ORIGINAL ARTICLE

# THE ROLE OF NT-PROBNP AND ST2 BIOMARKERS IN PATIENTS WITH ACUTE CORONARY SYNDROME

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**ABSTRACT**

**The aim:** To determine the diagnostic value of serum levels of ST2 in patients with the acute coronary syndrome (ACS) and its correlation with NT-proBNP levels.

**Materials and methods:** NT-proBNP and ST2 concentration in serum of patients was measured on admission to the hospital and on the 10th day of the treatment using NT-proBNP ELISA (Biomedica, Slovakia) and Presage ST2 assay (Critical Diagnostics, USA), respectively.

**Results:** Statistically significant direct correlations ($p<0.05$). The simultaneous increase of ST2 and NT-proBNP serum levels above their threshold in patients with ACSelST (sensitivity – 92.5 %, specificity – 74.2 %, AUC – 0.893, $p<0.05$) indicated a significant risk of cardiovascular (CV) complications of acute myocardial infarction (AMI) during the inpatient period, e.g. acute heart failure, acute LV aneurysm, recurrent AMI, as well as rhythm and conductivity disturbances.

**Conclusions:** The data suggest that both ST2 and NT-proBNP may prove useful in predicting unfavorable prognosis during the inpatient care of AMI, as the simultaneous increase of these biomarkers above their threshold values indicates a significant risk of CV complications.

**KEY WORDS:** acute coronary syndrome, heart failure, NT-proBNP, ST2

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## INTRODUCTION

Biomarkers play an important role in the diagnosis and prognosis of a number of cardiovascular (CV) diseases including coronary heart disease [1]. They are divided into several groups: myocardial stretch (natriuretic peptide), cardiomyocyte injury (highly sensitive troponins (hs-cTn), heart-type fatty acid-binding protein (H-FABR), glutathione-S-transferase P1 (GSTP1), markers of myocardial remodeling (Galectin-3, ST2) and inflammation (growth differentiation factor 15 (GDF-15)), heat shock proteins (highly conserved proteins (Hsp100, Hsp90, Hsp70, Hsp60, Hsp40) and small proteins (Hsp27, Hsp10) ), hypoxia-induced factor (HIF-1α), Klotho protein, as well as endothelial NO-synthase gene, and others [2].

Analyzing numerous studies on the deleterious effects of pro-inflammatory cytokines and markers of myocardial injury, we found that ST2 not only plays a crucial role in the course of chronic heart failure (HF) but also complements the information obtained when determining NT-proBNP levels [3]. The evaluation of ST2 is included in the recommendations of the European Society of Cardiologists (ESC, 2016) for stratification of CV risk in patients with acute or chronic HF. Using the combination of several biomarkers will help to optimize the treatment of HF in the future [4].

## THE AIM

The aim of this study was to determine the diagnostic value of serum levels of ST2 in patients with the acute coronary syndrome (ACS) and its correlation with NT-proBNP levels.

## MATERIALS AND METHODS

The study was performed in the settings of communal noncommercial enterprise "Lviv City Clinical Hospital of Emergency Care". Total 186 patients with ACS were examined, including 81 individuals (64 males and 17 females, mean age 61.67±1.13 years) with ST-segment elevation (ACSelST)- group I, and 86 patients (60 males and 16 females, mean age 61.80±1.13 years) without ST-segment elevation (ACSnelST) – group II. In patients of both groups the prevalence of concomitant pathology and comorbid conditions were analyzed from anamnesis (Table I).

The study was designed in adherence to ethical, moral, and legal principles and was approved by the Bioethics Committee of Danylo Halytstky Lviv National Medical University (Protocol No. 8 dated October 21, 2019). Each subject provided informed written consent before participation and was aware of the right to withdraw from the study for any reason without prejudice. The entire protocol was performed in accordance with the declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

All patients underwent standard laboratory tests (common blood and urine tests, biochemical studies assessing lipid profile), 12-lead ECG at rest, EchoCG as well as selective coronary angiography to assess the condition of the coronary arteries. Additionally, NT-proBNP and ST2 serum concentrations were determined on admission to hospital and on the 10$^{th}$ day of treatment using the NT-proBNP ELISA (Biomedica, Slovakia) and Presage ST2 assay (Critical Diagnostics, USA).

**Table I.** The prevalence of comorbidity and main risk factors in patients with ACS (P±mp, %)

| Consequences | Group I (n=81) | | Group II (n=86) | |
|---|---|---|---|---|
| | N | P±m$_p$, % | N | P±m$_p$, % |
| MI in anamnesis | 9 | 11,11±3,49 | 20 | 23,26±4,56* |
| Hypertension | 77 | 95,06±2,41 | 72 | 83,72±3,98 |
| Dyslipidemia | 43 | 53,09±5,54 | 58 | 67,44±5,05* |
| Diabetes mellitus | 19 | 23,46±4,71 | 12 | 13,95±3,74 |
| Smoking | 51 | 62,96±5,37 | 40 | 46,51±5,38 |
| Excessive alcohol consumption | 25 | 30,86±5,13 | 21 | 24,42±4,63 |
| Heredity | 23 | 28,40±5,01 | 22 | 25,58±4,70 |
| Professional harm | 19 | 23,46±4,71 | 34 | 39,53±5,27* |

Note: * - p<0,05 – the difference between the indicators in groups I and II

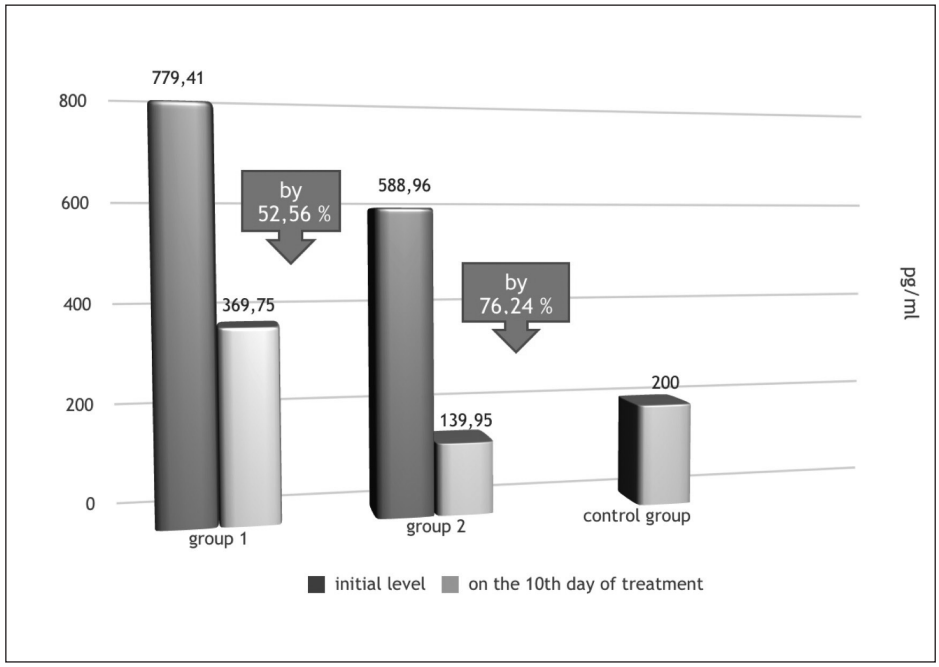


**Fig. 1.** Changes in serum levels of NT-proBNP on admission and on the 10th day of the treatment
Note. * – p<0.05 difference between indicators of groups I and II

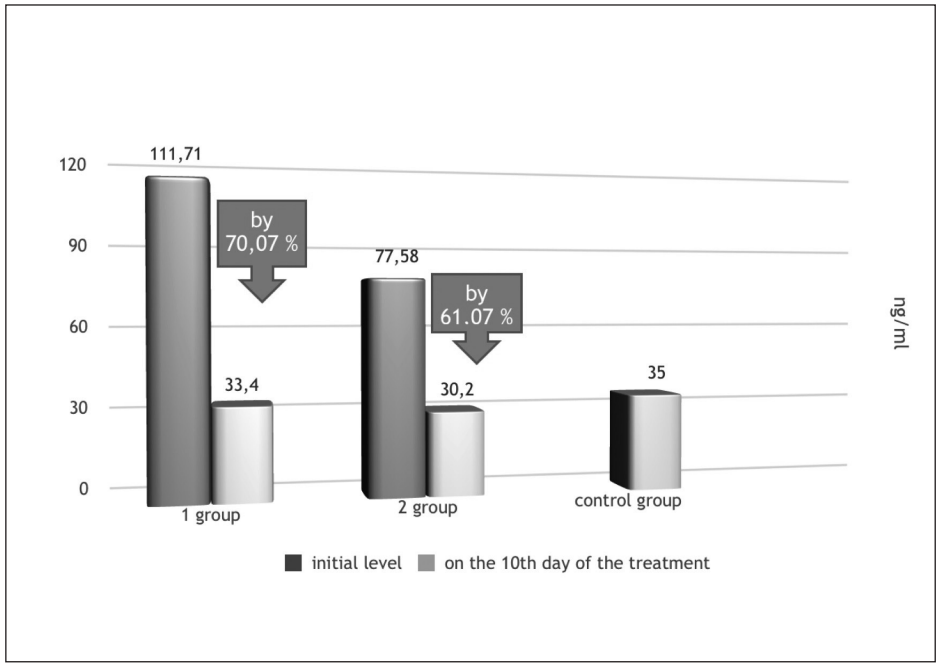


**Fig. 2.** Changes in serum levels of ST2 on admission and on the 10th day of the treatment
Note. * – p<0.05 difference between indicators of groups I and II

**Table II.** Mean values (M±m) of ST2 (ng/ml) and NT-proBNP (pg/ml) in patients of groups I and II depending on the course of the disease

| Consequences | No complications | | Early CV complications | |
|---|---|---|---|---|
| | Group I | Group II | Group I | Group II |
| | NT-proBNP, pg/ml | | | |
| On admission to the hospital | 713,55±93,26 *** | 419,73±116,16 * | 823,31±75,6 *** | 680,08±110,76 *** |
| On the 10th day of treatment | 235,86±52,18 * # | 219,2±49,14 | 503,65±85,97 *** # | 295,92±56,32 ** # |
| | ST2, ng/ml | | | |
| On admission to the hospital | 87,1±19,1 ** | 57,06±11,04 | 129,07±16,25 *** | 84,68±7,92 *** |
| On the 10th day of treatment | 22,63±1,39 *** # | 27,05±3,33 * # | 41,52±6,87 # | 31,29±2,58 # |

Note. * - p<0,05; **- p<0,01; ***- p<0,001 - differences between indicators and their reference values;
# - p<0,01 - differences in groups on admission and on the 10th day of the inpatient treatment.

Medical-statistical analysis of the obtained data was performed using Microsoft Excel 2016, Statistica 10 and IBM SPSS Statistics 20 software. Gaussian distribution was established allowing us to determine the standard deviation (SD) and error (M±m) for each of the studied mean values (Mean). The comparison of two sets of mean values was performed using the unpaired Student's t-test (t). Pearson's $\chi 2$ criterion was used to compare the two sets by categorical variables and frequencies. The calculation of the correlation dependence between the studied parameters was performed by the method of linear Pearson correlation (r). The results were considered significant with a minimum significance level of p<0.05.

## RESULTS

On admission to the hospital, mean NT-proBNP levels were higher in patients with ACSelST (779.41±57.86 pg/ml (I)) when compared with ACSnelST patients (588.96±82.47 pg/ml (II), p>0.05), albeit this difference was not statistically significant. On the 10th day of the hospitalization serum levels of NT-proBNP decreased to 369.75±55.22 pg/ml (I) and 139.95±19.57 pg/ml (II), respectively and the difference between two patient groups became statistically significant (p<0.05) (Fig. 1).

On admission the ST2 level in the serum of the patients with ACSelST significantly exceeded the corresponding values in patients with ACSnelST (111.71±12.41 ng/ml (I) vs. 77.58±6.5 ng/ml (II), p<0.05) (Fig. 2). After 10 days of the treatment the mean ST2 level decreased by 70,07% and 61,07% respectively (group I - 33.43±4.38 ng/ml; group II - 30.20±2.05 ng/ml) and there were no statistically significant differences between the two groups (p>0.05). The obtained results confirmed the observation that an increase in the ST2 concentration correlates with the size of the necrosis site and the severity of ACS, and the NT-proBNP levels – with the presence of acute or chronic HF.

Significant direct correlations of moderate and high strength were also found between ST2 and NT-proBNP levels in patients with ACSelST (I) on admission and on the 10th day of treatment (r=0.43; p=0, 03 and r=0.85; p=0.0001, respectively). Patients with ACSnelST (II) had only direct correlations of moderate and low strength (p>0.05) between these biomarkers and of left ventricular myocardial remodeling (r=0.35; p=0.11 and r=0.01; p=0.96, respectively).

Depending on the course of the disease, during the hospital stay the patients were divided into 2 subgroups: patients whose ACS ran without complications and patients whose course of disease was complicated by the appearance of acute HF, acute aneurysm LV, recurrence of AMI, rhythm and conductivity disturbances (see Table II).

On the first day of inpatient treatment the concentration of NT-proBNP in the serum of patients with ACSelST (I), who later showed the appearance of early CV complications, were 15.38% higher compared to the same indicator in patients without CV complications and 62.03% higher than in patients with ACSnelST (II) (p>0.05). On the 10th day of the treatment the concentration of NT-proBNP in patients with ACSelST (I) with early CV complications was 2,14 times higher than in patients without CV complications (p<0.01), and 1.35 times higher than in patients with ACSnelST (II) however there was no statistical significance. (p>0.05).

During inpatient treatment serum levels of NT-proBNP in ACSelST patients (I) with early CV complications significantly decreased but only by 38.83% (p<0.007), whilst in patients whose course of disease ran without complications the decrease was 66.95% (p<0.001). In the serum of the group II patients (ACSnelST), who in course of treatment showed early CV complications, a 56.49% (p<0.01) decrease of NT-proBNP concentration was detected, and a 47.78% (p>0.05) decrease was seen in serum of patients with positive disease dynamics.

Therefore, serum NT-proBNP biomarker levels decrease in both groups during the inpatient treatment. However, even on the 10th day of the treatment NT-proBNP levels exceeded the reference values regardless the course of ACS.

Upon admission to the hospital the ST2 concentration in serum of the patients with ACSelST (I), who later have showed early CV complications, was higher by 32.52% (p>0.05) than corresponding value in patients without CV complications, and it remained higher by 45.5%

($p<0.01$) even on the 10th day of inpatient treatment. However, the patients with ACSelST (I) and with positive dynamics of the disease showed a significant decrease of ST2 levels by 3.85 times ($p<0.01$). Patients of the group I with early CV complications have also showed a decrease in these indications by 3.11 times ($p<0.001$).

Upon the first determinatoin, ST2 concentration in serum of patients with ACSnelST (II), who showed early CV complications, was 32.62% ($p<0.05$) higher compared to the same indication in patients without CV complications. After 10 days of inpatient treatment this difference was 13.55% ($p<0.05$) higher. In cource of treatment myocardial ST 2 remodeling marker in patients with ACSnelST (II) showed a tendency to decrease, regardless of the course of ACS. Patients of the group II with early CV complications had their ST2 concentration levels 2,71 times lower ($p<0.001$), and with the positive dynamics of disease 2.11 times lower ($p<0.05$). In both cases on the 10th day of the treatment, regardless the course of disease, average ST2 indications were not exceeding threshold values of this cardiomarker (35 ng/ml) ($p<0.05$).

Thus, in all patients serum levels of myocardial ST 2 remodeling marker showed the tendency to decrease with the treatment progression. Patients whose average values of this indication exceeded 35 ng/ml, exhibited a CV complications more frequently.

Analyzing the correlation relationship in patients with ACSelST (I) and ACSnelST (II) on admission, we found a significant direct moderate relationship between ST2 and NT-proBNP indices and the presence of early CV complications ($r=0.63$; $p=0.002$ and $r=0.45$; $p=0.014$, respectively), such as acute HF, acute left ventricular (LV) aneurysm, recurrent acute myocardial infarction, rhythm and conductivity disturbances. After the 10$^{th}$ day of treatment in the patients of the group I, a significant direct strong relationship (я б писала correlation а не relationship) between the ST2 and NT-proBNP ($r=0.92$; $p<0.001$) was found. No significant difference was found between two groups of patients with positive changes and the ST2 and NT-proBNP values ($p>0.05$).

ST2 and NT-proBNP indicators serve as predictors of adverse prognosis in AMI, since simultaneous increase of these indications above its threshold values indicates a significant risk of CV complications (sensitivity – 92.5 %, specificity – 74.2 %, AUC – 0.893, $p<0.05$). Thereby, ST2 and NT-proBNP values are closely linked to the severity of ACS course during the inpatient treatment stage.

## DISCUSSION

The increase in NT-proBNP concentration is directly proportional to the size of the necrosis site and the severity of acute myocardial infarction [5,6]. ENTIRE-TIMI 23 study has shown that the ST2 level correlates with future risk of the chronic HF death [7]. In the CLARITY-TIMI study, increase in ST2 was found to be a predictor of HF death after 30 days regardless of NT-proBNP values. The ST2 biomarker is known to be an independent predictor of overall patient mortality [8].

According to the PRIDE study [9] involving 593 patients, serum ST2 concentration was significantly higher in patients with chronic HF than in patients with non-cardiac diseases. High ST2 level correlates with NYHA class chronic HF, left ventricular (LV) ejection fraction, and creatinine clearance. As with NT-proBNP, there is a higher ST2 concentration in abnormal LV systolic function than in patients with preserved LV systolic function. It is important to note that ST2 was a less significant marker in the diagnosis of chronic HF than NT-proBNP [9].

Furthermore, in the PRIDE study, the ST2 concentration was a true predictor of chronic HF mortality during the year. The ST2 concentration correlated with the severity of symptoms regardless of the etiology of the disease. The combined increase in the ST2 and NT-proBNP concentration allows us to predict the adverse course of the disease accurately [10-11]. Similar results were obtained according to our observations.

Changes in the ST2 level during the course of illness is more predictive than a one-time measurement. The study, which included 150 patients with NYHA II-IV chronic HF, established the importance of determining the changes of concentration in the evaluation of chronic HF results [12], which was also confirmed by the results of our study.

However, it remains unclear whether the therapeutic approach aimed at reducing ST2 concentrations in chronic HF therapy is going to reduce the possible risk associated with high concentrations of this marker. It was found that the 2-week changes of ST2 concentration served as a predictor of death regardless of NT-proBNP concentration. Another study found that ST2 levels correlated with the risk of sudden death in chronic HF [13].

PRAISE-2 study involving 161 patients with NYHA class III or IV HF of non-ischemic origin found that changes in the course of the disease were associated with an increased risk of death (but not ST2 baseline values) [14]. As a result of our study, the reductions in ST2 myocardial remodeling marker in all patients tended to decrease whith the time. CV complications developed more frequently in subjects with the mean values that did not reach 35 ng/ml.

In a multi-center PHFS study [15] involving 1141 patients, ST2 was no less important than NT-proBNP alone when assessing individual patient risk. The combination of these two biomarkers significantly improved the ability to assess risk, according to our findings.

The results obtained are consistent with the results of the MUSIC study, in which an increase in ST2 and NT-proBNP levels above the threshold was associated with a high rate of sudden death (71%) [13]. These findings are vitally important considering that no other biomarker today correlates with the risk of sudden death in HF patients. The important prognostic value of sST2 in chronic HF was also confirmed in studies such as HF-ACTION [16] and CORONA [17].

## CONCLUSIONS

ST and NT-proBNP indicators are closely related to severe course of ACS during the inpatient treatment stage. Simultaneous in-

crease of ST2 and NT-proBNP levels above its threashold values in patients with ACSelST (sensitivity – 92.5 %, specificity – 74.2 %, AUC – 0.893, p<0.05) allows to predict a more severe course of the disease and the risk of cardiovascular complications (acute heart failure, acute left ventricular aneurysm, recurrent course of myocardial infarction, rhythm and conductivity disturbances) during the acute period of myocardial infarction.

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**Conflict of interest:**
*The Authors declare no conflict of interest.*

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