

# Baroreflex sensitivity but not microvolt T-wave alternans can predict major adverse cardiac events in ischemic heart failure

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## Abstract

**Background:** Major adverse cardiovascular events (MACE) constitutes the main cause of morbidity and mortality in ischemic heart failure (HF) patients. The prognostic value of the autonomic nervous system parameters and microvolt T-wave alternans (MTWA) in this issue has not been identified to date. The aim herein, was to assess the usefulness of the abovementioned parameters in the prediction of MACE in HF patients with left ventricular systolic dysfunction of ischemic origin.

**Methods:** Baroreflex sensitivity (BRS), heart rate variability (HRV), MTWA and other well-known clinical parameters were analyzed in 188 ischemic HF outpatients with left ventricular ejection fraction (LVEF)  $\leq 50\%$ . During 34 (14–71) months of follow-up, 56 (30%) endpoints were noted.

**Results:** Univariate Cox analyses revealed BRS (but not HRV), MTWA, age, New York Heart Association functional class III, LVEF, implantable cardioverter-defibrillator presence, use of diuretics and antiarrhythmic drugs, diabetes, and kidney insufficiency were defined as significant predictors of MACE. Pre-specified cut-off values for MACE occurrence for the aforementioned continuous parameters (age, LVEF, and BRS) were:  $\geq 72$  years,  $\leq 33\%$ , and  $\leq 3$  ms/mmHg, respectively. In a multivariate Cox analysis only BRS (HR 2.97, 95% CI 1.35–6.36,  $p < 0.006$ ), and LVEF (HR 1.98, 95% CI 0.61–4.52,  $p < 0.038$ ) maintained statistical significance in the prediction of MACE.

**Conclusions:** Baroreflex sensitivity and LVEF are independent of other well-known clinical parameters in the prediction of MACE in patients with HF of ischemic origin and LVEF up to 50%. BRS  $\leq 3$  ms/mmHg and LVEF  $\leq 33\%$  identified individuals with the highest probability of MACE during the follow-up period. (Cardiol J)

**Key words:** autonomic nervous system, baroreflex sensitivity, heart rate variability, microvolt T-wave alternans, heart failure, left ventricular dysfunction, ischemic cardiomyopathy

## Introduction

Major adverse cardiovascular events (MACE) constitutes the main cause of morbidity and mortality in heart failure (HF) patients, particularly when ischemic etiology is involved [1]. The role and prognostic value of the autonomic nervous system (ANS) indices: baroreflex sensitivity (BRS) and

heart rate variability (HRV), as well as microvolt T-wave alternans (MTWA), have been thoroughly confirmed in patients with HF concerning cardiovascular death (CVD) [2–8]. A robust body of the previous data focused on patients with HF and reduced ejection fraction, which have the most clinical evidence with regard to therapies, and guidelines clearly define management strategies

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[9, 10]. However, the latest recommendations for the management of acute and chronic HF have defined a new category — HF with mid-range ejection fraction (HFmrEF), i.e. with left ventricular ejection fraction (LVEF) in the range of 40–49%. Research on HFmrEF has recently begun to appear, although, data remain scarce and the management is not clearly defined. Estimates show that HFmrEF is responsible for 13% to 24% of all HF cases [11], so from a practical point of view, it seems important to include this group of patients in clinical studies.

The role and prognostic value of ANS indices and MTWA in prediction MACE (which beside CVD involves non-fatal myocardial infarction [MI] and non-fatal stroke), especially in patients with LVEF up to 50%, requires further investigations. In this study, the authors aimed to examine this issue in HF patients with left ventricular systolic dysfunction of ischemic origin.

## Methods

The protocol of the study was approved by the Local Ethics Committee at the Medical University of Gdansk, and written informed consent was obtained from all participants.

### Patient's selection

Between 2009 and 2018, 188 consecutive patients with stable ischemic HF (documented by prior MI, percutaneous coronary intervention, or coronary artery by-pass grafting) and LVEF  $\leq$  50% who visited the outpatient clinic, were enrolled in this single-center study. The protocol of the initial visit included anamnesis with particular emphasis on pharmacological treatment and comorbidities; information on the demographic status of the patients; physical examination; two-dimensional-transthoracic echocardiographic study; laboratory blood tests; ANS and MTWA assessment. Additional inclusion criteria were as follows: sinus rhythm; a stable clinical condition for at least 3 months before enrollment; optimal medical therapy for HF and complete coronary revascularization under current guidelines [9, 12–14]. The exclusion criteria were: age  $<$  18 years; a history of prior sustained ventricular arrhythmia or cardiac arrest; permanent atrial fibrillation/flutter; ventricular paced rhythm due to atrioventricular block; New York Heart Association (NYHA) functional class IV, clinical features of coronary instability; a revascularization (coronary angioplasty and/or surgery by-pass grafting) within 3 months before the study;

incomplete coronary revascularization status (scheduled coronarography, coronary angioplasty or surgery by-pass graft); diabetes complicated by documented symptomatic peripheral neuropathy; inability to perform exercise test; poor general condition or non-cardiologic comorbidities with potential unfavorable effect on survival.

### Studied parameters

**MTWA assessment.** Detailed skin preparation including mild abrasion was performed to reduce the impedance between skin and the electrode and minimize the risk of artifacts. Next, special electrodes (High-Res high-resolution electrodes, Cambridge Heart — Spacelab's Healthcare, Snoqualmie, WA, USA) were placed in three orthogonal Frank leads (X, Y, and Z). The exercise test was performed on a treadmill (Delmar Reynolds), in line with the protocol dedicated for MTWA testing i.e. with a gradual increment in heart rate, first to the range of 100–110 bpm and then to 110–120 bpm for at least 2 min. The data were analyzed with the CH2000 system utilizing a spectral method (Cambridge Heart, Inc., Bedford, MA, USA), and were finally verified by the physician performing the study. The detailed methodology was already precisely described in previous studies [2, 15, 16]. The results of the test were classified as negative (MTWA\_neg), positive (MTWA\_pos) or indeterminate (MTWA\_ind), and additionally, all non-negative results were classified jointly as MTWA\_non-neg and were included for further analysis.

**ANS assessment.** Autonomic parameters were analyzed in a quiet room with dimmed lights between 08.00 am and 1.00 pm, all patients were asked to fast (at least 4 h) and to refrain from smoking and drinking coffee (at least 12 h) before the examination. After adjustment of measuring devices, and a 15 min stabilization period, resting electrocardiogram (ECG) (Mingograf 720C) and beat-to-beat non-invasive arterial blood pressure (Finapres 2300, Ohmeda) were continuously recorded for 10 min during spontaneous breathing. The collected data were transferred to a PC workstation, processed with POLYAN software [17] and analyzed according to the described protocol [18, 19].

The information on RR interval (resolution 1 ms) and systolic arterial pressure (SAP) were obtained automatically. BRS (ms/mmHg) was computed by spectral analysis as the average value of the transfer function modulus (Blackman-Tukey method, 0.03 Hz-bandwidth Parzen window) be-

tween SAP and RR interval time series in low frequency (LF, 0.04–0.15 Hz) band, independently from coherence values [18]. Then, based on collected ECG data routine HRV frequency-domain indices such as LF (in  $\text{ms}^2$ ), high frequency (HF, 0.14–0.4 Hz, in  $\text{ms}^2$ ), LF to HF ratio (LF/HF), and relative spectral powers in LF bands expressed in normalized units (LFnu) were analyzed. Furthermore, time-domain HRV parameters were calculated based on RR data, such as the standard deviation of normal-to-normal RR intervals (SDNN), the square root of the mean of squared differences between successive intervals (RMSSD), and percentage of adjacent RR intervals differing by more than 50 ms (pNN50). Also, the mean heart period (HP in ms) value was included in the analysis [20].

### Follow-up

The routine assessment, which took place every 6 months (or earlier if clinically necessary) involved assessing the patient's clinical condition and recorded study if any had occurred. A decision on potential implantation on an implantable cardioverter-defibrillator (ICD) as a primary prevention of sudden cardiac death (or CRT-D if needed) was at the discretion of the physician in charge. The endpoint of the study was 3-point MACE, defined as non-fatal MI, non-fatal stroke and CVD [21, 22]. Non-fatal MI was recognized according to the Fourth Universal Definition of Myocardial Infarction Guidelines [23]. Non-fatal stroke was defined according to the World Health Organization (WHO) definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting 24 h (unless interrupted by surgery) with no apparent causes other than of vascular origin [24]. CVD included: fatal stroke or MI; death attributed to HF; any sudden death including unobserved and unexpected death; fatal pulmonary or systemic embolism; death following a vascular operation, vascular procedure, or amputation. All deaths were confirmed against the patient's death certificate information or medical documentation.

### Statistical analysis

Database construction and statistical analysis were performed with STATISTICA 12 software (StatSoft, Poland) and R 2.15.2 environment. Continuous data were presented as the median (25<sup>th</sup>–75<sup>th</sup> percentiles), categorical as a number and percentage. Differences between the MACE(+) and MACE(–) groups were calculated with the Mann-Whitney U-test and for qualitative data with the  $\chi^2$  or Yates  $\chi^2$  test. The accuracy of pre-

specified cut-off values for analyzed parameters was determined by area (AUC) under the receiver-operating characteristic (ROC) curve. An association between the analyzed parameters and the endpoint was assessed using the Cox univariate and multivariate proportional hazard models. The probabilities of reaching the primary endpoint over time, for pre-specified cut-off values for BRS and LVEF, were estimated using the Kaplan-Meier method and compared with the log-rank test. A p value of less than 0.05 was considered statistically significant.

## Results

### Clinical characteristics of the studied patients

Demographic, clinical and echocardiographic data, as well as parameters of the ANS and MTWA of the studied groups, are presented in Table 1. Briefly, the patients were approximately 64 (58–72) years old, most of them were males (92%), more than 90% underwent MI. During 34 (14–71) months of follow-up, 56 (30%) patients underwent MACE: 7 had a non-fatal stroke, 5 non-fatal MI, and 44 suffered from CVD. These patients were characterized by worse echocardiographic parameters, i.e. lower LVEF and larger atrial size, fewer negative results in MTWA assessment, worse results derived from ANS testing such as lower BRS, LFnu, and LF/HF ratio values. Furthermore, antiarrhythmic and diuretic drugs were used more frequently in these patients, and more often they had diabetes and chronic kidney disease (in stage III or higher).

### Predictors of the endpoint

Univariate Cox analyses revealed age, NYHA III functional class, LVEF, ICD presence, use of diuretics and antiarrhythmic drugs, diabetes and glomerular filtration rate  $< 60 \text{ mL/min/1.73 m}^2$  as significant predictors of the MACE (Table 2). Only BRS and MTWA<sub>non-neg</sub>, but not HRV indices (both time and frequency domain) proved to be statistically significant. Pre-specified cut-off values with a high predictive likelihood for MACE occurrence established by using area under ROC for the aforementioned continuous parameters (age, LVEF, and BRS) were:  $\geq 72$  years,  $\leq 33\%$ , and  $\leq 3 \text{ ms/mmHg}$ , respectively (Table 3). In a multivariate Cox analysis, which included all parameters which proved to be statistically significant in the univariate test, only BRS and LVEF maintained statistical significance in the prediction of MACE (Table 2). Figures 1 and 2 presents the Kaplan-

**Table 1.** Clinical, laboratory and echocardiographic characteristics of the study group and comparison between the major adverse cardiovascular events [MACE(+)] and MACE(-)] groups.

	All (n = 188)	MACE(+) (n = 56)	MACE(-) (n = 132)	P*
Age [years]	64 (58–72)	65 (60–74)	64 (58–70)	< 0.026
Male	173 (92%)	53 (95%)	120 (91%)	0.406
Myocardial infarction	171 (91%)	50 (89%)	121 (92%)	0.785
Revascularization	169 (90%)	53 (95%)	116 (88%)	0.195
ICD	113 (60%)	37 (66%)	76 (58%)	0.262
CRT-D	17 (9%)	5 (9%)	12 (9%)	1
<b>NYHA class</b>				< 0.001
NYHA I	34 (18%)	3 (5%)	31 (23%)	
NYHA II	122 (65%)	36 (64%)	86 (65%)	
NYHA III	32 (17%)	17 (30%)	15 (11%)	
<b>Laboratory parameters</b>				
Hemoglobin [g/dL]	14 (13–15)	13.9 (13.0–14.5)	14.1 (13.3–14.8)	0.368
BNP [pg/mL]	108 (77–300)	238 (104–918)	104 (66–201)	< 0.003
<b>Echocardiographic parameters</b>				
LADs [mm]	45 (41–48)	46 (41–50)	44 (40–48)	< 0.035
LVEF [%]	33 (27–40)	28 (23–32)	35 (30–42)	< 0.001
<b>MTWA results</b>				
MTWA_neg	59 (31%)	10 (18%)	49 (37%)	< 0.021
MTWA_pos	84 (45%)	32 (57%)	52 (39%)	< 0.021
MTWA_ind	45 (24%)	14 (25%)	31 (23%)	< 0.021
MTWA_non-neg	129 (69%)	46 (82%)	83 (63%)	< 0.010
<b>ANS parameters</b>				
Mean HP [ms]	1031 (948–1136)	1021 (950–1109)	1033 (949–1148)	0.230
SDNN [ms]	25.3 (16.8–37.9)	20.2 (11.5–47.0)	25.5 (18.8–36.4)	0.229
RMSDD [ms]	17.1 (10.3–29.9)	19.7 (7.5–41.4)	16.9 (10.9–27.6)	0.470
pNN50 [%]	0.68 (0–7.9)	0.81 (0.0–10.5)	0.63 (0.0–6.9)	0.321
LFnu	51 (26.7–69.8)	31.3 (23.4–61.6)	54.1 (29.5–70.6)	< 0.041
LF/HF	1 (0.38–2.31)	0.53 (0.3–1.6)	1.2 (0.4–2.40)	< 0.041
BRS [ms/mmHg]	4.2 (2.2–6.7)	2.6 (1.9–4.9)	4.6 (2.3–7.8)	< 0.001
<b>Medications</b>				
Beta-adrenolytics	179 (95%)	52 (93%)	127 (96%)	0.286
ACEI or ARB	173 (92%)	52 (93%)	121 (92%)	1
Spirolactone/eplerenone	98 (52%)	30 (54%)	68 (51%)	0.874
Antiplatelet therapy	171 (91%)	51 (91%)	120 (91%)	1
Statins	169 (90%)	52 (93%)	117 (89%)	0.596
Digoxin	6 (3%)	3 (5%)	3 (2%)	0.359
Diuretics	86 (46%)	39 (70%)	50 (36%)	< 0.001
Anti-arrhythmic	19 (10%)	11 (20%)	8 (6%)	< 0.006
<b>Concomitant diseases</b>				
Arterial hypertension	128 (68%)	35 (62%)	93 (70%)	0.313
Diabetes	51 (27%)	23 (41%)	28 (21%)	< 0.012
GFR < 60 (mL/min/1.73 m <sup>2</sup> )	41 (22%)	23 (41%)	20 (14%)	< 0.001
Hypercholesterolemia	128 (68%)	40 (71%)	92 (67%)	0.612
History of atrial fibrillation/flutter	39 (21%)	14 (25%)	25 (19%)	0.441
Smoking	139 (74%)	41 (73%)	98 (74%)	1

\*p value for comparison between MACE(+) and MACE(-) groups; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; BNP — B-type natriuretic peptide; BRS — baroreflex sensitivity; CRT-D — implantable cardioverter-defibrillator with cardiac resynchronization therapy; HP — heart period; LADs — left atrium diameter; LFnu — spectral power in low-frequency range expressed in normalized units; LF/HF — LF to high frequency ratio; LVEF — left ventricular ejection fraction; GFR — glomerular filtration rate; ICD — implantable cardioverter-defibrillator; MI — myocardial infarction; MTWA\_ind — indeterminate result for microvolt T-wave alternans; MTWA\_neg — negative result for microvolt T-wave alternans; MTWA\_non-neg — positive and indeterminate results for microvolt T-wave alternans; MTWA\_pos — positive result for microvolt T-wave alternans; NYHA — classification according to the New York Heart Association; pNN50 — proportion of successive R-R intervals that differ by more than 50 ms; QRS — QRS complex width; RMSDD — square root of the mean squared difference of successive R-R intervals; SDNN — standard deviation of the average R-R intervals of the sinus rhythm

**Table 2.** Univariate and multivariate Cox models estimating the likelihood of major adverse cardiovascular events (MACE).

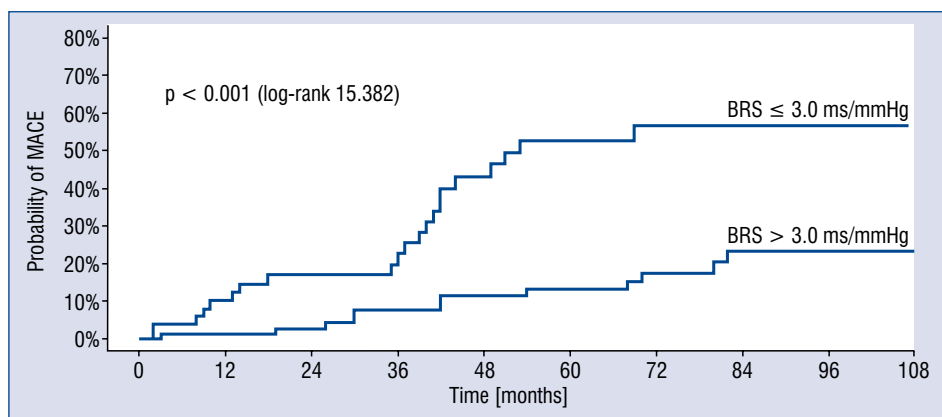
Parameter	Unadjusted		P*	Adjusted		P*
	HR	95% CI		HR	95% CI	
Age ≥ 72 [years]	2.03	1.17–3.51	< 0.012	0.90	0.38–2.11	0.801
NYHA class III	2.02	1.14–3.59	< 0.016	1.35	0.57–3.20	0.327
LVEF ≤ 33 [%]	3.65	1.93–6.93	< 0.001	1.98	0.61–4.52	< 0.038
MTWA_non-neg	2.15	1.08–4.27	< 0.029	1.86	0.66–5.26	0.242
BRS ≤ 3.0 [ms/mmHg]	3.78	1.85–7.73	< 0.001	2.97	1.35–6.36	< 0.006
Diuretics	2.38	1.34–4.21	< 0.003	1.37	0.56–2.77	0.410
Diabetes	1.76	1.03–3.00	< 0.039	1.78	0.77–4.69	0.165
GFR < 60 (mL/min/1.73 m <sup>2</sup> )	2.33	1.37–3.99	< 0.002	1.13	0.49–2.57	0.778

\*p value for comparison between MACE(+) and MACE(-) groups; BRS — baroreflex sensitivity CI — confidence interval; LVEF — left ventricular ejection fraction; GFR — glomerular filtration rate; HR — hazard ratio; MTWA\_non-neg — positive and indeterminate results for microvolt T-wave alternans; NYHA — classification according to the New York Heart Association

**Table 3.** Prognostic accuracy of the pre-specified cut-off values for analyzed parameters as the predictors of major adverse cardiovascular events during the follow-up.

Parameters	AUC (95% CI)	Characteristics (95% CI)		Predictive value (95% CI)	
		Sensitivity (%)	Specificity (%)	Positive (%)	Negative (%)
Age ≥ 72 [years]	0.59 (0.5–0.68)	81	36	76	43
LVEF ≤ 33 [%]	0.79 (0.72–0.85)	69	79	89	51
BRS ≤ 3.0 [ms/mmHg]	0.65 (0.55–0.76)	69	64	85	41

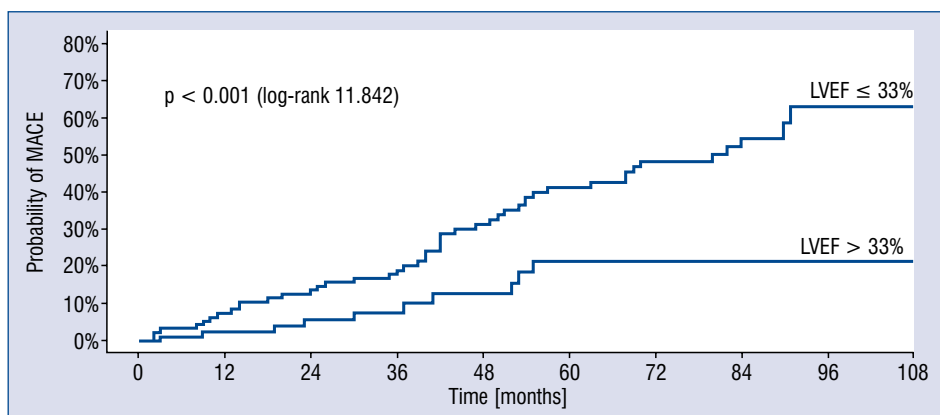
AUC — area under the curve; BRS — baroreflex sensitivity; CI — confidence interval; LVEF — left ventricular ejection fraction



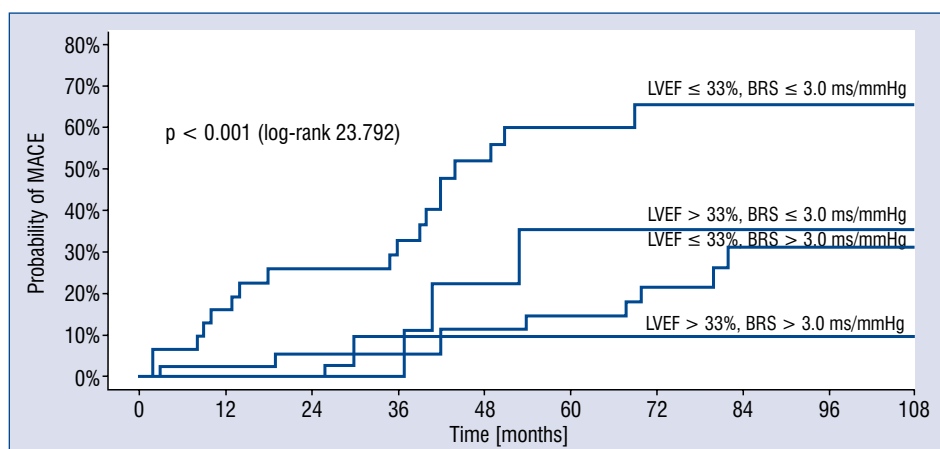
**Figure 1.** Kaplan-Meier curves illustrating the probability of major adverse cardiovascular events (MACE) during the follow-up period according to the cut-off value for baroreflex sensitivity (BRS).

-Meier curves illustrating the probability of MACE depending on pre-specified cut-off values for LVEF and BRS during the follow-up period, while Figure 3 illustrates the probability of endpoint for a com-

combined parameter (LVEF and BRS jointly). As it has been presented, both LVEF ≤ 33% and BRS ≤ 3 ms/mmHg assessed separately or jointly, can identify patients at highest risk of MACE occurrence.



**Figure 2.** Kaplan-Meier curves illustrating the probability of major adverse cardiovascular events (MACE) during the follow-up period according to the cut-off value for left ventricular ejection fraction (LVEF).



**Figure 3.** Kaplan-Meier curves illustrating the probability of major adverse cardiovascular events (MACE) during the follow-up period according to the combined parameter (left ventricular ejection fraction [LVEF] + baroreflex sensitivity [BRS]).

## Discussion

The observation that not only LVEF but also BRS can predict MACE in patients with ischemic left ventricular systolic dysfunction, even after adjusting for other clinical parameters (such as age, NYHA functional class, ICD presence, impaired renal function, diuretics and antiarrhythmic’s using, and diabetes), is the principal finding of the present study. The role of MTWA was proved only in univariate Cox analysis. According to available research, this is the first study analyses regarding the usefulness of ANS and MTWA parameters in the identification of high-risk individuals of MACE occurrence among patients with ischemic cardiomyopathy and LVEF up to 50%. Previous investigations concerning MACE risk assessment among

patients with coronary artery disease were dedicated to other well-known clinical parameters [25, 26], which were also confirmed in the present study. The role of ANS indices and MTWA was previously proven for arrhythmic, cardiac and all-cause mortality [2–7, 19, 27–34], however not for MACE, which are common and relevant in this population [1]. Moreover, the vast majority of cited studies omitted patients with ejection fraction 40–50%, who have similarly poor prognosis [35–39].

### Prognostic value of MTWA indices in the identification of MACE

Univariate Cox analysis showed that non-negative MTWA is a prognostic risk factor for MACE occurrence, yet it was not confirmed in the multivariate analysis (Table 2). This could be due

to the fact that abnormal MTWA, as a potential modulator of arrhythmic episodes, is mainly associated with the risk of these events [2, 31, 33, 40–42]. Several studies have shown the usefulness of MTWA in predicting cardiac and overall mortality mainly in patients with reduced LVEF [6, 7, 34, 43, 44]. However, in MACE, which is a complex endpoint, where the percentage of arrhythmias is relatively smaller, its prognostic value seems to be significantly lower. This was noted by Chow et al. [44], who stated that non-negative MTWA increases the risk of total and arrhythmic mortality but does not increase the risk of non-arrhythmic death. Another explanation may be the interpretation of indeterminate MTWA results. In patients with LVEF  $\leq 35\%$  indeterminate MTWA is associated with a poor prognosis — similar to the patients with positive MTWA [45]. Regarding the patients with higher LVEF, as it was shown in one of the largest meta-analyses, conducted by Merchant et al. [46], indeterminate MTWA results are not associated with such outcomes.

### Prognostic value of ANS indices in the identification of MACE

In the present study, it was shown in both uni- and multivariate Cox analyses, the role of BRS in the prediction of MACE occurrence in patients with HF of ischemic origin and LVEF up to 50%. The pre-specified cut-off value for BRS (3 ms/mmHg) is consistent with the results acquired by other researchers, where BRS was determined by both invasive and non-invasive methods [3, 4, 19, 27, 28, 47]. In the current study, patients with BRS below 3 ms/mmHg had a relative risk for MACE threefold higher than patients above the cut-off. Moreover, as Figure 3 presents, individuals with both LVEF  $\leq 33\%$  and BRS  $\leq 3$  ms/mmHg had the highest MACE probability over a 34-month follow-up period. In many previous studies, BRS was proved to have prognostic value in predicting various end-points, such as hospitalization due to HF exacerbation as well as arrhythmic, cardiovascular, or all-cause mortality [3, 4, 8, 19, 27, 28, 47]. The results of our research show that BRS also has an important role in the prediction of MACE, which proves the fact that autonomic imbalance could have an enormous impact on the development of various cardiovascular complications, and that this parameter should be taken into account in risk stratification and clinical evaluation of HF patients.

Two recently published studies [48, 49], put in question earlier data from the literature regarding the role of autonomic tone parameters. However,

the clinical characteristics of studied populations and duration of follow-up periods were different, therefore these results, as it was noticed in the commentary by Parati et al. [50] should be interpreted with caution and should not be extrapolated to HF patients with other clinical characteristics [49].

### Limitations of the study

The authors are well aware of the potential limitations of the study. Firstly, this was a fairly small, single-center study with strict inclusion criteria, and thus needs confirmation in larger trials. Secondly, although the percentage of patients with HFmrEF is similar to that in the general population of patients with HF, it should be noted that the group of patients with HFmrEF in this article was 50. Next, due to the nature of the methodology of ANS and MTWA evaluation, only patients with sinus rhythm were included in the study. Moreover, in this paper we primarily focused on the MACE assessment rather than assessing other important endpoints, e.g. hospitalization due to HF exacerbation. Finally, during the follow-up period, ANS or MTWA evaluation was not repeated, which makes it difficult to assess the impact of potential changes occurring at that time.

### Conclusions

Baroreflex sensitivity and LVEF are independent of other well-known clinical parameters (such as age, NYHA functional class, ICD presence, impaired renal function, diuretics and antiarrhythmic's using, and diabetes), in the prediction of MACE in patients with left ventricular systolic dysfunction of ischemic origin and LVEF up to 50%. BRS  $\leq 3$  ms/mmHg and LVEF  $\leq 33\%$  identified individuals with the highest probability of MACE during the follow-up period.

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**Conflict of interest:** None declared

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