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DYNAMICS OF HEART FAILURE MARKERS IN PATIENTS AFTER PAST MYOCARDIAL INFARCTION WITH THE USE OF POTASSIUM AND MAGNESIUM SALTS OF GLUCONIC ACID, EPLERENONE AND RIVAROXABAN

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Abstract. **The objective of the research** was to increase the efficiency of treatment of patients with chronic heart failure (CHF) and post-infarction cardiosclerosis by adding potassium and magnesium salts of gluconic acid, eplerenone and rivaroxaban to the background therapy taking into account the indices of growth differentiation factor 15 (GDF-15), aldosterone and galectin-3.

Materials and methods of the research. Emmunoenzymometric determination of the galectin-3, GDF-15 and aldosterone levels concentration in blood serum was conducted to achieve the stated objective. 42 patients with CHF and post-infarction cardiosclerosis after coronary artery stenting in the acute period of myocardial infarction (MI) were examined. The patients were randomized into four groups according to the peculiarities of treatment. Group I included patients with CHF and post-infarction cardiosclerosis treated with the background therapy (BT). Group II consisted of patients with CHF who were treated with BT and addition of potassium and magnesium salts of gluconic acid. Group III included patients with CHF who were prescribed eplerenone secondary to BT. Group IV consisted of patients who were treated with BT and rivaroxaban.

Results. The proposed treatment regimens were proved to be effective in reduction of GDF-15, aldosterone and galectin-3 indices in 12 months of treatment. Conducted therapy with the use of rivaroxaban secondary to BT led to more intensive decrease in GDF-15 concentration in comparison with the use of potassium and magnesium salts of gluconic acid or eplerenone on the background of BT. This index constituted (2110.21±107.4) pg/ml before the treatment in these patients and significantly decreased to (1286.75±109.6) pg/ml being significantly before the therapy. The performed treatment with the use of eplerenone secondary to BT was proved to be more effective for normalization of aldosterone and galectin-3 levels in blood serum compared to other studied treatment regimens. The average value of aldosterone changed in the treatment process by 67.24%. Thus, the average level of this index constituted (139.8±7.63) pg/ml before the treatment and was equal to (45.8±5.52) pg/ml at the end of the treatment course. The average value of galectin-3 in patients with CHF and post-infarction cardiosclerosis was noted to be (34.69±1.67) ng/ml before the treatment. It constituted (22.53±0.98) ng/ml after the end of treatment being significantly lower compared to the value before the treatment. The average value of this index changed in the course of twelve-month treatment by 35.05%. Lower risk of sudden cardiac arrest (SCA), acute coronary syndrome (ACS) and stroke was observed in the patients with CHF and post-infarction cardiosclerosis with the use of rivaroxaban secondary to BT.

Conclusions. Thus, the use of rivaroxaban combination therapy secondary to BT led to more intensive decrease in GDF-15 concentration in comparison with the use of potassium and magnesium salts of gluconic acid or eplerenone. Conducted therapy with the use of eplerenone on the background of BT was more effective for the normalization of galectin-3 and aldosterone levels in the blood compared to other studied treatment regimens.

Keywords: heart failure; growth differentiation factor 15; galectin-3; eplerenone; rivaroxaban.

Problem statement and analysis of the recent research

The frequency of hospitalization and mortality in case of CHF and post-infarction cardiosclerosis remains high despite the advances in modern medicine. In this regard the search for specific markers becomes more urgent. Their task consists in early diagnosis, prognosis of CHF course and its complications, monitoring of treatment efficacy and patients' risk stratification [1].

One of the achievements of modern medicine is the discovery of a new biomarker, namely GDF-15 [9] which is a stress-induced marker, macrophage-inhibitory cytokine-1. It belongs to super family of proteins of transforming growth factor I. It is an inflammatory marker and a marker of haemodynamic load as well as apoptosis and cardiac muscle remodeling. GDF-15 prognostic value in various periods of the disease was shown in several studies where its role in risk stratification of patients with MI (GUSTO-IV, FRISC-2, ASSENT-2, AMI) was evaluated [12, 13]. Retrospective study analyses have shown that high levels of GDF-15 are associated with increased risk of death and/or repeated AMI [14]. According to some data, this biomarker is a more accurate marker of CHF with preserved left ventricular (LV) ejection fraction while natriuretic peptide (NUP) better shows the course of systolic heart failure [15]. The level of GDF-15 correlates with the severity of CHF manifestations and LV diastolic dysfunction indices [8].

The role of aldosterone in CHF development including myocardial injury is beyond argument [7]. As a component of angiotensin aldosterone system, it significantly influences fluid retention and edema formation, potassium excretion and sodium retention, remodeling, fibroid heart and vessels sclerosis. It acts at the level of cell genome like other steroid hormones. According to modern concepts, weak inhibition of aldosterone activity is one of the possible reasons for insufficient efficacy of standard therapy in the treatment of chronic heart failure with post-infarction cardiosclerosis [10].

Galectin-3 is also CHF prospective marker which belongs to the family of I-galactoside-binding proteins and is expressed by many cells including neutrophils, macrophages, labrocytes, fibroblasts and osteoblasts. It is normally not observed in cardiomyocytes [4]. According the study of E. Grandin galectin-3 is associated with the risk of CHF development after AMI. This adds evidence in favor of its use as a biomarker of adverse LV remodeling [5]. In general, the study of galectin-3 properties was conducted with the participation of more than 16 900 patients. This provides an opportunity to consider this lectin to be the most studied cardiovascular biomarker after NUP [2]. However, the possibility of its application in clinical practice remains unexplained to this day [6].

The objective of the research was to increase the efficiency of treatment of patients with chronic heart failure (CHF) and post-infarction cardiosclerosis by adding potassium and magnesium salts of gluconic acid, eplerenone and rivaroxaban to the background therapy taking into account the indices of growth differentiation factor 15 (GDF-15), aldosterone and galectin-3.

Materials and methods of the research

The research was performed at the premises of Ivano-Frankivsk Regional Clinical Cardiology Dispensary. 42 patients with CHF and post-

infarction cardiosclerosis were examined. All examined patients were divided into the following groups. Group I included 9 patients with CHF after past AMI with conducted stenting 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 75 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/week). Group II consisted of 12 patients with CHF after past AMI with conducted stenting who were treated with BT and addition of potassium and magnesium salts of gluconic acid in a dose of 360 mg 3 times per day. Group III included 11 patients with CHF after past MI with the stenting who were prescribed eplerenone in a dose of 25 mg 2 times a day secondary to BT. Group IV consisted of 10 patients with CHF after past AMI with conducted stenting who received the combined treatment with BT medication together with rivaroxaban in a dose of 2.5 mg 2 times a day.

Emmunoenzymometric determination of the galectin-3, GDF-15 and aldosterone levels concentration in blood serum was conducted to achieve the stated objective. GDF-15 level in blood serum was determined using Human GDF-15/MIC-1 ELISA ("BioVendor", Czech Republic). Galectin-3 level in blood serum was determined with the use of BMS279/2TEN, Human Galectin-3 (Bender MedSystems, Austria). Aldosterone concentration was determined using the ELISA kit (EIA-4128, Aldosterone ELISA) for the direct quantitative determination in blood serum.

Results of the research and their discussion

The therapy impact on aldosterone and GDF-15 levels in the patients' blood was analyzed.

As Table 1 shows, all studied treatment regimens led to a significant decrease in the average level of aldosterone after therapy completion. The average aldosterone concentration was found to be (125.1 ± 6.23) pg/ml before the treatment and

Table 1. The therapy impact on GDF-15 and aldosterone levels in patients with CHF after past MI

Group of patients	Aldosterone level (pg/ml)		GDF-15 level (pg/ml)	
	Before the treatment	After the treatment	Before the treatment	After the treatment
Group I BT (n=9)	125.1±6.23	100.7±6.45 Δ-19.5 p<0.05 Δ-33,92	2069.78±101.8	1821.98±104.6 Δ-11.9 p>0.05
Group II BT + potassium and magnesium salts of gluconic acid (n=11)	135.3±7.18	105.1±8.44 Δ-22.3 p<0.05 p_{1-2}>0.05	2195.08±101.6	1845.97±100.9 Δ-15.9 p<0.05 p_{1-2}>0.05
Group III BT+ eplerenone (n=12)	127.4±6.79	37.1±4.67 Δ-70.9 p<0.001 p_{1-3}<0.001 p_{2-3}<0.001	2297.64±103.6	1785.65±104.7 Δ-22.3 p<0.01 p_{1-3}>0.05 p_{2-3}>0.05
Group IV BT + rivaroxaban (n=10)	131.7±8.53	98.2±7.84 Δ-25.4 p<0.01 p_{1-4}>0.05 p_{2-4}>0.05 p_{3-4}<0.001	2365.85±102.7	1464.23±105.8 Δ-38.1 p<0.001 p_{1-4}<0.05 p_{2-4}<0.05 p_{3-4}<0.05

Note. p – the probability of difference between average values before and after the treatment; p_{1-2} – the probability of difference between average values of Group I and II; p_{1-3} – the probability of difference between average values of Group I and III; p_{2-3} – the probability of difference between average values of Group II and III; p_{2-4} – the probability of difference between average values of Group II and IV; p_{3-4} – the probability of difference between average values of Group III and IV
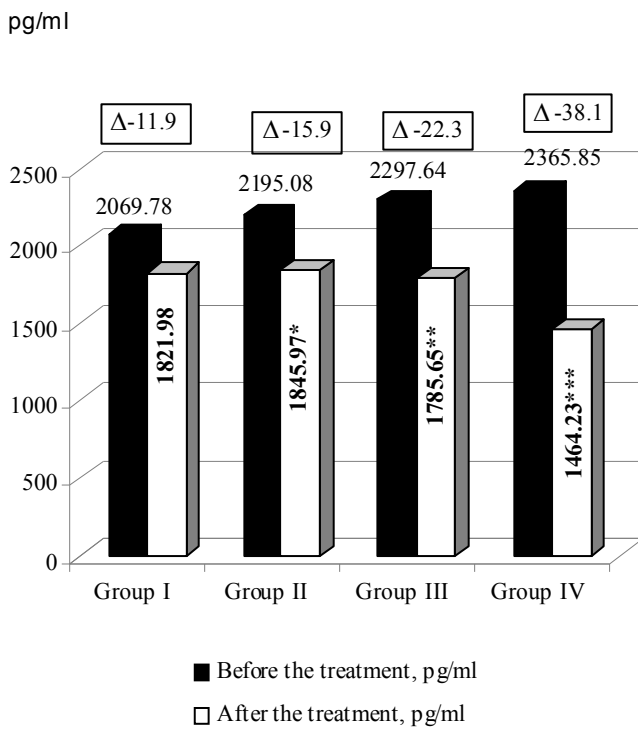
pg/ml

Fig.1. The influence of the conducted therapy on GDF-15 concentration
Note. **The probability of difference between average values before and after the treatment – *p<0.05; **p<0.01; ***p<0.001**
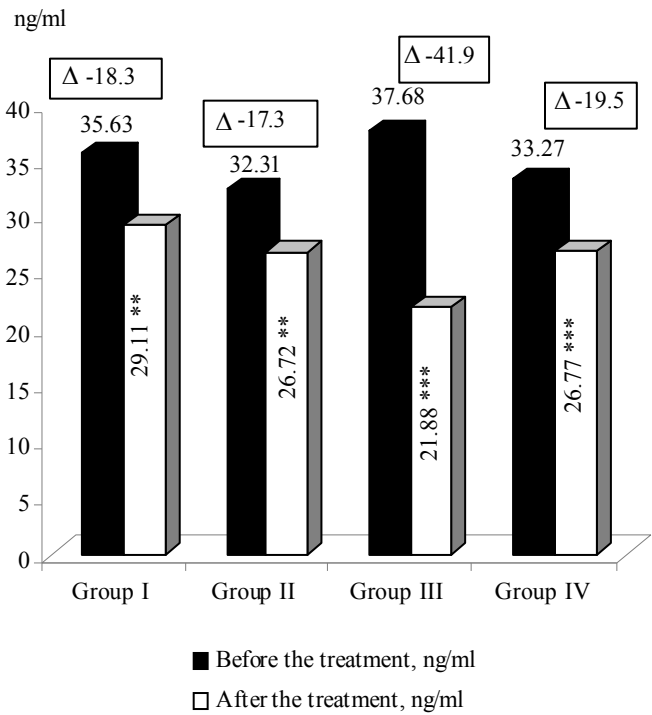
ng/ml

Fig.2. The influence of the conducted therapy on galectin-3concentration
Note. **The probability of difference between average values before and after the treatment – *p<0.05; **p<0.01; ***p<0.001**

significantly decreased under the influence of BT treatment to (100.7±6.45) pg/ml in the patients of Group I. In case of adding potassium and magnesium salts of gluconic acid to BT, the average value of this index in the patients of Group II constituted (135.3±7.18) pg/ml before the treatment and (105.1±8.44) pg/ml after the therapy (p<0.05). The application of the therapy with eplerenone in patients of Group III led to more intensive decrease in aldosterone concentration in comparison with other medications (p_{1-3}<0.001, p_{2-3}<0.001). The average value of this index changed in the course of treatment by 70.9%. Thus, the average level of this index constituted (127.4±6.79) pg/ml before the treatment and was equal to (37.1±4.67) pg/ml at the end of the treatment course. Aldosterone concentration in Group IV constituted (131.7±8.53) pg/ml before the treatment and decreased by 25.4% to the level of (98.2±7.84) pg/ml (p<0.01) under the influence of the treatment.

GDF-15 average value in the patients of Group I was found to constitute (2069.78±101.8) pg/ml before the treatment and significantly decreased to the level of (1821.98±104.6) pg/ml (p>0.05) under the influence of BT. In case of potassium and magnesium salts of gluconic acid adding to BT, the average value of this index in the patients of Group II constituted (2195.08±101.6) pg/ml before the treatment and (1845.97±100.9) pg/ml after the therapy completion which was significantly lower compared to the same value before the treatment. The average level of GDF-15 in the patients of Group III treated with eplerenone secondary to BT was (2297.64±103.6) pg/ml before the treatment and (1785.65±104.7) pg/ml (p<0.01) at the end of the treatment course. Thus, eplerenone was found to be more effective in reduction of this index concentration than potassium and magnesium salts of gluconic acid, GDF-15 level changed by 22.3% in the treatment course. Rivaroxaban therapy was determined to result in more intense decrease in GDF-15 concentration than potassium and magnesium salts of gluconic acid or eplerenone (p<0.001).

According to Fig.1, rivaroxaban treatment of group IV patients secondary to BT during 12 months contributed to a probable decrease in GDF-15 level to 38.1%. Thus, the average value of this index constituted (2365.85±102.7) pg/ml before the treatment and (1464.23±105.8) pg/ml after therapy completion which was significantly lower in comparison with the same value before the treatment. It should be noted that the application of rivaroxaban therapy secondary to BT led to a more intensive decrease in GDF-15 concentration compared to the application of potassium and magnesium salts of gluconic acid or eplerenone.

The therapy impact on galectin-3 level in the patients' blood was analyzed.

According to Fig.2, galectin-3 level was equal to (35.63±1.73) ng/ml before the treatment in patients treated with BT and significantly decreased by 18.3% to the level of (29.11±1.26) ng/ml after the course of treatment. Galectin-3 level in blood constituted (32.31±1.34) ng/ml before the treatment in the group of patients who underwent BT with the addition of potassium and magnesium salts of gluconic acid. It statistically changed after the therapy by 17.3% and constituted (26.72±1.16) ng/ml (p<0.01). Complex therapy with the use of eplerenone secondary to BT was the most effective for the normalization of galectin-3 in blood in comparison with other studied treatment regimens. Thus, this index constituted (37.68±1.53) ng/ml before the treatment in the patients of Group III and significantly decreased to (21.88±1.46) ng/ml. The average value of this index was changed in the treatment course by 41.9%. Galectin-3 level was (33.27±1.12) ng/ml before treatment and significantly decreased after therapy completion to (26.77±1.23) ng/ml (p<0.001) in the patients of Group IV who were treated with BT medication and rivaroxaban.

Odds ratio of SCA, ACS and stroke development in patients with CHF after MI depending on the characteristics of differentiated therapy were calculated.
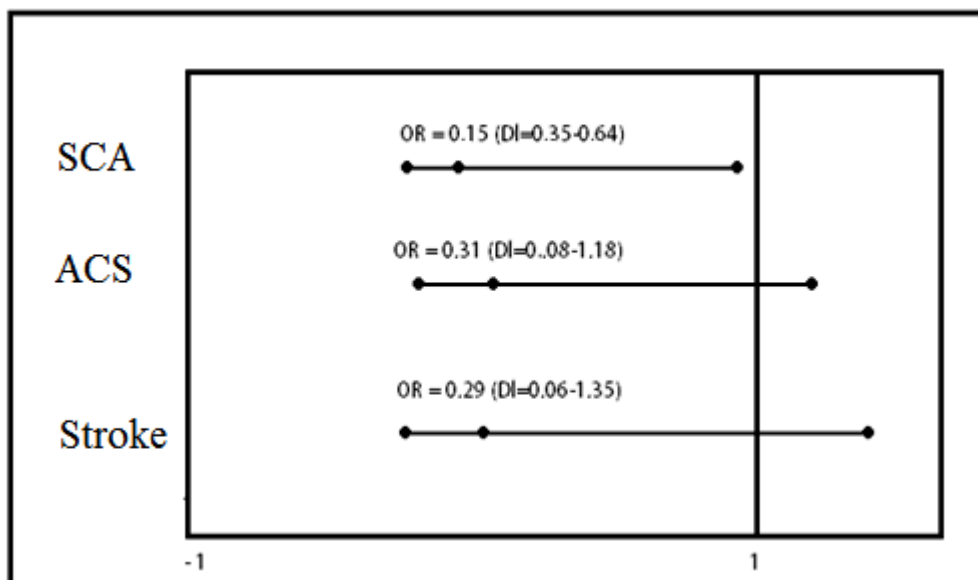
Fig.3. The odds of the studied events occurrence in the patients with CHF after MI under the influence of the background therapy
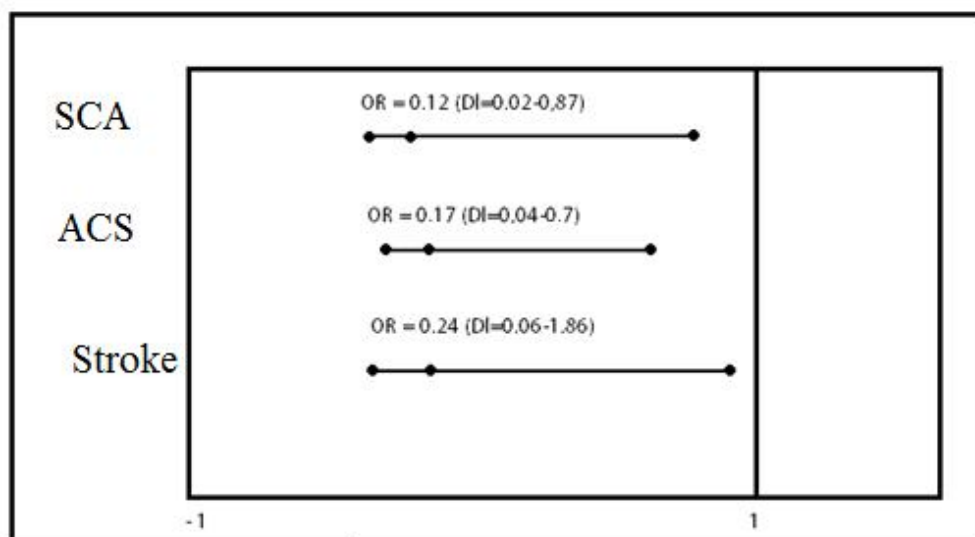

Fig. 4. The odds of the studied events occurrence in the patients with CHF after MI under the influence of the background therapy and rivaroxaban

in GDF-15concentration in comparison with the use of potassium and magnesium salts of gluconic acid or eplerenone.

2. Conducted therapy with the use of eplerenone secondary to BT was more effective for the normalization of galectin-3 and aldosterone levels in the blood compared to other studied treatment regimens.

3. Lower risk of SCA, ACS and stroke was observed in patients with CHF and post-infarction cardiosclerosis after stenting in the acute period of myocardial infarction in case of rivaroxaban use secondary to BT.

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Analysis of the odds of the studied events occurrence detected that BT application did not affect the odds of SCA (OR=0.31; CI=0.08- 1.18) and stroke (OR=0.29 (CI=0.06-1.35)) development. However, the risk of ACS development significantly decreased under BT influence (OR=0.15; CI=0.035-0.64).

At the same time the decrease in odds of not only SCA (OR=0.12 (CI=0.02-0.87)) but also of ACS (OR=0.17 (CI=0.04-0.7)) and stroke (OR=0.24; CI= 0.06-1.86) was observed in the patients of group IV in case of therapy application.

Thus, the higher efficiency of therapy in case of BT and rivaroxaban combination to prevent the development of certain complications in the postinfarction period was proved in comparison with use of BT solely in patients with CHF after MI.

Prospects for further research involve further studies aimed at the monitoring of the conducted treatment efficacy.

Conclusions

1. The use of combination therapy with rivaroxaban secondary to BT was found to lead to a more intensive decrease

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ІНДЕКСНА ХАРАКТЕРИСТИКА СТАНУ ОРГАНІВ РОТОВОЇ ПОРОЖНИНИ В ПАЦІЄНТІВ ІЗ ЧАСТКОВИМИ ДЕФЕКТАМИ ЗУБНИХ РЯДІВ

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ИНДЕКСНАЯ ХАРАКТЕРИСТИКА СОСТОЯНИЯ ОРГАНОВ РОТОВОЙ ПОЛОСТИ У ПАЦИЕНТОВ С ЧАСТИЧНЫМИ ДЕФЕКТАМИ ЗУБНЫХ РЯДОВ

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INDEXED STATE CHARACTERISTIC OF THE ORAL CAVITY IN PATIENTS WITH PARTIAL DEFECTS OF DENTITION

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Резюме. Ефективність ортопедичного лікування пацієнтів значною мірою залежить від клінічної ситуації в ротовій порожнині і, особливо, оральної гігієни. Обстежено 60 пацієнтів із частковими дефектами зубних рядів, в яких оцінювали стан гігієни ротової порожнини і тканин пародонту. Встановлений низький рівень догляду за органами ротової порожнини і високі показники запально-дистрофічних уражень тканин пародонта. Доортопедична підготовка таких пацієнтів вимагає належного догляду за ротовою порожниною на індивідуальному рівні, медикаментозну корекцію патологічних змін у тканинах пародонта.
Ключові слова: ротова порожнина, гігієна ротової порожнини, пародонт, індекси.

Резюме. Эффективность ортопедического лечения пациентов зависит от клинической ситуации в ротовой полости и, особенно, оральной гигиены. Обследовано 60 пациентов с частичными дефектами зубных рядов, в которых оценивали состояние гигиены ротовой полости и тканей пародонта.
Отмечен низкий уровень ухода за органами ротовой полости и высокие показатели воспалительно-дистрофических изменений тканей пародонта. Дооротопедическая подготовка таких больных требует особенного ухода за полостью рта на индивидуальном уровне, медикаментозной коррекции патологических изменений у тканях пародонта.
Ключевые слова: полость рта, гигиена полости рта, пародонт, индексы.

Abstract. The effectiveness of orthopedic treatment of patients is largely dependent on the clinical situation in the oral cavity, and especially in oral hygiene. It was examined 60 patients with partial defects of dentition, which assessed the state of oral hygiene and periodontal tissues. It was established the low level care by oral cavity and high rates of inflammatory and degenerative lesions of periodontal tissues. Orthopedic preparing of such patients requires proper oral care at the individual level, drug correction of pathological changes in periodontal tissues.
Key words: oral cavity, oral hygiene, paradontium, indexes.