HEART FAILURE AND DIABETES: A TREACHEROUS COMBINATION

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Heart failure with mid range ejection fraction, characteristics and prognosis in patients with and without type 2 diabetes

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Background: Patients with type 2 diabetes (T2DM) are at increased risk of developing heart failure (HF) however information on the recently instituted entity mid-range HF (HFmrEF) is so far lacking.

Purpose: To study characteristics and prognostic implications of T2DM in HFmrEF in a contemporary HF population.

Methods: Of 30 696 patients with clinically judged HF included in the Swedish Heart Failure Registry 2003–2011, we identified 6843 patients with HFmrEF (EF 40–49%). Patients were followed for mortality until 31 December 2014 (median 4 years). Differences in background characteristics were adjusted for in a Cox regression model.

Results: T2DM was present in 24%. Mean age was 74 years and 40% were women regardless of T2DM status. Patients with T2DM had a longer HF duration, more often NYHA class III–IV and a slightly higher median NT-pro-BNP (4789 vs. 4515 pg/mL, $p=0.01$). Further on, T2DM patients more often had reported ischemic heart disease (66 vs. 51%; $p<0.0001$), hypertension (63 vs. 45%; $p<0.0001$), pulmonary disease (20 vs. 17%; $p=0.007$) and compromised renal function (eGFR <60 mL/min/1.73 m²; 58 vs. 48%; $p<0.0001$) while atrial fibrillation (48 vs. 51%; $p=0.02$) and valvular heart disease (18 vs. 22; $p=0.0007$) were less common. Patients with T2DM had a compromised survival as depicted in the Kaplan Meier survival curve. T2DM independently predicted mortality before and after multivariate adjustment, unadjusted HRs (95% CI) 1.46 (1.36–1.57) and adjusted HR* 1.51 (1.39–1.65).

KM-survival in HFmrEF, T2DM vs. no T2DM. *Adjusted for diabetes, gender, age, duration of heart failure, level of care, weight, blood pressure, ischemic heart disease, co-morbidities, revascularisation, eGFR class, Hb class, pharmacological treatments.

Conclusion: Within the HFmrEF group, 24% had T2DM and these patients were burdened with more comorbidity especially ischemic heart disease and hypertension. Furthermore, the prognosis was more severe and T2DM increased mortality risk by 50%. This information is important for future planning of HF care and HF outcome studies.

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How does diabetes affect iron status in patients with heart failure?

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Both heart failure with reduced ejection fraction (HFrEF) and diabetes mellitus (DM) constitute co-morbidities significantly interfering with iron metabolism. It remains unclear whether and how the concomitance of DM in patients with HFrEF affects iron status.

Methods: We analysed the data of 622 men with stable HFrEF (age: 57±11 years, CAD: 71%, NYHA class III–IV: 41%, LVEF: 27±8%, DM: 30%). ID was defined as serum ferritin <100 µg/L, or serum ferritin 100–299 µg/L with transferrin saturation [TSAT] $<20\%$. Additionally, serum levels of hepcidin and soluble transferrin receptor [sTfR] were assessed as biomarkers of iron status.

Results: Patients with DM as compared with those without DM were older, more

obese, had more prevalent CAD, more symptomatic HF, more common hypertension and worse kidney function (all $p<0.05$), but with no difference in LVEF, uric acid, hsCRP, NT-proBNP and haemoglobin level between these 2 groups. Regarding iron status, men with HFrEF and DM as compared with those without DM demonstrated a similar prevalence of ID (33% vs 34%, $p>0.2$), and a trend towards a higher prevalence of IDA (13%, vs. 9%, $p=0.08$). There were no differences in either serum ferritin or TSAT between DM and non-DM men with HFrEF ($p>0.2$), whereas DM was accompanied by reduced sTfR (1.19 (0.96–1.60) vs. 1.31 (1.01–1.83) mg/L, $p<0.05$), and a borderline higher hepcidin (65 (33–123) vs. 55 (22–111) ng/mL, $p=0.07$). sTfR ≥ 1.32 mg/L was found in 50% vs 41% of DM vs non-DM men with HFrEF, respectively ($p<0.05$), whereas serum hepcidin <14.5 ng/mL was found in 18% vs 5% of DM vs non-DM men with HFrEF, respectively ($p<0.001$).

In non-DM men with HFrEF, lower hepcidin was related to younger age, whereas such relationship was not seen in DM subjects. In non-DM men with HFrEF, higher sTfR correlated with lower LVEF, sodium, GFR, and total cholesterol, and higher hs-CRP, NT-proBNP and uric acid (all $p<0.05$), whereas in DM subjects sTfR was related only to hs-CRP, NT-proBNP, uric acid and total cholesterol (all $p<0.05$).

Conclusions: DM does not differentiate iron status in men with HFrEF based on standard biomarkers (ferritin, TSAT), however the measurements of sTfR and hepcidin suggest the higher prevalence of intracellular ID (reflected by high sTfR) and depleted iron stores (reflected by low hepcidin). Importantly, there are different clinical correlates of novel iron status biomarkers in DM vs non-DM subjects with HFrEF, which might indicate the different pathophysiological mechanisms related to these iron derangements.

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Empagliflozin reduces mortality in analyses adjusted for control of blood pressure, low density lipoprotein cholesterol and HbA1c over time

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Background: In EMPA-REG OUTCOME, empagliflozin given in addition to standard of care significantly reduced the risk of cardiovascular (CV) (HR 0.62 [95% CI 0.49, 0.77]) and all-cause (0.68 [0.57, 0.82]) mortality vs placebo in patients with type 2 diabetes and established CV disease. We investigated the effects of controlling blood pressure (BP), low density lipoprotein cholesterol (LDL-C) and HbA1c on the treatment difference in mortality.

Methods: Patients were randomised to empagliflozin 10 mg, empagliflozin 25 mg, or placebo. CV and all-cause mortality were assessed in the pooled empagliflozin group vs placebo adjusting for control of BP, LDL-C and HbA1c at baseline and during the study as time-dependent covariates. Control was defined as systolic BP <140 mmHg and diastolic BP <90 mmHg, LDL-C <100 mg/dL, and HbA1c $<7.5\%$.

Results: Adjusting for control of BP, LDL-C, HbA1c and all these covariates at baseline and during the study, HRs for CV death with empagliflozin vs placebo were 0.61 (0.49, 0.76), 0.59 (0.47, 0.75), 0.62 (0.49, 0.78) and 0.61 (0.48, 0.76), and for all-cause mortality were 0.67 (0.56, 0.81), 0.66 (0.55, 0.79), 0.67 (0.56, 0.81) and 0.67 (0.56, 0.81), respectively (Figure).

Cox regression analysis in patients treated with ≥ 1 dose of study drug. Control of BP, LDL-C and HbA1c were defined as systolic BP <140 mmHg and diastolic BP <90 mmHg, LDL-C <100 mg/dL, and HbA1c $<7.5\%$.

Conclusion: Empagliflozin reduced CV and all-cause mortality to the same extent when analyses were adjusted for control of BP, LDL-C and HbA1c over time, suggesting that the mortality reductions were not driven by controlling or not controlling these CV risk factors during the study.

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NOVELTIES IN LEFT ATRIAL INTERVENTIONS

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Acute hemodynamic and echocardiographic effects of percutaneous ventricular restoration therapy using the Parachute device in patients with severe ischemic cardiomyopathy: a single center experience

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Background: In patients with ischemic heart failure following antero-apical myocardial infarction (MI) the concept of ventricular partitioning by percutaneous ventricular restoration (PVR) using the Parachute device (Cardiokinetix, Inc., Menlo Park, California) has demonstrated long-term safety and efficacy as a result of left ventricular remodeling.

Purpose: This single center study sought to evaluate if PVR therapy might influence acute hemodynamic and functional parameters in subjects with apical wall motion abnormalities such as dyskinesia or aneurysm after antero-apical MI.

Methods: In 22 consecutive patients (age 67.6±8.7 years, 15 male) with severe ischemic cardiomyopathy (ejection fraction (EF): 27.1±5.5%) after previous antero-apical MI intra-procedural invasive right and left heart hemodynamics before and after PVR as well as pre- and post-procedural echocardiographic parameters were compared.

Results: Immediately after Parachute implantation invasive measurements demonstrated a significant increase in cardiac output, cardiac index and stroke volume, whereas the remaining hemodynamic parameters did not significantly change. Post-procedural echocardiographic left ventricular (LV) parameters showed a significant reduction of left ventricular end-diastolic volume and left ventricular end-systolic volume as well as a non-significant increase in LV-EF (Table 1).

	Pre-implantation	Post-implantation	p-value
Cardiac output (l/min)	4.08±1.1	5.09±1.38	p<0.0001
Cardiac index (l/min/m ²)	2.12±0.42	2.60±0.64	p=0.001
Stroke volume (ml)	65.9±15.06	74.2±18.61	p=0.001
Systolic PAP (mmHg)	46.7±20.4	51.33±18.5	p=ns
Mean PAP (mmHg)	32.4±11.52	35.6±10.02	p=ns
PCWP (mmHg)	21.9±5.5	23.05±5.32	p=ns
Systolic blood pressure (mmHg)	104.4±17.8	111.9±19.6	p=ns
Diastolic blood pressure (mmHg)	56.9±11.8	59.1±11.7	p=ns
LVEDV (ml)	212.9±45.5	189.4±37.5	p=0.0001
LVESV (ml)	155.2±40.9	136.7±35.9	p=0.0001
Echocardiographic EF (%)	27.1±5.5	27.8±5.9	p=ns

EF: ejection fraction, PAP: pulmonary arterial pressure, PCWP: pulmonary capillary wedge pressure.

Conclusion: The current data indicate favorable acute hemodynamic effects of PVR using the Parachute device and thus underline the potential therapeutic impact of this innovative technology in selected patients with ischemic heart failure.

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Right ventricular papillary muscles approximation for functional tricuspid regurgitation treatment - in-vitro feasibility study

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Introduction: Treatment of functional tricuspid regurgitation (FTR) is considered challenging and currently available techniques are limited mainly to the tricuspid annuloplasty. However, unaddressed ventricular dilation can progress, leading to FTR recurrence. In case of mitral regurgitation, the papillary muscles (PM) approximation concomitant with annuloplasty showed superior long term results over annuloplasty alone and its transcatheter approach was feasible.

Purpose: To evaluate the effect of PM approximation in case of FTR in an ex-vivo passive beating heart platform.

Methods: The FTR was simulated in 6 porcine hearts in a system comprising a piston pump and a Windkessel model. The FTR model exploited the tendency of right ventricle to dilate under pressure which was enough to induce the pathology. Constrain bands were placed externally at the annulus and PM level to obtain competent valve. The system was set to 70bpm, 70ml of stroke volume and 25mmHg of mean arterial pressure.

Three stitches were passed from anterior PM towards: i) posterior PM (A-P), ii) septal PM (A-S) and iii) septal wall (A-SW, in between A-P and A-S). They were fixed from one end to the septal wall and at the other to a ratchet (see Fig. 1A) which rotation allowed for fine-controllable shortening of the intraventricular distance selectively for each position (A-P, A-S and A-SW). Cardiac output (CO) and

tricuspid regurgitation fraction (TRF) were evaluated at baseline, FTR and at 30% and 60% of PM approximation between evaluated positions.

Results: The results are summarized in Table 1. The induction of FTR resulted in a significant drop of CO (63%) and a double increase of TRF. The treatment induced a recovery of CO up to around 78% and 91% in respect to the baseline after 30% and 60% of the approximation, respectively. As expected, TRF had reverse trend. There were no statistical differences between approximation positions. Fiberscope and 3D echocardiography provided additional insight into the valve competency (see Fig. 1B and C showing exemplary approximation at A-P position).

Table 1

	Baseline	FTR	PM approximation 30%			PM approximation 60%		
			A-S	A-P	A-SW	A-P	A-SW	
CO, l/min	4.6±0.4	2.9±0.4*	3.5±0.8*	3.6±0.8*	3.6±0.7*	4.0±0.8*	4.2±0.9*	4.4±0.5*
FTR, %	25±3	51±6*	44±10*	42±9*	42±9*	38±7*	34±9*	32±5*

*p<0.05 vs. Baseline; †p<0.05 vs. FTR.

Figure 1

Conclusions: The experimental evaluation showed that the PM approximation is a feasible approach to treat FTR. As all approximation positions had comparable effects on the valve functioning it offers an additional degree of versatility encouraging to translate the procedure into an interventional approach.

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Insertable cardiac monitor in older patients candidates to percutaneous PFO closure. Preliminary results of a perspective registry study

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Background: Many relationships between patent foramen ovale (PFO) and atrial fibrillation (AF) may explain the causal link between atrial septal abnormalities and cryptogenic brain ischemia, besides trans-cardiac paradoxical emboli. An underlying atrial vulnerability in some PFO patients (pts) or a pre-existing misdiagnosed AF may lead to an unnecessary percutaneous intervention. The remarks that the ischaemic recurrences after device implantation affect mainly over 55 years old pts, usually in the absence of a significant residual shunt, stress the need of an improvements in AF detection algorithms.

Purpose: To define the additional rate of paroxysmal AF detection over the standard 24 hours to 7 days external monitoring, through a 6-months prolonged insertable cardiac "loop recorder" monitoring (ICM), in patients over 55 years old with cryptogenic stroke and candidates to percutaneous PFO closure.

Methods: Pts with a cryptogenic stroke (CS) and a PFO associated to a significant right-to-left shunt were considered candidate to percutaneous closure, if they presented one or more of the following high-risk features: permanent right-to-left shunt, atrial septal aneurysm, prominent Eustachian valve, recurrent brain ischemia, previous deep vein thrombosis, thrombophilia. The over 55 years old candidates to PFO closure underwent a 6-months ICM protocol, if they showed one or more of the following AF risk factors: heart failure, hypertension, age ≥65 years, diabetes, atrial runs, left atrium dilatation, left ventricle hypertrophy, pulmonary disease, thyroid disease, obesity. An ICM-detected AF threshold of ≥5 minutes was considered clinically meaningful, indicating oral anticoagulation and excluding a percutaneous treatment.

Results: From January 2008 to July 2016, 132 pts suffering CS underwent to ICM monitoring. 55 pts presented a PFO with high-risk features and were considered candidate to closure. In this group, the 6-months paroxysmal AF detection rate was 10% (5/55 pts). 21 pts (42%) underwent to a percutaneous PFO closure (group A) and 29 (58%) were medically treated (group B). The following AF detection rate was 24% in group A and 10% in group B. The mean time-to-AF detection was 4.5 months. The 36-months cumulative AF-free survival was 48%.

Conclusion: An occult pre-existing AF may lead to an unnecessary percutaneous intervention in a significant proportion of pts over 55 years old suffering