

## **Study of the effectiveness of fructose-1,6-diphosphate in coronary heart disease with heart rhythm disorders**

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**Abstract:** The article presents data on the effectiveness the drug fructose-1,6-diphosphate in patients with chronic forms of coronary heart disease. Drugs of this class provide reduction of oxygen demand of ischemic myocardium by optimizing energy exchange at a certain residual level of blood supply (including in the peri-infarction zone) by reducing fatty acid oxidation in mitochondria and stimulating glycolysis, requiring 13% fewer oxygen molecules. This preserves myocardial viability in the ischaemic zone. The results of the study showed that the inclusion of the drug fructose-1,6-diphosphate in the complex therapy of coronary heart disease makes it possible to accelerate the dynamics of ECG, has anti-inflammatory, antiarrhythmic, antianginal and anti-ischemic effect, thereby improving the quality of life of patients with chronic forms of coronary heart disease.

**Keywords:** ischemic heart disease, chronic coronary syndromes, antiarrhythmic, antianginal and anti-ischemic effect.

**Relevance.** Ischemic heart disease (CHD) can be classified as a pathology in which chronic hypoxic disorders play an important role. Chronic hypoxia in the myocardium leads to impaired utilization of fatty acids, which are a substrate for energy production [1, 2, 24]. Acetyl -I- CoA and acylated carnitine accumulate in mitochondria, and the function of cell membranes is disrupted. Damage to mitochondria leads to an increase in the level of calcium ions in the cytoplasm. This, in turn, changes the action potential in cardiomyocytes and can lead to arrhythmias [3, 5, 19, 20]. Therefore, it is important to search for means of optimizing therapy for this category of patients, among which drugs that affect the metabolic status in patients with coronary artery disease deserve special attention [4,6,7, 13, 15, 18].

These drugs include fructose-1,6-diphosphate. Fructose-1,6-diphosphate in pharmacological doses interacts with cell membranes, accelerates the absorption of potassium from circulating blood by cells and stimulates an increase in the intracellular supply of high- energy phosphates and the accumulation of 2,3-diphosphoglycerate. In addition, according to research data, the drug improves the pumping function of the heart and exhibits an antiarrhythmic effect.

**Objective :** to study the effect of fructose-1,6-diphosphate on the quality of life, lipid metabolism, structural and functional state of the left ventricular myocardium and vasomotor function of the endothelium in arrhythmias in patients with coronary heart disease.

**Materials and research methods.** 95 patients with coronary artery disease and heart rhythm disorders aged 39 to 64 years, who were under dynamic observation in the medical clinic of Sabo Darmon LLC and on an outpatient basis at the Department

of Cardiology and Gerontology, were examined, with a course of interventional cardiology and arrhythmology of the CRPCMR. The criteria for inclusion of respondents in the study were as follows: a diagnosis of stable HF I, II and III FC with the presence of arrhythmia, confirmed by clinical and instrumental studies.

The diagnosis of coronary artery disease, exertional angina was verified on the basis of anamnesis and bicycle ergometry (VEM). *Inclusion criteria*: verified diagnosis of coronary artery disease based on complaints, anamnestic data, clinical picture, results of an objective study. *Exclusion criteria* : severe concomitant pathology - ecompensation of diabetes mellitus, oncological diseases, fever, accompanied by inflammatory changes in the blood, renal, hepatic insufficiency and severe widespread CNS lesions. Cardiac arrhythmias were confirmed by HMECG studies. Of the 95 patients, 45 (47%) had atrial fibrillation (AF), 50 (53%).

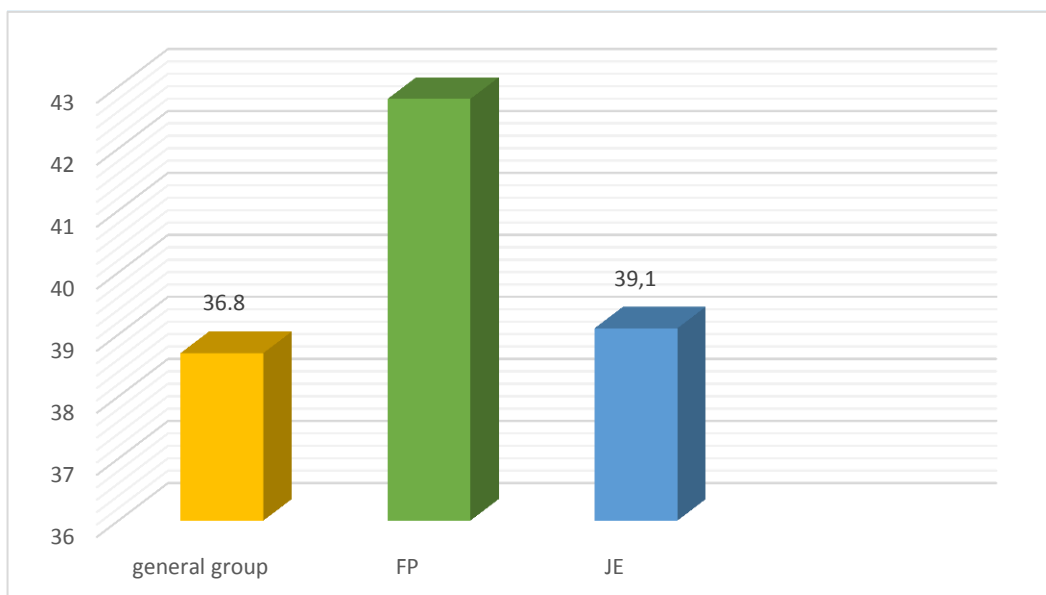
All patients, depending on the therapy performed, were divided into 2 groups; Group 1 (main, n=60) received fructose-1,6-diphosphate ( Ezafosfin produced by Biomedica Foscoma Group SPA (Ferentino, Italy) on the background of basic therapy for 5.0 days for 15 days against the background of basic therapy for coronary artery disease, group 2 (control, n = 35) who received only basic therapy (beta-blockers, antiplatelet agents, statins, if necessary, short-acting nitrates and amiodarone).

The duration of the study was 2 months, after which a second study was conducted according to the original protocol.

*Exclusion criteria*: symptomatic arterial hypertension, exacerbation of chronic or acute inflammatory diseases during the study, severe liver and kidney disease, recent myocardial infarction, high functional classes of chronic heart failure (III-IV).

*Research methods*: quality of life (QOL) was studied using the SF 36 questionnaire, blood lipid composition, ECG, HMECG, ECHOCC, endothelial vasomotor function (EVD) was assessed using the Celermajer method on an ultrasound machine. When statistically processing the results of the examination, Student's t-test was used; differences were considered significant at  $p \leq 0.05$ .

**The results of the study** showed that in the examined patients with coronary artery disease and cardiac arrhythmia, according to the questionnaire, the average quality of life was  $38.7 \pm 6.2$  points. Different directions in QoL were revealed in patients with coronary artery disease, depending on the clinical variant of cardiac arrhythmia. In the group of patients with PVC, the QOL index was  $39.1 \pm 7.2$  points, and in the group of patients with AF it was  $42.8 \pm 8.3$  points, that is, QOL in the group of patients with AF in relation to the general group of patients by 10% ( $p < 0.05$ ) is significantly low (Fig. 1).

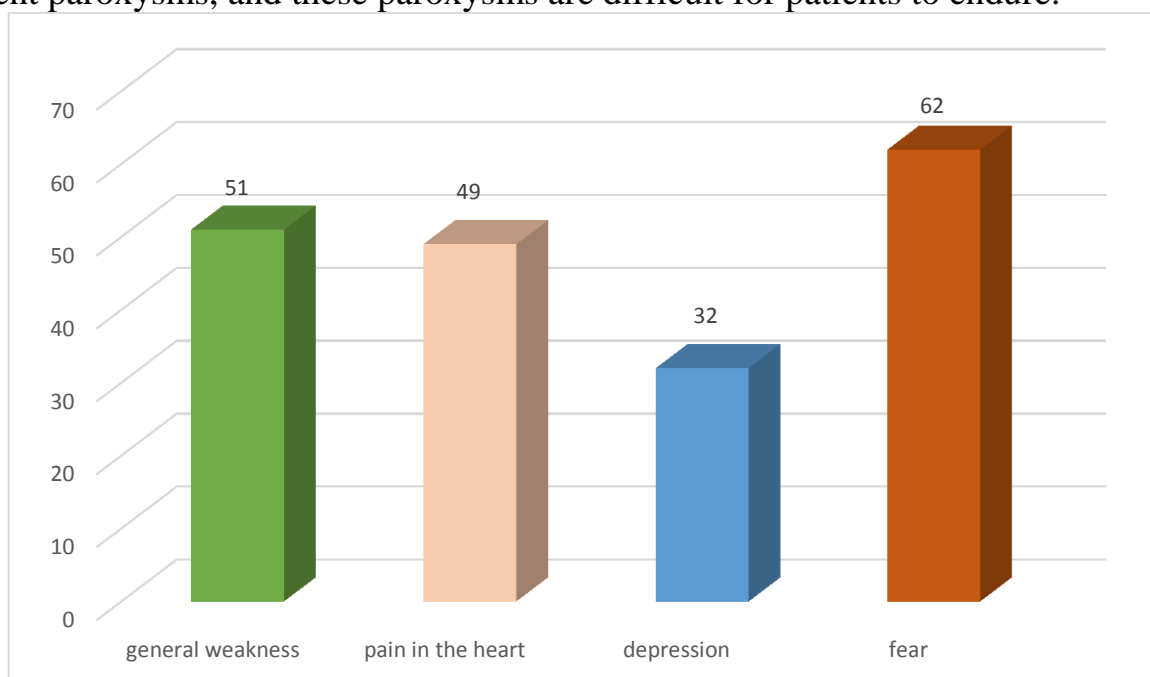


Note: \* p

<0.05 significance of differences in relation to the total group

**Figure 1. QoL in the examined individuals (score)**

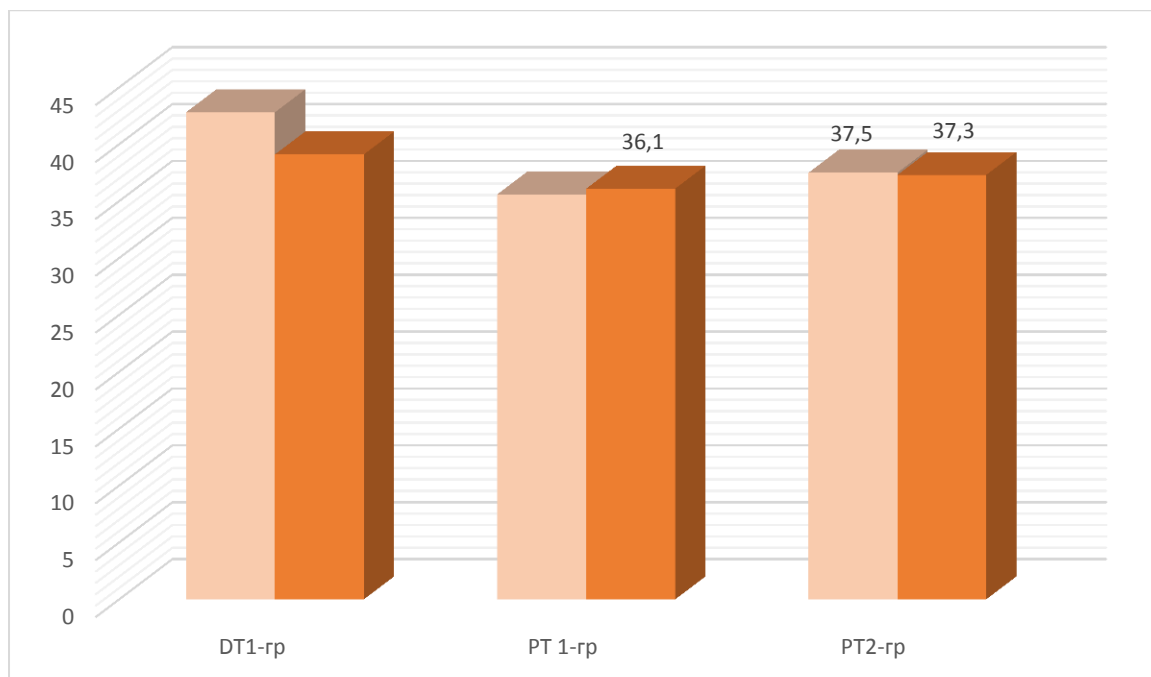
Violation of QoL in these patients apparently occurs due to the presence of frequent paroxysms, and these paroxysms are difficult for patients to endure.



**Figure 2. Clinical status of patients ( n )**

Along with this, we analyzed the clinical status of patients. The first place is occupied by fear - 65%, general weakness was detected in 54%, pain in the heart area in 51% and depression in 34%, respectively. All these clinical indicators could reduce QoL in patients with coronary artery disease (Fig. 2.).

During therapy in the main group of patients, the QoL of patients significantly and significantly changed in the group of patients with AF; in the group of patients with PVC, there is also a positive trend, but it does not have statistical significance. In the group of patients who received only basic therapy, a relative non-significant improvement in QoL was revealed.



Note: \*  $p < 0.05$  significance of differences in relation to the general group, DT-before therapy, PT - after therapy

**Figure 3. QoL in the examined individuals during therapy**

On the part of the clinical status, a noticeable positive trend was revealed in terms of anginal pain, which was manifested by a decrease in the number of angina attacks in the main group of patients. Along with a decrease in the number of angina attacks, there was a positive trend in relation to a decrease in the number of nitroglycerin tablets consumed, which indicates the effectiveness of antianginal therapy (by 31% ( $p < 0.05$ )).

**Table 1 .**

**Clinical status of patients before and after therapy**

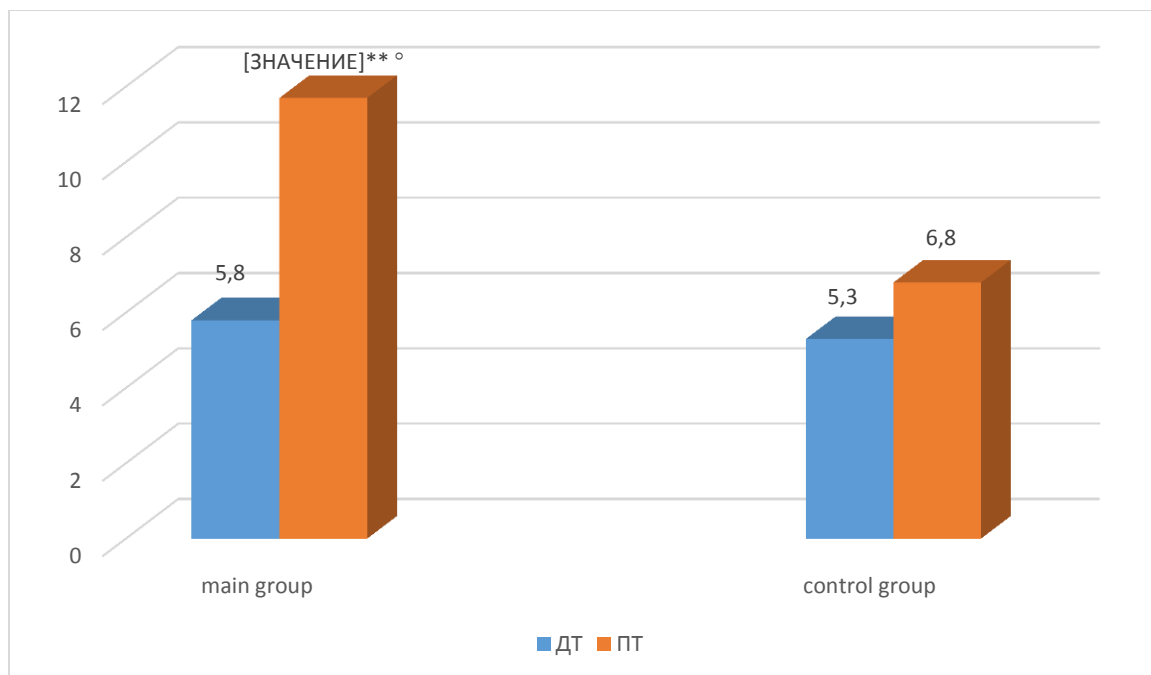
No.	Indicators studied	Main group		Control group	
		DT	Fri	DT	Fri
1	KPS	5.3±3.2	2.5±1.7*°	5.1±3.0	3.4±2.7
2	KTN	1.4±0.71	1.04±0.62	1.35±0.72	1.2±0.65

Note: \*  $p < 0.05$  significance of differences in relation to baseline data, °  $p < 0.05$  significance of differences between groups, CPS-number of angina attacks, CTH-number of nitroglycerin tablets

Evaluation of the effectiveness of the therapy in the main group of patients in relation to the baseline by 47% ( $p < 0.05$ ) demonstrated the decrease in CPS, respectively, CTN also decreased, although the results showed only a trend of positive dynamics with an unreliable character. At the same time, less significant positive dynamics is observed in the control group.

An analysis of the EZVD indicators showed that in patients suffering from coronary artery disease with the presence of cardiac arrhythmia, there is a high frequency of vasoconstrictor reactions of the brachial artery.

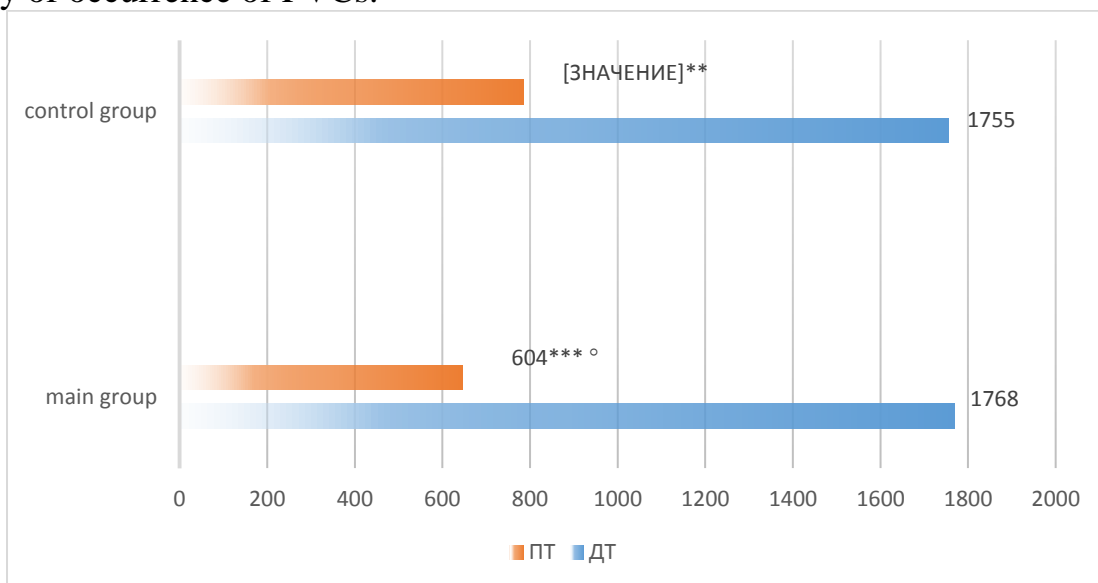
Thus, EDVR improves significantly in the main group, i.e. in relation to the initial data by 49.6% (  $p < 0.01$ ), while in the control group, the restoration of endothelial function was 28% (Fig. 4).



Note: \*  $p < 0.05$  significance of differences in relation to the original data, °  $p < 0.05$  significance of differences between groups

**Figure 4. EDVD values during therapy (%)**

According to HMECG data, we also observe positive dynamics in the frequency of occurrence of PVCs.

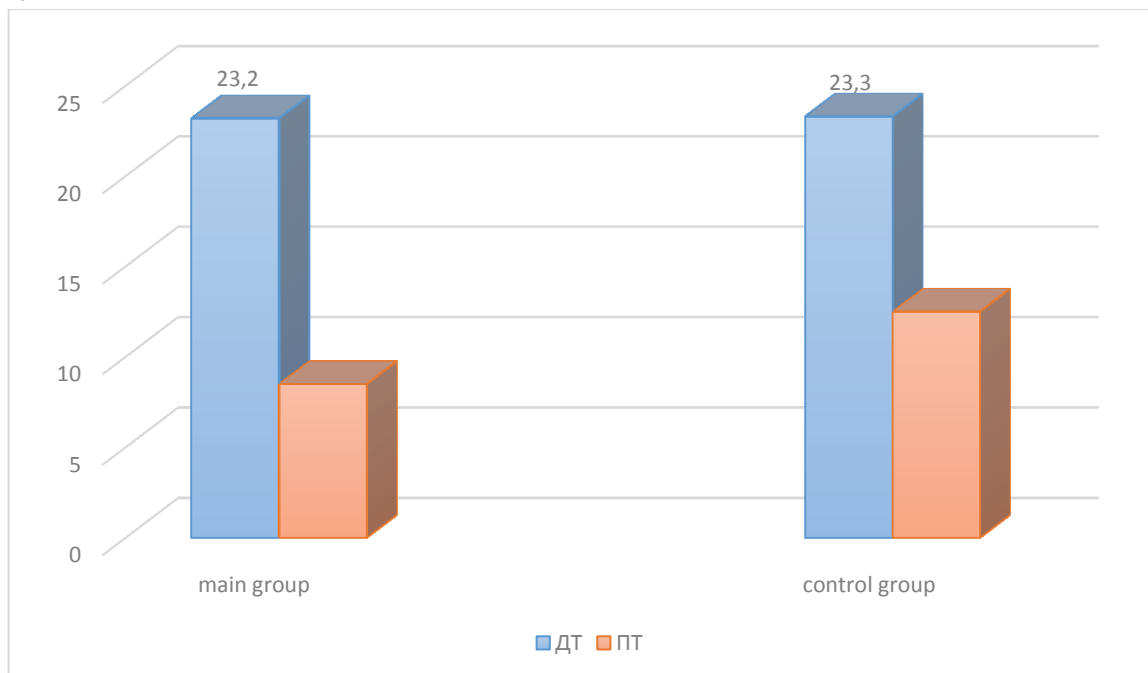


Note: \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  significance of differences in relation to the original data, °  $p < 0.05$  significance of differences between groups

**Figure 5. Frequency of occurrence of PVC during therapy**

It should be emphasized that in the main group the statistical significance of the results was higher in relation to the control group. As for episodes of atrial fibrillation in the main group,  $8.5 \pm 7.6$  versus  $23.2 \pm 27.1$  (  $p < 0.001$ ) were recorded per day in the control group, from  $23.3 \pm 19.6$  to  $12.5 \pm 10, 6$  (  $p < 0.01$ ). In the main

group of patients, the statistical significance of the result was an order of magnitude greater.



Note: \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  significance of differences in relation to the initial data, °  $p < 0.05$  significance of differences between groups

**Figure 6. AF paroxysms during therapy**

We have studied the parameters of the structural and functional state of the myocardium in the examined individuals. When analyzing ECHOCG against the background of therapy in the main group, there was a tendency to increase the contractility of the left ventricular myocardium, characterized by a decrease in the end-systolic and diastolic volume of the left ventricle.

At the same time, ESV in the main group significantly decreases from  $56.7 \pm 14.6$  ml to  $48.2 \pm 11.7$  ml ( $p < 0.05$ ), CVD from  $143.1 \pm 29.4$  ml to  $132.6 \pm 31.2$  ml ( $p < 0.05$ ), in the control group from  $55.8 \pm 13.2$  ml to  $53.1 \pm 12.5$  ml, from  $142.7 \pm 25.6$  ml to  $138.6 \pm 28.2$  ml, respectively.

When comparing the parameters of the left ventricular ejection fraction, a more significant increase was also noted in the main group from  $54.5 \pm 4.2$  to  $61.3 \pm 5.8\%$ , and in the control group from  $55.2 \pm 4.5$  to  $57, 3 \pm 5.2\%$ .

**Table 2.**

**Dynamics of blood lipid levels during therapy (M ± m )  
(DT is the numerator and PT is the denominator)**

Indicators	Main group	Control group
	Exodus	Exodus
	After treatment	After treatment
Total cholesterol, mg / dl	$222.0 \pm 6.3$	<b><math>219.5 \pm 5.0</math></b>
	$169.1 \pm 7.3^{*\circ}$	<b><math>184.0 \pm 7.1</math> *</b>
TG, mg/dl	$202.2 \pm 13.0$	<b><math>208.2 \pm 10.1</math></b>
	$172.0 \pm 11.4^{*\circ}$	<b><math>181.2 \pm 13.5^*</math></b>

<b>LDL cholesterol, mg/dl</b>	140.2±5.2	<b>141±4.5</b>
	121.4 ± 5.2	<b>131±5.0</b>
<b>HDL cholesterol, mg/dl</b>	39.1±1.0	<b>40.1 ± 1.4</b>
	42.0 ± 1.8	<b>41.5 ± 2.2</b>
<b>KA, rel.</b>	4.1±0.19	<b>4.1 ± 0.18</b>
	3.1±0.11	3.6±0.15
	<b>3.4 ± 0.18 ^^</b>	<b>3.0 ± 0.2 ^^^***</b>

Note: \* P <0.05 significance of differences in relation to baseline values,  
° P <0.05 significant differences between groups.

From the side of the lipid composition of the blood, there is also a positive trend, but in the main group it was more significant.

#### Conclusions:

1. The use of fructose-1,6-diphosphate in the complex therapy of patients with coronary heart disease with chronic coronary syndromes manifesting heart rhythm disturbances helps to reduce angina attacks, reduce the number of nitroglycerin tablets consumed, increasing stress tolerance, which is manifested by an improvement in quality of life indicators.

2. The effectiveness of the studied drug against the background of standard therapy on clinical, hemodynamic, laboratory, instrumental parameters in patients with coronary artery disease with cardiac arrhythmias is observed, therefore, given the cardioprotective effect, it can be recommended for use in patients with ischemic heart disease and stable angina pectoris .

3. The inclusion of fructose-1,6-diphosphate in complex therapy has a positive effect on endothelial function indicators, significantly increasing the indicator of endothelial-dependent vasodilation in patients with coronary artery disease with arrhythmia.

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