ISSN 1607-419X
УДК 612.172.1:615.03

Rosuvastatin and ezetimibe in patients with ischemic heart disease after coronary artery bypass grafting

I. T. Abesadze, M. Z. Alugishvili, N. L. Lokchovinina, I. V. Titenkov, K. V. Korzhenevskaya, R. Y. Nilk, A. V. Panov

Federal Almazov Medical Research Centre, St Petersburg, Russia

Corresponding author:
Marianna Z. Alugishvili,
MD, PhD, Federal Almazov Medical Research Centre, scientific research department of coronary heart disease, 15 Parkhomenko street, St Petersburg, 194156 Russia.
E-mail: marianna-alugishvili@yandex.ru

Received 29 October 2014; accepted 20 November 2014.

Abstract

Objective. To evaluate the relationship between endothelial dysfunction, proinflammatory activity of leucocytes and pleiotropics effects of hypolipidemic therapy by rozuvastatin vs. simvastatin (as monotherapy and in combination with ezetimibe) in patients with coronary artery disease undergoing coronary artery bypass surgery (CABG). **Design and methods.** Altogether 92 patients with coronary artery disease (study group) and 22 healthy individuals (a control group) were enrolled. Vascular endothelial function was evaluated by brachial artery response assessment (endothelium-dependent vasodilatation test, the method by D. Celermajer and co-authors, Vingmed CPM 800). Proinflammatory activity of leucocytes was measured by chemiluminescent microscopy, and the severity of atherosclerotic coronary lesions was assessed by invasive coronary angiography. Endothelial function, leucocytes activity and lipid levels were determined before CABG and 12 months after revascularization. **Results.** Patients with coronary artery disease showed more complex disorders involving endothelial dysfunction and higher levels of leucocytes activity. The clinical effect of CABG (absence of angina pectoris and negative result of stress-echo test during 1-year of follow-up) was found in 80.6%. Combination lipid lowering therapy (simvastatin 20 mg and ezetimibe 10 mg) and monotherapy by rosuvastatin 10 mg compared to monotherapy by simvastatin 20 mg demonstrated higher efficiency regarding target lipid levels achievement and improvement of endothelial function and stimulated oxidant activity of leucocytes.

Key words: endothelial dysfunction, oxidant activity of leukocytes, coronary artery bypass surgery, rosuvastatin, ezetimibe

For citation: Abesadze IT, Alugishvili MZ, Lokhovinina NL et al. Rosuvastatin and ezetimibe in patients with ischemic heart disease after coronary artery bypass grafting. Arterial'naya Gipertenziya = Arterial Hypertension. 2014:20(6):591–599.

Розувастатин и эзетимиб у больных ишемической болезнью сердца после коронарного шунтирования

И. Т. Абесадзе, М. З. Алугишвили, Н. Л. Лоховинина, И. В. Титенков, К. В. Корженевская, Р. Я. Нильк, А. В. Панов

Федеральное государственное бюджетное учреждение «Федеральный медицинский исследовательский центр имени В. А. Алмазова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия

Контактная информация:
Алугишвили Марианна Захариевна, ФГБУ «Федеральный медицинский исследовательский центр имени В. А. Алмазова» Минздрава России, пр. Пархоменко, д. 15, Санкт-Петербург, Россия, 194156.
E-mail: marianna-alugishvili@yandex.ru

Статья поступила в редакцию 29.10.14 и принята к печати 20.11.14.

Резюме

Цель исследования — динамическая оценка функционального состояния эндотелия и оксидантной активности лейкоцитов после коронарного шунтирования с точки зрения гиполипидемического и возможного плейотропного эффектов розувастатина и эзетимиба. **Материалы и методы.** У 92 пациентов с ишемической болезнью сердца и выполненной операцией прямой реваскуляризации миокарда с помощью коронарного шунтирования определена динамика функционального состояния эндотелия и оксидантной активности лейкоцитов на фоне гиполипидемической терапии симвастатином и эзетимибом. Сосудодвигательную функцию эндотелия оценивали путем определения величины эндотелийзависимой вазодилатации (Vingmed CPM 800, линейный датчик 5,5–7,5 МГц) по методике D. Celermajer с соавторами. Оксидантную активность лейкоцитов изучали методом хемилюминесценции на хемилюминометре IKB 1251. Группу контроля составили практически здоровые мужчины — 22 человека (средний возраст 51,3 ± 1,6 года). **Результаты.** Исходно у обследованных пациентов с ишемической болезнью сердца выявлено увеличение стимулированной оксидантной активности лейкоцитов и нарушение эндотелийзависимой дилатации плечевой артерии. Установлено, что в комплексном лечении пациентов с ишемической болезнью сердца на протяжении первого года после хирургической реваскуляризации миокарда назначение в дополнение к симвастатину селективного блокатора всасывания холестерина эзетимиба 10 мг/сутки или его замена на розувастатин 10 мг/сутки сопровождается дополнительным снижением холестерина липопротеинов низкой плотности, показателей стимулированной оксидантной активности лейкоцитов и положительной динамикой величины эндотелийзависимой дилатации плечевой артерии.

Ключевые слова: дисфункция эндотелия, оксидантная активность лейкоцитов, коронарное шунтирование, розувастатин, эзетимиб

Для цитирования: Абесадзе И. Т., Алугишвили М. З., Лоховинина Н. Л. и др. Розувастатин и эзетимиб у больных ишемической болезнью сердца после коронарного шунтирования. Артериальная гипертензия. 2014;20(6):591–599.

Introduction

Coronary artery bypass grafting (CABG) is the main method of invasive treatment of coronary heart disease (CHD). Surgical revascularization leads to a great reduction or complete elimination of angina pectoris and increases the life expectancy of patients with severe multivessel coronary disease. Meanwhile, patients with CHD after CABG surgery are at risk of symptom recurrence due to progression of atherosclerotic lesions of non-graft coronary arteries and closure of the aorto-coronary and mammary-coronary anastomoses. The occlusion of venous aorto-coronary bypass grafts occurs approximately in 10 % patients 2 months after CABG, and in 10 % — within 1 year after surgery [1, 2]. In one prospective study of patients after CABG recurrent angina pectoris developed in 30 % patients during the first year, in 46 % — after 3 years, and in 50 % — 8 years after surgery. Thus, secondary prevention is of particular importance in these patients. Firstly, these patients having severe multivessel and/or stem coronary disease initially are at high risk of myocardial infarction (MI) and sudden death. Secondly, in case of symptom recurrence after surgical revascularization medical treatment is often ineffective, and the re-operation (re-CABG) is associated with high risk and considerable technical difficulties. Today, endovascular intervention on native coronary arteries and/or shunt are being actively developed as a treatment option in patients with recurrent symptomatic CHD after CABG. However, their immediate and long-term efficiency requires clarification. Thus, conventional prevention and control of risk factors are highly relevant in patients after CABG regarding progressing and severe atherosclerotic lesion and limitation for the followed invasive treatment.

For secondary prevention of CHD, by European Society of Cardiology (ESC), American College of Cardiology, and American Heart Association (ACC/AHA) recommend long-term use of aspirin after CABG, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), and in high-risk patients — beta blockers and angiotensin converting enzyme inhibitors [4, 5]. The recently published clinical studies forced to set stricter target level of low density lipoprotein cholesterol (LDL–C) in patients with CHD after CABG at ≤ 1.8 mmol/L, or at least its reduction of more than 50 % of the baseline that is included in the latest edition of EOC guidelines (2014). In clinical practice, the achievement of such low levels of LDL–C is possible with novel statins in high doses or with combination therapy.

Rozuvastatin is highly effective even at initial daily dose (10 mg/day), and its hypolipidemic activity increases with the dose increase up to a maximal one (40 mg/day). Clinical efficacy of rosuvastatin proved in a large program GALAXY, included 18 multicenter trials divided into three large categories: 1) studies of the effects of rosuvastatin on lipids and inflammatory markers: COMETS, DISCOVERY, ECLIPSE, EXPLORER, LUNAR, MERCURY I, MERCURY II, ORBITAL, POLARIS, PULSAR, STELLAR; 2) studies of the effects of rosuvastatin on coronary and carotid artery atherosclerosis: ASTEROID, METEOR, ORION, and 3) studies of the effect of rosuvastatin on cardiovascular risk, cardiovascular and total mortality: AURORA, CORONA, JUPITER [6]. These studies showed a positive effect of rosuvastatin on all stages of the atherosclerotic process. A major step towards dyslipidemia management and improving outcomes after surgical revascularization is the introduction of ezetimibe — a drug that inhibits cholesterol absorbtion from the intestines thus reducing its circulation levels and can potentially enhance the effects of statins. The clinical efficiency of lipid-lowering drugs also depends on their nonlipid, so-called pleiotropic effects.

In recent years, endothelial dysfunction of the vascular wall is believed to play a major role in the pathogenesis of atherosclerosis. Endothelium dilation of the brachial artery in reactive hyperemia test (EDVD) is considered an integral indicator of endothelial function [7]. White blood cells are the first to react to to the functional impairment of endotheliocytes [9, 10]. Active phagocytes possess the greatest ability to produce oxygen free radicals, oxidative stress, resulting in an excessive blood cell adhesion, migration and their accumulation in the subendothelial space. Endothelial-leukocyte interaction is the initial

stage of the inflammatory response, which plays an important role in the formation of atherosclerotic plaques, as well as in the damage of a stable atheroma with subsequent thrombotic occlusion and the development of acute coronary syndromes, including those occurring after CABG [11]. Given the important role of endothelial-leukocyte interaction in the mechanisms of CHD and progression a prospective assessment of endothelial function and oxidative activity of white blood cells after CABG appears to be relevant in terms of potential lipid-lowering and pleiotropic effects of rosuvastatin and ezetimibe and was the purpose of the present study.

Design and methods

The study included patients with stable angina pectoris II–IV functional class (FC), referred to the hospital for the surgical myocardial revascularization. Altogether 92 patients were enrolled. Na important inclusion criterion was the simvastatin intake at baseline in a dose of 20 mg/day. The average age of patients was 51.4 ± 7.9 years, altogether we included 80 (87%) men and 12 (13%) women. Mean duration of CHD (angina pectoris of different FC) before the enrollment in the study was 3.8 ± 3.4 years. Exertional angina FC II was diagnosed in 16 patients (17%), FC III — in 58 (63%), and 18 (20%) patients had angina pectoris FC IV, so on the average the severity of angina pectoris was 2.96 ± 0.2 FC. The exclusion criteria were: a history of Q-MI, stroke, significant hypertension, type 1 or 2 diabetes mellitus, systemic diseases, disorders of kidney or liver function, congestive heart failure and left ventricular dysfunction (ejection fraction < 40%).

Enrolled patients were divided into 3 groups. Forty patients were randomized into 2 groups: Group A included 20 patients who got the prescription for rosuvastatin 10 mg instead of simvastatin; Group B included 20 patients, who took 20 mg of ezetimibe and simvastatin at a daily dose of 10 mg. The remaining 52 patients of the comparison group continued taking simvastatin 20 mg/day. In addition, before CABG the patients received standard therapy including antiplatelet (canceled before CABG), beta-blockers and/or calcium channel blockers and if necessary, nitrates.

In all patients the following parameters were assessed: blood lipids, vascular endothelial function by brachial artery EDVD and oxidant activity of white blood cells. Vasomotor endothelial function was assessed by ultrasound scanner Vingmed CPM 800 5.5–7.5 MHz linear transducer according to the method described by Celermajer D. et al. [7] Normally, there is a more than 10% increase in the diameter of brachial artery. Oxidant activity of leukocytes was studied by chemiluminescence on chemiluminometer IKB 1251. A formyl peptide — formylmethionyl-leucine-phenylalanine — was used to determine the induced chemiluminescence. The results are presented in millivolts (B). As a control group 22 healthy men (mean age 51.3 ± 1.6 years) were examined (brachial artery EDVD and oxidative activity of leukocytes).

An active follow-up was 12 months. The following parameters were evaluated: clinical effect of surgery (elimination of angina pectoris, recurrent angina, acute coronary syndrome development), blood lipids, EDVD of the brachial artery and oxidant activity of white blood cells, liver enzymes and creatinphosphokinase.

The mathematical processing of the primary data was performed using the software Statistica ver. 6.0. Data are presented as arithmetic means and error of the mean (M ± m). The critical level of significance of the statistical null hypothesis (no difference) was set at 0.05. The differences were assessed by Student t-test for independent samples and paired measurements; relationship between the studied parameters was evaluated by Spearman and Pearson correlation analysis.

Results and discussion

The mean EDVD of the brachial artery in patients with CHD was lower than in healthy men (6.0 ± 1.2 vs. 12.1 ± 1.4, respectively, p = 0.04), which reflects the modern concept of the role of endothelial dysfunction in the development of CHD (Table 1).

Thus, 56 (61%) patients showed insufficient dilation of brachial artery at the reactive hyperemia test (less than 10%), 20 (22%) patients demonstrated a paradoxical vasoconstriction, while in 16 (17%) patients had normal values of the brachial artery EDVD.

Development of radial artery spasm during reactive hyperemia test is considered as a mani-

Table 1

ENDOTHELIUM-DEPENDENT DILATION OF THE BRACHIAL ARTERY AND OXIDATIVE ACTIVITY OF WHITE BLOOD CELLS IN PATIENTS WITH CORONARY HEART DISEASE

Parameter	Control group (n = 22)	CHD patients (n = 92)
EDVD, %	12.1 ± 1.4	6.0 ± 1.2*
SpChL, MB	2.1 ± 0.8	4.08 ± 0.95
StChL, mV	14.4 ± 2.9	17.6 ± 2.4*

Note: CHD — coronary heart disease; EDVD — endothelium-dependent vasodilation; SpChL — spontaneous chemiluminescence of white blood cells; StChL — stimulated chemiluminescence of white blood cells; * — $p < 0.05$ versus control.

festation of severe endothelial dysfunction. Vasospasm occurred more frequently in patients with CHD than in the control group (22 and 14%, respectively; $p = 0.002$). This may indicate a coexistent endothelial and autonomic dysfunction in patients with CHD.

There were no significant associations between EDVD and LDL cholesterol ($r = 0.114$, $p = 0.2$), EDVD and triglyceride levels ($r = –0.110$, $p = 0.3$), and EDVD and total cholesterol ($r = 0.051$, $p = 0.6$).

Indicators of spontaneous (SpChL) and stimulated (StChL) chemiluminescence of white blood cells, reflecting the generation of oxygen free radicals in patients with different course of CHD, are shown in Table 1.

In CHD patients, StChL indicators reflecting the oxidant activity of leukocytes were higher than reference values. SpChL indicator in CHD patients did not differ from reference values. There were no significant correlations between the StChL of white blood cells and serum lipids. There was a significant negative correlation between StChL of white blood cells and brachial artery EDVD in patients with CHD ($r = –0.3$, $p = 0.01$).

One month after CABG mean severity of angina pectoris corresponded to 0.2 ± 0.13 FC. At one-year follow-up there was no angina pectoris in 74 (80.4%) patients, while ischemic test was positive in 18 (19.6%) patients: 7 subjects demonstrated exertional angina pectoris FC I, 6 patients had II FC angina pectoris, and only 1 patients developed angina pectoris FC III. The mean severity of angina pectoris corresponded to 0.4 ± 0.07 FC. Reduction in angina pectoris was 86.5% one year after CABG.

Table 2

THE EFFECTS OF ROSUVASTATIN MONOTHERAPY AND A COMBINATION OF SIMVASTATIN AND EZETIMIBE ON LIPID METABOLISM IN PATIENTS AFTER CORONARY ARTERY BYPASS GRAFTING WHO PREVIOUSLY RECEIVED SIMVASTATIN 20 MG/DAY

Groups	Rosuvastatin 10 mg (n = 20)		Simvastatin 20 mg + 10 mg ezetimibe (n = 20)	
	Baseline	After 12 months	Baseline	After 12 months
ОХ, ммоль/л	5.5 ± 0.5	4.5 ± 0.4**	5.4 ± 0.6	4.8 ± 0.2**
ТГ, ммоль/л	1.6 ± 0.2	1.4 ± 0.1*	1.7 ± 0.4	1.5 ± 0.2
ХС ЛПВП, ммоль/л	1.2 ± 0.7	1.2 ± 0.5	1.2 ± 0.5	1.1 ± 0.9
ХС ЛПНП, ммоль/л	3.6 ± 0.4	2.7 ± 0.2**	3.7 ± 0.2	3.0 ± 0.2**

Note: TC — total cholesterol; TG — triglycerides; HDL — high density lipoprotein cholesterol; LDL — low-density lipoprotein cholesterol; * — $p < 0.05$; ** — $p < 0.001$.

Table 3

THE EFFECTS OF ROSUVASTATIN MONOTHERAPY AND COMBINATIONS WITH EZETIMIBE ON ENDOTHELIUM DILATION OF THE BRACHIAL ARTERY AND OXIDANT ACTIVITY OF WHITE BLOOD CELLS IN PATIENTS AFTER CORONARY BYPASS SURGERY WHO PREVIOUSLY RECEIVED SIMVASTATIN 20 MG/DAY

Groups	Rosuvastatin 10 mg (n = 20)		Simvastatin 20 mg + 10 mg ezetimibe (n = 20)	
	Baseline	After 12 months	Baseline	After 12 months
EDVD, %	6.0 ± 1.2	10.4 ± 1.6%*	5.72 ± 0.52	9.8 ± 1.5%*
SpChL, MB	4.05 ± 0.84	4.0 ± 0.90	4.05 ± 0.84	4.0 ± 0.90
StChL, mV	17.6 ± 2.4*	13.3 ± 2.2*	18.1 ± 3.6	15.2 ± 2.2*

Note: EDVD — endothelium-dependent vasodilation; SpChL — spontaneous chemiluminescence of white blood cells; StChL — stimulated chemiluminescence of white blood cells; * — $p < 0.05$ compared with the original data.

Twelve months of therapy with rosuvastatin led to an additional decrease in LDL cholesterol by 25% down to 2.5 mmol/L an lower in 10 patients (50%). In 4 patients (20%), treatment resulted in a decrease in LDL cholesterol below 1.8 mmol/l that is the target level according to the most recent international recommendations. All patients in this group completed the study, which indicates good tolerability.

In a selected group of 20 patients, twelve-month combination therapy with simvastatin (20 mg/day) and ezetimibe (10 mg/day) resulted in the decrease of LDL cholesterol below 2.5 mmol/L in 11 patients (55%); in 3 patients LDL cholesterol it decreased below 1.8 mmol/L. The total additional reduction in LDL cholesterol constituted 22%. In one patient, lipid-lowering therapy was canceled due to the significant increase in liver enzymes. Thus, replacement of simvastatin 20 mg/day by rosuvastatin 10 mg/day as well as additional therapy by ezetimibe resulted in a further reduction of LDL cholesterol by 20–25%.

The change in indicators of endothelial function and oxidative activity of leukocytes after lipid-lowering therapy are shown in Table 3.

Combination of simvastatin and ezetimib, like rosuvastatin, resulted in a significant improvement of endothelial function and reduction of stimulated oxidative activity of white blood cells in patients previously treated with simvastatin monotherapy. There was an increase in brachial artery EDVD index in both patients receiving combination of simvastatin and ezetimibe and in those receiving rosuvastatin. Furthermore, paradoxical vasoconstrictor response was no longer determined in these groups.

Analysis of the clinical effects of different modes of lipid-lowering therapy showed no significant differences in clinical outcomes for CABG at 12 months in all groups. This may be also due to the insufficient sample size and relatively short follow-up.

Thus, analysis of the literature data and the results of our study demonstrate new opportunities of novel lipid-lowering therapy in patients with CHD undegoing CABG. Current American clinical guidelines of ACC/AHA on lipid-lowering therapy (2013) consider patients after myocardial revascularization as high-risk group, requiring high-dose statin monotherapy, in addition to traditional atorvastatin 80 (40) mg/day and rosuvastatin 40 (20) mg/day [12]. Our data showed a significant effect of rosuvastatin even at initial dose of 10 mg/day on the endothelial function and oxidative activity of leukocytes that suggests its potential favourable effect on the long-term prognosis in post-CABG patients. A more active introduction of maximal tolerated dose statin treatment in high-risk patients is obviously required. It is important to note that

pharmacoeconomic aspects of rosuvastatin therapy were analyzed in 2004 [13]. In models based on the results of several trials — STELLAR, MERCURY I, HeFT — rosuvastatin 1 mg was shown to have higher clinical efficacy and to be an optimal drug therapy in light of cost effectiveness compared to other original statins. This trend was observed in all subgroups, but it was the most significant in patients at high risk.

From another point of view, according to the recent recommendations of ACC/AHA ezetimibe can be also used, for example, in those patients who do not tolerate statins or who do not achieve target levels of LDL–C with statin therapy (50%). The results of IMPROVE-IT trial, which involved 39 countries and included more than 18 000 patients with acute coronary syndrome < 10 days prior to randomization in stable condition, have been recently published [14]. Patients were randomized to receive either monotherapy by simvastatin 40 mg or combination of simvastatin 40 mg and ezetimibe 10 mg. The median follow-up was 7 years. Ezetimibe in combination with simvastatin 40 mg was associated with the 6.4% lower cardiovascular mortality, lower rate of myocardial infarction, unstable angina, re-hospitalization, stroke and coronary revascularization by 6.4% in comparison with those patients who received only simvastatin ($p = 0.016$). The number of patients needed to treat to prevent one of the mentioned events within 7 years was 50. This is the first study that showed clinical benefit of adding any other lipid-lowering drugs to statins. An interesting issue of the trial IMPROVE-IT is a major change in medical care over the years since its design was developed and the first patient was enrolled. This statement also applies to our study. Simvastatin, which is a moderately active statin, is prescribed considerably less frequently now than a few years ago. Moreover, it is not considered an optimal choice in patients at high risk. The trial IMPROVE-IT does not answer the question how ezetimibe added to atorvastatin and rosuvastatin would influence the therapy effectiveness, which is obviously a promising direction of future studies of lipid-lowering therapy. In any case, currently there is a need for more active use of high-dose lipid-lowering drugs in the maximal tolerable doses in high-risk patients, including patients after CABG.

Conclusions

High stimulated chemiluminescence of white blood cells, a smaller increase in brachial artery diameter during reactive hyperemia test and high frequency of vasoconstriction are more common in patients with CHD and multivessel involvement than patients with atherosclerotic lesions of only one coronary artery.

Additional administration of ezetimibe for 12 months after CABG enhances the lipid-lowering effect of simvastatin, reduces oxidant-stimulated activity of white blood cells and improves endothelial function.

Rosuvastatin even at initial daily dose of 10 mg/day leads to greater reduction in LDL cholesterol and improves endothelial dysfunction and oxidant activity of leukocytes in patients after CABG previously treated with simvastatin 20 mg/day.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The article is published with the support of the company AstraZeneca (UK).

References

1. ACC/AHA 2004 Guideline update for coronary artery bypass graft sur-gery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation. 2004;110(9):1168–1176.

2. Bourassa MG, Fisher LD, Campeau L, Gillespie MJ, McConney M, Lespérance J. Long-term fate of bypass grafts: the Coronary Artery Surgery Study (CASS) and Montreal Heart Institute experiences. Circulation. 1985;72 (Suppl V):71–78.

3. Frey RR, Bruschke AV, Vermeulen FE. Serial angiographic evaluation 1 year and 9 years after aorta-coronary bypass: a study of 55 patients chosen at random. J Thorac Cardiovasc Surg. 1984;87(2):167–174.

4. The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) (2014) ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2014;35 (35):2383–2431.

5. Fihn SD, Cardin JM, Abrams J et al. CF/AHA/ ACP/FCP/AATS/PCNA/SCAI/SNS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. J Am Coll Cardiol. 2012;60(24):44–164.

6. Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk. Expert Rev Cardiovasc Ther. 2007;5(2):177–193.

7. Celermajer D. Testing endothelial function using ultrasound. J Cardiovasc. Pharmacol. 1998;32 (Suppl 3): 29–32.

8. Vanhoutte PM. How to assess endothelial function in human blood vessels. J Hypertens. 1999;17(8):1047–1058.

9. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135–1143.

10. Libby P. Current concepts of the pathogenesis of the acute coronary syn-dromes. Circulation. 2001;104 (3):365–372.

11. Libby P. Molecular bases of the acute coronary syndromes. Circulation. 1995;91(11):2844–2850.

12. Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2): S1-S45. doi: 10.1161/01.cir.0000437738.63853.7a

13. Rudakova AV. Rozuvastatin: pharmacoeconomic issues. Klinicheskaya Farmakologiya i Terapiya. 2004;13 (4):29–32.

14. Blazing MA, Giugliano RP, Cannon CP et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. Am Heart J. 2014;168 (2):205–212.