Research Article

https://doi.org/10.23934/2223-9022-2021-10-3-493-503

Evaluation of Clinical Efficiency of Cardioprotective Therapy in Patients with Acute Myocardial Infarction

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AIM To evaluate the efficiency of cardioprotective therapy using intravenous metoprolol in combination with a high dose of atorvastatin in the prevention of myocardial remodeling (MR) and heart failure (HF) in patients with acute ST-segment elevation myocardial infarction (STEMI).

MATERIAL AND METHODS A prospective study included 100 STEMI patients who underwent primary percutaneous intervention (PCI). Depending on the regimens of drug cardioprotection, three groups of patients were formed: the first (2014–2015) — 34 patients who received 80 mg atorvastatin as a part of the basic therapy on the first day of STEMI, then 20–40 mg/day for 30 days. The second group (2017–2018) — 34 patients who received atorvastatin 80 mg/day for a month from the onset of STEMI. The third group (2018–2019) — 32 patients who received intravenous metoprolol tartrate (5–15 mg) and atorvastatin 80 mg/day before PCI for a month from the onset of STEMI. On days 1 and 2 of STEMI and one month later, patients were assessed for serum levels of cardiac biomarkers; on the 1st, 7th days and one month later, echocardiographic studies (EchoCG) were performed. At the end of the observation, clinical and imaging outcomes (MR and HF) were assessed, which were compared with the dynamics of biomarkers between the groups of patients.

RESULTS The combined use of atorvastatin 80 mg/day for a month from the onset of STEMI and a single intravenous injection of metoprolol tartrate (5–15 mg) in the acute phase of STEMI before PCI showed the most significant effects in the prevention of the development of structural and functional myocardial disorders and clinically severe heart failure, and also caused the minimal serum activity of cardiomarkers in the third group of patients in comparison with the first and second groups of patients without this drug combination. Also, correlations between biomarkers and echocardiography indicators were established in the third group of patients who received cardioprotective therapy.

CONCLUSION The combined use of high-dose atorvastatin for a month with a single intravenous injection of metoprolol tartrate in acute STEMI before PCI prevents the formation of MR and clinically significant HF in the post-infarction period. Comprehensive dynamic assessment of cardiac biomarkers and echocardiography parameters within a month after post-STEMI is a highly informative tools for monitoring the efficiency of cardioprotective therapy.

Keywords: metoprolol tartrate, atorvastatin, myocardial infarction, myocardial remodeling, heart failure, biomarkers

For citation Astrakhantseva ID, Vorobyov AS, Nikolayev KYu, Urvantseva IA. Evaluation of Clinical Efficiency of Cardioprotective Therapy in Patients with Acute Myocardial Infarction. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2021;10(3):493–503. https://doi.org/10.23934/2223-9022-2021-10-3-493-503 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study has no sponsorship.

State Assignment No. AAAA-A17-117112850280-2, Research Institute of Therapy and Preventive Medicine – Branch of the Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russian Federation

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BP – blood pressure
PS – pain syndrome
HS-*C*RP – highly sensitive *C*-reactive protein
Hc-TnT – highly sensitive troponin T
DBP – diastolic blood pressure
IHD – ischemic heart disease
IEDV – end-diastolic volume index
IESV – index of end-systolic volume
MI – myocardial infarction
MMI – myocardial mass index
STEMI – ST-segment elevation myocardial infarction
BMI – body mass index
INLS – index of violation of local contractility
LV – left ventricle (heart)
HDLC – high density lipoprotein cholesterol
LDLC – low density lipoprotein cholesterol
MRI – Magnetic Resonance Imaging
ACS – acute coronary syndrome
AHF – acute heart failure
RM – myocardial remodeling
eGFR – estimated glomerular filtration rate according to the *EPI* calculator
SBP – systolic blood pressure
HF – heart failure
EF – ejection fraction
FC – functional class
PCI – percutaneous coronary intervention
HR – heart rate
ECG – electrocardiogram
EchoCG – echocardiographic examination
E / A TMBF – the ratio of the peak velocities of the E / A transmitral blood flow
NT-proBNP — aminoterminal fragment of the brain natriuretic peptide precursor
M – mean value
Me – median
N – number of patients
SD – standard deviation

INTRODUCTION

In the structure of morbidity and mortality of the population of Russia and most countries of the world due to diseases of the circulatory system, the largest specific weight belongs to ischemic heart disease (IHD). The most severe in the course and prognosis of the acute form of this disease is myocardial infarction (MI) with ST segment elevation (STEMI) on the electrocardiogram (ECG) [1].

Large-focal MI is characterized by the formation of early and distant disorders of the structure and function of the myocardium and heart chambers, referred to in the international medical literature as "postinfarction myocardial remodeling" (RM). Depending on the time interval from the onset of myocardial infarction, the early (from the first hours to 3-4 weeks) and later (in more distant terms) RM are isolated. This

phenomenon, in the absence of adequate therapeutic approaches, inevitably leads to chronic heart failure (HF) in patients at postinfarction stages [2, 3].

Despite a significant number of studies devoted to the effects of "aggressive" statin therapy regimens on clinical outcomes in postinfarction patients, as well as the corresponding provisions of clinical guidelines for their use in patients with acute coronary syndrome (ACS), a number of aspects concerning the effect of different doses of this class of drugs on key pathophysiological mechanisms (RM, myocardial stress, inflammation and ischemic damage to cardiomyocytes) remain poorly understood [4, 5].

At the same time, the pharmacological effects of "intense" β1-adrenergic blockade using intravenous metoprolol on the indicated structural-functional and molecular-biological processes in the myocardium under conditions of acute ischemia / infarction, as well as clinical outcomes in these patients, are still unclear [6–10]. Another limitation of the validity of the use of injectable forms of beta-blockers in modern clinical practice is the fact that the main studies in patients with acute myocardial infarction were carried out in the "pre-reperfusion" era (1990-2000) [11, 12]. The latest major studies by *METOCARD-CNIC* and *EARLY-BAMI* show conflicting evidence regarding the effect of intravenous metoprolol tartrate before percutaneous coronary intervention (PCI) on myocardial complications and clinical outcomes in persons with STEMI. [13–16].

In the clinical guidelines for the management of patients with acute STEMI (European Society of Cardiology - 2017, Russian Society of Cardiology - 2020, Eurasian Association of Cardiology - 2020), as indications for the use of intravenous injectable metoprolol for STEMI, there are no positions on the prevention of the formation of myocardial remodeling and heart failure in patients in postinfarction period [17–19].

Thus, the aim of the study was to evaluate the effectiveness of cardioprotective therapy using intravenous metoprolol in combination with a high dose of atorvastatin in the prevention of RM and HF in patients with acute STEMI.

MATERIAL AND METHODS

A prospective single-center clinical study included 100 patients with STEMI, who were sequentially included in it on the first day from the onset of pain and ECG registration at the stage of admission to the admission department of BU KhMAO - Yugra "District Cardiological Dispensary Center for Diagnostics and Cardiovascular vascular surgery" for the period from 2014 to 2019. The study period was 37 ± 5 (from 30 to 44) days from the onset of myocardial infarction. At the time of enrollment in the study, written informed consent was obtained from all patients. The study was approved by the local ethics committee at the place of its conduct, the provisions of which were in accordance with the requirements of biomedical ethics, the national standard of the Russian Federation on good clinical practice and the Declaration of Helsinki.

Inclusion criteria: acute STEMI; age 30–70 years; acute HF according to *Killip* class I or II.

Exclusion criteria: atrioventricular block I – III degree; complete bundle branch block; an implanted pacemaker; acute heart failure according to *Killip* III or IV; systolic blood pressure (BP) less than 100 mm Hg; the heart rate (HR) less than 60 beats / min, the duration of the P – R interval more than 240 ms on the ECG; history of bronchial asthma; severe obstructive peripheral arterial disease; patient refusal to participate in the study; intolerance to iodine, statins, beta-adrenergic blockers.

Depending on the treatment regimens, 100 STEMI patients were divided into three groups. The first group included persons who were admitted to the hospital for the period 2014–2015, who, according to the previous clinical guidelines (2012) for the management of patients with ACS with ST segment elevation after emergency thrombolysis / PCI [20], received atorvastatin as part of basic drug therapy. 80 mg on the first day of STEMI, then 20-40 mg in the post-myocardial infarction period. The second group (2017–2018) included patients who received, in accordance with the updated clinical guidelines (2017) [17–19], therapy that included atorvastatin at a dose of 80 mg / day in the acute phase of STEMI and for one month observations in the postinfarction period. In the third group (included in 2018–2019), patients were observed who received a single intravenous injection of metoprolol tartrate at a dose of 5–15 mg in the admission department under the control of blood pressure and heart rate, followed by a switch to metoprolol succinate in tablet form (25–100 mg / day) on a regular basis; these patients, as well as in the second group, received atorvastatin 80 mg / day in the acute phase of STEMI and for one month in the postinfarction period.

As a part of clinical and laboratory examination on the 1st and 2nd days, as well as one month after the onset of MI, blood samples were taken from all patients to assess the serum concentrations of cardiac biological markers [high-sensitivity troponin T (hs-TnT), aminoterminal fragment brain natriuretic peptide precursor (NT-proBNP), highly sensitive *C*-reactive protein (hs-*C*RP)]. Serum levels of NT-proBNP (*Roche Cobas* test systems, Switzerland), as well as hf-TNT (*Roche Elecsys* test system, Switzerland) were determined by enzyme immunoassay on an analyzer for laboratory express diagnostics *COBAS* E411 (*Roshe*, Switzerland); hf-CPR values were determined on an *IMMULITE* 1000 immunochemiluminescence analyzer (*Siemens*, Germany). In this case, the reference levels were considered: hf-TnT - up to 1.0 ng / ml; hf-SRP - up to 3.0 mg / l, NT-proBNP - up to 125 pg / ml. Serum levels of NT-proBNP (*Roche Cobas* test systems, Switzerland), as well as hf-TNT (*Roche Elecsys* test system, Switzerland) were determined by enzyme immunoassay on an analyzer for laboratory express diagnostics *COBAS* E411 (*Roshe*, Switzerland); hf-CPR values were determined on an IMMULITE 1000 immunochemiluminescence analyzer (*Siemens*, Germany). In this case, the reference levels were considered: hf-TnT - up to 1.0 ng / ml; hf-SRP - up to 3.0 mg / l, NT-proBNP - up to 125 pg / ml.). According to the data of echocardiographic parameters in dynamics, the presence and severity of early structural and functional remodeling of the myocardium were established in accordance with the criteria of *F. Flachskampf et al.* [2, 21]: (1) an increase in the end-diastolic volume index (ICDV) of the left ventricle (LV) of the heart by 20% or more from the initial values; (2) achieving an LV end-systolic volume index (ICSO) of 35 ml / m^2 or more; decrease in the ejection fraction (EF) of the LV less than 40%.

Statistical analysis of the data obtained was carried out using parametric and nonparametric methods in *Microsoft Excel* and *Statistica* version 13.0. In the case of a normal distribution, the mean (*M*) and standard deviation (*SD*) were calculated; when comparing two normally distributed samples, Student's *t*-test was used. In the absence of a normal distribution of data, the median (*Me*), 25% and 75% percentiles were calculated [25%; 75%], the differences between nonparametric indicators were assessed using the Wilcoxon, Mann – Whitney, and Kruskal – Wallis methods. When assessing the contingency of categorical characteristics, the Pearson β2 criterion was used. The presence and severity of associations between the studied indicators were established using the Spearman's rank correlation method. For all statistical procedures, the significance level for rejecting the null statistical hypothesis was taken at *p* values less than 0.05.

RESULTS

Clinical and anamnestic characteristics of the observed persons with MI are presented in Table. 1. No statistically significant differences were found among the three selected groups of patients. It should be noted that patients in group 3 were statistically insignificantly more likely to have anterior myocardial infarction and intermediate LV ejection fraction, but less frequently preserved LV ejection fraction. At the same time, in the second group, in comparison with the other two ones, there were more people with type 2 diabetes mellitus, and in the first group the highest frequency of smoking patients was found.

Table 1

Clinical and anamnestic data of patients with acute myocardial infarction with ST segment elevation

Indicators	Patients, *n*=100	Group 1, *n*=34	Group 2, *n*=34	Group 3, *n*=32
Age, years *(M±SD)*	56,9±8,4	55,7±9,8	57,7±7,5	57,3±7,7
BMI, кг/м^2 *(M±SD)*	28,4±4,6	28,7±5,2	28,1±4,0	28,3±4,7
HR per min *(M±SD)*	76,0±15,0	74,6±14,6	74,4±15,3	79,2±15,1
SBP, mm Hg. (*Me* [25%; 75%])	132 [120; 144]	130 [120; 150]	140 [124; 146]	133 [121; 140]
DBP, mm Hg. (*Me* [25%; 75%])	80 [80; 90]	80 [75; 90]	80 [80; 90]	80 [80; 90]
Male gender, *n* (%)	89 (89,0%)	32 (94,1%)	29 (85,3%)	28 (87,5%)
LV anterior wall MI, *n* (%)	49 (49,0%)	15 (44,1%)	14 (41,2%)	20 (62,5%)
Time from the beginning of the PS, *n* (%): 1-3 hours 3-12 hours	 51 (51,0%) 49 (49,0%)	 18 (52,9%) 16 (47,1%)	 19 (55,9%) 15 (44,1%)	 14 (43,8%) 18 (56,3%)

AHF by *Killip*, *n* (%): Class I Class II	 97 (97,0%) 3 (3,0%)	 32 (94,1%) 2 (5,9%)	 33 (97,1%) 1 (2,9%)	 32 (100%) 0 (0%)
LV EF, *n* (%): 50% and more 40–49% less than 40%	 53 (53,0%) 38 (38,0%) 9 (9,0%)	 19 (55,9%) 12 (35,3%) 3 (8,8%)	 22 (64,7%) 10 (29,4%) 2 (5,9%)	 12 (37,5%) 16 (50,0%) 4 (12,5%)
eGFR 60 or less ml / min, *n* (%)	10 (10,0%)	3 (8,8%)	3 (8,8%)	4 (12,5%)
Thrombolysis before PCI, *n* (%)	34 (34,0%)	13 (38,2%)	10 (29,4%)	11 (34,4%)
Taking drugs before MI, *n* (%)	20 (20,0%)	7 (20,6%)	6 (17,6%)	7 (21,9%)
Arterial hypertension, *n* (%)	79 (79,0%)	26 (76,5%)	27 (79,4%)	26 (81,3%)
Diabetes, *n* (%)	17 (17,0%)	3 (8,8%)	8 (23,5%)	6 (18,8%)
Obesity, *n* (%)	36 (36,0%)	13 (38,2%)	11 (32,4%)	12 (37,5%)
Smoking, *n* (%)	59 (59,0%)	24 (70,6%)	17 (50,0%)	18 (56,3%)

Notes: PS— pain syndrome; DBP — diastolic blood pressure; MI — myocardial infarction; BMI — body mass index; LV — left ventricle; AHF — acute heart failure; eGFR — estimated glomerular filtration rate according to the EPI calculator; SBP — systolic blood pressure; LV EF — left ventricular ejection fraction; AHF – acute heart failure; PCI — percutaneous coronary intervention; HR — heart rate; M — mean value ± SD — standard deviation; n number of patients; Me — median; [25%; 75%] — 25% and 75% percentiles.

When analyzing the lipid profile (Table 2), there were no differences in the initial levels of total cholesterol, low-density lipoprotein (LDL) and high (HDL) density. However, after one month of observation, there was a statistically significant decrease in all three groups of patients in the indicated fractions of cholesterol with a dose-dependent effect of atorvastatin: from the first group (20-40 mg / day) to groups 2 and 3 (80 mg / day). Triglyceride levels differed between the first and third groups of persons, but in dynamics there were no significant differences.

Table 2

Lipid panel indices in patients with myocardial infarction at the hospital stage and one month after discharge

Indicators	Group 1, *n*=34	Group 2, *n*=34	Group 3, *n*=32	*p*
Total cholesterol-1, mmol / l *(M±SD)*	5,0±1,4	4,6±0,9	4,6±1,2	все $p \geq 0,05$
Total cholesterol-2, mmol / l *(M±SD)*	4,6±0,7	3,7±1,2	3,7±0,6	$p_{1-2}<0,05$; $p_{1-3}<0,05$
Δ- Total cholesterol, mmol / l (%)	−0,4 (−8,0)*	−0,9 (−19,6)*	−0,8 (−17,8)*	*$p<0,05$
LPLD-1, mmol / l *(M±SD)*	3,0±1,3	2,9±0,7	3,1±1,6	все $p \geq 0,05$
LPLD -2, mmol / l *(M±SD)*	2,6±0,7	1,8±0,4	2,0±0,5	$p_{1-2}<0,05$; $p_{1-3}<0,05$; $p_{2-3}<0,05$
Δ- LPLD , mmol / l (%)	−0,4 (−13,3)*	−1,1 (−37,9)*	−1,1 (−35,5)*	*$p<0,05$
HDL-1, mmol / l *(M±SD)*	1,1±0,4	1,0±0,3	1,1±0,4	все $p \geq 0,05$
HDL-2, mmol / l *(M±SD)*	1,0±0,2	1,1±0,2	1,2±0,4	$p_{1-2}<0,05$; $p_{1-3}<0,05$
Δ- HDL, mmol / l (%)	(−0,1; −9,0)	(0,1; 9,0)	(0,1; 9,0)	все $p \geq 0,05$
Triglycerides-1, mmol / l *(M±SD)*	1,9±0,9	1,6±0,8	1,3±0,6	$p_{1-3}<0,05$
Triglycerides-2, mmol / l *(M±SD)*	1,9±1,1	1,7±0,7	1,4±0,6	$p_{1-3}<0,05$
Δ- Triglycerides, mmol / l (%)	(0; 0)	(0,1; 6,3)	(0,1; 7,7)	все $p \geq 0,05$

Notes: *p<0,05 — statistically significant change in the indicator compared to its initial value; p_{1-2} is a statistically significant difference when comparing the corresponding indicators between the first and second groups of patients; p_{1-3} — statistically significant difference when comparing the corresponding indicators between the first and third groups of patients; p_{2-3} is a statistically significant difference when comparing the corresponding indicators between the second and third groups of patients. LPLD — low density lipoprotein cholesterol; HDL — high density cholesterol lipoproteins; indicator-1 — the value of the indicator at the beginning of observation in acute myocardial infarction; indicator-2 — the value of the indicator in a month of observation; Δ-indicator — dynamic change of the indicator in the process of observation; M — mean value; ± SD — standard deviation; n — number of patients

Among the biochemical parameters (Table 3), it is necessary to note a significant decrease in the level of aminotransferase during the observation in all three studied groups of patients.

Table 3

Biochemical parameters in patients with myocardial infarction at the hospital stage and after one month

Indicators	Group 1, *n*=34	Group 2, *n*=34	Group 3, *n*=32	*p*
Blood glucose-1, mmol / l *(M±SD)*	5,6±1,8	5,9±2,9	7,3±2,3	p_{1-3}<0,05; p_{2-3}<0,05
Blood glucose-2, mmol / l *(M±SD)*	5,7±1,6	6,3±2,2	5,7±1,2	p_{1-2}<0,05
Δ- Blood glucose, mmol / l (%)	0,1 (1,8)	0,4 (6,8)*	−1,6 (−21,9)*	*p<0,05
Blood creatinine-1, μmol / l *(M±SD)*	87,6±15,3	84,5±20,5	89,6±25,9	all p≥0,05
Blood creatinine-2, μmol / l *(M±SD)*	92,6±17,6	91,1±22,5	87,9±26,8	all p≥0,05
Δ- Blood creatinine, μmol / l (%)	5,0 (5,7)	6,6 (7,9)	−1,7 (−1,9)	all p≥0,05
eGFR-1, μmol / ml / 1.73 m^2 *(M±SD)*	83,9±18,0	84,6±16,3	82,1±20,1	p_{1-3}<0,05; p_{2-3}<0,05
eGFR-2, μmol / ml / 1.73 m^2 (M±SD)	81,4±19,3	79,7±16,9	83,5±19,9	all p≥0,05
Δ- eGFR, μmol / ml / 1.73 m^2 (%)	−2,5 (−3,0)	−4,8 (−5,6)	−1,4 (−1,7)	все p≥0,05
Alanine aminotransferase-1, U / L *(M±SD)*	46,8±16,7	38,7±8,2	44,5±14,2	all p≥0,05
Alanine aminotransferase-2, U / L *(M±SD)*	32,0±9,4	33,8±7,4	31,8±6,4	all p≥0,05
Δ- Alanine aminotransferase, U / L (%)	−14,8 (−31,6)*	−4,9 (−12,7)*	−12,7 (−28,5)*	* p<0,05
Aspartate aminotransferase-1, U / L *(M±SD)*	89,2±18,8	85,8±17,5	52,4±8,2	p_{1-3}<0,05; p_{2-3}<0,05
Aspartate aminotransferase-2, U / L *(M±SD)*	23,4±10,3	28,3±13,4	26,2±5,7	all p≥0,05
Δ- Aspartate aminotransferase, U / L (%)	−65,8(−73,8)*	−57,5 (−67,0)*	−26,2 (−50,0)*	* p<0,05

Notes:*p<0,05 — statistically significant change in the indicator compared to its initial value; p_{1-3} — statistically significant difference when comparing the corresponding indicators between the first and third groups of patients; p_{2-3} is a statistically significant difference when comparing the corresponding indicators between the second and third groups of patients. EGF — estimated glomerular filtration rate according to the EPI calculator; indicator-1 — the value of the indicator at the beginning of observation in acute myocardial infarction; indicator-2 — the value of the indicator in a month of observation; Δ-indicator — dynamic change of the indicator in the process of observation; M — mean value ± SD — standard deviation; n — number of patients

The serum level of hs-TNT, determined upon admission of patients to the admission department, and 24 hours after PCI, are shown in Fig. 1. Baseline biomarker levels in the third group were statistically significantly higher (59.0 [25.0; 121.7] ng / ml versus 29.7 [19.5; 48.9] ng / ml, p = 0.028), and repeated the values of statistically significant are lower (85.5 [68.3; 141.0] ng / ml versus 218.1 [144.0; 684.0] ng / ml, p=0,0004), than in patients of the first group. nitial and repeated levels of hs-TnT (36.3 [18.2; 104.3] ng / ml and 165.9 [111.7; 735.3] ng / ml, respectively) of the second group took an intermediate position, but without statistically significant difference from the values of this biomarker in the other two groups.

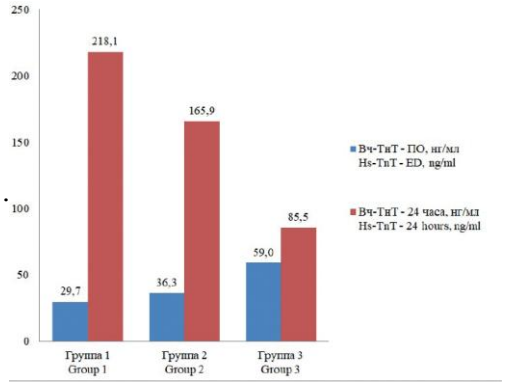

Fig. 1. Serum levels (ng/ml) of high-sensitivity troponin T (Hs-TnT) in patients in the acute phase of myocardial infarction upon admission to the emergency department and in 24 hours of observation

The dynamics of Hs-CRP levels in patients of the studied groups is shown in Fig. 2. When analyzing these values, it was found that the initial concentrations of the biological marker were significantly higher in group three (8.2 [3.5; 25.5] mg / l) in comparison with groups one and two (5.1 [2, 9; 7.4] mg / l, p = 0.012 and 4.3 [3.3; 6.7] mg / l, p = 0.008, respectively). It is important to note that the levels of Hs-CRP, determined one day after PCI, significantly differed between the three groups with the highest values in the first group (30.1 [16.7; 38.3] mg / L) and the lowest in the third group 12.3 [9.2; 18.0] (p<0,05). This trend continued after one month of observation: the levels decreased statistically significantly from the first group (4.8 [3.3; 6.0] mg / l) to the second (3.6 [2.2; 4.8] mg / l) and the third group of patients with MI (2.6 [1.6; 3.4] mg / l) (p<0,05).

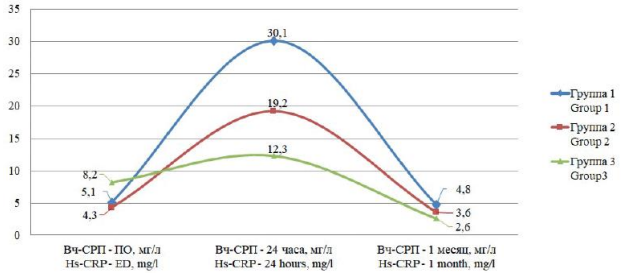

Fig. 2. Serum levels (mg/l) of highly sensitive C-reactive protein (Hs-CRP) in patients in the acute phase of myocardial infarction upon admission to the emergency department (ED), in 24 hours and 1 month of observation

We did not find statistically significant differences between the initial NT-proBNP concentrations in the patients of the three groups (Fig. 3). However, within a day there was an active increase in the biomarker values in the individuals of the first group (839.1 [462.0; 1706.1] pg / ml) in comparison with the second (594.2 [348.7; 916.0] pg / ml, p = 0.03) and the third (376.0 [198.5; 622.5] pg / ml, p = 0.0004) groups of patients. After one month, the NT-proBNP values were still the highest in patients of the first group (703.5 [290.3; 917.2] pg / ml).

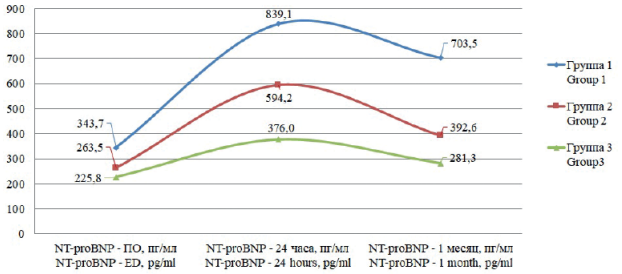

Fig. 3. Serum levels (pg/ml) of the aminoterminal fragment of the brain natriuretic peptide precursor (NT-proBNP) in patients in the acute phase of myocardial infarction upon admission to the emergency department (ED), in 24 hours and in 1 month of observation

Compared to group 1, the levels of the biomarker in group 2 (392.6 [276.2; 811.0] pg / ml) were statistically insignificantly lower the levels of NT-proBNP concentration of the third group (281.3 [169.0; 587.0] pg / ml, p = 0.0003).

Further, in Table 4 we present the dynamic changes in the echocardiographic parameters of myocardial remodeling and central hemodynamics in patients in the acute phase of MI and in postinfarction period. Thus, the baseline values between LV IEDV were comparable between the three groups without statistically significant differences. The dynamics of the increase in LV IEDV was insignificant in groups 2 and 3, however, the increase in this parameter in group 1 turned out to be statistically significant in patients of the first group (p = 0.01). Initial values of LV IESV did not differ significantly, but the repeated values in group 1 were significantly higher than in group 3 (p=0.04). At the same time, the dynamics of LV IESV is multidirectional in these groups: in group 1 there was a distinct increase in this parameter (p = 0.04), and in group 3, on the contrary, there was a statistically significant decrease in LV IESV (p = 0.027). Initial values of LV EF in group 3 were statistically significantly lower than in group 2 (p = 0.0013). In the dynamics of observation, there were no significant changes in the indicators of LV EF, however, it is important to note a significant increase in the indicators of LV EF in group 3 after a month. (p=0.0000001). When assessing the levels of LV myocardial

hypertrophy, a statistically significant increase in the dynamics of the LV myocardial mass index in the first group (p = 0.03) and in the second group (p = 0.007) and a slight decrease in LV myocardial mass index in the third group was found. When assessing violations of the regional contractility of the LV myocardium, a statistically significant decrease in the values of the index of disorders of local myocardial contractility (IDLMC) of the LV was revealed in the second (p = 0.04) and third (p = 0.02) groups of patients. Changes in LV diastolic function were assessed by the dynamics of the ratio of peak velocities *E/A* of transmitral blood flow (*E/A* TBF). The initial values of this ratio did not differ between all groups of patients, however, upon repeated measurements in the first group, we determined statistically significantly lower values of this parameter, in contrast to the third group (p = 0.028). In the dynamics of the study, in the first group, there was a statistically significant decrease in the ratio *E/A* TBF (p = 0.04), and, on the contrary, a significant increase in this parameter in the third group (p = 0.0001).

Table 4

Echocardiographic parameters in patients during follow-up (one month)

Indicators	Group 1, *n*=34	Group 2, *n*=34	Group 3, *n*=32	*p*
ICDV - 1 LV, ml / m^2 *(M±SD)*	61,4±8,8	65,1±8,5	65,6±11,3	все $p \geq 0,05$
ICDV - 2 LV, ml / m^2 *(M±SD)*	68,2±11,8	66,6±8,5	66,3±10,8	все $p \geq 0,05$
Δ- ICDV LV, ml / m^2 *(M±SD)* (%)	6,8 (11,1)*	1,4 (2,2)	0,7 (1,1)	*$p<0,05$
ICSV - 1 LV, ml / m^2 (M ± SD)	30,7±8,1	30,8±8,5	33,9±9,0	все $p \geq 0,05$
ICSV - 2 LV, ml / m^2 (M ± SD)	34,9±12,3	31,1±8,0	30,0±8,4	$p_{1-3}<0,05$
Δ- ICSV - LV, ml / m^2	4,2 (13,7)*	0,3 (1,0)	−4,9 (−14,7)*	*$p<0,05$
EF – 1 LV, % *(M±SD)*	50,5±8,8	53,4±7,7	47,2±7,2	$p_{2-3}<0,05$
EF – 2 LV, % *(M±SD)*	50,0±10,7	53,6±8,5	55,3±6,8	все $p \geq 0,05$
Δ-EF LV, % (%)	−0,5 (−1,0)	0,2 (0,4)	8,6 (18,2)*	*$p<0,05$
MMI- 1 LV, g / m^2 *(M±SD)*	108,8±24,2	119,6±29,0	119,6±23,8	все $p \geq 0,05$
MMI- 2 LV, g / m^2 *(M±SD)*	116,6±26,8	128,2±29,9	118,9±21,6	все $p \geq 0,05$
Δ- MMI- LV, g / m^2 (%)	7,7 (7,1)*	8,6 (7,1)*	−0,7 (−0,6)	*$p<0,05$
IVLC – 1 LV, ED. *(M±SD)*	1,19±0,13	1,13±0,11	1,16±0,11	все $p \geq 0,05$
IVLC – 2 LV, ED. *(M±SD)*	1,20±0,18	1,10±0,10	1,10±0,06	$p_{1-2}<0,05$
Δ- IVLC LV, ED. (%)	0,01 (0,8)	− 0,03 (− 2,7)*	− 0,06 (− 5,2)*	*$p<0,05$
E/A TBF – 1, ED. *(M±SD)*	0,82±0,11	0,80±0,21	0,84±0,35	все $p \geq 0,05$
E/A TBF – 2, ED. *(M±SD)*	0,78±0,14	0,94±0,48	1,00±0,34	$p_{1-3}<0,05$
Δ-*E/A* TBF, ED. (%)	−0,05 (−6,1)*	0,12 (15,0)	0,16 (19,0)*	*$p<0,05$

Notes: *p<0,05 — statistically significant change in the indicator compared to its initial value; p_{1-2} is a statistically significant difference when comparing the corresponding indicators between the first and second groups of patients; p_{1-3} — statistically significant difference when comparing the corresponding indicators between the first and third groups of patients; p_{2-3} is a statistically significant difference when comparing the corresponding indicators between the second and third groups of patients. IEDV — index of end-diastolic volume; IESV — index of end-systolic volume; MMI — myocardial mass index; IVLC— index of violation of local contractility; LV — left ventricle; EF – ejection fraction; indicator-1 — the value of the indicator at the beginning of observation in acute myocardial infarction; indicator-2 — the value of the indicator in a month of observation; E/A TBF — the ratio of the peak velocities of the E/A transmitral blood flow; M — mean value ± SD — standard deviation; n is the number of patients; Δ-indicator — dynamic change of the indicator in the process of observation

To assess the presence and severity of the relationship between echocardiography and biomarker levels in patients who received cardioprotective therapy (third group), a correlation analysis was performed (Table 5). Thus, we failed to identify statistically significant associations between the levels of all three biomarkers, determined upon admission to the PO, and echocardiography indicators at the hospital stage of treatment ($p \geq 0.05$). However, a relationship was established between the average strength between the concentrations of hf-TNT, determined after 24 hours, with the initial values of LV ICSO (r = 0.52, p = 0.016) and LVEF (r = -0.45, p = 0.043). The levels of hf-CRP, studied in patients one day after admission to the hospital, statistically significantly correlated with three baseline echocardiographic indices - LV ICDO (r = 0.67, p = 0.001), LV ICSO (r = 0.74, p = 0.0001) and LVEF (r = -0.51, p = 0.017); after one month, the values of hf-SRP were also

significantly associated with repeated measurements of LV ICSO (r = 0.46, p = 0.034) and LVEF (r = -0.54, p = 0.011). NT-proBNP levels, which were assessed 24 hours after patient admission, were clearly associated with LV ICDO (r = 0.62, p = 0.003) and LV ICSO (r = 0.61, p = 0.03). It is important to note the high severity of associations between the levels of NT-proBNP and all three echocardiographic parameters - LV ICDO (r = 0.65, p = 0.001), LV ICSO (r = 0.83, p = 0.0001) and LVEF (r = -0.72, p = 0.0001) - in their assessment in patients after one month of treatment.

Table 5

Correlation between the values of biomarkers and echocardiographic parameters in the dynamics of observation in the third group of patients who received cardioprotective therapy

Biomarcers	EhoCG indicators					
	EDVI — 1 LV	EDVI — 2 LV	ESVI — 1 LV	ICSO — 2 LV	EF — 1 LV	EF — 2 LV
	r	*r*	*r*	*r*	*r*	*r*
HSTT — AD	0,16	—	0,22	—	–0,22	—
Hs CRP — 24 hours	0,43	—	0,52*	—	–0,45*	—
Hs-CRP — AD	0,30	—	0,38	—	–0,33	—
Hs-CRP — 24 hours	0,67*	—	0,74*	—	–0,51*	—
Hs-CRP — 1 month	—	0,24	—	0,46*	—	–0,54*
NT-proBNP — AD	0,19	—	0,07	—	0,05	—
NT-proBNP — 24 hours	0,62*	—	0,62*	—	–0,40	—
NT-proBNP — 1 month	—	0,65*	—	0,83*	—	–0,72*

Notes: * — statistically significant correlation (p<0.05). HSTT — high-sensitivity troponin T; HS CRP — high-sensitivity C- reactive protein; EDVI — end-diastolic volume index; ESVI — end-systolic volume index; LV — left ventricle; EF — ejection fraction; echocardiographic indicator - 1 — the value of the indicator at the beginning of observation in acute myocardial infarction; echocardiographic indicator - 2 — the value of the indicator in a month of observation; NT-proBNP — aminoterminal fragment of the brain natriuretic peptide precursor; biomarkers were assessed in patients at the admission department (AD) stage, in 24 hours and in one month of follow-up; r - correlation coefficient

Based on the results of studying various options for myocardial remodeling and clinical outcomes in postinfarction patients at the end of observation, we established clear advantages of the treatment regimen of the third group, which is reflected in Table. 6. Thus, *de novo* myocardial remodeling in patients of the third group (3.1%) developed statistically significantly less frequently than in the first (26.5%, p = 0.0082) and the second (20.6%, p = 0, 03) observation groups.

Table 6

Clinical and instrumental outcomes in postinfarction patients at the end of follow-up (one month)

Outcomes	Group 1 (*n*=34)	Group 2 (*n*=34)	Group 3 (*n*=32)	*p*
Without MR, *n* (%)	14 (41,2%)	17 (50,0%)	17 (53,1%)	все $p \geq 0{,}05$
MR *de novo*, *n* (%)	9 (26,5%)	7 (20,6%)	1 (3,1%)	$p_{1-3}<0{,}05$, $p_{2-3}<0{,}05$
Initial MR with negative dynamics, *n* (%)	5 (14,7%)	3 (8,8%)	0 (0,0%)	$p_{1-3}<0{,}05$
Initial MR without positive dynamics, *n* (%)	3 (8,8%)	4 (11,8%)	3 (9,4%)	all $p \geq 0{,}05$
Initial MR with positive dynamics, *n* (%)	3 (8,8%)	3 (8,8%)	11 (34,4%)	$p_{1-3}<0{,}05$, $p_{2-3}<0{,}05$
LV aneurism, *n* (%)	4 (11,8%)	3 (8,8%)	1 (3,1%)	все $p \geq 0{,}05$
Symptomatic HF (FC II–IV), *n* (%)	16 (47,1%)	16 (47,1%)	5 (15,6%)	$p_{1-3}<0{,}05$, $p_{2-3}<0{,}05$
Stagnant HF (stages II–III), *n* (%)	4 (11,8%)	3 (8,8%)	2 (6,3%)	all $p \geq 0{,}05$

Notes: *p<0,05 — statistically significant change in the indicator compared to its initial value; p_{1-3} is a significant difference when comparing the corresponding indicators between the first and third groups of patients; p_{2-3} — statistically significant difference when comparing the corresponding indicators between the second and third groups of patients; LV — left ventricle; HF — heart failure; indicator-1 — the value of the indicator at the beginning of observation in acute myocardial infarction; indicator-2 — the value of the indicator in a month of observation; MR — myocardial remodeling; FC — functional class; M — mean value ± SD — standard deviation; n is the number of patients; Δ-indicator — dynamic change of the indicator in the process of observation

The same pattern was observed when assessing the incidence of clinically pronounced HF (II – IV functional classes, FC): the first group (15.6%) versus the second and third groups of patients (47.1% each, p = 0.0061). We also revealed a statistically significant greater number of patients with initial myocardial remodeling and positive dynamics of echocardiography in the third group (34.4%) compared with groups 1 and 2 (8.8% each, p = 0.011). The formation of negative dynamics of echocardiography indices against the background of initial myocardial remodeling in patients was not observed in group 3 with a statistically significant difference from individuals in the first group, in which this phenomenon took place in 14.7% of cases (p = 0.024).

DISCUSSION

Comparison of the obtained results with the data of large-scale studies on intravenous metoprolol *COMMIT / CCS-2, MIAMI, ISIS-1* does not seem correct, since these controlled studies were carried out in the so-called pre-reperfusion era, when patients in the acute phase of STEMI received metoprolol tartrate as part of the baseline drug therapy without pharmacoinvasive strategies (thrombolysis and / or PCI). The *TIMI-IIb* and *GUSTO I* trials (which already included thrombolytic therapy using intravenous metoprolol or atenolol) focused on hospital and long-term mortality in patients with MI, but the outcomes of myocardial remodeling and heart failure were not evaluated [6–12].

At the present stage, two large studies *METOCARD-CNIC* (2013, Spain) and *EARLY-BAMI* (2016, Holland-Spain) have been carried out to study the effects of metoprolol tartrate administered before PCI to persons with STEMI, with conflicting results. Thus, the *METOCARD-CNIC* study showed that early intravenous administration of metoprolol was associated with a decrease in the size of myocardial infarction according to magnetic resonance imaging (MRI) after 5-7 days in comparison with the placebo group and a higher LVEF after 6 months; the frequency of clinical events (recurrent MI, hospitalization for HF, life-threatening arrhythmias, cardiovascular death) was statistically insignificant after 2 years between the groups. The *EARLY-BAMI* study did not demonstrate any benefit in the intravenous metoprolol group versus control in reducing MI size on MRI or levels of damage biomarkers (troponin *T*, creatine phosphokinase *MB*); at the same time, early administration of metoprolol was associated with a close to significant decrease in the frequency of ventricular arrhythmias [13–17].

It is important to note that metoprolol tartrate in these studies was studied without background therapy with high doses of atorvastatin in patients with MI.

At the same time, the results of the *GALAXY* scientific program on rosuvastatin, as well as data from a meta-analysis of a number of controlled studies on atorvastatin, indicate a lower incidence of major cardiac events (death, stroke, reinfarction, repeated revascularization), proportional to the decrease in LDL and hf-*C*RP levels. High levels of the latter in postinfarction patients reflect the presence of a "residual" cardiovascular risk, despite the ongoing treatment, which is due to the persisting activity of arterial and myocardial inflammation [4, 17–20].

When planning the study, we assumed that the effects of metoprolol tartrate would be more pronounced in the prevention of postinfarction myocardial remodeling in patients with high-dose atorvastatin therapy.

Thus, we found that the combined use of atorvastatin in a high dose (80 mg / day) for one month after the onset of STEMI and a single intravenous injection of metoprolol tartrate (5-15 mg) in acute MI before PCI showed the most pronounced effects in the prevention of development structural and functional disorders of the LV (according to the dynamics of ICDO, ICSO, LVEF) and clinically pronounced heart failure, and also caused the minimum serum activity of all three cardiomarkers (hf-TnT, hf-SRP, NT-proBNP) in the third group of persons in comparison with the groups patients 1 and 2 without this drug combination.

With regard to the study of the "isolated" effects of atorvastatin in persons with MI, we revealed a dose-dependent positive effect of this drug on the dynamics of lipid profile (total cholesterol, LDL, HDL), values of hf-*C*RP and LV INL at all stages of the study, but without statistically significant positive effects on the key parameters of myocardial remodeling (ICDO, ICSO, LVEF), the levels of hs-TnT and NT-proBNP, as well as clinical outcomes in postinfarction patients, which is consistent with the data of the *CORONA* study and other large studies [4, 5, 22].

The associations established using correlation analysis indicate direct links between the dynamics of the levels of cardiac biomarkers and the values of echocardiography in patients with MI who received cardioprotective therapy. Similar results were obtained by other researchers. [23, 24].

CONCLUSION

The results presented in our study demonstrated new possibilities of drug prevention of myocardial remodeling and chronic heart failure in patients with coronary heart disease in the early post-infarction period, which provides a basis for conducting more large-scale controlled clinical trials in the long term.

FINDINGS

1. The use of atorvastatin at a dose of 80 mg / day for one month after acute *ST*-segment elevation myocardial infarction is effective in restoring regional myocardial contractility, reducing lipid profile and *C*-reactive protein levels.

2. The combined use of atorvastatin at a dose of 80 mg / day for one month with a single intravenous injection of metoprolol tartrate in acute myocardial infarction before percutaneous coronary intervention prevents the development of postinfarction left ventricular remodeling and clinically severe heart failure against the background of minimal serum activity of biomarkers of myocardial stress, myocardial stress in the early postinfarction period.

3. Comprehensive dynamic assessment of cardiac biomarkers and indicators of echocardiographic studies within a month after myocardial infarction with ST segment elevation is a highly informative means of monitoring the effectiveness of cardioprotective therapy.

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Received on 11.12.2020

Review completed on 11.03.2021

Accepted on 30.03.2021