

FEATURES OF THE STRUCTURAL AND FUNCTIONAL CONDITION OF THE MYOCARDIUM DEPENDING ON ST2 AND TROPONIN I PLASMA LEVELS IN NSTEMI PATIENTS

Introduction. The prevalence of myocardial infarction without ST-segment elevation and the risk of adverse events in the long term encourage the search for and study of non-invasive predictors of destabilization of the disease. ST2 is considered as one of such markers.

The aim of the study – to determine the features of the structural and functional condition of the myocardium depending on the levels of ST2 and troponin I in plasma in patients with NSTEMI.

Research Methods. The study involved 200 patients with NSTEMI aged 38 to 80 years. All patients were examined according to the current treatment protocol for patients with acute myocardial infarction without ST segment elevation, plasma levels of ST2 and troponin I were determined.

Results and Discussion. The dependence of ST2 level and the absence of such for troponin I level in plasma with the value of the left ventricular myocardial mass index was established. The results of the analysis show that the value of the left ventricular myocardial mass index $>115 \text{ g/m}^2$ in patients with NSTEMI is associated with a higher level of ST2 in plasma (median – 43.7 ng/ml). Analysis of the level of ST2 and troponin I in plasma in NSTEMI patients depending on the value of the relative myocardial wall thickness showed no statistically significant dependence of factors on its value. However, there was a tendency in the frequency of registration of cases of relative myocardial wall thickness of different sizes in the case of associations of relatively high levels of ST2 and troponin I. The data show that in the case of relatively high levels of ST2 parallel change in plasma with different values of the relative myocardial wall thickness.

Conclusions. ST2 levels, regardless of troponin I levels, are associated with an increase in left ventricular myocardial mass index as opposed to relative myocardial wall thickness. Determination of elevated ST2 levels in the early period tends to electrical instability of the myocardium, which requires appropriate preventive measures in this category of patients.

KEY WORDS: NSTEMI; ST2; troponin I; structural remodeling.

INTRODUCTION. Recently, great progress has been made in the diagnosis and treatment of myocardial infarction without ST-segment elevation (NSTEMI). However, the long-term prognosis of this category of patients remains disappointing. This is primarily due to the development of myocardial dysfunction resulting from post-infarction remodeling and the development of prognostically unfavorable arrhythmias on the background of electrically unstable myocardium [1]. Prevention of myocardial dysfunction and electrical instability of the myocardium provides an opportunity to prolong the duration and improve the quality of life of these patients. In this regard, the search for opportunities to predict the development of complications using non-invasive biomarkers and their impact on remodeling processes continues. One such biomarker currently being actively studied is the growth stimulating factor expressed by ST2 gene [2].

© V. I. Maslovskyi, 2022.

The aim of the study – to determine the features of the structural and functional state of the myocardium depending on the levels of ST2 and troponin I in plasma in NSTEMI patients.

RESEARCH METHODS. We examined 200 patients with acute myocardial infarction without ST-segment elevation (NSTEMI) aged 38 to 80 (mean 62.0 ± 0.71 , median – 62 and interquartile range – 55 and 70) years, who were hospitalized in the Municipal Non-Profit Enterprise “Vinnytsia Regional Clinical Medical and Diagnostic Center for Cardiovascular Pathology” with urgent indications.

The criteria for including patients in the study were:

- 1) verified NSTEMI, first diagnosed;
- 2) age up to 80 years;
- 3) the absence of contraindications to percutaneous coronary interventions and the use of the

main groups of pharmacological agents included in the basic therapy of NSTEMI;

4) informed consent of the patient to participate in the study.

The criteria for exclusion from the study were:

1) STEMI, transferred in the past and recurrent acute myocardial infarction;

2) age of patients 80 years and older;

3) the presence of sinoatrial or atrioventricular block degree II–III, implanted or the need for implantation of an artificial pacemaker;

4) chronic heart failure NYHA-III, IV before the incident of acute myocardial infarction;

5) diseases of the respiratory system, kidneys and liver, which were accompanied by signs of pulmonary, renal and hepatic failure; anemic conditions with a hemoglobin level below 110 g/L;

6) the presence of rheumatic and congenital heart defects, idiopathic and inflammatory myocardial lesions;

7) malignancies, severe neuropsychiatric disorders, alcohol abuse;

8) the presence of contraindications to percutaneous coronary interventions and the use of the main groups of pharmacological agents included in the basic therapy NSTEMI;

9) reluctance and refusal of the patient to participate in the study.

All patients were examined according to the NSTEMI protocol [3]. Determining of the plasma ST2 levels was performed by enzyme-linked immunosorbent assay in all patients on the first day of hospitalization before hospital coronary angiography [4].

We selected ST2 gradation methods by the method of variation statistics. Conditionally allocated relatively low risk (RL) corresponded to less than 25, and relatively high (RH) ST2 level – more than 75 percent of the percentage of indicator, respectively. Therefore, the levels were <26 and >56 ng/ml, respectively. In turn, the relatively moderate level (RM) of ST2 for these patients was 25–56 ng/ml [5].

Similar calculations made for the level of troponin I (Tp I) in plasma showed that the average level of the factor was 7.07 ng/ml at the minimum and maximum values of 0.31 and 18.41 ng/ml, respectively, and the standard deviation of the mean value (σ) – 4.84. The median was 5.96 and the interquartile range was 3.49 and 10.11 ng/ml, respectively. Therefore, the obtained data showed that in 75 % of the examined NSTEMI patients the level of troponin I in plasma ranged from 3.49 to 10.11 ng/ml.

RESULTS AND DISCUSSION. To assess changes in ST2 and Tp I levels in plasma in NSTEMI patients depending on the structural and functional condition of the myocardium, determined by echocardiography, we conducted an analysis in several areas: 1 – assessment of changes in ST2 and Tp I levels depending on the index left ventricular myocardial mass (LVMI); 2 – assessment of changes in the level of ST2 and Tp I depending on the value of the relative wall thickness of the LV myocardium (RWT). Analysis of plasma ST2 levels in NSTEMI patients depending on the value of LVMI (Fig. 1) showed a significant increase in the level of the factor in the group with LVMI >115, compared

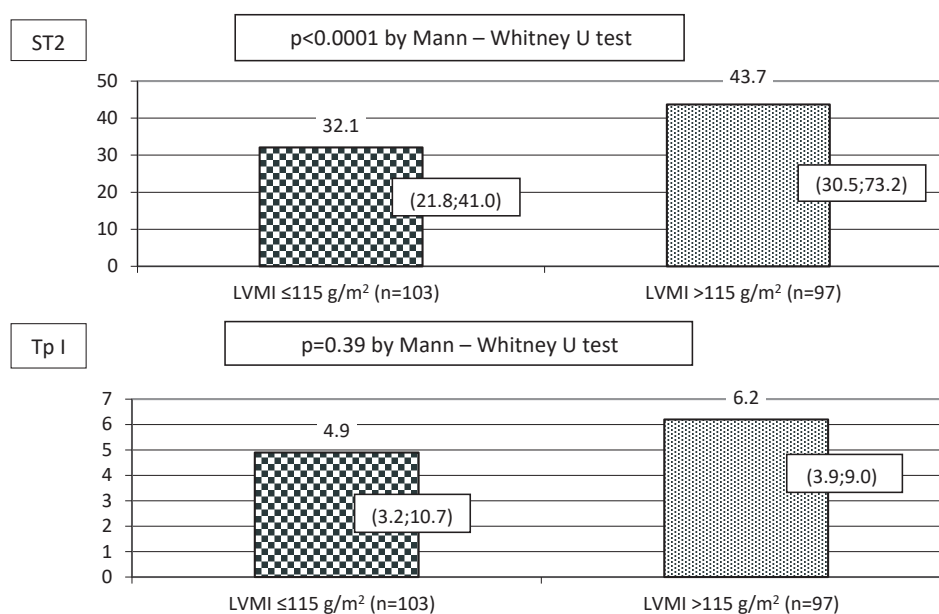


Fig. 1. Levels of growth stimulating factor expressed by gene 2 and troponin I in plasma (in ng/ml) in patients with NSTEMI depending on the value of the left ventricular myocardial mass index.

Notes: The results are presented as the median and interquartile range.

with its value $\leq 115 \text{ g/m}^2$ (43.7 vs. 32.1 ng/ml, $p < 0.0001$ for the Mann-Whitney U test). Instead, the analysis of the level of Tp I in plasma showed only a tendency to increase the level of the factor at the value of LVMI $> 115 \text{ g/m}^2$ (4.9 vs. 6.2 ng/ml, $p = 0.39$).

The distribution of cases with LVMI ≤ 115 and $> 115 \text{ g/m}^2$ at different associations of ST2 and Tp I levels in plasma (Fig. 2) showed that the frequency of cases with LVMI $\leq 115 \text{ g/m}^2$ was the highest (71.7 %) in the case of the association RL ST2/RL Tp I (group 1), it progressively decreased from the 1st to the 4th group and in the latter (association RH ST2 / RH Tp I) acquired a minimum value (31.9 %). The reverse pattern of changes was determined in the distribution of cases with LVMI $> 115 \text{ g/m}^2$. Thus, their minimum frequency (28.3 %) was found in the case of the association RL ST2/RL Tp I (group 1), it progressively increased from group 1 to group 4 and in the latter (association RH ST2/RH Tp I) acquired its maximum value (68.1 %).

Thus, in patients with NSTEMI, the dependence of ST2 levels and the absence of dependence for the level of Tp I in plasma with LVMI was determined. The results of the analysis show that the value of LVMI $> 115 \text{ g/m}^2$ in patients with NSTEMI is associated with higher levels of ST2 in plasma (median – 43.7 ng/ml). In addition, it is statistically proven that the biochemical association RH ST2/RH Tp I (ST2 $> 36 \text{ ng/ml}$ + Tp I $> 6 \text{ ng/ml}$ in plasma) and, to a lesser extent, the association of RH ST2/RL Tp I (ST2 $> 36 \text{ ng/ml}$ + Tp I $\leq 6 \text{ ng/ml}$ in plasma) are accompanied by the highest frequency of cases with LVMI $> 115 \text{ g/m}^2$ and the lowest, respectively, with LVMI $\leq 115 \text{ g/m}^2$, which a priori implies more severe structural modeling LV myocardium in this category of patients.

Analysis of ST2 and Tp I levels in plasma of NSTEMI patients depending on the value of RWT (Fig. 3) showed no statistically significant dependence ($p = 0.71$ and 0.26 , respectively, according to the Mann – Whitney U test) of factors with the

value of RWT (analyzed groups with RWT ≤ 0.45 and > 0.45).

The results of the distribution of cases with RWT values ≤ 0.45 and > 0.45 depending on different associations of ST2 and Tp I levels in plasma in NSTEMI patients (Fig. 4) showed no significant % difference between different associations. Instead, it was determined the tendency to reliability ($p = 0.06$ according to the criterion χ^2) in the frequency of registration of RWT cases of different magnitude in the case of associations RH ST2/RL Tp I and RH ST2/RH Tp I (56.9 % vs. 38.3 % for RWT ≤ 0.45 and 43.1 % vs. 61.7 % for RWT > 0.45 , respectively). The obtained data show that in the case of RH ST2 a parallel change in the level of Tp I in plasma fundamentally affects the frequency of cases with different values of RWT.

Therefore, the results of this analysis suggest that changes in plasma ST2 and Tp I levels in NSTEMI patients have no definite association with LV geometry variant.

The results of the study indicate a clear relationship between elevated ST2 levels and LVMI in contrast to Tp I. In our opinion, this is due to the greater sensitivity of ST2 in the acute period of myocardial infarction, while Tp I has a period to increase the concentration of blood, which depends not only on the extent of myocardial damage, but also on the duration of ischemia. Similar patterns have been obtained in a number of studies, but in association with NT-proBNP [6]. Also, RH ST2/RH Tp I level associations have a clear association with an increase in LVMI $> 115 \text{ g/m}^2$. The obtained results suggest more severe structural remodeling of the LV myocardium in the examined category of patients. At the same time, analysis of the level of ST2 and Tp I in plasma in NSTEMI patients depending on the value of RWT showed no statistically significant dependence of factors on the value of RWT. The results of the distribution of cases with RWT values ≤ 0.45 and > 0.45 depending on the different associations of ST2 and Tp I levels in plasma in

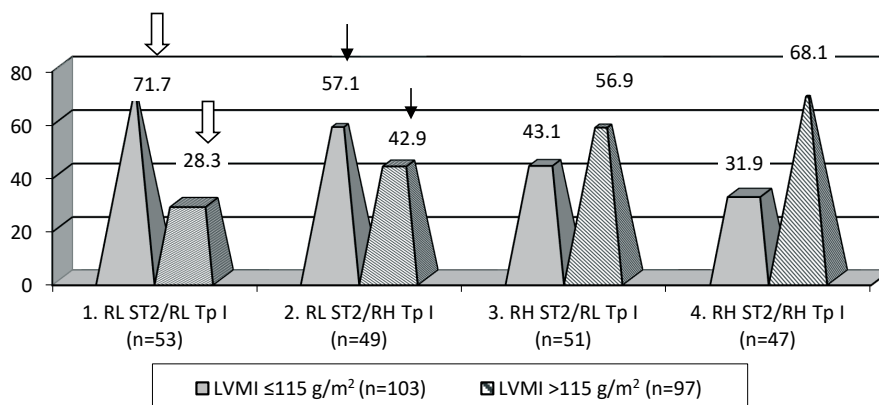


Fig. 2. Distribution of cases with different values of LVMI (in %) depending on the association of levels of growth stimulating factor expressed by gene 2 and troponin I in plasma in patients with NSTEMI.

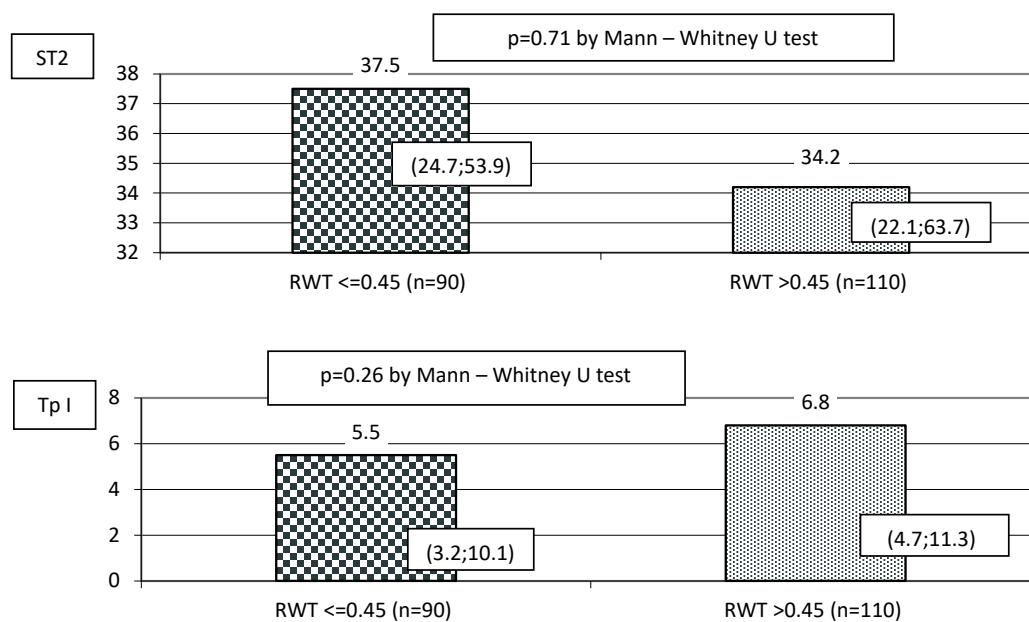


Fig. 3. Levels of growth stimulating factor expressed by gene 2 and troponin I in plasma (in ng/ml) in patients with NSTEMI depending on the value of the relative wall thickness of the myocardium.

Notes:

1. The results are presented as the median and interquartile range.
2. RWT – relative wall thickness of the left ventricular myocardium.

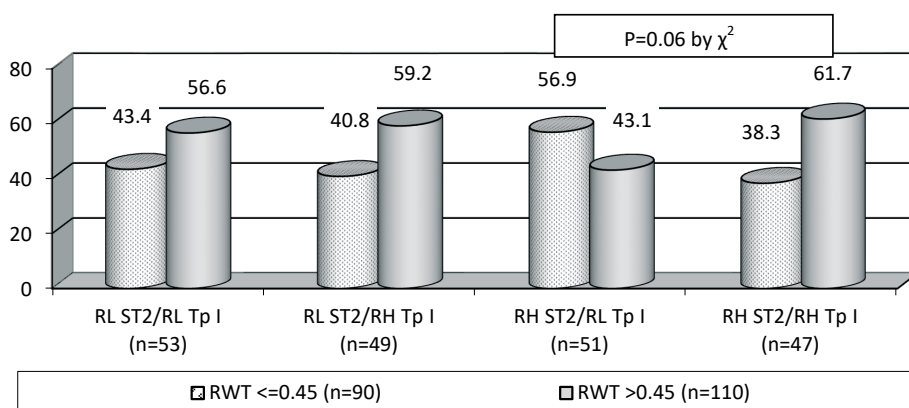


Fig. 4. Distribution of cases with different values of RWT (in %) depending on the association of levels of growth stimulating factor expressed by gene 2 and troponin I in plasma in patients with NSTEMI.

NSTEMI patients also showed the absence of a significant % difference between the different associations. However, despite the obtained data, there is a tendency to reliability in the frequency of registration of RWT cases of different magnitude in the case of associations RH ST2/RL Tp I and RH ST2/RH Tp I. The data show that in the case of RH ST2 parallel change in Tp I plasma fundamentally affects the frequency of cases with different values of RWT. The identified structural changes, in the future, tend to manifestations of electrical instability of the myocardium in the early period of infarction [7], as well as a tendency to unfavorable prognosis, which, accordingly, should be reflected in preventive measures.

CONCLUSIONS. 1. It was found that the level of ST2, regardless of the level of Tp I, is associated with an increase in the myocardial mass index of the left ventricle, in contrast to the relative wall thickness of the myocardium.

2. ST2/Tp I associations did not show a relationship with the parameters of structural myocardial remodeling, however, the change in indicators towards a relatively high level tended to be reliable in the values of the studied indicators.

3. Determination of elevated ST2 levels in the early period tends to electrical instability of the myocardium, which requires appropriate preventive measures in this category of patients.

LITERATURE

1. Physiological implications of myocardial scar structure / W. J. Richardson, S. A. Clarke, T. A. Quinn, J. W. Holmes // *Compr. Physiol.* – 2015. – **5**, Issue 4. – P. 1877–1909.
2. Biomarkers for heart failure prognosis: proteins, genetic scores and non-coding RNAs / A. Shrivastava, T. Haase, T. Zeller, C. Schulte // *Front. Cardiovasc. Med.* – 2020. – No. 7. – 601364.
3. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation / J. P. Collet, H. Thiele, E. Barbato [et al.] // *Eur. Heart J.* – 2021. – **42**, Issue 14. – P. 1289–1367.
4. Mueller T. The Presage®ST2 Assay: analytical considerations and clinical applications for a high-sensitivity assay for measurement of soluble ST2 /

T. Mueller, B. Dieplinger // *Expert Rev. Mol. Diagn.* – 2013. – **13** (1). – P. 13–30.

5. Mezhiievska I. ST2 plasma level in patients with acute myocardial infarction without st elevation and different clinical characteristics / I. Mezhiievska, V. Ivanov, V. Maslovskiy // *EUREKA: Health Sci.* – 2020. – No. 1. – P. 47–54.

6. Serum soluble ST2 and adverse left ventricular remodeling in patients with ST-Segment elevation myocardial infarction / M. Kercheva, T. Ryabova, A. Gusakova [et al.] // *Clin. Med. Insights Cardiol.* – 2019. – No. 13. – 1179546819842804.

7. Restoring heart function and electrical integrity: closing the circuit / L. M. Monteiro, F. Vasques-Nóvoa, L. Ferreira [et al.] // *NPJ Regen. Med.* – 2017. – No. 2. – P. 9.

REFERENCES

1. Richardson, W.J., Clarke, S.A., Quinn, T.A., & Holmes, J.W. (2015). Physiological implications of myocardial scar structure. *Compr. Physiol.*, 5 (4), 1877-1909. DOI: 10.1002/cphy.c140067.
2. Shrivastava, A., Haase, T., Zeller, T., & Schulte, C. (2020). Biomarkers for heart failure prognosis: proteins, genetic scores and non-coding RNAs. *Front. Cardiovasc. Med.*, 7, 601364. DOI: 10.3389/fcvm.2020.601364.
3. Collet, J.P., Thiele, H., Barbato, E., Barthélémy, O., Bauersachs, J., Bhatt, D.L., ..., & Sibbing, D. (2021). 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.*, 42 (14), 1289-1367. DOI: 10.1093/eurheartj/ehaa575.
4. Mueller, T., & Dieplinger, B. (2013). The Presage®ST2 Assay: analytical considerations and clinical applications for a high-sensitivity assay for measurement

of soluble ST2. *Expert Rev. Mol. Diagn.*, 13, (1), 13-30. DOI: 10.1586/erm.12.128.

5. Mezhiievska, I., Ivanov, V., & Maslovskiy, V. (2020). ST2 plasma level in patients with acute myocardial infarction without st elevation and different clinical characteristics. *EUREKA: Health Sci.*, 1, 47-54. DOI: 10.21303/2504-5679.2020.001098.

6. Kercheva, M., Ryabova, T., Gusakova, A., Suslova, T.E., Ryabov, V., & Karpov, R.S. (2019). Serum soluble ST2 and adverse left ventricular remodeling in patients with ST-Segment elevation myocardial infarction. *Clin. Med. Insights Cardiol.*, 13, 1179546819842804. DOI: 10.1177/1179546819842804.

7. Monteiro, L.M., Vasques-Nóvoa, F., Ferreira, L., Pinto-do-Ó, P., & Nascimento, D.S. (2017). Restoring heart function and electrical integrity: closing the circuit. *NPJ Regen. Med.*, 2, 9. DOI: 10.1038/s41536-017-0015-2.

В. Ю. Масловський

ВІННИЦЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ ІМЕНІ М. І. ПИРОГОВА

ОСОБЛИВОСТІ СТРУКТУРНО-ФУНКЦІОНАЛЬНОГО СТАНУ МІОКАРДА ЗАЛЕЖНО ВІД РІВНІВ ST2 І ТРОПОНІНУ І У ПЛАЗМІ ПАЦІЄНТІВ З NSTEMI

Резюме

Вступ. Розповсюдженість інфаркту міокарда без елевації сегмента ST і ризик виникнення несприятливих подій у віддалений період спонукають до пошуку та вивчення неінвазивних предикторів дестабілізації перебігу захворювання. Одним з таких маркерів є ST2.

Мета дослідження – визначити особливості структурно-функціонального стану міокарда залежно від рівнів ST2 і тропоніну I у плазмі пацієнтів з NSTEMI.

Методи дослідження. У дослідженні взяли участь 200 пацієнтів з NSTEMI віком від 38 до 80 років. Усіх хворих обстежено відповідно до діючого протоколу лікування пацієнтів з гострим інфарктом міокарда без елевації сегмента ST, визначено плазмові рівні ST2 і тропоніну I.

Результати й обговорення. Встановлено залежність рівня ST2 та відсутність такої для рівня тропоніну I у плазмі з величиною індексу маси міокарда лівого шлуночка. Результати аналізу доводять, що величина індексу маси міокарда лівого шлуночка $>115 \text{ г/м}^2$ у пацієнтів з NSTEMI асоційована з вищим рівнем ST2 у плазмі (медіана показника – 43,7 нг/мл). Аналіз рівнів ST2 і тропоніну I у плазмі хворих на NSTEMI залежно від величини відносної товщини міокарда показав відсутність статистично значущої залежності чинників з її величиною. Однак мала місце тенденція до достовірності в частоті реєстрації випадків відносної товщини міокарда різної величини в разі асоціації відносно високих рівнів ST2 і тропоніну I. Отримані дані показують, що при відносно високому рівні ST2 паралельна зміна рівня тропоніну I у плазмі принципово впливає на частоту випадків з різною величиною відносної товщини міокарда.

Висновки. Рівень ST2, незалежно від рівня тропоніну I, пов'язаний із збільшенням індексу маси міокарда лівого шлуночка, на відміну від відносної товщини міокарда. Визначення підвищеного рівня ST2 в ранній період має тенденцію до електричної нестабільності міокарда, що потребує відповідних профілактичних заходів у цієї категорії пацієнтів.

КЛЮЧОВІ СЛОВА: NSTEMI; ST2; тропонін I; структурне ремоделювання.

Received 01.02.22

Address for correspondence: V. I. Maslovskyi, Keletska Str. 50b, ap. 127, Vinnytsia, 21021, Ukraine, e-mail: vmaslovskyi@gmail.com.