ORIGINAL ARTICLE

Association of galectin-3 and soluble ST2 with in-hospital and 1-year outcomes in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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KEY WORDS

biomarkers, heart failure, hospitalization, independent predictor, prognosis

ABSTRACT

INTRODUCTION Galectin-3 (Gal-3) and soluble interleukin-1 receptor-like 1 (sST2) have known prognostic value in already diagnosed heart failure (HF).

OBJECTIVES To investigate the association of Gal-3 and sST2 with prognosis in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI).

PATIENTS AND METHODS The analysis was based on data collected in a prospective observational BIOSTRAT (Biomarkers for Risk Stratification After STEMI; ClinicalTrials.gov identifier, NCT03735719) study. Analysis included 117 patients with first-time STEMI treated with pPCI. Serum for Gal-3 and sST2 was sampled 72 to 96 hours after admission due to STEMI. The patients were followed for the primary endpoint (cardiovascular [CV] death or HF hospitalization at 1 year).

RESULTS Both biomarkers correlated with N-terminal pro-B-type natriuretic peptide (NT-proBNP); Gal-3 correlated with older age. Data on the primary endpoint were available for 104 patients (89%). At 1-year follow-up, 9 patients (8.7%) reached the primary endpoint. In univariate Cox proportional hazards regression analysis, both Gal-3 and sST2 as continuous variables, as well as their newly-established cutoffs (≥9.57 ng/ml for Gal-3 and ≥45.99 ng/ml for sST2, based on the Youden index) were predictors of the primary endpoint, and of HF hospitalizations alone. Gal-3 also predicted CV death. After adjustment for age and NT-proBNP, Gal-3 and sST2 remained predictors of the primary endpoint in multivariate models.

CONCLUSIONS In patients with first-time STEMI treated with pPCI, baseline Gal-3 and sST2 predicted the composite of CV death and HF hospitalization at 1 year. Both biomarkers may play an important role in CV risk stratification after STEMI, although Gal-3 may be considered preferable.

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Received: September 7, 2019.
Revision accepted: October 23, 2019.
Published online: October 23, 2019.
Pol Arch Intern Med. 2019; 129 (11): 770-780
doi:10.20452/pamw.15030

INTRODUCTION Despite modern reperfusion strategies and evidence-based pharmacotherapy, acute myocardial infarction (AMI) causes pathological left ventricular remodelling (LVR) and heart failure (HF), and therefore leads to adverse cardiovascular (CV) outcomes.[1-4] AMI represents a major cause of HF.[1,5-7] According to a Polish nationwide database of acute coronary syndromes (AMI-PL database), HF is one of the most frequent causes of recurrent hospitalization in patients after AMI in 1-year follow-up,[8] indicating a need for an intensification of secondary prevention programs (including cardiac rehabilitation, smoking cessation, and improvement of risk stratification).[3,4,9] Therefore, it is important to explore new sensitive

WHAT'S NEW?

Despite modern reperfusion strategies, myocardial infarction leads to deleterious processes resulting in left ventricular remodeling (LVR) and heart failure (HF). Galectin-3 (Gal-3) and soluble ST2 (sST2) are involved in LVR as a result of inflammation and fibrosis. There is an evidence of a prognostic value of both biomarkers in predicting outcomes in HF patients. However, studies evaluating the role of Gal-3 and sST2 in patients after ST-segment elevation myocardial infarction (STEMI) are insufficient. The study aimed to investigate the association of Gal-3 and sST2 with prognosis in patients with STEMI treated with primary percutaneous coronary intervention. We also established new cutoffs for Gal-3 and sST2 (based on the Youden index) for prediction of the primary endpoint. The results of the study showed that both biomarkers reflect prognosis after STEMI, with particular focus on Gal-3.

and specific biomarkers that could help identify patients at risk of developing HF and adverse CV outcomes after AMI.

Galectin-3 (Gal-3) and soluble interleukin-1 receptor-like 1 (sST2) are promising biomarkers involved in LVR, resulting from inflammatory processes and fibrosis.[10-14] There is evidence for a high prognostic value of both biomarkers in predicting outcomes in patients with chronic and acute HF.[15] Biomarkers of myocardial fibrosis (including sST2 and Gal-3) were recommended as useful tools for additional risk stratification in the American guidelines for the management of HF.[16]

However, studies evaluating the role of Gal-3 and sST2 and their relationship with adverse outcomes in patients after AMI are insufficient. Therefore, we aimed to evaluate the association of Gal-3 and sST2 in patients with first-time ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) with in-hospital and 1-year CV outcomes.

PATIENTS AND METHODS

Study population

The analysis was based on data collected in a prospective observational BIOSTRAT (Biomarkers for Risk Stratification After STEMI; ClinicalTrials.gov identifier, NCT03735719) study. The BIOSTRAT study included 117 consecutive white patients with first-time STEMI treated with primary PCI in the 1st Department of Cardiology, Medical University of Warsaw from October 2014 to April 2017. STEMI was diagnosed in accordance with the applicable guidelines.[17] Main inclusion criteria were age 18 years or older and first-time STEMI treated with primary PCI. Main exclusion criteria were previous AMI, pre-existing HF (history of LV ejection fraction [LVEF] <50% or diagnosed HF with preserved LVEF), severe renal dysfunction (plasma creatinine level >220 mmol/l (approx. 2.5 mg/dl), and/or creatinine clearance <30 ml/min), severe liver disease, chronic inflammatory disease, current neoplastic disease, and life expectancy less than 1 year.

Informed written consent was obtained from each study participant. The trial protocol complied with the Declaration of Helsinki and was approved by the local ethics committee of the Medical University of Warsaw (decision no. KB/97/2014).

Baseline tests and measurements

Routine laboratory parameters, including complete blood count, glycemia, lipid profile, electrolytes, serum creatinine, and biomarkers such as cardiac troponin I, creatine kinase myocardial band, high-sensitive C-reactive protein (hs-CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured using standard methods in the hospital laboratory. The concentration of NT-proBNP was measured using the Roche Elecsys 1010 analyzer (Roche Diagnostics, Mannheim, Germany). The concentration of hs-CRP was assessed using Cobas Integra 800 (Roche Diagnostics).

The highest concentrations of cardiac troponin I, NT-proBNP, and hs-CRP were subsequently included in the analyses.

Electrocardiogram, transthoracic echocardiogram and clinical examination were performed in each patient during index hospitalization. Demographic data, details on previous and current pharmacotherapy, clinical and angiographic characteristics, and medical history were also prospectively gathered.

Gal-3 and sST2 measurements

Additionally, blood samples were collected from all recruited patients for further measurements of serum Gal-3 and sST2 concentrations. To avoid the potential impact of PCI on biomarker concentration, we sampled blood after 72 to 96 hours after hospital admission, as per previous studies.[18,19] Serum was prepared from blood samples by allowing the blood to clot for 60 min, followed by centrifugation at 3500 rpm for 15 min. Serum samples were then stored at –80°C. Measurements were performed after all patients had entered the study. Serum concentrations of Gal-3 were measured using Human Galectin-3 Quantikine ELISA Kit (BIOKOM, Janki, Poland), and plasma sST2, using Presage ST2 Assay (Genloxa, Puck, Poland).

Study endpoints

Patients were followed for 12 months. The primary endpoint was CV death or hospitalization for HF during 1-year follow-up. CV death was defined as deaths related to AMI, HF, sudden cardiac death, or stroke. Hospitalization for HF was considered as hospitalization with a primary diagnosis of HF supported by evidence of clinical signs of HF (rales, peripheral edema), pulmonary congestion on a chest radiograph, or a need for intravenous diuretics.

Secondary endpoints concerned in-hospital outcomes including 1) total length of index hospitalization, 2) length of stay in intensive cardiac care unit during index hospitalization, 3) in-hospital death; and events that occurred in 1-year follow-up including 4) CV death, 5) hospitalization for HF, and 6) MI.

Statistical analysis

For a between-group comparison, we used the Fisher exact test and

TABLE 1 Clinical correlates of Gal-3 and sST2 in patients with ST-segment elevation myocardial infarction treated with primary coronary intervention

Variable	Baseline Gal-3		Baseline sST2	
	Rho	*P* value	Rho	*P* value
Baseline characteristics				
Age, y	0.38	<0.001	0.09	0.32
BMI, kg/m^2	0.14	0.15	0.01	0.93
Clinical status, laboratory, and angiographic findings on admission				
Killip class	0.20	0.03	0.10	0.27
Hemoglobin, g/dl	–0.26	0.004	–0.14	0.12
hs-CRP, mg/dl	0.18	0.05	0.19	0.047
Troponin I, ng/ml	–0.45	0.64	0.03	0.74
NT-proBNP, pg/ml	0.36	0.001	0.38	<0.001
Gal-3, ng/ml	–	–	0.48	0.04
sST2, ng/ml	0.48	0.04	–	–
eGFR, ml/min/1.73 m^2	–0.30	0.001	–0.11	0.23
Serum sodium, mmol/l	–0.09	0.36	–0.20	0.03
Total cholesterol, mg/dl	–0.23	0.01	–0.24	0.01
LDL, mg/dl	–0.12	0.07	–0.19	0.059
TIMI score	0.34	<0.001	0.12	0.19
GRACE score	0.38	<0.001	0.10	0.26
Baseline TIMI grade flow	0.10	0.31	–0.16	0.04
Final TIMI grade flow	–0.05	0.63	–0.16	0.045
Echocardiographic and laboratory findings at discharge				
Hemoglobin, g/dl	–0.19	0.05	–0.03	0.78
Serum creatinine, mg/dl	0.13	0.18	0.19	0.054
eGFR, ml/min/1.73 m^2	–0.36	<0.001	–0.24	0.01
Outcomes				
Hospitalization length, d	0.18	0.055	0.35	<0.001
Time in ICCU, d	0.35	<0.001	0.45	<0.001

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Gal-3, galectin-3; GRACE, Global Registry of Acute Coronary Events; hs-CRP, high-sensitive C-reactive protein; ICCU, intensive cardiac care unit; LDL, low-density lipoprotein; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; sST2, soluble interleukin-1 receptor-like 1; TIMI, Thrombolysis in Myocardial Infarction

the Mann–Whitney test for categorical and continuous variables, respectively. Categorical data were presented as numbers and percentages of patients. Normally distributed continuous data were expressed as mean (SD), while non-normally distributed continuous data were presented as median with an interquartile range (IQR). Pearson and Spearman correlation coefficients were used for parametric and nonparametric variables, respectively. The Cox proportional hazards regression model was performed to identify predictors of the primary endpoint. Receiver operating characteristic (ROC) curves were plotted for baseline Gal-3 and sST2 in relation to the primary endpoint. In addition, the Youden J statistic was performed to determine the optimal biomarker cutoff point for the prediction of the primary endpoint. A *P* value of less than 0.05 was considered significant. All tests were 2-tailed. SPSS software, version 22 (IBM SPSS Statistics 22, New York, New York, United States) was used for analysis.

RESULTS

Baseline characteristics A total of 117 consecutive first-time STEMI patients were included in the study. The median (IQR) age was 61.0 (50.5–67.0) years and 70% of patients were men. Median (IQR) baseline LVEF was 48% (41%–53%). Median (IQR) Gal-3 and sST2 concentrations were 7.1 (5.6–8.8) ng/ml and 23.4 (18.0–32.0) ng/ml, respectively.

Correlation analysis with baseline parameters We also performed correlation analysis of baseline Gal-3 and sST2 concentrations with clinical parameters (TABLE 1). A correlation was found between Gal-3 and sST2 levels. Both Gal-3 and sST2 correlated positively with stay at an intensive cardiac care unit, NT-proBNP, and hs-CRP and inversely with glomerular filtration rate. Gal--3 correlated positively with age, Killip class, as well as the Thrombolysis in Myocardial Infarction (TIMI) and the Global Registry of Acute Coronary Events (GRACE) scores. sST2 correlated negatively with sodium level on admission and inversely with baseline and final TIMI Coronary Grade Flow. There was a nonsignificant correlation between sT2 and age.

One-year follow-up Data on survival was available for all patients (5 out of 117 patients [4.3%] died). Thirteen patients were lost to follow--up in terms of hospitalization for HF, leaving 104 patients (89%) for the composite primary endpoint analyses at 1 year. During 1-year follow-up, 9 patients (8.7%) reached the primary endpoint (3 died due to CV causes and 6 were hospitalized for HF). Among CV causes of death, HF-related death occurred in 2 patients and AMI-related death, in 1 patient (including 1 patient who died during index hospitalization after recruitment).

Patients who experienced the primary endpoint during follow-up had higher levels of baseline Gal-3 and sST2 (for sST2 nonsignificant). Baseline characteristics of patients who reached and who did not reach the primary endpoint at 1 year are presented in Supplementary material, *Table S1*.

Comparison of baseline characteristics, laboratory findings, clinical presentations, in-hospital and 1-year outcomes in patients with high and low Gal-3 and sST2 levels ROC analysis revealed that the area under the curve (AUC) for Gal-3 and sST2 (for prediction of the primary endpoint) was 0.85 and 0.64, respectively (FIGURE 1). Gal-3 concentration of 9.57 ng/ml or higher had a sensitivity of 41%, a specificity of 91%, a negative predictive value of 92%, and a positive predictive value of 36% for prediction of the primary endpoint at follow--up (the Youden index). sST2 concentration of 45.99 ng/ml or higher had a sensitivity of 44%, a specificity of 97%, a negative predictive value of 95%, and a positive predictive value of 57% for prediction of the primary endpoint at follow-up (the Youden index).

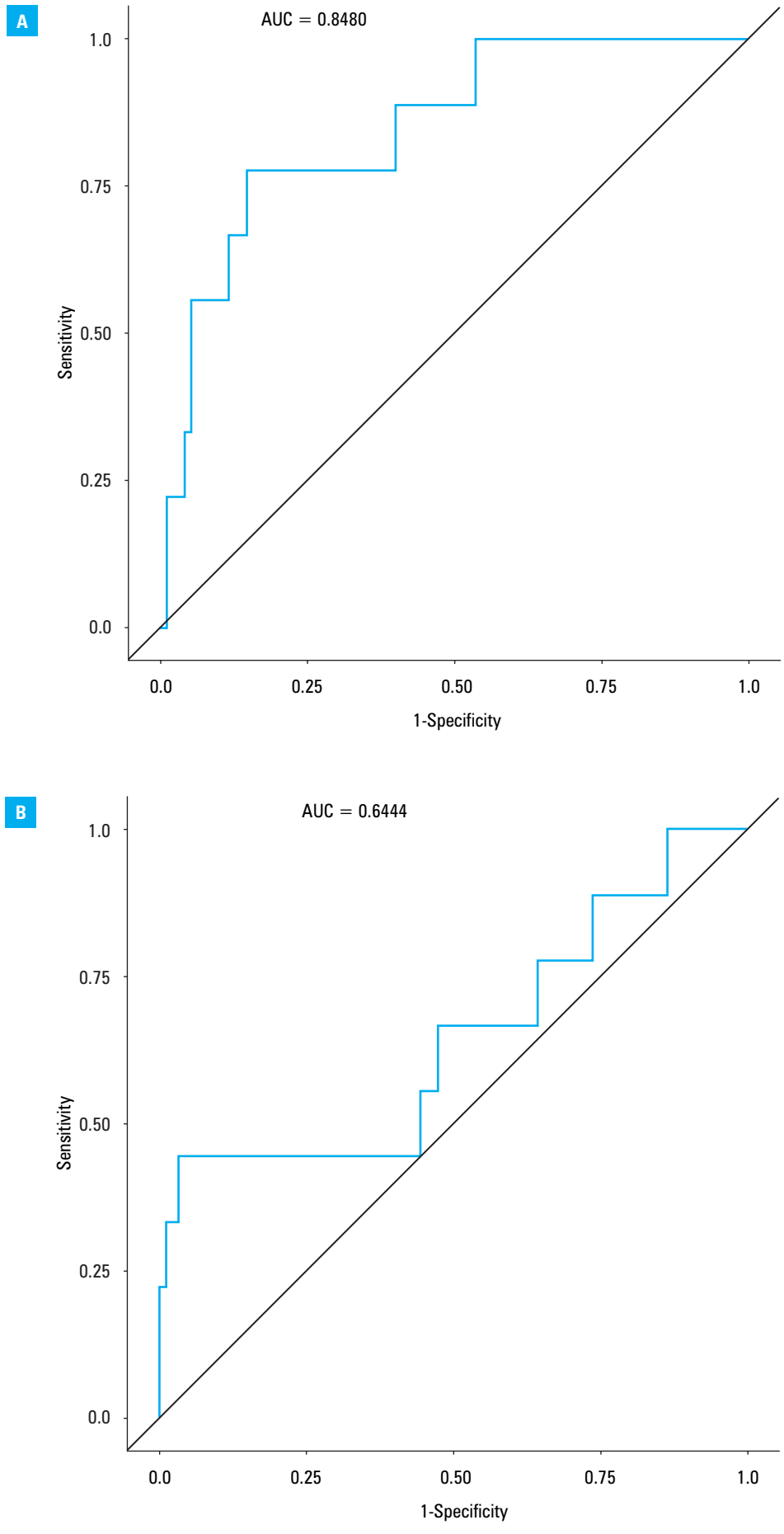

FIGURE 1 **A** – receiver operating characteristic curve for galectin-3 concentration in relation to the primary endpoint; **B** – receiver operating characteristic curve for the concentration of soluble interleukin-1 receptor-like 1 (sST2) in relation to the primary endpoint
Abbreviations: AUC, area under the curve

Baseline characteristics, laboratory findings, clinical presentations, in-hospital and 1-year outcomes of patients with high and low Gal-3 and sST2 levels depending on established cutoffs are presented in TABLES 2 and 3. Twenty-four patients (20.5%) had baseline Gal-3 levels equal to or above the upper limit of the established cutoff value of 9.57 ng/ml. Eight patients (6.8%) had baseline sST2 levels equal to or above the upper limit of the established cutoff value of 45.99 ng/ml. Higher concentrations of both biomarkers (above the cutoffs) were associated with a longer hospital stay (including a longer stay in intensive cardiac care unit) and more frequent occurrence of the primary endpoint. Patients with a Gal-3 level above the cutoff also experienced CV death more frequently.

Predictors of the primary endpoint In the univariate Cox proportional hazards regression analysis, both baseline Gal-3 and sST2 (as continuous variables, as well as their newly-established cutoffs) were predictors of the primary endpoint (CV death or HF hospitalization), and of HF hospitalizations (TABLE 4). Furthermore, in contrast to sST2, Gal-3 predicted CV death.

Gal-3 and sST2 remained significant predictors of the primary endpoint even after adjustment for age and NT-proBNP in multivariate analyses (FIGURE 2, TABLE 5).

DISCUSSION

In our study, concentrations of both Gal-3 and sST2 were higher in those with worse clinical presentation at baseline. Both Gal-3 and sST2 were associated with unfavorable in-hospital outcomes and were independent predictors of CV death or hospitalization for HF in 1-year follow-up (when regarded as continuous variables). However, if the newly-established cutoffs of both biomarkers were included in one multivariate model (together with age), only Gal-3 remained an independent predictor of the primary endpoint. Moreover, Gal-3 also predicted CV death alone. Furthermore, there was no difference in sST2 concentration between those who did and did not reach the primary endpoint during follow-up. Therefore, Gal-3 might be preferable to ST2 in risk stratification after STEMI.

In our study there was a small number of events, but the results are in line with a recent study assessing the same composite endpoint in patients with a first anterior STEMI treated with pPCI. In this study, 20 out of 103 patients (19.4%) died or were admitted for HF within a 6-month follow-up. Gal-3, measured within 48 hours after STEMI, significantly predicted the composite endpoint after adjustment for age, gender, renal and ventricular function as well as troponin and NT-proBNP values.[20]

Gal-3 plays an important role in various biological processes, but the most acknowledged role of Gal-3 is participation in fibrosis.[10,21,22] Gal-3 is produced by activated macrophages that stimulate inflammation and proliferation of myofibroblasts and collagen deposition.[10] Sanchez-Mas et al[23] observed based on experimental data that Gal-3 increases in myocardium after AMI with the maximum concentration achieved in the infarcted area during the first week, with a gradual decrease over the following weeks. It appears that the increase in concentration of Gal-3 in the early phase after myocardial infarction contributes to the activation of repair functions in the damaged zone in order to maintain the geometry and function of the heart. However, in a longer perspective, chronic activation leads to tissue fibrosis and accelerates adverse LVR.[23]

The ST2 molecule is a soluble glycoprotein belonging to the interleukin-1 receptor family, and is secreted by inflammatory cells, cardiomyocytes, and endothelium.[11] ST2 has 2 clinically relevant isoforms—transmembrane (ST2 ligand) and soluble (sST2) circulating in the bloodstream.[11,24] The balance between these 2 forms of ST2 guarantees an appropriate biological effect. Elevated sST2 triggers myocardial fibrosis.[11,24] In an experimental study, sST2 concentrations increased steadily after AMI with maximum expression on the first day.[11]

It is also known that Gal-3 and interleukin 33 / ST2 pathways are involved in the pathogenesis of atherosclerosis, in which the inflammatory substrate is one of the main causes of instability of atherosclerotic plaques.[24,25] Tsai et al[26] showed that Gal-3 levels were significantly higher in patients with AMI than in healthy controls. In our study, we observed lower median Gal-3 concentrations (7.1 ng/ml) in patients following first-time AMI than was reported previously by Szadkowska et al[27] and van der Velde et al[28] (13.0 and 13.4 ng/ml, respectively). However, these differences can be explained by more restrictive exclusion criteria related to potential fibrosis processes (ie, exclusion of patients with neoplasms, advanced chronic kidney disease, previous HF) in our study. We also only enrolled patients with STEMI, excluding patients with non–ST-segment elevation myocardial infarction. In addition, previously, it has also been shown that elevated Gal-3 and sST2 concentrations were observed in patients with hypertension, diabetes, prior AMI, and prior HF—factors which may bias the biomarkers' measurements between studies.[19,29]

The first studies on Gal-3 and sST2 were in the field of HF and showed that higher levels of circulating Gal-3 and sST2 were associated with worse prognosis in those patients.[15,29,30] The American Heart Association recommendations have even considered Gal-3 and sST2 to be valuable prognostic markers in acute and chronic HF (class IIb recommendation, level of evidence B).[16] The Food and Drug Administration approved threshold values of 17.8 ng/ml for Gal-3 and 35.0 ng/ml for sST2 for additional risk stratification in patients with chronic and acute HF.[28] However, there is still a need to assess the clinical

TABLE 2 Baseline characteristics and clinical course of index hospitalization of patients (n = 117) with ST-segment elevation myocardial infarction treated with primary coronary intervention with reference to baseline Gal-3 and sST2 cutoffs (continued on the next page)

Variable		sST2 <45.99 ng/ml (n = 109)	sST2 ≥45.99 ng/ml (n = 8)	*P* value	Gal-3 <9.57 ng/ml (n = 93)	Gal-3 ≥9.57 ng/ml (n = 24)	*P* value
Baseline characteristics							
Age, y		60 (50.5–67)	69.5 (51–78.8)	0.19	59 (50–64.5)	66.5 (55.3–78.8)	0.01
Male sex, n (%)		77 (70.6)	5 (62.5)	0.69	70 (75.3)	12 (50)	0.02
BMI, kg/m^2		28.4 (24.6–30.5) n = 98	33.3 (29.3–34.7) n = 7	0.07	28.1 (24.4–30.4) n = 87	30.0 (28.6–33.7) n = 18	0.02
Moderate valve disease, n (%)		4 (3.7)	1 (12.5)	0.30	3 (3.2)	2 (8.3)	0.27
Hypertension, n (%)		65 (59.6)	6 (75.0)	0.48	55 (59.1)	16 (66.7)	0.64
Atrial fibrillation, n (%)		3 (2.8)	2 (25)	0.04	2 (2.2)	3 (12.5)	0.058
Diabetes, n (%)		21 (19.3)	2 (25)	0.66	17 (18.3)	6 (25)	0.57
Chronic kidney disease, n (%)		15 (13.8)	5 (62.5)	0.04	12 (12.9)	8 (33.3)	0.03
COPD, n (%)		4 (3.7)	3 (37.5)	0.01	4 (4.3)	3 (12.5)	0.15
Prior stroke or TIA, n (%)		4 (3.7)	2 (25)	0.054	3 (3.2)	3 (12.5)	0.10
Peripheral artery disease, n (%)		4 (3.7)	3 (37.5)	0.01	2 (2.2)	5 (20.8)	0.004
Current or former smoking, n (%)		80 (73.4)	6 (75)	1.00	70 (75.3)	16 (66.7)	0.44
Clinical status and laboratory findings on admission							
Heart rate, bpm		80 (70–90)	90 (71–98.8)	0.24	80 (70–90)	80 (70–89)	0.80
SBP, mm Hg		130 (120–141)	142.5 (120–168.5)	0.18	130 (120–140)	132.5 (120–149.8)	0.49
DBP, mm Hg		77 (70–90)	83 (62.5–94.8)	0.52	77 (70–90)	80 (62.5–85)	0.93
Intravenous diuretics, n (%)		33 (30.3)	6 (75)	0.02	26 (28)	13 (54.2)	0.03
Killip class		1 (1–2)	2 (1–3)	0.01	1 (1–1)	2 (1–2)	<0.001
TIMI score		3 (2–5)	5 (3–7)	0.02	3 (2–4)	5 (3–7)	<0.001
GRACE score		110 (95–127)	135 (100.0–171)	0.17	109 (94–123)	132 (102–158)	0.002
Laboratory findings on admission							
Hemoglobin, g/dl		14.3 (13.5–15.6)	13.2 (12.2–13.8)	0.02	14.3 (13.6–15.7)	13.7 (12.6–14.3)	0.01
hs-CRP peak, mg/dl		3.2 (1.7–7.4) n = 104	91.6 (3.2–208)	0.01	3 (1.5–6.7) n = 88	7 (2.2–43.2)	0.03
Troponin I peak, ng/l		31.91 (3.73–82.31) n = 105	40.04 (16.92–102.07)	0.37	29.63 (3.58–82.31) n = 89	47.26 (16.92–95.67)	0.12
CK-MB peak, U/l		74.55 (12.68–178.68) n = 108	116 (48.25–428.20)	0.26	71.05 (7.13–173.20) n = 92	112.70 (55.95–241.18)	0.07
NT-proBNP peak, pg/ml		886 (329–1945) n = 75	7194 (2343.3–14701.5)	<0.001	884 (283.8–1926.5) n = 64	3520 (762–5986) n = 19	0.003
Serum creatinine, mg/dl		0.93 (0.86–1.06)	1.15 (0.87–1.31)	0.12	0.94 (0.86–1.06)	0.95 (0.81–1.22)	0.90
eGFR, ml/min/1.73 m^2		92.8 (64.2–117.9)	84.3 (58.1–107.9)	0.30	96.3 (68.8–117.9)	74.1 (58.4–102.2)	0.06
Serum sodium, mmol/l		140.0 (138.4–141.9)	138.5 (135.4–139.8)	0.03	140 (137.9–142)	139.5 (138.7–141.2)	0.34
Serum potassium, mmol/l		3.9 (3.6–4.2)	4 (3.7–4.3)	0.53	3.97 (3.62–4.18)	3.94 (3.55–4.38)	0.76
Total cholesterol, mg/dl		187 (162–223) n = 105	145.5 (121.3–162.8)	0.002	188 (163.8–226.5) n = 90	153 (140–188) n = 23	0.004
LDL, mg/dl		113 (84–145) n = 95	77 (61.8–95.3)	0.01	115.5 (85–148) n = 80	84 (75–121) n = 23	0.03
HDL, mg/dl		44.5 (34.3–52) n = 104	43.5 (15.5–58.8)	0.78	45 (35–53.5) n = 89	40 (33–50) n = 23	0.34
Triglycerides, mg/dl		136 (93–177) n = 103	103 (85.5–227.3)	0.67	135.5 (91.3–181.3) n = 88	134 (91–157) n = 23	0.63
Angiographic characteristics							
Infarct-related artery, n (%)	RCA	46 (42.2)	5 (62.5)	0.29	39 (41.9)	12 (50.0)	0.50
	LAD	48 (44.0)	3 (37.5)	1.00	42 (45.2)	9 (37.5)	0.65
	Cx	15 (13.8)	0	0.59	12 (12.9)	3 (12.5)	1.00
Extent of CAD, n (%)	1-vessel	64 (58.7)	3 (37.5)	0.28	55 (59.1)	12 (50.0)	0.49
	2-vessel	28 (25.7)	5 (62.5)	0.04	24 (25.8)	9 (37.5)	0.31
	3-vessel	17 (15.6)	0	0.60	14 (15.1)	3 (12.5)	1.00

TABLE 2 Baseline characteristics and clinical course of index hospitalization of patients (n = 117) with ST-segment elevation myocardial infarction treated with primary coronary intervention with reference to baseline Gal-3 and sST2 cutoffs (continued from the previous page)

Variable		sST2 <45.99 ng/ml (n = 109)	sST2 ≥45.99 ng/ml (n = 8)	*P* value	Gal-3 <9.57 ng/ml (n = 93)	Gal-3 ≥9.57 ng/ml (n = 24)	*P* value
Angiographic characteristics							
TIMI grade flow	Baseline	0 (0–1)	0 (0–0)	0.12	0 (0–1)	0 (0–1)	0.35
	Final	3 (3–3)	3 (2–3)	0.13	3 (3–3)	3 (3–3)	0.52
Stent implantation, n (%)	1 stent	72 (66.1)	6 (75.0)	1.00	61 (65.6)	17 (70.8)	0.81
	≥2 stents	31 (28.4)	2 (25.0)	1.00	27 (29.0)	6 (25.0)	0.80
	Complete revascularization	63 (57.8)	3 (37.5)	0.29	55 (59.1)	11 (45.8)	0.26
Echocardiography							
Ejection fraction, %		48 (42–53)	38 (29–49)	0.03	48 (41–54)	46 (35–51)	0.15
LVEDD, mm		4.8 (4.5–5.2) n = 108	5.3 (4.5–5.4)	0.19	4.8 (4.5–5.2) n = 92	5.0 (4.3–5.4)	0.62
LVEDV, ml		104 (80–127)	130 (65–131)	0.99	105 (79–124)	112 (74–131)	0.86
LVESV, ml		53 (40–70)	86 (32–95)	0.46	53 (41–70)	59 (34–92)	0.77
LVH[a], n (%)		31 (32.6)	3 (50.0)	0.40	24 (28.6)	10 (58.8)	0.02
LA dimension, mm		3.8 (3.5–4.2) n = 108	4.1 (3.6–5.2)	0.18	3.8 (3.5–4.2) n = 92	4.1 (3.6–4.2)	0.08
Clinical status and laboratory findings at discharge							
Heart rate, bpm		70.0 (64.0–76.0) n = 108	80.0 (72.8–84.5)	0.01	70.0 (64.0–80.0)	71.0 (67.0–80.0) n=23	0.43
SBP, mm Hg		120.0 (110.0–130.8) n = 108	132.0 (103.8–138.8)	0.55	120.0 (110.0–130.0)	130.0 (105.0–141.0) n = 23	0.41
DBP, mm Hg		73.5 (60.0–80.00) n = 108	80.0 (65.5–80.00)	0.64	75.0 (62.5–80.0)	70.0 (60.0–80.00) n = 23	0.49
Hemoglobin, g/dl		13.7 (12.6–14.7) n = 99	12.9 (11.0–14.5)	0.17	14.0 (12.7–14.8) n = 86	12.9 (11.5–14.2) n = 21	0.01
Serum creatinine, mg/dl		0.93 (0.81–1.10) n = 97	1.24 (0.83–1.45)	0.054	0.95 (0.81–1.05) n = 84	0.93 (0.81–1.25) n = 21	0.42
eGFR, ml/min/1.73 m^2		91.36 (74.75–120.25) n = 97	57.14 (37.94–121.55)	0.10	92.59 (78.17–112.06) n = 84	65.07 (54.60–106.38) n = 21	0.01
Serum sodium, mmol/l		141.3 (139.5–143.3) n = 97	140.8 (137.3–142.9)	0.47	141.0 (139.5–143.3) n = 84	141.6 (139.4–143.0) n = 21	0.64
Serum potassium, mmol/l		4.4 (4.1–4.6) n = 97	4.6 (4.1–5.0)	0.34	4.45 (4.19–4.69) n = 84	4.3 (4.1–4.7) n = 21	0.34
Pharmacotherapy at hospital discharge[b]							
ASA, n (%)		108 (100)	8 (100)	1.00	93 (100)	23 (100)	1.00
Clopidogrel, n (%)		95 (88.0)	7 (87.5)	1.00	83 (89.2)	19 (82.6)	0.47
Ticagrelor, n (%)		13 (12.0)	1 (12.5)	1.00	10 (10.8)	4 (17.4)	0.47
Anticoagulants, n (%)		7 (6.5)	2 (25.0)	0.12	6 (6.5)	3 (13.0)	0.38
Loop diuretics, n (%)		24 (22.2)	5 (62.5)	0.02	18 (19.4)	11 (47.8)	0.01
ACEI, n (%)		104 (96.3)	8 (100)	1.00	89 (95.7)	23 (100)	0.58
ARB, n (%)		6 (5.6)	1 (12.5)	0.40	6 (6.5)	1 (4.3)	1.00
β-Blocker, n (%)		101 (93.5)	8 (100)	1.00	87 (93.5)	22 (95.7)	1.00
Aldosterone antagonist, n (%)		37 (34.3)	1 (12.5)	0.27	32 (34.4)	6 (26.1)	0.62
Ivabradine, n (%)		2 (1.9)	0	1.00	2 (2.2)	0	1.00
Statin, n (%)		104 (96.3)	7 (87.5)	0.31	89 (95.7)	22 (95.7)	1.00

Data presented as median (IQR) unless otherwise indicated.

a LVH was based on LVMI: LVMI >95 g/m^2 for women, LVMI >115 g/m^2 for men; **b** In patients who survived to hospital discharge (n = 108)

SI conversion factors: to convert hemoglobin to g/l, multiply by 100; hs-CRP to nmol/l, by 95.24; troponin to µg/l, by 1; CK-MB to µ/l, by 0.0167; serum creatinine to µmol/l, by 76.25; total cholesterol and LDL and HDL cholesterol to mmol/l, by 0.0259; triglycerides to mmol/l, by 0.0113.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid; CAD, coronary artery disease; CK-MB, creatine kinase-muscle/brain; COPD, chronic obstructive pulmonary disease; Cx, circumflex artery; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LA, left atrium; LAD, left anterior descending artery; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; RCA, right coronary artery; SBP, systolic blood pressure; TIA, transient ischemic attack; others, see **TABLE 1**

TABLE 3 In-hospital and 1-year outcomes of patients with ST-segment elevation myocardial infarction treated with primary coronary intervention with reference to baseline Gal-3 and sST2 cutoffs

Variable	sST2 <45.99 ng/ml (n = 109)	sST2 ≥45.99 ng/ml (n = 8)	*P* value	Gal-3 <9.57 ng/ml (n = 93)	Gal-3 ≥9.57 ng/ml (n = 24)	*P* value
In-hospital outcomes						
Hospitalization length, median (IQR), d	8.0 (7.0–10.0)	15.5 (12.3–24.8)	<0.001	8.0 (6.5–10.0)	9.5 (7.3–13.8)	0.03
Time in ICCU, median (IQR), d	4.0 (3.0–5.0)	11.0 (7.5–17.0)	<0.001	3.0 (3.0–5.0)	5.5 (4.3–10.8)	<0.001
In-hospital death, n (%)	1 (0.9)	0	1.00	0	1 (4.2)	0.21
1-year outcomes						
CV death or HF hospitalization, n (%)	5 (5.2) n = 97	4 (57.1) n = 7	0.001	2 (2.4) n = 83	7 (33.3) n = 21	<0.001
CV death, n (%)	2 (1.8)	1 (12.5)	0.19	0	3 (12.5)	0.01
HF hospitalization, n (%)	3 (3.1) n = 97	4 (57.1) n = 7	<0.001	2 (2.4) n = 83	5 (23.8) n = 21	0.003
MI, n (%)	4 (4.1) n = 97	0 n = 7	1.00	2 (2.4) n = 83	2 (9.5) n = 21	0.18

Abbreviations: CV, cardiovascular; HF, heart failure; MI, myocardial infarction; others, see TABLE 2

TABLE 4 Association of Gal-3, sST2, NT-proBNP and age with the primary endpoint in univariate analysis

Variable	HR (95% CI)	*P* value
Age, per 10 years	1.97 (1.02–3.71)	0.04
NT-proBNP, per 1000 pg/ml	1.14 (1.04–1.25)	0.01
Gal-3, per 1 ng/ml	1.34 (1.17–1.54)	<0.001
Gal-3 ≥9.57 ng/ml	15.94 (3.31–76.82)	0.001
sST2, per 10 ng/ml	1.63 (1.22–2.16)	0.001
sST2 ≥45.99 ng/ml	12.62 (3.37–47.20)	<0.001

Abbreviations: HR, hazard ratio; others, see TABLE 1

utility and specific cutoffs of both biomarkers to help clinicians conduct better risk stratification in patients with AMI but without previous HF. Only few studies have described the impact of Gal-3 and sST2 on outcomes after AMI.

Subanalysis of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial showed that Gal-3 concentrations above median value of 16.7 µg/l, measured within 7 days after acute coronary syndrome (100 patients after AMI or unstable angina), were associated with a higher risk of HF development in a 2-year follow-up.[19] In our study, the cutoff Gal-3 level for the primary endpoint occurrence was equal to or above 9.57 ng/ml. This Gal-3 threshold was associated with a worse clinical condition during index hospitalization, as well as a higher rate of unfavorable outcomes during index hospitalization and follow-up. Similarly, the study performed by Tsai et al[26] (196 patients with first-time STEMI) revealed that a Gal-3 level equal to or above 7.67 ng/ml was the most powerful predictor of death and development of HF in a 30-day postinfarction period. Moreover, this association was observed regardless of the severity of coronary artery lesions, LVEF, and serum creatinine.[26] Of note, in our study patients with higher Gal-3 concentrations had higher risk in GRACE and TIMI scores, which identify high-risk patients after MI.

In our study, median sST2 concentration in the study group was 23.4 ng/ml, while in a study by Jenkins et al[29] (1401 patients after AMI) the median sST2 value was 48.7 ng/ml. However, their study relied on heterogeneous diagnoses—79% of patients had non–ST-segment elevation myocardial infarction. Increased concentrations of sST2 were associated with an increased risk of death and HF development during 5 years of follow-up, independently of other prognostic factors.[29] Liu et al[31] showed that sST2 concentrations above 58.7 ng/ml have highest specificity in predicting either MACEs (defined as the composite of all-cause death, HF, and nonfatal AMI) or mortality at 1-year after STEMI. In our study, the cutoff sST2 value of 45.99 ng/ml identified patients at high risk of the primary endpoint.

Another analysis based on the BIOSTRAT study assessed the association of Gal-3 and sST2 and changes in their concentrations after 1 year with the development of HF which showed that baseline Gal-3 and sST2 concentrations have higher clinical value than measurements obtained after 1 year.[32]

In the CORONA study, Gal-3 was not correlated with worse prognosis after adjusting for NT-proBNP in older patients with ischemic chronic HF, hence Gal-3 may have limited the application of risk stratification in older patients.[33] However, our study showed that this does not apply to patients after STEMI. Gal-3 (but not sST2) correlated with age but both Gal-3 and sST2 were independent predictors of the primary endpoint even after adjusting for age.

In our study, there was no association between sST2 and Gal-3 concentrations and maximum troponin I. An explanation for this is that these biomarkers are involved in distinct

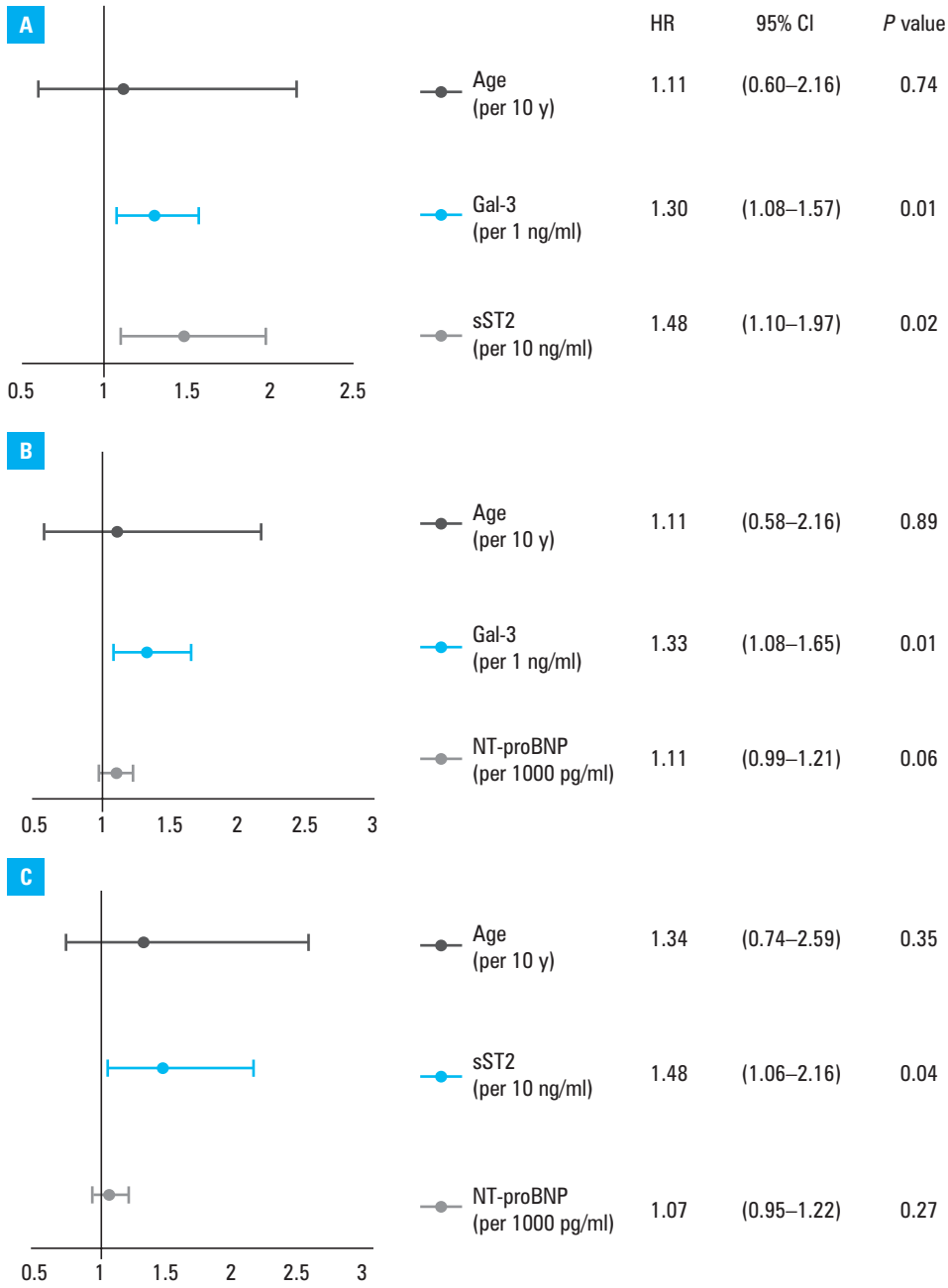

FIGURE 2 Forest plots of multivariate analyses of predictors of the primary endpoint
Abbreviations: see **TABLES 1** and **4**

pathophysiological pathways than that which are already known. AMI provokes an inflammatory response with the migration of a multitude of cells and regulators into the infarcted and non-infarcted areas. This process initiates reparative changes in the early phase after AMI.[2] This could be the reason for higher values of hs-CRP in both groups of sST2 and Gal-3 upper cutoffs values. However, chronic activation of these processes leads to tissue fibrosis, adverse LVR, and development of HF. Szadkowska et al[27] found that elevated Gal-3 (>16 ng/ml) concentrations during hospitalization in patients after AMI were associated with a higher risk of HF and atrial fibrillation. In our study, patients with higher levels of Gal-3 and sST2 were more likely to have a higher Killip class on admission, and more frequently required diuretics intravenously during hospitalization and orally at discharge. Consequently, elevated Gal-3 and sST2 concentrations were associated with increased risk of combined endpoint—CV death and HF hospitalization—as well as the risk of HF hospitalization itself.

Therefore, it may be concluded that increased levels of Gal-3 and sST2 after AMI reflect myocardial damage and may help in the early identification of patients at higher risk of HF development. It may have important implications for postdischarge follow-up and highlights the need for therapies which impact adverse cardiac remodeling, such as angiotensin-converting enzyme inhibitors, aldosterone receptor blockers or mineralocorticoid receptor antagonists. There are several studies showing the potential advantageous influence of renin-angiotensin-aldosterone antagonists, as well as genetic therapies on the reduction of biomarker levels.[34-38] Other mediators of inflammatory processes (ie, leukotrienes) have recently been

TABLE 5 Predictors of the primary endpoint in multivariate analyses

Variable	Multivariate analyses		
	HR	95% CI	*P* value
Age, per 10 years	1.22	0.74–2.16	0.44
Gal-3 ≥9.57 ng/ml	8.65	1.45–51.70	0.02
sST2 ≥45.99 ng/ml	3.15	0.72–13.81	0.13
Age, per 10 years	1.22	0.66–2.16	0.62
Gal-3 ≥9.57 ng/ml	14.51	1.46–143.95	0.02
NT-proBNP, per 1000 pg/ml	1.05	0.94–1.25	0.36
Age, per 10 years	1.34	0.74–2.59	0.36
sST2 ≥45.99 ng/ml	11.79	1.52–91.26	0.02
NT-proBNP, per 1000 pg/ml	0.99	0.85–1.16	0.95

Abbreviations: see TABLES 1 and 4

intensively studied for their role in coronary artery disease. Further studies will show if novel anti-inflammatory strategies added to conventional therapy will reduce cardiovascular risk.[39]

Limitations The main limitations of our study relate to the small sample size and relatively short follow-up which translated into a small number of events. Additionally, 13 patients (11.1% of the 117 patients) were lost to follow-up in terms of hospitalization for HF. Therefore, in order to maintain an adequate events per predictor variable value, we were not able to include more potentially significant variables in the Cox proportional hazards regression model.[28] Moreover, a certain proportion of data (including NT-proBNP concentrations) for some of the patients was missing (as indicated in tables). Still, given the correlation of both Gal-3 and sST2 with NT-proBNP, as well as the fact that NT-proBNP concentration predicted the primary endpoint, we decided it was important to include NT-proBNP in our multivariate models. However, we also performed a separate multivariate analysis including age and both of the studied biomarkers (Gal-3 and sST2), but not NT-proBNP. Gal-3 and sST2 remained significant predictors of the primary endpoint in all those models.

Further studies with longer follow-up are still needed to determine the predictive value and clinical utility of serum levels of sST2 and Gal-3 in patients with AMI.

Conclusion In patients with first-time STEMI treated with primary PCI, Gal-3 and sST2 predicted CV death or hospitalization for HF at 1 year. Concentrations of both biomarkers above the established cutoffs (≥9.57 ng/ml for Gal-3 and ≥45.99 ng/ml for ST2) were associated with worse clinical presentation at baseline, as well as adverse in-hospital and 1-year outcomes. Assessment of these 2 biomarkers of inflammation and fibrosis may play an important role in CV risk stratification after AMI; however, Gal-3 may be considered a more preferable option.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS The BIOSTRAT study is supported by 2 grants from Medical University of Warsaw (1WR/NM2/14, to AT; 1WR/NM4/16, to AW).

CONTRIBUTION STATEMENT All authors made substantial contributions to the concept and design of the study. AT, AKC, KO, MB, AW, PS, and JM researched data, conducted data interpretation. AT, KO, and MP performed statistical analysis. AT, KO, and AKC wrote manuscript. All authors reviewed the manuscript and approved its final version.

CONFLICT OF INTEREST None declared.

HOW TO CITE Tymińska A, Kapłon-Cieślicka A, Ozierański K, et al. Association of galectin-3 and soluble ST2 with in-hospital and 1-year outcomes in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. Pol Arch Intern Med. 2019; 129: 770-780. doi:10.20452/pamw.15030

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