https://doi.org/10.38109/2225-1685-2018-2-28-41

ISSN 2225-1685 (Print)
ISSN 2305-0748 (Online)

Check for updates

Semenova A.E., Sergienko I.V.

ROSUVASTATIN – THE MOST POTENT STATIN IN CARDIOVASCULAR DISEASE PREVENTION

Federal State Budgetary Institution "National Medical Research Center of Cardiology" of the Ministry of Health of Russia, Moscow, Russia

ABSTRACT

Rosuvastatin is a statin with maximum hypolipidemic effect, to date, which makes it one of the most frequently prescribed lipid-lowering medications. The drug has been widely studied in large international randomized clinical trials and proven to be highly effective. Administration of rosuvastatin at doses of up to 40 mg/day allows to decrease low-density lipoprotein cholesterol (LDL-C) levels by 55-63%, triglyceride levels by 28% and to significantly increase the level of high-density lipoprotein cholesterol by 10-14%. The effectiveness of rosuvastatin for primary prevention of CV complications has been indicated in high and very high risk patients, as well as in intermediate-risk persons and patients with mildly elevated base LDL-C level. The ability of rosuvastatin to suppress the progression of atherosclerosis has been demonstrated by intravascular ultrasound of coronary arteries and by magnetic resonance imaging of carotid arteries. Rosuvastatin is a hydrophilic statin with high hepatoselectivity, low systemic bioavailability (very limited penetration of rosuvastatin into extrahepatic tissues and, hence, lower risk of myotoxicity) and minimal involvement of P450 cytochrome in its metabolism (mostly mediated by 2C9 enzyme), which provides for good tolerability of the drug. High hepatoselectivity and the absence of any significant interaction with cytochrome P450 system mitigate the likelihood of side effects and drug interactions. The above mentioned characteristics of rosuvastatin enable its effective and safe use in treating a wide range of patients..

Key words: *rosuvastatin, hypercholesterolemia, atherosclerosis, cardiovascular disease, cardiovascular risk.*

Information about authors:

Sergienko I.V.	MD, PhD, DMSc, cardiologist, leading clinical research fellow of Atherosclerosis department, National medical research center of cardiology, 121552, Moscow, 3rd Cherepkovskaya Street, 15a E-mail: igorcardio@mail.ru, тел 8 (903) 149-2253
Corresponding author: Semenova A.E.	MD, PhD, cardiologist, clinical research fellow of Atherosclerosis department, National medical research center of cardiology, 121552, Moscow, 3rd Cherepkovskaya Street, 15a E-mail: an.sem@mail.ru, тел 8 (926) 239-4171

✉ **an.sem@mail.ru**

For citation: Semenova A.E., Sergienko I.V. Rosuvastatin – the most potent statin in cardiovascular disease prevention. Eurasian heart journal. 2018, May 25; 2:36-41.

At present statins continue to hold a dominant position in the treatment of patients with cardiovascular (CV) diseases [1, 2]. Their ability to improve prognosis in subjects with CV diseases and at high risk for their occurrence is confirmed by results of large-scale randomized studies that compares statins favorably with other lipid-lowering drugs [3, 4]. It has been established that clinical efficacy of lipid-lowering therapy depends on the achieved level of low density lipoprotein cholesterol (LDL-C) [5]. Results of analysis of 26 randomized clinical studies which included over 170 000 patients (a meta-analysis by Cholesterol Treatment Trialists) have shown that across all 26 studies, per each 1 mmol/L LDL-C reduction on statin therapy there were further proportional reductions in the incidence of cardiovascular death, i.e., deaths due to coronary heart disease (CHD) were reduced by 20%, all-cause mortality by 10%, risk of major vascular events by 23% and risk of stroke by 17% [5]. The initial "starting" statin dose has the most pronounced effect on LDL-C level (Table 1). If the dose of a statin is doubled then there is an additional reduction in LDL-C level though only by 3-7% (the so-called "six percent rule"). For that reason the success of lipid-lowering therapy is largely determined by the choice of a drug at the beginning of treatment.

When active therapy is required, the maximum effect can be achieved using rosuvastatin (original drug Crestor, AstraZeneca, United Kingdom). The effect of rosuvastatin is well studied thanks to the GALAXY program which included 23 multicenter, randomized, controlled clinical studies named after cosmic objects [7]. Notably, the studies COMETS, DISCOVERY, LUNAR, MERCURY-I, MERCURY-II, ORBITAL, POLARIS, STELLAR, PULSAR, ECLIPSE, EXPLORER, CENTAURUS and GRAVITY aimed at evaluating drug effect on lipid profile and inflammation markers; studies ASTEROID, METEOR, ORION, COSMOS and SATURN aimed at the assessment of atherosclerosis progression in coronary and carotid arteries; studies AURORA, CORONA and JUPITER aimed at the effect on disease prognosis; PLUTO study evaluated safety and tolerability of

rosuvastatin in children and PLANET I/II study assessed the statin nephroprotective properties.

EFFICACY OF ROSUVASTATIN THERAPY

Lipid-lowering effect

Administration of rosuvastatin at doses of 5-40 mg/day enables to decrease LDL-C levels by 39-55% (to 52-63% according to meta-analyses data) [8, 9]. This is the most potent statin in terms of its ability to reduce the level of total cholesterol (TC) and LDL-C, also its proven ability to decrease triglyceride (TG) level and increase the level of high-density lipoprotein cholesterol (HDL-C) [10]. Rosuvastatin at doses of 10-40 mg/day can increase the HDL-C level to 14% and reduce the TG level to 28% in patients with hypercholesterolemia. That said, 90% of the maximally possible rosuvastatin lipid-lowering effect is achieved at 2 weeks after the start of treatment. The intensity of lipid-lowering effect makes rosuvastatin the drug of choice for the treatment of familial hypercholesterolemia (FH) [11]. Rosuvastatin has been approved in the USA for use in children with FH aged 10 years and older [12] and in Europe for children with FH aged 6 years and older [13]. Treatment can be started at the earlier age in children with severe FH [14].

Use for primary prevention in case of mildly raised LDL-C

Rosuvastatin efficacy in patients with mildly raised LDL-C at baseline was demonstrated in a multinational randomized, double-blind, placebo-controlled trial JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) which included subjects with elevated levels of highly- sensitive C-reactive protein (hs-CRP) [15]. The study participants were men ≥ 50 years old and women ≥60 years old without CHD or diabetes mellitus (DM), with LDL-C level <3.4 mmol/L and hs-CRP level ≥2 mg/dL. All participants were randomly assigned to the rosuvastatin 20 mg/day group (n=8901) or placebo group (n=8901). Participating medical centers were located in 26 countries. After 12 months of treatment with rosuvastatin 20 mg/day the levels of LDL-C, hs-CRP and TG decreased by 50%, 37% and 17%, respectively, and the level of HDL-C raised by 4% [16]. After a 2-year follow-up the number of myocardial infarction (MI) cases decreased by 46%, number of strokes by 52%, revascularization requirements and episodes of unstable angina by 53% and MI+stroke+cardiovascular death combinations by 53% [16]. On the whole, over a 2-year follow-up of patients receiving rosuvastatin 20 mg/day there was a 44% reduction in the probability of reaching the primary endpoints (MI, stroke, unstable angina, revascularization, CV death) (OR 0.56; 95% CI: range 0.46-0.69, p<0.00001) and a 20% reduction in the probability of reaching the secondary endpoints (all-cause mortality) (OR 0.80; 95% CI: range 0.67-0.97, p<0.02) as compared to placebo [16]. Results of the JUPITER trial open up a wide perspective for primary prevention of CHD and atherosclerosis in subjects with normal cholesterol level and elevated level of hs-CRP. However, the measurement of the hs-CRP level is not included in the commonly used scales for risk stratification, and the expedience of its use in order to solve the issue of statin administration to decrease the risk of CV diseases has not been established. Moreover, despite there is an association between hs-CRP elevation and CHD, there is no compelling evidence regarding reduced frequency of CV complications as a function of lower level of hs-CRP [17]. In the JUPITER trial the majority of patients either had hypertension (57%) or had been smokers (15%), i.e., had the risk factors which should be paid attention to in the first place [18]. In support of the abovementioned data, a recently completed HOPE-3 trial in the intermediate risk subjects not suffering from CV disease failed to demonstrate that the difference in efficacy of statin therapy is related to elevated hs-CRP level at baseline [19].

The later analysis of the JUPITER trial results has shown a similar reduction in the relative risk of a composite cardiovascular endpoint against the backdrop of rosuvastatin therapy for subjects under and over 70 years of age. The number of subjects who had to be treated with rosuvastatin for 4 years to prevent one major cardiovascular event was 24 subjects in a group over 70 years of age and 36 subjects in a group under 70 years of age [20]. Therefore, the JUPITER trial demonstrated the significance of rosuvastatin as a drug for primary prevention of CV diseases among subjects with originally mildly elevated LDL-C level, that may be explained by additional reduction of LDL-C level and pleiotropic drug effect which results in stabilization of the atherosclerotic process.

Table 1. Lipid-lowering efficacy of statins according to STELLAR study [6]

The dose of statin	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin
LDL-C				
10 mg	-46%	-37%	-28%	-20%
20 mg	-52%	-43%	-35%	-24%
40 mg	-55%	-48%	-39%	-30%
80 mg	-	-51%	-46%	-
TG				
10 mg	-20%	-20%	-12%	-8 %
20 mg	-24%	-23%	-18%	-8%
40 mg	-26%	-27%	-15%	-13%
80 mg	-	-28%	-18%	-
HDL-C				
10 mg	+8%	+6%	+5%	+3%
20 mg	+10%	+5%	+6%	+4%
40 mg	+10%	+4%	+5%	+6%
80 mg	-	+2%	+7%	-

Note: LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, TG – triglycerides.

Primary prevention in intermediate risk subjects

The HOPE-3 trial demonstrated the effectiveness of rosuvastatin for primary prevention of CV diseases in intermediate risk subjects from different populations. A total of 12705 subjects from 21 countries were randomly assigned to rosuvastatin 10 mg/day group or placebo group. The primary composite endpoints were CV death, non-fatal MI or non-fatal stroke. The secondary composite endpoints were revascularization, heart failure and resuscitated cardiac arrest counted in addition to the primary endpoint events. The median follow-up was 5.6 years. The mean level of LDL-C in rosuvastatin group was lower by 26.5%. There was a significant superiority of rosuvastatin in terms of reduction of primary (3.7% versus 4.8%, p=0.002) and secondary (4.4% versus 5.7%, p<0.001) composite endpoints as compared to placebo [19].

SUPPRESSION OF ATHEROSCLEROTIC PROCESS

Effect on atherosclerotic plaques

The ability of rosuvastatin to suppress the progression of coronary atherosclerosis was demonstrated in the ASTEROID study (A Study

To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden). A total of 349 patients with CHD who received no statins at study entry have been enrolled in the study. The state of atherosclerotic plaques (ASP) was monitored in blood vessels which did not undergo prior endovascular treatment and were narrowed to a degree not exceeding 50% of luminal dimension. Administration of rosuvastatin 40 mg/day resulting in a 53% reduction of LDL-C from the baseline (mean LDL-C level was 1.6 mmol/L) after 2 years of the follow-up (n=349) led to significant reduction of ASP volume according to results of the intravascular ultrasound imaging [21]. Table 2 presents the dynamics of ASP volume as a function of the achieved LDL-C level. The reduction of normalized total ASP volume and reduction in ASP buildup in the 10-mm-long arterial segment was noted in 78% of patients and the reduction of relative ASP volume in 64% of patients.

A small randomized, double-blind ORION study was carried out to evaluate the dynamics of ASP volume and composition in carotid arteries after 24 months of treatment with rosuvastatin using magnetic resonance imaging [22]. The comparison of ASP parameters was performed in 33 patients receiving rosuvastatin whose baseline level of LDL-C was ≥2.6 and <6.5 mmol/L. Over the 24-month treatment period the LDL-C level was decreased by 38.2% in rosuvastatin 5 mg/day group and by 59.9% in rosuvastatin 40/80 mg/day group ($p<0.001$). There was a 41.4% reduction in the mean wall-to-lumen ratio in a zone originally occupied by a lipid-rich necrotic core of ASP ($p=0.005$). No significant changes in ASP volume have been observed at that.

The SATURN study (The Study of coronary Atheroma by inTravascular Ultrasound: the effect of Rosuvastatin vs. atorvastatiN) was composed of several consequential evaluations of indices reflecting the composition of coronary atherosclerotic plaques (ASP) obtained by intravascular ultrasound with radio frequency spectral analysis in patients receiving rosuvastatin 40 mg/day for 24 months (n=71) [23]. A direct relationship was found between the reduction of LDL-C, CRP and elevation of HDL-C levels on the one hand and regression of atheroma volume with reduction of its fibro-lipid component and increase of its calcification on the other. No changes in the volume of fibrous cap and necrotic core have been found.

The ability of intensive statin therapy (rosuvastatin 40 mg/day) to decrease the size of the atheromatous lipid core was proposed in the YELLOW study (Reduction in YEllow Plaque by Aggressive Lipid LOWering Therapy) in which drug effect was evaluated after 7 weeks of therapy in patients (n=87) undergoing percutaneous coronary intervention due to multiple coronary lesions [24]. However, from the authors' perspective, their findings need to be confirmed in a larger trial with a longer follow-up period.

An additional evaluation of morphological changes of coronary ASP in patients receiving rosuvastatin 40 mg/day for 8-12 weeks (n=85) was performed using the intravascular optical coherence tomography in the YELLOW II (Reduction in Coronary Yellow Plaque, Lipids and Vascular Inflammation by Aggressive Lipid Lowering) study [25]. An independent relationship was found between the atheroma fibrous cap thickening and improvement of reverse cholesterol transport that could contribute to morphologic changes associated with ASP stabilization. Also, changes in the transcriptome profile of peripheral blood mononuclear cells have been found that needs further investigation in order to establish the mechanisms of ASP stabilization in patients receiving high-dose statin therapy.

Table 2. Dynamics of ASP volume as a function of the achieved LDL-C level as found in the ASTEROID study

LDL-C	Patient number	Change in ASP volume (% median)	p
< 1,8 mmol / l	254	-0,9	<0,001
1,8-2,6 mmol / l	78	-0,3	0,09
≥ 2,6 mmol / l	17	-0,2	NS

Note: ASP – atherosclerotic plaque;
LDL cholesterol – low-density lipoprotein cholesterol;
NS – non-significant.

In conclusion, the ALTAIR study from Japan (Aggressive Lipid-Lowering Treatment Approach Using Intensive Rosuvastatin for Vulnerable Coronary Artery Plaque Randomized Trial) which also carried out the assessment of coronary ASP using angioscopy and intravascular ultrasound imaging (n=37), has shown the increased stabilization of ASP for both high-dose rosuvastatin (20 mg/day) and low-dose rosuvastatin (2.5 mg/day) administered for 48 weeks [26]. However, high-dose rosuvastatin appeared to be more effective in the initiation of ASP volume regression.

Slowing the changes in the intima-media complex

The ability of rosuvastatin 40 mg/day to slow progression of intima-media thickness (IMT) in patients with elevated LDL-C level and asymptomatic carotid atherosclerosis who are in the low cardiovascular risk group was demonstrated in a 24-month randomized, double-blind, placebo-controlled METEOR (Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin) study [27]. The study cohort comprised 984 patients including 702 patients in rosuvastatin group and 282 patients in placebo group with maximum IMT ranging between 1.2 mm and 3.5 mm. After a 2-year follow-up period the IMT progression was observed in placebo group whereas a trend toward the IMT regression was found in rosuvastatin group.

Slower carotid IMT progression was also found after 2 years of rosuvastatin therapy in children with heterozygous form of FH (n=197) aged 6 years or older as shown in the CHARON (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label) study [28]. It should be noted that currently there is no compelling reason to use the IMT parameter in clinical practice for evaluation of CV risk in FH or treatment efficacy although this parameter might come in handy from a scientific standpoint [13].

TREATMENT SAFETY

Pharmacological particulars of rosuvastatin

Rosuvastatin is a hydrophilic statin with high hepatoselectivity, low systemic bioavailability (very limited penetration of rosuvastatin into extrahepatic tissues and, hence, lower risk of myotoxicity) and minimal involvement of P450 cytochrome (CYP) in the metabolism of rosuvastatin (mostly mediated by 2C9 enzyme) that determines good tolerability of rosuvastatin [29]. There is no evidence of clinically significant pharmacokinetic drug-drug interactions between rosuvastatin and other drugs known to inhibit CYP enzymes [30]. Administration of rosuvastatin does not limit consumption of grapefruit juice, nor is there an increased risk of rhabdomyolysis as rosuvastatin is a non-CYP3A4-metabolized statin [31].

Rosuvastatin is excreted largely unchanged [32]. Hepatic elimination of rosuvastatin from the serum involves transporter proteins (hepatobiliary transporters) which secure its hepatic uptake and biliary clearance. The examples of transporter proteins responsible for transport of rosuvastatin, and medications affecting

the transporters are presented in Table 3. The elimination half-life of rosuvastatin is approximately 20 hours. About 10% of the drug is excreted by the kidneys. Pharmacodynamics and pharmacokinetics of rosuvastatin does not depend on the time of day the drug is administered [33].

Altogether, it has been found that the range of tolerance and safety of rosuvastatin therapy is comparable to that of other statins [10]. Analysis of data has shown that the frequency of complications does not significantly increase when a more aggressive approach to lipid-lowering statin therapy is used [35]. Rosuvastatin dosing adjustments toward reduction in drug dose may be preferable for Asian people or patients with stage 4 chronic kidney disease (CKD) (severe kidney failure) and patients receiving protease inhibitors or cyclosporine [10]. For statin-intolerant subjects with high risk for CV disease the possibility of an intermittent dosing regimen must be considered. Significant reduction of LDL-C levels due to rosuvastatin administration every other day or twice weekly has been reported [36].

Rosuvastatin drug-drug interactions

Caution should be exercised when rosuvastatin is co-administered with cyclosporine, gemfibrozil and protease inhibitors (used in the treatment of HIV infection) because of the risk of toxicity due to potential pharmacokinetic interactions

[37]. The above mentioned drugs are inhibitors of transporter proteins which mediate the hepatic uptake of rosuvastatin (Table 3). Co-administration of rosuvastatin 20 mg/day with combined protease inhibitor lopinavir/ritonavir 400/100 mg/day in healthy volunteers resulted in a 5-fold increase in maximum rosuvastatin plasma concentration [38]. Therefore, rosuvastatin is not recommended for HIV patients receiving treatment with protease inhibitors.

Co-administration of rosuvastatin with cyclosporine leads to a 11-fold increase in rosuvastatin plasma concentration without any effect on cyclosporine plasma concentration [39]. Use of cyclosporine is a contraindication for prescribing rosuvastatin at a dose of 10 mg/day and higher. Co-administration of rosuvastatin with gemfibrozil leads to a 2-fold increase in peak rosuvastatin plasma concentration [40]. It was shown that the combination lipid-lowering therapy with statins and fibrates or statins and nicotinic acid increases the risk of myopathy perhaps because each drug may cause myopathy on its own. Although there is no evidence in favor of possible pharmacokinetically significant interaction between rosuvastatin and fenofibrate, the possibility of their pharmacodynamic interaction cannot be ruled out. As a precautionary measure, concomitant administration of fibrates with rosuvastatin at a dose of 40 mg/day is contraindicated. When taken concurrently with gemfibrozil, fibrates or nicotinic acid, the recommended initial dose of rosuvastatin is 5 mg/day.

Table 3. Rosuvastatin transporter proteins and their affecting medicinal products [34]

Proteins-carriers	Substrate	Inhibitors
BCRP	rosuvastatin	ciclosporin, elthrombopag, gefitinib
OATP1B1		ciclosporin, elthrombopag, gemfibrozil, rifampicin, HIV protease inhibitors (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir)
OATP1B3		ciclosporin, rifampicin, HIV protease inhibitors (atazanavir, lopinavir, ritonavir, saquinavir)
OAT3		diclofenac, probenecid, cimetidine

Rosuvastatin can enhance the anticoagulant effect of warfarin although the mechanism of such drug interaction is so far obscure. Currently, a careful monitoring of international normalized ratio is recommended when rosuvastatin is co-administered with warfarin [41].

Co-administration of rosuvastatin with erythromycin results in a 20% decrease in AUC (area under the plasma concentration-time curve) of rosuvastatin and reduction by 30% of peak rosuvastatin plasma concentration [42]. Such effect is due to enhanced intestinal motor response to erythromycin.

It has been established that co-administration of rosuvastatin with oral contraceptives results in increased AUC of ethinylestradiol and AUC of norgestrel by 26% and 34%, respectively [43]. This must be taken into account during selection of oral contraceptive dose.

Rifampicin (antibiotic which is highly active against Mycobacterium tuberculosis) can affect the function of CYP enzymes and transporter proteins. Some data imply the possibility of interaction between statins and rifampicin. Experimental data have shown that rifampicin significantly inhibits hepatobiliary transport of rosuvastatin whereas imatinib has no effect on rosuvastatin plasma elimination [44]. Co-administration of rosuvastatin with rifampicin had no significant effect on pharmacokinetics of rosuvastatin in a small group (n=18) of healthy men [45]. Considering the data on rifampicin ability to suppress the activity of transporter proteins OATP1B3 and OATP1B1 involved in transport of rosuvastatin, a combination of these drugs can be fraught with the risk of drug interaction and occurrence of side effects (Table 3).

Combination of rosuvastatin with fenofibrate, ezetimibe, omega-3 fatty acids, azole-based antifungal compounds or clopidogrel seems to be safe considering the known pharmacokinetics and pharmacodynamics of these drugs, which attests against the likelihood of their interaction [37]. A clinically significant interaction between rosuvastatin and digoxin can be hardly anticipated. Therefore, rosuvastatin can be considered as a relatively safe and well tolerated drug which side effects are commonly associated with statin therapy.

TOLERANCE IN SPECIAL POPULATIONS

Chronic kidney disease

Rosuvastatin therapy in patients with end-stage chronic kidney disease (CKD) was studied in the AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events) trial, the first large international trial aimed at evaluating the efficacy of statin therapy on CV morbidity and mortality in a given category of patients. Administration of rosuvastatin 10 mg/day for patients with stage 5 CKD (n=2776) undergoing hemodialysis therapy for at least three months before the AURORA study entry, did not show any benefits in terms of the lower risk for CV complications as compared to placebo [46]. Results of other clinical studies leave the expediency of statin therapy for patients with stage 5 CKD in abeyance. Statin therapy is considered reasonable if patients with CV disease and CKD have already been taking it at the time when hemodialysis therapy was commenced [47]. Although patients with stage 3-5 CKD are at high or very high CV risk, according to clinical guidelines statins are mainly indicated for subjects who are not in need for hemodialysis therapy. Creatinine clearance <30 mL/min is a contraindication for administration of rosuvastatin.

Chronic heart failure

Good tolerance of rosuvastatin has been shown in such a difficult category of patients with New York Heart Association (NYHA) class III-IV heart failure as demonstrated by the CORONA (Controlled Rosuvastatin multinational study in heart failure) trial [48]. This study included more than 5 000 patients (average age - 73 years) with severe ischemic heart disease who have been randomly assigned to rosuvastatin 10 mg/day group (n=2514) or placebo group. The study duration was just under 3 years. No significant differences in mortality rate between the active therapy group and placebo group have been found although the number of hospitalizations due to CV diseases was significantly reduced. According to its authors, the study main positive outcome was good tolerance and safety of a long-term administration of rosuvastatin 10 mg/day in the population of patients with NYHA class III-IV heart failure. Similar results were obtained in the GISSI-HF study where administration of rosuvastatin 10 mg/day in subjects with NYHA class II-IV heart failure (n=2285), regardless of the etiology, did not affect disease outcome and was characterized by good treatment tolerance [49]. For that reason, according to clinical guidelines, the occurrence of heart failure in subjects already receiving statins bespeaks no need for their withdrawal. It should only be borne in mind that statin therapy on its own is not recommended for patients with heart failure (although it does no harm) unless there are no other indications for its prescription.

Conclusion

A pronounced lipid-lowering effect of rosuvastatin and its good tolerability made it one of the most frequently prescribed drugs which are used in clinical practice to diminish the risk of cardiovascular complications. High efficacy of rosuvastatin was demonstrated in large international and multinational randomized clinical trials using the original drug Crestor (AstraZeneca, United Kingdom). Its high hepatoselectivity and the absence of any significant interaction with cytochrome P450 system mitigate the likelihood of side effects and drug interactions. This provides the possibility of effective and safe rosuvastatin use across a broad spectrum of patients.

REFERENCES

1. *2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Catapano A.L., Graham I., De Backer G., et al.; Authors/Task Force Members; Additional Contributor. Eur Heart J. 2016;37(39):2999-3058.*
2. *Diagnosis and correction of lipid disorders for the prevention and treatment of atherosclerosis. Russian guidelines. VI revision. Moscow: 2017;44p. [in Russian].*
3. *Grundy S.M., Cleeman J.I., Mertz C.N., et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110(2):227-239.*
4. *Mills E.J., Rachlis B., Wu P., et al. Primary prevention of cardiovascular mortality and events with statin treatments. A network meta-analysis involving more than 65,000 patients. J Am Coll Cardiol. 2008;52:1769-1781.*
5. *Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C., Blackwell L., Emberson J., et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-1681. DOI: 10.1016/S0140-6736(10)61350-5.*
6. *McKenney J.M., Jones P.H., Adamczyk M.A., et al.; STELLAR Study Group. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. Curr Med Res Opin. 2003;19(8):689-698.*
7. *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.*
8. *Barter P.J., Brandrup-Wognsen G., Palmer M.K., Nicholls S.J. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. J Lipid Res. 2010;51(6):1546-1553. DOI: 10.1194/jlr.P002816.*
9. *Jones P.H., Davidson M.H., Stein E.A., et al.; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003;92(2):152-160.*
10. *Toth P.P., Dayspring T.D. Drug safety evaluation of rosuvastatin. Expert Opin Drug Saf. 2011;10(6):969-986.*
11. *2016;4(25):21-29. / Ezhov M.V., Sergienko I.V., Rozhkova T.A., et al. Russian Guidelines on Familial Hypercholesterolemia Diagnosis and Treatment. Atherosclerosis and dyslipidaemias. 2016;4(25):21-29. [in Russian].*
12. *Watts G.F., Gidding S., Wierzbicki A.S., et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation. Int J Cardiol. 2014;171:309-325.*
13. *Wiegman A., Gidding S.S., Watts G.F., et al.; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36(36):2425-2437. DOI: 10.1093/eurheartj/ehv157.*
14. *Reiner Z. Impact of early evidence of atherosclerotic changes on early treatment in children with familial hypercholesterolemia. Circ Res. 2014;114:233-235.*
15. *Ridker P.M.; JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation. 2003;108(19):2292-2297.*
16. *Ridker P.M., Danielson E., Fonseca F.A., et al.; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-2207.*
17. *Buckley D.I., Fu R., Freeman M., et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(7):483-495.*
18. *US Preventive Services Task Force, Bibbins-Domingo K., Grossman D.C., Curry S.J., et al., Pignone MP. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;316(19):1997-2007. DOI: 10.1001/jama.2016.15450.*
19. *Yusuf S., Bosch J., Dagenais G., et al.; HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374(21):2021-2031.*
20. *Glynn R.J., Koenig W., Nordestgaard B.G., et al. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol*

levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010;152:488-496,W174.

21. *Nissen S.E., Nicholls S.J., Sipahi I., et al.; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295(13):1556-1565.*
22. *Underhill H.R., Yuan C., Zhao X.Q., et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. Am Heart J. 2008;155(3):584. e1-8. DOI: 10.1016/j.ahj.2007.11.018.*
23. *Puri R., Libby P., Nissen S.E., et al. Long-term effects of maximally intensive statin therapy on changes in coronary atheroma composition: insights from SATURN. Eur Heart J Cardiovasc Imaging. 2014;15(4):380-388. DOI: 10.1093/ehjci/jet251.*
24. *Kini A.S., Baber U., Kovacic J.C., et al. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). J Am Coll Cardiol. 2013;62(1):21-29. DOI: 10.1016/j.jacc.2013.03.058.*
25. *Kini A.S., Vengrenyuk Y., Shameer K., et al. Intracoronary Imaging, Cholesterol Efflux, and Transcriptomes After Intensive Statin Treatment: The YELLOW II Study. J Am Coll Cardiol. 2017;69(6):628-640. DOI: 10.1016/j.jacc.2016.10.029.*
26. *Takayama T., Komatsu S., Ueda Y., et al.; ALTAIR study group. Comparison of the Effect of Rosuvastatin 2.5 mg vs 20 mg on Coronary Plaque Determined by Angioscopy and Intravascular Ultrasound in Japanese With Stable Angina Pectoris (from the Aggressive Lipid-Lowering Treatment Approach Using Intensive Rosuvastatin for Vulnerable Coronary Artery Plaque [ALTAIR] Randomized Trial). Am J Cardiol. 2016;117(8):1206-1212. DOI: 10.1016/j.amjcard.2016.01.013.*
27. *Crouse J.R. 3rd, Raichlen J.S., Riley W.A., et al.; METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007;297(12):1344-1353.*
28. *Braamskamp M.J.A.M., Langslet G., McCrindle B.W., et al. Effect of Rosuvastatin on Carotid Intima-Media Thickness in Children With Heterozygous Familial Hypercholesterolemia: The CHARON Study (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label). Circulation. 2017;136(4):359-366. DOI: 10.1161/CIRCULATIONAHA.116.025158.*
29. *McTaggart F. Comparative pharmacology of rosuvastatin. Atherosclerosis. 2003;Suppl4:9-14.*
30. *Neuvonen PJ. Drug interactions with HMG-CoA reductase inhibitors (statins): the importance of CYP enzymes, transporters and pharmacogenetics. Curr Opin Investig Drugs. 2010;11(3):323-332.*
31. *Bailey D.G., Dresser G.K. Interactions between grapefruit juice and cardiovascular drugs. Am J Cardiovasc Drugs. 2004;4(5):281-297.*
32. *Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19:117-126.*
33. *Martin P.D., Mitchell P.D., Schneck D.W. Pharmacodynamic effects and pharmacokinetics of a new HMG-CoA reductase inhibitor, rosuvastatin, after morning or evening administration in healthy volunteers. Br J Clin Pharmacol. 2002;54(5):472-477.*
34. *http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#substrates. The University of Washington Drug Interaction Database. 2011.*
35. *Benes L.B., Bassi N.S., Davidson M.H. The Risk of Hepatotoxicity, New Onset Diabetes and Rhabdomyolysis in the Era of High-Intensity Statin Therapy: Does Statin Type Matter? Prog Cardiovasc Dis. 2016;59(2):145-152.*
36. *Keating A.J., Campbell K.B., Guyton J.R. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. Ann Pharmacother. 2013;47:398-404.*
37. *Kostapanos M.S., Milionis H.J., Elisaf M.S. Rosuvastatin-associated adverse effects and drug-drug interactions in the clinical setting of dyslipidemia. Am J Cardiovasc Drugs. 2010;10(1):11-28.*
38. *Kiser J.J., Gerber J.G., Predhomme J.A., et al. Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. J Acquir Immune Defic Syndr. 2008;47(5):570-578.*
39. *Simonson S.G., Raza A., Martin P.D., et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. Clin Pharmacol Ther. 2004;76(2):167-177.*
40. *Bergman E., Matsson E.M., Hedeland M., et al. Effect of a single gemfibrozil dose on the pharmacokinetics of rosuvastatin in bile and plasma in healthy volunteers. J Clin Pharmacol. 2010;50(9):1039-1049.*
41. *Simonson S.G., Martin P.D., Mitchell P.D., et al. Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. J Clin Pharmacol. 2005;45(8):927-934.*
42. *Cooper K.J., Martin P.D., Dane A.L., et al. The effect of erythromycin on the pharmacokinetics of rosuvastatin. Eur J Clin Pharmacol. 2003;59(1):51-56.*
43. *Simonson S.G., Martin P.D., Warwick M.J., et al. The effect of rosuvastatin on oestrogen & progestin pharmacokinetics in healthy women taking an oral contraceptive. Br J Clin Pharmacol. 2004;57(3):279-286.*
44. *Bergman E., Hedeland M., Bondesson U., Lennern s H. The effect of acute administration of rifampicin and imatinib on the enterohepatic transport of rosuvastatin in vivo. Xenobiotica. 2010;40(8):558-568.*
45. *Zhang W., Deng S., Chen X.P., et al. Pharmacokinetics of rosuvastatin when coadministered with rifampicin in healthy males: a randomized, single-blind, placebo-controlled, crossover study. Clin Ther. 2008;30(7):1283-1289.*
46. *Fellstr m B.C., Jardine A.G., Schmieder R.E., et al.; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360(14):1395-1407.*
47. *Tonelli M., Wanner C.; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. Ann Intern Med. 2014;160:182.*
48. *Fonarow GC. Randomized clinical outcome trials of statins in heart failure. Heart Fail Clin. 2008;4(2):225-229.*
49. *Tavazzi L., Maggioni A.P., Marchioli R., et al.; Gissi-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372(9645):1231-1239. DOI: 10.1016/S0140-6736(08)61240-4*

Approved for publication: April 23, 2013