Research Results in Pharmacology

Research Results in Pharmacology 10(3): 17–23
UDC: 615.036.8
DOI 10.18413/rrpharmacology.10.506

Research Article

Efficacy of various combined treatment regimens in patients with stable effort angina, functional classes II-III

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Academic editor: Mikhail Korokin ♦ **Received** 11 May 2024 ♦ **Accepted** 18 June 2024 ♦ **Published** 17 August 2024

Citation: Dorofeeva SG, Konoplya EN, Mansimova OV (2024) Efficacy of various combined treatment regimens in patients with stable effort angina, functional classes II-III. Research Results in Pharmacology 10(3): 17–23. https://doi.org/10.18413/rrpharmacology.10.506

Abstract

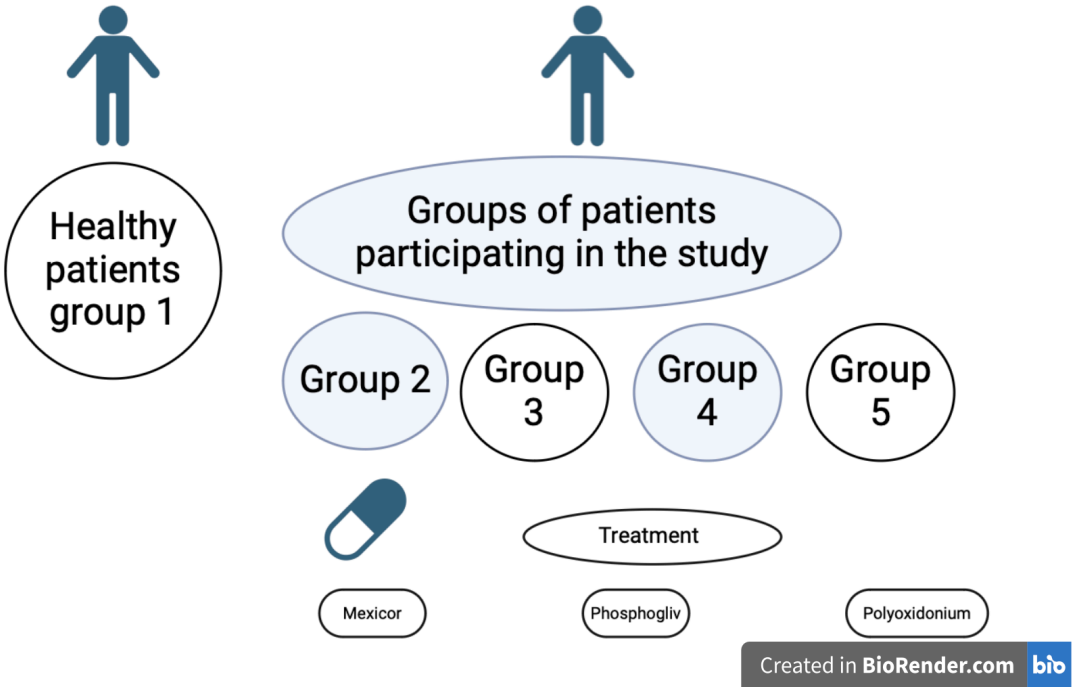
Introduction: Inflammation and metabolic disorders of cardiomyocytes are undoubtedly important pathogenetic links in the development of coronary heart disease and its complications. Our study assessed the effect of various combined treatment regimens on cycle ergometry performance and plasma concentrations of pro- and anti-inflammatory interleukins in patients with stable effort angina, functional classes II-III.

Materials and Methods: The clinical study included 120 patients diagnosed with coronary heart disease: stable effort angina, functional classes II–III, and 40 healthy participants who met the inclusion criteria. Further, four groups were randomly formed: a group receiving the standard treatment; a group receiving Mexicor for 10 days in addition to the standard treatment; a group receiving Mexicor and Phosphogliv for 10 days in an addition to the standard treatment; and a group receiving Mexicor and Polyoxidonium for 10 days in addition to the standard treatment. After the treatment, cycle ergometry performance and plasma concentrations of pro- and anti-inflammatory cytokines were assessed in the patients. Mathematical statistical analysis was carried out using Statistica 10.0 software. The statistical significance of differences between the qualitative indicators was assessed using the $\chi 2$ test. The results of the statistical analysis were considered statistically significant at $p<0.05$.

Results: The combined treatment with using the above-mentioned pharmacological agents resulted in a statistically significant improvement in cycle ergometry indicators: Mexicor made it possible to increase the threshold load power by 43.0% and the total load power – by 70.3%. In the groups of patients with coronary heart disease who had received Mexicor and Phosphogliv or Mexicor and Polyoxidonium, there was an increase in the load duration by an average of 69.0% and in the rate-pressure product – by 25%, respectively. When analyzing the dynamics of plasma concentrations of pro-inflammatory cytokines, it was found that a statistically significant decrease in the concentrations of tumor necrosis factor-α, interleukin-1ß, interleukin-6 and interleukin-10 was registered only in the groups receiving Mexicor and Phosphogliv or Mexicor and Polyoxidonium in addition to the standard treatment.

Conclusion: Applying the combined treatment regimens using Mexicor and Phosphogliv or Polyoxidonium results in the most effective improvement of the cycle ergometry performance and the dynamics of plasma concentrations of pro- and anti-inflammatory interleukins in patients with stable effort angina, functional classes II-III.

Graphical abstract



Keywords

correction, coronary heart disease, stable effort angina, cycle ergometry, interleukins, cytokines

Introduction

Coronary heart disease (CHD) is a serious disease characterized by impaired blood supply to the heart muscle due to damage to the coronary arteries. Lindstrom et al. (2022), who conducted a large-scale study of the epidemiological issues of cardiovascular diseases, found that CHD is the leading cause of death in the world among all cardiovascular diseases with an indicator of 9,440,000 (8,820,000-9,960,000) deaths in 2021. In the Russian Federation in 2021, according to The Russian Federal State Statistics Service (Rosstat), the number of deaths from coronary heart disease was 507,793 people. Moreover, the vast majority of those patients had suffered from chronic forms of coronary heart disease.

As of today, treatment for CHD includes various pharmacological and surgical methods aimed at improving blood flow to the heart and reducing the formation of atherosclerotic plaques and blood clots (RSC 2020). However, in spite of significant advances in these areas, the existing approaches to treating such patients require further study and consideration in order to be optimized (Zyryanov et al. 2020; Pribylov et al. 2024). One of the promising directions is the search for pharmacological and biotechnological agents to help reduce the inflammatory response supported by immune cells, platelets, endothelial cells, etc. (Pello Lázaro et al. 2021).

On the other hand, an important link in the CHD pathogenesis is a change in metabolic processes in the myocardium, characterized by impaired energy metabolism, formation of oxidative stress and acidosis, and, as a result, apoptosis of cardiomyocytes (Yehualashet et al. 2020). Thus, metabolic modulation is also a promising strategy for treating CHD, since changes in energy metabolism are involved in disease progression.

Materials and Methods

The protocol of the study conducted on the basis of the private clinic hospital “RZD-Medicine” and regional state-financed healthcare facility “City Hospital No. 3” in Kursk City, Russia, was approved by the Regional Ethics Committee (Minutes No. 2 dated 18 February 2013).

Experimental design

The study included 40 healthy participants (22 women and 18 men aged 40-65 years), and 120 participants diagnosed with coronary heart disease (62 women and 58 men aged 40-65 years). The criteria for including patients into and excluding them from the study are shown in Table 1.

Using a simple unrestricted method, the patients were randomized into four groups, the characteristics of which are shown in Table 2.

Table 1. Inclusion and exclusion criteria for patients

Criteria for including patients in the study	Criteria for excluding patients from the study
• men and women aged 40-65 years; • voluntary informed consent of patients to conduct the study; • presence of coronary heart disease: stable effort angina (functional classes II-III) confirmed clinically and through cycle ergometry test; • diagnosis documented by a history of myocardial infarction and positive results of exercise tests; • regular use of antianginal medication before the study initiation; • neither alcohol nor drug addiction; • patient's ability to independently fill out the questionnaire.	• hemodynamically significant rhythm and conduction disturbances; progressive or unstable angina; • stenting surgery; • stable effort angina (functional class IV); • echocardiography data: LV-EF <40%; • uncontrolled diabetes mellitus; • acute cerebrovascular disease, persistent functional disorders due to previous vascular accidents; • history of angioedema; • renal, hepatic and respiratory failure; counterindications for the prescription or hypersensitivity to any of the drugs used in the study; • need for other cardiovascular treatment; • presence of side effects and/or obvious ineffectiveness of the prescribed drugs; • participation in another clinical drug trial over the last 3 months; • presence of an inflammatory process of any etiology and its localization or relief at least 7 days before blood sampling to qualify for the study.

Table 2. Characteristics of the groups participating in the study

No.	Group characteristics	Group name	Intervention characteristics
1.	19 men 21 women; aged 51.18±0.75 years on average	Standard treatment	Metoprolol: 50±25 mg/day; Acetylsalicylic acid: 75±25 mg/day; Perindopril: 8 mg/day; Nitroglycerine: 0.5 mg as needed
2.	20 men 20 women aged 51.18±0.75 years on average	Standard treatment + Mexicor	Interventions of the standard treatment group + Ethylmethylhydroxypyridine succinate: 250 mg/day for 10 days
3.	10 men 11 women aged 51.18±0.75 years on average	Standard treatment + Mexicor + Phosphogliv	Interventions of the standard treatment group + Ethylmethylhydroxypyridine succinate: 250 mg/day for 10 days + Phospholipids and sodium glycyrrhizinate: 5 g/day for 10 days
4.	9 men 10 women aged 51.18±0.75 years on average	Standard treatment + Mexicor + Polyoxidonium	Interventions of the standard treatment group + Ethylmethylhydroxypyridine succinate: 250 mg/day for 10 days + Azoximer bromide: 6 mg/day for 10 days

Determination of cytokine levels

On the 11th day of the treatment, in the morning on an empty stomach, blood was sampled into vacuum tubes with heparin, then centrifuged and, in order to obtain red blood cell membrane samples, blood plasma was frozen at a temperature of -70 °C. Next, plasma concentrations of pro-inflammatory cytokines were assessed: interleukin 1β (IL-1β), interleukin 6 (IL-6), tumor necrosis factor α (TNFα) and anti-inflammatory cytokines – interleukin 4 (IL-4) and interleukin 10 (IL-10). For that, the enzyme-linked immunosorbent assay using the Vector-Best (Russia) and e-Biosciences (USA) kits was applied. The results of the analysis were measured spectrophotometrically by means of an Anthos spectrophotometer (Biohrom Ltd., UK).

Exercise tolerance assessment

The patients' exercise tolerance was assessed by using the method of paired cycle ergometer tests with an intermittent, stepwise-increasing loading. The study was carried out on an empty stomach in the morning or 1.5-2 hours after a meal; the interval between the paired tests was at least 24 hours. Submaximal load was calculated according to the R. Shephard nomogram. The total load duration was limited to 16 minutes, with the duration of each stage and the pause between them being 4 minutes.

The following indicators were calculated: threshold load power (W_{th}, W), total load power (W_t, W), load duration (min), rate-pressure product (RPP) according to the well-recognized methods.

Statistical processing

A mathematical statistical analysis was performed by means of Statistica 10.0 software (StatSoft Inc., USA). The normality of distribution was tested using the Kolmogorov-Smirnov test. The results were described with the arithmetic mean M and its standard deviation ±σ. The mean and standard error of the mean were determined for a normal distribution of the parameter. Otherwise, the quartile intervals (25^{th}, 50^{th} and 75^{th} percentiles) were determined.

Statistical analysis was performed with the nonparametric Mann-Whitney test. The statistical significance of differences between the qualitative indicators was assessed using the $\chi 2$ test. The results of the statistical analysis were considered statistically significant at $p<0.05$.

Results

Studying the cycle ergometry performance in patients with CHD (stable effort angina, functional classes II-III) yielded the following results: there was a decrease in exercise tolerance during the cycle ergometry test (CET). The average W_{th} was 77.3 W. At the same time, there was a decrease in W_t by an average of 448.9 W and a sharp decrease in load duration by an average of 6.4 minutes. RPP was 174.5±3.5 RU. The use of the traditional pharmacotherapy made it possible to increase the threshold load power in patients by 17.8% and the total load power by 58.6% as compared to those before treatment. At the same time, the load duration increased to 9.3±0.4 minutes, and RPP increased on average to 190.7 RU. Adding Mexicor to the standard treatment regimen in patients with CHD: stable effort angina (functional classes II-III) made it possible to increase W_{th} to 106.3±1.6 W, which is 43.0% higher than in the group before treatment, and W_t to 764.5±45.1, which is 70.3% higher than before treatment.

Along with an increase in the level of threshold load power and the total load power, in the group of CHD patients who had received Mexicor with Phosphogliv, there was an increase in the load duration by 68.0% and in RPP by 24.3%, respectively, as compared to the indicators before treatment.

In the group of CHD patients who had additionally received Mexicor and Polyoxidonium, the load duration increased by 70.0% and RPP increased by 26.4%, respectively, as compared to those before treatment. All the studied indicators in the group of patients treated with Mexicor and Polyoxidonium were significantly higher than in the group who had received only the standard treatment.

An assessment of pro- and anti-inflammatory cytokines in blood plasma and biochemical markers of inflammation in the experimental groups was also carried out.

Unlike in healthy controls, in CHD patients there was a statistically significant increase in the concentration of pro-inflammatory cytokines: TNFα increased 3.6 times, IL-1β – 2.9 times, and IL-6 – by 26.0%, whereas the concentration of the anti-inflammatory cytokine IL-4 decreased by 30.0%. However, the concentration of IL-10 did not decrease, but rather increased 2.1 times.

After 10 days of treatment, there were observed changes in the immune status indicators (Table 4).

Adding Mexicor and Phosphogliv to the standard treatment in patients with CHD: stable effort angina (functional classes II-III) made it possible in this category of patients, unlike other groups, to normalize the level of IL-1β to the level of healthy controls and to correct the levels of IL-6, IL-4, TNFα and to reduce the level of IL-10 almost to the norm.

Adding Polyoxidonium and Mexicor to the standard treatment in patients with CHD: stable effort angina (functional classes II-III) reduced the concentrations of proinflammatory cytokines (TNFa, IL-1β, IL-6) in blood plasma. At the same time, the level of TNFα was corrected to that of healthy controls, and the level of IL-1β decreased, but not to the level of healthy controls. The use of an immunomodulators made it possible to increase the level of anti-inflammatory cytokine – IL-4.

Table 3. Dynamics of changes in CET indicators in patients with CHD: stable effort angina (functional classes II-III) in different pharmacological regimens (M±m)

Indicators	Patients with CHD: stable effort angina (functional classes II-III)				
	Before treatment	After ST	After ST + Mexicor	After ST + Mexicor + Phosphogliv	After ST + Mexicor + Polyoxidonium
W_{th}, W	74.3±2.9	87.5±2.6	106.3±1.6*	110.2±1.23*¹	112.5±1.01*¹
W_t, W	448.9±37.5	711.8±49.4	764.5±45.1*	778.1±20.23*¹	780.1±12.23*¹
Load duration, min	6.4±0.4	9.3±0.4	10.5±0.3*	13.2±0.2*¹	14.4±0.1*¹
RPP, RU	174.5±3.5	190.7±5.3	209.9±5.1*	216±4.7*¹	220±3.6*¹

***Note*:** * – $p<0.05$-0.001 as compared to the indicators of patients who received standard treatment (10 days); *¹ – $p<0.05$ as compared to the indicators of patients who received standard treatment in combination with Mexicor (10 days); ST – standard treatment; W_{th}, W – threshold load power, W_t, W – total load power, RRP – rate-pressure product, CHD – coronary heart disease, CET – cycle ergometry test.

Table 4. Indicators of plasma concentrations of key cytokines in patients with CHD: stable effort angina (functional classes II-III) in different treatment regimens (M+m)

Indicators	Patients with CHD: stable effort angina (functional classes II-III)					
	Healthy	Before treatment	After ST	After ST + Mexicor	After ST + Mexicor + Phosphogliv	After ST + Mexicor + Polyoxidonium
TNFα, pg/mL	5.85±0.73	22.1±1.4	21.3±1.2	15.9±0.27*	9.73±0.34*¹	5.73±0.77*¹
IL-1ß, pg/mL	3.33±0.21	14.61±1.16	10.3±1.06	9.8±0.67	3.29±0.26*¹	4.09±0.96*¹
IL-6, pg/mL	7.8±1.01	19.09±1.18	9.46±0.87	8.03±0.4	7.45±0.55*¹	7.23±1.08*¹
IL-4, pg/mL	2.02±0.08	0.87±0.07	0.89±0.31	1.94±0.03	2.51±0.06*¹	2.11±0.06*¹
IL-10, pg/mL	0.54±0.09	1.12±0.2	2.41±0.27	2.16±0.08	1.88±0.21*¹	1.07±0.06*¹

Note: * – p<0.05-0.001 as compared to the indicators of patients who received standard treatment (10 days); *¹ – p<0.05 as compared to the indicators of patients who received standard treatment in combination with Mexicor (10 days); ST – standard treatment; CHD – coronary heart disease.

Discussion

Inflammation plays an important role at various stages of the cardiovascular continuum. In recent decades, a great number of studies have emphasized the role of inflammation in atherogenesis, atherothrombosis, two-way interactions with various cardiovascular risk factors, and characterized its further influence on these dynamic processes (Amin et al. 2020; Lawler et al. 2021; Vilela and Fontes-Carvalho 2021). Another factor to influence the course and outcomes of CHD, in addition to atherogenesis, is a pathogenetic interaction between the inflammatory reaction activity and the hemostatic system, which can lead to the formation of a prothrombotic state (Stark and Massberg 2021; Dimitroglou et al. 2023).

Some of the key components of the inflammatory response is the synthesis of chemokines, including interleukins, both pro- and anti-inflammatory (Amin et al. 2020). Like in a number of clinical studies and evaluation of their results (Zhang and Dhalla 2024), we have also demonstrated an increase in plasma concentrations of the key pro-inflammatory cytokines – IL-1ß by 2.9 times, necrosis factor alpha by 2 times, and interleukin 6 by 2.2 times. According to researchers, interleukin 6 has a special place in the pathogenesis of cardiovascular diseases, including coronary heart disease (Ridker and Rane 2021). Due to this, a search is under way for strategies aimed at reducing its production (including the application of the standard treatment by means of statins, acetylsalicylic acid and agents affecting the renin-angiotensin-aldosterone system) and selectively influencing the IL-6 system through using monoclonal antibodies to the human receptor for this cytokine, developed for the treatment of rheumatological patients (Dimitroglou et al. 2023). A new IL-6 ligand inhibitor, ziltivekimab, has entered a clinical trial stage (Ridker and Rane 2021; Dimitroglou et al. 2023).

Conspicuous is not only the increase in the production of pro-inflammatory cytokines, but also of such an anti-inflammatory cytokine as interleukin 10 – it doubled as compared to that in healthy controls. Similar results were obtained by Welsh et al. (2011), who demonstrated the link between an increased IL-10 concentration and the development of cardiovascular diseases in seniors. It can be assumed that an increase in the level of this chemokine can be associated with the activation of the endogenous system aimed at relieving low-grade inflammation and serves as a surrogate marker of a pro-inflammatory environment.

One of the new directions of drug therapy for coronary heart disease is the use of anti-inflammatory drugs (Pello Lázaro et al. 2021) and drugs with metabolic effect (Yehualashet et al. 2020), as these processes significantly contribute not only to atherogenesis, but also to the formation of blood clots and the development of complications. One of such drugs is ethylmethylhydroxypyridine succinate. Golikov et al. (2004) found that in patients with acute myocardial infarction, Mexicor contributed to a reduction in areas of akinesia and restoration of segmental contractility, and in patients with unstable angina, it contributed to a more pronounced reduction in the frequency, duration and severity of myocardial ischemia and to the stabilization of the patients' condition. The present study has also identified its ability to favorably influence the clinical course of stable effort angina: in comparison with the standard treatment group, the addition of Mexicor contributed to a statistically significant improvement in the cycle ergometry performance: the increase in the total load power was over 41%.

Another study showed the ability of Mexicor to reduce the severity of an acute exacerbation of chronic obstructive pulmonary disease in patients with comorbidity (Nastroga 2014). The administration of a 5% solution for 15 days helped reduce the patients' stay in the hospital and statistically significantly improved their quality of life.

In our study, along with Mexicor, two other drugs with metabolic and anti-inflammatory properties: Phosphogliv and Polyoxidonium – demonstrated protective effects, which resulted in a decreased level of pro-inflammatory cytokines among others. The earlier studies found that one of the components of Phosphogliv, glycyrrhizic acid, exhibits both anti-atherosclerotic and anti-inflammatory

properties (Zhao et al. 2021; Zhu et al. 2024), among other things through a decrease in the activity of macrophages, as well as the expression of α-SMA in smooth muscle cells of blood vessels and inflammatory factors.

In a clinical study by Aleinikova et al. (2021), the ability of Mexicor and Polyoxidonium in combination with the background treatment was proved to statistically significantly improve both clinical and functional, as well as electrophysiological parameters in patients with cardiorespiratory pathology (Aleinikova et al. 2021), which was attributed to an increased functional activity of cardiomyocytes and a decreased inflammatory response in the lung tissue.

Thus, the results of the present study indicate an increased effectiveness of pharmacotherapy for coronary heart disease by using Mexicor, Phosphogliv, Polyoxidonium and their combinations. This is evidenced by a statistically significant improvement in cycle ergometry performance and the dynamics of changes in plasma combinations of pro- and anti-inflammatory cytokines.

Conclusion

The present study evaluated the indicators of cycle ergometry performance and cytokine status when using different combined treatment regimens in patients with coronary heart disease: stable effort angina (functional classes II-III).

In the group of patients with stable effort angina (functional classes II-III) when applying the standard treatment, no improvement in the levels of either basic pro-inflammatory cytokines IL-1β and IL-6, the factor of tumor necrosis α, or anti-inflammatory cytokines – IL-4 and IL-10 was observed. In patients of this group, when Mexicor and Phosfoglyv, as well as Mexicor and Polyoxidonium were added to the standard treatment, the levels of major pro-inflammatory and anti-inflammatory cytokines were reliably reduced or corrected.

A statistically reliable improvement in cycle ergometry performance was also noted. In the group of patients with coronary heart disease who additionally received a combined treatment, the duration of physical activity increased in comparison with the indicators before the treatment, and the rate pressure product also went up.

Therefore, it is reasonable to include the combined regimen in the standard treatment of patients with stable effort angina (functional classes II-III).

Conflict of interests

The authors declare no conflict of interests.

Data availability

All of the data that support the findings of this study are available in the main text.

References

- Aleinikova KS, Efremova OA, Kamyshnikova LA, Pogurelskaya EP (2021) Effect of combination therapy on parameters of cardiovascular system in patients with cardiorespiratory pathology. Bulleting of Surgut State University. Medicine [Vestnik SurGU. Meditsina] 1(47): 36–41. https://doi.org/10.34822/2304-9448-2021-1-36-41 [in Russian]
- Amin MN, Siddiqui SA Ibrahim M, Hakim ML, Ahammed MS, Kabir A, Sultana F (2020) Inflammatory cytokines in the pathogenesis of cardiovascular disease and cancer. SAGE Open Medicine 8: 2050312120965752. https://doi.org/10.1177/2050312120965752 [PubMed] [PMC]
- Dimitroglou Y, Aggeli C, Theofilis P, Oikonomou E, Chasikidis C, Tsioufis K, Tousoulis D (2023) Novel anti-inflammatory therapies in coronary artery disease and acute coronary syndromes. Life (Basel) 13(8): 1669. https://doi.org/10.3390/life13081669 [PubMed] [PMC]
- Golikov AP, Mikhin VP, Polumiskov VY, Boĭtsov SA, Boguslovskaya EN, Vesel'eva NV, Lukyanov MM, Rudnev DV, Frolov AA (2004) Efficacy of cytoprotective agent Mexicor in urgent cardiology. Therapeutic Archives [Terapevticheskiy Arkhiv] 76(4): 60–65. [PubMed] [in Russian]
- Lawler PR, Bhatt DL, Godoy LC, Lüscher TF, Bonow RO, Verma S, Ridker PM (2021) Targeting cardiovascular inflammation: next steps in clinical translation. European Heart Journal 42(1): 113–131. https://doi.org/10.1093/eurheartj/ehaa099 [PubMed]
- Lindstrom M, DeCleene N, Dorsey H, Fuster V, Johnson CO, LeGrand KE, Mensah GA, Razo C, Stark B, Varieur Turco J, Roth GA (2022) Global burden of cardiovascular diseases and risks collaboration. 1990-2021. Journal of the American College of Cardiology 80(25): 2372–2425. https://doi.org/10.1016/j.jacc.2022.11.001 [Pubmed]
- Nastroga TV (2014) Effectiveness of cytoprotective therapy in the complex treatment of patients with chronic coronary heart disease with concomitant COPD. Bulletin of Problems of Biology and Medicine 2(4): 157–161.
- Pello Lázaro AM, Blanco-Colio LM, Franco Peláez JA, Tuñón J (2021) Anti-inflammatory drugs in patients with ischemic heart disease. Journal of Clinical Medicine 10(13): 2835. https://doi.org/10.3390/jcm10132835 [PubMed] [PMC]
- Pribylov SA, Leonidova KO, Pribylov VS, Gavrilyuk EV, Pribylova NN (2024) Approaches to therapy Amlodipine/Indapamide/Perindopril therapy of high arterial hypertension in ischemic heart disease patients with chronic kidney disease stage 1-3 after coronary stenting. Research Results in Pharmacology10(2): 49–55. https://doi.org/10.18413/rrpharmacology.10.475
- Ridker PM, Rane M (2021) Interleukin-6 signaling and anti-interleukin-6 therapeutics in cardiovascular disease. Circulation Research 128(11): 1728–1746. https://doi.org/10.1161/CIRCRESAHA.121.319077 [PubMed]
- RSC – Russian Society of Cardiology (RSC) (2020) Clinical practice guidelines for stable coronary artery disease. Russian Journal of Cardiology [Rossijskij Kardiologicheskij ZHurnal] 25(11): 4076. https://doi.org/10.15829/29/1560-4071-2020-4076 [in Russian]
- Stark K, Massberg S (2021) Interplay between inflammation and thrombosis in cardiovascular pathology. Nature Reviews Cardiology 18(9): 666–682. https://doi.org/10.1038/s41569-021-00552-1 [PubMed] [PMC]
- Vilela EM, Fontes-Carvalho R (2021) Inflammation and ischemic heart disease: The next therapeutic target? Revista Portugesa Cardiologia (English Ed). 26: S0870-2551(21)00321-8. https://doi.org/10.1016/j.repc.2021.02.011 [PubMed]
- Welsh P, Murray HM, Ford I, Trompet S, de Craen AJM, Jukema JW, Stott DJ, McInnes IB, Packard CJ, Westendorp Naveed Sattar RGJ (2011) Circulating interleukin-10 and risk of cardiovascular events: a prospective study in the elderly at risk. Arteriosclerosis, Thrombosis, and Vascular Biology 2011; 31(10): 2338–2344. https://doi.org/10.1161/ATVBAHA.111.231795 [PubMed]
- Yehualashet AS, Belachew TF, Kifle ZD, Abebe AM (2020) Targeting cardiac metabolic pathways: a role in ischemic management. Vascular Health and Risk Management 16: 353–365. https://doi.org/10.2147/VHRM.S264130 [PubMed] [PMC]
- Zhang H, Dhalla NS (2024) The role of pro-inflammatory cytokines in the pathogenesis of cardiovascular disease. International Journal of Molecular Sciences 25(2): 1082. https://doi.org/10.3390/ijms25021082 [PubMed] [PMC]
- Zhao Y, Li W, Zhang D (2021) Gycyrrhizic acid alleviates atherosclerotic lesions in rats with diabetes mellitus. Molecular Medicine Reports 24(5): 755. https://doi.org/10.3892/mmr.2021.12395 [PubMed] [PMC]

- Zhu K, Fan R, Cao Y, Yang W, Zhang Z, Zhou Q, Ren J, Shi X, Gao Y, Guo X (2024) Glycyrrhizin attenuates myocardial ischemia reperfusion injury by suppressing Inflammation, oxidative stress, and ferroptosis via the HMGB1-TLR4-GPX4 pathway. Experimental Cell Research 435(1): 113912. https://doi.org/10.1016/j.yexcr.2024.113912 [PubMed]
- Zyryanov SK, Fitilev SB, Vozzhaev AV, Shkrebniova II, Klyuev DA (2020) Critical aspects of the management of stable coronary artery disease in primary care practice or how to increase the efficacy of evidence-based pharmacological therapy?. Research Results in Pharmacology 6(3): 15–20. https://doi.org/10.3897/rrpharmacology.6.53615

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