Original Research Article: full paper

(2022), «EUREKA: Health Sciences»
Number 5

ST2 AND COPEPTINE – MODERN BIOMARKERS FOR MONITORING THE EFFECTIVENESS OF TREATMENT OF DECOMPENSATED HEART FAILURE IN PATIENTS AFTER ACUTE MYOCARDIAL INFARCTION

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Abstract

The aim of the study was to increase the efficiency of diagnostic methods to find means to improve the treatment of patients with decompensated heart failure in the post-infarction period.

Materials and methods. This study is based on an examination of 120 patients with decompensated HF (60 patients with STEMI and 60 with non-STEMI). Patients with previous STEMI complicated by decompensated heart failure were divided into groups, depending on their treatment. The studied groups were homogeneous in terms of age, sex, the severity of the course of the disease, duration of the post-infarction period, and the presence of clinical manifestations of decompensation. The patients were observed on the first day after hospitalization, after 1 and 2 months after treatment. Copeptin serum levels were assayed using the EK 065-32, EIA Copeptine kit (RayBiotech, Inc., USA). ST-2 in blood serum was determined with the help of the Presage ST-2 kit (Critical Diagnostics, USA). The level of ST2 was determined in ng/ml.

Results. We analysed the effect of therapy on the level of ST2 in the blood serum of examined patients with STEMI and non-STEMI complicated by decompensated heart failure. All the treatment regimens we proposed led to a significant decrease in the level of this peptide in blood serum after the end of the treatment. In patients of group I who received basic therapy drugs, the average ST2 concentration was (49.47±1.77) ng/ml before treatment. After 1 and 2 months of therapy, it was (44.92±1.22) ng/ml and (41.67±1.18) ng/ml, respectively ($p<0.05$). The patients with decompensated heart failure after non-STEMI from group I had a copeptin level of (18.13±0.10) pg/ml before treatment and probably decreased to levels of (16.29±0.15) pg/ml and (15.09±0.14) pg/ml after 1 and 2 months under the influence standard therapy.

Conclusions. We found the dependence of copeptin and ST2 levels on decompensated HF in the early and late post-infarction periods. It was established that the use of the therapy with a combination of the studied drugs led to a more intense decrease in serum copeptin, compared to therapy with succinic acid, arginine drugs, and standard therapy ($p<0.05$). Using a differentiated treatment algorithm for patients with decompensated heart failure in the post-infarction period, copeptin and ST2 in blood serum increases the effectiveness of treatment and prevents complications.

Keywords: myocardial infarction, decompensated heart failure; ST2, copeptin succinic acid, arginine preparations.

DOI: 10.21303/2504-5679.2022.002683

1. Introduction

Our understanding of the causes, diagnosis and treatment of acute myocardial infarction (AMI) has evolved significantly over the last 40 years [1]. Over the last 10 years, the definition of this pathological condition has been formulated. According to the definition, this diagnosis requires a rising and/or falling pattern of a sensitive muscle-injury marker - troponin T or I, with at least one value exceeding the 99th percentile upper reference limit and supportive evidence in the form of clinical signs [2]. Even though the significant advances in treating AMI, post-infarction heart failure (HF) remain one of the leading causes of readmission and death [3].

HF is a chronic and progressive clinical syndrome caused by structural and functional cardiac abnormalities displaying the altered function of the left ventricle (LV) [4]. Despite the ambiguity of a definition, clinical presentation similar to other cardiac disorders, undeniably high risk of cardiovascular mortality, recurrence of decompensation worsening the patient's condition, and rehospitalizations, this specific condition is of great importance. These factors and the high risk of adverse cardiovascular events emphasize the importance of improving the diagnostic methods for this syndrome at its development and decompensation stages, especially in patients with a history of AMI [5, 6].

The sudden onset and progression of HF symptoms characterizes decompensated HF. Although HF is the most common cause of hospital admissions, especially in older patients, knowledge of its pathophysiology and treatment is scarce [7]. Despite the widespread availability of evidence-based pharmacological treatments and therapeutic methods, many patients suffer from a functional impairment, poor quality of life, and early HF-related deaths. Patients with HF may experience a wide range of symptoms associated with increased cardiac filling pressure and/or decreased cardiac output, ranging from asymptomatic to severe functional impairment [8, 9]. Patients with decompensated HF are readmitted due to hypotonia, deterioration of renal function, dyspnea at rest, hemodynamically insignificant arrhythmia, increased congestion, and electrolyte disturbances [10]. As the patient's condition deteriorates rapidly, the search for measures that would help determine the need for readmission to choose the further strategy for managing this cohort of patients is of great relevance. For this purpose, biomarker diagnosis of decompensated HF in the post-infarction period is promising.

Suppression tumorigenicity 2 (ST2) is a member of the interleukin (IL)-1 receptor superfamily. The main biologic isoforms are the transmembrane which affects cardiomyocytes via IL-33 ligand with its antihypertrophic and antifibrotic properties, and the soluble isoform (sST2), which acts as a decoy receptor blocking IL-33 signalling [11].

ST2 has not previously been considered a diagnostic marker of HF; however, elevated levels of this indicator point to acute and chronic HF-related deaths, irrespective of the cause of HF development. The level of sST2, along with other biomarkers, provides additional value in predicting sudden death in patients with HF and LV failure [12]. IL-33 can function as both pro- and anti-inflammatory cytokine depending on the costimulatory factors. In addition, IL-33 exerts cardioprotective functions [13]. The soluble form of ST2 is released into the bloodstream and acts as a decoy receptor for IL-33 blocking its effects. Thus, an increased concentration of ST2 weakens the systemic and biological effects of IL-33 [14], while sST2 may exacerbate cardiac hypertrophy, fibrosis, and LV dysfunction [15]. This peptide has a clear prognostic value in patients with decompensated HF and acute coronary syndrome [16].

Copeptin is a C-terminal fragment of the precursor pre-pro-vasopressin and a surrogate marker of vasopressin [17]. In contrast to vasopressin, copeptin is very stable in plasma at room temperature and easy and robust to measure. In the Leicester Acute Myocardial Infarction Peptide (LAMP) study, the prognostic value of copeptin and its precursor – pro-atrial natriuretic peptide, was evaluated. The study has found that patients after MI have marked activation of the vasopressin system and copeptin is a prognostic predictor of HF development and death, independent of traditional risk factors. Copeptin as a diagnostic parameter is relevant in cardiovascular and renal diseases; its determination is currently considered a positive method compared to arginine-vasopressin [18].

Vasopressin is a hormone released in response to stress to adapt and renew homeostatic balance; its main function is regulating the body's intravascular pressure and water balance [19]. After AMI, vasopressin is thought to enhance peripheral vasoconstriction, thereby increasing ventricular wall afterload and tension and protein synthesis in the cell, leading to LV hypertrophy and coronary artery narrowing [20].

From the standpoint of evidence-based medicine, significant progress has been made in the treatment of CHF, as well as its decompensation. The main treatment directions of this pathological condition include inotropic stimulation of the myocardium and hemodynamic and neurohumoral unloading of the heart [21].

Energy deficit and various electrophysiological, vascular, and hemodynamic effects lead to even greater neurohumoral activation, cytokine activation, development of immune inflammation, disruption of fibrinolysis, and even greater damage to cardiomyocytes and intercellular space. The consequence of these complications is the progression of LV remodelling with subsequent progression of cardiac dysfunction [22].

Among synthetic cardioprotectors, the group of oxypyridines attracts attention. Succinic acid (butanedioic acid, ethane-1,2-dicarboxylic acid) is a product of the fifth reaction and a substrate of the sixth reaction of the tricarboxylic acid cycle is constantly formed in the body and is oxidized in the citrate cycle with the formation of a large amount of energy that is stored in the form of ATP, as well as preparations of the L-arginine group [23].

Modern therapeutic approaches are still aimed at reducing the load on the heart and improving its contractility, which undoubtedly increases the energy expenditure of an already energy-depleted heart. In this focus, it is appropriate to search for means to determine the effectiveness and receptivity of treatment by a specific patient to improve his condition.

The aim of the research is to increase the efficiency of diagnostic methods aimed at finding means to improve the treatment of patients with decompensated heart failure in the post-infarction period.

2. Materials and methods

The study was performed based on the Regional Clinical Cardiology Centre, infarction department No2 and rehabilitation during the 2017–2020 years.

This study is based on an examination of 120 patients with decompensated HF (60 patients with STEMI and 60 with non-STEMI). Patients with previous STEMI complicated by decompensated heart failure were divided into groups: Group I: patients with STEMI who received standard therapy (ST) following the protocols of the Ministry of Healthcare of Ukraine (beta-blockers, ACE inhibitors, double antiplatelet therapy (acetylsalicylic acid + clopidogrel), nitrates, statins) (n=15); Group II: patients with previous STEMI, who, in addition to ST, got added succinic acid 100 mg intravenously by drip infusion 3 times a day (5 days), intramuscularly 100 mg 3 times a day (from 6th to 14th day) with the transition to taking the drug orally 100 mg (1 capsule) 3 times a day from the 15th day of treatment up to 2 months. (n=15); Group III: patients with previous STEMI who were prescribed L-arginine 100 ml intravenously as a drip once a day during the first 10 days, with the transition to the internal administration of 5 ml (one measuring spoon) 3 times a day from 11th day of treatment up to two months in addition to the standard therapy (n=15); Group IV: patients with STEMI who were treated with a combination of the standard therapy, L-arginine and succinic acid according to the proposed scheme (n=15).

60 patients with non-STEMI were divided into 4 similar groups.

The studied groups were homogeneous in terms of age, sex, the severity of the course of the disease, duration of the post-infarction period, and the presence of clinical manifestations of decompensation.

The members of the Ethics Commission (extract from protocol No. 10 dated January 11, 2019) at the Ivano-Frankivsk National Medical University decided that this study would not contradict the main provisions of the GCP, Convention Council of Europe on human rights and biomedicine, the Helsinki Declaration of the World Medical Association on ethical principles for the conduct of scientific medical research with the participation of man and the Law of Ukraine «On Medicines». Therefore, all patients signed an informed consent to participate in a clinical trial.

The patients were observed on the first day after hospitalization, after 1 and 2 months after treatment.

The study did not include patients with acute and chronic inflammatory diseases of the cardiovascular system (endocarditis, myocarditis, pericarditis), severe heart rhythm and conduction disorders, a history of stroke and transient ischemic attack, severe renal failure, with a high risk of bleeding (thrombocytopenia, cranial-brain injury in the anamnesis, gastrointestinal bleeding up to one year ago and any internal bleeding at present).

Copeptin serum levels were assayed using the EK 065-32, EIA Copeptine kit (RayBiotech, Inc., USA).

ST-2 in blood serum was determined with the help of the Presage ST-2 kit (Critical Diagnostics, USA). The level of ST2 was determined in ng/ml.

3. Research results

We analysed the effect of therapy on the level of ST2 in the blood serum of examined patients with STEMI and non-STEMI complicated by decompensated heart failure.

According to the data in **Table 1**, all the treatment regimens proposed by us led to a significant decrease in the level of this peptide in blood serum after the end of the treatment.

In patients of group I who received basic therapy drugs, the average ST2 concentration was (49.47±1.77) ng/ml before treatment. After 1 and 2 months of therapy, it was (44.92±1.22) ng/ml and (41.67±1.18) ng/ml, respectively ($p<0.05$).

When succinic acid was added to the basic therapy, the value of this indicator before treatment was equal to (49.00±1.25) ng/ml and probably decreased by 22.31 % and 26.67 % after 1 and 2 months of therapy and was (38.07±2.28) ng/ml and (35.93±1.79) ng/ml ($p<0.05$).

In the examinees of group III, who, along with standard treatment, used arginine preparations, the level of ST2 was (37.07±1.91) ng/ml after two months of treatment, which was reliably lower by 22.98 % from the corresponding values before the start of therapy (48.13±0.99) ng/ml ($p<0.05$).

In patients of group IV, the concentration of ST2 was (49.40±1.12) ng/ml before treatment and probably decreased by 28.80 % and 41.30 % and amounted to (35.13±2.47) ng/ml and (29.00±2.98) ng/ml, respectively ($p<0.05$) after 1 and, especially, after 2 months of therapy with the combined use of succinic acid and arginine preparations.

Table 2 shows the results of the analysis of the therapeutic effect in patients after non-STEMI complicated by decompensated HF on the ST2 level.

As it is indicated in the **Table 2**, in patients who received basic therapy, the level of ST2 in blood serum was (48.93±1.83) ng/ml and probably decreased by 18.11 % to the level of (40.07±2.43) ng/ml ($p<0.05$) after the end of treatment.

We also noted a decrease in the ST2 level in patients who received succinic acid besides standard therapy.

Table 1

Dynamics of ST2 indicators in patients with decompensated heart failure after ST-elevation myocardial infarction in the course of treatment

Group of patients	Standard treatment (n=15)			Standard treatment + succinic acid (n=15)			Standard treatment + arginine preparations (n=15)			Standard treatment + succinic acid + arginine preparations (n=15)		
Value	Before treatment	1 mon	2 mon	Before treatment	1 mon	2 mon	Before treatment	1 mon	2 mon	Before treatment	1 mon	2 mon
ST2, ng/ml	49.47±1.77	44.92±1.22 p*	41.67±1.18 p*, p1*	49.00±1.25 p*	38.07±2.28 p*	35.93±1.79 p*, p1*	48.13±0.99	42.13±2.61 p*	37.07±1.91 p*, p1*	49.40±1.12	35.13±2.47 p*	29.00±2.98 p*, p1*
Δ, %		–9.19	–15.77		–22.31	–26.67		–12.47	–22.98		–28.80	–41.30

*Note: difference probability: p compared to indicators before treatment, p1 compared to indicators after 1 month of treatment; * – $p<0.05$, ** – $p>0.05$. Δ is an increase or decrease (-) of the value during the treatment as a percentage of the values before the start of treatment*

Here, this indicator was (48.80±3.32) ng/ml before treatment and (37.13±1.92) ng/ml and (34.13±2.03) ng/ml, respectively ($p<0.05$).

In patients of group III, the level of ST2 was (48.93±2.43) ng/ml before the start of therapy; and (39.80±2.86) ng/ml and (36.07±2.25) ng/ml ($p<0.05$) after one and two months of its course, which was lower by 18.66 % and 26.28 % compared to the initial data.

In group IV of examinees, the concentration of ST2 in blood serum was (48.53±3.93) ng/ml before treatment and probably decreased by 32.15 % and 42.30 % after 1 and 2 months of therapy and was (32.93± 2.12) ng/ml and (28.00±2.39) ng/ml, respectively ($p<0.05$).

Table 2

Dynamics of ST2 indicators in patients with decompensated heart failure after a non-ST elevation myocardial infarction during treatment

Group of patients	Standard treatment (n=15)			Standard treatment + succinic acid (n=15)			Standard treatment + arginine preparations (n=15)			Standard treatment + succinic acid + arginine preparations (n=15)		
Value	Before treatment	1 mon	2 mon	Before treatment	1 mon	2 mon	Before treatment	1 mon.	2 mon.	Before treatment	1 mon	2 mon
ST2, ng/ml	48.93±±1.83	43.33±1.80 p*	40.07±2.43 p*, p1*	48.80±±3.32	37.13±1.92 p*	34.13±2.03 p*, p1*	48.93±±2.43	39.80±2.86 p*	36.07±2.25 p*, p1*	48.53±±3.93	32.93±2.12	28.00±2.39
Δ, %		–11.45	–18.11		–23.91	–30.06		–18.66	–26.28		–32.15	–42.30

*Note: probability of difference: p compared to indicators before treatment, p1 compared to indicators after 1 month of treatment; * – p<0.05, ** – p>0.05. Δ is an increase or decrease (-) of the value during the treatment as a percentage of the values before the start of treatment*

We analysed the effect of therapy on the copeptin level in blood serum.

As it is shown in **Fig. 1**, the patients of group I had the average copeptin value in blood serum (18.13±0.12) pmol/l before treatment and probably decreased to (16.47±0.07) pmol/l and (15.23±0.11) pmol/l under the influence of treatment with standard therapy after 1 and 2 months (p<0.05).

The combination of standard therapy and succinic acid contributed to a more intensive reduction in this value from (18.07±0.13) pmol/l to (13.15±0.18) pmol/l after the end of treatment (p<0.05).

In the subjects of group III who received arginine preparations on the background of standard therapy, the average copeptin level in blood serum was (18.15±0.06) pmol/l before the start of treatment. At the end of the therapeutic course, this indicator was (14.11±0.21) pmol/l (p<0.05).

Thus, the use of succinic acid contributed to a more significant decrease in the copeptin level than arginine preparations.

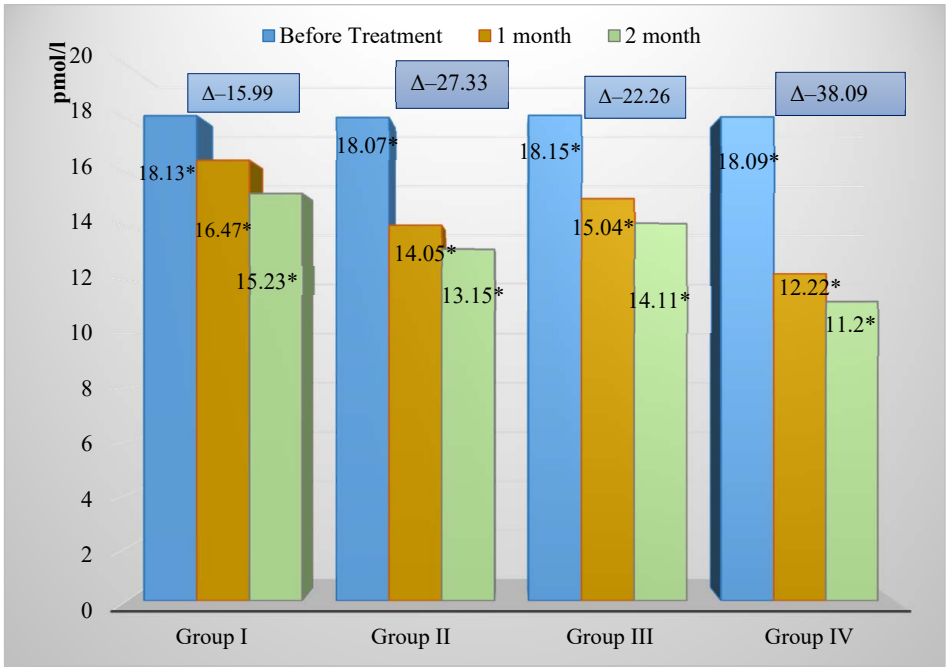

Fig. 1. The effect of therapy on the concentration of copeptin in the blood serum in patients with STEMI and decompensated HF. Probability of difference before and after treatment: * – p<0.05, ** – p>0.05; Δ is an increase or decrease (-) of the indicator during the treatment as a percentage of the values before the start of treatment

The average value of this value was (18.09±0.15) pmol/l before treatment and decreased by 32.45 % and 38.09 % after 1 and 2 months of therapy and was (12.22±0.14) pmol/l and (11.20±0.17) pmol/l, respectively ($p<0.05$).

As it is shown in **Fig. 2**, the patients with decompensated heart failure after non-STEMI from group I had the copeptin level (18.13±0.10) pmol/l before treatment and probably decreased to levels of (16.29±0.15) pmol/l and (15.09±0.14) pmol/l after 1 and 2 months under the influence standard therapy.

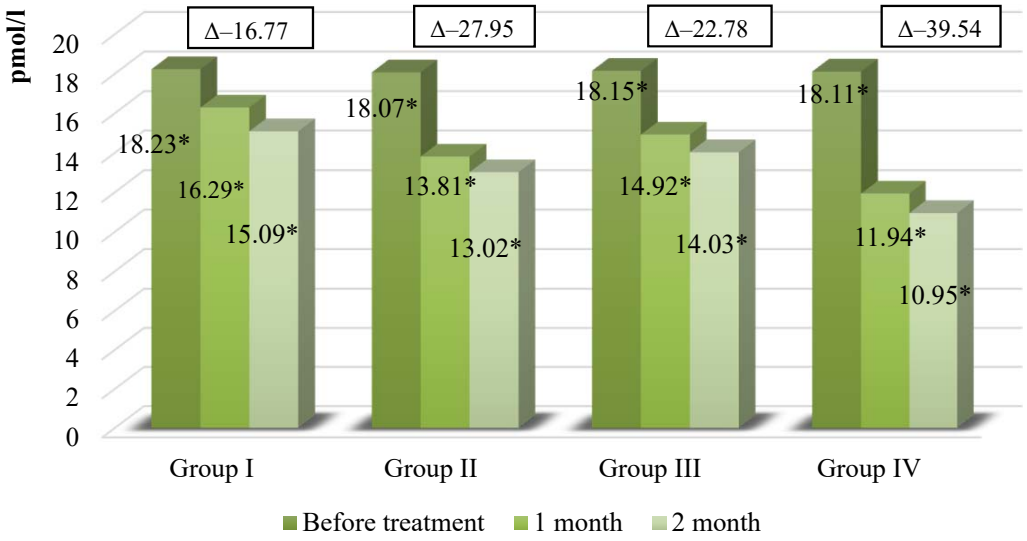

Fig. 2. The influence of therapy on the copeptin concentration in the blood serum in patients with previous non-STEMI and decompensated HF. Probability of difference before and after treatment: * – $p<0.05$, ** – $p>0.05$; Δ is an increase or decrease (-) of the indicator during the treatment as a percentage of the values before the start of treatment

The combination of standard therapy and succinic acid contributed to the more intense reduction of this value from (18.07±0.15) pmol/l to (13.02±0.14) pmol/l after the end of treatment ($p<0.05$).

In patients of group III who received arginine preparations on the background of standard therapy, the average copeptin level was (18.15±0.06) pmol/l before the start of therapy and (14.03±0.24) pmol/l ($p<0.05$) at the end of the treatment course.

Therefore, succinic acid turned out to be more effective along with arginine drugs and standard drugs for reducing the concentration of this value.

It was established that the use of the therapy with a combination of the studied drugs led to a more intense decrease in serum copeptin, compared to therapy with succinic acid, arginine drugs, and standard therapy ($p<0.05$).

Thus, the average value of this indicator before treatment was (18.11±0.14) pmol/l. However, after the completion of the two-month course of therapy, it was (10.95±0.09) pmol/l, which was probably lower compared to similar values before treatment.

4. Discussion

In the post-infarction period, the ventricular wall undergoes stress-induced hypertrophic changes. Molecular mechanisms involved in post-infraction remodelling have yet to be fully understood [24]. Therefore, a clear prediction of HF decompensation development is critical for the timely referral of such patients to speciality cardiac hospitals, proper management of their condition, and appropriate patient follow-up. Several strategies to evaluate the risk of adverse events in patients with HF in the post-infarction period have been developed; however, they are significantly limited from the perspectives of physicians making decisions on such patients' hospitalization, emergency physicians, family physicians, and cardiologists [25].

Even though patients with HF and its decompensation have a clear diagnostic and therapeutic strategy, there is a constant progression of both the clinical stage and its FC [26]. Therefore, an expanded understanding of HF management in the post-infarction period includes the management of patients in whom the symptoms of its decompensation remain pronounced, despite correct treatment and intermediate LV systolic function, according to the LVEF index [27].

A clear prediction of the development of HF decompensation is especially important for the timely referral of such patients to specialized cardiology centres, proper treatment planning, and follow-up of such individuals [28].

Several strategies concerning the risks of adverse events in patients with HF in the post-infarction period have been developed. However, they are significantly limited from the point of view of physicians who make decisions about the hospitalization of such patients, emergency and family care physicians, and cardiologists [29].

A possible clinical application in patients with HF, which should be taken into account when evaluating a biomarker, is the using diagnostic assessment and risk stratification for such patients in detecting the development of HF from the point of view of monitoring the prognosis of the response to the treatment [30].

Study limitations. A limitation of the study is that immunoenzymatic markers are trying to occupy and play their role in diagnosing the appearance of decompensated heart failure that occurred in the post-infarction period. The possibility, expediency and necessity of their use for quality control and the possibility of personalizing the treatment of this contingent of patients are important.

Prospects of further research. The study of changes in these parameters on the background of managing decompensated HF in the post-infarction period is promising to personalize and improve treatment strategies for this cohort of patients.

5. Conclusions

Decompensated HF in the post-infarction period is characterized by an aggravated clinical course manifested by a deterioration in the clinical condition, a decrease in exercise tolerance, a deterioration in its perception, a decrease in cardiac bioelectric activity, higher HF functional class, signs of LV hypertrophy, more frequent rhythm and conduction disorders.

We found the dependence of copeptin and ST2 levels on decompensated HF in the early and late post-infarction periods.

It was established that the use of the therapy with a combination of the studied drugs led to a more intense decrease in serum copeptin, compared to therapy with succinic acid, arginine drugs, and standard therapy ($p<0.05$).

The use of a differentiated treatment algorithm for patients with decompensated heart failure in the post-infarction period, depending on the presence of concomitant pathology, indicators of central hemodynamics and geometry of left ventricular contraction, tolerance to physical exertion, copeptin and ST2 in blood serum increases the effectiveness of treatment and prevents the occurrence of complications.

Conflicts of interest

The authors declare that there is no conflict of interest in relation to this paper, the published research results, the financial aspects of conducting the research, obtaining and using its results, and any non-financial personal relationships.

Funding

The study was performed without financial support.

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Received date 16.08.2022
Accepted date 20.09.2022
Published date 30.09.2022

How to cite: *Vakaliuk, I., Levandovska, K., Tymochko, N. (2022). ST2 and copeptine – modern biomarkers for monitoring the effectiveness of treatment of decompensated heart failure in patients after acute myocardial infarction. EUREKA: Health Sciences, 5, 30–38. doi: http://doi.org/10.21303/2504-5679.2022.002683*