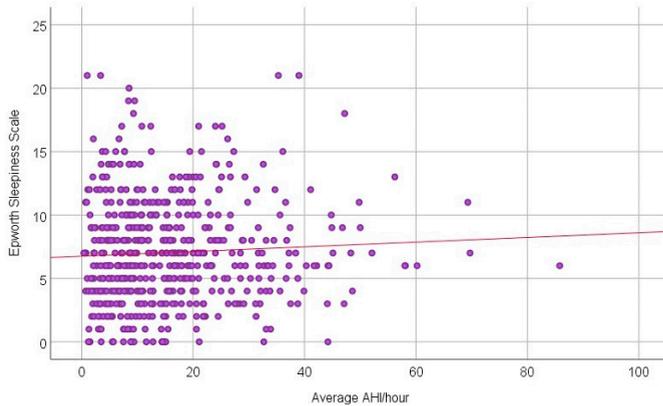
Methods: We prospectively studied 578 patients with paroxysmal AF scheduled for catheter ablation at two centers. SA was diagnosed using portable respiratory polygraphy two nights at home. Sleep studies were analyzed by an experienced specialist, using standard American Academy of Sleep Medicine definitions. The degree of subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS), with scores ranging from 0 to 24 (most sleepy). We calculated differences in variables between SA categories by Chi-Square Test or ANOVA as appropriate (Table).

Results: 158 women (27 %) and 420 men (73 %) were enrolled. Mean age was 59.9 (9.6) years, with a mean BMI of 28.6 (4.4) kg/m². 477 (83 %) of the patients had an apnea-hypopnea index (AHI) = 5/h, while moderate/severe SA (AHI = 15/h) was diagnosed in 243 patients (42 %). Men had a higher prevalence of moderate/severe SA (47 %) than women (30 %). The type of SA was predominantly obstructive, with mean AHI 15.3/h (12.1) (range 0.4/h-85.8/h). Mean central apnea index was 0.8/h (2.1). AHI increased with age, BMI, weight, neck-and waist circumference. Mean ESS score was 7 (4.1), indicating normal daytime sleepiness. There was no association between ESS and AHI/h, Spearman rho = 0.08.

Conclusion: In our AF population we found no correlation between the ESS and SA severity. The prevalence of moderate/severe SA was 42 %, which is several times higher than in the general population (8 %). The high prevalence of SA in this study may indicate that SA is under-recog-

	AHI < 5 No SA	AHI 5-15 Mild SA	AHI 15-30 Moderate SA	AHI ≥30 Severe SA	P-value
Total n=578 (%)	101 (17.5)	234 (40.5)	174 (30)	69 (12)	
Male n (%)	59 (58)	165 (71)	144 (83)	52 (75)	< 0.001
Age, years	54.9 (11.9)	59.4 (9.5)	62 (7.7)	63.6 (6.9)	< 0.001
BMI, kg/m ²	26.7 (3.8)	28.1 (4.1)	29.2 (4.4)	31.4 (4.8)	< 0.001
Neck circumference, cm	37.2 (3.2)	38.6 (3.3)	39.7 (3.3)	40.6 (2.9)	< 0.001
Waist circumference, cm	92.6 (11.9)	98.5 (11.3)	102.5 (11.6)	106.3 (12.4)	< 0.001
Waist-Hip Ratio	0.93 (0.09)	0.97 (0.08)	0.99 (0.07)	1.00 (0.07)	<0.001
Epworth Sleepiness Scale	6.8 (4.4)	6.9 (4.1)	7.4 (3.7)	7.1 (4.2)	< 0.532

Data are mean with standard deviation, or otherwise stated.



nized in patients with AF. More studies are needed to evaluate if treatment of SA can reduce the burden of AF.

After initial improvement, left ventricular ejection fraction remains stable in long-term survivors with dilated cardiomyopathy

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Purpose: Over the last decades, survival in patients with heart failure has improved with the introduction of beta-blockers, inhibitors of the renin-angiotensin-aldosterone system and implantable devices. We and others have reported a substantial improvement in left ventricular ejection fraction (LVEF) after the initiation of optimal therapy in patients with recent-onset dilated cardiomyopathy (DCM). In a prospective cohort study, we aimed to evaluate whether this initial improvement presaged enduring left ventricular competence or repre-

sented a honeymoon phenomenon.

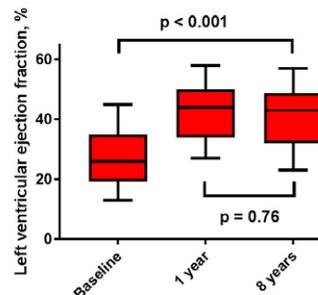
Methods: We included 102 consecutive patients referred to our tertiary care hospital with DCM and an LVEF < 40 %. Patients with significant coronary disease, primary valvular disease, congenital disease, hypertensive cardiomyopathy, myocarditis

and specific causes of DCM were excluded. After extensive baseline work-up, follow-up was performed after 1 and 8 years. LVEF was determined by echocardiography.

Results: At baseline, the mean age was 51 ± 14 years. 74 (73%) patients were male. The average duration of symptoms prior to inclusion was 7 (1-13) months, the average LVEF was 26 ± 10 % . The mean New York Heart Association (NYHA) functional class prior to enrollment was 3.2 ± 0.9. At follow-up after 7.8 (IQR 6.3 - 9.0) years, 26 (26%) patients were either dead or

had received heart transplants. In long-term survivors, the average LVEF increased from 28 ± 10 % to 42 ± 10 % after one year and remained stable until 7.8 years, (t 41 ± 10 % ; Figure). Circulating levels of NT-proBNP fell substantially from baseline to 1 year (1238 [423-2427] pg/ml vs 320 [121-609] pg/ml, p < 0.001), with no significant difference after that (320 [121-609] pg/ml vs 288 [86 - 919] pg/ml, p = 0.06). Likewise, the average NYHA class improved from 3.2 ± 0.9 prior to inclusion to 1.4 ± 0.6 after one year (p for difference < 0.001), and remained at 1.6 ± 0.6 at 8 years (p for difference from 1 year, 0.10).

Conclusion: After a substantial initial improvement, left ventricular function, natriuretic peptides and functional class remains stable in long-term survivors of dilated cardiomyopathy.



Long term outcomes in asymptomatic patients with severe aortic stenosis

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Objective: Patients with asymptomatic, severe aortic stenosis (AS) are presumed to have a benign prognosis. Current guidelines therefore do not recommend aortic valve replacement (AVR) for isolated, asymptomatic, severe AS. The aim of this study was to explore the natural history of patients with severe AS advised against surgery due to lack of symptoms.

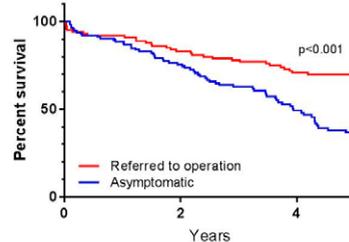
Methods: Patients who were referred for diagnostic evaluation for severe AS were identified through a search in the hospital database. We reviewed the medical records of every patient with the ICD-10-code for AS (I35) between Dec 1st, 2002 and Dec 31st, 2016. Clinical data, biochemistry and imaging data were procured for the patients categorised as asymptomatic and 100 age- and gender matched patients referred to AVR. By March 2017, mortality data were obtained from the national Norwegian Cause of Death Registry. This study was approved by the Regional Ethical Committee, which waived the need for patient consent because of the retrospective nature of the study.

Results: Among the 3454 patients with the code for AS, 2341 patients were evaluated by the heart team for possible AVR due to severe AS during the period in question. 1953 patients were referred to AVR. 388 patients received conservative treatment due to either a lack of symptoms (n=114), patient refusal (n=49) or a high risk-benefit ratio or because they had comorbidities presumed to reduce life expectancy significantly (n=225). The asymptomatic patients had a median age of 83.4 (IQR: 76.5-87.0). 42 % were male. The peak aortic jet velocity was 4.4 ± 0.8 m/s, and the aortic valve opening area was 0.68 ± 0.16 cm². During a mean duration of follow up of 4.0 ± 2.5 years (median 4.1 years, IQR: 2.10-5.4), 72 of the 114 patients died (63%). Survival at 1, 2 and 3 years for the asymptomatic patients was 88%, 75% and 63% respectively, compared with 91%, 82% and 77% in those who were referred to AVR ($p < 0.001$) (Figure 1). 28 patients received AVR at a median 1.6 (IQR:1.1,-2.8) years after they were initially advised against surgery. When censoring the

asymptomatic patients at the time of AVR, 1, 2 and 3 years survival was 88%, 72% and 57%. Cox regression analysis identified Troponin T as an independent predictor of mortality in patients with asymptomatic severe AS, $p = 0.029$. Age, valvular disease severity, NT-ProBNP, diabetes and coronary artery disease were not predictors of mortality.

Conclusions: Patients with severe AS who were advised against surgery due to lack of symptoms, had significantly higher mortality than patients referred for AVR. Troponin T was an independent predictor of mortality. Our results suggest that in patients with severe AS, AVR should be considered even in «asymptomatic» patients, particularly if Troponin T is elevated.

Figure 1. Survival analysis. Kaplan-Meier curve reflecting survival in asymptomatic patients with severe aortic stenosis compared to 100 age- and gender matched patients referred to operation.



The secreted matrix glycoprotein ADAMTSL3 is up-regulated in heart failure and mediates anti-fibrotic effects in cardiac fibroblasts

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Background/Introduction: Fibrosis is a central remodelling process in heart failure where cardiac fibroblasts (CFB) become activated, trans-differentiate into myofibroblasts, and produce excessive amounts of extracellular matrix (ECM) constituents. The ADAMTSL (a disintegrin and metalloproteinase with thrombospondin motif like) protein family consists of seven glycoproteins secreted into the ECM. They are structurally similar to the matrix metalloproteinase and ADAMTS protein families, yet lack a catalytic domain. Despite suggested roles in ECM microfibril formation and connective tissue disorders, the function of ADAMTSL proteins remain largely unknown, including in the heart.

Purpose: The purpose of this study was to investigate the regulation and role of ADAMTSL3 in heart failure.

Methods: Expression level of ADAMTSL3 was examined in myocardial biopsies from patients with aortic stenosis (AS) and ischemic dilated cardiomyopathy (iDCM). ADAMTSL3 levels were also examined in mouse hearts after aortic banding (AB) and in primary cultures of CFB and cardiomyocytes (CM) from neonatal rats. Finally, adenoviral overexpression of ADAMTSL3 was performed in CFBs to investigate the effects of increased ADAMTSL3 levels on fibrosis.

Results: In cardiac biopsies from patients with AS and iDCM, ADAMTSL3 mRNA was increased 2-fold and 1.5-fold, respectively, compared to controls, suggesting that ADAMTSL3 levels are increased in the heart of patients with heart failure. Similarly, mice subjected to AB showed elevated left ventricular mRNA levels of ADAMTSL3 during concentric hypertrophic remodelling and dilated, end-stage heart failure (1.5-fold and 2-fold, respectively). In rat heart cell cultures, mRNA expression of ADAMTSL3 was 3-fold higher in CFB than in CM, suggesting that CFBs are the main producers of ADAMTSL3 in the heart. CFBs overexpressing ADAMTSL3 showed reduced mRNA levels of the stiff fibrillar collagen type I (70% of control) and reduced total collagen protein synthesis to 50% of controls, measured by radioactive proline incorporation, suggesting anti-fibrotic effects. In line with this, ADAMTSL3 overexpression reduced mRNA levels of the collagen cross-linking enzyme lysyl oxidase (80% of control). Furthermore, expression of the ECM scaffold proteins fibrillin-1 and fibronectin was reduced to 80 and 50% of control, respectively, and the myofibroblast signature gene, alpha smooth muscle actin, was reduced to 80% of control. These anti-fibrotic effects of ADAMTSL3 overexpression was likely mediated through reduced TGF β -signaling, as ADAMTSL3 overexpressing CFB showed reduced phosphorylation of the TGF β -directed transcription factor SMAD2.

Conclusion: Our results suggest that ADAMTSL3 mediates anti-fibrotic effects in the heart. This will be investigated further in ADAMTSL3-knock out mice subjected to heart failure.

Long-term survival in contemporary patients with dilated cardiomyopathy

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Purpose: Historically, the prognosis in patients with dilated cardiomyopathy has been poor. Outcomes have improved substantially over the last decades due to advances in medical therapy and the development of implantable devices for the treatment of heart failure. We report long-term survival data from a prospective cohort of contemporary patients with dilated cardiomyopathy.

Methods: Between October 2008 and December, 2012, we recruited 102 patients referred to our tertiary care hospital with a left ventricular ejection fraction (LVEF) < 40 % and a diagnosis of idiopathic DCM based on patient history, echocardiography and coronary angiography. We performed an extensive baseline evaluation, and the patients were included in a prospective cohort study. During follow-up, vital status, device implantation and heart transplantations were recorded.

Results: Baseline characteristics are provided in the Table. After a median follow-up of 7.8 (IQR 6.3 – 9.0) years, 12 patients had received cardiac allografts. One of these patients later died from acute allograft rejection. In addition, 15 patients died. Transplant-free survival was 74 %, and over-all survival was 84 % (Figure). At follow-up after 7.8 years, the average LVEF in the long-term, transplant-free survivors was 41 \pm 10 %. Baseline age and left ventricular size and ejection fraction did not differ between survivors and non-survivors. The longer the duration of symptomatic heart failure prior to inclusion, the higher the risk of heart transplantation or death

Age - years	51 \pm 14
Male gender - no (%)	74 (73)
Duration of symptoms - months	7 (3 - 16)
NYHA class prior to inclusion - no I/II/III/IV	4/15/25/58
Systolic blood pressure - mm Hg	116 \pm 20
Left ventricular ejection fraction - %	26 \pm 10
Peak oxygen consumption - ml/kg/min	19.7 \pm 7
N-terminal pro-B-type natriuretic peptide - pg/ml	1332 (584 - 2903)
Pulmonary capillary wedge pressure - mmHg	15 \pm 8

NYHA = New York Heart Association

(Cox regression $p < 0.001$), suggesting that late initiation of therapy or a lack of response to therapy for heart failure predicts a poor outcome.

Conclusion: In contemporary patients with dilated cardiomyopathy, survival is better than previously reported.

