

## Prognostic significance of a combination of novel biomarkers in the long-term stratification of adverse outcomes in patients with ST-segment elevation myocardial infarction

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A multi-marker approach for assessing the prognosis of patients with ST-segment elevation myocardial infarction (STEMI) is a promising strategy.

**Aim.** To assess the potential prognostic power of soluble growth stimulation gene-2 (sST2), pentraxin 3 (Ptx-3), and N-terminal pro-brain natriuretic peptide (NT-proBNP) in stratification of the risk of major cardiovascular events (CVE) during 2-year follow-up after STEMI.

**Material and methods.** In 154 patients with STEMI, serum concentrations of NT-proBNP, sST2, and Ptx-3 were determined upon admission to hospital. During the two-year follow-up period (734,2±61,2 days), correlation of biomarker concentrations with the risk of a composite endpoint (myocardial infarction + stroke + hospitalization due to cardiovascular disease + cardiovascular death) was analyzed.

**Results.** In the 2-year follow-up, CVE were observed in 81 (55,1%) patients (CV death (n=33; 22,1%), recurrent MI (n=28; 18,8%), stroke (n=8; 5,4%), hospitalization due to cardiovascular disease other than MI, stroke or cardiovascular death (n=12; 8,2%)). NT-proBNP (HR, 1,19; 95% CI, 1,018-1,32, p<0,001) and sST2 (HR, 1,000013; 95% CI, 1,00-1,001, p=0,007) correlated with CVE in contrast to Ptx-3 (HR, 1,178; 95% CI, 0,798-1,73, p=0,434). The most accurate prediction of CVE was shown in the model with three biomarkers (AIC=831, BIC=843, LR=12,45, p=0,033).

**Conclusion.** After STEMI, NT-proBNP and sST2, but not Ptx-3, predicted CVE, while 3-marker analysis showed higher accuracy compared to single- and double-marker.

**Keywords:** STEMI, cardiovascular events, cardiovascular death, risk stratification, sST2, NT-proBNP, pentraxin-3.

**Relationships and Activities:** none.

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Despite the development of new therapeutic strategies, coronary artery disease remains one of the prioritized healthcare problems all across the globe. ST-segment elevation myocardial infarction (STEMI) leads to both long-term complications and unfavorable cardiovascular diseases (CVDs) over a long period [1]. Thus, one of the most important goals in routine clinical practice is to identify such patients from the risk group.

Using cardiospecific markers facilitates improvement in diagnostics and allows for complication risk stratification and CVD monitoring both during hospitalization and over a long (1–5 years) period [2]. Their concentration correlates with the severity of a cardiovascular event, shows the dynamic of disease and the efficiency of ongoing therapy. Alongside traditionally used biomarkers such as creatine-phosphokinase MB, aspartate aminotransferase, and now commonly used in clinical practice troponins T and I, “new” serum biomarkers rise to popularity: a soluble form of a stimulating growth factor (sST2), pentraxin 3 (Ptx-3), N-terminal pro-brain natriuretic peptide (NT-proBNP). Their concentration allows for the identification of different damage mechanisms affecting myocardial tissues [3, 4]. Indeed, high levels of NT-proBNP are prognostically important for the evaluation of sudden death risks, repeated MI, and chronic heart failure (CHF) not only in patients with MI but also in patients with unstable angina [4]. Nevertheless, the sensitivity and specificity of such markers remain low [5]. Thus, we need additional instruments for cardiovascular outcomes evaluation.

It is proven that multimarker analytical approaches increase the sensitivity and specificity of a prognosis. Therefore, they can be a more efficient instrument for estimating unfavorable CVDs in patients with MI. “New” serum biomarkers such as sST2 and Ptx-3 have been recently presented as a potentially efficient instrument for CVD risks stratification improvement [6]. Ptx-3 is related to the family of pentraxins, while sST2 is a member of the interleukin-1 receptor family and a stimulating growth factor. An increase in its concentration in the blood indicates a higher risk of unfavorable outcomes for patients with MI and heart failure [7]. A Ptx-3 increase is common in patients with coronary artery disease including acute coronary syndrome (ACS) while its high concentration in plasma is a predictor of negative clinical outcomes in patients with HF both with reduced and preserved ejection fraction (EF) [8]. Nevertheless, the prognostic ability of both biomarkers to evaluate outcomes in patients surviving MI remains a highly debated topic. While Ptx-3 levels in blood plasma predict clinical outcomes in patients with HF, its prognostic

ability for patients with MI in the long run is still unclear. In our previous studies, we discovered that in patients with STEMI high presence of sST2, Ptx-3, and NT-proBNP were associated with mortality from cardiovascular diseases while the multimarker approach improved the stratification accuracy of this endpoint [9]. Whether a combination of “new” biomarkers such as NT-proBNP, sST2, and Ptx-3 in patients with STEMI can improve the long-term prognostic accuracy for the composite endpoint, remains unclear.

The aim was to evaluate the potential of stratification of the composite endpoint in patients with STEMI using a combination of serum biomarkers NT-proBNP, sST2, and Ptx-3. Throughout the 2-year follow-up period, we determined the interrelation between initial concentrations of biomarkers in the blood serum and the prevalence of unfavorable cardiovascular events such as MI, stroke, cardiovascular-related hospitalizations, and deaths.

### Material and methods

In this prospective randomized single-center study we included 154 patients hospitalized due to STEMI to the vascular center. The diagnosis was produced using data from electrocardiography (ECG) and verified clinically using follow-up ECG, echocardiography, coronary angiography, and laboratory results according to guidelines of the European Society of Cardiology (ESC) [10].

Depending on the timeframe of symptoms manifestation and availability of coronary angiography, patients were treated with immediate coronary angiography or thrombolysis. Thrombolysis before admission was due to a fraction of patients from remote regions requiring more time to be delivered to the hospital. Thrombolytic therapy only was used for patients who declined coronary angiography or had nephropathy (13 patients out of 147). In cases of inefficient thrombolytic therapy, coronary angiography was performed as soon as possible (Table 1). During coronary angiography, stenting of the infarct-related artery was performed for all 134 patients. Drug therapy and recommendations for further treatment following an MI were conducted according to ESC guidelines [10].

This study is the continuation of our previous study published in January 2020 in the Journal of Clinical Medicine [9] for the same cohort of patients. It contained an analysis of the predictive abilities of the biomarker in relation to cardiovascular mortality.

The study was conducted in accordance with Good Clinical Practice standards and principles of the Declaration of Helsinki. The protocol was approved by

the Local Ethics Committee. Before the inclusion, all participants provided a written informed agreement.

There were following inclusion criteria: age over 18 years and STEMI in accordance with ESC guidelines. Exclusion criteria were as follows: over 48 hours after the ACS onset, severe valvular dysfunction such as severe regurgitation or stenosis, dilated cardiomyopathy, severe atrial fibrillation and/or atrial flutter, second- and third-degree atrioventricular block based on anamnesis or ECG, implanted cardiac pacemaker, acute pulmonary embolism, and recent (<3 years) severe disease, chronic obstructive pulmonary disease or bronchitis; acute infectious diseases at admission, renal failure with glomerular filtration rate less than 30 ml/min/1,72m<sup>2</sup>, pregnancy and lactation.

The design of the study is presented in Figure 1. During the first 3 hours after the arrival, venous blood from patients was collected, centrifuged, and the serum was frozen for further analysis. The concentration of NT-proBNP, sST2, and Ptx-3 was analyzed using enzyme-linked immunosorbent assay (Critical diagnostics, USA, Biomedica, Slovakia, Hycult Biotech, USA). Follow-up analysis was conducted after 2 years  $\pm$  3 months (734,2 $\pm$ 61,2 days) from STEMI using the regional informational analytical system PROMED. This program allows to remotely monitor releases from hospitals and death certificates. In cases when no such entries existed, patients were contacted via telephone to prevent data loss.

The composite endpoint (negative cardiovascular events) was determined as the frequency of repeated MI + stroke + cardiovascular-related hospitalizations + cardiovascular mortality during the follow-up period. Patients who died within the first 6 days of the initial hospitalization, patients died from other reasons (trauma, cancer, suicide, etc.), and patients with whom contact was lost were excluded from the analysis. There were 9 such patients: 2 died due to traumas, 1 patient died from cancer, and 2 patients died within 5 days after hospitalization. Also, contact was lost with 4 other patients due to moving. These patients were also excluded from the analysis.

The statistical analysis was conducted using SPSS 21 and R Studio software. Data are presented as median values (M) and standard deviation. The Mann-Whitney test were used to determine differences between subgroups since it has the highest statistical power among non-parametric tests for small sample pools. Qualitative traits were analyzed using standard statistical chi-squared test. To evaluate the prognostic value of parameters, the area under the ROC curve (AUC) was determined while threshold values were also calculated using ROC

**Table 1**  
**Parameters of the studied group**

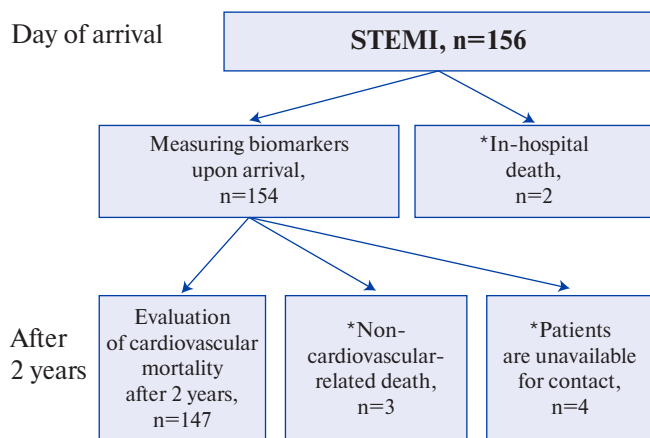
Parameter	Value
N	147
Sex (Male), n (%)	118 (80,3)
Age, years	60,9 $\pm$ 12,1
LVEF (%)	52,8 $\pm$ 7,2
Stroke, n (%)	5 (3,4)
Prior MI, n (%)	34 (23,1)
CABG, n (%)	1 (2,9)
Coronary angiography and artery stenting, n (%)	15 (44,1)
Smoking, n (%)	86 (58,5)
Hypertension, n (%)	138 (93,9)
Type II diabetes, n (%)	23 (15,6)
<i>Revascularization strategy</i>	
Immediate TLT, n (%)	13 (8,8)
Immediate TLT with following CAG, n (%)	22 (15,0)
Immediate CA, n (%)	112 (76,2)
<i>Affected arteries during CAG:</i>	
LCA, n (%)	1 (0,7)
AIA, n (%)	51 (38,1)
CA, n (%)	12 (8,9)
RCA, n (%)	48 (35,8)
Multiple lesion, n (%)	12 (8,9)
<i>Therapy after release</i>	
ACE inhibitors/sartans, n (%)	143 (97,3)
B-blockers, n (%)	139 (94,6)
Diuretics, n (%)	51 (34,7)
Aldosterone antagonists, n (%)	37 (25,2)
Ivabradine, n (%)	12 (8,1)
Statins, n (%)	139 (94,6)
Acetylsalicylic acid, n (%)	142 (96,0)
Thienopyridine, n (%)	138 (93,8)
— Clopidogrel, n (%)	110 (78,7)
— Ticagrelor, n (%)	28 (21,3)
DOAC and Warfarin, n (%)	7 (4,8)

**Abbreviations:** CABG — coronary artery bypass grafting, ACE — angiotensin-converting-enzyme, MI — myocardial infarction, LCA — left coronary artery, DOAC — direct oral anticoagulants, RCA — right coronary artery, AIA — anterior interventricular artery, LVEF — left ventricular ejection fraction, TLT — thrombolytic therapy.

curves. The differences were considered significant at  $p < 0,05$ . The statistical processing was conducted using SPSS 2 and MedCalc 8.2.0.3 software.

## Results

Table 1 contains parameters of the studied cohort as well as examinations and treatments during the hospitalization period and recommendations given upon release from the hospital. Men ( $n=118$ ) prevailed over women ( $n=29$ ). Among comorbidities,

**Figure 1.** Study design.

**Note:** \* — patients were excluded from the study.

**Abbreviations:** STEMI — ST-elevation myocardial infarction, CV — cardiovascular.

hypertension (n=167, 92%), prior MI (42,23%), type II diabetes (31,17%) were observed. Drug therapy during and after hospitalization was in accordance with current ESC guidelines [10].

During statistical analysis, we obtained median values for relevant biomarkers. These results are presented in Table 2. For the time being, normative values for Ptx-3 are not established. All values in patients with ACS from the general group were increased several folds, especially troponin I.

Over 2 years ( $734,2 \pm 61,2$  days), the composite endpoint for cardiovascular events (MI + stroke + cardiovascular-related hospitalizations + cardiovascular mortality during) was observed in 81 patients (55,1%: cardiovascular mortality, 33 (22,1%), repeated MI, 28 (18,8%), stroke, 8 (5,4%), cardiovascular-related hospitalizations, 12 (8,2%)) (Table 3).

The statistical analysis was conducted using the described mathematical model. Two years after a STEMI, ROC-analysis was used to evaluate cut-off points of studied biomarkers depending on cardiovascular events (Table 4, Figure 2). The logarithmic criterion and Gehan-Wilcoxon test showed a reliable cardiovascular events biomarker cut-off point only for NT-proBNP ( $>2247$  pg/ml,  $p=0,02$ ) (Table 5).

Kaplan-Meier survival curves were created for cardiovascular events frequency after 2 years above and below cut-off points for biomarkers NT-proBNP, sST2, and Ptx-3 (Figure 3). We observed a slight divergence in survival between cardiovascular events frequency for NT-proBNP and sST2 while Ptx-3 curves were nearly identical.

During the next stage, endpoints of biomarkers were analyzed using the Cox regression. NT-proBNP

**Table 2****Biomarker parameters in the general group**

Parameter	Value	Reference value
n	147	
Creatinine, mmol/l	$100,97 \pm 25,28$	male — 80-115, female — 53-97
CPK-MB, mmol/l	$112,16 \pm 94,47$	5-24
Troponin I, ng/ml	$1625,4 \pm 2882,1$	0-0,1
NT-proBNP, pg/ml	$1342,8 \pm 1648,2$	0,5-30
sST2, ng/ml	$58,17 \pm 60,03$	male — 8,5-49,3, female — 7,1-33,5
Ptx-3, ng/ml	$170,9 \pm 117,29$	-

**Abbreviations:** CPK-MB — creatine phosphokinase-MB, NT-proBNP — N-terminal pro-brain natriuretic peptide.

**Table 3****Cardiovascular events in the group after 2 years**

	STEMI, n=147
Deceased, n	33 (22,1%)
MI, n	28 (18,8%)
Stroke, n	8 (5,4%)
Hospitalization, n	12 (8,2%)
Composite endpoint (CVE)	81 (55,1%)

**Abbreviations:** MI — repeated myocardial infarction, STEMI — ST-segment elevation myocardial infarction, CVE — cardiovascular events.

and Ptx-3 values were presented in logarithmic form and sST2 — in quadratic. Table 4 presents Cox regression coefficients for cardiovascular events for studied biomarkers. To evaluate mortality coefficients in the Cox model, we used the Efron approximation (partial likelihood). Indeed, in Cox regression, biomarkers NT-proBNP and sST2 were able to predict cardiovascular events ( $p<0,01$ ). The NT-proBNP (AUC=0,8,  $p<0,001$ ) demonstrated a higher prognostic value for cardiovascular events compared to sST2 (AUC=0,625,  $p=0,02$ ).

Using Gehan-Wilcoxon tests and logarithmic analysis, parameters of patients (Table 1 and 2) were analyzed to evaluate control variables associated with cardiovascular events throughout the follow-up period ( $p<0,1$ ). It was discovered that the following parameters were associated with cardiovascular events with  $p<0,1$ : NT-proBNP, sST2, Ptx-3, age over 5 years, male sex, and a high level of troponin I. Biomarkers NT-proBNP, sST2, and Ptx-3 were binarized and transformed into fictitious variables according to cut-off points obtained above using ROC analysis. It was done to analyze the combined effect of risk factors (RF) on cardiovascular

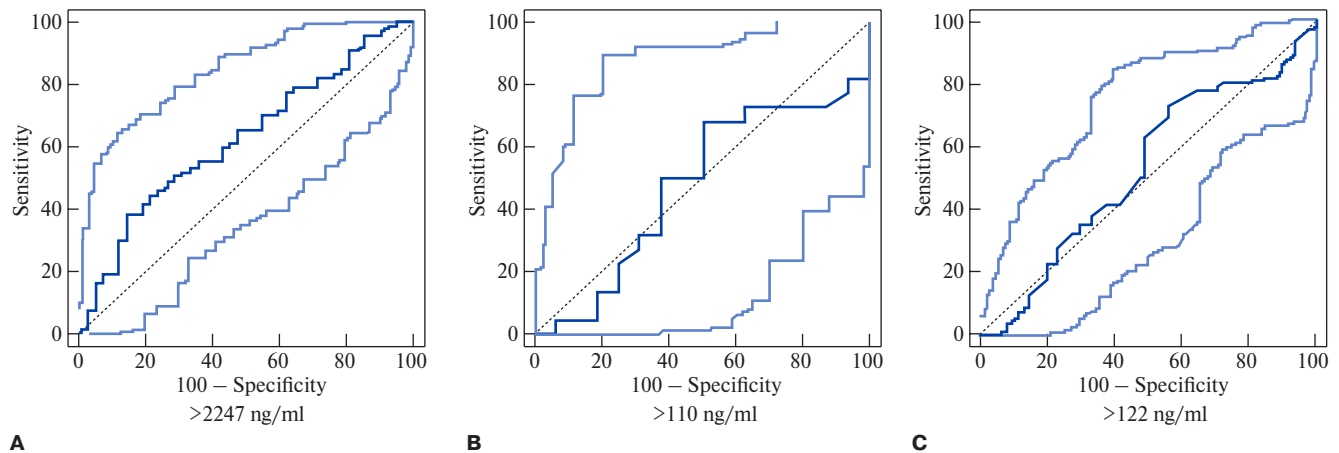


Table 4

## Cut-off points for biomarkers for CVE over the 2 years after STEMI

Biomarker	CVE				
	Cut-off point	Sensitivity, %	Specificity, %	AUC	p
NT-proBNP, pg/ml	>2247	38,8	85,7	0,625	0,020
sST2, ng/ml	>110	68,2	50,0	0,477	0,814
Ptx-3, ng/ml	>122,0	72,5	44,3	0,526	0,593

**Abbreviations:** NT-proBNP — N-terminal pro-brain natriuretic peptide, sST2 — soluble suppression of tumorigenicity 2, Ptx-3 — pentraxin 3, CVE — cardiovascular events.



**Figure 2.** ROC analysis of cut-off points for cardiovascular events for NT-proBNP (A), sST2 (B), and Ptx-3 (C) after a 2-year follow-up period after STEMI.

Table 5

## Cox regression for biomarkers and CVE prevalence after STEMI

Biomarker	Coefficient±SD	Hazard ratio	AUC	95% CI	P
Log (NT-proBNP)	0,1781±0,051	1,19	0,526	1,08-1,32	0,0006
sST2 <sup>2</sup>	a,000013±0,000000007	1,000013	0,625	1,00-1,001	0,007
Log (Ptx-3)	0,167±0,20	1,178	0,477	0,798-1,73	0,4344

**Abbreviations:** CI — confidence interval, NT-proBNP — N-terminal pro-brain natriuretic peptide.

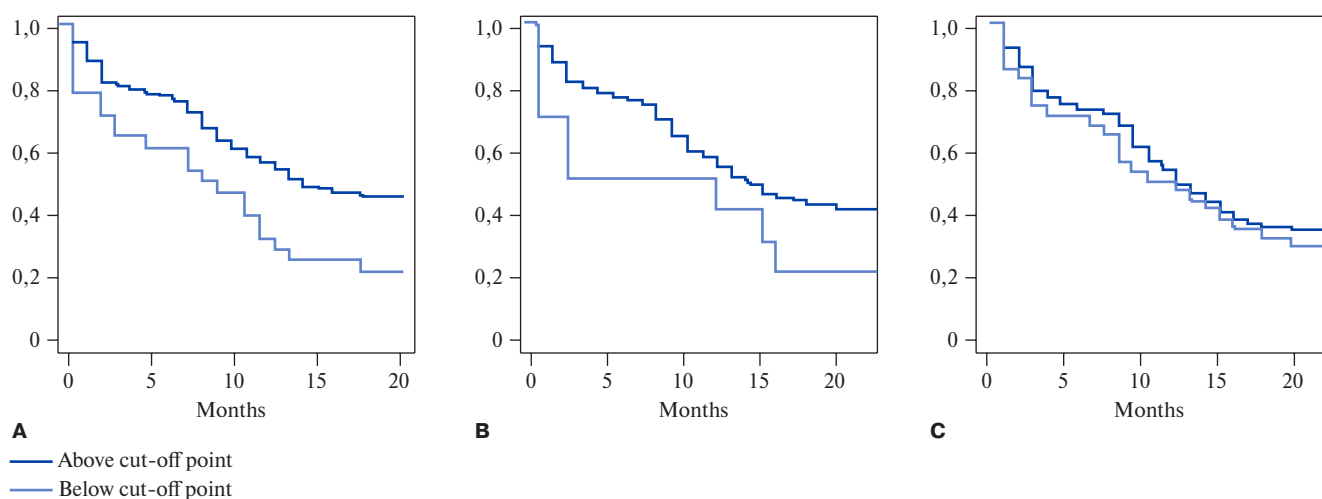
events throughout the 2-year follow-up period with a comparatively small volume of initial data. Additionally, discrete variables allow for a more accurate interpretation of the risk ratio in the Cox model.

During the next stage, we conducted a comparison of prognostic power between multimarker approaches (various combinations of NT-proBNP, sST2, and Ptx-3) for cardiovascular events based on information criteria Akaike (AIC) and Schwartz (BIC) with control variables. Variables of NT-proBNP, sST2, and Ptx-3 biomarkers were transformed into binary form for both models. The comparison between two biomarker models (sST2 + NT-proBNP, sST2 + Ptx-3, and NT-proBNP + Ptx-3) and the model with three biomarkers allowed us to find the most accurate variant according

to AIC and BIC statistical parameters. Table 5 presents the results for coefficients and multifactor analysis of risks in the Cox model for cardiovascular events over the 2-year follow-up analysis. The most accurate prognosis was found for the model with three biomarkers although with a low likelihood ratio (LR) of 12,45 ( $p=0,034$ ). It should be noted that the combination of NT-proBNP and sST2 was only slightly behind the three-component cut-off point with LR 12,44 ( $p=0,034$ , Table 6).

## Discussion

For rational risk stratification in patients with STEMI and to acquire additional prognostic information, it was suggested to use a combination of serum biomarkers involved in a variety of pathological reactions associated with cardiovascular



**Figure 3.** Kaplan-Meier survival curves for cardiovascular events during a 2-year analysis for NT-proBNP (A), sST2 (B), and Ptx-3 (C).

**Table 6**  
**Multivariable regression analysis of RF for different combinations of biomarkers 2 years after STEMI**

Biomarker and cut-off values	Coefficient±SD	HR	95% CI	p
Combination NT-proBNP + sST2 + Ptx-3 (AIC=831, BIC=843, LR=12,45, p=0,033)				
NT-proBNP >2247 pg/ml	0,54±0,26	1,72	1,03-2,86	0,037
sST2 >110 ng/ml	-0,04±0,33	0,96	0,51-1,82	0,902
Ptx-3 >122 ng/ml	0,31±0,24	1,37	0,85-2,20	0,199
Age >65 years	0,31±0,24	1,17	0,84-2,21	0,219
Male	0,121±0,22	1,13	0,72-1,74	0,599
Troponin I	0,35±0,21	1,42	1,15-1,75	0,174
Combination NT-proBNP + Ptx-3 (AIC=828, BIC=838, LR=10,76, p=0,034)				
NT-proBNP >2247 pg/ml	0,54±0,26	1,72	1,03-2,86	0,037
Ptx-3 >122 ng/ml	0,31±0,24	1,36	0,86-2,15	0,196
Age >65 years	0,31±0,24	1,36	0,84-2,21	0,214
Male	0,111±0,21	1,12	0,91-1,38	0,606
Troponin I	0,37±0,20	1,45	1,19-1,77	0,160
Combination NT-proBNP + sST2 (AIC=830, BIC=840, LR=12,44, p=0,034)				
NT-proBNP >2247 pg/ml	0,58±0,26	1,78	1,07-2,96	0,023
sST2 >110 ng/ml	0,08±0,32	1,08	0,58-2,04	0,805
Age >65 years	0,33±0,25	1,39	0,85-2,26	0,185
Male	0,15±0,23	1,16	0,92-1,46	0,521
Troponin I	0,41±0,21	1,51	1,22-1,86	0,091
Combination sST2 + Ptx-3 (AIC=833, BIC=843, LR=8,27, p=0,081)				
sST2 >110 ng/ml	-0,048±0,32	1,72	0,50-1,79	0,881
Ptx-3 >122 ng/ml	0,36±0,24	1,43	0,89-2,29	0,137
Age >65 years	0,48±0,23	1,61	1,04-2,52	0,034
Male	0,15±0,22	1,13	0,72-1,74	0,599
Troponin I	0,40±0,21	1,49	1,20-1,84	0,101

**Abbreviations:** CI — confidence interval, HR — hazard ratio, LR — likelihood ratio, NT-proBNP — N-terminal pro-brain natriuretic peptide.

events [11]. The majority of multimarker approaches include an addition of new promising biomarkers to the pool of well-studied RFs [12, 13]. Patients with high-risk experience longer hospitalization,

higher hospitalization rate, higher frequency of ICD implantations, and thus they are recommended a different strategy of secondary prophylaxis, rehabilitation, etc.

Alongside standard biomarkers, the prognostic value of “new” biomarkers NT-proBNP (myocardial stress marker), sST2 (myocardial fibrosis and remodeling marker), and Ptx-3 (inflammation marker) was analyzed in 147 patients with STEMI in terms of negative cardiovascular events (after 2 years). In this study, for the cardiovascular endpoint, the sST2 cut-off point was  $>47$  ng/ml (hazard ratio (HR), 1,000012, 95% confidence interval (CI), 1,000-1,001,  $p=0,071$ , 68,2%, 50,7%), NT-proBNP  $>463,0$  (HR, 1,19, 95% CI 1,018-1,32,  $p<0,01$ , 38,8%, 85,7%). Kaplan-Meier survival curves above and below the cut-off point revealed a divergence between curves for NT-proBNP and sST2, but not for Ptx-3.

In the Bayes-Genis A, et al. (2015) study, in 1015 patients with HF with reduced EF, sST2 showed long-term risk stratification in patients with different concentrations of biomarkers of other pathogenetic classes in the blood serum [10]. Hence, the death risk ratio based on the sST2 was 1,22 (95% CI, 1,08-1,37;  $p=1,001$ ) in the upper tercile of NT-proBNP and 2,02 (95% CI, 1,61-2,52;  $p=1,001$ ) in the lower tercile of NT-proBNP. A multicenter study with 1141 outpatients with systolic heart failure revealed that the risk of cardiovascular endpoints was higher when the concentration of sST2 was  $\geq 36,3$  ng/ml compared to when it was  $sST2 < 22,3$  ng/ml (HR, 1,9; 95% CI, 1,3-2,9;  $p=0,002$ ) [12]. This fact suggests that sST2 on its own cannot be considered an RF which was confirmed in the CLARITY-TIMI study [4]. Ehab K, et al. (2016) determined the level of serum Ptx-3 in STEMI patients. In patients with STEMI, the level of Ptx-3 was significantly higher compared to the control group and it was recommended to use it as an early MI marker [13]. The cut-off point was 4,35 ng/ml, also lower than in our study. As pointed out above, during MI, the low specificity of sST2 in relation to endpoints can be observed [4]. However, the prognostic ability was

high for the combination of sST2 and NT-proBNP. It increased from 0,82 (95% CI, 0,77-0,87) to 0,86 (95% CI, 0,81-0,90;  $p=0,017$ ). The combination of sST2 and NT-proBNP significantly improved the risk stratification accuracy. High levels of Ptx-3 predicted long-term mortality in several prospective observational studies [14, 15]. In our previous studies, the significance of biomarker combination (sST2 + Ptx-3 + NT-proBNP) in patients with STEMI for cardiovascular mortality diagnosis was already demonstrated [9, 16]. In another, similar in terms of design with ours, study, AUC was 0,872 for sST2 (sensitivity, 76,27%; specificity, 85,92%) and 0,902 for NT-proBNP (96,61%, 77,69%) while levels of sST2 in serum and NT-proBNP were independent RF for cardiovascular events [17]. In 1401 patients with STEMI, the median sST2 was 48,7 ng/ml and higher values were associated with higher excessive mortality risk and heart failure independent from other prognostic parameters over the course of 5-year follow-up [7].

In this study, in 147 patients with STEMI throughout 2-year follow-up analysis, we studied the ability of serum biomarkers sST2, Ptx-3, and NT-proBNP to stratify risks of unfavorable cardiovascular events. Two years after MI, NT-proBNP and sST2 separately predicted cardiovascular events while the two-marker combination of NT-proBNP and sST2 was significant in cardiovascular events prognosis (LR=12,44,  $p=0,033$ ). The three-component endpoint NT-proBNP + sST2 + Ptx-3 (LR=12,45,  $p=0,033$ ) slightly prevailed over the combination of NT-proBNP and sST2. Thus, we demonstrated the efficiency of new biomarkers for 2-year cardiovascular events prognosis after MI.

The study limitations are a comparatively small sample pool and a short follow-up period, both limiting the statistical potential of analysis.

**Relationships and Activities:** none.

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