Liječenje zasnovano na dokazima s Krkinim rosuvastatinom u primarnoj i sekundarnoj prevenciji kardiovaskularnih bolesti

Evidence-based therapy with Krka's rosuvastatin in primary and secondary prevention of cardiovascular disease

Darja Milovanovič Jarh, Mateja Grošelj, Breda Barbič-Žagar*

Krka, d. d., Novo mesto, Slovenija
Krka, d. d., Novo mesto, Slovenia

SAŽETAK: Kardiovaskularne bolesti vodeći su uzrok smrti u svijetu. Od svih čimbenika rizika za tu skupinu bolesti pokazalo se da je hiperlipidemija povezana s najvišim populacijskim rizikom. Usprkos dokazano djelotvornim lijekovima koji se primjenjuju već desetljećima, učestalost kardiovaskularnih događaja i dalje ostaje visoka. Međunarodne su smjernice identificirale probleme propisivanja najniže jačine statina, a često se ti lijekovi ne titriraju kako bi se postigle ciljne vrijednosti. Činjenica da se većina bolesnika liječi niskom početnom jačinom statina i da liječnici rijetko posežu za višim jačinama upućuje na potrebu za srednjim jačinama. Krka je uvela širok raspon jačina rosuvastatina kako bi premostila tu prazninu, uključujući one srednje jačine od 15 i 30 mg. Te, dodatne jačine omogućuju prilagodbu liječenja prema potrebama pojedinih bolesnika te postizanje željene, ciljne razine lipida u većeg postotka pacijenata.

SUMMARY: Cardiovascular disease is the leading cause of death worldwide. Among the risk factors, hyperlipidemia has been associated with the highest population attributable risk for cardiovascular disease. Despite many proven therapies and decades of their use, cardiovascular event rates remain high. International guidelines have identified the problem of statins being prescribed at the lowest dose and often not up-titrated to attain the goal of treatment. The fact that a majority of patients are treated with the initial low doses of statins and that doctors rarely reach for the higher doses indicates a need for intermediate doses. In order to bridge this gap, Krka produces a wide range of rosuvastatin strengths, including the intermediate strengths of 15 and 30 mg. This additional strengths enables treatment to be adjusted to the requirements of individual patients and increase the percentage of patients reaching target lipid levels.

KLJUČNE RIJEČI: rosuvastatin, kardiovaskularne bolesti, LDL kolesterol, djelotvornost, sigurnost, dodatne jačine.

KEYWORDS: rosuvastatin, cardiovascular disease, LDL cholesterol, efficacy, safety, additional strengths.

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***ADDRESS FOR CORRESPONDENCE:** Breda Barbič-Žagar, Krka d. d., Dunajska 65, SLO-1000 Ljubljana, Slovenia
Phone: +386-1-4751-339 / E-mail: breda.zagar@krka.biz

ORCID: Darja Milovanovič Jarh, http://orcid.org/0000-0001-5085-9823 • Mateja Grošelj, http://orcid.org/0000-0002-4035-7691
Breda Barbič-Žagar, http://orcid.org/0000-0002-1173-7361

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Kardiovaskularne bolesti (KVB) vodeći su uzrok smrti u svijetu. Svake godine od KVB-a umire više od 17 milijuna ljudi. Među čimbenicima rizika za tu skupinu bolesti pokazalo se da je hiperlipidemija povezana s najvišim populacijskim rizikom za KVB.[1] Usprkos mnogim dokazanim opcijama liječenja i desetljećima njihove primjene, učestalost kardiovaskularnih događaja i dalje ostaje visoka.[2,3] Kao što je pokazala nedavno obavljena studija EUROASPIRE IV, više od 80 % bolesnika s visokim ili vrlo visokim rizikom ne postigne ciljne vrijednosti lipida u plazmi te stoga oni ne dobivaju najveću moguću korist od liječenja.[4]

Cardiovascular disease (CVD) is the leading cause of death worldwide. More than 17 million people die from CVD each year. Among the risk factors, hyperlipidemia is associated with the highest population attributable risk for CVD.[1] Despite many proven therapies and decades of their use, cardiovascular event rates remain high.[2,3] As evidenced by the recently published EUROASPIRE IV survey, more than 80% of high- or very-high-risk patients do not attain the target levels of plasma lipids and thus do not get the maximum benefit of statin therapy.[4]

As recognised by international guidelines, statins are usually prescribed at the lowest dose and often not up-titrated to attain the therapeu-

Kao što se navodi i u međunarodnim smjernicama, statini se obično propisuju u najnižoj jačini te se često ne titriraju do ciljnih vrijednosti. Slabo je i dugoročno pridržavanje liječenja, a trećina ili više bolesnika prekine liječenje statinima unutar godine dana. Posljedično tomu, takvi pacijenti ne dobivaju najveću moguću korist od primjene ovakve preventivne strategije.[5] Oni ostaju pod povećanim rizikom za razvoj ili progresiju KVB-a usprkos primanju liječenja.

Statini su uobičajeno dostupni u jačinama od 10, 20, 40 i 80 mg, uz iznimku rosuvastatina koji je na raspolaganju u jačinama od 5 do 40 mg.[6,7] Podatci iz kliničke prakse pokazuju da liječnici obično ne propisuju najviše jačine te da većina bolesnika prima jednu od dviju najnižih jačina. To upućuje na potrebu za srednjim jačinama.

Na tržište su uvedene dvije nove jačine (15 i 30 mg) Krkina rosuvastatina (Roswera®) sa svrhom primjene optimalnog i učinkovitog liječenja hipolipemicima. Širok raspon jačina rosuvastatina omogućuje prilagodbu liječenja prema potrebama pojedinih pacijenata te u konačnici povećava vjerojatnost postizanja ciljne razine lipida.[8]

Iako se klinička djelotvornost jačina od 15 i 30 mg može predvidjeti linearnom ekstrapolacijom iz podataka o već odobrenim jačinama rosuvastatina, bilo je potrebno prikupiti kliničke podatke kao dodatne potkrepljujuće dokaze.

Djelotvornost i sigurnost titracije jačina rosuvastatina u liječenju bolesnika s hiperlipidemijom (klinička studija ROSU-PATH)

Međunarodna, randomizirana, multicentrična, otvorena, prospektivna klinička studija ROSU-PATH (*The efficacy and safety of ROSUvastatin dose titration in the treatment of PATients with Hyperlipidemia*) provedena je kako bi se utvrdile djelotvornost i sigurnost dodatnih jačina rosuvastatina od 15 i 30 mg u bolesnika s primarnom hiperkolesterolemijom ili miješanom dislipidemijom te odredio postotak pacijenata koji postižu ciljne vrijednosti LDL kolesterola (LDL-K) prema smjernicama Europskoga kardiološkoga društva i Europskoga društva za aterosklerozu iz 2011. godine, koje su bile aktualne u razdoblju provedbe studije.

U toj međunarodnoj, randomiziranoj, multicentričnoj, otvorenoj, prospektivnoj kliničkoj studiji provedenoj u 30 zdravstvenih ustanova u Hrvatskoj, Češkoj, Mađarskoj, Rumunjskoj, Rusiji, Sloveniji i Ukrajini, 494 pacijenta (prosječne dobi od 56,9 ± 9,9 godina) randomizirana su u standardnu (10 mg – 20 mg – 40 mg rosuvastatina) ili alternativnu titracijsku skupinu (15 mg – 30 mg – 40 mg rosuvastatina).

Nakon početne procjene pacijentima su u trima posjetima (u 4., 8. i 12. tjednu) mjerene razine lipida i sigurnosni parametri. Pri svakom je posjetu titrirana jačina rosuvastatina prema standardnoj ili alternativnoj titracijskoj shemi kako bi se postigle ciljne razine LDL-K-a (**slika 1**).

Usporedba djelotvornosti i sigurnosti jačina rosuvastatina od 15 i 10 mg

Na početku studije nije bilo znatnih razlika među skupinama, samo što je u alternativnoj titracijskoj skupini bilo više muškaraca nego u standardnoj skupini (57% prema 47%; P < 0,05).

U 4. tjednu pacijenti u alternativnoj titracijskoj skupini pokazali su mnogo veće sniženje vrijednosti LDL-K-a u usporedbi s pacijentima u standardnoj titracijskoj skupini (**tablica 1**).[9]

tic goal.[1] In addition, treatment adherence over the long term is poor, with up to a third of patients or more stopping their statin treatment within a year. As a consequence, these patients are not getting the maximum benefit of this preventive strategy.[5] They remain at an increased risk for the development and/or progression of CVD despite receiving treatment.

Statins are normally available in 10 mg, 20 mg, 40 mg and 80 mg strengths, with the exception of rosuvastatin, which is available in strengths from 5 mg to 40 mg.[6,7] Data from clinical practice show that usually physicians do not reach for the highest doses and that a majority of patients are treated with one of the two lowest doses. This indicates the need for intermediate doses.

Two new strengths (15 mg and 30 mg) of Krka's rosuvastatin (Roswera®) have been introduced on the market with the aim to facilitate optimal and effective hypolipidemic therapy. The wide range of rosuvastatin strengths enables treatment adjustment to the requirements of individual patients and ultimately increases the likelihood of reaching the target lipid level.[8]

Although the clinical efficacy of the 15 mg and 30 mg strengths is predictable from the linear extrapolation of data on already approved rosuvastatin doses, clinical evidence was required as supporting evidence.

The efficacy and safety of ROSUvastatin dose titration in the treatment of PATients with Hyperlipidemia (the ROSU-PATH clinical study)

The international, randomised, multicentre, open-label, prospective clinical study ROSU-PATH (The efficacy and safety of ROSUvastatin dose titration in the treatment of PATients with Hyperlipidemia) was performed to establish the efficacy and safety of the additional doses of 15 mg and 30 mg of rosuvastatin in patients with primary hypercholesterolemia or mixed dyslipidemia and to determine the percentage of patients reaching the target LDL-cholesterol (LDL-C) levels as defined by the 2011 ESC/EAS guidelines current at the time of the study.

In this international, randomised, multicentre, open-label, prospective clinical study conducted at 30 healthcare institutions in Croatia, the Czech Republic, Hungary, Romania, Russia, Slovenia and Ukraine, 494 patients (aged 56.9 ± 9.9 years) were randomised to either the standard (10 mg – 20 mg – 40 mg of rosuvastatin) or the alternative titration arm (15 mg – 30 mg – 40 mg of rosuvastatin).

Baseline assessment was followed by three visits (at weeks 4, 8 and 12) where lipid levels and safety parameters were measured. At each visit the dose of rosuvastatin was titrated according to the standard or alternative titration scheme to achieve target LDL-C levels (**Figure 1**).

Comparison of the efficacy and safety of rosuvastatin 15 mg vs 10 mg

At baseline, there were no significant differences between the groups, except that there were more men in the alternative than in the standard titration arm (57% vs 47%; P < 0.05).

At week 4, patients in the alternative titration arm showed a significantly greater LDL-C reduction compared to patients in the standard titration arm (**Table 1**).[9]

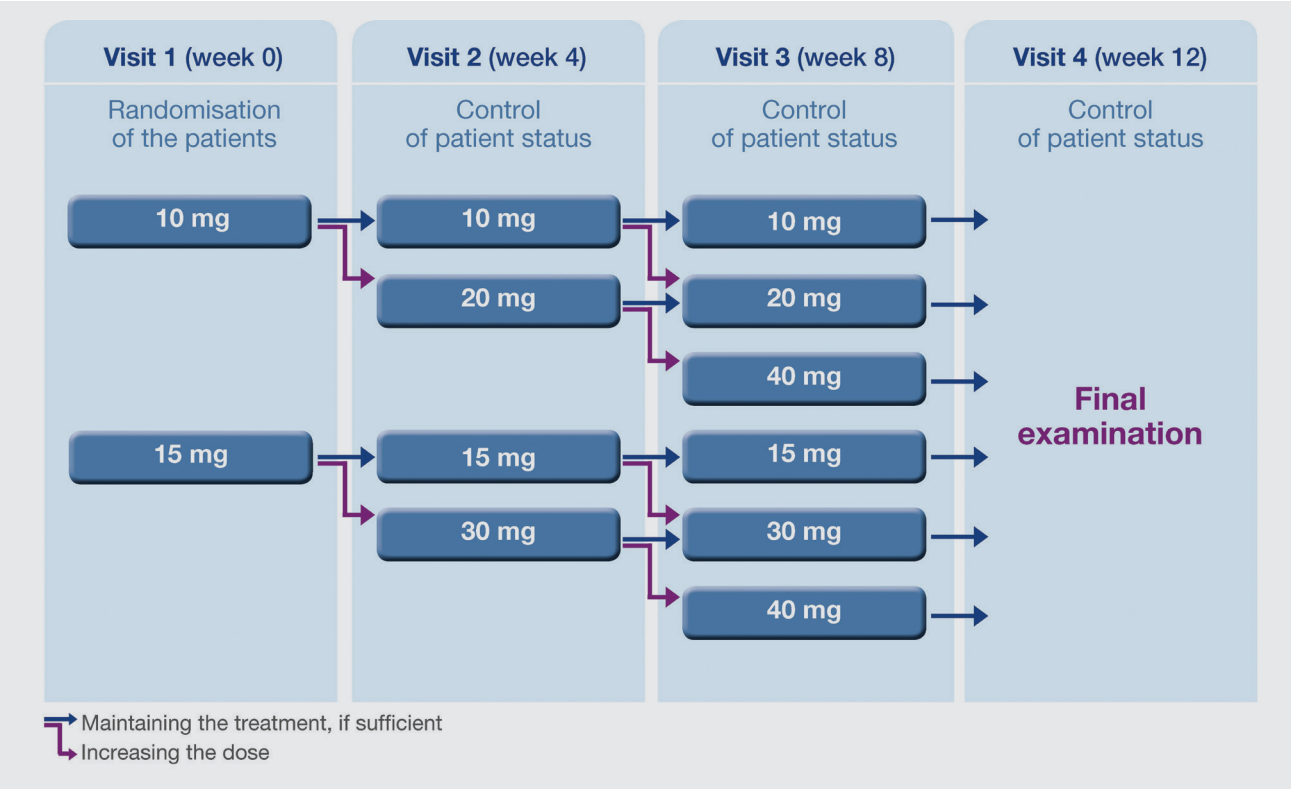

FIGURE 1. ROSU-PATH (The efficacy and safety of ROSUvastatin dose titration in the treatment of PATients with Hyperlipidemia) dosage diagram.

TABLE 1. LDL-cholesterol (LDL-C) values at baseline and at week 4.

LDL-C value	Standard titration arm	Alternative titration arm
Baseline (mmol/l)	4.33 ± 1.11	4.44 ± 1.02
Week 4 (mmol/l)	2.64 ± 0.93	2.52 ± 0.80
Baseline – Week 4 (mmol/l) (absolute change)	–1.69 ± 0.99	–1.95 ± 0.98
	P < 0.005	
Baseline – Week 4 (%) (relative change)	–37.5 ± 21.7	–42.6 ± 17.3
	P < 0.01	

Mnogo je više bolesnika na rosuvastatinu od 15 mg postiglo ciljne razine lipida u usporedbi s pacijentima na jačini od 10 mg (81% prema 67%; P < 0,0001) (**slika 2**), pri čemu su profili podnošenja i sigurnosti bili slični za obje skupine.[9]

Postizanje ciljne razine LDL-K-a u pacijenata s različitim razinama KV rizika

Analiza prema namjeri liječenja (engl. *intention-to-treat analysis*) uključivala je 469 pacijenata, od kojih 166 s umjerenim, 78 s visokim i 225 s vrlo visokim KV rizikom. Evaluacija postizanja ciljnih vrijednosti LDL-K-a u tim skupinama pod KV rizikom pokazala je stope uspješnosti od 83,4, 66,7 i 33,0 % za te tri skupine. U pacijenata s vrlo visokim rizikom, 22,7 % njih nije uspjelo postići ciljnu vrijednost LDL-K-a od < 1,8 mmol/L,

Significantly more patients on rosuvastatin 15 mg reached target lipid levels compared to patients on rosuvastatin 10 mg (81% vs 67%; P < 0.0001) (**Figure 2**), while the tolerance and safety profiles were comparable in both arms.[9]

Target LDL-C level attainment rate in patients at different CV risk levels

An intention-to-treat analysis included 469 patients; 166, 78 and 225 patients at moderate, high and very high CV risk, respectively. Evaluation of the target LDL-C level attainment in these CV risk groups revealed success rates of 83.4%, 66.7% and 33.0%, respectively. Among very-high-risk patients, there were 22.7% of patients who failed to reach the target LDL-C level of < 1.8 mmol/l, but had a ≥ 50% LDL-C reduction com-

ali su imali smanjenje ≥ 50 % LDL-K-a u usporedbi s početnom razinom, što znači da je 55,5 % pacijenata s vrlo visokim rizikom dosegnulo ciljnu razinu LDL-K-a. Prosječne dnevne jačine bile su 18,7 mg za pacijente s umjerenim rizikom, 21,8 mg za pacijente s visokim rizikom i 25,3 mg za pacijente s vrlo visokim rizikom (**slika 3**). Evaluacija prosječnih razlika od ciljnih razina LDL-K-a za skupine s različitim KV rizikom pokazala je da samo bolesnici s vrlo visokim rizikom nisu uspjeli postići ciljnu vrijednost (**tablica 2**).[10]

pared to baseline, resulting in 55.7% of very-high-risk patients reaching the LDL-C goal. The mean daily doses were 18.7 mg, 21.8 mg and 25.3 mg for moderate-, high- and very-high-risk patients, respectively (**Figure 3**). Evaluation of the mean differences from the target LDL-C levels for different CV risk groups showed only the very-high-risk patients failed to reach the target (**Table 2**).[10]

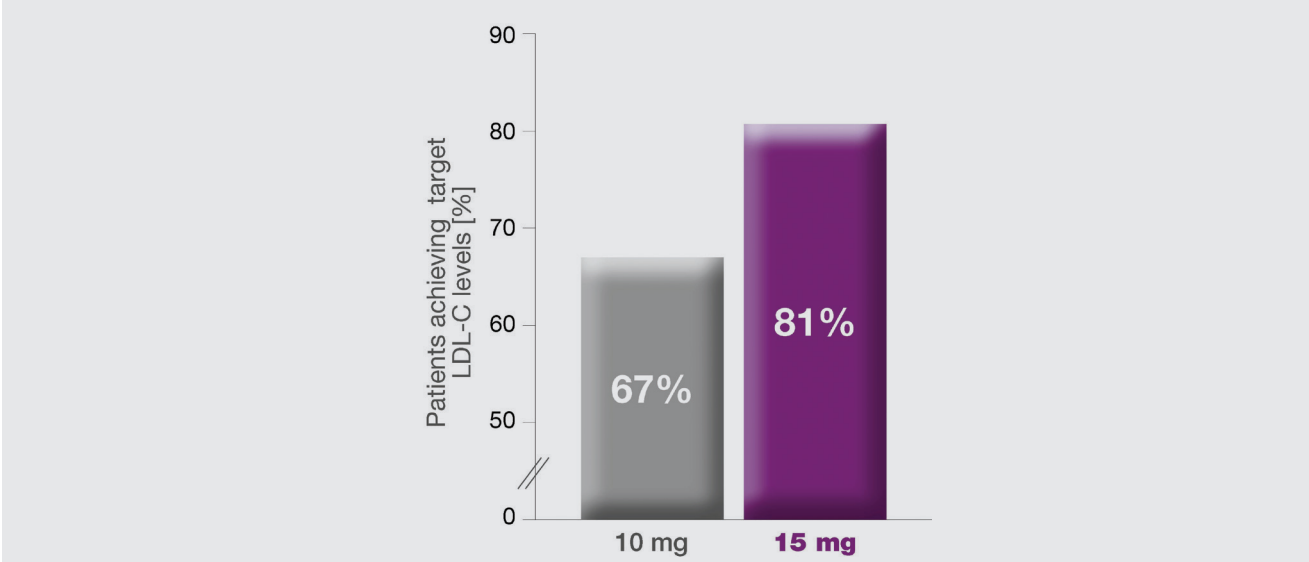

FIGURE 2. Percentage of patients with LDL-cholesterol reaching target levels after 10 mg and 15 mg doses at the end of the study.

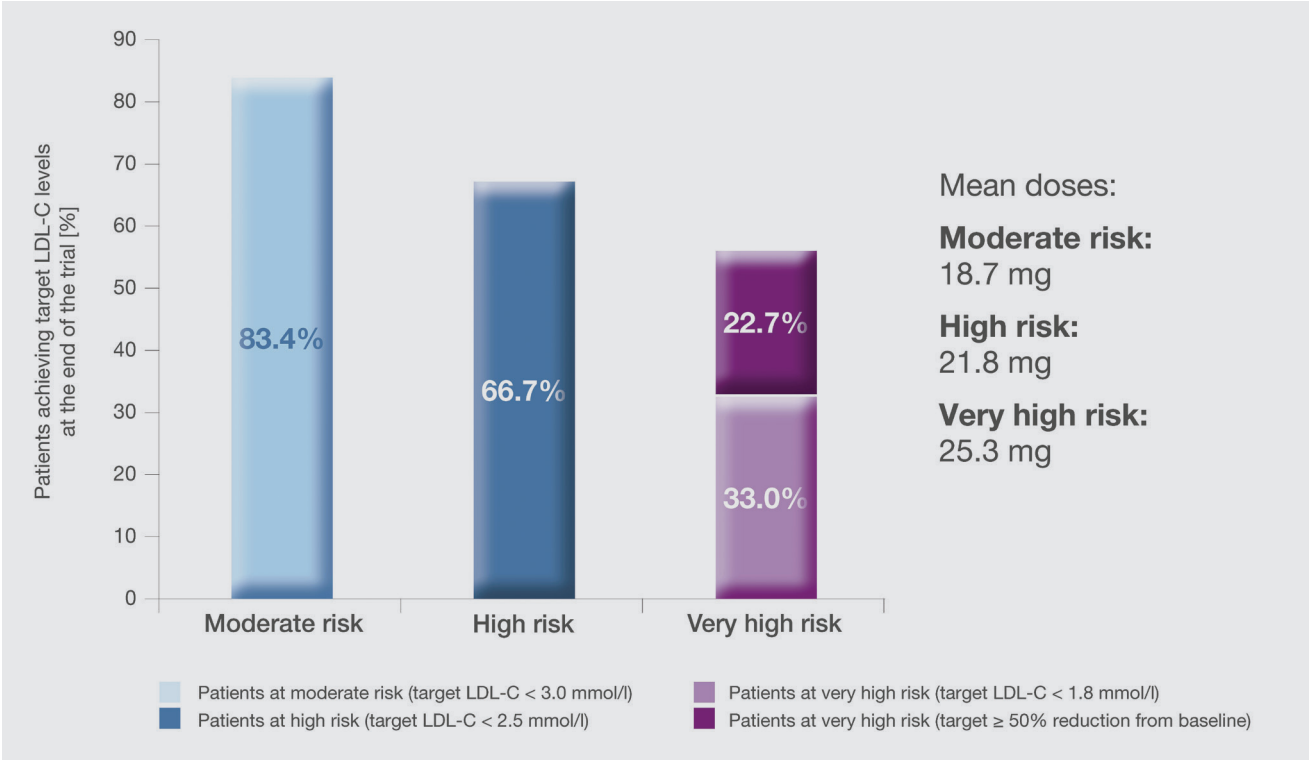

FIGURE 3. Evaluation of LDL-cholesterol goal attainment by cardiovascular risk group.

Zaključci i implikacije rezultata

Klinička studija ROSU-PATH bila je prva klinička procjena uporabe rosuvastatina jačine 15 mg u kliničkoj praksi. Terapija bilo kojom od istraženih jačina rosuvastatina procijenjena je kao učinkovita i sigurna za široki raspon bolesnika s hiperlipidemijom. Mnogo više pacijenata u alternativnoj skupini – na rosuvastatinu od 15 mg – postiglo je ciljne razine lipida u usporedbi s pacijentima na rosuvastatinu od 10 mg. Usto, u alternativnoj skupini titriranja bio je potreban mnogo manji broj titracija. Možemo zaključiti da je jačina rosuvastatina od 15 mg učinkovita i sigurna početna doza rosuvastatina koja više bolesnika dovodi do ciljne vrijednosti LDL-K-a.[9]

Procjena prosječnih razlika između ciljnih razina LDL-K-a pokazala je da su pacijenti s umjerenim i visokim rizikom dosegnuli svoje ciljne vrijednosti, a bolesnici s vrlo visokim rizikom nisu, upućujući na to da je prosječna jačina rosuvastatina u ovoj skupini (25,3 mg) bila preniska.[10] Dodatne jačine rosuvastatina od 15 i 30 mg mogle bi biti dobrodošla alternativa za bolesnike koji ne dobivaju najveću moguću korist od liječenja statinima zbog toga što se ne liječe optimalnom jačinom.

Conclusions and implications of the findings

The clinical study ROSU-PATH was the first clinical evaluation of the use of the rosuvastatin 15 mg strength in clinical practice. Therapy with any of the investigated strengths of rosuvastatin was evaluated as effective and safe in a wide range of patients with hyperlipidemia. Significantly more patients in the alternative arm, on rosuvastatin 15 mg, reached target lipid levels compared to patients on rosuvastatin 10 mg. Moreover, significantly fewer dose titrations were needed in the alternative dosing arm. We can conclude that the 15 mg dose of rosuvastatin is an effective and safe initial dose of rosuvastatin, bringing more patients to target LDL-C level.[9]

Evaluation of mean differences from target LDL-C levels showed that moderate- and high-risk patients reached their targets, while the very-high-risk patients failed, suggesting that the mean dose of rosuvastatin in this group (25.3 mg) was too low.[10] The additional strengths of rosuvastatin of 15 mg and 30 mg might be a welcome alternative for patients not getting the greatest possible benefit from statin treatment due to not being treated with the optimal dose.

TABLE 2. Mean absolute differences from target LDL-cholesterol in different cardiovascular risk groups [mmol/l].

Group	Baseline	Week 4	Week 8	Week 12	Significance (Baseline : week 12)
Moderate risk (target LDL-C < 3.0 mmol/l)	**1.64**	**–0.35**	**–0.53**	**–0.50**	**P < 0.0001**
High risk (target LDL-C < 2.5 mmol/l)	**2.05**	**0.28**	**0.18**	**–0.11**	**P < 0.0001**
Very high risk (target LDL-C < 1.8 mmol/l)	**2.33**	**0.66**	**0.30**	**0.34**	**P < 0.0001**

LITERATURE

1. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al; Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016 Aug 1;37(29):2315-81. https://doi.org/10.1093/eurheartj/ehw106
2. Zoungas S, Curtis A, McNeil J, Tonkin A. Treatment of dyslipidemias and cardiovascular outcomes: the journey so far. Is this the end for statins? Clin Pharmacol Ther. 2014 Aug;96(2):192-205. https://doi.org/10.1038/clpt.2014.86
3. Mendis S, Puska P and Norrving B. Global atlas on cardiovascular disease prevention and control. [internet] Published by the World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. Geneva 2011. [cited 2017 March 14]. Available at: http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf
4. Kotseva K, Wood D, De Bacquer D, De Backer G, Rydén L, Jennings C, et al; EUROASPIRE Investigators. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016 Apr;23(6):636-48. https://doi.org/10.1177/2047487315569401
5. Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, et al; EUROACTION Study Group. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. Lancet. 2008 Jun 14;371(9629):1999-2012. https://doi.org/10.1016/S0140-6736(08)60868-5
6. Kendrach MG, Kelly-Freeman M. Approximate equivalent rosuvastatin doses for temporary statin interchange programs. Ann Pharmacother. 2004 Jul-Aug;38(7-8):1286-92. https://doi.org/10.1345/aph.1D391
7. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, https://doi.org/10.1016/S0002-9149(03)00530-7
8. Brus S, Barbič-Žagar B. Clinical Evidence of the Efficacy of Krka's Rosuvastatin in the Treatment of Hyperlipidemia with Focus on Additional Dosage Strengths. Cardiol Croat. 2014;9(7-8):320-323. https://doi.org/10.15836/ccar.2014.320
9. ESC Congress 365. Cevc M. Comparison of efficacy and safety of rosuvastatin 15 mg vs. 10 mg: subanalysis of the ROSU-PATH trial. Available at: http://congress365.escardio.org/Presentation/140210 (14.3.2017).
10. ESC Congress 2016. Poster session 2: Cardiovascular prevention outcomes I. Presentations list. Available at: http://spo.escardio.org/SessionDetails.aspx?eevtid=1127&sessId=19169&subSessId=5564 (14.3.2017).