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Early prescription of trimetazidine in patients with acute coronary syndrome after incomplete myocardial revascularization: the assessment of the prognosis

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Abstract

Objective. *To assess the effectiveness of the early prescription of trimetazidine in patients with acute coronary syndrome (ACS) and established multivessel coronary artery disease syndrome after incomplete myocardial revascularization.*

Materials and methods. *This open-label randomized study included 100 patients with multivessel coronary artery disease syndrome. The randomization was blind into two equal groups: the study group (received 70 mg/day trimetazidine during the entire observation period) and the control group (did not receive trimetazidine). Echocardiography (EchoCG) was performed according to generally accepted technique on the ACUSON 128 XP 10 apparatus (USA) with the study of the following characteristics: left atrium and right ventricle anterior-posterior diameter, end-systolic and end-diastolic diameter of the left ventricle (LV), interventricular septal thickness, left ventricular (LV) posterior*

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wall thickness, end-systolic and end-diastolic volumes, as well as LV ejection fraction (EF) according to the Simpson method.

Results. *According to the results of EchoCG, mean LV EF was 50.72±6.89 % in the modified-release trimetazidine (trimetazidine- MR) group and 52.69± 7.5 % in the comparison group. In addition, significant changes in the Echo CG linear dimensions were diagnosed, and in 100 % of cases there were LV diastolic dysfunction of varying severity. Patients with ACS with early prescription of trimetazidine, required significantly fewer repeat myocardial revascularizations. According to statistical analysis, the Kaplan — Meier curves significantly diverged at the 12th month of study. Thus, the survival coefficient in actively treated patients was 0.72, and 0.54 — in the control group, the differences between groups were 18 % in favor of the trimetazidine-MR use.*

Conclusion. *Early prescription of trimetazidine-MR in patients with ACS and incomplete myocardial revascularization is associated with the decrease of cardiovascular complications during the first year of treatment, which should be considered as an important component of rehabilitation after endovascular intervention.*

Keywords: *trimetazidine-MR, acute coronary syndrome, incomplete myocardial revascularization.*

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Introduction

Today cardiovascular complications (CVCs) are the main causes of death according to the statistics of the most countries including Russian Federation. Coronary heart disease (CHD) and many other atherosclerotic complications are still the leading causes of death and disability. Surgical treatment of coronary revascularization can improve the survival rate of patients with CHD and today are the primary treatment choice for patients with this pathology [1]. However, despite the improvement of the technology of invasive cardiology, there are still several unresolved issues in clinical practice, including the so-called incomplete revascularization. This approach is commonly observed in patients with acute coronary syndrome (ACS) and multivessel coronary artery disease, at the early stages of its onset, and is associated with the resumption of blood flow in the target artery. This type of revascularization has a number of advantages, but also has significant number of disadvantages, therefore, it has both supporters and opponents. The controversy about the effectiveness or ineffectiveness of incomplete revascularization can continue indefinitely, which will not make it easier for the clinical practitioners who will receive such patients for further treatment. Currently, these patients receive standard therapy, often independent of the degree of restoration of coronary blood flow. However, it should be noted that in this case, even in patients with pronounced positive clinical effect, areas of ischemic myocardial tissue still remain, therefore, additional pathogenetic medications should be considered. Pharmacological therapy prescribed for patients with CHD primary include symptomatic agents. For example, "metabolic" antianginal medication, the modified-release (MR) formulation of trimetazidine, that has been used for a long time in the complex therapy of CHD and showed its effectiveness [2]. Moreover, in recent years, the effect of trimetazidine-MR on cumulative survival rate and quality of life in patients with CHD has become the subject of separate study [3]. Therefore, studies evaluating the prognostic value of this medication in patients with CHD seem to be very relevant.

Objective

To assess the effectiveness of the early prescription of trimetazidine in patients with ACS, established multivessel coronary artery disease and incomplete revascularization.

Materials and methods

The study was conducted in accordance with Good Clinical Practice standards and Declaration of Helsinki principles. The study protocol was approved by the Ethics Committees of all participating clinical centers. Written informed consent was waived from all participants prior to the inclusion into the study.

This open randomized study included 100 patients with multivessel CHD that was defined as at least one hemodynamically significant stenosis (over 50 % in diameter) in at least two main arteries (anterior interventricular artery (AIA), right coronary artery, circumflex artery (CA) in patients with the right type of coronary circulation or AIA and CA — in patients with

the left type) and / or the presence of over 50 % stenosis of the main trunk of the left coronary artery. In all cases, ACS was identified, confirmed by the clinical picture, ECG data and/or significant increase of specific cardiac enzymes. Patients were divided into groups after percutaneous transluminal angioplasty (PTA) and stenting at least in 24 hours after the manifestation of symptoms.

The exclusion criteria were: the presence of concomitant diseases that could affect the final results, including decompensation of diabetes mellitus (DM), uncontrolled arterial hypertension (AH), kidney and liver diseases accompanied by the impaired function of these organs. The exclusion criterion was any planned surgical intervention (primarily cardiac surgery) within 4–6 months after the onset of ACS symptoms. The inclusion criterion was optimal pharmacological treatment.

Randomization was performed in blind manner into two equal groups: the study group (received 70 mg/day trimetazidine during the entire observation period) and the control group (did not receive trimetazidine). The follow-up period was 365 days. The clinical characteristics of the patients are presented in Table 1.

EchoCG was performed according to the generally accepted technique on the ACUSON 128 XP 10 apparatus (USA) and assessed the following parameters: anteroposterior dimension of the left atrium, right ventricle, end-systolic and end-diastolic dimensions of the left ventricle (LV), interventricular septal thickness, LV posterior wall, end-systolic and end-diastolic volumes and left ventricular ejection fraction (LV EF) according to Simpson's method.

Statistical analysis was performed using STATISTICA v.10.0, MS Excel 7.0 software. The normally distributed data were presented as M±m, where M is the mean, m is the standard error, the χ^2 criterion was used to assess the differences between the frequency of certain categorial variables between groups. The probability of adverse event was investigated using the Kaplan-Meier method; the differences between groups were assessed using the Log-Rank test, Breslow, and Taron-Ware tests. The following parameters were assessed in the long-term period: CVC frequency, death, myocardial infarction (MI), repeated interventions. The method of four-field table for case-control studies by Mantel — Haenzel was used to calculate the relative risk coefficient and 95 % confidence interval (CI).

Results

All study participants were divided into equal groups, 50 of them received 35 mg of trimetazidine-MR 2 times a day; 50 patients were included into the control group. The average age of patients from group 1 was 59.54±7.47 years, from group 2–60.36±7.05 years ($p>0.05$). The groups did not differ significantly by the main clinical data, including morphofunctional cardiac parameters (Tables 1, 2). According to the results of EchoCG, average LV EF was 50.72±6.89 % in the trimetazidine-MR group and 52.69±7.5 % in the comparison group. In addition, significant difference in the linear dimensions of the heart chambers were detected, and all the patients had LV diastolic dysfunction of various severity.

The groups included patients with unstable angina and acute myocardial infarction (AMI) with and with-

Table 1. **Initial clinical characteristics of the studied groups**

Parameter	Trimetazidine, n=50		Control, n=50		p
Age	59.32±7.71		59.84±7.3		0.896
The duration of CHD, years	3.2±1.6		2.9±1.9		0.224
Body mass index (kg/m^2)	23.7±2.2		22.9±2.5		0.894
Female gender	17	34 %	15	30 %	0.668
Male gender	43	86 %	45	90 %	0.538
The history of MI	8	16 %	7	14 %	0.701
The history of AH	23	46 %	27	54 %	0.322
Diabetes mellitus	4	8 %	5	10 %	0.175
Smoking	11	22 %	10	10 %	0.788
Statins	18	36 %	23	46 %	0.118
Aspirin	31	62 %	34	68 %	0, 554
ACE inhibitors	22	44 %	24	48 %	0.721
Calcium antagonists	11	22 %	13	26 %	0.483

Table 2. **The main clinical and instrumental parameters of patients with ACS included into the study**

Parameter	Trimetazidine, n=50		Control, n=50		χ^2	p
SBP (mmHg)	138.6± 7.4		141.7± 8.3		0.076	0.775
DBP (mmHg)	78.3± 9.0		77.4± 7.8		69	0.813
Average BP (mmHg)	104.5± 3.4		106.0± 2.7		0.048	0.917
HR (beats/min)	72.2± 4.9		76.1± 3.8		0.376	0.527
LV EF (%)	50.72± 6.89		52.69± 7.5		0.048	0.911
Unstable angina	11	22 %	10	20 %	0.060	0.806
Acute MI with ST-segment elevation	30	60 %	29	58 %	0.041	0.839
Acute MI without ST-segment elevation	9	18 %	11	22 %	0.250	0.617
Anterior MI	18	46.2 %	20	50 %	0.328	0.511
Posterior MI	21	53.9 %	20	50 %	0.367	0.532

Table 3. **The severity of CHD in study participants**

Parameter	Trimetazidine-MR, n=50		Control, n=50		χ^2	p
Killip class I acute heart failure	32	64 %	30	60 %	0.170	0.680
Killip class II acute heart failure	7	14 %	10	20 %	0.638	0.424
Killip class III–IV acute heart failure	0	0 %	0	0 %	—	—
Hemodynamically significant stenoses (LCA trunk>50 %, other arteries>75 %) of two vessels	26	52 %	20	40 %	1.449	0.229
Hemodynamically significant stenoses (LCA trunk>50 %, other arteries>75 %) of three vessels	13	26 %	18	36 %	1.169	0.280
Hemodynamically significant stenoses (LCA trunk>50 %, other arteries>75 %) of more than three vessels	11	22 %	12	24 %	0.056	0.812

out ST-segment elevation. The groups were comparable by the frequency the pathology, and its severity. Acute heart failure (AHF) severity class 1 prevailed in patients with AMI, which was diagnosed in over 60 % of patients in each group; the rest of the patients had AHF severity class II. LV EF in group I: min. — 28 %, max. — 70 %, average — 50.72± 6.89 %. EF in group II: min. — 30 %, max. — 79 %, average — 53.62±7.51 %. According to coronary angiogram (CAG) data, hemodynamically significant stenoses (left coronary artery trunk> 50 %, other arteries>75 %) of two vessels were detected in most patients (Table 3).

Initially, 50 PTA with stenting and incomplete revascularization (mainly target coronary artery) were performed in both groups. During 1-year follow-up CAG was additionally required in 8 patients from in group I (16 %), in 18 (36 %) from group II (χ^2=5.19, p= 0.023). PTA was performed in 6 (12 %) patients from the main group and in 15 (30 %) — from the control group (χ^2= 4.88; p=0.027). As the result, patients with ACS with early prescription of trimetazidine, required significantly fewer repeat myocardial revascularizations. The use of sirolimus-eluting stents was comparable in both groups — in group I they were used in 3 (5.36 %) patients out of 56 (100 %), in group II — in 5 (7.69 %) out of 68 (100 %) (χ^2= 0.203, p= 0.653).

The surgical intervention with complete myocardial revascularization including coronary artery bypass grafting with *cardiopulmonary bypass machine* was required in 8 (16%) patients from the main group and in 7 (14%) patients from the control group (χ^2 = 0.460, p = 0.498). Repeated hospital admissions due

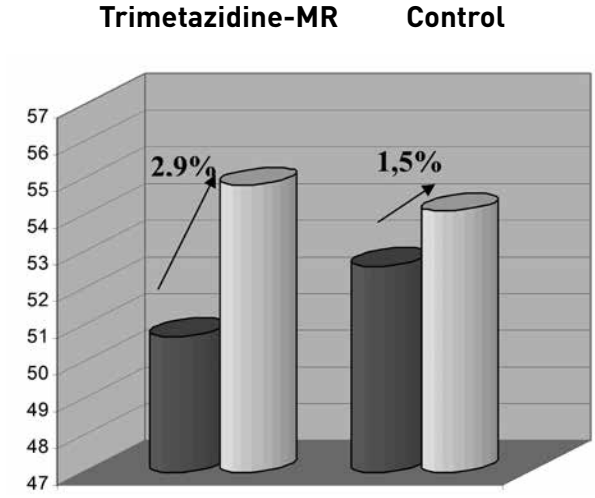

Figure 1. The dynamics of LV EF in study participants

to CHD decompensation were required in 9 (18%) patients from the main group, and in 21 (42%) patients from the control group (χ^2 = 3.673, p = 0.055). During the 12-month follow-up period, the LV EF increased in both groups, mostly in patients receiving trimetazidine (2.9% and 1.5%), but without statistically significant difference (Figure 1). The survival rate during admission was 100% in both groups. The incidence of MI also did not differ between groups – 6 (12%) patients from the main group and 11 (22%) – from the control group (χ^2 = 1.772, p = 0.183).

During the 12-month follow-up, we assessed the survival rate of patients after ACS without adverse events. The analysis was carried out by the Kaplan — Meier method. The observation period was set as the period from the beginning to the end of the follow-up or until the endpoint for each individual patient. The endpoints were: all-cause death, nonfatal MI, acute cerebrovascular accident, decompensation of angina pectoris, the need for cardiac surgery, any admission due to CVD.

According to statistical analysis, the Kaplan — Meier curves significantly diverged at the 12th month of observation. Thus, the coefficient of survival in patients during active treatment was 0.72, and in the control group — 0.54, the difference between the groups was 18 % with the superiority of trimetazidine-MR group (Fig. 2). The probability of error was assessed by the Log-Rank test p= 0.048, with RR — 0.61; 95 % CI 0.36–0.98 (p<0.05). Therefore, in our study, there was significantly lower frequency of CVC in patients with ACS who were administered with "metabolic" antianginal medication after PTA and stenting with incomplete revascularization.

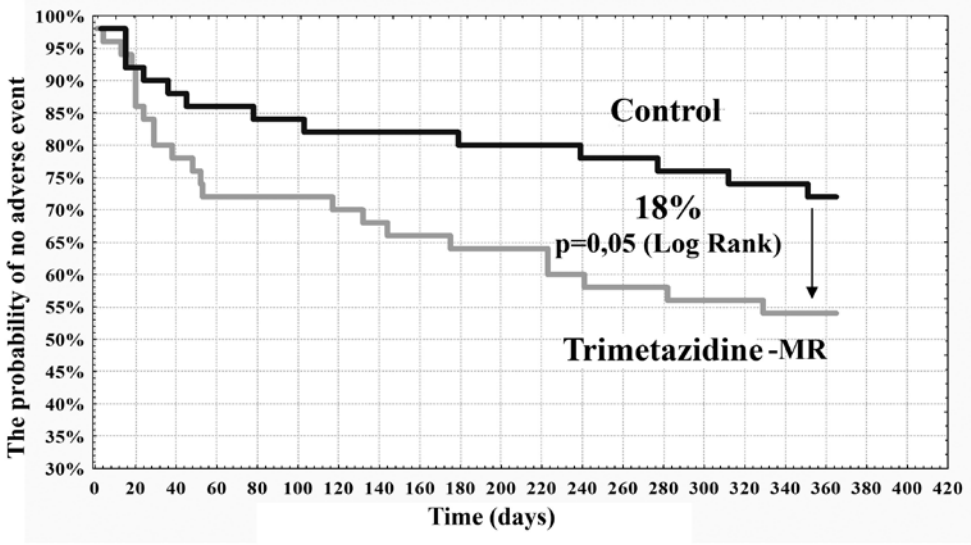

Figure 2. The probability of no adverse cardiovascular events in the study

Discussion

Anti-ischemic agent used in myocardial protection trimetazidine has been successfully used for a long time. Its high efficiency has been proven, but it is usually used as additional tool to enhance basic pharmacotherapy [4]. According to Russian guidelines for the diagnosis and treatment of stable CHD, trimetazidine-MR can be used at any stage of treatment to enhance the antianginal efficacy of hemodynamically active medications, as well as an alternative in case of their intolerance or the presence of contraindications for their use. Thus, the additional prescription of trimetazidine-MR to β-blockers leads to significantly more pronounced antianginal effect compared with the additional prescription of long-acting nitrate. Trimetazidin-MR increases the coronary flow reserve, prevents the consequences of ischemia, reduces the frequency of angina episodes, improves myocardial contractility and increases exercise tolerance in patients with CHD [5, 6]. The mechanism of trimetazidine-MR anti-ischemic effect is associated with the increase of glucose metabolism compared with the metabolism of fatty acids, with the suppression of fatty acid ß-oxidation and the increase of pyruvate oxidation — a glucose metabolite during the ischemia, and, therefore, it maintains of the required level of adenosine triphosphate in cardiomyocytes, decreases intracellular acidosis and excessive accumulation of calcium ions [7].

The use of trimetazidine in patients with ACS is being actively investigated. It is known that this medication can limit cardiac reperfusion injury and, accordingly, reduce myocardial hibernation processes, as well as the frequency of reperfusion arrhythmias [8]. In addition, the preventive use of this cytoprotector reduces the manifestations of transmural ischemia that develops during PTA, and can minimize ECG signs of reperfusion injury[9] and its severity, assessed by the levels of cardiac-specific biomarkers after coronary artery bypass graft surgery, and, therefore, positively affects the prognosis [10].

According to the " Consensus on the role and place of the myocardial cytoprotector Trimetazidine in the treatment of patients with chronic forms of CHD" [11], the use of this antianginal agent before surgical interventions (coronary artery bypass graft surgery, percutaneous coronary intervention) reduces the severity of myocardial injury, that is confirmed by the significant decrease of cardiac-specific biomarkers in the blood and the frequency of perioperative cardiac arrhythmias. Long-term therapy with trimetazidine after surgery has positive effect on the frequency of angina episodes and admissions due to ACS, significantly reduces the severity of myocardial ischemia, including silent myocardial ischemia, the rate of coronary artery restenosis, increases exercise tolerance, quality of life and, consequently, affects the survival rate of patients [12, 13].

Trimetazidine is the most studied "metabolic" antianginal medication. Several clinical studies have revealed the significant range its therapeutic mechanisms of action that are not limited only by its effect on cardiomyocytes. To this date, it is known that trimetazidine inhibits LV remodeling by the reduction of oxidative stress, apoptosis and inflammation, and affects the expression of endothelial nitric oxide synthase. It has been shown that trimetazidine can reduce inflammation in the arterial intima. At least two

clinical studies have shown the significant decrease of the serum C-reactive protein concentration during the therapy with this myocardial cytoprotector [14, 15].

Recently, very successful attempts have been made to study the effect of trimetazidine on the elastic properties of the large arteries. The preclinical trials have demonstrated positive effect of trimetazidine-MR on vascular endothelial cells in patients with arterial hypertension, including refractory hypertension, that reduces the severity of endothelial dysfunction. It has been shown that this effect is associated with intracellular signaling pathways, the intracellular calcium ions in particular, the activity of mitogen-activated protein kinases, the decrease of intracellular concentration of free radicals and the increase of the production of vascular endothelial growth factor [16]. Previously, we found that the use of 70 mg / day trimetazidine-MR for 4 months led to significant improvement of endothelium-dependent reactivity in the radial artery by over 32%, compared with the initial parameters. Improvement of the endothelial function developed along with the increase of the myocardial metabolic equivalent of oxygen uptake and the increase of exercise tolerance [17, 18].

The evaluation of the effect of metabolic antianginal therapy on the survival rate and quality of life in patients with cardiac pathology has been performed in number of studies. It should be noted that only one medication from this group, trimetazidine, has an impressive evidence base on its impact on cumulative survival. The METRO study showed that the early prescription of trimetazidine as antianginal therapy in patients with stable angina pectoris (before the development of myocardial infarction) significantly reduces the 6-month risk of death from ACS by 64% compared with other antianginal agents [19]. The KAMIR study included approximately 10 thousand patients with stable CHD with the history of myocardial infarction, and showed that the additional prescription of trimetazidine-MR to basic therapy during one-year follow-up increased survival rate by 69%, due to the decrease of cardiovascular events and mortality [2]. P. Di Napoliet al., according to 2-year follow-up, noted the increase of cumulative survival in patients with ischemic cardiomyopathy after the additional prescription of this myocardial cytoprotector to traditional therapy [3].

According to the results of the meta-analysis by D. Gao et al., that analyzed results of 4 studies, trimetazidine therapy was associated with lower mortality compared with placebo (7.5% of patients versus 27.5%, respectively). The reduction in the risk of death due to chronic heart failure was 0.29 with 95% CI 0.17–0.49 ($p<0.01$). Cardiovascular events and admissions significantly decreased — RR in the trimetazidine group was 0.42 with 95% CI 0.30–0.58 ($p<0.01$) [20]. Previously, we estimated the 6-year survival rate of patients with CHD and heart failure (LV EF less than 40%). The main endpoint in the active treatment group decreased by 15% ($p= 0.044$) with the 0.51 RR and 95% CI of 0.25–0.92 ($p<0.05$). The combined endpoint, that included all-cause mortality, the occurrence of nonfatal MI and stroke during entire observation period, decreased by 15.5% ($p= 0.025$) with RR 0.61 and 95% CI 0.97–0.35 ($p<0.05$) [4].

In this study we investigated the effect of early administration of the myocardial cytoprotector trimetazidine-MR in patients with ACS and incomplete revascularization after PTA and stenting. Currently, this method of blood flow partial restoration is used due to the number of reasons, including technical difficulties with complete revascularization (distal stenosis, the presence of extended occlusions, multivessel lesions in patients with ACS, etc.). Today, there are no clear recommendations for the management of patients after incomplete revascularization; in most cases, standard therapy is recommended after PTA and stenting that initially implies complete restoration of the blood flow. It should be noted that our study included patients with persistent myocardial ischemia. The additional prescription of trimetazidine to standard therapy led to the significant decrease of absolute risk of CVC by 18%.

Conclusion

Thus, early prescription of trimetazidine-MR in patients with ACS and incomplete revascularization is associated with the decrease of CVC during the first year of treatment, which should be considered as an important component of rehabilitation after endovascular intervention.

Conflict of interest: None declared.

References

1. Kotseva K., Wood D., De Backer G. et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. European Journal of Preventive Cardiology. 2016. 23(6): 636–48.
2. Kim J.S., Kim C.H., Chun K.J., Kim J.H., Park Y.H., Kim J., Choi J.H., Lee S.H., Kim E.J., Yu D.G., Ahn E.Y., Jeong M.H. Effects of trimetazidine in patients with acute myocardial infarction: data from the Korean Acute Myocardial Infarction Registry.Clin Res Cardiol. 2013 Dec;102(12): 915–22.
3. Di Napoli P., Di Giovanni P., Gaeta M.A. et al. Trimetazidine and reduction in mortality and hospitalization in patients with ischaemic dilated cardiomyopathy: a post hoc analysis of the Villa Pini d'Abruzzo Trimetazidine Trial. J Cardiovasc Pharmacol. 2007;50 (5): 585–589.
4. Ilyukhin O.V., Tarasov D.L., Ilyukhina M.V., etc. Effect of Trimetazidine on cumulative survival rates in patients with coronary heart disease complicated by chronic heart failure. Heart: a journal for medical practitioners. 2013;12 (6): 355–359. Russian.
5. Vasyuk Yu.A., shalnova S. A., Kulikov K.G., et al. study of PRIMA: Trimetazidine with modified release of the active substance in the treatment of patients with stable angina who have suffered a myocardial infarction. Epidemiological clinical stages. Cardiology. 2008; 48 (12): 10–13. Russian.
6. Zhang N., Lei J., Liu Q., Huang W., Xiao H., Lei H. The effectiveness of preoperative trimetazidine on myocardial preservation in coronary artery bypass graft patients: a systematic review and meta-analysis. Cardiology. 2015;131(2): 86–96.
7. Kallistratos M.S., Poulimenos L.E., Giannitsi S., Tsinivizov P., Manolis A.J. Trimetazidine in the Prevention of Tissue Ischemic Conditions. Angiology. 2019 Apr;70(4): 291–298.
8. Effect of 48-h intravenous trimetazidine on short- and long-term outcomes of patients with acute myocardial infarction, with and without thrombolytic therapy; A double-blind, placebo-controlled, randomized trial. The EMIP-FR Group. European Myocardial Infarction Project-Free Radicals. Eur Heart J. 2000;21 (18): 1537–1546.
9. Ferrari R., Ford I., Fox K., Challeton J.P., Correges A., Tendera M., Widimský P., Danchin N.; ATPCI investigators. Efficacy and safety of trimetazidine after percutaneous coronary intervention (ATPCI): a randomised, double-blind, placebo-controlled trial.Lancet. 2020 Sep 19;396(10254): 830–838.
10. Aksun M., Aksun S., Kestelli M., Kuru V., Tanyeli H.F., Girgin S., Damar E., Golboyu B.E., Karahan N. The postoperative effects of use of trimetazidine before the coronary artery bypass graft surgery. Niger J Clin Pract. 2019 Jul;22(7): 997–1001.
11. Aronov D.M. expert Consensus on the role and place of the myocardial cytoprotector Trimetazidine (Preduktal MV) in the treatment of patients with chronic forms of IHD. Heart: a journal for medical practitioners. 2015; 84(4): 256–260. Russian.
12. Chen J., Zhou S., Jin J. Chronic treatment with trimetazidine after discharge reduces the incidence of restenosis in patients who received coronary stent implantation: A 1-year prospective follow-up study. Int J Cardiol 2014; 174 (3): 634–9.
13. Lopatin Yu.M., Dronova E.N. Clinical and pharmacoeconomical assessment of long-term use of modified release Preductal in patients with ischemic heart disease who underwent percutaneous coronary interventions. Heart: a journal for medical practitioners. 2011; 10(1): 67–7. Russian.
14. Costa L.M.A, Rezende P.C, Garcia R.M.R, Uchida A.H, Seguro L.F.B.C., Scudeler T.L., Bocchi E.A., Krieger J.E., Hueb W., Ramires J.A.F., Filho R.K. Role of Trimetazidine in Ischemic Preconditioning in Patients With Symptomatic Coronary Artery Disease. Medicine (Baltimore). 2015 Aug;94(33): e1161.
15. Marzilli M., Vinereanu D., Lopaschuk G., Chen Y., Dalal J.J., Danchin N., Etriby E., Ferrari R., Gowdak L.H., Lopatin Y., Milicic D., Parkhomenko A., Pinto F., Ponikowski P., Seferovic P., Rosano G.M.C. Trimetazidine in cardiovascular medicine. Int J Cardiol. 2019 Oct 15;293:39–44.
16. Dézsi C.A. Trimetazidine in Practice: Review of the Clinical and Experimental Evidence. Am J Ther. 2016 May-Jun;23(3): e871–9.
17. Inzhutova A.I., Bykov V.V., Novikova T.V., et al. Improvement of endothelial function cytoprotector Trimetazidine in essential and iatrogenic arterial hypertension, called sunitinib. Bulletin of science of Siberia. 2012;4 (3): 291–306. Russian.
18. Lopatin Y.M., Ilyukhin O.V., Ilyukhina M.V. et al. Trimetazidine, but not isosorbide dinitrate, improves endoteliumdependent reactivity of muscular tape arteries in patients with stable angina and heart failure. European Heart Journal. 2014. T. 35. № Suppl. 1. C. 162.
19. Iyengar S.S., Rosano G.M. Effect of antianginal drugs in stable angina on predicted mortality risk after surviving a myocardial infarction: a preliminary study (METRO). Am J Cardiovasc Drugs. 2009;9(5): 293–297.
20. Gao D., Ning N., Niu X. et al. Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. Heart. 2011;97 (4): 278–286.