ORIGINAL ARTICLE

INFLUENCE OF COMPLEX TREATMENT WITH MAGNESIUM AND POTASSIUM SALTS OF GLUCONIC ACID, EPLERENONE AND RIVAROXABAN ON DYNAMICS OF INDICATORS OF ISCHEMIA AND MYOCARDIAL REMODELING IN PATIENTS WITH CHRONIC HEART FAILURE AFTER MYOCARDIAL INFARCTION

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ABSTRACT

The aim: To increase the treatment effectiveness of CHF patients after MI with stenting by using magnesium and potassium salts of gluconic acid, eplerenone, and rivaroxaban in complex therapy.

Materials and methods: The research was performed at the premises of Ivano-Frankivsk Regional Clinical Cardiology Centre, Ukraine. 84 patients with CHF after past MI were examined.

Results and conclusions: A more pronounced anti-ischemic effect has been linked to the use of combination therapy with rivaroxaban on the background of basic therapy (BT) in patients with CHF after MI, compared with the use of magnesium and potassium salts of gluconic acid or eplerenone. The use of eplerenone in the complex treatment of these patients on the background of BT has been proven to provide a pronounced reverse remodeling of the left myocardium in the postinfarction period.

KEY WORDS: stenting, heart failure, postinfarction cardiosclerosis, remodeling, eplerenone, rivaroxaban

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INTRODUCTION

Despite significant advances in therapy over the past decade, mortality in patients with CHF after MI is quite high the quality of life is often unsatisfactory, which encourages to search for new approaches to treat this disease [1, 2].

The cause of recurrence of ischemia after myocardial infarction was studied in a prospective study PROSPECT, which included 697 patients who successfully underwent coronary stenting. The number of deaths from cardiac causes, cardiac arrest, myocardial infarction, or hospitalization due to CNS for 3 years was 20.4% and was the highest in the first year after myocardial infarction [3]. It turned out that only half of the cases of recurrent unfavorable course of the postinfarction period are due to stenosis responsible for the occurrence of the acute coronary syndrome (ACS), while in other patients the deterioration was associated with the damage to other segments of the coronary artery. Obviously, this suggests that efforts to prevent secondary ACS should focus not only on the prevention of stent thrombosis in stenosis, which has caused instability but also on the prevention of thrombotic complications in other areas of the coronary artery. From this point of view, ACS can be considered as a marker of increased risk of atherosclerosis thrombotic complications as a systemic disease, and long-term enhanced antithrombotic treatment – as an attempt to prevent clinically pronounced thrombosis in cases of vulnerable atherosclerotic plaques rupture [4]. Thus, there is a need to improve approaches to long-term secondary prevention of coronary thrombosis after MI [5]. One of the methods to improve the prognosis of this disease is to increase the effectiveness of antithrombotic treatment.

Rivaroxaban has been approved by the European Medicines Agency for use in acute coronary syndrome following the results of a large (15,526 patients) prospective multicenter, double-blind, placebo-controlled study ATLAS ACS 2-TIMI 51 [6]. This clinical trial was preceded by a similar smaller study ATLAS ACS-TIMI 46 (3491 patients), which resulted in the selection of two doses of rivaroxaban from many options, prospective for further study in addition to acetylsalicylic acid and its combination with clopidogrel – 2.5 mg or 5mg 2 times a day [7].

According to modern ideas, weak inhibition of aldosterone activity is one of the possible reasons for standard therapy effectiveness lack in the treatment of CHF with postinfarction cardiosclerosis [8, 9]. Aldosterone blockade can slow the progression of myocardial fibrosis, postinfarction remodeling, and improve the prognosis in patients who have suffered MI [10, 11].

THE AIM

To increase the effectiveness of CHF patients treatment after MI with stenting by using magnesium and potassi-

um salts of gluconic acid, eplerenone, and rivaroxaban in complex therapy.

MATERIALS AND METHODS

The research was performed at the premises of Ivano-Frankivsk Regional Clinical Cardiology Centre, Ukraine. The research was based on the results of the examination of 84 patients with CHF II stage A by the classification of V.Kh. Vasylenko and M.D. Strazheska II-III functional class according to the New York Heart Association (NYHA) with the preserved ejection fraction of the LV, which occurred in persons with the experienced MI. The criterion for the patients' enrollment was the Q, QS-MI experienced not earlier than 28 days before the research.

The patients underwent outpatient observation after 1, 3, 6, and 12 months. The study groups were homogeneous by age, sex, disease severity, duration of postinfarction period, the intensity of clinical manifestations, peculiarities of coronary arteries lesion, risk factors, which became the basis for randomization.

All examined patients were divided into the following groups. Group I consisted of 20 patients with CHF after past MI who underwent BT (metoprolol succinate in a dose of 25 mg/day, clopidogrel in a dose of 75 mg/day, aspirin-cardio in a dose of 100 mg/day, atorvastatin in a dose of 20 mg/day, enalapril in a dose of 5 mg/day, trimetazidine in a dose of 70 mg/day, torasemide in a dose of 10 mg/day). Group II included 21 patients with CHF after past MI who were treated with BT and the addition of potassium and magnesium salts of gluconic acid in a dose of 360 mg 3 times per day. Group III included 23 patients with CHF after past MI who were prescribed eplerenone in a dose of 25 mg 2 times a day secondary to BT. Group IV included 20 patients with CHF after past MI who received the treatment with BT together with rivaroxaban in a dose of 2.5 mg 2 times a day.

The ischemic genesis of CHF was verified based on a history of Q, QS-MI with positive biological markers, ECG results, echocardiography, coronary angiography, according to the recommendations of the European Society of Cardiology (2017). Holter monitoring (HM ECG) was performed using the Cardiolab system manufactured by HAI-MEDICA (Kharkiv, Ukraine). Intracardiac and systemic hemodynamics was studied by echocardiography (EchoCG) on the CARIS-PLUS device (Biomedice, Italy).

RESULTS

Table I shows myocardial ischemia dynamics in patients with CHF after myocardial infarction with stenting under the influence of therapy according to HM ECG.

According to Table I, the average daily number of ischemic episodes in group I before the examination was equal to 2.69 ± 0.13 and decreased after completion of therapy by 6.69% to 2.51 ± 0.13 ($p > 0.05$). In group II the average number of ischemia episodes during the day decreased by 6.25% and was 2.10 ± 0.1 after treatment ($p > 0.05$; p1-2 <0.05). It should be mentioned that the addition of eplerenone to BT in group III patients was accompanied by a more pronounced anti-ischemic effect, reducing the average daily number of ischemic episodes by 22.78% ($p < 0.01$). Worth noting that anti-ischemic treatment of group IV patients using a combination of BT with rivaroxaban led to the statistically greatest change of this indicator in the subjects ($p < 0{,}001$). Thus, in patients before the examination, the level of the average number of ischemic episodes was 3.38 ± 0.17 and decreased by 46.15% after 12 months of therapy to the level of 2.11 ± 0.08 ($p < 0.001$), significantly different from the same indicator in groups I, II ($p < 0.05$) and III ($p < 0.001$).

Indicators of maximum and average values of ST-segment depression depth were analyzed. According to Table I, the positive dynamics of decrease in these indicators was observed in all groups of patients with CHF after the MI with the carried out stenting. Twelve-month treatment of group I patients with BT drugs was accompanied by a decrease in the average value of depression of the ST segment by 13.53% to (1.15 ± 0.11) mm ($p > 0.05$). The maximum value of the ST-segment depression has decreased by 10.5% ($p > 0.05$). In groups II and III patients, the dynamics of ST-segment depression depth was improved by 20.51% and 37.78%, respectively. Maximum ST-segment depression in the study groups decreased by 21.5 and 38.46%, respectively. In the group I of the study, the total duration of myocardial ischemia per day after therapy was (31.2 ± 1.56) min/day, which is significantly higher than in patients treated with BT and eplerenone – (21.14 ± 1, 06) min/day (p1-3 <0.001).

When analyzing the average daily duration of myocardial ischemia in patients of groups II, III, and IV, the value of this indicator was statistically lower compared to the BT group (Fig. 1). At the same time, the most pronounced anti-ischemic effect was observed in the therapy group with rivaroxaban (group IV). The use of treatment in group IV patients has led to a decrease in the total duration of myocardial ischemia per day by 51.93%, which is significantly higher than the same indicator of groups I, II, and III patients ($p < 0.001$; p1-4 <0.001; p2-4 < 0.001; p3-4 <0.001). Thus, the high efficiency of the studied drugs in reducing the frequency and duration of myocardial ischemia was established.

The influence of the therapy on the indicators of cardiac hemodynamics in patients with CHF after myocardial infarction was studied (Table II). Under the influence of treatment, was observed positive dynamics of the main indicators of echocardiography. In the group I patients, the level of LV ejection fraction (EF) before treatment was (57.54 ± 2.87)% and statistically increased after 12 months of therapy to (66.43 ± 3.45)%. The use of BT together with magnesium and potassium salts of gluconic acid or eplerenone contributed to a significant increase in LV EF in groups II and III patients, respectively. In the examined group II, the level of LV EF before the beginning of therapy was equal to (54.02 ± 2.37)% and increased after 12 months of therapy with magnesium and potassium salts of gluconic

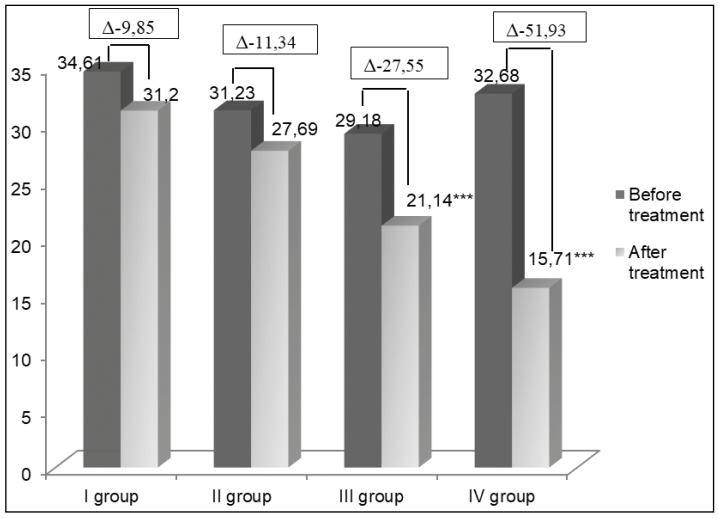

Fig.1. Indicators of ischemia daily duration after a therapy course in different study groups patients
Note. Probability of difference compared to almost healthy – *p<0,05; ***p<0,001.

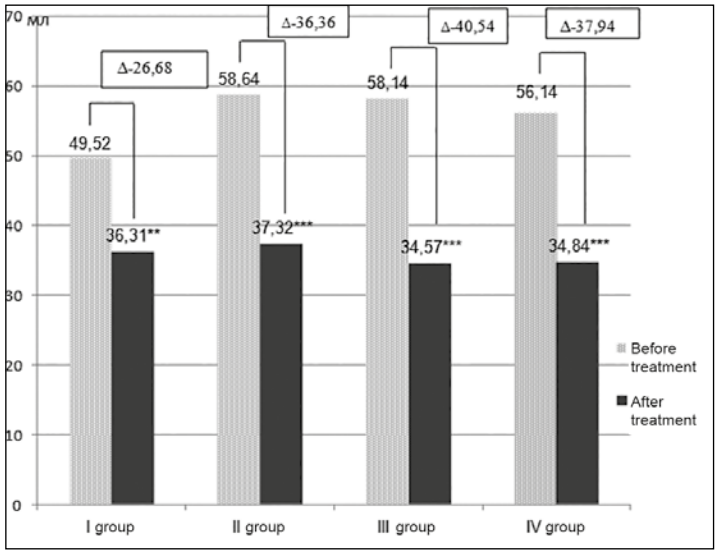

Fig. 2. End-systolic volume dynamics in the examined patients
Note. Difference probability in comparison with indicators before treatment: *- p<0,05, **- p<0,01, *** – p<0,001.

acid to (63.67 ± 1.91)%. When using BT with eplerenone in group III patients, was also noted a significant improvement in LV systolic function. LV EF in these patients was (55.73 ± 2.64)% before treatment and increased to (64.67 ± 1.92)% after twelve months of treatment (p <0.01). Treatment of group IV patients with rivaroxaban on the background of BT for 12 months contributed to a significant increase in EF by 10.73%. Thus, the average value of EF in the subjects of group IV before therapy was (56.21 ± 1.39)% and increased to (62.14 ± 1.86)% (p <0.01). At the same time, it should be noted that the change in the mean values of LV EF after 6 months of treatment was statistically unlikely in all survey groups.

The dynamics of end-systolic volume (ESV) and end-diastolic volume (EDV) of LV were analyzed under the influence of the studied drugs (Table II). The use of BT drugs in the treatment of patients with CHF after myocardial infarction led to a decrease in LV ESV and LV EDV after 6 and 12 months of therapy. So, in patients of group I, the LV ESV before treatment was (49.52 ± 2.97) ml, and after 6 and 12 months of treatment decreased to (37.65 ± 2.75) ml (p <0.01) and (36.31 ± 2.86) ml (p <0.01), respectively. The mean level of LV EDV in patients of this group before the examination was (109.51 ± 8.72) ml and statistically significantly decreased to (90.67 ± 2.54) ml after 12 months.

A significant decrease in LV ESV and LV EDV was also noted after 6 months of therapy in group II. In patients receiving magnesium and potassium salts of gluconic acid on the background of BT, the mean value of LV ESV before treatment was (58.64 ± 2.76) ml and significantly decreased to (46.87 ± 1.2) ml at the end of six months of treatment and up to (37.32 ± 1.4) ml after 12 months of therapy. It should be pointed out that the treatment of group III patients with the use of eplerenone on the background of BT has led to the most statistically significant change in ESV and EDV. Thus, LV ESV was equal to (58.14 ± 2.64) ml before examination start and significantly decreased to (44.51 ± 1.9) ml after 6 months of therapy by 40.54%, to the level of 34.57 ± 1, 8) ml after 12 months. The mean level of EDV in these patients was (129.74 ± 4.53) ml before treatment and noticeably decreased to (104.8 ± 4.75) ml after 6 months of treatment and by 21.06% to the level of 102.42 ± 4.75) ml at the end of twelve months of treatment.

Table I. Ischemia dynamics in patients with heart failure according to Holter ECG monitoring

Patients' groups / Numbers	I group (basic therapy), n=20		II group (BT+ magnesium and potassium salts of gluconic acid), n=21		III group (BT+ eplerenone), n=23		IV group (BT+ rivaroxaban), n=20	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Average number of ischemia episodes during the day	2,69±0,13	2,51±0,13 Δ-6,69 p>0,05	2,24±0,11	2,10±0,1 Δ-6,25 p>0,05 p1-2<0,05	3,16±0,2	2,44±0,12 Δ-22,78 p<0,01 p1-3>0,05 p2-3<0,05	3,38±0,17	1,82±0,08 Δ-46,15 p<0,001 p2-4<0,05 p3-4<0,001
Total duration of ST segment displacement, min./day	34,61±1,7	31,2±1,56 Δ-9,85 p>0,05	31,23±1,56	27,69±1,38 Δ-11,34 p>0,05 p1-2>0,05	29,18±1,54	21,14±1,06 Δ-27,55 p<0,001 p1-3<0,001 p2-3<0,01	32,68±1,65	15,71±0,78 Δ-51,93 p<0,001 p2-4<0,001 p3-4<0,001
Average value of ST depression depth, мм	1,33±0,05	1,15±0,11 Δ-13,53 p>0,05	1,17±0,06	0,93±0,04 Δ-20,51 p<0,01 p1-2>0,05	1,35±0,07	0,84±0,03 Δ-37,78 p<0,001 p1-3<0,05 p2-3>0,05	1,29±0,07	0,65±0,03 Δ-49,61 p<0,001 p2-4<0,001 p3-4<0,001
Average value of maximum displacement of ST segment, мм	2,19±0,1	1,96±0,09 Δ-10,5 p>0,05	2,14±0,11	1,68±0,08 Δ-21,5 p<0,01 p1-2<0,05	2,21±0,11	1,36±0,07 Δ-38,46 p<0,001 p1-3<0,001 p2-3<0,01	2,31±0,12	1,11±0,06 Δ-51,95 p<0,001 p2-4<0,001 p3-4<0,05
Average heart rate during ST segment depression, per min.	74,1±2,91	64,9±2,51 Δ-12,42 p<0,05	71,5±2,62	62,23±2,51 Δ-12,97 p<0,05	73,25±2,65	63,24±2,69 Δ-13,67 p<0,05	72,31±2,78	61,46±2,45 Δ-15,0 p<0,01

Note. p – probability of indicators changes before treatment.

The average ESV in group IV patients after a twelve-month therapy course with rivaroxaban was equal to (34.84 ± 1.9) ml, which is statistically lower compared to its value before treatment – (56.14 ± 1.63) ml. EDV in these patients before treatment was equal to (125.32 ± 4.12) ml and decreased to (100.9 ± 3.56) ml after 6 months of treatment and to the level of (99.8 ± 4.76) ml after 12 months of therapy. These treatment plans did not lead to a significant dynamics of end-diastolic size (EDS) and end-systolic size (ESS) indicators in all survey groups.

The influence of the studied treatment regimens on the echocardiography of left ventricular hypertrophy (LVH) was analyzed. Table I shows that in group II patients who received BT with magnesium and potassium salts of gluconic acid, the mean value of the left ventricular myocardial mass index (LVMI) was (113.23 ± 3.52) g/m2 before treatment and decreased to (99.31 ± 2.13) g/m2 after 12 months under the influence of treatment (p <0.01). The decrease of LVMI mean value in group II patients after 6 months of therapy was not likely, which can be explained by the insufficient duration of therapy.

The mean value of LVMI was (217.71 ± 6.62) g/m2 before treatment and significantly decreased to the level (190.43 ± 5.89) g/m2 after 6 months under the influence of treatment and by 15.17% to the level (184.68 ± 5.31) g/m2 after 12 months of therapy (p <0.001) in group III patients, who received BT with eplerenone.

A similar trend was observed for left ventricular mass (LVM) in groups II and III patients. Using BT treatment with rivaroxaban in subjects from group IV has also led to a noticeable reduction in LVM and LVMI.There was noticed a statistically unreliable decrease in LVMI and LVM levels when analyzing the effect of BT on LVM indicators in patients with CHF having MI during 6 and 12 months. As can be seen from Fig. 2, the highest intensity of LV reverse remodeling processes was observed in patients who received eplerenone in addition to BT.

DISCUSSION

We have evaluated the influence of our therapy on the indicators of myocardial ischemia in patients with CHF after MI. Changes in ECG parameters in patients with CHF after MI with revascularization depending on the intended treatment medication mediators combination schemes are presented in this article. Our study has shown the proposed

Table II. Hemodynamic parameters dynamics in chronic heart failure patients after treatment

Patients' groups	EDD, cm	ESD, cm	EDV, ml	ESV, ml	УО, ml	EF, %	LVMI, g/m2	LVM, g
Healthy (n=15)	4,25±0,15	2,97±0,07	98,65±4,16	36,72±1,88	61,75±2,17	62,4±2,65	92,4±1,71	184,08±3,2
I group (n=20)								
- before treatm.	5,23±0,59	3,58±0,54	109,51±8,72	49,52±2,97	61,64±2,32	57,54±2,87	112,62±3,57	220,32±6,94
- in 6 months	5,24±0,78 Δ-0,19	3,45±0,42 Δ-3,63	107,65±2,87 Δ-1,70	37,65±2,75** Δ-23,97	60,77±2,85 Δ-1,41	59,86±2,84 Δ+4,03	108,51±3,13 Δ-3,65	215,14±6,32 Δ-2,35
- in 12 months	5,13±0,52 Δ-1,91	3,64±0,57 Δ-1,68	90,67±2,54* Δ-17,20	36,31±2,86** Δ-26,68	60,98±2,16 Δ-1,07	66,43±3,45* Δ+15,45	104,53±3,12 Δ-7,18	213,14±6,25 Δ-3,26
II group (n=21)								
- before treatm.	5,17±0,71	3,38±0,13	133,17±2,81	58,64±2,76	73,81±2,13	54,02±2,37	113,23±3,52	227,12±6,91
- in 6 months	5,79±0,84 Δ-12,0	3,34±0,56 Δ-1,18	112,6±4,42** Δ-15,45	46,87±1,2*** Δ-20,07	70,54±1,76 Δ-4,43	56,42±2,98 Δ+4,44	109,32±2,87 Δ-3,45	211,62±6,83 Δ-6,82
- in 12 months	4,99±0,21* Δ-3,48	3,35±0,42 Δ-0,89	104,82±3,45*** Δ-21,29	37,32±1,4*** Δ-36,36	66,32±1,15* Δ-10,15	63,67±1,91** Δ+17,86	99,31±2,13** Δ-12,29	196,06±6,12** Δ-13,18
III group (n=23)								
- before treatm.	5,23±0,34	3,32±0,15	129,74±4,53	58,14±2,64	71,32±2,53	55,73±2,64	109,63±3,96	217,71±6,62
- in 6 months	4,83±0,45 Δ-7,65	3,23±0,25 Δ-2,71	104,8±4,75* Δ-19,22	44,51±1,9*** Δ-23,44	67,73±2,83 Δ-5,03	58,84±1,75 Δ+5,58	96,12±3,72* Δ-12,32	190,43±5,89* Δ-12,53
- in 12 months	4,74±0,12* Δ-9,37	3,12±0,14 Δ-6,02	102,42±4,75*** Δ-21,06	34,57±1,8*** Δ-40,54	65,54±2,29* Δ-8,10	64,67±1,92** Δ+16,04	92,34±3,27** Δ-15,77	184,68±5,31*** Δ-15,17
IV group (n=20)								
- before treatm.	4,79±0,25	3,31±0,74	125,32±4,12	56,14±1,63	70,53±2,65	56,21±1,39	110,42±4,47	214,52±6,26
- in 6 months	4,76±0,24 Δ-0,63	3,36±0,36 Δ-1,51	100,9±3,56*** Δ-19,49	43,42±1,5*** Δ-22,66	61,43±3,41* Δ-12,90	58,67±1,57 Δ+4,38	100,1±3,12 Δ-9,35*	199,23±4,12 Δ-7,13*
- in 12 months	4,74±0,14 Δ-1,04	3,28±0,13 Δ-0,91	99,8±4,76*** Δ-20,76	34,84±1,9*** Δ-37,94	63,81±2,83** Δ-9,53	62,14±1,86** Δ+10,73	93,96±2,91** Δ-14,91	185,32±5,53** Δ-13,87

Note. Difference probability in comparison with indicators before treatment: *- $p<0,05$, **- $p<0,01$, *** – $p<0,001$.

treatment regimens' effectiveness in reducing ischemic events after 6 and 12 months of treatment. The following patterns were obtained while comparing baseline values and data obtained from the above-mentioned methods of patients observation: the average number of myocardial ischemia episodes during the day, the total duration of ischemia, mean and maximum depth of ST-segment depression, mean heart rate during ST-segment depression decreased in all four groups.

Treatment with rivaroxaban has proved to provide the most intense antiischemic effect. It should be noted that treatment of group IV patients with rivaroxaban on the background of BT has led to the most statistically significant change in the total duration of ST-segment displacement by 51.93% ($p < 0.001$) and in the average number of myocardial ischemia episodes in the subjects, namely by 46.15 % ($p < 0.001$). JL Mega, E. Braunwald, SA Murphy in the rivaroxaban group proved a probable reduction in the risk of stent thrombosis by 35%, cardiovascular and overall mortality by 34% and 32%, respectively, which prevented 17 cases of cardiovascular death, myocardial infarction, or stroke, 16 deaths from all causes and 7 stent thromboses [12, 13].

The use of BT with magnesium and potassium salts of gluconic acid, eplerenone, or rivaroxaban has led to the activation of the left ventricle reverse remodeling processes. However, the results showed that the highest intensity of LV reverse remodeling processes was observed in patients receiving eplerenone in addition to BT and supported by a significant decrease in mean levels of left ventricular EDD, ESD, and LVMMI in patients with CHF after MI, compared with the use of magnesium and potassium salts of gluconic acid or rivaroxaban on the background of BT. G. Mak, N. Edwards, and co-authors noted that aldosterone antagonist therapy prevents increased markers of collagen metabolism and improves diastolic function in this category of patients [14].

Thus, the use of the studied treatment plans had a positive effect on improving the left ventricle systolic function, reducing the average values of left ventricular ESD and LDD, suggesting the ability of the studied drugs to normalize cardiohemodynamics.

CONCLUSIONS

1. We have compared the initial data and data obtained after 6 and 12 months of patient follow-up and have obtained the following patterns: the total ischemia duration, frequency of daily episodes, mean and maximum value of ST-segment depression decreased in all study groups.
2. The use of combination therapy with rivaroxaban on the background of BT in patients with CHF after MI has provided a more pronounced anti-ischemic effect, compared with the use of magnesium and potassium salts of gluconic acid or eplerenone on the background of BT.
3. The use of eplerenone in the complex treatment of these patients on the background of BT has proved to provide a pronounced reverse left ventricular myocardium remodeling in the postinfarction period.

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