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Effect of β-blocker therapy on the level of soluble ST2 protein in the blood serum in patients with heart failure with preserved and mildly reduced ejection fraction

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ABSTRACT

Aim. To study the prognostic value of high serum concentration of soluble ST2 protein (sST2) in the development of cardiovascular events after endovascular myocardial revascularization and the possibility of using this biomarker as a target for β-blocker therapy in patients with chronic heart failure (CHF) with preserved (HFpEF) and mildly reduced (HFmrEF) left ventricular ejection fraction.

Materials and methods. The study included 72 patients (aged 57–69 years, 81.94% were men) with class I–III CHF of ischemic etiology with HFpEF and HFmrEF. The patients were admitted to the cardiology department for endovascular myocardial revascularization. Before myocardial revascularization, serum concentrations of sST2 and N-terminal pro-brain natriuretic peptide (NT-proBNP) in all patients were analyzed by enzyme-linked immunosorbent assay (ELISA). Doses of β-blockers used in all patients were recalculated into a total daily dose equivalent to metoprolol succinate. Patients were divided into 2 groups depending on the median equivalent dose of metoprolol succinate ("high" ≥ 100 mg / day and "low" < 100 mg / day).

Results. In patients of group 1, the serum concentration of sST2 was 30.7% higher ($p < 0.001$) than in patients of group 2 (40.26 [34.39; 48.92] ng /ml and 27.9 [23.05; 35.27] ng / ml, respectively), the serum NT-proBNP level in group 1 was 22.8% higher ($p = 0.049$) than in group 2 (167 [129; 330] ng / ml vs. 129 [125; 147] ng / ml, respectively). In patients receiving an equivalent dose of metoprolol succinate < 100 mg / day, the incidence of cardiovascular events was 34% higher ($p = 0.002$) than in patients receiving an equivalent dose of metoprolol succinate ≥ 100 mg/day. The ROC analysis showed that serum sST2 level ≥ 34.18 ng / ml (sensitivity 78.0%, specificity 90.0%, area under the curve (AUC) 0.906; $p < 0.0001$) predicts a high risk of cardiovascular events within one year. However, the serum NT-proBNP level was not an informative predictor of cardiovascular events.

Conclusion. It was confirmed that increased sST2 serum concentration has high prognostic value in the development of cardiovascular events within a year after endovascular myocardial revascularization. The possibility of using this biomarker as a target for β-blocker therapy in patients with HFpHF and HFmrEF was substantiated. Aggressive use of β-blockers in the group of patients with HFpEF and HFmrEF and sST2 overexpression is preferable in order to reduce the incidence of cardiovascular events.

Keywords: chronic heart failure, left ventricle, preserved and mildly reduced ejection fraction, β-blockers, biomarkers, soluble ST2, N-terminal pro-brain natriuretic peptide, prognosis, endovascular revascularization

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Влияние терапии β-адреноблокаторами на уровень растворимой формы белка st2 в сыворотке крови пациентов с сердечной недостаточностью с сохраненной и умеренно сниженной фракцией выброса

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РЕЗЮМЕ

Цель – изучение прогностического значения высокой концентрации в сыворотке крови растворимой формы белка ST2 (sST2) в развитии сердечно-сосудистых событий после эндоваскулярной реваскуляризации миокарда и возможности использования этого биомаркера в качестве мишени для терапии β-блокаторами у пациентов с хронической сердечной недостаточностью (ХСН) с сохраненной (СНсФВ) и умеренно сниженной (СНусФВ) фракцией выброса левого желудочка.

Материалы и методы. В исследование включены 72 пациента (в возрасте 57–69 лет, 81,94% мужчин) с ХСН I–III функционального класса ишемической этиологии с СНсФВ и СНусФВ, госпитализированных в кардиологическую клинику для выполнения эндоваскулярной реваскуляризации ишемизированного миокарда. У всех пациентов перед реваскуляризацией миокарда анализировали концентрацию в сыворотке крови sST2 и N-терминального промозгового натрийуретического пептида (NT-proBNP) с помощью иммуноферментного анализа (ELISA). Дозы применяемых у всех пациентов β-блокаторов были пересчитаны в общую суточную дозу, эквивалентную метопрололу сукцинату. Больные были разделены на две группы в зависимости от медианы эквивалентной дозы β-блокатора метопролола сукцината («высокая» ≥100 мг/сут и «низкая» <100 мг/сут).

Результаты. У пациентов первой группы сывороточная концентрация sST2 была на 30,7% ($p < 0,001$) больше, чем у больных, вошедших во вторую группу (40,26 [34,39; 48,92] нг/мл и 27,9 [23,05; 35,27] нг/мл соответственно), уровень NT-proBNP в сыворотке крови больных первой группы также был выше (на 22,8%; $p = 0,049$), чем у пациентов второй группы (167 [129; 330] нг/мл против 129 [125; 147] нг/мл соответственно). У пациентов, получавших эквивалентную дозу метопролола сукцината <100 мг/сут, частота сердечно-сосудистых событий была выше на 34% ($p = 0,002$), чем у пациентов, получавших эквивалентную дозу метопролола сукцината ≥ 100 мг/сут. По данным ROC-анализа установлено, что сывороточный уровень sST2 ≥ 34,18 нг/мл (чувствительность 78,0%, специфичность 90,0%, AUC 0,906; $p < 0,0001$) позволяет прогнозировать высокий риск развития сердечно-сосудистых событий в течение ближайшего года. Уровень NT-proBNP в сыворотке крови при этом не являлся информативным предиктором сердечно-сосудистых событий.

Заключение. Подтверждено высокое прогностическое значение повышения концентрации в сыворотке крови sST2 в развитии сердечно-сосудистых событий в течение года после эндоваскулярной

реваскуляризации миокарда и обоснована возможность использования этого биомаркера в качестве мишени для терапии β-блокаторами у пациентов с СНсФВ и СНусФВ. Агрессивное применение β-блокаторов в группе пациентов с СНсФВ и СНусФВ и гиперэкспрессий sST2 предпочтительнее с целью снижения частоты сердечно-сосудистых событий.

Ключевые слова: хроническая сердечная недостаточность, левый желудочек, сохраненная и умеренно сниженная фракция выброса, β-блокаторы, биомаркеры, растворимый ST2, N-терминальный промозговой натрийуретический пептид, прогноз, эндоваскулярная реваскуляризация

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Chronic heart failure (CHF) is a serious public health problem with the prevalence of 5.8 to 6.5 mln individuals in the United States, about 8.1 mln individuals in the Russian Federation, and 26 mln people worldwide [1–3]. Despite the advances made in the study of the pathogenesis, course features, clinical manifestations, and treatment methods, the prognosis in CHF patients remains unfavorable [4, 5]. One of the key indicators of the myocardial dysfunction severity in CHF patients is the value of the left ventricular ejection fraction (LVEF), which characterizes its contractility [6].

Based on the data of large epidemiological studies of the last few decades, scientists have come to the conclusion that CHF can also develop in preserved LVEF. CHF with preserved ejection fraction (HFpEF) is detected in about half of all patients with heart failure – they account for 51–63% of the general population [7, 8]. Since life expectancy in economically developed countries tends to increase, the prevalence of HFpEF will continue to grow. Epidemiological data from population-based studies in the United States show that if current trends continue, 8.5 mln Americans will be diagnosed with HFpEF by 2030, with about 70% of them being over 65 years old (6 mln) [9]. Over the past decade, the rate of increase in HFpEF incidence has grown on average by 10–20% relative to the same indicator for heart failure with reduced ejection fraction (HFrEF) [10–14].

Beta-blockers (β-blockers) are a class of drugs used to control CHF symptoms and improve survival, especially in patients with left ventricular (LV) systolic dysfunction [15]. Co-administration of this group of drugs with other drugs that are commonly used to treat CHF, such as angiotensin-converting enzyme (ACE) inhibitors, diuretics, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists, regresses LV remodeling and decelerates the progression of systolic CHF [15, 16]. In theory, β-blockers can also be used to treat patients with diastolic CHF, which is characterized by an increase in LV myocardial stiffness. In this case delayed or incomplete ventricular relaxation leads to slowdown in diastolic filling and an increase in ventricular filling pressure. The LV filling is never complete during diastole, although the pumping function remains preserved [17]. Considering the fact that diastolic dysfunction and LV remodeling also play a key role in the mechanisms of CHF progression up to the terminal stage of heart disease and death [18, 19], there is every reason to expect that the use of β-blockers in patients with preserved LVEF will lead to a decrease in CHF manifestations and symptoms and better survival. It is possible due to a decrease in heart rate and an increase in the time for a more complete LV filling and, as a consequence, an increase in blood volume during diastole [20]. However, now there is no con-

vincing evidence that the use of β-blockers in CHF patients with HFpEF and HFmrEF is effective.

Currently, soluble ST2 protein (sST2) is a new biomarker. Along with natriuretic peptides, it plays an important role in the mechanisms (cardiomyocyte and interstitial remodeling of the heart, myocardial dysfunction, and cardiomyocyte apoptosis, etc.) of cardiovascular diseases [21–23]. In contrast to N-terminal pro-brain natriuretic peptide (NT-proBNP), synthesis and secretion of which is determined by increased stretching of cardiomyocytes, the sST2 level also reflects the activity of inflammatory and fibrotic processes in the cardiac muscle tissue [23, 24], which may be more useful for risk stratification and monitoring of treatment efficacy in patients with HFpEF. There is evidence that the dynamic changes in ST2 concentrations during CHF treatment correlate with the frequency of long-term outcomes [25]. Therefore, it can be assumed that comprehensive treatment that slows down LV remodeling or provides its "reverse" remodeling, which ultimately leads to a decrease in the incidence of cardiovascular complications, will significantly improve the prognosis for HFpEF patients with an initially elevated sST2 level [18].

The aim of the study was to evaluate the prognostic value of high serum concentration of sST2 in the development of cardiovascular events after myocardial revascularization and the possibility of using this biomarker as a target for β-blocker therapy in patients with HFpEF and HFmrEF.

MATERIALS AND METHODS

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee at Cardiology Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences. All patients signed an informed consent to participate in the study.

This study was a prospective, observational, single-center study. The study included 72 patients (aged 57–69 years, 81.9% were men) with CHF of ischemic etiology corresponding to functional class (FC) I–III according to the classification of the New York Heart Association (NYHA), with preserved and mildly reduced LVEF. Patients were admitted to hospital for endovascular revascularization (Table 1).

Table 1

Clinical and demographic characteristics of patients at the time of inclusion in the study

Parameter	Group 1, $n = 40$ BB ≥100 mg / day	Group 2, $n = 32$ BB <100 mg / day	p
Age, years, *Me* (Q_{25}; Q_{75}) Men, *n* (%)	62 (57; 69) 32 (80.0)	61.5 (53.5; 68.5) 27 (84.4)	0.426 0.631
CHF duration, months, *Me* (Q_{25}; Q_{75})	12 (6; 17)	11 (7; 18)	0.374
IHD duration, years, *Me* (Q_{25}; Q_{75})	5 (2; 11)	5 (2; 10)	0.861
6-minute walk test, m, *Me* (Q_{25}; Q_{75})	335 (275; 385)	300 (225; 385)	0.439
FC of CHF by NYHA, *n* (%) I II III	 2 (5.0) 29 (72.5) 9 (22.5)	 3 (9.4) 17 (53.1) 12 (37.5)	 0.835 0.089 0.056
GFR, ml / min/1.73 m^2, *Me* (Q_{25}; Q_{75})	42.4 (29.3; 59)	77 (72; 87)	0.492
Body mass index, *Me* (Q_{25}; Q_{75})	27.1 (24.9; 31.0)	28.8 (25.9; 30.9)	0.439
Hypertension, *n* (%)	34 (85.0)	26 (81.2)	0.778
Type 2 diabetes mellitus, *n* (%)	8 (20.0)	5 (15.6)	0.631
COPD, *n* (%)	3 (7.5)	2 (6.2)	0.872
Atrial fibrillation, *n* (%)	6 (15.0)	2 (6.2)	0.665
History of myocardial revascularization, *n* (%)	23 (57.5)	20 (62.5)	0.667
Systolic blood pressure, mm Hg, *Me* (Q_{25}; Q_{75}) Diastolic blood pressure, mm Hg, *Me* (Q_{25}; Q_{75}) Heart rate, bpm, *Me* (Q_{25}; Q_{75})	120 (120; 130) 80 (70; 80) 61 (55; 67)	120 (110; 130) 80 (80; 80) 66 (61; 82)	0.779 0.624 0.061
Smoking, *n* (%)	12 (30.0)	4 (12.5)	0.327
History of acute CVA, *n* (%)	6 (15.0)	3 (9.4)	0.331

Table 1 (continued)

Parameter	Group 1, n = 40 BB ≥100 mg / day	Group 2, n = 32 BB <100 mg / day	p
Family history of CVD, n (%)	7 (17.5)	5 (15.6)	0.823
Therapy, n (%)			
ACE inhibitors or ARBs	36 (90.0)	27 (84.4)	0.435
Spironolactone / eplerenone	11 (27.5)	9 (28.1)	0.471
Loop diuretics	13 (32.5)	8 (25.0)	0.660
Amiodarone	4 (10.0)	2 (6.2)	0.675
Statins	38 (95.0)	29 (90.6)	0.912
Total cholesterol, mmol / l	4.65 (3.67; 5.25)	4.65 (3.67; 5.11)	0.932
LDL, mmol / l	3.03 (1.95; 3.41)	2.49 (2.25; 3.43)	0.856
HDL, mmol / l	1.07 (0.85; 1.31)	1.06 (0.96; 1.26)	0.889
Triacylglycerols, mmol / l	1.44 (1.13; 1.93)	1.67 (1.22; 1.92)	0.870
Hemoglobin, g / l	142 (131; 153)	147 (138; 152)	0.464
hsCRP, mg / l	6 (5; 7)	6 (4; 7)	0.596
HbA1c, %	4.8 (4.5; 6.6)	5.1 (4.7; 6.7)	0.445
sST2, ng / ml	27.9 (23.05; 35.27)	40.26 (34.39; 48.92)	<0.001
NT-proBNP, pg /l	129 (125; 147)	167 (129; 330)	0.049

Note: HbA1c – glycated hemoglobin; NT-proBNP – N-terminal pro-brain natriuretic peptide; NYHA – New York Heart Association; sST2 – soluble ST2; BP – blood pressure; BB – β-blockers, ARBs – angiotensin-II receptor blockers; hsCRP – highly sensitive C-reactive protein; CHF – chronic heart failure; ACE inhibitors – angiotensin-converting enzyme inhibitors; IHD – ischemic heart disease; HDL – high-density lipoproteins; LDL – low-density lipoproteins; GFR – glomerular filtration rate; HR – heart rate; COPD – chronic obstructive pulmonary disease; FC – functional class; CVD – cardiovascular disease.

According to modern criteria, CHF with preserved and mildly reduced LVEF was diagnosed in the presence of signs and / or symptoms of heart failure, preserved LV systolic function (LVEF ≥ 40%), NT-proBNP level ≥125 pg / ml, as well as signs of LV diastolic dysfunction [26].

Exclusion criteria were age older than 75 years, GFR lower than 50 ml / min / 1.73 m^2 (CKD-EPI equation), bronchial asthma and severe chronic obstructive pulmonary disease, autoimmune diseases, pregnancy, malignant neoplasms, less than six months after acute coronary or cerebrovascular events or failure to sign an informed consent form.

All patients received standard treatment and were followed up for 12 months after myocardial revascularization. Patients were divided into 2 groups depending on the median equivalent dose of the β-blocker metoprolol succinate ("high" ≥ 100 mg / day and "low" < 100 mg / day). Doses of β-blockers used in all patients were converted into a total daily dose equivalent to controlled-release metoprolol succinate (in accordance with the data of the PROTECT study) in the following ratios: immediate-release metoprolol tartrate, carvedilol × 4, bisoprolol × 20, propranolol × 0.833, and sotalol × 1.2. Group 1 included 40 patients who received an equivalent dose of metoprolol succinate ≥ 100 mg / day, group 2 included 32 patients who received < 100 mg / day (Table 1).

The primary composite endpoint was considered a set of events: cardiovascular death, fatal or non-fatal stroke, any coronary event (sudden cardiac death, fatal or non-fatal myocardial infarction, myocardial revascularization or hospitalization for unstable angina), aggravation of CHF (appearance of new symptoms / signs or progression of symptoms / signs requiring unplanned intensification of diuretic therapy or hospitalization). In total, two deaths were recorded: in the first case – due to acute myocardial infarction 11 months after revascularization, in the second case – in the postoperative period, one month after coronary artery bypass grafting performed due to the CHF progression.

Blood samples were obtained by venipuncture from 8 AM to 9 AM and the corresponding blood serum samples after centrifugation were stored at –24 ° C with one freeze – thaw cycle. Serum sST2 and NT-proBNP levels were analyzed from the same blood sample by enzyme-linked immunosorbent assay (ELISA) prior to myocardial revascularization. Soluble ST2 was measured using a high-

ly sensitive monoclonal sandwich immunoassay (Presage® ST2 assay, Critical Diagnostics, USA). NT-proBNP levels were determined using a sandwich immunoassay (Biomedica, Austria).

Statistical processing of the study results was carried out using the STATISTICA 10.0 (StatSoft, Inc., USA) and MedCalc 11.5.0.0 (MedCalc Software Ltd, USA) programs. To test statistical hypotheses when comparing two independent groups, the Mann – Whitney U test was used. The Wilcoxon W test and the sign test were used to compare two dependent variables. When analyzing qualitative features, contingency tables were analyzed using the Pearson's χ^2 test or the Fisher's exact test, when the expected value in any of the table cells with specified boundaries was below 10. A ROC analysis was performed to identify predictors of unfavorable cardiovascular events. The characteristic curves were constructed and the area under the curve (AUC) was calculated. An AUC value exceeding 0.70 was considered significant. To identify factors that have a significant impact on the disease course and prognosis, the odds ratio (OR) and a 95% confidence interval (CI) were calculated. The data were presented as the median and interquartile range *Me* (Q_{25}; Q_{75}). The critical level of statistical significance (p) in all analyses was equal to 0.05.

RESULTS

Therapy with low doses of β-blockers was associated with high serum levels of sST2 and NT-proBNP (Table 1). In group 1, sST2 serum concentration was 30.7% higher ($p < 0.001$) than in group 2 (40.26 (34.39; 48.92) and 27.9 (23.05; 35.27) ng / ml, respectively). The NT-proBNP level in group 1 was also 22.8% higher ($p = 0.049$) than in group 2 (167 (129; 330) ng / ml vs. 129 (125; 147) ng / ml, respectively). Echocardiographic parameters in the groups did not differ significantly at the time of inclusion in the study (Table 2).

Table 2

Echocardiographic characteristics of patients at the time of inclusion in the study, *Me* (Q_{25}; Q_{75})

Parameter	Group 1, $n = 40$ beta-blocker ≥ 100 mg / day	Group 2, $n = 32$ beta-blocker < 100 mg / day	p
Left ventricular ejection fraction, %	64 (50.5; 65.0)	61 (48.5; 65.0)	0.083
End-systolic dimension, mm	33.0 (31.5; 35.0)	33.0 (32.5; 40.5)	0.524
End-diastolic dimension, mm	50.25 (48.0; 52.5)	51.0 (48.7; 53.0)	0.307
End-systolic volume, ml	43.0 (36.5; 48.0)	44.5 (39.5; 64.0)	0.065
End-diastolic volume, mm	116 (100.5; 125.5)	116.5 (108.5; 129.0)	0.224
LVMI, g / m^2	94.5 (88.0; 105.0)	98.0 (88.5; 114.5)	0.276
EDVI, ml / m^2	57.3 (53.3; 64.45)	60.4 (56.5; 72.9)	0.056
ESVI, ml / m^2	20.9 (19.2; 24.1)	23.1 (20.4; 27.6)	0.276

Note. LVMI – left ventricular mass index; EDVI – end-diastolic volume index, ESVI – end-systolic volume index.

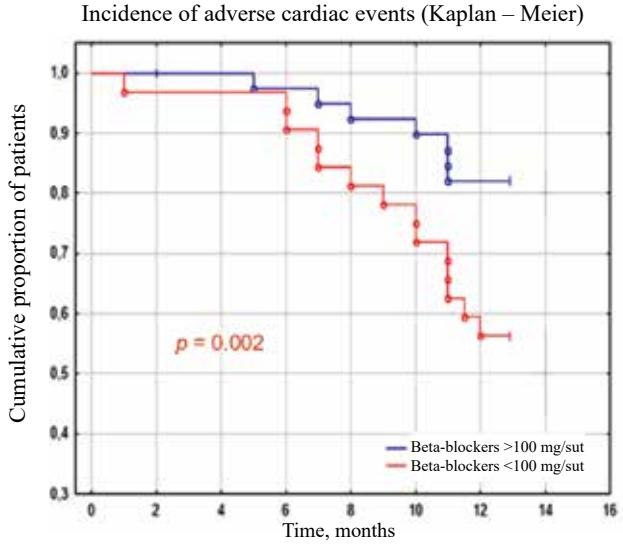

Fig. 1. Development of cardiovascular events within a year in groups of CHF patients with preserved and mildly reduced ejection fractions, formed depending on the β-blocker dosage (the Kaplan – Meier method)

Intergroup differences were found in the incidence of cardiovascular events within a year after endovascular revascularization (Fig. 1). Patients who received an equivalent dose of metoprolol succinate < 100 mg / day had a 34% higher rate of cardiac events ($p = 0.002$) than patients who received an equivalent dose of metoprolol succinate ≥ 100 mg / day.

According to the ROC analysis, it was found that an increase in the level of sST2 ≥ 34.18 ng / ml (sensitivity 78.0%, specificity 90.0%, AUC 0.906; $p < 0.0001$) predicted a high risk of cardiovascular events within the following 12 months. Serum NT-proBNP levels did not have any predictive value for risk stratification (Fig. 2).

Data analysis showed that in patients with sST2 overexpression ≥ 34.18 ng / ml who received a low dose of β-blockers, cardiovascular events developed more frequently (OR 4.18; $p < 0.0001$), while in patients with the level of the studied biomarker in the blood lower than 34.18 ng / ml and a high dose of β-blockers, no adverse events were recorded in any of the cases during the 12-month follow-up. Patients with sST2 < 34.18 ng / ml who received a low dose of β-blockers and patients with overexpression of sST2 ≥ 34.18 ng / ml who received β-blockers at a high dose had intermediate incidence of cardiovascular events (OR 1.79; $p = 0.003$ and 2.09; $p = 0.023$, respectively). The addition of NT-proBNP to sST2 analysis models did not increase the accuracy of risk stratification.

After 12 months, in patients receiving low doses of β-blockers, LVEF decreased by 6.3% ($p = 0.043$), and end-systolic dimension increased by 10.8% ($p = 0.049$) (Table 3), which indicated the progression of LV remodeling and, as a consequence, manifestations of heart failure.

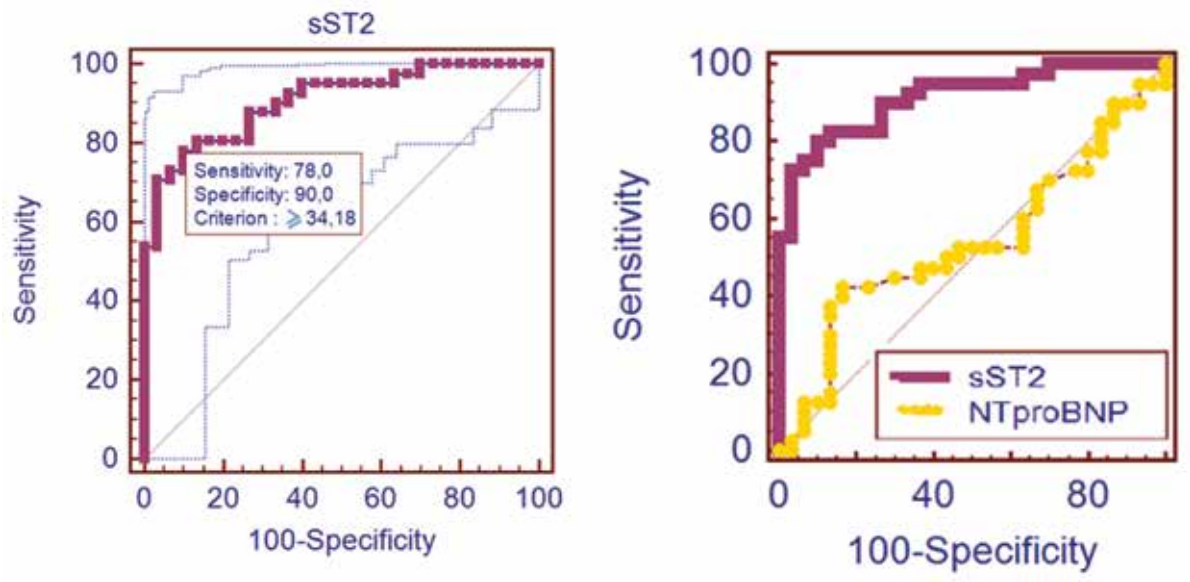

Fig. 2. Sensitivity and specificity of sST2 values in cardiovascular event risk stratification in CHF patients with preserved and mildly reduced ejection fraction (ROC analysis)

Table 3

Echocardiographic and laboratory data in groups of CHF patients during the 12-month follow-up depending on the dose of β-blockers, *Me* (Q_{25}; Q_{75})

Parameter	Baseline		After 12 months		
	Group 1 (BB ≥ 100 mg/day) $n = 40$	Group 2 (BB < 100 mg/day) $n = 32$	Group 1 (BB ≥ 100 mg/day) $n = 40$	Group 2 (BB < 100 mg/day) $n = 32$	p
LVEF, %	64 (60.5; 65.0)	63 (58.5; 65.0)	64 (61; 65)	59 (52.0; 62.0)#	0.043
ESD, mm	33.0 (31.5; 35.0)	33.0 (32.5; 40.5)	33.0 (32.0; 34.0)	37.0 (32.0; 40.0)#	0.052
EDD, mm	50.25 (48.0; 52.5)	51.0 (48.7; 53.0)	50.5 (49; 52)	53.0 (50.0; 54.0)	0.057

Table 3 (continued)

Parameter	Baseline		After 12 months		
	Group 1 (BB ≥ 100 mg/day) *n* = 40	Group 2 (BB < 100 mg/day) *n* = 32	Group 1 (BB ≥ 100 mg/day) *n* = 40	Group 2 (BB < 100 mg/day) *n* = 32	*p*
ESV, ml	43.0 (36.5; 48.0)	44.5 (39.5; 64.0)	41.5 (37.0; 44.5)	45.5 (40.0; 60.0)	0.085
EDV, ml	116 (100.5; 125.5)	116.5 (108.5; 129.0)	115.5 (102; 119.5)	118.0 (111.0; 126.0)	0.144
LVMI, g / m^2	94.5 (88.0; 105.0)	98.0 (88.5; 114.5)	93.5 (86.5; 102.0)	98.0 (89.0; 105.0)	0.237
EDVI, ml / m^2	57.3 (53.3; 64.45)	60.4 (56.5; 72.9)	58.4 (53.2; 64.15)	60.6 (57.1; 65.5)	0.066
ESVI, ml / m^2	20.9 (19.2; 24.1)	23.1 (20.4; 27.6)	21.35 (19.2; 23.85)	24.4 (21.4; 31.4)	0.076
sST2 (ng / ml)	27.9 (23.05; 35.27)	40.26 (34.39; 48.92)	27.98 (23.4; 30.17)	39.6 (32.61; 49.66)	0.001
NT-proBNP (ng / l)	129 (125; 147)	167 (129; 330)	–	–	–

Note. LVEF – left ventricular ejection fraction; EDD – end-diastolic dimension; ESD – end-systolic dimension; ESV – end-systolic volume; EDV – end-diastolic volume.

DISCUSSION

Currently, β-blockers are a class of drugs widely used for the treatment of heart failure which undoubtedly improve survival in patients with LV systolic dysfunction and reduce the incidence of adverse cardiovascular outcomes and hospitalizations for decompensated heart failure [15]. However, there are contradictory data on their effectiveness in CHF patients with preserved LVEF.

The OPTIMIZE-HF registry evaluated the endpoints of over 7,000 elderly patients hospitalized with heart failure. It was shown that β-blockers did not have a significant effect on mortality or the risk of rehospitalization for CHF decompensation in patients with preserved LV systolic function [21]. At the same time, it should be noted that the number of patients included in the registry was small in order to evaluate this fact properly. In 2015, S. Prijic et al. performed a systematic review and meta-analysis of 17 studies with 27,099 heart failure patients. Based on the data obtained, it was shown that the use of β-blockers reduced mortality from all causes by 19%, however, the analysis in the subgroups did not reveal this effect in elderly patients over 75 years of age [27].

Another study, which included 538 HFpEF patients, evaluated the effect of β-blocker therapy on the course of this pathology. At the same time, this group of drugs had no obvious positive effect on CHF severity in patients with preserved LVEF. The exception was patients with IHD and atrial fibrillation, where the use of β-blockers led to a decrease in the CHF FC (according to the NYHA) and the level of brain natriuretic peptide as well as an increase in exercise tolerance [28].

Maladaptive myocardial remodeling is a central feature of heart failure progression. This process can be modulated by various factors and includes hypertrophy and cardiomyocyte apoptosis, which leads to a significant change in the structure and function of the myocardium [29, 30]. One of the most important factors in myocardial remodeling is activation of the sympathetic nervous system. Increased concentrations of norepinephrine cause death of cardiac cardiomyocytes and stimulate gene expression and protein synthesis in fibroblasts, which contribute to CHF progression [15, 31, 32]. Acting directly through β-adrenergic receptors, β-blockers deactivate the sympathetic nervous system and prevent CHF progression, slowing down the processes of unfavorable remodeling. Over the past decade, several randomized clinical trials have shown that the use of β-blockers improves LV function and reduces morbidity and mortality in patients with both acute and chronic heart failure [29, 32, 33].

Soluble ST2 is currently considered a new biomarker involved in the pathophysiology of processes occurring in the myocardium, such as maladaptive cardiac remodeling, ischemic and non-ischemic dysfunction and myocardial apoptosis, and arrhythmogenesis, leading to the development of heart failure and sudden cardiac death [18, 27, 34–38]. Unlike the concentration of NT-proBNP and brain natriuretic peptide (markers of myocardial stress or myocardial dysfunction), the level of sST2 expression does not depend on factors, such as body mass index, gender, age, smoking status, and presence of comorbidities (mainly renal dysfunction), and has the lowest intra- and interindividual variabili-

ty among the main cardiac biomarkers. Taking into consideration the above points, ST2 may be more useful than NT-proBNP for risk stratification and monitoring of treatment effectiveness in HFpEF patients [22].

It was found that sST2 overexpression in the blood serum of patients is closely associated with autoimmune and inflammatory processes, in particular, with type 2 CD4 + cells [39]. It is also known that elevated sST2 levels can be used as a marker for predicting cardiovascular mortality and rehospitalization rates in patients with heart failure [35, 40]. It has been shown that increased baseline sST2 levels and achieved doses of β-blockers are associated with the incidence of cardiovascular events in patients with heart failure with preserved and mildly reduced LVEF, regardless of NT-proBNP concentrations. At the same time, the mechanisms of action of β-blockers on the ST2 interleukin receptors remain unclear.

The study by J. Xia et al. (2017) suggested that β-blocker therapy modulates IL-33 / sST2 signaling, thereby slowing down the processes of ventricular remodeling, but these data were obtained in the animal model of acute myocardial infarction [41]. B-blocker therapy was found to significantly improve LV function, decrease infarction size and enhance IL-33 / ST2 signaling, leading to a decrease in sST2 expression. It is interesting that in this study β-blocker treatment reduced sST2 levels but did not affect elevated IL-33 levels. Thus, it was concluded that β-blocker therapy may play an important role in modulating IL-33 / ST2 signaling and in ventricular remodeling [41].

Analysis of the prospective, randomized PROTECT trial revealed the relationship between changes in β-blocker doses and sST2 levels and the risk of cardiovascular events [42]. The authors of this study analyzed the use of the β-blocker at a wide range of doses and identified the role of sST2 in risk stratification. In this study, patients were randomized into four groups according to the baseline sST2 values (≤ 35 ng / ml versus > 35 ng / ml) and a final β-blocker dose (≥ 50 mg versus < 50 mg daily) in patients with LVEF ≤ 40%. As a result, it was found that β-blocker therapy had a dose-dependent effect, and the measurement of sST2 helped to identify patients with CHF. Higher doses of these drugs may be especially useful for such patients, as they can reduce the incidence of adverse events.

At the same time, the results of the EPHESUS study evaluating the effectiveness of eplerenone on the survival of patients with heart failure after acute myocardial infarction showed that adverse LV remodeling in patients with normal ST2 expression is less common regardless of therapy [20]. The study by W.P. Huang et al. found that patients after ST-segment elevation myocardial infarction and higher baseline sST2 concentrations, which were not titrated with high doses of β-blockers ($p < 0.0001$) before therapy, had higher incidence of cardiovascular events [42].

The data obtained help to understand the mechanisms of involvement of ST2 receptors in the pathogenesis of cardiac remodeling, fibrosis, and apoptosis leading to the onset and progression of CHF with preserved and mildly reduced LVEF. Long-term therapy with β-blockers has anti-ischemic and hemodynamic effects in patients with CHF with preserved and mildly reduced LVEF. It is probably due to an increase in time allowing for more complete LV filling during diastole, which causes an increase in stroke volume. Another effect of β-blockers is their influence on the increased tone of the sympathetic nervous system and the level of catecholamines. As a result, CHF progression is prevented by inhibiting adverse remodeling.

It should be noted that our data in no way suggest that β-blocker therapy should be abandoned if sST2 expression is normal. Moreover, we have shown that in patients with physiological sST2 values, the incidence of cardiovascular events was further reduced due to the use of high doses of β-blockers.

CONCLUSION

Therefore, the study results confirm high prognostic value of the increase in the sST2 serum concentration in the development of cardiovascular events within a year after endovascular myocardial revascularization and substantiate the possibility of using this biomarker as a target for β-blocker therapy in HFpEF and HFmrEF patients. Aggressive use of β-blockers is preferable in the group of patients with sST2 overexpression and HFpEF and HFmrEF in order to reduce the incidence of cardiovascular events.

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