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Cardiac biomarkers for risk stratification of arrhythmic death in patients with heart failure and reduced ejection fraction

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ABSTRACT

Objectives. Patients with heart failure and reduced left ventricular ejection fraction (HFrEF) are prone to ventricular tachyarrhythmias. We tested whether biomarkers C-terminal Endothelin 1 (CT-ET1), midregional pro atrial natriuretic peptide (MR-proANP) and midregional pro adrenomedullin (MR-proADM) might improve risk stratification for arrhythmic death.

Methods: This prospective observational study included 160 heart failure patients with ischaemic cardiomyopathy (ICM) or non-ischaemic, dilated cardiomyopathy (DCM) and 30 control patients without heart disease. Primary endpoint was arrhythmic death (ArD) or resuscitated cardiac arrest (resCA).

Results: A total of 61 patients died during the median follow-up of 7.0 [5.2–8.4] years. An ArD or resCA was observed in 48 patients. Plasma levels of CT-ET1 ($p = 0.002$), MR-proANP ($p < 0.001$) and MR-proADM ($p = 0.013$) were significantly higher in ICM or DCM patients compared to controls. MR-proANP levels in ICM patients were associated with a significantly increased risk for ArD or resCA (hazard ratio (HR) = 1.42, [95%CI: 1.08–1.85], $p = 0.011$) in a multivariable Cox regression model. Plasma levels of CT-ET1 (HR = 1.07 [0.98–1.17], $p = 0.113$) and MR-proADM (HR = 1.80 [0.92–3.55], $p = 0.087$) were not associated with ArD or resCA in ICM patients. No significant association with ArD or resCA was found in DCM patients. Multivariable Cox regression showed that CT-ET1 (HR = 1.14 [1.07–1.22], $p < 0.001$), MR-proANP (HR = 1.64 [1.29–2.08], $p < 0.001$) and MR-pro ADM (HR = 2.06 [1.12–3.77], $p = 0.020$) were associated with a higher risk for overall mortality.

Conclusion: Patients with HFrEF had elevated levels of CT-ET1, MR-proANP and MR-proADM. Plasma levels of MR-proANP are useful as predictor for arrhythmic death in patients with ICM.

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Sudden cardiac death; risk stratification; biomarker; ventricular tachycardia; arrhythmic death; overall mortality

Introduction

Fatal ventricular tachyarrhythmias are a dreaded complication in patients with heart failure and reduced ejection fraction (HFrEF) [1–3]. Sudden cardiac death is responsible for a significant part of this patient population's mortality [4]. Consequently, current guidelines recommend primary prevention of sudden cardiac death with an implantable cardioverter defibrillator (ICD) in patients with heart failure and left ventricular ejection fraction (LVEF) ≤35% [5,6]. Risk stratification for arrhythmic events has been extensively investigated [7–9], but LVEF reduction remains the only clinical parameter used for arrhythmic risk prediction in clinical practice [5,6]. Nevertheless, LVEF as a sole risk stratifier is unsatisfactory in terms of sensitivity and specificity and only provides limited discrimination between the risk of fatal ventricular arrhythmias and the risk of death due to progressive HF [6,7,10]. Additional variables are crucial for an improved and more accurate identification of patients at high risk for fatal arrhythmic events.

Cardiac biomarkers might improve risk stratification for arrhythmic death in HFrEF patients. C-terminal proendothelin-1 (CT-proET-1), midregional pro-atrial natriuretic peptide (MR-proANP) and midregional pro-adrenomedullin (MR-proADM) are released in response to increased cardiovascular stress, pressure and volume overload, increased wall tension and endothelial shear stress [11–13]. Elevated plasma levels of these prohormone fragments are associated with increased all-cause mortality, cardiovascular mortality and adverse outcome in patients with HF [14–20]. However, the role of these biomarkers in the prediction of arrhythmic death alone has not been investigated. The present study tests the null hypothesis that the biomarkers CT-proET-1, MR-proANP and MR-proADM are not associated with an increased risk for arrhythmic death and all-cause mortality in HFrEF patients with ischaemic or non-ischaemic, dilated cardiomyopathy.

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Materials & methods

This present study is a prospective, observational long-term investigation performed at the Medical University of Vienna, Department of Cardiology. The study included 108 patients with ischaemic cardiomyopathy, 52 patients with non-ischaemic, dilated cardiomyopathy and 30 control patients without heart disease and normal LVEF. Patient recruitment was conducted between 2002 and 2004 with regularly planned follow-up visits until 2013.

Patients were eligible for study participation if coronary angiography was recently performed in these patients due to typical symptoms or abnormal LV function.

Transthoracic echocardiography or magnetic resonance imaging was used in all patients to assess LVEF after a minimum of eight weeks of optimal medical therapy. Patients with a history of sustained ventricular tachycardia, permanent atrial fibrillation or dependency on cardiac pacing were excluded from study participation. Written informed consent was obtained from all participants prior to study inclusion. The local ethics committee of the Medical University of Vienna approved the study which was conducted in compliance with all national regulations and the tenets of the Helsinki declaration.

Arrhythmic death or resuscitated cardiac arrest was the primary endpoint, overall mortality was the secondary outcome parameter. An adapted form of the of the Hinkle classification [21] was applied to categorize deaths. Patients with already implanted ICDs: appropriate ICD therapy without ventricular tachycardia acceleration that failed to save the patient's life during the arrhythmic event was classified as an arrhythmic death. Ventricular fibrillation or ventricular tachycardia >240 bpm (beats per minute) leading to syncope before ICD therapy and multiple slower ventricular tachycardia episodes (electrical storm) leading to syncope and ICD discharge without ICD therapy related acceleration was classified as resuscitated cardiac arrest All other ICD discharges because of ventricular tachycardia <240 bpm were not taken as a surrogate for resuscitated cardiac arrest [8,9,22,23].

Venous blood samples were collected from all patients at study inclusion. An automated immunofluorescent assay (KRYPTOR System, BRAHMS AG, Hennigsdorf/Berlin, Germany) was used to determine CT-proET-1, MR-proADM and MR-proANP as described by us previously [24]. Intra- and inter-assay coefficients of variation (CV) of the three analysed markers are provided in Table 1.

Descriptive statistics of all variables of interest were calculated. Continuous variables are presented as median and interquartile range (IQR) and were compared using student's t-test. Categorical variables are presented as counts and percentages and were compared using Fisher's exact test. Univariable Cox regression analysis was performed to investigate the association between the three biomarkers (CT-ET1, MR-proANP and MR-proADM) and the two outcome parameters ArD or resCA and overall survival. If a significant association was found, a multivariable Cox regression was fit adjusted for age, sex, LVEF ≤35%, chronic kidney disease and presence of an implantable cardioverter-defibrillator. Kaplan Meier plots and log-rank tests were calculated to analyse the time to ArD or resCA and overall mortality in the groups stratified to the upper tertile and the combined two lower tertiles of the three biomarkers. All analysis was conducted using SPSS software program (version 25.0, SPSS Inc, Chicago, IL, USA).

Results

The baseline clinical characteristics of the study population stratified to the underlying heart disease are depicted in Table 2. Sixty-one patients died during the median follow-up time of 7.0 [5.2–8.4] years. Arrhythmic death or resuscitated cardiac arrest was observed in 48 patients. Median levels of CT-ET-1, MR-pro-ANP and MR-proADM in the overall study population were 61 pmol/l [52–86], 136 pmol/l [84–233] and 0.66 nmol/l [0.55–0.94], respectively.

Patients with ICM or DCM showed significantly higher plasma levels of CT-ET1, MR-proANP, and MR-proADM compared to controls (Table 2). Female patients represented a significantly higher (p = 0.023) proportion of patients in the DCM group compared with the ICM group.

Stratified to the underlying heart disease, univariable Cox regression showed that CT-ET1 [HR/95% 1.07

Table 1. Intra- and inter-assay coefficients of variation (CV) of the three analysed markers*.

	Intra-Assay CV	Inter-Assay CV
CT-proET1	< 4% for concentrations > 44 pmol/L	< 6% for concentrations > 80 pmol/L
	< 10% for concentration > 10 pmol/L	< 10% for concentration > 44 pmol/L
MR-proANP	≤5% from 10 pmol/L to 20 pmol/L	≤6,5% from 10 pmol/L to 20 pmol/L
	< 3,5% from 20 pmol/L to 1 000 pmol/L	< 6,5% from 20 pmol/L to 1 000 pmol/L
	< 3,5% for concentrations >1000 pmol/L	< 6,5% for concentrations > 1 000 pmol/L
MR-proADM	≤10,8% from >0,2 nmol/L to ≤0,5 nmol/L	≤17,5% from >0,2 nmol/L to ≤0,5 nmol/L
	≤ 3,1% from >0,5 nmol/L to ≤2 nmol/L	≤ 10,4% from >0,5 nmol/L to ≤2 nmol/L
	≤ 1,2% from >2 nmol/L to ≤6 nmol/L	≤ 7,3% from >2 nmol/L to ≤6 nmol/L
	≤ 3,0% from >6 nmol/L to ≤10 nmol/L	≤ 5,6% from >6 nmol/L to ≤10 nmol/L
	≤ 6,3% for concentrations >10 nmol/L	≤ 6,8% for concentrations >10 nmol/L

* CV = coefficients of variation, CT-proET1 = C-terminal pro-Endothelin, MR-proADM = midregional pro-adrenomedullin, MR-proANP = midregional pro-atrial natriuretic peptide

Table 2. Clinical characteristics and comparison of the three study groups.

	Controls (n = 30)	ICM (n = 108)	DCM (n = 52)	p-value
Age (years)	56 ± 11.5	60.1 ± 9.0	56.3 ± 10.3	0.077
Female	13 (43.3)	11 (10.2)	12 (23.1)	<0.001[a]
Follow-up [years]	9.0 [8.9–9.0]	7.04 [4.5–8.0]	6.8 [2.3–7.0]	<0.001[a]
LVEF (%)	67 [65–71.5]	34 [28–38]	32 [28–36]	<0.001[a]
ICD	0 (0)	59 (54.6)	9 (17.3)	<0.001[a, b]
CRT-P	1 (3.3)	12 (11.1)	10 (19.2)	0.074
Hypertension	23 (76.7)	93 (86.1)	44 (84.6)	0.453
Diabetes	2 (6.7)	42 (38.9)	13 (25.0)	0.002 [a]
Hyperlipidaemia	10 (33.3)	82 (75.9)	27 (51.9)	<0.001[a, b]
CKD	0 (0)	29 (26.9)	15 (28.8)	0.004[a]
NYHA 1	15 (50.0)	27 (25.0)	20 (38.5)	0.020[a]
NYHA 2	15 (50.0)	58 (53.7)	22 (42.3)	0.402
NYHA 3	0 (0)	23 (21.3)	10 (19.2)	0.022[a]
BMI (kg/m^2)	27 ± 6.2	28.0 ± 4.3	28.3 ± 4.4	0.274
ACE/ARB	19 (63.3)	104 (96.3)	49 (94.2)	<0.001[a]
Beta blocker	18 (60.0)	97 (89.8)	46 (88.5)	<0.001[a]
Amiodarone	0 (0)	17 (15.7)	8 (15.4)	0.067
Digitalis	0 (0)	16 (14.8)	14 (26.9)	0.005 [a]
Diuretics	7 (23.3)	77 (71.3)	32 (61.5)	<0.001[a]
Spironolactone	0 (0)	35 (32.4)	28 (53.8)	<0.001[a, b]
CT-proET1 [pmol/l]	54 [48–62]	65 [56–99]	62 [51–78]	0.002[a]
MR-proANP [pmol/l]	63 [33–93]	167 [112–274]	130 [66–235]	<0.001[a]
MR-proADM [nmol/l]	0.57 [0.53–0.72]	0.72 [0.57–0.96]	0.70 [0.61–0.97]	0.013[a]

[a]significant difference between the three groups. [b] significant difference between ICM and DCM patients

* ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, BMI = body mass index, CKD = chronic kidney disease, CRT-P = cardiac resynchronization therapy pacemaker, CT-proET1 = C-terminal pro-Endothelin 1, DCM = dilative cardiomyopathy, ICD = implantable cardioverter-defibrillator, ICM = ischaemic cardiomyopathy, LVEF = left ventricular ejection fraction, MR-proADM = mid-regional pro-adrenomedullin, MR-proANP = midregional pro-atrial natriuretic peptide, NYHA = New York heart association

(1.00–1.15) p = 0.045] and MR-proANP [1.52 (1.22–-1.89), p < 0.001] were associated with a significantly increased risk for arrhythmic death or resuscitated cardiac arrest in patients with ICM. There was no association with MR-proADM [HR/95%CI 1.8 (0.92–3.55), p = 0.087]. In a multivariable model adjusted for age, sex, LVEF <35%, CKD and implanted ICD, MR-pro ANP [1.42 (1.08–1.85), p = 0.011] remained a significant predictor for arrhythmic death or resuscitated cardiac arrest, but not CT-ET1 [1.07 9 (0.98–1.17), p = 0.113]. None of the three biomarkers showed a significant association with arrhythmic death or resuscitated cardiac arrest in patients with DCM: CT-ET1 [1.00 (0.81–-1.24), p = 0.973], MR-proANP [1.08 9 (0.79–1.49), p = 0.619] and MR-proADM [1.24 (0.29–5.34) p = 0.776].

Kaplan Meier curves were calculated stratified for plasma levels in the upper tertile or the combined two lower tertiles of CT-ET-1 (76 pmol/l), MR-proANP (213 pmol/l) and MR-proADM (0.86 nmol/l). Patients with plasma levels of MR-proANP in the upper tertile had a significantly higher risk for arrhythmic death or resuscitated cardiac arrest compared to patients in the two lower tertiles (Figure 1(b)). No difference was found for CT-ET1 (Figure 1(a)) or MR-proADM (Figure 1(c)).

Univariable Cox regression demonstrated that CT-ET -1 [HR/95% CI 1.14 (1.09–1.20), p < 0.001], MR-proANP [1.74 (1.42–2.14), p = <0.001] and MR-proADM [3.16 (2.00–4.98), p < 0.001] were associated with a significantly higher risk for overall mortality in patients with ICM. In the adjusted model for age, sex, LVEF <35%, CKD and implanted ICD, the three biomarkers remained significantly predictive for overall mortality: CT-ET1 [HR/95%CI 1.14 (1.07–1.22), p < 0.001], MR-proANP [1.64 (1.29–2.08), p < 0.001] and MR-proADM [2.06 (1.12–3.77), p = 0.020]. In patients with DCM, CT-ET1 [1.23 (1.11–1.36), p < 0.001], MR-proANP [1.41 (1.18–-1.69), p < 0.001] and MR-proADM [4.91 (2.38–10.13), p < 0.001] were significantly predictive for overall mortality. After adjustment for relevant clinical parameters, MR-proANP [HR/95% CI 1.29 (1.08–1.53), p = 0.005] and MR-proADM [3.37 (1.20–9.46), p = 0.021] remained significant predictors for overall mortality, but not CT-ET1 [1.13 (0.97–1.30), p = 0.107].

Kaplan Meier curves were calculated stratified to the upper and the combined two lower tertiles of plasma levels of CT-ET1, MR-proANP and MR-proADM. Patients in the upper tertiles of CT-ET1 (Figure 2(a)), MR-proANP (Figure 2(b)) or MR-proADM (Figure 2(c)) had a significantly higher risk for overall death.

Discussion

Our data provides evidence that MR-proANP is a significant predictor for arrhythmic death or resuscitated cardiac arrest in patients with ICM (after adjustment for relevant clinical confounders), and confirms that plasma levels of the prohormones CT-ET1, MR-proANP and MR-proADM are significantly elevated in patients with ICM or DCM compared to healthy individuals. All three biomarkers were significantly associated with an increased risk for overall mortality in HFrEF patients, regardless of the underlying aetiology.

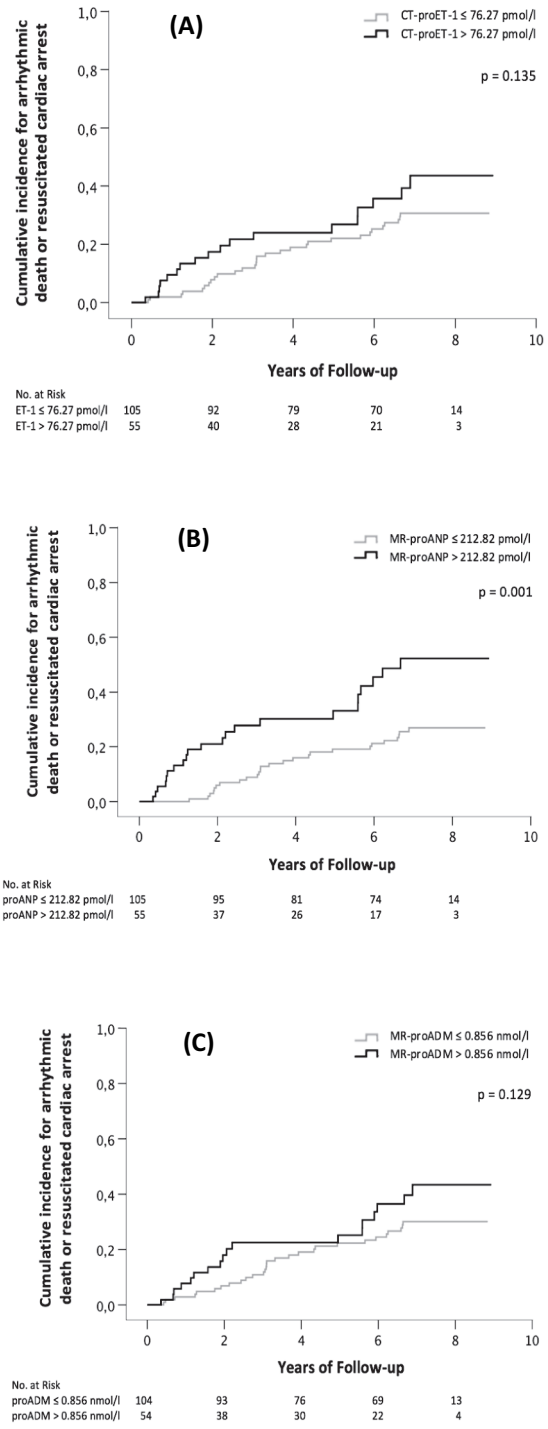

Figure 1. Kaplan Meier curves demonstrating the association between ArD or resCA and plasma levels of (a) CT-proET-1 (b) MR-proANP and (c) MR-proADM stratified to the upper and the combined two lower tertiles. ArD = arrhythmic death, CT-proET-1 = C terminal pro Endothelin 1, MR-proANP = midregional pro atrial natriuretic peptide, MR-proADM = midregional pro Adrenomedullin, resCA = resuscitated cardiac arrest.

The precursor fragments CT-ET1, MR-proANP and MR-proADM show more stable plasma levels than the active hormones and are recommended to be used for quantitative measurements [25]. The biomarkers ET1, proANP and proADM have previously been associated with adverse cardiovascular outcome. ET1 is a vasoconstrictive agent released from endothelial cells [26] and is associated with adverse cardiovascular remodelling [27–29]. Previous studies showed that elevated levels of CT-ET1 are associated with increased overall mortality after myocardial infarction and poor prognosis in patients with congestive heart failure [14,15,30]. Pro-ANP is the precursor molecule from ANP that is released by atrial myocytes in response to increased volume load and wall stretch [11]. Elevated plasma levels of MR-proANP have been associated with adverse outcome in patients with coronary heart disease and heart failure [19,31,32]. MR-proADM is a precursor peptide of ADM that is involved in the function of endothelial cells, causes long-lasting vasodilatation, carries natriuretic properties and might have positive inotropic effects on the contractility of the myocardium [33–35]. Elevated plasma levels of adrenomedullin have been proposed to be upregulated as a protective mechanism in patients with advanced cardiac disease [36,37]. Previous studies demonstrated that elevated levels of MR-proADM are associated with a poor prognosis in patients with acute and chronic heart failure [17,18,38]. So far, the potential role of these biomarkers in risk stratification for arrhythmic death was unclear.

Patients with heart failure and LVEF reduction are considered a high-risk population with considerably high annual death rates [1,2]. A significant part of this high mortality is caused by fatal ventricular arrhythmias, but risk prediction of arrhythmic death remains unsatisfactory [5,7]. While the reduction of LVEF remains the most important risk predictor for arrhythmic events, quantitative measurement of biomarkers might contribute to a more accurate arrhythmic risk prediction [5].

Although previous studies demonstrated that MR-proANP is associated with an increased overall mortality in heart failure [32,39], we add to the literature, showing that MR-proANP is associated with a significantly increased risk for arrhythmic death or resuscitated cardiac arrest. This association is independent of clinical parameters and the degree of LVEF reduction and might contribute to an improved risk stratification for fatal ventricular arrhythmias. In addition, the underlying study corroborates previous investigations that elevated levels of CT-ET1, MR-proANP and MR-proADM are associated with a significantly increased risk for overall death in patients with coronary heart disease and heart failure [14,15,19,31,38].

We acknowledge certain limitations, notably the relatively small sample size that limits the power of the underlying study. Further prospective studies with significantly larger study cohorts are

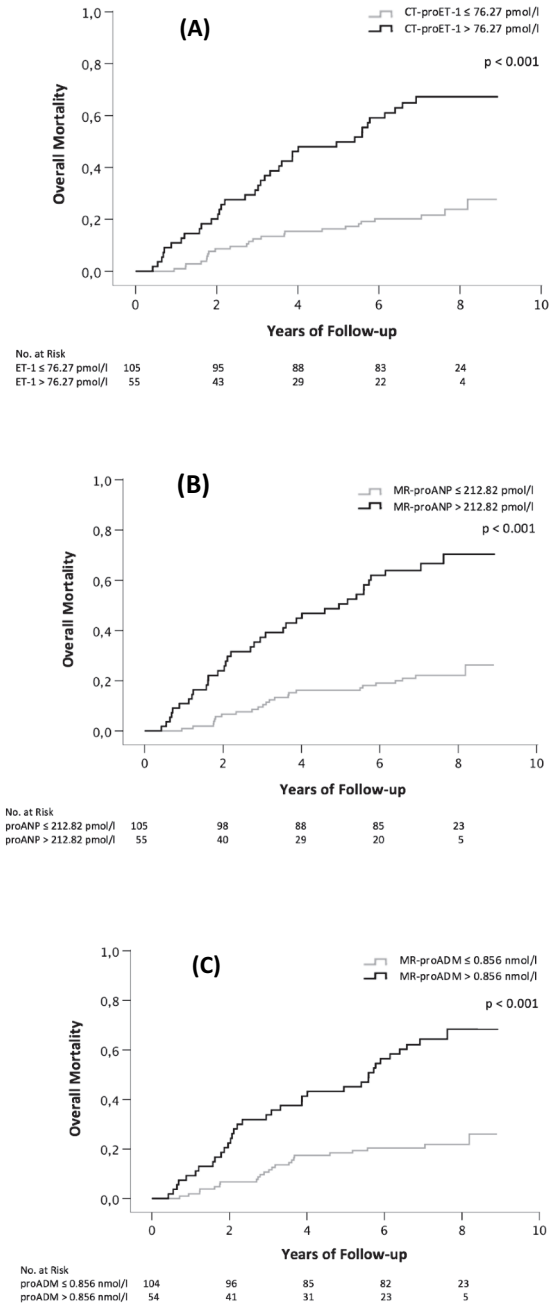

Figure 2. Kaplan Meier curves demonstrating the association between overall mortality and plasma levels of (a) CT-proET-1 (b) MR-proANP and (c) MR-proADM stratified to the upper and the combined two lower tertiles. ArD = arrhythmic death, CT-proET-1 = C terminal pro Endothelin 1, MR-proANP = midregional pro atrial natriuretic peptide, MR-proADM = midregional pro Adrenomedullin, resCA = resuscitated cardiac arrest.

required to confirm results and the clinical predictive value of MR-pro ANP for arrhythmic death. Events of the primary outcome parameter arrhythmic death or resuscitated cardiac arrest were carefully evaluated. However, we cannot rule out that some events that were classified as resuscitated cardiac arrest might not have led to death.

Our data represent an advance in biomedical science as it points to the value of measuring plasma levels of CT-ET1, MR-proANP and MR-pro ADM, as they are elevated in patients with HFrEF and predict for fatal arrhythmic events in patients with ICM.

Summary table

What is known about this subject:

- Heart failure patients with reduced left ventricular ejection fraction (LVEF) are at high risk for ventricular arrhythmias.
- Current risk stratification for arrhythmic events based on LVEF reduction lacks sensitivity and specificity.

What the study adds:

- Plasma levels of MR-proANP are associated with a significantly increased risk for ventricular arrhythmias.
- This finding is independent from the degree of LVEF reduction and might contribute to an improved risk stratification for arrhythmic death.

Disclosure statement

No potential conflict of interest was reported by the authors.

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None declared.

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