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Can Statins Help „Good Cholesterol“ to Become Even Better

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Abstract

Background: Ischemic heart disease (IHD) is a most common manifestation of generalised atherosclerosis. Hyperlipidemia is one of the most significant risk factors causing atherosclerosis. Becouse of this, statin therapy is the ″guideline″ in therapy of hyperlipoproteinemia.

Aim: The aim of this study was to show the hypolipemic effect of statins.

Material and Methods: The research included 74 patients with hyperlipoproteinemia type II and III, with (59 patients) or without (15) coronary disease diagnosis. All patients have been treated with statins. In all patients, we analizing statins hypolipemic effects, and the research was carried out: before therapy, after 2 and 6 weeks, 3 months, and than every 3 months during 2 years of treatment.

Results: Target value of lipoprotein profile parameter is achieved after 3-6 months of statin treatment. According to the results HDL-cholesterol was changed with the statins for 12.5% average; the highest average value change of 27.5% was recorded at the end of follow-up, and the minimal mean change, observed 2 weeks after therapy initiation was 4.59%.

Conclusion: The statin therapy has significant effect on lipoprotein profile and atherogenic index. That effect is the most intensive after 3 month therapy, and target level of lipoprotein parameter are achieved after 3-6 months of statin treatment.

Introduction

Numerous epidemiological studies have shown that cardiovascular diseases account for 50% of the total mortality rate, and the pronounced atherosclerosis is verified in about 90% of cases in these diseases [1]. Ischemic heart disease is caused by atherosclerosis in over 90% of cases. So far, 250 risk factors were found to be responsible or to contribute in the development of atherosclerosis, and beside smoking and hypertension, hyperlipidaemia have shown to be one of the most important risk factor [2].

Hyperlipidaemia is a disorder of lipid metabolism, or individual lipoprotein fractions with consequential increase in their concentrations in the blood and accumulation in the human body. Ethiopathogeneticly, they are divided into primary (which according to Fridricson can be divided into 6 types) and secondary [3]. However, only types II and III are clinically manifested by fast developing atherosclerosis. This classification can be useful to provide information about phenotypic disorders, but the clinical classification is used more often. According to this classification primary hyperlipoproteinemia is divided into: primary hypercholesterolemia (type IIa, IIb partly), hypertriglyceridemia (I, IV, V), mixed hypercholesterolemia and hypertriglyceridemia (III) and rare lipoprotein disorders. The diagnosis of hyperlipidaemia is based on medical history, clinical manifestations and diagnostic methods, primarily laboratory findings. The first step in diagnosis is to determine the levels of triglycerides, total cholesterol, and the refrigerator test; as well as to determine the level of HDL-cholesterol. The main goal of treatment is slowing down the development of atherosclerosis and reducing the frequency of its consequences via diets, medicaments, and in extreme cases, surgery [3]. Medical treatment involves the use of statins, fibrates, nicotinic acid and ion exchange medicines [4].

Statins (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin) are specific reversible inhibitors of HMG-CoA reductase, key enzyme in endogenous cholesterol synthesis, and they are considered to be the most powerful hypolipemics. These drugs have a dose dependent effect on lowering total cholesterol levels for 30%, triglycerides for 35%, LDL-cholesterol for 40%, and increasing of HDL-cholesterol for 10% [4, 5]. Pharmacological effects are manifested after only 2 weeks of medication use, the maximum therapeutic effect occurs after 4-6 weeks, and remains constant over the entire therapy. Dosage is individual and depends on presence of coronary heart disease beside hyperlipidemia [4]. In patients with coronary heart disease initial treatment usually starts with 20-40 mg daily of atorvastatin, simvastatin or rosuvastatin, and further dose adjustments should be made at intervals not less than 4 weeks, up to a maximum dose of 80 mg (40 mg of rosuvastatin).

With this research we wanted to investigate the effect of early diagnosis and modern treatment methods of hyperlipidaemia on the coronary heart disease. We focused on the use of atorvastatin in the majority of patients, because of its lipid lowering, and non lipid lowering effects, especialy antiathero-sclerotic. The aim was also to investigate in which period the first benefitial effects of the treatment can be observed, whether they remain constant during the treatment or not, and compare obtained results with the published data.

Matherials and Methods

This controlled clinical research included 74 patients with primary hyperlipoproteinaemia type II and III, 59 patients with and 15 without diagnosed coronary heart disease. Two patients, in the group with coronary heart disease, had familial homozygous hypercholesterolemia. Research included 58 male and 16 female patients, aged 30 to 55 years. All patients were treated in Department of Cardiology, University Clinical Center Kragujevac from 2000-2003. Before treatment initiation, all patients were informed about the purpose of research and drug effects, and signed the informed consent. The research lasted for three years and period of treatment for each individual patient was two years. Every patient had 11 follow-ups at appropriate intervals: before therapy, after 2 weeks, 6 weeks, 3 months and then in every 3 months (6, 9, 12, 15, 18, 12 and 24 months after the beginning of the research) so cumulative period of treatment for every patient was 2 years.

The severity and manifestations of coronary artery disease, and differences in the level of lipoprotein fractions in secondary hyperlipidemia are dependent on the primary disease, which is the cause of lipid metabolism disorder [2]. Therefore is difficult to investigate the effect of any medicine or treat hyperlipidemia as an independent risk factor for atherosclerosis. In order to achieve valid results of the study, we included only patients with primary hyperlipoproteinemia type II and III.

Appropriate drug and dose selection was dependent on a number of associated risk factors and levels of lipid fractions. According to Rote list [6], and the recommendations of great clinical, world [7-10] and national studies, all patients were treated using statins. Due to the characteristics of atorvastatin, and benefits in the treatment of hyperlipidemia presented in the same list [6], the majority, 70 patients, were treated with this medicine, while 4 patients used simvastatin for personal reasons. All patients included in this research had low-fat diet in addition to the statin treatment. Dosing of statins was conducted individually, depending on the presence of coronary artery disease. In patients with coronary disease treatment started with 20 mg of atorvastatin daily (same dose of simvastatin in 4 patients), in acute coronary syndrome 40 mg, a further dose adjustment was performed at intervals, not less than 4 weeks, up to a maximum dose of 80 mg [4, 5, 7]. In patients with hyperlipidemia, without coronary heart disease (15 patients) treatment started with 10 mg or even 5 mg daily (7 patients). Patients with diagnosed familial homozygous hypercholesterolemia (2 patients) were treated with 40 mg in the evening and then 80 mg daily (40 mg in the morning and at noon, and 40 mg in the evening).

We comply the CURVES and GRACE Study recommendations concerning the criteria for dose reduction or discontinuation of treatment (but not the study exclusion): ten-fold increase in phospho-creatine kinase, persistent threefold increase in serum transaminase levels (verified with 2 measurements within one week), decrease of total cholesterol levels below 3.6 mmol/l or LDL-cholesterol levels lower than 1.94 mmol/l, or with the adverse effects of these drugs [4, 11]. Reasons for patient withdrawal were: renal insufficiency, acute hepatitis, statin hypersensitivity, pregnancy and lactation, drug and alcohol abuse, myopathy or rhabdomyolysis. Statin adverse effects were not recorded and none of the patients had criteria for the withdrawn. Five patients stopped treatment voluntarily so they were excluded from the process of further investigation. So, out of the 74 patients included in the research, 69 patients have reached the end of the research and were treated for 2 years.

Following parameters of statin effects were investigated: Lipid profile components (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, atherogenic indices: LDL/HDL ratio and total cholesterol/HDL ratio); the rate of achieving desired values of individual lipoprotein profile components. Desirable values were determined according to the recommendations applied in clinical practice (total cholesterol < 5.2 mmol/l; LDL < 3.5 mmol/l; HDL > 1.3 mmol/l; triglycerides < 1.7 mmol/L; LDL/HDL < 2.5 and total cholesterol/HDL < 4.5) and

European Society for Atherosclerosis-EAS recommendations [3].

According to the pharmacodynamic and pharmacokinetic characteristics of the statins [4, 12], pharmacological effects were analyzed for the first time 2 weeks after the treatment initiation (which corresponds to the beginning of the treatment effect manifestations), then 6 weeks after the initiation (which corresponds to the time of achieving maximum therapeutic effect); after 3 months (which corresponds to the clinical benefits) and then in three-month periods (because drug effect remains constant over the entire therapy). In order to avoid the adverse effects of drugs, patients were controlled after 6 weeks, and then every three months during the first year of therapy, and in the same intervals after each dose increase; and then twice a year for all patients, except those who were treated with a dose of 80 mg, and those who had to undergo a three-month test during the entire treatment period [4, 11].

General patient characteristics, and the results obtained with tests that were performed, were described using the methods of descriptive statistics: absolute numbers and proportions, measures of central tendency (mean, median), measures of variability (standard deviation, minimum and maximum), confidence interval, and graphical and tabular presentation. Factor analysis of variance with repeated measures, Friedman's test and Cochran's Q test were used as the methods of inferential statistics. First method was used in investigating the impact of factors on the resulting feature during the period (several measurements), in case of numerical data with normal distribution. When the type of data different from the normal distribution was present, we used Friedman's test and Cochran's Q test in the case of features with a dichotomy result.

Results

HDL-cholesterol measured before the statin application and in observed intervals after the onset of drug use, showed a statistically significant difference. Two and six weeks after the treatment initiation, after 3 months, and then in equal, three-months intervals to the end of the second year of treatment, levels of this parameter significantly increased (ANOVA, p = 0.000).

Factors that caused the difference in HDL-cholesterol levels showed a statistically significant difference in the values of each patient as a result of the statin use, and different lengths of its application (Tests of within-subjects effects, p = 0.000), as well as the variability of values between respondents in all observed intervals (Tests of between-subjects effects, p = 0.000). Based on the factors that influence differences we can conclude that the dynamics of changes in this lipoprotein levels showed some variability between respondents. All patients had increase in HDL-cholesterol values with different levels of change over time.

Table 1: HDL-cholesterol levels measured in determined time intervals (before applied statin therapy, 2, 6 weeks after, than in 3 months intervals (3, 6, 9, 12, 15, 18, 21 and 24) after the applied therapy.

Observed parameters	Measurement time of applied therapy	Observed statistical parameters			
		(X ± SD)	95% CI	Min	Max
HDL	Before	0.94 ± 0.18	0.89-0.98	0.6	1.6
	2 weeks	0.98 ± 0.19	0.93-1.02	0.6	1.6
	6 weeks	1.07 ± 0.21	1.02-1.12	0.6	1.7
	3 months	1.156 ± 0.2	1.11-1.2	0.7	1.7
	6 months	1.159 ± 0.2	1.11-1.21	0.6	1.7
	9 months	1.156 ± 0.2	1.11-1.2	0.6	1.7
	12 months	1.15 ± 0.21	1.1-1.2	0.6	1.6
	15 months	1.16 ± 0.21	1.11-1.21	0.6	1.7
	18 months	1.165 ± 0.21	1.12-1.21	0.7	1.7
	21 months	1.17 ± 0.21	1.12-1.22	0.6	1.8
	24 months	1.18 ± 0.21	1.13-1.23	0.6	1.7

A significant increase of HDL-cholesterol levels was recorded during the first four measurements, or up to 3 months of treatment. There was a constant, statistically significant increase in the value in every measurement conducted from the second week until the third month of treatment. From 3rd month to the end of 21st month of statin use, there was a constant, but not statistically significant, increase in value. A significant increase was recorded again between the 21st month and second year of treatment.

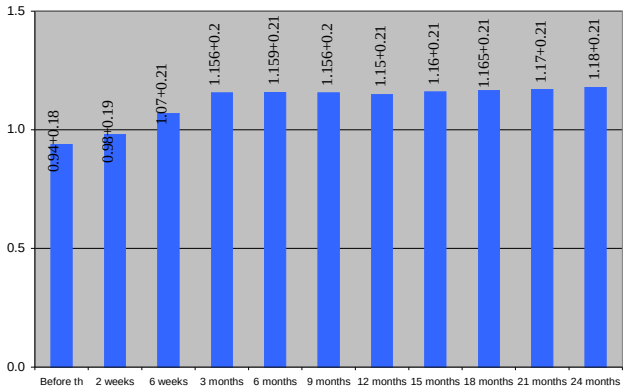

Figure 1: Mean HDL-cholesterol levels measured in determined time intervals during the two-years follow-up.

Number of patients with normal or low HDL-cholesterol significantly changed in the observed intervals over a two-year treatment period (Cochran's Q test, p = 0.000). With longer use of statins there was a significant increase in the number of patients with normal values, but even so, after two years of taking the statins, more than half of the subjects still had lower values. The most pronounced changes in the number of patients occurred during the first 3 months of statin use. After 2 and 6 weeks, there was less than 5% increase in the number of subjects with normal values. A significant increase in the number of patients with normal values was at the end of 3rd month of statins use, when the normal level of HDL-cholesterol was found in 44.6% of patients. The number of patients with normal values did not change

significantly until the 21st month after treatment initiation, when we found an increase on 47.3% and 48.6% with HDL-cholesterol > 1.3 mmol/L, after two years of statin use.

Table 2: Number of subjects with normal or low HDL-cholesterol levels measured in determined time intervals during the two-years follow-up period.

Observed parameter	Measurement time	Number of subjects N (%)	
		Normal values	Low values
HDL	Before th	4 (5.4%)	70 (94.6%)
	2 weeks of applied th	6 (8.1%)	68 (91.9%)
	6 weeks of applied th	7 (9.5%)	67 (90.5%)
	3 months of applied th	33 (44.6%)	41 (55.4%)
	6 months of applied th	34 (45.9%)	40 (54.1%)
	9 months of applied th	32 (43.2%)	42 (56.8%)
	12 months of applied th	31 (41.9%)	43 (58.1%)
	15 months of applied th	34 (45.9%)	40 (54.1%)
	18 months of applied th	34 (45.9%)	40 (54.1%)
	21 months of applied th	35 (47.3%)	39 (52.7%)
	24 months of applied th	36 (48.6%)	38 (51.4%)

The highest average change in HDL-cholesterol was 27.5% and it was observed at the end of follow-up, or 2 years after the use of statins. The minimal individual change was 9.09%, observed after 2 weeks of therapy. Six weeks after treatment initiation with these medications, minimal change was 0%, which means that the parameter values in some subjects were the same as before taking the drug, without any change. The maximum increase was found after 21 months, and after 2 years of treatment, increase was 100%. In those intervals, some subjects had HDL-cholesterol two times higher than the initial values.

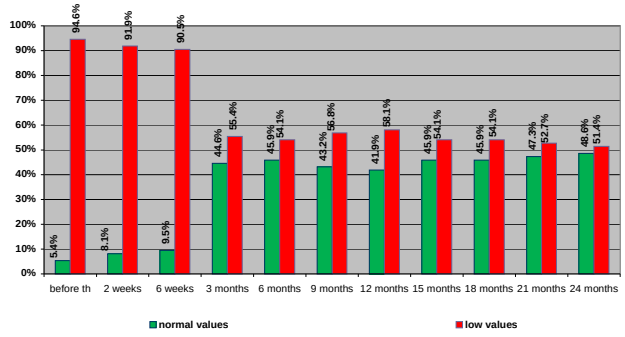

Figure 2: Number of subjects with normal or low HDL-cholesterol levels during the two-years follow-up period.

Desirable levels of HDL-cholesterol, with statin use, have been achieved in half of the patients, with 5.3% of respondents having the desirable levels even before taking the therapy. Two weeks after treatment with these medications started, and in period from 2 to 6 weeks of taking the drug, 1.4% of subjects achieved the desirable levels, thereby, after a month and a half of therapy use, 8.1% of respondents had the desirable level of HDL-cholesterol.

Table 3: Percentage of change of HDL-cholesterol levels in determined time intervals during the two-years follow-up period.

Observed parameter	Measurement time	Observed statistical parameters			
		X	SD	Min	Max
% of HDL level change	2 weeks of applied th	4.59%	7.42%	9.09%	28.57%
	6 weeks of applied th	14.96%	11.17%	0%	42.86%
	3 months of applied th	24.78%	15.36%	18.75%	62.5%
	6 months of applied th	24.98%	16.18%	18.75%	62.5%
	9 months of applied th	24.86%	16.25%	18.75%	71.43%
	12 months of applied th	24.54%	19.45%	18.75%	85.71%
	15 months of applied th	25.18%	18.61%	18.75%	85.71%
	18 months of applied th	25.95%	18.57%	18.75%	85.71%
	21 months of applied th	26.37%	19.35%	18.75%	100%
	24 months of applied th	27.5%	19.34%	18.75%	100%

Majority of the respondents (36.3%) achieved desirable value by the end of 3rd month of using the drug, making 44.4% of respondents. The remaining 5.6% of the respondents achieved the desirable HDL-cholesterol levels by the end of 2-year follow-up, by 1.4% on each following control visit (after 6, 9, 12 and 24 months of therapy).

The most important average value of the reduced total with the use of statins was registered after 18 months of treatment and it was 38.1%. The highest average change in LDL-cholesterol, compared to the values before the treatment, was recorded after 18 months of therapy (48.07%), and the highest change of triglyceride levels was recorded two years after treatment started (38.35%).

Disscusion

Modern cardiology studies in the U.S are comparing morbidity and mortality before and after the so-called “statins era”, and the “implementing healthy lifestyle era” that involves a smoking cessation, daily physical activity and the use of adequate diets. Considering the fact that type IIb hyperlipidemia is the most common of all hereditary diseases [3], logical step in the prevention and treatment of coronary artery disease, is diagnosis and appropriate treatment of lipid metabolism disorders. Importance of early detection of potentially modifiable risk factors for coronary heart disease, especially primary hypercholesterolemia, is explained with the fact that the National Cholesterol Education Program (NCEP) recommends lipid screening every 5 years for all persons older than 20 years [13, 14].

The importance of the application of lipid-lowering agents in modern cardiology is discussed in many new, clinical studies that recommend the use of these drugs in patients with coronary artery disease, even when they are normolipidemic [15]. Many other studies put these drugs in a central place in the primary prevention of coronary heart disease. The

significance of these drugs use in coronary artery disease is showed with the fact that many studies are investigating their effects when the lipid status of the patient is not an indication for their use [15].

Pasternak and associates gave the primacy of statin treatment in normolipidemic patients with coronary artery disease comparing to other lipid-lowering agents [15]. The results of their, and few other studies showed that statins are lowering total cholesterol for 22% in normolipidemic patients, and in hyperlipidemic for 35%, LDL-cholesterol for 32% and a maximum of 61%, triglycerides for 15% and 19-37%, and they increase HDL -cholesterol for 8% and 12% [15-17]. Comparing our results with these studies that investigate the use of statins in normolipidemic patients with established coronary heart disease, we can conclude that the effect of these drugs on the change of certain lipoprotein fractions is far more pronounced in hypercholesterolemia [18], than in normolipidemia [6, 15, 19, 20]. This research demonstrated a significant effect of statins on the decrease of total cholesterol levels by an average of 38.1%, decrease in LDL-cholesterol up to 48.07%, an increase in HDL-cholesterol levels for 12.5-27.5%, and decrease in triglycerides levels for 34.7%.

This phenomenon cannot be explained by the simple fact that the lipid-lowering medicaments effect of changing lipoprotein fractions in hypercholesterolemia is far more pronounced than in normolipidemia. The effect depends also on the initial values of individual lipoprotein parameters, normal or disordered lipid metabolism, but it can be assumed that the applied dose was adequate to specified values, and the hypocholesterolemic effect was at least partly dose dependent.

Framingham study suggests that an increase in HDL-cholesterol for 0.026 mmol/l reduces the risk of coronary events by 2% in men and up to 3% in women. In addition, the Helsinki study suggests that increase in HDL-cholesterol levels by only 1% reduces the incidence of myocardial infarction by 3%, while lowering levels of LDL-cholesterol by only 1% reduces the incidence of myocardial infarction in 2% [2, 3]. According to the results of this study 2/3 of patients who recovered from myocardial infarction have HDL-cholesterol lower than borderline-normal range, which highlights the importance of analysis and normalization of this lipoprotein fraction.

Observing the changes in HDL-cholesterol levels influenced by statins use, we found a statistically significant difference, which was time dependent. The trend of maintaining the values achieved after three months of statin use lasted until the 21st month of treatment, when we registered a gradual, constant increase of HDL-cholesterol with no statistical significance. The increase in value is recorded again in the period between the 21st month and the second year of treatment. According to the results of our study, HDL-cholesterol improved with the statins for 12.5% average which is consistent with the previous results [16].

Number of patients with normal or low HDL-cholesterol changed significantly during the treatment with statins over a two-year period. With longer use of statins there was a significant increase in the number of patients with normal values, but even so, after two years of taking the statins, more than half of the subjects still had lower values. The most pronounced changes in the number of patients occurred during the first 3 months of statin use. The above mentioned results are consistent with the results of other clinical studies that investigate the effect of statins on some lipoprotein fractions, especially with the results of Rote list. Similar results are obtained from other studies [19-23].

The results of comparative clinical studies investigating the intensity of the pharmacological effects of various drugs from a group of statins, and the other groups of lipid-lowering agents, are indicating that atorvastatin has the strongest effect on LDL-cholesterol decrease, while increase in HDL-cholesterol levels is higher with simvastatin use [24, 25] and niacin, which increases the value of this parameter for 75% [22]. Gemfibrozil causes a much more significant decrease in triglyceride levels, but its effect on LDL-cholesterol has no clinical importance, which favours the use of statins considering the extreme atherogenity of LDL-cholesterol. Fibrates have more favorable effect on HDL-cholesterol increase comparing to statins [4, 11, 25], but that is their only advantage over these drugs, when it comes to the treatment of hypercholesterolemia.

Ballanthyne points out that the most favorable effects on the increase in HDL-cholesterol between statins have atorvastatin and simvastatin [24, 25], with priority given to simvastatin (desirable levels of HDL-cholesterol achieved in 53% of patients) compared to atorvastatin (desirable levels of HDL-cholesterol achieved in 45%). The use of this drug increased transaminase to a level that requires a brief interruption in application only in 0.4% cases; compared to simvastatin, which increased them in 2.8% cases. Since we used atorvastatin in majority of our patients we can't confirm or deny the better effect of this drug in increasing HDL-cholesterol levels compared to simvastatin. However, our results, showing that more than 45% of patients achieved desirable levels of HDL-cholesterol during the treatment, are consistent with the results of the previous study.

In order to achieve desirable level of HDL-cholesterol with statins, some authors suggest the use of combination of these drugs with other lipid-lowering agents, primarily ion exchange agents and niacin [4, 11, 15, 22, 26] or even fibrates [26], which have the most intense effect on this lipoprotein fraction. However, the same authors suggest the possibility of reducing the safety of therapy, because the combination of statin and niacin increases possibility of developing myopathy, as side effect by 25% [4].

When we compare results of our research with other studies, especially comparing the effects of statins on some lipoprotein fractions and their level changes, we must be careful in a certain way, because other studies showed results obtained by highly aggressive therapy [28-31]. Our study was based primarily on individualization and dosing the statins dependent on coronary heart disease risk, as well as on the registered values of lipoprotein profile components [3, 4, 7].

Our study was, according to the treatment method, strictly individualized dosing, and the NCEP criteria [13, 32] to achieve the target value, based on principles used in GREACE study (The Greek Atorvastatin and Coronary heart disease Evaluation Study) from 2002 [7], so our result can be compared to the results of this study. GREACE study was not using the aggressive lipid-lowering therapy, with high doses of medications for all patients. As in our study, their research was based according to the criteria of NCEP [13, 32] and on pharmacological principles of treatment, started with a diet, then with 10 mg of atorvastatin, which was doubled in strictly determined intervals up to maximal of 80 mg, if the desired results were not achieved in previous intervals [3, 4, 7].

In five patients who have stopped treatment voluntarily, because of which they were excluded from the process of further investigation, total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol levels returned to the level before treatment in a very short period. Return to the baseline values was registered after 3 months when patients voluntarily made the control of lipoprotein status, but we can assume that the period was significantly shorter, and almost all changes occured in the interval of 1.5-2 months after the cessation of drug use.

These results represent the opposite view to the earlier findings that patients should be treated with statins until the significant changes in the values of lipoprotein fractions are registered, which is followed with the rest interval of 1-2 months without drug application, and then the treatment is implemented again in cycles [5]. This form of treatment had intervals without lipid-lowering medications, which were called “empty intervals” or “windows” [5] and the aim was to reduce the side effects of these drugs, but the results of our study showed that this attitude should be abandoned. This is especially true for the treatment of patients with primary hyperlipidemia. In the “empty intervals” or “windows” lipoprotein fractions were returned to baseline, after reaching the desirable, target values, thereby, applying the new therapy leads to discontinuation, and the maximum effect, and thus the goal of treatment, could not be reached.

Time to achieve the desirable or target value of these lipoprotein fractions, according to the results of our study, was significantly longer than the time of first manifestation of the pharmacological effects of statins, and in our study it was 3 to 6 months. Nearly half of all patients achieved the desirable values of all lipoprotein profile components after three months of therapy, and 90% after six months of statin therapy, except for the desirable level of HDL-cholesterol, that was achieved by 50% of patients during the research.

The criteria used in this study were based on the European Society for Atherosclerosis-EAS recommendations [3, 33, 34] and the National Cholesterol Educational Program-NCEP [3, 13, 32], which are somewhat the “guidelines” in the treatment of hyperlipidaemia, and coronary artery disease [13, 17, 32-34]. During the research, we came across more stringent criteria based on the initial values of total cholesterol, LDL-cholesterol and HDL-cholesterol, and to studies that used strictly individual approach to each case in determining the desirable values [16, 17, 35].

It was experimentally demonstrated for hyperlipoapoproteinaemia E7 the corresponding phenotype, with clinical expression of hyperlipidemia in 50% of patients, with dramatically successful results of the treatment using only antiatherosclerotic diets. Using of diets in the treatment of hyperlipoproteinemia has undivided opinions [36], but there are some disagreements in terms of prescribing medicines or food rich in omega-3-fatty acids [3, 37]. All patients included in our study had mandatory antiatherosclerotic diet. According to the results of studies that were available to us, use of restrictive diets and foods rich in omega-3-fatty acids found in fish oil, combined with the use of statins, not only is the necessary form of treatment for all patients with hyperlipoproteinemia [27, 36, 37], but according to the results of modern clinical studies, this combination prolongs life in patients after myocardial infarction and reduce mortality from coronary heart disease [38].

In our study there were no cases of sudden cardiac death or fatal myocardial infarction, for the entire period of research, so that the mortality rate cannot be compared with the results of other studies, though, the fact underreport fatal myocardial infarction, speaks for itself. Based on these results, it can be concluded that statins may have a beneficial effect on reducing the number of fatal myocardial infarction.

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