Heart Failure – Chronic Heart Failure, Diagnostic Methods, Biomarkers

Pro-adrenomedullin may guide decongestive therapy in acute heart failure patients

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Background: Congestion is a major determinant of outcomes in acute heart failure. Its assessment is complex, rendering sufficient decongestive therapy a challenge. Consequently, residual congestion is frequent at discharge, increasing the risk of re-hospitalisation and death. Mid-regional pro-adrenomedullin mirrors vascular integrity and may therefore be an objective marker to quantify congestion and to guide decongestive therapies in patients with acute heart failure.
Methods: Observational, prospective, single centre study in unselected patients presenting with acute heart failure. This study aimed to assess the potential capability of mid-regional pro-adrenomedullin in guiding decongestion therapy. Congestion was assessed applying clinical scores. Baseline pro-adrenomedullin concentrations were related to in-hospital (all-cause) death and in-hospital worsening heart failure. Discharge pro-adrenomedullin concentrations were related to post-discharge (all-cause) mortality. Worsening heart failure was defined by the RELAX-AHF-2 trial criteria. Cox and logistic regression models with adjustment for clinical features were fitted.
Results: Overall, 233 patients were analysed (median age 77 years, 148 male (63.5%)). Ischaemic cardiomyopathy was the most common cause of heart failure affecting 85 patients (40.5%). The present hospitalisation was the first heart failure event in 47 patients (20.9%). Frequent presumed triggers were tachyarrhythmia (68 patients, 29.4%), hypertensive crisis (60 patients, 26.4%), infections (52 patients, 22.6%) and acute myocardial infarction (30 patients, 12.9%). Median NT-proBNP concentration was 7,332 ng/l (IQR 3,425, 14,854) and pro-adrenomedullin 2.0 nmol/l (1.4, 2.9). Overall, 8 patients (3.5%) died in hospital, 100 (44.1%) experienced in-hospital worsening heart failure and 60 patients (36.6%) died after discharge over a median follow-up of 1.92 years. Pro-adrenomedullin concentrations (logarithmised) were significantly associated with congestion, both at baseline as well as during the hospital stay (Figure 1). Baseline pro-adrenomedullin was associated with in-hospital worsening heart failure (OR 4.23, 95% Confidence Interval 1.87, 9.58; $p < 0.001$), pro-adrenomedullin at discharge with post-discharge death (HR 3.93, 95% CI 1.86, 8.67; $p < 0.001$) (Figure 2).
Conclusion: In patients admitted with decompensated heart failure, elevated pro-adrenomedullin is associated with congestion, in-hospital worsening heart failure and with death during follow-up. Pending external validation, these results identify pro-adrenomedullin as a promising biomarker to quantify cardiac congestion.

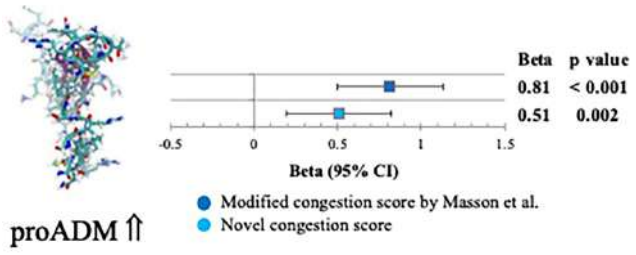

Figure 1: Association of pro-adrenomedullin with change of score values. Beta (95% CI): Beta value (95% Confidence Interval).

Figure 1

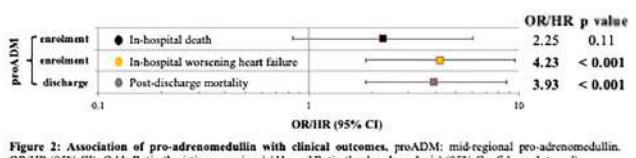

Figure 2: Association of pro-adrenomedullin with clinical outcomes. proADM: mid-regional pro-adrenomedullin. OR/HR (95% CI): Odds Ratio (logistic regressions) / Hazard Ratio (landmark analysis) (95% Confidence Interval).

Figure 2

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Predictors of kidney-related outcomes in chronic heart failure patients with concomitant type 2 diabetes mellitus treated with dapagliflozin

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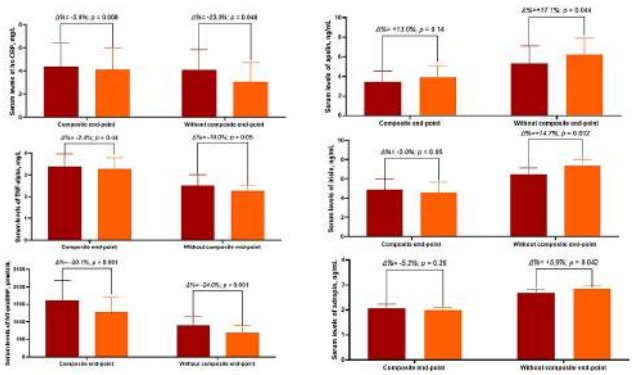
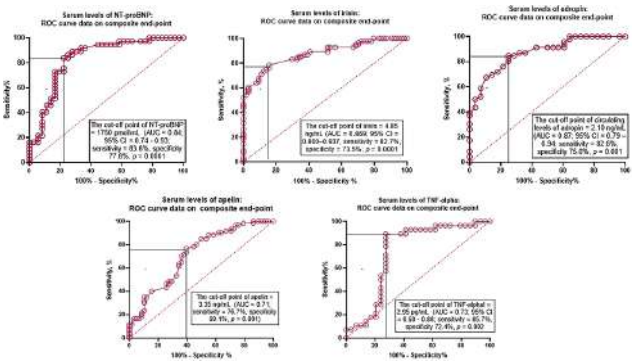
Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have a favorable impact on the kidney function in patients with heart failure (HF), while there is no clear evidence of what factors predict this effect. The aim of the study was to identify plausible predictors for kidney function outcome among patients with HF and investigate their association with SGLT2i.
Methods: We prospectively enrolled 480 patients with type 2 diabetes mellitus (T2DM) treated with diet and metformin and concomitant chronic HF and followed them for 52 weeks. All patients were treated with individually adjusted diet and metformin and had well-controlled T2DM (HbA1c > 6.9%), which did not require insulin therapy. On this occasion, we excluded the patients with T2DM treated with insulin because it previously was found to be a powerful trigger for changes in irisin, adropin and apelin regardless of chronic kidney disease (CKD) progression. In the study, we determined kidney outcome as a composite of ≥ 40% reduced estimated glomerular filtration rate from baseline, newly diagnosed end-stage CKD or kidney replacement therapy. The relevant medical information and measurement of the biomarkers (N-terminal natriuretic pro-peptide, irisin, apelin, adropin, C-reactive protein, tumor necrosis factor-alpha) were collected at baseline and at the end of the study.
Results: The composite kidney outcome was detected in 88 (18.3%) patients of the entire population. All patients received guideline-recommended optimal therapy, which was adjusted to phenotype/severity of HF, cardiovascular risk and comorbidity profiles, and fasting glycaemia. Levels of irisin, adropin and apelin significantly increased in patients without clinical endpoint, whereas in those with composite endpoint the biomarker levels exhibited a decrease with borderline statistical significance ($p = 0.05$) (Figure 1). Well-balanced optimal cutoff points for



The dynamic changes of the biomarkers



The optimal cutoffs for biomarkers

biomarkers are reported by Figure 2. Multivariate logistic regression revealed that use of SGLT2i (OP = 0.92; p = 0.048), baseline serum levels of irisin ≤ 4.50 ng/ml (OR = 1.51; p = 0.001) and adropin ≤ 2.10 ng/ml (OR = 1.15; p = 0.001) along with and a ≤ 15% increase in the levels of these biomarkers (OR = 1.60; p = 0.001) and ≤ 6% (OR = 1.21; p = 0.001), respectively, remained an independent predictor for composite kidney endpoint. We noticed that irisin ≤ 4.50 ng/ml at baseline and a ≤ 15% increase in irisin serum levels added more valuable predictive information than the reference variable. However, the combination of irisin ≤ 4.50 ng/ml at baseline and ≤ 15% increase in irisin serum levels (area under curve = 0.91; 95% confidence interval = 0.87-0.95) improved the discriminative value of each biomarker alone. Conclusion: We suggest that low levels of irisin and its inadequate increase during administration of SGLT2i are promising predictors for unfavorable kidney outcome among patients with T2DM and concomitant HF.

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Circulating levels of erythrocytes-derived vesicles related to poor glycaemia control in heart failure patients with type 2 diabetes mellitus

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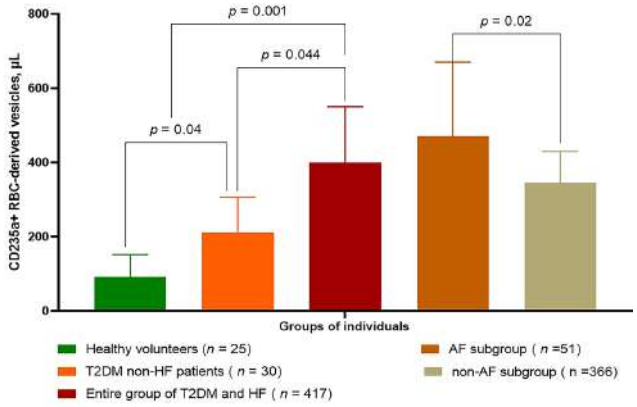
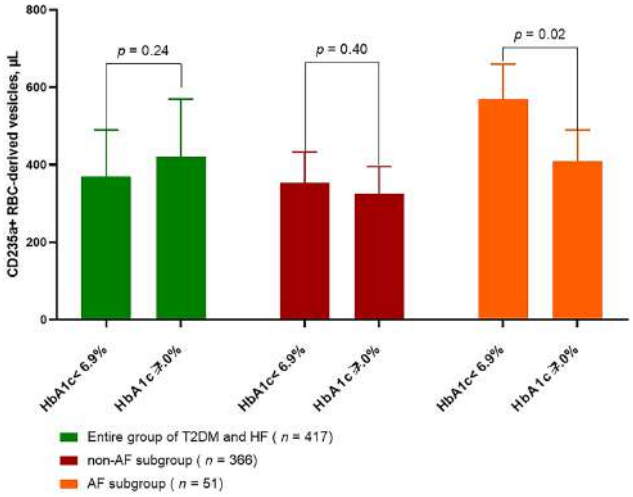
Background: Previous studies demonstrated that insulin resistance, hyperglycemia contribute to the development of a pro-thrombotic state characterized by increased platelet activation, activation of coagulation cascade and elevated number of extracellular vesicles (EVs) in type 2 diabetes mellitus (T2DM) patients. There is a less known impact of glycaemia control in T2DM patients with concomitant heart failure (HF) and atrial fibrillation (AF) on a number of erythrocytes-derived EVs. The aim of the study was to elucidate whether glucose control in T2DM patients with HF and AF affect a circulating number of erythrocytes-derived EVs.
Methods: The entire patient population composes of 417 patients (231 male, 55.4% and 186 female, 44.6%) with average age of 53 years as well as 25 healthy volunteers and 30 T2DM non-HF individuals. As inclusion, age ≥ 18 years, T2DM, established HF, and written consent to participate in the study was used. Patients after successful ablation procedure (mainly radiofrequency ablation) were included in the group non-AF in 6 weeks after procedure if cardiac rhythm is sinus. All patients were divided into two groups depending on criteria of poor glycemic control (HbA1c < 6.9% and ≥7.0%, respectively). Hemodynamics features, conventional biochemistry parameters and EVs measure were performed at the baseline. Flow cytometry was performed according to conventional protocol with FMO standards to detect and measure EVs.
Results: Circulating levels of CD235a+ PS+ erythrocytes-derived vesicles differed amongst T2DM patients depending on HF presentation when compared with healthy volunteers (Figure 1). Figure 2 illustrated the differences in circulating amount of CD235a+ PS+ RBC-derived vesicles in AF and non-AF patients with T2DM and HF depending on glycaemia control. There were significantly lower levels of CD235a+ PS+ RBC-derived vesicles were detected in those with HbA1c < 6.9% than in patients with HbA1c ≥ 7.0%. To note, there were no significant differences in circulating amount of CD235a+ PS+ erythrocytes-derived vesicles between patients in entire cohort (p = 0.24) and in non-AF sub-cohort (p = 0.40) with HbA1c < 6.9% and HbA1c ≥ 7.0%, respectively. The Receive Operation Characteristics curve analysis revealed that the well-balanced cut-off point for circulating amount of CD235a+ PS+ erythrocytes-derived vesicles (HbA1c ≥ 7.0% versus HbA1c < 6.9%) were 545 particles in μL (area under curve = 0.91, sensitivity = 74.2%, specificity = 90.3%; p = 0.0001). Multivariate linear regression yielded that NT-proBNP (OR = 1.07; 95% CI = 1.02-1.10, p = 0.04) and CD235a+ PS+ erythrocytes-derived vesicles ≥ 545 particles in μL (OR = 1.06; 95% CI = 1.01-1.11, p = 0.044) remained independent predictors for HbA1c ≥ 7.0%.
Conclusion: Poor glycaemia control is associated with elevated levels of CD235a+ PS+ EVs, which were found to be independent predictor for AF presentation in T2DM patients with HF.



Circulating levels of EVs



EVs in AF and non-AF patients

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Novel biomarkers associated with worsening renal function among patients hospitalized for acute heart failure

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Background: Worsening renal function is associated with poor prognosis in patients with heart failure. Osteopontin (OPN) and Matrix extracellular phosphoglycoprotein (MEPE) are both proteins involved in bone mineralization processes and have also been implicated in renal function. Ostepontin has been associated with kidney function markers worsening and a higher risk for adverse outcomes in patients with chronic kidney disease, and MEPE has been shown to promote renal phosphate excretion by influencing FGF23 expression.
Purpose: To explore if MEPE and OPN are associated with worsening renal function in patients with acute heart failure.
Methods: Worsening renal function was defined as an increase in plasma creatinine of >26.5 mmol/L, or 50% higher than the admission concentration within 48 hours of admission. OPN and MEPE were analyzed using a proximity extension assay in 324 patients, of whom 321 had complete data. Logistic regression analyses were performed to explore the associations between MEPE, OPN and worsening renal function. The model was adjusted for age, sex, systolic blood pressure, NT-proBNP, NYHA-classification, prevalent diabetes and treatment with diuretics and RAAS-blockade. Correlations were assessed using Spearman's correlations.
Results: The study population characteristics are presented in Table 1. Mean age was 74.5 years (±12.1) and 32.3% were women. In the fully adjusted logistic regression analyses MEPE and OPN were significantly associated with worsening renal function (OR 2.89; 95%CI 1.56-5.34; p < 0.001, and OR 1.91; 95%CI 1.11-3.31; p = 0.020, respectively). Furthermore, both MEPE and OPN were significantly correlated with each other (Spearman rho 0.52, p < 0.001). MEPE was correlated with Cystatin C (Spearman rho 0.52; p < 0.001), and with estimated glomerular filtration rate (eGFR) (Spearman rho -0.55; p < 0.001). OPN was also correlated with Cystatin C (Spearman rho 0.59; p < 0.001) and with eGFR (Spearman rho -0.57; p < 0.001).