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COMPARATIVE EFFICIENCY OF DIFFERENT LIPID-LOWERING DRUGS COMBINATIONS FOR THE TREATMENT OF CORONARY ATHEROSCLEROSIS

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Summary: *The article presents a study results on the dynamics of lipid spectrum under the influence of combination regimens of lipid-lowering therapy (statin + fibrate and a statin + ω-3 PUFA). The data shown a significant lipid-lowering effect of combinated therapy by fibrate with a statin on all the atherogenic fractions. Integrated application of statin with ω-3 PUFA allowed not only to reduce the atherogenic lipid fractions, but also achieve a higher level of HDL. The results indicate a greater effectiveness of the medication complex as compared with statin monotherapy, as well as the need for a differentiated approach to lipid-corrective therapy based on blood lipid fractions baseline.*

Keywords: ischemic heart disease, dyslipidemia, lipid-corrective therapy.

The main cause of ischemic heart disease (IHD) is atherosclerosis (AS) due to dyslipidemia IIa, IIb or III type by Fredrickson [1]. According to modern concepts, hypercholesterolemia, and especially an increasing of serum low-density lipoprotein (LDL) level, is a one of the most important factors in the development of cardiovascular disease [2, 3].

However, modern researching datas on the field of Lipidology shows that high cholesterol and increased LDL are not the only leading mechanisms, which is the trigger of atherogenesis. The convincing data, that obtained in last time, show that the decrease of high-density lipoprotein (HDL) involved in the transport of cholesterol (LDL) from tissues back to the liver, promotes to the atherogenicity of the blood and become an independent risk factor for coronary heart disease [4].

The degree of AS risk is increased if an increase of LDL cholesterol and low levels of HDL-C connect with the hypertriglyceridemia [5, 6]. With this in mind, the choice of

lipid-lowering drugs important is their ability to correct the levels of triglycerides (TG) and HDL.

At present the correction of LDL with statins is considered modern clinical protocols as a key element of the strategy to reduce the risk of coronary heart disease (primary prevention) or cardiovascular events (secondary prevention). [5] At the same time, in accordance with European and Ukrainian recommendations for the prevention of AS in patients with increased cardiovascular risk should strive to achieve optimal levels of blood lipids [5]. However, after statin monotherapy, even at maximum doses, there is often a problem of residual cardiovascular risk, which is estimated by various authors at the level of 30-70% [7, 8]. Also, the effect of statins on TG and HDL not so great as in other atherogenic fraction. More important is the effect expressed in other classes of lipid-lowering drugs, such as fibrates and a ω-3 polyunsaturated fatty acids (PUFA) [5, 9, 10].

It is evident that a combination of small doses of drugs from different groups can be not only more efficient but also better tolerated than vysokodozovaya monotherapy. In this regard, actual is now a comparative study of the efficacy of different combined therapy strategies. And if research on the issue of comparing combination therapy with statin monotherapy, appeared only the last years and, as a consequence, very few in number, the comparative studies of combinations of lipid-lowering drugs, we have not found.

Objective: To compare the efficiency of the combination regimens of lipid-lowering therapy (statin + fibrate and a statin + ω-3 PUFA).

Materials and Methods:

The subjects of the study were 71 patients with stable angina I-III functional class (FC), who was treated at the cardiology department of the Military Medical Clinical Centre of South region and therapeutic department of the Yuzhnyi city hospital (Odessa region). The diagnosis of stable angina was esteblished in accordance with the recommendations of the Association of Cardiologists of Ukraine (2007),and the classification of the Canadian Cardiology Society of [6].

Inclusion criteria: signed patient's informed consent form and verified diagnosis of stable angina pectoris I - III FC.

Exclusion criteria: acute coronary syndrome, chronic heart failure above FC IV by NYHA and severe comorbidities (decompensation of chronic diseases, septic status, cancer, hematological diseases, etc.).

Patients have been divided for three groups:
Group I - 25 patients (control group). Treatment by the standard complex regimens for the treatment of stable angina pectoris (beta-blockers, aspirin, ACE inhibitors, nitrates, statins - atorvastatin in a daily dose of 20 mg).
Group II - 25 patients. Standart complex regimen swith atorvastatin (daily dose 10 mg) plus fenofibrate (Tricor in a daily dose 145 mg) for the entire of observation period.
Group III - 21 patients. Standart complex regimen swith atorvastatin (daily dose 10 mg) plus ω-3 PUFA (omega-3 vitrum cardio, daily dose - 2 g).

The treatment groups were broadly representative of the age (Gr. I:63,2±2,6 y.o, Gr.: II 62,1±2,49 y.o., Gr.III: 59,17±2,63 y.o.) and angina range (Gr. I:1,91±0,15 FC, Gr.II: 1,87±0,12 FC and Gr.III: 2,25±0,18 FC). On average, the duration of treatment was 6-8 weeks.

Blood samples from the all patients were collected before and after treatment from a peripheral vein. We analyzed the following parameters: total cholesterol (TC), triglycerides, LDL, VLDL, HDL, atherogenic index (AI). Components of lipid spectrum (total cholesterol, triglycerides, LDL, VLDL, HDL) were studied on an automatic biochemical analyzer Cobas Mira Plus (Switzerland) using reagent kits firm "BIOLATEST" (Czech Republic). The content of VLDL and AI was determined by the following formulas:

VLDL = total cholesterol - HDL cholesterol - LDL cholesterol

AI = total cholesterol - HDL cholesterol / HDL-C

The resulting material was processed using the statistical program «STATISTICA 6.0». The data were processed by the method of variation statistics using the Student t-test. Results are presented as mean and SEM (M ± m). The differences between the studied parameters were considered statistically significant between $p < 0.05$.

Results and discussion:

The first results showed that in all groups of patients the mean values of atherogenic fractions (total cholesterol, triglycerides, LDL, VLDL, IA) were much higher than normal, which coincides with the opinion of other authors [11]. The results obtained under the influence of a complex with standard medical atorvastatin are shown in Table 1. The table shows a significant decrease of more atherogenic lipid fractions: TC and LDL (p = 0,002 and p = 0,0003). However, necessary to emphasize that the decrease of this fraction did not reach the required level for patients with coronary heart disease [5], and, accordingly, require further decline.

Thus, as a result of treatment with standard drugs complex with atorvastatin, even though they were marked by a significant positive change in the attitude of total cholesterol and LDL, these indicators not achieved target levels for patients with coronary artery disease, and make a difference in the treatment of dyslipidemia on indicators such as HDL, TG and EA did not succeed.

Table 1- **Dynamics of the blood lipid spectrum under the influence of standard medical complex with the atorvastatin**

Parameter	Before the treatment	After the treatment	p1
Total cholesterol (mmol / L)	6,07±0.24	5.26±0.24	0.002
LDL (mmol / L)	3.76±0.29	2.99±0.22	0.0003
VLDL (mmol / L)	1.01±0.14	1.2±0.18	0.1
TG (mmol / L)	1.72±0.12	1.93±0.27	0.47
HDL (mmol / l)	1.3±0.15	1.07±0.09	0.2
IA (un.)	5.1±0.72	4.68±0.49	0.55

These data show that the proposed scheme is given a positive impact on the main range of blood atherogenity of patients with coronary artery disease, but has an insignificant effect on a number of factions lipid profile, and therefore need to be optimized.

Considering the data obtained by us about the weak effect of statins on some lipid fractions, as well as the authors report about the a more expressed effect of fibrates on TG and HDL-C [5, 12], the expected results of the combined treatment with statins with

fibrates applied a more pronounced positive effect on all indicators of lipid metabolism. Results are shown in Table. 2.

Table. 2 **- Dynamics of blood lipid profile under the standard medication complex - combination of atorvastatin and fenofibrate**

Parameter	Group I standart therapy			Group II standart therapy + atorvastatin and fenofibrate			p1-2
	before the treatment	after the treatment	p1	before the treatment	after the treatment	p2	
Total cholesterol (mmol/L)	6,07±0.24	5.26±0.24	0.002	6.44±0.24	5.26±0.17	0.0001	0.27
LDL (mmol / L)	3.76±0.29	2.99±0.22	0.0003	3.53±0.26	2.98±0.26	0.045	0.46
VLDL (mmol/L)	1.01±0.14	1.2±0.18	0.15	1.54±0.17	0.97±0.14	0.009	0.003
TG (mmol/L)	1.72±0.12	1.93±0.27	0.47	2.63±0.16	1.48±0.10	0.0001	0.0003
HDL (mmol/l)	1.3±0.15	1.07±0.09	0.2	1.25±0.10	1.28±0.09	0.69	0.18
IA (un.)	5.1±0.72	4.68±0.49	0.55	4.97±0.49	3.42±0.30	0.0004	0.16

As seen from Table 2, the use of combined treatment (standard complex with inclusion of statins and fibrates) achieved a significant reduction of total cholesterol concentration (6,44 ± 0,24) mmol / L to (5,26 ± 0,17) mmol / l (p = 0,0001), more pronounced than in the control group. Also, a significant decrease was observed in LDL cholesterol (p = 0.04), although significant intergroup differences are controlled by these parameters were observed (p = 0.27 and p = 0.46).

The most distinctive in this group of patients was significant (p = 0,0001 and p = 0.009) reduction TG levels (2,40 ± 0,18 to lech. And 1,43 ± 0,08 after lech., P = 0,0001) and VLDL (1,54 ± 0,17 to lech. and 0,97 ± 0,14 after lech., p = 0.009) were significantly different from the control group (p = 0.003 and p = 0.003). In accordance with the decline in the major atherogenic fractions also decreased significantly IA (p = 0,0004) - from 4,97 ± 0,49 to 3,42 ± 0,30, preferably by reducing the total cholesterol, while the decrease in the control group IA was not statistically significant (p = 0.55).

In difference from published data about the increasing of HDL cholesterol by an average of 10.5% under the fibrates [5, 12], we did not mark any positive dynamics of

their level in this group of patients (1,28 ± 0,09 to lech. 1 and , 27 ± 0,07 after lech.). In summary, we can conclude that it is a significant lipid-lowering effect of fenofibrate in combination with a statin at a daily dose of 10 mg, noting the marked effect on TG and virtually no effect on HDL.

A substantial effect on TG and HDL and also tend to ω-3 PUFAs [10], which allowed expect a more pronounced efficacy in all lipid fractions. The results are shown in Table. 3.

Table 3 - **Dynamics of lipid profile under the influence of a standard medical complex with the inclusion of atorvastatin and ω-3 PUFA**

Parameter	Group I standart therapy			Group III standart therapy + atorvastatin and ω-3 PUFA			p1-3
	before the treatment	after the treatment	p1	before the treatment	after the treatment	p3	
Total cholesterol (mmol/L)	6,07±0.24	5.26±0.24	0.002	6,14±0,25	5,16±0,20	0,006	0.6
LDL (mmol / L)	3.76±0.29	2.99±0.22	0.0003	3,47±0,33	2,14±0,22	0,002	0.08
VLDL (mmol/L)	1.01±0.14	1.2±0.18	0.15	1,32±0,13	0,84±0,08	0,001	0.0002
TG (mmol/L)	1.72±0.12	1.93±0.27	0.47	2,90±0,29	1,83±0,17	0,001	0.001
HDL (mmol/l)	1.3±0.15	1.07±0.09	0.2	1,38±0,16	2,23±0,33	0,005	0.001
IA (un.)	5.1±0.72	4.68±0.49	0.55	4,21±0,71	1,73±0,31	0,0001	0.02

The table shows that, despite the absence of a significant between-group differences with the control group (p = 0.6) under the influence of combined treatment with statins, and the inclusion of ω-3 PUFA total cholesterol was significantly reduced from (6,14 ± 0,25) mmol / L to (5,16 ± 0,20) mmol / L (p = 0,006). There was also a significant reduction in LDL cholesterol (p = 0.002), VLDL (p = 0.001), and triglycerides (p = 0.001) were significantly different from the control group (p = 0.08, p = 0.0002, p = 0.001). Synchronously with the reduction of atherogenic fractions decreased by 59.0% and IA - from 4,21 ± 0,71 to 1,73 ± 0,31 (p = 0,0001), were also significantly different from the control group (p = 0, 02).

In contrast to the other groups was statistically significant (p = 0.005) positive trend levels of HDL - from (1,38 ± 0,16) mmol / L to (2,23 ± 0,33) mmol / L, significantly different from the control group (p = 0.001). Based on the foregoing, it can be concluded a significant lipid-lowering effect combination ω-3 fatty acids with a statin in a daily dose of

10 mg, expressed in relation to both of atherogenic and antiatherogenic fraction.

After receiving of information about a positive effect on the lipid profile of lipid-lowering combinated herapy, the most interesting to compare the effectiveness of two of the studied combinations (Table 4)

Table 4 - **The dynamics of blood lipid profile under the studied therapeutical combinations**

Parameter	Group II standart therapy+ atorvastatin and fibrate			Group III standart therapy+ atorvastatin and ω-3 PUFA			p2-3
	before the treatment	after the treatment	p2	before the treatment	after the treatment	p3	
Total cholesterol (mmol/L)	6.44±0.24	5.26±0.17	0.0001	6,14±0,25	5,16±0,20	0,006	0.55
LDL (mmol / L)	3.53±0.26	2.98±0.26	0.045	3,47±0,33	2,14±0,22	0,002	0.04
VLDL (mmol/L)	1.54±0.17	0.97±0.14	0.009	1,32±0,13	0,84±0,08	0,001	0.70
TG (mmol/L)	2.63±0.16	1.48±0.10	0.0001	2,90±0,29	1,83±0,17	0,001	0.78
HDL (mmol/l)	1.25±0.10	1.28±0.09	0.69	1,38±0,16	2,23±0,33	0,005	0.004
IA (un.)	4.97±0.49	3.42±0.30	0.0004	4,21±0,71	1,73±0,31	0,0001	0.13

As the table shows, the total cholesterol significantly decreased in both groups, however, are more pronounced degree of reduction was observed in the group with the fibrate, although significant between-group differences were observed (p = 0.55). LDL cholesterol decreased significantly in both groups, however, significantly greater in the group with the addition of ω-3 PUFAs, which confirms the accuracy of the intergroup difference (p = 0.04). VLDL concentration was significantly decreased in both groups, and the absence of inter-group differences (p = 0.70), the effect was more pronounced when using ω-3 PUFA (p = 0.001 vs. p = 0.009). In contrast, under the influence of fibrates observed greater effects on TG (p = 0.0001 vs. p = 0.001), but considering the significance of the results reliable intergroup difference was observed (p = 0.78).

Thus, our data shows that statin monotherapy does not have a positive effect on HDL cholesterol, and there was even a mild tendency to deterioration (p = 0.2). Upon acceding to fibrate therapy, this orientation has disappeared and HDL levels remained unchanged (p = 0.69), and when used in treatment of ω-3 PUFA, the indicator changed its

focus to improve, and the difference was significant (p = 0.005) , and that led to a significant difference between groups II and III (p = 0.004). Based on the foregoing, it can be concluded about the impact of inadequate treatment in the control group at the level of HDL, the positive, but insufficient to normalize when joining a fibrate and a significant positive effect of ω-3 PUFA.

Of the above data allows us to conclude not only to strengthen the effect of the studied hypolipidemic therapeutic complexes compared with statin monotherapy, but also of a "tropism" of fibrates and ω-3 fatty acids to reducing of TG greater in fibrates, and ω-3 PUFA – to reducing of HDL. This, in turn, led to the dynamics and the integral index of the IA, who had only a slight downward trend in the group using statin monotherapy (p = 0.55) and a significant decrease in the two groups with combined therapy (p = 0.0004 and p = 0 , 0001).

Thus, these studies have shown that as a result of treatment with a standard medication complex using atorvastatin 20 mg daily, although it was observed a significant reduction in major atherogenic fractions (total cholesterol and LDL), they do not reach their target levels, and their effect on HDL , TG, VLDL and the EA complex in general was virtually ineffective.

The combination of a fibrate with a statin had a significant lipid-lowering effect in respect of all atherogenic fractions, with the exception of HDL, and he was most pronounced with respect to total cholesterol and triglycerides. Under the influence of an integrated treatment with ω-3 PUFA has been achieved not only the reduction of all atherogenic lipid fractions, but also the best result in terms of the level of HDL. Based on the foregoing, one can conclude that a greater effectiveness of the combinations versus statin monotherapy. Moreover, given the different efficiencies combination regimens for individual fractions of lipids (triglycerides, HDL), requires a different approach in the assignment schemes lipid corrective therapy for patients based on baseline lipid levels.

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