Original Article

Comparative Benefits of Statins in Coronary Heart Disease

Viktoriya Ermakova[1]*, Hizir Bataev[2], Natalya Semenenko[1]

[1]I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation, [2]Federal State Budgetary Institution of Higher Education Chechen State University, Grozny, Russian Federation

Abstract

Hyperlipidemia is one of the main risk factors for coronary heart disease (CHD), thus the treatment of the lipid metabolism disorders is the main measure to prevent the development and progression of this disease. The purpose of the research is a comparative study of atorvastatin, rosuvastatin, and simvastatin's hypolipidemic effect by determining the content of a lipoprotein fraction in the dynamics of statin therapy, as well as to study their negative effect on glucose metabolism. For the study, 150 people aged (57.86±4.59) years were examined for CHD (stable angina pectoris II functional class). All patients received basic CHD therapy: one 5-mg tablet of bisoprolol a day, one 75-mg tablet of aspirin a day, and short-acting nitrates for angina attacks. The patients had also been receiving statin therapy, depending on which the patients were divided into three groups (in each of 50 people): group 1 - one 20-mg tablet of simvastatin a day; group 2 - one 20-mg tablet of atorvastatin a day; group 3 - one 10-mg tablet of rosuvastatin a day. The patients taking simvastatin were observed with a significant decrease of cholesterol at the end of the 12-week treatment, by 24.7% ($p<0.05$) compering to the atorvastatin group by 34.75% ($p<0.05$) and rosuvastatin – by 36.96% ($p<0.05$); triglycerides – by 16.2% ($p<0.05$), 20.1% ($p<0.05$), and 22.7% ($p<0.05$), respectively; low density lipoproteins – by 24.5% ($p<0.05$), 35% ($p<0.05$), and 38.7% ($p<0.05$) while the increase of high density lipoproteins was noted – by 20.4% ($p<0.05$), 28.2% ($p<0.05$), and 39.5% ($p<0.05$), respectively, and AIP significantly decreased by 34% ($p<0.05$), 41.8% ($p<0.05$), and 64.1% ($p<0.05$). Statin therapy with atorvastatin and rosuvastatin is more effective compared with simvastatin according to lipid profile, and rosuvastatin is more effective than atorvastatin based on the increase of high-density lipoproteins.

Keywords: blood lipid spectrum correction, comparative characteristics of statins, side effects of statins, statin therapy in coronary heart diseases

Introduction

Diseases of the cardiovascular system are a leading cause of death among non-communicable diseases globally, except for the African continent (Peters *et al.*, 2016). Although mortality from cardiovascular diseases has declined in recent years, they still make up one-third of all deaths among people over 35 years of age (Sanchis-Gomar *et al.* 2016). Thus, according to the WHO, 17.5 million people died from cardiovascular pathology and its complications in 2012, which is about 31% of all deaths, 7.4 million of them from chronic coronary heart disease (CHD), and 6.7 million - from myocardial infarction (MI) (World Health Organization, 2017). According to the American Heart Association in the United States, more than 15.5 million people over 20 have CHD, and every 42 seconds one American suffers myocardial infarction (Sanchis-Gomar *et al.*, 2016; World Health Organization, 2017).

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CHD is a myocardial pathology due to circulatory disorders in the coronary arteries (Chen & Levy, 2016; Abbasi *et al.*, 2018). The cause of CHD in 95% of cases is the atherosclerotic lesion of the coronary arteries (Morbach *et al.*, 2017; Humphries *et al.*, 2018; Batty *et al.*, 2019; Safonov, 2020). It is known that the main factors for the development and progression of CHD are atherogenic dyslipidemia, high systolic blood pressure, obesity, diabetes, smoking, a sedentary lifestyle as well as male gender, and heredity (Khukhlina *et al.*, 2010; Jousilahti *et al.*, 2016; Menotti *et al.*, 2019). Moreover,

***Address for correspondence:** Viktoriya Ermakova. I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation. Email: ermakova.viktoriya.yurievna@mail.ru

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the prevalence is associated with socio-economic status (Bajekal *et al.*, 2012; Zhu *et al.*, 2016). According to studies from the US, the prevalence of CHD among people with a low socioeconomic status in the United States was twice as high, and mortality was respectively higher than the other sector of people (Zhu *et al.*, 2016; World Health Organization, 2017; Menotti *et al.*, 2019).

The main metabolic abnormalities associated with the development of CHD is atherogenic dyslipidemia – a persistent increase of cholesterol, low density lipoproteins (LDL), triglycerides (TG) (Kirichuk & Tsymbal, 2011; Koopman *et al.*, 2016; Menotti *et al.*, 2020), as well as a decrease in high density lipoproteins (HDL) (Reiner *et al.*, 2016; Saito *et al.*, 2017). A high lipid level is associated with an increased risk of development of myocardial infarction (about 50%) (Wadhera *et al.*, 2016). The decisive effect of dyslipidemia on the course of CHD was proved by a study on the correlation of serum cholesterol and mortality from CHD over 50 years in ten study cohorts of seven countries. The study included 9063 men aged 40–59 years who were diagnosed with CHD. The relationship between the cholesterol level and mortality was proved, and it was observed at the individual level (Menotti *et al.*, 2020).

The fact remains that the basis for preventing CHD and its complications should be measures normalizing the blood lipid spectrum (Koopman *et al.*, 2016; Saito *et al.*, 2017; Menotti *et al.*, 2020). The drugs that are effective in eliminating atherogenic dyslipidemia include statins. Studies have shown that changes in lifestyle and the systematic use of lipid-lowering drugs have contributed to a decrease in the occurrence of cardiovascular pathology (Trialists, 2010; Chowdhury *et al.*, 2013). The use of lipid-lowering drugs for primary prevention in people at low risk of cardiovascular diseases is less appropriate from an economic point of view. However, they should undoubtedly be used for secondary prevention in patients with CHD (Koopman *et al.*, 2016). Large-scale studies have found that changes in drug therapy reduce mortality from CHD by 25–50% (Bajekal *et al.*, 2012). The randomized controlled trials have proved that lowering of LDL with statins reduces the risk of cardiovascular diseases reoccurring in patients with CHD, and normalization of this fraction of lipoproteins can be achieved with a lower dose of statins or a less powerful statin, thus provides effective prevention of CHD (Trialists, 2010; Reiner *et al.*, 2016). That is why the American recommendations for the CHD treatment emphasize the need to lower LDL by at least 50%, which can be achieved by statin therapy of high-intensity (Stone *et al.*, 2013), and the target level of LDL should be less than 1.8 mmol/L according to the recommendations of the European Society of Cardiology (Knuuti *et al.*, 2019; Mach *et al.*, 2019).

Statins are among the best-selling drugs in the world (Cohen *et al.*, 2012; Oldridge & Taylor, 2019). Beside the lipid-lowering, statins slow antihypertensive, anti-inflammatory, and antioxidant effects, and can also reduce thromboxane-dependent platelet activation. There is the possibility of using statins in the field of immunology, transplantology, nephrology (Bedi *et al.*, 2016).

Statins are not class effect drugs, since their chemical structure, the severity of lipid-corrective effects, pharmacokinetics properties are different, and therefore they have a different safety profile and their own spectrum of side effects. Typically, statin tolerance is quite good, but they have a number of side effects associated with glucose metabolism, the nervous system (Preiss, 2011; Thongtang *et al.*, 2011), and skeletal muscle (Ganga *et al.*, 2014; Taylor & Thompson, 2015; Du Souich *et al.*, 2017). The most common side effect is a statin-associated muscle syndrome, manifested by myalgia, muscle twitching and muscle weakness, and, according to research results, it occurred in 10–25% of people who regularly received statins for a long time (Ganga *et al.*, 2014; Taylor & Thompson, 2015). The immune-mediated necrotizing myopathy and rhabdomyolysis are severe statin-associated muscle syndromes (Cziraky *et al.*, 2013; Thompson *et al.*, 2016). The rhabdomyolysis is extremely rare, thus, in a study of medical insurance data of 473,343 people receiving statin therapy, only 144 cases of rhabdomyolysis were recorded, of which 44 were confirmed by a doctor's examination (Cziraky *et al.*, 2013). According to a systematic analysis of 1012 works studying the effects of statins, the rhabdomyolysis occurred in 0.10% of people who received statins, and 0.04% from the placebo group (Ganga *et al.*, 2014). The studies have proved that statin therapy is a risk factor for diabetes, since it influences on insulin levels and insulin resistance (Preiss, 2011; Thongtang *et al.*, 2011; Thompson *et al.*, 2016). Other possible side effects of prolonged statin therapy include impaired kidney and liver function (Bangalore *et al.*, 2014; Thompson *et al.*, 2016). The data on impaired liver function due to the use of statins are contradictory. Moreover, there is evidence of a positive effect of statins on the course of chronic liver diseases – a decrease in portal pressure, inhibition of fibrogenesis, elimination of endothelial dysfunction, and a decrease in sensitivity to endotoxin-mediated liver damage (Bosch *et al.*, 2020). The survey of 10,138 people taking statins showed that 60% respondents had statin-induced myalgia, and 62% stopped taking statins because of side effects (Cohen *et al.*, 2012). Stopping statins is associated with worsening of cardiovascular events. Particularly, a recent meta-analysis of 15 studies on statins showed a 45% increase in all-cause mortality and a 15% increase in adverse cardiovascular events in patients taking less than 80% of prescribed statin therapy compared with those who received it fully (Chowdhury et al., 2013).

Despite the fact that statins are the main drugs in the treatment and the prevention of cardiovascular pathology, they remain the subject of a large number of studies that allow obtaining more accurate data on their therapeutic properties, studying in detail the possible side effects for more effective use with minimal harm to patients.

The purpose of the research is a comparative study of atorvastatin, rosuvastatin, and simvastatin's hypolipidemic effect by determining the content of a lipoprotein fraction in the dynamics of statin therapy, as well as to study their negative effect on glucose metabolism.

Material and research methods

The study included 150 people (82 [54.7%] men and 68 [45.3%] women) diagnosed with CHD (stable angina pectoris II functional class [FC]) and 30 healthy individuals. The average age of the studied patients was (57.86±4.59) years. All patients received basic CHD therapy: one 5-mg tablet of bisoprolol a day, one 75-mg tablet of aspirin a day, short-acting nitrates for angina attacks. The patients had been also receiving statin therapy, depending on which the patients were divided into three groups (in each of 50 people): group 1 - one 20-mg tablet of simvastatin a day; group 2 - one 20-mg tablet of atorvastatin a day; group 3 - one 10-mg tablet of rosuvastatin a day. The patient groups were randomized by age, gender, and disease duration. The duration of monitoring was 12 weeks. Each patient signed an informed consent to participate in the study.

The inclusion criteria are the age of 45–70 years old, a diagnosis of CHD (stable angina pectoris II FC), and an agreement of the patient to participate in the study.

The exclusion criteria are heart failure, acute myocardial infarction, unstable angina pectoris, cardiomyopathy, a chronic disease in the acute stage or a chronic disease in the substage/decompensation stage, drug polyallergy, a history of statin intolerance, hepatocellular dysfunction, renal failure, mental illness, cancer, pregnancy, lactation, and poor adherence to treatment.

The diagnosis of CHD (stable angina pectoris II FC) was verified in accordance with the recommendations of the European Society of Cardiology from 2019 (Knuuti *et al.*, 2019), based on complaints from patients, medical history, and physical examination, results of an electrocardiogram (ECG), echocardiography (Echo), and bicycle ergometry testing, Holter monitor ECG test.

The study of the blood lipid spectrum was carried out by determining the content of C, LDL, TG, HDL in the blood and calculating the atherogenic index (IA), using the formula: IA=(C-HDL)/HDL. The carbohydrate metabolism parameters were determined by fasting plasma glucose (2 h after eating) and insulin, glycated hemoglobin (HbA1c), and the IR index (HOMA2IR), using the HOMA Calculator Version 2.2 Diabetes Trials Unit University of Oxford (UK). The lipid spectrum and carbohydrate metabolism examinations were carried out in dynamics: before treatment, after 4 and 12 weeks of treatment.

ECG was recorded with SE-601 (Edan, China), daily ECG monitoring was performed with Card (X) Plore (Meditech, Hungary) under normal patient physical activity, a bicycle ergometry testing was performed with Corival cpet (Holland), and echocardiography with Siemens Acuson X150 (Germany).

Statistical data processing was carried out using Wilcoxon's T and U criteria using SPSS 13.0 software package and Microsoft Excel 2013 (Microsoft, USA). The differences were considered statistically significant at $p<0.05$. The Past3 program was used for comparing qualitative characteristics between groups.

The results of the study

The study revealed differences in the hypolipidemic effect of statins (Table 1). Particularly, at the end of the fourth week of treatment, the blood oxygen content significantly decreased by 8.6% ($p<0.05$) among patients receiving simvastatin, by 13.2% ($p<0.05$) among patients receiving atorvastatin, and by 13.6% ($p<0.05$) receiving rosuvastatin; thus, the differences between one and two ($p<0.05$), one and three ($p<0.05$) were statistically significant. More significant changes were in the decrease of cholesterol at the end of the 12th week of treatment: in the simvastatin group cholesterol decreased by 24.7% (1.33 times) ($p<0.05$), atorvastatin by 34.75% (1.53 times) ($p<0.05$), rosuvastatin by 35.96% (1.56 times) ($p<0.05$) with a statistically significant difference between one and two ($p<0.05$), one and three ($p<0.05$) groups. The level of cholesterol at the end of the 12th week of treatment in patients of the second group (atorvastatin group) and the third group (rosuvastatin group) did not statistically differ from the healthy individuals ($p>0.05$). A similar dynamic was observed in the decrease of TG and LDL. At the end of the fourth week of treatment in group 1, there was only a tendency ($p>0.05$) to decrease the content of TG in the blood; while in group 2, this indicator significantly decreased by 7.4% ($p<0.05$), in group 3 by 9.7% ($p<0.05$), and at the end of the 12th week of therapy, the content of TG in group 1 significantly decreased by 16.2% ($p<0.05$), group 2 by 20.1% ($p<0.05$), group 3 by 22.7% ($p<0.05$) with a statistically significant difference between groups 1 and 2 ($p<0.05$) as well as groups 1 and 3 ($p<0.05$). At the end of the fourth week of treatment, the LDL significantly decreased in patients of group 1 by 5.1% ($p<0.05$), group 2 by 11.8% ($p<0.05$), groups 3 by 14 3% ($p<0.05$), at the end of the 12th week of treatment, by 24.5% (1.3 times) ($p<0.05$), 35% (1.54 times) ($p<0.05$), and 38.7% (1.63 times) ($p<0.05$), respectively, with a statistically significant difference between groups 1 and 2 ($p<0.05$), as well as groups 1 and 3 ($p<0.05$).

The content of antiatherogenic HDL significantly increased in patients of all comparison groups ($p<0.05$); however, rosuvastatin turned out to be the most effective in this aspect. Thus, at the end of the fourth week of treatment, the content of HDL in the blood of patients of the first group increased by 10.2% ($p<0.05$), group 2 by 11.36% ($p<0.05$), group 3 by 14.68% ($p<0.05$), and at the end of the 12th week of treatment - by 20.37% (1.2 times) ($p<0.05$), by 28.1% (in 1, 28

Table 1: Dynamics of lipid metabolism in patients with stable CHD treated with statins, M ± m

Indicators	Healthy individuals	Group	Before treatment	At the end of the fourth week of treatment	At the end of the 12th week of treatment
C, mmol/L	4.20±0.14	1	6.97±0.13*	6.36±0.048*/**	5.24±0.57*/**
		2	7.06±0.11*	6.12±0.05*/**/***	4.55±0.10**/***
		3	6.99±0.10*	6.03±0.054*/**/***	4.46±0.05**/***
TG, mmol/L	1.27±0.034	1	3.15±0.04*	3.03±0.032*	2.64±0.016*/**
		2	3.13±0.06*	2.89±0.027*/**/***	2.46±0.02*/**/***
		3	3.12±0.05*	2.78±0.03*/**/***	2.38±0.02*/**/***
LDL, mmol/L	1.69±0.026	1	2.80±0.026*	2.64±0.02*/**	2.10±0.037*/**
		2	2.80±0.03*	2.46±0.018*/**/***	1.81±0.031**/***
		3	2.81±0.03*	2.37±0.04*/**/***	1.70±0.025**/***
HDL, mmol/L	1.85±0.04	1	1.09±0.01*	1.19±0.01*/**	1.30±0.018*/**
		2	1.10±0.02*	1.25±0.013*/**/***	1.41±0.01*/**/***
		3	1.09±0.01*	1.32±0.02*/**/***/#	1.52±0.01*/**/***/#
AIP	1.24±0.025	1	5.44±0.16	4.32±0.06*/**	3.02±0.05*/**
		2	5.41±0.09	3.90±0.08*/**/**	2.26±0.07*/**/***
		3	5.40±0.14	3.61±0.07*/**/**	194±0.04*/**/***/#

* - the difference is statistically significant compering to healthy individuals ($p<0.05$); ** - the difference is statistically significant with the indicator before treatment ($p<0.05$); *** - the difference is statistically significant compering to the indicator after treatment of group 1 ($p<0.05$); the difference is statistically significant compering to the indicator after treatment of group 2 ($p<0.05$); Group 1 (n=50) individuals who took simvastatin 20 mg/day; Group 2 (n=50) individuals who took atorvastatin 20 mg/day; Group 3 (n=50) individuals who took rosuvastatin 10 mg/day.

times) ($p<0.05$) and by 39.5% (1.4 times) ($p<0.05$), respectively. Therefore, at the end of the fourth week of therapy, there was a statistically significant difference in the content of HDL between groups 1 and 2 ($p<0.05$), 1 and 3 ($p<0.05$), as well as 2 and 3 ($p<0.05$). With the increase of HDL due to statin therapy, the patients with CHD were noted with significant decrease of AIP: at the end of the fourth week of statin therapy in group 1 by 20.59% (1.26 times) ($p<0.05$), group 2 by 27.9% (1.4 times) ($p<0.05$), group 3 by 33.1% (1.5 times) ($p<0.05$), at the end of the 12th weeks of treatment by 34.5% (1.7 times) ($p<0.05$), 41.8% (2.4 times) ($p<0.05$), and 64.1% (2, 8 times) ($p<0.05$), respectively, with the presence of a statistically significant difference between groups 1 and 2 ($p<0.05$), 1 and 3 ($p<0.05$), as well as 2 and 3 ($p<0.05$).

Studying the effect of statin therapy on carbohydrate metabolism, it was found that at the end of the fourth week of treatment, there was only a tendency of increase in fasting plasma glucose, insulin levels, and the IR index (HOMA2IR) for all groups ($p>0.05$) (table 2). The negative effect of the studied drugs on glucose homeostasis was observed only at the end of the 12th week of statin treatment, while simvastatin proved to be the worst. Particularly, at the end of the 12th week of therapy, the level of fasting plasma glucose significantly increased by 29.3% ($p<0.05$) in patients of group 1 compering to that before treatment, in group 2 by 16.27% ($p<0.05$) while in patients of the group 3, there was only a tendency of increase in fasting plasma glucose ($p>0.05$). The statistically significant difference was between groups 1 and 2 ($p<0.05$), 1 and 3 ($p<0.05$). The similar changes were observed for level of postprandial glucose: in patients of group 3, at the end of treatment, there was only a tendency to increase ($p>0.05$), while in group 1 this indicator significantly increased by 18.06% ($p<0.05$), groups 2 by 14.1% ($p<0.05$) with statistically significant difference between groups 1 and 2 ($p<0.05$), 1 and 3 ($p<0.05$). The study of the insulin content showed an increase at the end of the 12th week of treatment only in group 1 by 20.9% ($p<0.05$), while in groups 2 and 3, only a tendency to increase by 12.07% ($p>0.05$) and 9.35% ($p>0.05$) with significant difference between groups 1 and 2 ($p<0.05$), groups 1 and 3 ($p<0.05$). The statistically significant increase in IR index (HOMA2IR) occurred at the end of treatment in all the studied groups: by 28.9% ($p<0.05$) in group 1, by 16.7% ($p<0.05$) in group 2, by 13.16% ($p<0.05$) in group 3 with statistically significant difference between groups 1 and 2 ($p<0.05$), 1 and 3 ($p<0.05$). There was a tendency of glycosylated hemoglobin increase in all comparison groups at the end of the 12th week of statin therapy, but without statistically significant differences ($p>0.05$).

Analyzing other side effects (except for a negative effect on glucose metabolism) that are possible with statin therapy, we rarely encountered statin-associated myalgia. Particularly, myalgia was observed in four (8%) people of the first group, in two (4%) of the second group, and in only one (2%) of the third group. There were no statistically significant intergroup differences in the case of myalgia ($p>0.05$): the odds ratio for groups 1 and 2 were OR=2.09, 95% CI [0.36–11.95]; OR=4.26, 95% CI [0.46–39.55] for groups 1 and 3; and OR=2.04, 95% CI [0.18–23.27] for groups 2 and 3. Among our patients, not a single case of rhabdomyolysis was detected. Moreover, none of the examined patients receiving statin therapy had an increased hepatic transaminases and/or nitrogen metabolism (urea, creatinine).

Table 2: The effect of statin therapy on carbohydrate homeostasis, M ± m

Indicators	Healthy individuals	Group	Before treatment	At the end of the fourth week of treatment	At the end of the 12th week of treatment
Fasting glucose mmol/L	4,08±0,13	1	4,19±0,18	4,60±0,12*	5,42±0,10*/**
		2	4,24±0,20	4,48±0,17	4,93±0,14*/**/***
		3	4,25±0,15	4,39±0,21	4,81±0,17*/***
Glucose 2 h after a meal, mmol/L	6,13±0,26	1	6,20±0,33	6,55±0,24	7,32±0,13*/**
		2	6,17±0,21	6,41±0,28	7,04±0,20*/**
		3	6,16±0,24	6,32±0,30	6,79±0,11*/***
Insulin, u/l	8,53±0,45	1	9,24±0,37	10,03±0,22	11,17±0,25*/**
		2	9,20±0,41	9,56±0,36	10,31±0,14*/***
		3	9,22±0,42	9,45±0,40	10,06±0,27*/***
HbA1c, %	5,25±0,20	1	5,36±0,17	5,48±0,18	5,83±0,11*
		2	5,31±0,21	5,41±0,26	5,72±0,16
		3	5,30±0,21	5,37±0,23	5,67±0,12
HOMA2-IR	1,05±0,04	1	1,14±0,04	1,27±0,019*	1,47±0,02*/**
		2	1,14±0,03	1,20±0,02*	1,33±0,023*/**/***
		3	1,14±0,03	1,18±0,026	1,29±0,03*/**/***

* - the difference is statistically significant compering to healthy individuals ($p<0.05$); ** - the difference is statistically significant with the indicator before treatment ($p<0.05$); *** - the difference is statistically significant compering to the indicator after treatment of group 1 ($p<0.05$); HbA1c - glycosylated hemoglobin; HOMA2-IR - HOMA insulin resistance index; Group 1 (n=50) - individuals who took simvastatin 20 mg/day; Group 2 (n=50) - individuals who took atorvastatin 20 mg/day; Group 3 (n=50) - individuals who took rosuvastatin 10 mg/day.

Discussion

The study results proved that all the drugs are effective in the blood lipid spectrum correlation in patients with CHD (stable angina pectoris II functional class) based on the statistically significant decrease ($p<0.05$) of cholesterol, TG, LDL, and AIP, as well as an increase of anti-atherogenic HDL at the end of treatment. Simvastatin turned out to be less effective compering to other statins, according to a statistically significant difference ($p<0.05$) associated with cholesterol, TG, LDL, HDL, as well as AIP levels between groups receiving simvastatin and atorvastatin ($p<0.05$), as well as rosuvastatin and simvastatin ($p<0.05$). The efficacy of atorvastatin and rosuvastatin is approximately the same, since there was no statistically significant difference ($p>0.05$) between the two groups regarding the main indicators of the blood lipid spectrum at the end of treatment, only anti-atherogenic HDL at the end of treatment was significantly higher in the rosuvastatin group ($p<0.05$), and AIP, respectively, lower ($p<0.05$). Such a lipid-lowering efficiency of statins is related to their mechanism of action, namely blocking the access of the natural substrate HMG-CoA to the catalytic site. Thus, there is an increase in the expression of LDL receptors on hepatocytes, which leads to an increase in cholesterol catabolism, contained in the LDL, and with a decrease of LDL and TG, the HDL content increases (Bedi *et al.*, 2016; Timoshin *et al.*, 2018; Knuuti *et al.*, 2019). Moreover, statins have a number of pleiotropic properties important for patients with CHD: stabilization of atherosclerotic plaques, elimination of endothelial dysfunction, anti-inflammatory, anticoagulant, and antioxidant effects, which ultimately leads to a significant reduction in adverse cardiovascular events (Bedi *et al.*, 2016; Arzukanyan *et al.*, 2020). Despite a similar mechanism of action, the differences in efficiency of the drugs studied are explained by chemical structure (simvastatin is an "older" semi-synthetic drug, atorvastatin, and rosuvastatin are synthetic statins of the third generation), as well as pharmacokinetic properties. Simvastatin is a lactone prodrug, subjected to hydrolysis with the formation of pharmacologically active hydroxy acids, which occur with the participation of non-specific carboxylases. Atorvastatin and rosuvastatin do not require endogenous activation, so their effect is faster and more effective. The rosuvastatin has the lowest lipophilicity, the highest selectivity for hepatocytes among the studied statins, it is the least metabolized and has the lowest risk of drug–drug interaction (Lee *et al.*, 2012). The study results are comparable with studies comparing the efficacy of the lipid-lowering effects of simvastatin, atorvastatin, and rosuvastatin (Nicholls *et al.*, 2010; Lee *et al.*, 2012; Karlson *et al.*, 2016). The recent meta-analysis on the VOYAGER database of 32,258 patients from 37 clinical trials, provided a comparative analysis of the lipid-lowering effects of simvastatin, atorvastatin, and rosuvastatin, depending on their dose. The significantly higher efficacy ($p<0.05$) of atorvastatin and rosuvastatin compared with simvastatin has been found, while rosuvastatin showed the highest lipid-lowering effect, and an increase in the dose of each drug contributed to a 4–7% increase in all major aspects of the atherogenic lipids. In addition, it was found that baseline lipid levels ($p<0.0001$) and increased statin doses ($p<0.0001$) were close to achieving treatment goals in patients at high risk for cardiovascular diseases (Karlson *et al.*, 2016; Utyuzh *et al.*, 2016).

The study of the negative effects of prolonged statin therapy on carbohydrate homeostasis showed that the use of simvastatin is the most unfavorable in this aspect. Consequently, at the end of treatment with simvastatin, there was a significant increase ($p<0.05$) in fasting plasma glucose and insulin, as

well as IR index (HOMA2IR), and the growth of these indicators was significantly higher compering to the groups receiving atorvastatin ($p<0.05$) and rosuvastatin ($p<0.05$), which indicates better safety profile of these drugs. No statistically significant differences ($p>0.05$) were found between the atorvastatin and rosuvastatin based on glucose metabolism parameters, that is probably associated with a rather short observation period (3 months) and requires more detailed study with longer statin therapy (more than 6 months). Generally, the results on the negative effects of statin therapy on carbohydrate metabolism are consonant with the research data known today (Preiss, 2011; Thongtang *et al.*, 2011; Thompson *et al.*, 2016). Therefore, simvastatin greatly ($p<0.05$) increases fasting plasma glucose and insulin comparing to atorvastatin ($p<0.05$) and rosuvastatin ($p<0.05$), while rosuvastatin is safer ($p<0.05$) compared with atorvastatin. The mechanisms of statins' negative effects on glucose metabolism are still unclear. It is known that they reduce the concentration of such metabolites as isoprenoids, farnesyl pyrophosphate, ubiquinone, formed during cholesterol biosynthesis, which may lead to a deterioration in the glycemic profile and a decrease in sensitivity to insulin. Isoprenoids activate glucose transporter 4, which leads to increased absorption of the latter. Depletion of ubiquinone leads to a delay in the synthesis of adenosine triphosphate, thus, the secretion of insulin by the cells is impaired. Lipophilic statins (simvastatin, atorvastatin) easily penetrate extra-hepatocytic cells, inhibiting the synthesis of isoprenoids (Thongtang *et al.*, 2011).

Conclusions

Thus, a 12-week therapy with statins contributed to the blood lipid spectrum correction in patients with CHD. Statin therapy with atorvastatin and rosuvastatin was significantly more effective compared with simvastatin: patients receiving simvastatin were observed with a significant decrease of cholesterol by 24.7% ($p<0.05$) compering to the atorvastatin group— by 34.75% ($p<0.05$) and rosuvastatin—by 36.96% ($p<0.05$); triglycerides - by 16.2% ($p<0.05$), 20.1% ($p<0.05$) and 22.7% ($p<0.05$), respectively; LDL by 24.5% ($p<0.05$), 35% ($p<0.05$), and 38.7% ($p<0.05$) while the increase of high density lipoproteins was noted by 20.4% ($p<0.05$), 28.2% ($p<0.05$) and 39.5% ($p<0.05$), respectively, and AIP significantly decreased by 34% ($p<0.05$), 41.8% ($p<0.05$), and 64.1% ($p<0.05$). When comparing rosuvastatin and atorvastatin, the rosuvastatin is proved to be significantly more effective by increasing HDL ($p<0.05$) and, accordingly, reducing AIP ($p<0.05$), and simvastatin significantly ($p<0.05$) inferior to rosuvastatin and atorvastatin in all aspects of lipid metabolism correction for patients with CHD. Atorvastatin and rosuvastatin had the largest safety profile for use with a relatively negative effect on glucose metabolism, while simvastatin ($p<0.05$) significantly increased fasting plasma glucose and insulin, and contributed to an increase in the primary insulin resistance index.

The prospect for further research is a comparative study of the safety profile of long-term statin therapy (more than 6 months) in patients suffering from CHD along with obesity.

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