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SYNTHETIC AND PLANT-BASED CARDIOPROTECTORS

Actuality. *In diseases and emergencies of the cardiovascular system, cardioprotectors are included in complex pharmacotherapy – drugs that eliminate metabolic disorders. Along with synthetic drugs, a large group is made up of herbal preparations, including those of complex composition. These drugs cause changes in cellular metabolism, membrane transport, membrane structure and function.*

Purpose of the study. *To establish the mechanisms of action of cardioprotectors of synthetic and plant origin.*

Materials and research methods. *Based on domestic and foreign literature and online publications SCOPUS, «Web of Science», Google Scholar, determine the mechanism of action and pharmacodynamics of synthetic and herbal cardioprotectors.*

Research results and their discussion. *As a result of the conducted research, the main groups of synthetic drugs were identified, which include mildronate, nitrates and especially nicorandil, trimetazidine, ranolazine, ATP-long, succinic acid preparations, thiotriazoline, quercetin, coenzyme Q, arginine. Among herbal remedies – polyphenols, thiols. Separately, such herbal preparations as resveratrol, quercetin are highlighted.*

Conclusions. *The work defines the classification of cardioprotectors, provides the main aspects of the pharmacodynamics of synthetic and a number of herbal preparations, which will contribute to their targeted use in clinical practice.*

Key words: *cardioprotectors, synthetic, herbal, phytopreparations, cardiovascular system.*

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СИНТЕТИЧНІ ТА РОСЛИННІ КАРДІОПРОТЕКТОРИ

Актуальність. *При захворюваннях та невідкладних станах серцево-судинної системи в комплексну фармакотерапію включають кардіопротектори – лікарські засоби, які усувають порушення метаболізму. Поряд із синтетичними лікарськими засобами велику групу становлять рослинні препарати, у тому числі комплексного складу. Ці препарати викликають зміни клітинного метаболізму, мембранного транспорту, структури та функції мембрани.*

Мета дослідження *– установити механізми дії кардіопротекторів синтетичного та рослинного походження.*

Матеріал і методи. *На підставі вітчизняної, зарубіжної літератури та Інтернет-видань SCOPUS, Web of Science, Google Scholar визначити механізм дії та фармакодинаміку синтетичних та рослинних кардіопротекторів.*

Результати дослідження. *У результаті проведених досліджень виділено основні групи синтетичних лікарських засобів, до яких належать мілдронат, нітрати й особливо нікорандил, триметазидин, ранолазин, АТФ-лонг, препарати бурштинової кислоти, тіотриазоліну, кверцетину, коензиму Q, аргініну. Серед рослинних засобів – поліфеноли, тіоли. Окремо зупиняються на таких рослинних препаратах, як ресвератрол, кверцетин.*

Висновок. *У роботі визначено класифікацію кардіопротекторів, надано головні аспекти фармакодинаміки синтетичних та низки рослинних препаратів, що сприятиме їх цілеспрямованому застосуванню у клінічній практиці.*

Ключові слова: *кардіопротектори, синтетичні, рослинне, фітопрепарати, серцево-судинна система.*

Introduction. Cardioprotectors are drugs that eliminate disorders, primarily of metabolism and membrane functions, and prevent their irreversible consequences. Drugs that have a cardioprotective effect should affect:

– cellular metabolism;

– ion homeostasis;

– the structure and function of membranes, preventing the development of their irreversible damage during reperfusion.

We consider another definition possible: cardioprotectors are agents that optimize heart function both under normal physiological conditions and in pathology, and also prevent the effects of damaging exogenous and endogenous factors.

Classical cardioprotectors (cytoprotectors) protect cardiomyocytes from ischemia-reperfusion at the cellular level and thus have a positive effect on hemodynamics.

Based on the definition, two groups of drugs with a cardioprotective effect can be distinguished: direct action (reduce the severity of the impact of exogenous and endogenous factors directly on cardiomyocytes in normal and pathological conditions of the heart muscle) and indirect action (reduce the load on the heart muscle by affecting other organs and systems).

The effect of direct cardioprotectors is due to both local (membrane stabilization, effect on metabolism directly in cardiomyocytes, vasodilator effect) and central (regulation of vascular tone via the CNS) action.

Direct cardioprotectors include drugs that affect mainly the myocardium:

1. Selective slow calcium channel blockers (calcium antagonists): verapamil, nifedipine, amlodipine, felodipine, lacidipine, diltiazem.

2. Drugs with a predominant effect on energy processes: trimetazidine, mildronate, ATP-long (ATP-forte), neoton (creatine phosphate), asparkam (K^+-Mg^{2+} asparaginate), combined drug rhythmocor (K^+-Mg^{2+} gluconate), cardonate (lysine hydrochloride, carnitine chloride, pyridoxal phosphate, cocarboxylase chloride, cobamamide), kratal (taurine, thick hawthorn fruit extract, stinging nettle extract), glutargin (glutamic acid, arginine).

3. Anabolic steroids and non-steroidal agents: nandrolone, methandienone, potassium orotate, riboxin, magnerot, corargin (riboxin, L-arginine).

4. Antiarrhythmic agents that stabilize the membrane of myocardial cells: amiodarone, ajmalin, disopyramide, lidocaine, mexiletine, propafenone, flecainide.

5. Agents that reduce the myocardium's need for oxygen and improve its blood supply are organic nitrates (nitroglycerin, isosorbide dinitrate, isosorbide mononitrate) and coronary dilators with a similar mechanism of action - molsidomine.

6. β-adrenergic blockers (bisoprolol, metoprolol, nebivolol, etc.) and α- and β-adrenergic blockers (carvedilol, etc.).

7. Antioxidants: tocopherol, ascorbic acid, quercetin, corvitin (soluble quercetin), lipoflavone (liposomal form of quercetin), thiotriazolin, ceruloplasmin, mexidol, mexicor, stimol (citrulline maleate), emoxipin, vitamin and adrenopeptide complexes.

8. Electron acceptors: cytochrome C, riboflavin, coenzyme Q.

9. Na^+/H^+ channel inhibitors: amiloride.

10. Agents that open ATP-dependent K^+ channels: nicorandil, etc.

11. Phytopreparations of vitamins, amino acids.

There are three pathophysiological variants of heart failure:

1. Overload failure («afterload»): develops in diseases that cause increased resistance to cardiac output in a certain part of the heart.

2. Insufficiency due to myocardial damage. Causes may include intoxication, infection, vitamin deficiency, hypoxia.

3. Heart failure caused by reduced venous return («preload»): in venous diseases, vascular paresis, significant blood loss, etc.

4. Mixed form.

The positive effect is the uncoupling of the processes of excitation and contraction. In addition, due to the inhibition of the ATPase enzyme, the utilization of macroergic phosphates and oxygen consumption are reduced. These effects are due to the following mechanisms:

1. Selective inhibition of the transmembrane current of calcium ions into the heart cell: verapamil.

2. Reducing the number of functioning calcium channels: nifedipine, amlodipine, felodipine, lacidipine, lercanidipine.

3. Decreased activity of Na^+/K^+-ATPase: procainamide, quinidine sulfate, moracizin and other membrane stabilizers.

4. Increasing membrane permeability for potassium ions: lidocaine, phenytoin.

5. Inhibition of Na^+/H^+ exchange: amiloride, trimetazidine.

Drugs that stabilize cardiomyocyte membranes:

1. Prevention of accumulation of underoxidized fatty acid metabolism products: mildronate.

2. Normalization of the composition of membrane phospholipids and blocking of free radical oxidation catalysts: carnosine.

3. Neutralization of free radicals: tocopherol, quercetin.

4. Superoxide radical scavenging: ceruloplasmin, etc.

5. Increasing glutathione levels: glutamic acid, methionine, taurine, acetylcysteine, trimetazidine, etc.

6. Reducing the intensity of free radical reactions in mitochondria: mildronate, trimetazidine, neoton.

Drugs that affect myocardial metabolism:

1. Decrease in the content of acyl-coenzyme A in the myocardium: mildronate, trimetazidine.

2. Acceleration of glucose metabolism: mildronate, trimetazidine, etc.

3. Increasing glucose oxidation: L-carnitine preparations.

4. Reducing the flow of fatty acids into the myocardium: nicotinic acid, insulin.

5. Reducing the intensity of free radical reactions: mildronate, trimetazidine, exogenous creatine phosphate.

Areas of hibernated («sleeping») myocardium can recover their function under the influence of revascularization or the use of drugs (Hassan et al., 2023). Risk factors include hyper- and dyslipidemia, accumulation of free fatty acids (FFA) and their detergent metabolites (acyl- and β-hydroxyacyl-CoA, acylcarnitine) in the myocardium (N. Rong et al., 2023). β-oxidation of fatty acids occurs in mitochondria with the participation of a multienzyme complex(X.-Y. Wei et al., 2023). Carnitine (γ-trimethylamino-β-oxybutyrate) is a carrier of acyl groups. Acyl-CoA and acylcarnitine can have a damaging effect on plasma membranes and are arrhythmogenic agents (N. Rong et al., 2023). In ischemia, it is important to shift the balance of ATP production towards glucose oxidation (aerobic glycolysis)(X.-Y. Wei et al., 2023). Such a pharmacological drug is mildronate (N. Rong et al., 2023).

Research objective– to provide a modern pharmacotherapeutic characteristic of cardioprotectors of synthetic and plant origin.

Research methods. Based on domestic and foreign literature and online publications SCOPUS, Web of Science, Google Scholar, determine the mechanism of action and pharmacodynamics of synthetic and herbal cardioprotectors.

Research results. Mildronate. According to its chemical structure, mildronate – 3-(2, 2, 2-trimethylhydrazinium) propionate – is a structural analogue of the direct precursor of carnitine – γ-butyrobetaine. The specific activity of mildronate is due to its ability to inhibit carnitine-dependent oxidation of fatty acids, reducing the content of carnitine and its metabolically active fraction (acylcarnitine) in the myocardium. The following possible mechanisms of action of the drug have been proposed (Chen et al., 2024):

Inhibition of γ-butyrobetaine hydroxylase activity by a non-competitive type; by inhibiting the enzyme that catalyzes the last stage of carnitine biosynthesis – hydroxylation of γ-butyrobetaine, mildronate reduces carnitine levels and thereby prevents the accumulation of long-chain acylcarnitines and acyl-CoA.

Inhibition of carnitine acyltransferase activity by competitive type, which serves as additional mechanisms for inhibiting acylcarnitine accumulation.

Decreased activity of acyl-CoA synthetase, which catalyzes the process of formation of the «active form» of FA – acyl-CoA.

When the concentration of carnitine in the cytosol decreases, the rate of fatty acid transport in the mitochondria also decreases, which, in turn, contributes to the restoration of the transport of already produced ATP into the cytosol. An increase in the concentration of fatty acids in the cytosol is a kind of signal to the cell that the

oxidation of fatty acids is impossible for some reason. The body responds to such a signal by turning on the mechanisms of glucose oxidation.

In experimental testing of the mechanism of action of mildronate, it was shown that prophylactic ten-day administration of mildronate significantly prevents the disruption of the process of aerobic glucose oxidation in the isolated perfused rat heart. The same is observed in vivo. Thus, in a model of myocardial infarction in dogs, prophylactic 10-day administration of mildronate reduces the accumulation of lactate in the ischemic zone of the myocardium by more than 50%. This indicates that mildronate prevents acidosis of the ischemic zone of the myocardium (N. Xu et al., 2023).

Evidence that glucose oxidation is the main source of energy for maintaining myocardial functional capacity in ischemia caused by cardiac stimulation, under the influence of both mildronate and insulin, was obtained in isolated rat hearts (after a previous ten-day administration of mildronate).

Normally, the potential of energy charge (PEZ) is close to unity, which means that ATP prevails among macroergic phosphates in the myocardium. In the ischemic zone, this indicator sharply decreases (by approximately 35%). At the same time, in the group of animals that received mildronate, the energy potential of cells in the ischemic zone of the myocardium is almost completely preserved.

It has been established that mildronate activates both of the most important enzymes of the aerobic glucose oxidation cycle (Chen et al., 2024):

Hexokinase, which involves not only glucose but also other hexoses in the oxidation process.

Pyruvate dehydrogenase, which involves pyruvate formed from sugars in the Krebs cycle, thereby preventing the formation of lactate (acidosis).

It should be especially emphasized that under the influence of mildronate, not only the activity of these enzymes increases, but also their biosynthesis is induced, i.e. the number of these most important enzymes in cardiomyocytes increases. Mildronate reversibly inhibits the conversion of gamma-butyrobetaine to carnitine after ten days of administration of the drug.

A significant amount of data on the biochemical pharmacodynamics of mildronate in the experiment has been accumulated. Thus, when mildronate is administered to rats (50 mg/kg, intraperitoneally, 10 days), the concentration of free carnitine in the myocardium decreases by 42%, and when 150 mg/kg is administered, by 70%. The concentration of acid-insoluble acylcarnitine in the latter case decreases by 84%. In rats fed a high-fat diet, the administration of the drug inhibits the oxidation of ^{14}C-palmitic acid by 16% and 50%, respectively (X. Wu et al., 2022), does not affect the increased amount of ATP and reduces the concentration of lactate in the myocardium (Aguayo-Morales et al., 2024). When administered to white rats, the drug increases the concentration of VFA in the blood serum by almost 2 times, without affecting their level in the myocardium, which is apparently caused by the limitation of their uptake from the blood. The content of triglycerides in the myocardium tends to increase (by 1.25 times), which can be considered as a compensatory reaction in response to the excess of VFA under the conditions of course administration of mildronate (X. Wu et al., 2022).

In experiments on rats subjected to starvation, it was shown that mildronate, when administered in courses, has an antiketogenic effect both in carnitine-dependent ketogenesis (starvation) and in carnitine-independent formation of ketone bodies (octonoate loading under conditions of mildronate inhibition of carnitine-dependent ketogenesis), in which short- and medium-chain FAs are utilized. These effects may be useful in the correction of pathological conditions accompanied by increased ketogenesis (obesity, diabetes) (Aguayo-Morales et al., 2024).

Protection of the heart of rats perfused according to Langendorff, prevention of contractile function impairment is noted only with course use of mildronate. Prophylactic long-term administration of mildronate in doses of 50–150 mg/kg prevents isadrine-induced myocardial metabolism impairment (accumulation of acylcarnitine, decrease in ATP content) against the background of an even more pronounced decrease in the concentration of free carnitine and the absence of accumulation of AMP and lactate. Along with this, the damaging effect of membranotropic products of metabolic activation of fatty acids on hepatocytes and cardiomyocytes is weakened, which is confirmed by the absence of isadrine-stimulated release of CPK-MB isoform and LDH into the blood. In animals with myocardial infarction, mildronate inhibits lipid peroxidation in the myocardium and erythrocytes (reduces the level of malondialdehyde, diene conjugates), increases total antioxidant activity, restoring the activity of Ca^{2+}-ATPase, alkaline phosphatase, creatine phosphokinase, and enhancing reparative processes (X. Wu et al., 2022).

Given the nature of the effect of mildronate on the metabolism of fatty acids and carnitine, as well as the peculiarities of the biochemistry of ischemic myocardium, it seemed appropriate to use the drug in this type of pathology (Chen et al., 2024).

Thus, in rabbits treated with mildronate (250 mg/kg, intraperitoneally, 10 days), after hypoxic exposure during three-minute oxygenation, isolated atria developed

the initial force of contractions. In animals of the control group, this force was lower than the initial force throughout the entire observation period (Shinde et al., 2023). The drug protected the heart of rats perfused according to Langendorff from damage to contractile function caused by ischemia and prolonged exposure to palmitic acid. At the same time, during postischemic perfusion with palmitate, the recovery of the heart relaxation rate of rats treated with mildronate was significantly more pronounced at all observation periods compared to the control. The effect of the drug was manifested only with course administration to animals and was not observed with direct administration into the perfusate (N. Xu et al., 2023).

Mildronate has been shown to have a cardioprotective effect in isadrine-induced myocardial damage, which is most similar in pathogenesis and manifestations to the human disease (Rong et al., 2023). Pretreatment of mildronate in rats prevents isadrine-induced myocardial metabolic disorders: accumulation of acylcarnitine and reduction of ATP content against the background of an even more pronounced decrease in free carnitine concentration, prevents accumulation of AMP and lactate. The content of ornithine in the myocardium under the influence of cardioprotective doses of the drug (50–150 mg/kg) decreases (by 70%) with a decrease in acylcarnitine concentration by 56% and an increase in the concentration of fatty acids in the myocardium by 80% (Hassan et al., 2023).

Thus, under the influence of mildronate, the concentration of VFA in the myocardium increases even more while limiting the content of free carnitine. In this case, the intensification of VFA metabolism in the liver is possible, as indicated by a decrease in the level of VFA in the blood serum. Along with this, the damaging effect of membranotropic products of metabolic activation of FA on hepatocytes and cardiomyocytes is weakened, which is confirmed by the absence of isadrin-stimulated release of CPK-MB isoform and hepatic LDH into the blood (Chen et al., 2024).

Compared to other inhibitors of beta-oxidation of fatty acids, mildronate has a number of advantages. For example, unlike oxyphenicin, the drug does not cause the accumulation of fatty acids, triglycerides and cholesterol in the myocardium. The use of mildronate is not accompanied by the accumulation in the heart of long-chain acyl-CoA and acylcarnitine, which is fixed by the action of oxirane-2-carboxylic acid derivatives (N. Xu et al., 2023).

Studies have established the beneficial effect of mildronate on the energy metabolism of the myocardium of rats with isadrine myocardial infarction in the scarring stage (Zhang et al., 2024). In animals with this pathology, metabolic disorders were observed, which were manifested by significant changes in energy metabolism - a decrease in the level of ATP, ADP and AMP, the amount of adenyl nucleotides, a decrease in the total content of nicotinamide coenzymes due to a decrease in the level of oxidized and an increase in reduced forms. Under the influence of mildronate (50 mg/kg, intramuscularly, 21 days) in the myocardium of animals, the level of all components of the adenyl system and their sum increased, the proportion of oxidized forms of nicotinamide coenzymes increased and the reduced forms decreased.

The effectiveness of mildronate in preventing myocardial energy metabolism disorders caused by isadrine can be explained by the compensatory increase in glycolysis due to the release of proton acceptors, as evidenced by a decrease in the content of glucose-6-phosphate and pyruvate. A similar effect occurred with a significant decrease in the concentration of free carnitine (by 36–60%) (Chiari et al., 2024). The decrease in the utilization of VFA under the influence of mildronate is accompanied in normoxic conditions by the activation of the succinate oxidase oxidation pathway in rat lymphocytes, which is manifested by an increase in the activity of succinate dehydrogenase and glucose-6-phosphate dehydrogenase, and in hypoxic conditions by the preferential activation of glycolysis with an increase in the activity of LDH (Ybanez et al., 2026). According to the authors, the antihypoxic effect of mildronate is due to its ability to inhibit the synthesis of endogenous carnitine and thereby inhibit carnitine-dependent oxidation of fatty acids, which leads to a decrease in tissue oxygen demand. A single administration of mildronate (40 mg/kg) to rats with cerebral hypoxia of circulatory genesis significantly reduced the severity of neurological disorders and their EEG manifestations (Qayyum et al., 2022).

Further studies revealed the antioxidant properties of mildronate. It was found that the activation of lipid peroxidation processes in isadrine myocardial infarction was effectively prevented by the administration of mildronate. The drug reduced the concentration of DC, MDA, which is associated with its ability to reduce the level of reduced forms of nicotinamide coenzymes, the excess of which stimulates lipid peroxidation. As a result of the inhibitory effect of the drug on the metabolism of fatty acids and their membrane-toxic detergent metabolites, the AOA index increased by 20%. The level of cholesterol in the blood, which increased by 29% due to the activation of lipid peroxidation, decreased by 21%.

Normalization of myocardial metabolism was accompanied by positive dynamics of the bioelectrical activity of the heart, which was manifested by the normalization of the T wave and the S-T segment, and the growth of the R wave (Méndez-Valdés et al., 2022).

In rats with adrenocortical myocardial dystrophy, mildronate reduced the intensity of lipid peroxidation in erythrocytes, restored the activity of Ca^{2+}-ATPase, which was 11% higher than the activity of control animals, suppressed the activity of Mg^{2+}-ATPase with a slight decrease in total activity, and affected the restoration of the activity of alkaline phosphatase, creatine phosphokinase, and succinate dehydrogenase. This effect of the drug was more pronounced than that of the well-known antioxidant α-tocopherol, and was accompanied by an improvement in the condition of contractile fibers, an increase in the number of intact mitochondria, and an increase in intracellular reparative processes (Fallah et al., 2024). Normalization of the functioning of cardiomyocyte ATPases under the action of mildronate contributes to full-fledged diastole and the creation of favorable conditions for the restoration of myocardial functional activity.

It was found (Fallah et al., 2024) that the administration of the drug to white rats with chronic nonspecific lung diseases (CNLD) contributed to the preservation of histamine reserves in the myocardium, in particular, its bound fraction. These properties of the drug are important in the treatment of CNLD, in the process of which there is an increased influx of histamine and other biologically active substances into the blood.

Experimental studies of the effect of mildronate on coronary blood flow (Măgureanu et al., 2026) have shown that in an acute study in dogs, administration of the drug (0.01–0.06 mg/kg) into the circumflex branch of the left coronary artery increased the volumetric velocity of coronary blood flow and pO_2 in the blood of the coronary sinus. This suggests that the cause is active dilation of the coronary arteries.

Studies conducted (Niewiadomska et al., 2023) in a chronic experiment on dogs with a model of pulmonary heart failure (CHF) showed for the first time that mildronate (50 mg/kg body weight for 3 weeks) has a pronounced effect on blood circulation in the small circle. The drug helps to eliminate the pulmonary hypertension syndrome, reducing systolic (by 28%) and diastolic (by 47%) pressure in the pulmonary artery, as well as total pulmonary resistance by 52%. In conditions of reduced pulmonary vascular resistance, mildronate optimized the work of the right ventricle of the heart (by reducing its overload by 40%). By affecting the postcapillary capacitive channel, mildronate significantly limited blood flow to the heart (decreased CVT by 37%) without a noticeable change in the precapillary resistive channel.

A feature of the action of mildronate is a negative inotropic effect, which mainly affects the RV. Under the influence of the drug, both the force and speed parameters of the RV contractile activity decreased. The decrease in the relaxation properties of the RV indicated that mildronate is not able to eliminate one of the early signs of heart failure - the syndrome of «incomplete» diastole.

The drug did not significantly affect LV function indicators. The pumping function of the heart did not change significantly after a course of pharmacotherapy, although a unidirectional trend towards an increase in IOC by 25% and improvement in heart function was observed.

To study the mechanism of the negative inotropic effect of mildronate on the RV myocardium, its effect in the concentration range from 10^{-7} to 10^{-4} mol/l on the main parameters of isometric contraction was investigated. Under the influence of all studied concentrations, a significant decrease in the maximum developed contraction force was established. A significant (by 48%) decrease in this indicator was noted at a drug concentration of 10^{-4} mol/l. Only at a concentration of 10^{-6} mol/l was a significant decrease in the time indices of contraction and relaxation observed (Zhang et al., 2024).

Thus, when studying the effect of mildronate on the kinetics of isometric contraction, its negative effect on the maximum developed force of contraction was established. The data obtained indicate that mildronate has a direct negative inotropic effect. This gives reason to consider its use in combination with cardiotonic agents as appropriate.

In experiments on dogs, it was shown (Wang et al., 2023) that combined pharmacotherapy with mildronate and strophanthin allows avoiding the negative consequences of monotherapy with each of the drugs. These results allow us to recommend the inclusion of mildronate in the complex therapy of LSN, carried out using cardiac glycosides.

Of great interest are the data on the effect of the drug on energy metabolism. Experiments have shown that mildronate has the ability to optimize the metabolism of the right ventricle of the heart and lungs, eliminate their energy deficit by increasing the content of all components of the adenylyl system (Kampa et al., 2023). At the same time, the drug has practically no effect on the bioenergetic processes of the left ventricle and significantly reduces the number of macroergs in the liver.

The high ability of mildronate to correct the process of energy metabolism of the myocardium of the right ventricle may be due to its vasoactivity in relation to the small circle of blood circulation, which leads to a decrease in the degree of overload of the right ventricle. Due to this, the latter works in a more optimal mode, which balances the resynthesis and decay of macroergs.

In a model of erythrocyte membranes, it was shown (Hosseini et al., 2023) that the course administration of mildronate did not have a positive effect on the permeability of biomembranes. A further increase in cellular permeability under the influence of this drug is observed. The lack of a positive effect justifies the conclusion about the feasibility of combining mildronate with α-tocopherol.

In a cat model of CHF, it was found that prior administration of mildronate prevented the development of failure, preventing a decrease in left ventricular contractility and contributing to the stabilization of basic hemodynamic parameters (Zhang et al. 2024).

The drug has also been shown to have adaptogenic properties to strenuous exercise. Mildronate administration increased the running time of mice by 290–325% compared to baseline. The delayed effect persisted for up to 7 days (Măgureanu et al., 2026).

Due to its high efficacy in experimental studies, the drug is widely used in clinical practice. Initially, mildronate was used as a means of increasing the endurance of athletes. Taking the drug was accompanied by an increase in endurance and the speed of recovery processes, which was recorded by biochemical blood parameters (Kampa et al., 2023).

The presence of mildronate cardioprotective and antiischemic properties led to its use in the treatment of coronary artery disease. Monotherapy with mildronate in patients with angina pectoris was accompanied by a pronounced antianginal effect. A decrease in the number of attacks, shortness of breath and nitroglycerin consumption was noted. This led to positive dynamics of spirocycle ergometric indicators and an increase in the anaerobic threshold of work (Dar et al., 2025).

After administration of mildronate, cardiac output increased in most patients with coronary artery disease. With course treatment, the indicators stabilized, which coincided with the development of an antianginal effect. The drug increased exercise tolerance and the volume of work performed (Das et al., 2024).

Radiocardiographic indicators indicated a positive effect on central and peripheral hemodynamics. Course administration normalized nitrogen metabolism and ATPase activity. The antioxidant effect was manifested by a decrease in lipid peroxidation in erythrocyte membranes (Arandhara et al., 2024). The drug also eliminated some adverse effects of nitro drugs (Pagliaro et al., 2025).

Long-term administration contributed to a decrease in glycolysis intensity and activated aerobic processes (Soltani et al., 2022). Follow-up data confirmed the high efficacy of the drug, which reduced the frequency of recurrent infarctions by 9.2 times (Gu et al., 2025).

The administration of mildronate during the rehabilitation period caused a significant decrease in cholesterol and atherogenic index, as well as an increase in antioxidant protection (Lim et al., 2023). These effects were enhanced when combined with α-tocopherol. This regimen normalizes energy and lipid metabolism, improves trophism and promotes scarring. Clinically, this has been shown to improve the condition of patients and increase exercise tolerance (Gu et al., 2025).

Of particular interest are the properties of mildronate as an immunomodulator. After a course of treatment, the main indicators of cellular and humoral immunity normalized (Khoso et al., 2024).

In recent years, a significant number of publications have appeared confirming the clinical efficacy of mildronate in chronic heart failure (CHF) in patients with coronary artery disease, chronic heart failure in patients in the early post-infarction period, with stable angina, etc.

A modern and promising direction in the treatment of CHF is the use of drugs that do not have a direct inotropic effect, but have a cytoprotective and direct metabolic effect at the cellular level and contribute to increasing the efficiency of myocardial function by optimizing ATP synthesis in cardiomyocyte mitochondria with lower oxygen consumption.

A multicenter, double-blind, placebo-controlled, parallel, randomized study examined the clinical efficacy and safety of mildronate compared with digoxin in 120 patients with functional class II heart failure on the background of chronic forms of ischemic heart disease (Naik et al., 2025). Compared with placebo on the background of course treatment with mildronate (1–1.5 g/day):

– the total clinical effectiveness score increases by 42%;

– the contractile activity of the left ventricle increases;

– physical performance increases (increase in the duration of the load by 34% and the amount of work performed by 47%);

– in 78% of patients, the functional class of heart failure decreases.

In patients with initially low values of ejection fraction (EF) and minute blood volume (MCV), mildronate had a normalizing effect on these parameters. It is characteristic that increased tolerance to exercise was noted within 2–4 weeks after the end of the course of treatment with mildronate, which was not observed in the case of discontinuation of digoxin therapy. Unlike digoxin, when used in 29% of patients at the peak of bicycle ergometric load, angina attacks and ischemic ST-segment changes were observed, in patients receiving mildronate, these negative effects were not detected.

In addition, in no less than 70% of patients, the number of extrasystoles decreased by 50% or more.

Similar data were obtained in special studies on the use of mildronate in the complex therapy of heart failure (II–IV functional class according to the NYHA classification) that developed due to coronary artery disease (Morariu-Briciu et al., 2026). All patients (80 people) received standard therapy (enalapril, furosemide, cardicet, digoxin). It was found that the addition of mildronate (500 mg/day) improved the results of classical therapy by 10% according to the criterion of transition of patients to a lower functional class according to the NYHA, and also contributed to a significant decrease in end-systolic volume (ESV). This effect was accompanied by the normalization of the content of ATP and the amount of adenyl nucleotides in erythrocytes.

A study (Alonazi et al., 2024) involving 96 patients after myocardial infarction showed that the inclusion of mildronate in the treatment regimen had a positive effect on: the functional state of patients (increase in exercise capacity), a decrease in the number of angina attacks, myocardial metabolic indicators, and renal status.

Elderly patients (117 people) who took mildronate for 12 weeks showed a 33% reduction in LDL lipid peroxidation products and a 26% increase in LDL oxidation resistance. An average 1.4-fold increase in NO metabolite concentrations was also recorded (Thomas et al., 2023).

The use of mildronate in stable angina pectoris on the background of standard antianginal therapy led to an improvement in subjective and objective indicators. According to single-photon emission computed tomography (SECT), a decrease in stress-induced myocardial ischemia was noted (Khoso et al., 2025). The authors suggest that the increase in ATP production under the influence of mildronate enhances its capture by cardiomyocytes.

Molecular mechanisms and cell signaling

To understand the action of mildronate as a modulator of endogenous cardioprotection mechanisms, its effect on universal cellular signaling cascades – adenylate cyclase (C_1) and calcium-mobilizing polyphosphoinositide (C_2) – was studied (Khoso et al., 2025).

Blood rheology: Mildronate exhibits a slight dose-dependent inhibitory effect on platelet aggregation, similar to that of the Ca^{2+} channel blocker nifedipine. This may indicate an effect of the drug on platelet Ca^{2+} channels.

Immunomodulatory activity: In a model of T-lymphocyte rosette formation, it was found that mildronate has a pronounced immunosuppressive effect (maximum - a 48% reduction in the number of rosettes at a concentration of 1×10^{-5} mol/dm³).

Inflammatory mediators: Studies have shown that the drug at high concentrations reduces the release of leukotriene (LT) C_4 from macrophages by 38%, indicating inhibition of the biosynthesis of LTC_4 from endogenous arachidonic acid via the lipoxygenase pathway.

Overall, the results indicate that mildronate is a representative of a group of pharmacological agents – inhibitors of the polyphosphoinositide cell signaling system with pronounced polytropy of action. The direct metabolic effects of the drug may be mediated by its «signaling» effect on the control systems of lipid metabolism in the cell.

Application prospects Meldonium and adenyl nucleotides are considered an important approach to metabolic protection of the myocardium through optimization of energy metabolism. Meldonium is distinguished by the presence of additional positive effects that expand the possibilities of its use in pulmonology (including bronchial asthma) and in the relief of alcohol withdrawal syndrome (Alonazi et al., 2024). **Nicorandil and Ranolazine.** Nicorandil is a drug based on nitrates and nicotinamide, which is compared with another cardioprotector, ranolazine (Soltani et al., 2022).

Modern approaches to antianginal therapy: a comparative analysis of ranolazine and nicorandil. Today, the strategy for the treatment of ischemic heart disease (IHD) is based on adapting therapy to the individual patient profile, taking into account the pathophysiological mechanisms of ischemia, hemodynamic status and concomitant diseases. The main task is to eliminate the imbalance between myocardial oxygen supply and its demand, which arises as a result of coronary stenosis, microvascular dysfunction or vasospasm. Among modern second-line agents, ranolazine and nicorandil attract special attention, which, having different pharmacodynamic profiles, allow for a personalized approach to the treatment of angina. Mechanisms of action and hemodynamic effects Nicorandil is characterized by a unique dual mechanism of action. Acting simultaneously as an activator of adenosine triphosphate-dependent potassium KATP channels and a donor of nitric oxide NO, it provides balanced dilation of the arterial and venous bed. This leads to a decrease in both pre- and afterload on the myocardium, improving coronary blood flow, especially in the diastolic phase (Lim et al., 2023). In contrast, ranolazine acts mainly as a selective inhibitor of the late sodium current INa, which prevents intracellular calcium overload. This mechanism improves myocardial relaxation and reduces diastolic tension of the left ventricular walls, with virtually no effect on blood pressure and heart rate (Gu et al., 2025). Pharmacokinetic features and safety. An important aspect of clinical choice is the metabolic pathway of drugs. Ranolazine is extensively metabolized in the liver by the cytochrome P450

(CYP3A4) system, which poses a risk of significant drug interactions, especially with inhibitors of this enzyme, such as diltiazem or clarithromycin. In addition, ranolazine may be associated with QTc prolongation, which requires caution when administered to patients receiving antiarrhythmics or antidepressants (Lim et al., 2023). Nicorandil (including under the trade name Nicorel®) is devoid of first-pass metabolism, and its metabolites are not pharmacologically toxic. Due to the lack of significant effects on the cytochrome system and the presence of renoprotective properties, the drug can be administered to patients with liver and kidney pathology without dosage adjustment. However, its ability to lower blood pressure limits its use in patients with baseline hypotension or cardiogenic shock (Morariu-Briciu et al., 2026). Pleiotropic properties and additional benefits. Both drugs demonstrate significant non-cardiac effects. Ranolazine has been shown to have a positive effect on carbohydrate metabolism by reducing glycosylated haemoglobin levels in patients with diabetes. The pleiotropic spectrum of nicorandil is more extensive: it includes antiplatelet activity, protection of the microvascular bed from ferroptosis and the ability to prevent contrast-induced nephropathy during coronary angiography (Alonazi et al., 2024). Evidence base and clinical application. The results of large randomised trials confirm the effectiveness of both drugs in reducing the frequency of angina attacks and increasing exercise tolerance. However, the IONA study demonstrated the advantage of nicorandil in reducing the risk of cardiovascular events, including non-fatal myocardial infarction and hospitalisation. Current guidelines consider nicorandil as the first choice for vasospastic and microvascular angina, while ranolazine is appropriate for patients with decompensated diabetes in the absence of renal failure (Ullah et al., 2024). A promising direction is the combination of nicorandil with trimetazidine. Such a combination provides synergy between vascular dilation and myocardial cytoprotection, which allows achieving a stable clinical effect even in patients with refractory forms of ischemia and a high risk of endothelial dysfunction.

Observational studies and clinical efficacy of metabolic therapy. Observational studies conducted in real-world clinical practice provide strong evidence in favor of the combined use of nicorandil and trimetazidine. In particular, it was found that such a combination demonstrates significantly higher therapeutic efficacy compared to monotherapy. Comparative efficacy and prognosis. According to retrospective trials, the proportion of patients who reported «excellent» and «good» efficacy of combination therapy was 57.69% and 36.54%, respectively. In comparison, similar indicators against the background of taking trimetazidine alone were significantly lower (41.18% and 23.53%, respectively; $p < 0.05$) (Khoso et al., 2025). In a large study involving over 11,000 people, the incidence of major adverse cardiovascular events (MACE), stroke and myocardial infarction (MI) was analyzed over 1–3 years. The results of the 3-year follow-up showed: The incidence of MACE in the nicorandil+trimetazidine combination group was significantly lower (OR 0.85; 95% CI 0.74–0.97; $p = 0.017$). The risk of stroke was reduced by 42% compared with the trimetazidine group (OR 0.58; 95% CI 0.48–0.71; $p < 0.0001$). During the first year of follow-up, stroke was also diagnosed significantly less frequently in the combination therapy group (Dubey et al., 2026). Chinese scientists state that such a combination can be considered an effective strategy for reducing the risk of cardiovascular complications and improving short-term survival after acute MI (Chen et al., 2022).

An important aspect is the treatment of patients with diabetes mellitus (DM), in whom sympathetic hyperactivation and increased regional vascular tone in the kidneys or heart are often observed. The appointment of beta-blockers (BB) to such patients is pathogenetically justified, especially in the presence of coronary artery disease, previous infarction, or heart failure with reduced left ventricular ejection fraction (LVEF < 40%). BBs in this situation act as a measure that saves the patient from death and cardiovascular complications (Jalali et al., 2025). A separate category is young women with arterial hypertension (AH) who are planning pregnancy. For them, the use of ACE inhibitors or angiotensin II receptor blockers is unacceptable due to teratogenic effects, so BBs remain the drugs of choice for safe control of the condition (Grewal et al., 2023).

Trimetazidine. Trimetazidine ensures the preservation of energy metabolism in cells suffering from ischemia. It inhibits beta-oxidation of fatty acids by blocking 3-ketoacyl-CoA thiolase (3-CAT), which stimulates glucose oxidation. Since this process requires less oxygen, it allows maintaining the level of intracellular ATP and the proper functioning of ion pumps (Paulino et al., 2024). Clinical studies (TRIMPOL-II, SELLIER, VASCO) have confirmed that trimetazidine significantly increases the duration of physical exertion and the time to the appearance of ischemic changes on the ECG, without changing hemodynamic parameters (Pirdhankar et al., 2023). A stable concentration of trimetazidine in blood plasma is achieved by the 60th hour of administration. The drug is excreted mainly by the kidneys, so the half-life increases in patients over 65 years of age to 12 hours (compared to 7 hours in young volunteers), which directly correlates with creatinine clearance (S. Stank-

ovic et al., 2025). Based on the above data, the combination of nicorandil and trimetazidine demonstrates high potential in the treatment of patients with coronary artery disease. It allows to significantly reduce the risk of MACE and stroke, improve the functional state of the myocardium and provide kidney protection (in particular, from contrast-induced nephropathy). The use of such a strategy is pathogenetically justified for leveling endothelial dysfunction and suppressing the chronic inflammatory process.

Modern pharmacotherapy is moving towards multitarget strategies. The combination of classical metabolic agents (thiotriazoline) with amino acids or plant extracts allows not only to more effectively treat the underlying disease, but also to provide systemic protection of the body from inflammation, ischemia, and side effects of aggressive therapy.

Modern medical science is actively exploring the possibilities of expanding the indications for known drugs and creating synergistic combinations that can reduce the toxicity of basic therapy and increase its effectiveness.

Cardioprotective 1,2,4-triazole derivatives

1,2,4 triazole derivatives have a wide spectrum of pharmacological activity: antihypoxic, antiischemic, antioxidant, growth-stimulating, antiviral, anti-inflammatory (Ziyaev et al., 2025; Strzelecka et al., 2021; Hotsulia et al., 2024).

The greatest interest is in 1,2,4-triazole derivatives as potential cardioprotectors. Thus, among 3-methyl-1,2,4-triazolyl-5-carboxylic acids and their salts, compounds have been identified that exhibit cardioprotective activity in a model of myocardial infarction in rats. Among this subgroup, the following salts have been identified: morpholine, sodium, monoethanolammonium salts of 3-methyl-1,2,4-triazolyl-5-thioacetic acid, and its most prominent representative is thiotriazoline. Thiotriazoline, which is the first representative of the class of metabolitotropic cyto- and cardioprotectors, exhibits anti-ischemic, cardioprotective, antioxidant, energotropic, membraneprotective, and immunomodulatory properties. (Mazur et al., 2021; Belenichev et al., 2022).

Thiotriazoline. The pharmacological effect of thiazide acid is due to its anti-ischemic, membrane-stabilizing, antioxidant, and immunomodulatory effects.

The effect of the drug is realized by enhancing the compensatory activation of anaerobic glycolysis and activation of oxidation processes in the Krebs cycle with the preservation of the intracellular ATP pool. The presence in the structure of the thiazolidinedione molecule of sulfur thiol, which is characterized by redox properties, and tertiary nitrogen, which binds excess hydrogen ions, causes the activation of the antioxidant system. The strong reducing properties of the thiol group cause a reaction with reactive oxygen species and lipid radicals. Reactivation of antiradical enzymes - superoxide dismutase, catalase and glutathione peroxidase - prevents the initiation of reactive oxygen species.

The effect of thiazide acid leads to inhibition of lipid oxidation processes in ischemic areas of the myocardium, reduction of myocardial sensitivity to catecholamines, prevention of progressive inhibition of cardiac contractile function, stabilization and reduction of the necrosis and ischemia zones of the myocardium, respectively. Improvement of the rheological properties of the blood is achieved by activating the fibrinolytic system. Improvement of myocardial metabolic processes, increase of its contractility, promotion of normalization of heart rhythm allow us to recommend thiazide acid for the treatment of patients with various forms of ischemic heart disease.

In parallel with the use of the drug in cardiology, thiazide acid is used in the treatment of diseases of the liver and other internal organs, given its high hepatoprotective properties. The drug prevents the destruction of hepatocytes, reduces the degree of fatty infiltration and the spread of centrilobular necrosis of the liver, promotes the processes of reparative regeneration of hepatocytes, normalizes protein, carbohydrate, lipid and pigment metabolism in them. Increases the rate of synthesis and secretion of bile, normalizes its chemical composition. The introduction into medical practice of a new original domestic drug of a metabolic nature - thiotriazoline is of significant theoretical and practical interest for experimental and clinical medicine.

The presence of sulfur, triazole rings, and a methyl group in the chemical structure contributed to the manifestation of the pharmacological activity of this medication, in particular, cardioprotective properties.

Studies have shown that doxorubicin has a toxic effect on myocardial function and metabolism in the body, causing doxorubicin cardiomyopathy (Belenichev et al., 2022). The main mechanism of development of doxorubicin cardiomyopathy is dystrophic changes in the heart muscle, which lead to impaired function, metabolism in the myocardium and the development of energetic and dynamic heart failure.

The effect of doxorubicin and thiotriazoline on the following indicators of cardiac activity and systemic hemodynamics of rabbits was studied: Pmax (maximum pressure) in the left ventricle (LV), SI (cardiac index), SII (systolic index), cardiac output (CVO), stroke volume (SVO), left ventricular work index (LVWI), left ventricular work stroke index (LVWI), blood output (B),

systemic arterial pressure (SAP), total peripheral resistance (TPR), heart rate (HR).

In doxorubicin cardiomyopathy, the most pronounced inhibition of myocardial contractile activity is observed, as evidenced by a significant drop in LV pressure by 20.5%, as well as a decrease in the working index and working stroke index by 29% and 26.5%, respectively.

Less pronounced disorders were detected in the central hemodynamics. Thus, cardiac and systolic indices decreased by only 9.8% and 5%, respectively. The tendency to change the CBC by 10.6% and the systolic pressure by 11.6% leads to a decrease in SBP by 16.4% ($p < 0.05$). The heart rate practically did not change.

Analysis of the results showed that in doxorubicin cardiomyopathy, myocardial contractile activity is significantly reduced; to a lesser extent, such changes concern the indicators of central hemodynamics: SI, SiI, HOC, ZPO, SAT.

Thiotriazoline, when administered in courses, prevents the deterioration of most of the parameters that have undergone changes in the conditions of doxorubicin cardiomyopathy. This primarily concerns the maximum pressure in the LV, systemic arterial pressure, left ventricular working index, left ventricular working stroke index, which remained practically at the level of the control group (Belenichev et al., 2024).

Adenyl nucleotides play a significant role in the energy supply of the myocardium. ATP deficiency is one of the causes of violations of the ion gradient and other vital processes in the cardiac muscle. As is known, the level of adenyl nucleotides (ATP, ADP, AMP) is a regulatory link between the systems of aerobic oxidation and glycolysis, which is due not only to the acceptor effect, but also to a direct effect on individual stages of energy formation in the cell (Belenichev et al., 2024).

The level of nicotinamide coenzymes is also significant, which, in turn, contribute to the transfer of electrons of oxidation substrates in the respiratory chain and participate as a cofactor in the formation of energetic phosphorus-containing compounds. This allows us to analyze changes in the adenylyl system in relation to changes in pyridine nucleotides (Mazur et al., 2025).

Thus, it is the adenyl nucleotide system, which acts as a reservoir of biological energy, as well as the nicotinamide coenzyme system, which performs the functions of the energy transport chain, that serve as informative indicators of pathological changes in myocardial functioning and can contribute to the disclosure of mechanisms of interaction of toxic agents with metabolic correction drugs.

The level of ATP in the myocardium of rats under conditions of doxorubicin cardiomyopathy decreased by 40%, ADP and AMP – by 44% and 38%, respectively. The amount of adenyl nucleotides decreased by 41%. Analyzing the state of nicotinamide coenzymes in the studied pathology, it should be noted that the level of oxidized forms also decreases – by 21.7%, and the amount of nicotinamide coenzymes (NAC) – by 16%. No significant difference between the reduced forms of NAC in animals of the control and experimental groups was found. At the same time, the ratio of oxidized and reduced forms decreased (by 15%).

Thus, intoxication caused by the action of doxorubicin is accompanied by a decrease in the synthesis of macroergic compounds, impaired tissue respiration, and energy deficiency of myocardial cells.

The results of the effect of thiotriazoline on the content of adenyl nucleotides and nicotinamide coenzymes in the myocardium of rats with doxorubicin cardiomyopathy indicate that thiotriazoline, when administered in a course, intensifies oxidative metabolism and increases the level of macroergs in the myocardium of rats with doxorubicin cardiomyopathy. An increase in the level of ATP by 44%, ADP and AMP – by 24% and 34%, respectively, was noted. The amount of adenyl nucleotides increased by 34%, the ATP/ADP ratio increased by 20%. This fact indicates a decrease in the level of coenzyme recovery, which reflects a positive effect on the functioning of various chains of cell metabolism. The AEZ indicator practically did not differ from that in the control group (Belenichev et al., 2024).

Analysis of the obtained data showed that doxorubicin causes a sharp activation of lipoperoxidation in both the myocardium and the liver of rats. At the same time, the intensity of spontaneous uninitiated LPO significantly increases: in the liver – by 41%, in the myocardium of rats – by 21%.

The intensity of enzyme-dependent lipoperoxidation processes significantly increases in the myocardium by 70%, in the liver by 24%.

In the myocardium of rats under the influence of thiotriazoline, a significant decrease in the level of MDA (by 30%) was observed in enzymatically dependent lipoperoxidation. In spontaneous lipoperoxidation, the level of MDA decreases by 15%. In the liver of rats under the influence of thiotriazoline, this indicator decreases by 24% in spontaneous lipoperoxidation, and by 21% in enzymatically dependent lipoperoxidation (Belenichev et al., 2024).

The results of the conducted studies indicate a significant increase in the accumulation of MDA in the myocardium (by 70%) in the induced enzyme-dependent process. This can be explained by the tropism of doxorubicin to cardiolipin, which is a phospholipid of

the mitochondrial membranes of cardiomyocytes (Belenichev et al., 2025). The high level of MDA in the myocardium of the studied rats also indicates an increase in the saturation of the myocardium with fatty acids, which are the main substrates of POL. Thiotriazoline normalizes the fatty acid composition of myocardial and liver lipids in doxorubicin cardiomyopathy (Belenichev et al., 2024). Acidosis occurs in the heart tissues, the permeability of cell membranes increases and an additional amount of Ca2+ ions enters the cells. A vicious circle of interdependent disorders of lipid and ion homeostasis is formed. There is additional activation of proteases, phospholipases, formation of free fatty acids, production of prostaglandins and leukotrienes (Strzelecka et al., 2021).

The biochemical pharmacodynamics of thiotriazoline in doxorubicin cardiomyopathy are similar to nicotinamide (Belenichev et al., 2019). In an experiment using the fluorescent dye thioflavin, as well as histologically, the property of thiotriazoline to reduce the area of myocardial ischemia and necrosis by 42% was established. The appointment of thiotriazoline in the acute period of experimental myocardial infarction led to a significant decrease in electrocardiographic and biochemical indicators of ischemic myocardial damage - MV-CPK, LDH (Belenichev et al., 2019).

Based on the data of experimental studies, which established the property of thiotriazoline to reduce the area of myocardial ischemia and necrosis, significantly reduce electrocardiographic and biochemical indicators of ischemic myocardial damage, a blind clinical study was conducted at the N.D. Strazhesk Institute of Cardiology (Mazur et al., 2025). The effect of thiotriazoline therapy against the background of basic treatment with nitrates and beta-blockers on the pumping function of the heart, the dynamics of electrocardiographic and biochemical markers of myocardial damage in patients with acute myocardial infarction was studied. The study involved 40 patients aged 38–56 years with a diagnosis of «acute Q-wave myocardial infarction», who were admitted to the clinic within the first 24 hours from the onset of the disease. At this time, treatment was started. As basic therapy, all patients received nitrosorbide at a dose of 40–80 mg per day, propranolol – 60–160 mg per day. Analgesics and antiarrhythmic drugs were used according to indications in traditional dosages. All patients were randomly divided into two groups – 20 people in each. Patients in the first group were prescribed thiotriazoline according to the following scheme: from the 1st to the 5th day from the onset of the disease – 2 ml of 1% solution intramuscularly three times a day, from the 6th to the 20th day – orally one tablet of the drug three times a day (daily dose – 300 mg).

Patients in the second group were given saline as a placebo for the injectable form of thiotriazoline; no placebo was provided for the oral form. To assess the effectiveness of therapy, objective research data, ECG, EchoCG, serum MV-fraction activity of CPK, LDH were used.

Analysis of the results showed that in the group of patients receiving thiotriazoline, not a single case of myocardial infarction recurrence was registered, while in two patients of the second group, on the 4th and 5th days of the disease, a myocardial infarction recurrence occurred with the formation of an acute aneurysm of the anterior wall of the left ventricle.

When analyzing the dynamics of pain syndrome, a faster regression was observed in people who received thiotriazoline. Thus, by the 5th day of the disease, pain syndrome was noted only in one patient of the first group and in four – in the second group. By the 10th day, pain syndrome was not noted in any of the patients who received thiotriazoline, but it persisted in one patient of the second group. In the group of patients who received thiotriazoline, a significantly lower frequency of ventricular extrasystoles was also recorded – one of the manifestations of electrical instability of the myocardium. At the same time, by the 10th day of observation, no high-grade extrasystoles were recorded in any patient of the first group. In the second group, which received only basic therapy, ventricular arrhythmias were more common, and three patients had short paroxysms of ventricular tachycardia. In general, ventricular arrhythmia persisted in the group until the 20th day of observation. Moreover, the appointment of thiotriazoline was more effective than riboxin.

The cardioprotective effect of thiotriazoline was realized primarily through the effect on ischemic changes in bioenergetic metabolism in the myocardium. Thus, in the experiment, an increase in the level of endogenous glycogen and a decrease in the content of free fatty acids were observed in the myocardium of animals receiving thiotriazoline compared to the control group. At the same time, a decrease in lactate hyperproduction, increased oxidative processes with increased lipid utilization and energy production were recorded. In the myocardium of animals with myocardial infarction receiving thiotriazoline, there was an increase of 66.6% in the activity of cytochrome C oxidase - the key enzyme of the electron transport (respiratory) chain. Maintenance of oxidative metabolism by thiotriazoline in the ischemic myocardium determined an increase in the level of macroergic phosphate compounds: ATP – by 37.1%, creatine phosphate – by 51.4%. The second important fact confirming the effect of thiotriazoline on bioenergetics processes in ischemic myocardium is an

87.5% increase in the level of malate - a component of the malate-aspartate transport system, which reflects the intensification of the Krebs cycle due to the transport of carbohydrate flows with the formation of reduced equivalents to the substrate site of the electron transport chain. In the group of animals receiving riboxin, normalization of bioenergetics processes was also observed, but to a much lesser extent.

In clinical practice, when thiotriazoline was used in the complex therapy of acute myocardial infarction, the severity of markers of ischemic myocardial damage was significantly reduced, and positive dynamics of cardiohemodynamic characteristics were noted, which was confirmed by several works (Belenichev et al., 2024).

The results of multicenter randomized studies indicate the feasibility of including Thiotriazolin in the complex treatment of cardiovascular diseases as a metabolitotropic cardioprotector. Thiotriazolin reduces the number and duration of episodes of ischemia, heart rhythm disturbances, increases tolerance to physical exertion, and also improves the quality and duration of life of patients with stable angina, myocardial infarction, post-infarction myocardial remodeling, CHF, therefore, improves the prognosis and quality. Good tolerability and safety of course use (8 weeks) have been shown. Thiotriazolin in a daily dose of 600 mg for the treatment of coronary artery disease, stable angina pectoris of II-III functional class and CHF. Thus, during clinical trials of Thiotriazolin, it was found that the percentage of side effects was low – about 3%, and they were not serious (mild and moderate) and were not associated with taking the drug (Belenichev et al., 2019). The mechanism of action of Thiotriazolin is to increase the expression of antioxidant enzymes, reduce the concentration of free radicals, activate the compensatory malate-aspartate shunt of energy production, normalize the Krebs cycle, and initiate Red/Oxi-dependent expression of transcription factors under conditions of ischemia (Belenichev et al., 2024; R(Opazova et al., 2023)).

Thiotriazoline: cytoprotection in post-covid syndrome and dentistry. Thiotriazoline (thiazotic acid) demonstrates broad multiorgan activity. Researchers have made an important observation about the absence of side effects in thiotriazoline; this allows us to believe that it is currently one of the most effective means of metabolic myocardial protection, which is used to optimize the therapy of patients with myocardial infarction and post-infarction angina

COVID-19 leads to a violation of the blood coagulation system, thrombosis, hypercoagulation, as a result, to an increased risk of strokes and heart attacks. During COVID-19, endothelial dysfunction develops, associated with a deficiency of NO with a decrease in the level of SH-compounds. Thiazide acid (thiotriazoline) has immunomodulatory, anti-inflammatory, antioxidant, anti-ischemic, cardio- and endothelioprotective, antiplatelet, hepatoprotective activity. Our studies were conducted at the National Research Medical Center «University Clinic of ZDMU» with the participation of 57 patients (from 30 to 65 years old) with post-covid syndrome, who received thiotriazole with basic therapy either in tablets (200 mg) or in suppositories for 0 days. During treatment with thiotriazoline, a significant increase in eNOS content was recorded, which indicated the presence of endothelioprotective activity of the drug. Thiotriazoline significantly reduced the level of D-dimer in the blood of patients, and also led to the normalization of INR. The established effects indicated the presence of antiplatelet and fibrinolytic effects of thiotriazoline and its ability to reduce the risks of heart attacks and strokes in post-covid syndrome. Thiotriazoline led to an objective improvement in general clinical indicators in patients with post-covid syndrome, complaints of palpitations disappeared, and blood pressure stabilized (Belenichev et al., 2022).

Dental practice: The combination of thiotriazoline with L-arginine (1:4) has shown high efficacy in the treatment of chronic generalized periodontitis. The therapy leads to a decrease in the concentration of pro-inflammatory cytokines (IL-1beta by 56.1% and TNF-alpha by 71%) and a significant increase in the expression of heat shock protective proteins (HSP70) in periodontal tissues (Mazur et al., 2025, Nagorna et al., 2018). In models of allergic alveolitis on a background of stress, the combination of Corvitin + Thiotriazoline showed an immunocorrective effect: activation of the cellular component (T-lymphocytes) and suppression of the humoral component (circulating immune complexes), which prevents depletion of the immune system (Mazur et al., 2025). After oral administration, thiotriazoline is rapidly absorbed, its absolute bioavailability is 53%. The maximum concentration in blood plasma is reached 1.6 hours after a single dose of 200 mg. The half-life is almost 8 hours.

The development of combined tablets of paracetamol with thiotriazoline is a promising step for leveling the side effects of antipyretics on the liver (Belenichev I. et al., 2024). Further modification of the thiotriazoline molecule allowed to obtain a new molecule of the following structure – L-lysinium 3-methyl-1,2,4-triazolyl-5-thioacetate, which was named Angiolin. Angiolin has a fragment of the molecule similar to Thiotriazoline – 3-methyl-1,2,4-triazolyl-5-thioacetate, revealing new links of the mechanism of cardioprotective action, which are absent in Thiotriazoline (Belenichev et al., 2022; Chekman et al., 2024).

1. Angiolin increases the bioavailability of NO, normalizes the expression of eNOS and iNOS mRNA, and also increases the density of endothelial cells of myocardial vessels against the background of increased expression of vascular endothelial growth factor (VEGF) and decreased expression of molecular markers of endothelial dysfunction C-reactive protein, interferon-gamma (INF-g) in myocardial infarction, myocardial ischemia, chronic heart failure, and alcoholic cardiomyopathy. Everything indicates the presence of an endothelioprotective mechanism (absent in all known cardioprotectors) in the cardioprotective action of Angiolin.

2. Angiolin leads to a redistribution of cell density with varying degrees of fibrosis – it reduces the density of cardiocytes with a moderate degree of fibrosis, increases the density of cells with a slight degree of fibrosis, and completely prevents the appearance of cells with a pronounced degree of fibrosis in chronic heart failure.

3. Angiolin leads to the elimination of left ventricular dysfunction, which was expressed in an increase in the left ventricular working index and the left ventricular working stroke index, and an increase in left ventricular pressure in chronic heart failure.

4. Angiolin preserves the ultrastructure of cardiomyocyte mitochondria in arterial hypertension and activates additional energy shunts (malate-aspartate) both in arterial hypertension and in myocardial infarction, chronic heart failure, alcoholic cardiomyopathy, and rabies myopathy.

5. Angiolin inhibits reactions of not only oxidative but also nitrosative stress.

6. Angiolin enhances the expression of the endogenous cytoprotector heat shock protein HSP70

7. Angiolin inhibits TNF-α-dependent apoptosis of cardiomyocytes. Angiolin, according to the concept of creating cationic-anionic drugs, combines in its structure 3-methyl-1,2,4-triazolyl-5-thioacetate, which is responsible for antioxidant, energotropic and anti-ischemic properties, and L-lysine, which is able to regulate the expression of eNOS, as well as influence on. We have established that Angiolin exhibits good endothelioprotective, anti-ischemic, cardioprotective, neuroprotective, antioxidant and anti-inflammatory properties. Angiolin also exhibits cardioprotective effects, increasing cardiomyocyte survival and improving ECG results, general and cardiohemodynamics in acute and chronic myocardial ischemia – normalizes systolic blood pressure, reduces manifestations of ischemic dysfunction of the left ventricle – increases cardiac. Laboratory and industrial synthesis methods and standardization methods for Angiolin have been developed (Nagorna, 2018).

Cardioprotective properties have also been found in derivatives of 4-amino-1,2,4-triazole. Thus, the greatest interest is represented by derivatives of 1-alkyl-, 1-(1-carboxyalkyl)-4-amino-1,2,4-triazolium (Drapak et al., 2019). Of which, the most active compound 1-(b-phenylethyl)-4-amino-1,2,4-triazolium bromide was isolated, which showed high cardioprotective activity and was classified as low-toxic substances (LD50 295 mg/kg, intraperitoneally) (Patent for invention No. 28494 of Ukraine). Employees of the departments of pharmaceutical chemistry and pharmacology and medical formulation with a course of normal physiology of the ZDMFU under the guidance of Professor I.O. Mazur developed the original drug Hypertril based on a derivative of 4-amino-1,2,4-triazole, namely 1-(b-phenylethyl)-4-amino-1,2,4-triazolium bromide. Hypertril is a cardioselective β-adrenoblocker with NO-mimetic effect, which exhibits antihypertensive, antianginal, antiischemic, fibrinolytic and antioxidant properties. (Patent No. 84351 Ukraine). Hypertril at a dose of 2.5 mg/kg exhibits a pronounced cardioprotective effect in conditions of acute myocardial ischemia and reperfusion in rats, reducing the values of markers of ischemic myocardial damage - MV-CPK hyperenzymemia, ΣΔST interval shift, as well as the volume of myocardial necrosis. Experimentally, the ED50 of Hypertril was determined in a myocardial infarction model with intraperitoneal (2.5 mg/kg) and intramuscular (3.5 mg/kg) routes of administration. It was shown that intraperitoneal administration of Hypertril at a dose of 2.5 mg/kg to rats in parallel with the formation of acute myocardial infarction led to a 100% reduction in mortality and improvement of ECG parameters. Administration of Hypertril to animals with myocardial infarction led to a decrease in the myocardial necrosis zone, a decrease in the density of apoptotic and destructively altered cardiomyocytes, an increase in the density of cardiocyte nuclei, and an increase in RNA in them compared to the group of untreated animals, which indicated the presence of a pronounced cardioprotective effect. As a result of experimental studies, Hypertril was found to have NO-mimetic properties - in the hearts of animals with myocardial infarction that received Hypertril, an increase in eNOS activity, an increase in its concentration and an increase in NO production were found. Hypertril reduced the manifestation of mitochondrial dysfunction of cardiomyocytes in acute myocardial infarction – it reduced the opening of the mitochondrial pore, increased the charge of the inner membrane of myocardial mitochondria. The administration of Hypertril to animals with myocardial infarction led to a significant reduction in oxidative stress reactions in the myocardium. In the myocardium of animals that received a course of Hypertril, a decrease in markers of

oxidative protein modification was found, as well as a significant increase in the activity of superoxide dismutase, catalase and glutathione reductase in the cytosolic and mitochondrial fractions of the hearts of rats with myocardial infarction. Hypertril showed effects on all the main processes that cause activation of thrombogenesis in acute myocardial infarction, but was more effective on fibrinolysis than on the blood coagulation and platelet aggregation systems. Hypertril at a dose of 2.5 mg/kg improved the main indicators of general and cardiohemodynamics in acute myocardial ischemia in rabbits, regulated heart rate, lowered blood pressure, and reduced total peripheral vascular resistance. Unlike traditional β-blockers, the therapeutic effect of Hypertril is not accompanied by a decrease in left ventricular function – the drug increases its working indices. Administration of Hypertril to animals with acute myocardial ischemia leads to an increase in stroke volume, systolic and cardiac indices. Hypertril, due to cardioprotective mechanisms aimed at reducing both pre- and afterload on the heart in conditions of acute ischemia, is apparently able to improve not only systolic, but also diastolic function of the left ventricle. The obtained data demonstrate the presence of Hypertril in the characteristics of a cardioselective β-blocker with the properties of a peripheral vasodilator. (Belenichev et al., 2021; Belenichev et al., 2024).

The potential drug Hypertril exhibits pronounced antihypertensive and cardioprotective properties when administered for 15 days at a dose of 5 mg/kg/day to SHR rats against the background of a persistent increase in blood pressure, which was expressed in a significant decrease in blood pressure and a decrease in damage to the target organ of the heart. Our studies have provided evidence of an improvement in myocardial energy metabolism in conditions of arterial hypertension with the course administration of Hypertril, associated with its mitoprotective effect. Hypertril reduces the manifestations of secondary mitochondrial dysfunction of cardiocytes in arterial hypertension in rats. Hypertril affects one of the causes of mitochondrial dysfunction – oxidative modification of mitochondrial protein structures under conditions of activation of oxidative stress reactions, reduces mPT pore insufficiency and eliminates antioxidant insufficiency in spontaneously hypertensive rats. Hypertril reduces disturbances in the myocardial L-arginine-NOS-NO system in arterial hypertension. Hypertril exhibits NO-mimetic properties, increasing NO synthesis by increasing the expression of endothelial NOS in the myocardium. Hypertril enhances the protective effects of NO, reducing its conversion to peroxynitrite and thereby increasing cardiomyocyte resistance to adverse effects. The appointment of Hypertril in arterial hypertension leads to a decrease in the density of cardiomyocyte nuclei to the value of normotensive rats and a significant increase in the content of RNA in the nuclei and cytoplasm of cardiomyocytes compared to the group of untreated animals (Mazur et al., 2019).

Based on comprehensive experimental studies and analysis of data on disorders of the electrical activity of the heart and autonomic regulation of heart rhythm, activation of oxidative stress, inhibition of energy metabolism and ATP production, and disorders of the nitroxidergic system, we have obtained new data on the role of disorders of mRNAiNOS expression, mRNAeNOS, and NOS deficiency. These works show that the severity of disorders of the electrical activity of the heart and autonomic regulation of heart rhythm, oxidative stress, and energy deficiency are associated with disorders in the myocardial NO system. We have experimentally substantiated and clinically confirmed the use of a new original b-blocker with an NO-mimetic effect – 1-(b-phenylethyl)-4-amino-1,2,4-triazolium bromide (Hypertril) for the treatment of CHF. The mechanism of protective action of Hypertril in experimental CHF is shown, namely in activation, normalization of eNOS/iNOS expression, increase in NO production, which leads to improvement of ECG parameters, reduction of oxidative stress and improvement of energy metabolism. The superiority of Hypertril over basic b-blockers of different generations in experimental CHF (metoprolol, carvedilol, bisoprolol and nebivalol) is shown (Belenichev et al., 2024; Goncharov et al., 2023).

Rilmenidine. Traditionally known as an antihypertensive agent, rilmenidine has shown unexpected chondroprotective properties. In osteoarthritis models, it demonstrates a reduction in thermal hyperalgesia (analgesic effect), a protective effect on the joint capsule and matrix, and regulation of bone turnover by reducing serum RANKL and osteoprotegerin (OPG) levels (Jalali et al., 2025).

Hawthorn extract. The use of plant extracts (hawthorn, stinging nettle, garlic) is becoming an important part of preventive cardiology. Hawthorn extract (Crataegus) contains flavonoids and terpenoids that protect the endothelium, promote vasodilation and prevent lipid accumulation in macrophages (foam cell formation). Clinical data indicate an improvement in left ventricular ejection fraction and exercise tolerance (Grewal et al., 2023).

Preductal – the first metabolic drug included in the official recommendations of the European Society of Cardiology, provides significant additional efficacy in the treatment of patients with various ischemic syndromes in combination with beta-blockers or calcium antagonists while maintaining good tolerability. The drug reorients energy

metabolism in myocardial cells from fatty acid oxidation to glucose oxidation and has a direct cardioprotective effect. It inhibits long-chain 3-ketoacyl-CoA thiolase (3-CAT) and is considered the ancestor of a new class of antianginal drugs – 3-CAT inhibitors. The European Recommendations for the Treatment of Stable Angina include two representatives of this class: Trimetazidine and Ranolazine. The latter, in addition to the main mechanism, additionally blocks sodium channels that are activated during ischemia and lead to overload of the myocardium with calcium ions. The mechanisms of energy replacement and cytoprotection of Trimetazidine are based on ensuring economical use of oxygen and preserving the integrity of cell membranes (Belenichev et al., 2012). Currently, there is evidence of its effectiveness in chronic heart failure and ischemic cardiomyopathy; in particular, in patients who have suffered a myocardial infarction with a Q wave, the drug reduces the incidence of post-infarction dilation (Goncharov et al., 2023). The change in energy metabolism during infarction formed the basis of the concept of substrate «switching», according to which the activation of glucose oxidation instead of free fatty acids plays a therapeutic role in ischemic heart disease (Belenichev et al., 2024). The excess fatty acids are directed to the synthesis of phospholipids, which determines membrane protective properties, and the mediated antioxidant effect reduces the activity of free radicals in macrophages and endothelial cells (Belenichev et al., 2024).

ATP drugs. At the same time, in cardiology, considerable attention is paid to drugs based on adenyl nucleotides. Although the sodium salt of ATP was the first to be used in the clinic, its effectiveness was limited due to rapid hydrolysis by the enzyme ATPase in the blood and the inability of transmembrane transport of the molecule (Belenichev et al., 2012). The advantages of the coordination compound ATP-Long lie in its unique structure, where the molecule ATP is combined with magnesium and potassium ions and the amino acid histidine. This structure provides stability to the action of deaminases and a significantly higher affinity for purine receptors compared to the usual salt (Patent for invention No. 28494 of Ukraine). The drug has a pronounced cardioprotective effect, increases the activity of the Na^+/K^+-ATPase and Ca^{2+}-ATPase ion transport systems and improves coronary blood flow. An important clinical difference of ATP-Long is the antiarrhythmic effect - it helps restore sinus rhythm in atrial flutter and stop paroxysmal tachycardia, which expands its therapeutic profile compared to Trimetazidine (Goncharov et al., 2023). Clinical regimens and safety of ATP-Long therapy are based on the fact that the drug consists of natural metabolites of the body, so it does not exhibit toxicity and side effects. In the relief of acute conditions, a positive result occurs 30–40 seconds after sublingual administration of 10–40 mg of the drug. For the treatment of paroxysmal supraventricular tachycardia, ATP-Long is administered intramuscularly (1–2 ml) or intravenously (1–5 ml) under the control of blood pressure. The drug can also be effectively combined with nitrates, beta-blockers and calcium antagonists for complex correction of disorders (Goncharov et al., 2023).

The use of ATP-Long is indicated for a wide range of cardiac pathologies, including paroxysmal supraventricular tachycardia, ischemic heart disease (stable angina), post-infarction cardiosclerosis, myocardial dystrophy and chronic fatigue syndrome. The clinical efficacy of ATP-Long is manifested when administered sublingually at a dose of 20 mg three times a day, starting from 3–5 days of regular use. In contrast to intramuscular administration of ATP sodium salt, this drug more effectively reduces the frequency of angina attacks (by 2 times versus 1.2 times) and increases exercise tolerance by 1.7 times. A slight decrease in systolic blood pressure by 7.5% and an increase in contractility index by 15.3% were also noted, which is associated with the vasodilator properties of adenosine.

Conclusions. The work defines the classification of cardioprotectors, provides the main aspects of the pharmacodynamics of synthetic and a number of herbal preparations. These facts will contribute to targeted application in clinical practice. Based on the analysis of the literature, it was found that over the past 20 years, an increase in survival, a decrease in the frequency of repeated hospitalizations and an improvement in clinical outcomes are achieved when properly selected basic therapy agents are included in the treatment regimen. New ideas about the molecular and biochemical mechanisms of cardiodestruction of various etiologies have allowed us to identify common mechanisms of damage – disorders in the NO system, substrate changes, disorders of energy metabolism, lactic acidosis A and B, mitochondrial dysfunction, ferroptosis. target links of cardioprotection. Based on this, new approaches to the pharmacotherapy of cardiovascular diseases include mitoprotection, NO modulation, improvement of myocardial energy metabolism, antioxidant modulation, membrane protection and antiapoptotic action. All of the above significantly increases the effectiveness of basic therapy and improves survival, quality of life and clinical condition of patients with cardiovascular pathology. This can be achieved by deeper study and understanding of the metabolotropic properties of basic therapy agents, as well as rational, targeted use of metabolotropic cardioprotectors and their combination with basic therapy agents.

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