Liječenje Krkinim statinima utemeljeno na dokazima u pacijenata u primarnoj i sekundarnoj prevenciji kardiovaskularnih bolesti

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

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SAŽETAK: Dokazano je da statini smanjuju kardiovaskularni pobol i smrtnost u primarnoj i sekundarnoj prevenciji kardiovaskularnih bolesti. No liječenje statinima još uvijek nije optimalno jer većina pacijenata ne postiže najveće moguće pozitivne učinke ovakve preventivne strategije. Krka ima širok raspon statina koji su iscrpno testirani. Studije donose jasne i opsežne dokaze o dobrobiti primjene atorvastatina (Atoris®) i rosuvastatina (Roswera®) u primarnoj i sekundarnoj prevenciji, uključujući uspješno liječenje ukupnoga lipidnog profila, postizanje ciljne razine lipida, prevencije ozbiljnih ishemijskih ishoda u pacijenata s akutnim koronarnim sindromom, preventivne pleiotropne učinke i dobar sigurnosni profil. Kliničke studije na Krkinim statinima važan su doprinos boljem liječenju hiperlipidemije u različinim skupinama pacijenata.

SUMMARY: Statins have been proven to reduce cardiovascular morbidity and mortality in primary and secondary prevention of cardiovascular disease. However, statin treatment is still not optimal, with the majority of patients not achieving the maximum benefits of this preventive strategy. Krka offers a wide range of statins that have been extensively studied. The studies have provided clear and conclusive evidence about the benefits of atorvastatin (Atoris®) and rosuvastatin (Roswera®) in primary and secondary prevention patients, including effective management of the total lipid profile, achievement of target lipid levels, prevention of severe ischemic outcomes in patients with acute coronary syndrome, protective pleiotropic effects and a good safety profile. Clinical studies with Krka's statins represent an important contribution to a better management of hyperlipidemia in different groups of patients.

KLJUČNE RIJEČI: statini, primarna prevencija, sekundarna prevencija, kliničke studije, učinkovitost, sigurnost.

KEYWORDS: statins, primary prevention, secondary prevention, clinical studies, efficacy, safety.

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Važnost primjene statina raste iz godine u godinu zbog povećane svijesti o potrebi liječenja povišene razine kolesterola u krvi. Važan korak u liječenju statinima dogodio se 1994. godine, kada je kliničko istraživanje *Scandinavian Simvastatin Survival Study* (4S) prvi put dokazalo dobrobiti liječenja statinima u pacijenata u sekundarnoj prevenciji. Istraživači su zaključili da je liječenje simvastatinom sigurno te da poboljšava stope preživljenja u pacijena-

With increased awareness about the need of treating elevated levels of blood cholesterol, the importance of statins is growing every year. A major milestone in the statin therapy was the year 1994, when the Scandinavian Simvastatin Survival Study (4S) for the first time demonstrated the benefits of statin treatment in secondary prevention patients. The investigators of the study suggested that treatment with simvastatin was

ta s koronarnom bolesti srca (KBS).[1] No dokazano je da statini smanjuju kardiovaskularni (KV) pobol i smrtnost ne samo u sekundarnoj prevenciji kardiovaskularnih bolesti (KVB) već i u drugim terapijskim područjima. Studija JUPITER potvrdila je 2003. godine pozitivne učinke liječenja statinima i kod pacijenata u primarnoj prevenciji.[2] Na temelju tih rezultata, prevencija KVB uvedena je kao nova indikacija za statine. Pozitivni učinci uporabe statina u primarnoj prevenciji kasnije su potvrđeni također i u Cochrane pregledu tijekom 2013. godine kod 56 934 pacijenta, koji je dokazao smanjenje ukupne smrtnosti, ozbiljnih KV zbivanja i revaskularizacije.[3] Zbog neupitnih dokaza i preporuka u smjernicama za liječenje, primarna je prevencija iz godine u godinu bivala sve važnijom. Prema Europskim smjernicama za prevenciju KVB u kliničkoj praksi iz 2012. god, više od 50 % primijećenog smanjenja stope smrtnosti od KBS povezano je s djelovanjem na čimbenike rizika, a 40 % je posljedica poboljšanog liječenja.[4] Ipak, liječenje statinima još uvijek nije optimalno. Četiri od pet pacijenata s visokim rizikom i, prema rezultatima nedavno objavljene studije EUROASPIRE IV, više od 80 % liječenih pacijenata s KBS ne postižu ciljne vrijednosti lipida te stoga ne dobiju najveći mogući pozitivni učinak od tog preventivnog liječenja.[5,6]

Liječenje hiperlipidemije i prevencija KVB među najvažnijim su područjima moderne medicine. Stoga, farmaceutska tvrtka Krka nudi statine koji su opsežno testirani u primarnoj i sekundarnoj prevenciji. U ovome ćemo članku ukratko iznijeti glavne podatke i rezultate najvažnijih kliničkih studija s atorvastatinom (Atoris®) i rosuvastatinom (Roswera®), koji su prikazani u **tablicama 1**, **2** i **3**.

Rezultati ostalih kliničkih studija s atorvastatinom, što se učinkovitosti tiče, u skladu su s podatcima iz sljedećih studija provedenih s Krkinim atorvastatinom: INTER-ARS, ATOP, ATLANTICA, FARVATER i OSCAR koje su prikazane u **tablici 1** i **tablici 2**. Ta su istraživanja dokazala učinkovitost tog lijeka u pacijenata u primarnoj i sekundarnoj prevenciji, njegov učinak na opći lipidni profil, učinak na smanjenje LDL-kolesterola (LDL-C) u linearnoj ovisnosti o dozi i jasne prednosti titriranja doze lijeka na smanjenje vrijednosti LDL-C.[7] Također, studija INTER-ARS potvrdila je usporedivu učinkovitost originalnom atorvastatinu u smanjenju LDL-C, ukupnog kolesterola (UK) i triglicerida (TG).[7,8]

Atorvastatin je prošao opsežnu kliničku procjenu koja je dokazala da je primjeren za liječenje pacijenata s različitim lipidnim poremećajima i dodatnim komorbiditetima.[7] Primjerice, studija ATOP uključivala je uz pacijente u primarnoj prevenciji također i pacijente s KBS, dijabetesom, metaboličkim sindromom i okluzivnom bolesti nekoronarnih arterija. Rezultati su pokazali znatno smanjenje UK za 26 %, LDL-C za 36 % i TG za 9 %. Učinak atorvastatina na razinu lipida bio je sličan u svim analiziranim skupinama pacijenata.[7,9,10]

Svakodnevna klinička praksa pokazuje da se statini najčešće propisuju u najmanjoj dozi te da je izostanak titriranja doze lijeka jedan od glavnih razloga zbog kojeg pacijenti ne postižu ciljne razine lipida.[5,7] Prednosti titracije atorvastatina jasno su pokazane u studiji ATLANTICA, koja je uključivala pacijente koji su uglavnom zadovoljavali kriterije u sekundarnoj prevenciji. To je istraživanje usporedilo učinkovitost i sigurnost atorvastatina kod pacijenata koji su dobivali lijek u

safe and improved survival rates in coronary heart disease (CHD) patients.[1] However, statins have been proven to reduce cardiovascular (CV) morbidity and mortality not only in secondary prevention of cardiovascular disease (CVD) but also in other therapeutic areas. In 2003 the JUPITER study confirmed the benefits of statin treatment also in primary prevention patients.[2] Based on its results, prevention of CVD was introduced as a new indication to statin labels. The benefits of statin treatment in primary prevention were later on also confirmed by a Cochrane review from 2013 of 56,934 patients, which demonstrated reductions in all-cause mortality, major vascular events and revascularizations.[3] Due to indisputable evidence and recommendations in treatment guidelines, primary prevention has become more and more important through the years. According to the European guidelines on CVD prevention in clinical practice from 2012, more than 50% of the reduction seen in CHD mortality relates to changes in risk factors and 40% to improved treatment.[4] However, statin treatment is still not optimal. Four out of five high risk patients and, as stated in the recently published EUROASPIRE IV study, more than 80% of treated coronary patients do not achieve the lipid goals and, as a consequence, do not gain the maximum benefit from this preventive strategy.[5,6]

The management of hyperlipidemia and the prevention of CVD are among the most important fields of modern medicine. Due to this fact, Krka offers statins that have been extensively studied in primary and secondary prevention patients. In this review, we will briefly outline the main data and results of the most important clinical studies with atorvastatin (Atoris®) and rosuvastatin (Roswera®), which are presented in **Tables 1**, **2** and **3**.

Findings from other atorvastatin clinical studies are, in terms of efficacy, consistent with those reported in the following clinical studies conducted with Krka's atorvastatin: INTER-ARS, ATOP, ATLANTICA, FARVATER, and OSCAR (**Tables 1** and **2**). These studies have demonstrated its efficacy in a wide range of primary and secondary prevention patients, its effects on the overall lipid profile, its LDL-C cholesterol (LDL-C) lowering effects in a linear dose-related manner and clear advantages of dose up-titration on the reduction of LDL-C.[7] In addition, the INTER-ARS study has indicated a similar efficacy to that of the originator's atorvastatin in decreasing LDL cholesterol, total cholesterol (TC) and triglycerides (TG).[7,8]

Atorvastatin has undergone extensive clinical evaluation which proved its suitability for the treatment of patients with various lipid disorders and additional comorbidities.[7] For instance, also the ATOP study included patients with CHD, diabetes mellitus, metabolic syndrome and occlusive disease of non-coronary arteries and patients in primary prevention. The results showed significant reductions of TC by 26%, LDL-C by 36% and TG by 9%. The effect of atorvastatin on lipid levels was similar in all analysed groups of patients.[7,9,10]

Everyday clinical practice shows that statins are usually prescribed at the lowest dose and that not up-titrating the dose is one of the main reasons why patients are not achieving the lipid goals.[5,7] Advantages of up-titrating atorvastatin were clearly shown in the ATLANTICA study, which included patients mostly eligible for secondary prevention. The study

TABLE 1. Key outcome studies with Krka's atorvastatin – part 1.

STUDY	PRIMARY OBJECTIVE	PATIENT PROFILES	NO. OF PATIENTS	DURATION	DOSE	STUDY RESULTS		MAIN CONCLUSION
						EFFICACY	SAFETY AND TOLERABILITY	
INTER-ARS8	To evaluate the hypolipidemic action of Krka's ATV compared to the originator's ATV as the reference agent.	High-coronary-risk patients with hyperlipidemia: - 40–65 years old - absolute coronary risk > 9.5% in 10 years - without diagnosed CVD	117	16 weeks	Initial dose: 10 mg/d or 20 mg/d After 6 weeks of treatment, the dose was doubled if the patient did not achieve the target LDL-C level.	LDL-C: - Krka's ATV: –37.8% - Originator's ATV: –38.4% No significant difference between treatment groups in LDL-C reduction was found. TC: - Krka's ATV: –30.3% - Originator's ATV: –29.2%	The safety of the study medicines was comparable. No increase of CK level > 10 times ULN was observed. No treatment discontinuations due to adverse reactions.	Fully comparable efficacy and safety of Krka's ATV and the originator's ATV.
ATOP9	To establish the efficacy and safety of **ATV** in a wide population of patients.	Patients with primary hypercholesterolemia and combined hyperlipidemia (+18 years old): - at high CV risk and without established CVD - metabolic syndrome - CHD - occlusive disease of non-coronary arteries and - diabetes mellitus	334	12 weeks	Initial dose: 10 mg/d or 20 mg/d After 6 weeks of treatment, the dose was doubled if the patient did not achieve the target cholesterol level.	LDL-C: –36% TC: –26% Among different groups of patients ATV had a similar effect on lipid parameters.	The treatment with ATV was well tolerated. No cases of ALT activity elevation > 3 times ULN and CK > 10 times ULN were reported. 1 case of AST activity elevation > 3 times ULN was reported. 3.3% of the patients discontinued the treatment due to adverse reactions.	ATV has been proven to be effective and safe in a wide population of patients.
ATLANTICA11	To demonstrate the efficacy and safety of **ATV** in long-term treatment.	Patients with dyslipidemia, 18–75 years old, with established CHD or with: - diagnosed atherosclerosis of the arteries - abdominal aortic aneurysm - type 2 diabetes mellitus - metabolic syndrome - transient ischemic attack - high CV risk	655	24 weeks	Group A: 10 mg/d Group B: 10–80 mg/d (the mean dose at the end of the study was 28.6 mg) Group C: conventional treatment	LDL-C: - Group A: –31.1% - Group B: –38.6% - Group C: –24.8% TC: - Group A: –23.1% - Group B: –28.6% - Group C: –18.2%	The treatment with ATV was well tolerated. No significant difference in the frequency of adverse events between groups in any phase of the study. The frequency of significant adverse reactions was 1.8% in group A and 0.5% in group B.	The study confirmed the effect of ATV on LDL-C and its dose dependence.

Abbreviations: ATV Đ atorvastatin, CVD Đ cardiovascular disease, CV Đ cardiovascular, CHD Đ coronary heart disease, LDL-C Đ low-density lipoprotein cholesterol, TC Đ total cholesterol, ALT Đ alanine transaminase, AST Đ aspartate transaminase, CK Đ creatine kinase, ULN Đ upper limit of normal

TABLE 2. Key outcome studies with Krka's atorvastatin – part 2.

STUDY	PRIMARY OBJECTIVE	PATIENT PROFILES	NO. OF PATIENTS	DURATION	DOSE	STUDY RESULTS		MAIN CONCLUSION
						EFFICACY	SAFETY AND TOLERABILITY	
ACS12	To investigate the role of **ATV** in the treatment of patients with ACS.	ACS patients with hyperlipidemia, 52–70 years old, with or without ST segment elevation.	98	4 weeks	40 mg/d	LDL-C: –54.4% TC: –43.5% Lowering of the functional class of effort angina (by 1 or more) in 53.6% of the patients. 29.4% increase of the microcirculation index. Reduction of total incidence of death, recurrent myocardial infarction, and early post-infarction angina by 8.2%. Reduction of overall incidence of ischemic events by 23.8% and mean duration of ischemic stroke by 29.4%.	The treatment with ATV was well tolerated. Clinically significant adverse events were not reported.	**ATV** at a dose of 40 mg/day is an effective medicine for the prevention of severe ischemic outcomes (CV death, stroke, myocardial infarction) and the progression of heart failure.
FARVATER16	To evaluate the effects of **ATV** on lipids, C-reactive protein, fibrinogen levels and vascular wall structure and function.	Patients with CHD and primary hyperlipidemia, 35–70 years old.	50	24 weeks	One group received 10 mg/d and the other 20 mg/d	LDL-C: - 10 mg/d: –34.9% - 20 mg/d: –43.9% TC: - 10 mg/d: –25.4% - 20 mg/d: –27.0% Endothelium-dependent vasodilatation: - 10 mg/d: +40.2% - 20 mg/d: +51.3% Common carotid artery distensibility: - 10 mg/d: +45.3% - 20 mg/d: +43.7% Vascular wall stiffness: - 10 mg/d: –23.3% - 20 mg/d: –25.7%	The treatment with ATV was well tolerated. No cases of AST or ALT activity elevation above > 3 times ULN and CK > 10 times ULN. Two adverse reactions (allergic reaction, elevation of CK activity) linked to ATV therapy were registered.	ATV is effective and **ATV** tolerated with proven pleiotropic effects.
OSCAR22	To identify high-risk patients and establish the efficacy of **ATV** and SIM in real-life clinical practice settings.	Patients with established CVD or at high CV risk, 35–75 years old.	7098	8 weeks	10 mg/d of ATV or 20 mg/d of SIM	LDL-C: - **ATV**: –26.7% - **SIM**: –25,0% TC: - **ATV**: –22.7% - **SIM**: –22.7% Reduction of total CV risk by 33%	The treatment was well tolerated; adverse reactions were documented in 2.7% of the patients.	**ATV** and SIM have been proven to be effective and safe in real-life clinical practice settings.

Abbreviations: ATV Ð atorvastatin, SIM Ð simvastatin, CVD Ð cardiovascular disease, CV Ð cardiovascular, CHD Ð coronary heart disease, LDL-C Ð low-density lipoprotein cholesterol, TC Ð total cholesterol, HDL-C Ð high-density lipoprotein cholesterol, TG Ð triglyceride, ALT Ð alanine transaminase, AST Ð aspartate transaminase, CK Ð creatine kinase, ULN Ð upper limit of normal

TABLE 3. Key outcome studies with Krka's rosuvastatin.

STUDY	PRIMARY OBJECTIVE	PATIENT PROFILES	NO. OF PATIENTS	DURATION	DOSE	STUDY RESULTS		MAIN CONCLUSION
						EFFICACY	SAFETY AND TOLERABILITY	
Non-interventional follow up of efficacy and safety of rosuvastatin (Sorvasta®) in patients with hyperlipidemia18	To evaluate the efficacy and safety of **RSV**, including the additional strengths 15 mg and 30 mg in normal clinical practice.	Patients with primary hypercholesterolemia or mixed hyperlipidemia (type IIb) or homozygous familial hypercholesterolemia.	6,366	12 weeks	Roswera in the whole range of strengths (5 mg – 40 mg) The dose of Roswera was individualised according to the lipid levels and goal of the therapy.	LDL-C: –37.5% TC: –28.7% HDL-C: +8.5% TG: –17.2% Established linear relationship between the dose and the reduction of LDL-C.	Adverse reactions were documented in 2.6% of the patients.	Study confirmed efficacy and good tolerability of RSV, including the 15 mg and 30 mg dose. Additionally, linear relationship between the dose and the reduction of LDL-C was established.
Post-authorisation study of efficacy and safety of titration of Sorvasta dose in the hyperlipidemia treatment19	To evaluate the efficacy and safety of **RSV**, including the additional strengths 15 mg and 30 mg in normal clinical practice.	Patients with primary hypercholesterolemia or mixed hyperlipidemia (type IIb) or homozygous familial hypercholesterolemia.	512	12 weeks	Roswera in the whole range of strengths (5 mg – 40 mg). The dose of Roswera was individualised according to the lipid levels and goal of the therapy.	LDL-C: –30.6% TC: –21.2% HDL-C: +6.2% TG: –21.0%	One adverse event was reported in one patient.	Study confirmed efficacy and good tolerability of **RSV**, including the 15 mg and 30 mg dose.
ROSUPATH*[20,21]	To establish the efficacy and safety of **RSV** dose titration in patients with hyperlipidemia and to place the additional strengths 15 mg and 30 mg into clinical practice.	Patients with high absolute risk for CVD in primary and secondary prevention.	329	12 weeks	Two titration schemes: Standard: 10 mg – 20 mg – 40 mg Alternative: 15 mg – 30 mg – 40 mg If the target LDL-C level was not achieved at the visit, the dose was titrated according to one of the schemes.	LDL-C: Standard: –33.5% Alternative: –34.6% TC: Standard: –45.1% Alternative: –48.1% HDL-C: Standard: –15.0% Alternative: –22.3% TG: Standard: +4.6% Alternative: +6.8% Significant difference in the reduction of LDL-C after first 4 weeks of the treatment between 10 mg and 15 mg (–37% vs. –43.7%, P < 0.005).	The total incidence of adverse reaction was 5.5% by the end of the study. No significant difference in the occurrence of adverse reactions was observed between standard and alternative titration arm. No patients with an increase of ALT > 3x ULN. Only one patient with an increase of AST > 3x ULN, which was resolved by the end of the study.	The study confirmed the efficacy and safety of **RSV** across the whole range of doses, including the additional doses of 15 mg and 30 mg.

* Interim results

Abbreviations: RSV Đ rosuvastatin, CVD Đ cardiovascular disease, LDL-C Đ low-density lipoprotein cholesterol, TC Đ total cholesterol, HDL-C Đ high-density lipoprotein cholesterol, TG Đ triglyceride, ALT Đ alanine transaminase, AST Đ aspartate transaminase, ULN Đ upper limit of normal

dozi od 10 mg i onih koji su dobivali atorvastatin u dozama od 10 do 80 mg te onih na konvencionalnom liječenju. Najznačajnije smanjenje razina LDL-C, UK, TG i povišenje HDL-kolesterola registrirani su kod pacijenata na višim dozama atorvastatina. To navodi povećanje doze statina može dovesti do većega smanjenja vrijednosti lipida i pomaže većem broju pacijenata da postignu ciljne razine lipida.[7,11]

Još je jedna studija istražila učinak atorvastatina u sekundarnoj prevenciji kod 98 pacijenata s akutnim koronarnim sindromom sa ili bez elevacije ST-segmenta i hiperlipidemijom. Atorvastatin u dozama od 40 mg/dan pokazao se učinkovitim lijekom za prevenciju ozbljinih ishemijskih ishoda u tih pacijenata. Tijekom razdoblja od jednog mjeseca u kojemu je provedeno istraživanje, atorvastatin je smanjio ukupnu učestalost ishemijskih zbivanja za 23,8 % i prosječno trajanje ishemijskog moždanog udara za 29,4 %. Nadalje, smanjio je i ukupnu smrtnost, ponovni infarkt miokarda te rane postinfarktne angine za 8,2 %.[12]

Uz hipolipemijski učinak, statini također imaju važnu ulogu u poboljšanju endotelne funkcije, smanjenja upalne aktivnosti i remodeliranja vaskularne stijenke, što može pridonijeti prevenciji KV zbivanja.[13-15] Ti se učinci nazivaju pleiotropnim učincima te su bili predmet studije FARVATER. Nakon 24 tjedna, liječenje atorvastatinom povećalo je vazodilataciju ovisnu o endotelu za 40 – 51 % i rastezljivost zajedničke karotidne arterije za 43 – 45 % te smanjilo krutost vaskularne stijenke za 23 – 26 %.[16] Analiza podskupine u studiji ATLANTICA također je pokazala da se takvi učinci pojavljuju pri većim dozama atorvastatina. Tijekom te studije broj pacijenata s izraženom disfunkcijom endotela značajno se smanjio za 26 % u skupini liječenoj višim dozama atorvastatina.[7,11]

U 2014. godini prikupili smo prve kliničke podatke o Krkinu rosuvastatinu, trenutačno najistraživanijem generičkom rosuvastatinu.[17] Već imamo rezultate dviju postautorizacijskih studija o učinkovitosti i sigurnosti, provedenih kod 6878 pacijenata. Obje studije dokazuju učinkovitost i sigurnost titriranja doze rosuvastatina kod liječenja hiperlipidemije, uključujući i primjenu doza od 15 i 30 mg. Rezultati dviju studija bili su slični: UK, LDL-C i TG bili su statistički značano niži, a vrijednost HDL kolesterola statistički značajno viša na kraju obiju studija (**tablica 3**).[18,19]

Studija ROSU-PATH još je jedna klinička studija koja je pokazala učinkovitost i sigurnost rosuvastatina u punom rasponu snaga doza, uključujući 15 mg i 30 mg (**tablica 3**). Ta je istraživanje još uvijek u tijeku, pa ovdje iznosimo prve privremene rezultate koji uključuju 329 pacijenata iz pet zemalja. Uspoređuju se dvije različite titracijske sheme – standardna (10 mg – 20 mg – 40 mg) i alternativna titracijska shema, koja uključuje dvije dodatne jačine doze (15 mg – 30 mg – 40 mg). Rezultati pokazuju da rosuvastatin poboljšava cjelokupni lipidni profil i smanjuje LDL-C sukladno doziranju. Nadalje, spomenuta studija pokazuje da pacijenti koji počnu liječenje s 15 mg rosuvastatina brže dostižu ciljne vrijednosti. Nakon prva četiri tjedna liječenja njihove su razine LDL-C bile značajno niže u usporedbi s pacijentima koji su dobivali 10 mg rosuvastatina (**slika 1**). Moguće je da su veća smanjenja na početku liječenja dovela do većega broja pacijenata u alternativnoj titracijskoj shemi koji su postigli ciljne razine lipida. Takvim je pacijenti-

compared the efficacy and safety of atorvastatin between patients receiving the 10 mg strength and those receiving atorvastatin in the strengths of 10 to 80 mg and those on conventional treatment. The most significant reductions of LDL-C, TC, TG and elevation of HDL cholesterol were seen in patients receiving more intensive atorvastatin treatment. This suggests that increasing the dose of statin can provide a greater reduction of blood lipids and help more patients to reach target lipid values.[7,11]

Another study that evaluated the effects of atorvastatin in secondary prevention was a study that included 98 patients with acute coronary syndrome with or without ST-segment elevation and hyperlipidemia. Atorvastatin in doses of 40 mg once daily proved to be an effective medicine for the prevention of severe ischemic outcomes in these patients. During the one-month study period atorvastatin reduced the overall incidence of ischemic events by 23.8% and the mean duration of ischemic stroke by 29.4%. Furthermore, it reduced the total incidence of death, recurrent myocardial infarction and early post-infarction angina by 8.2%.[12]

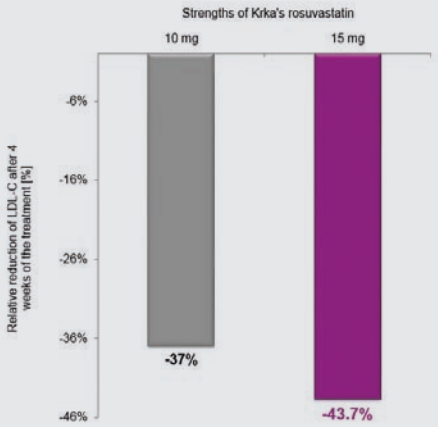
Apart from hypolipidemic effects, statins also play an important role in the improvement of the endothelial function, decrease of inflammatory activity and remodelling of the vascular wall, which can contribute to the prevention of cardiovascular events.[13-15] These effects are known as pleiotropic effects and were also evaluated in the FARVATER study. After 24 weeks, atorvastatin therapy increased endothelium-dependent vasodilatation by 40-51% and common carotid artery distensibility by 43-45% and reduced vascular wall stiffness by 23-26%.[16] Additionally, also a subgroup analysis of the ATLANTICA study has shown that these effects occur at higher doses of atorvastatin. During the study, the number of patients with pronounced endothelium dysfunction significantly decreased by 26% in the group treated with higher doses of atorvastatin.[7,11]

In 2014 we gathered the first clinical evidence for Krka's rosuvastatin, currently the most studied generic rosuvastatin.[17] We already have the results from two post-authorisation efficacy and safety studies, which included 6,878 patients. Both studies demonstrated the efficacy and safety of up-titrating the rosuvastatin dose, including the use of the 15 and 30 mg doses, in hyperlipidemia treatment. These two strengths were the first in the world offered by Krka with the intention to offer more possibilities in the treatment of hyperlipidemia. The results were similar between the two studies: TC, LDL-C and TG were statistically significantly reduced and HDL-C was statistically significantly increased at the end of each study (**Table 3**).[18,19]

Another clinical study that has demonstrated the efficacy and safety of rosuvastatin across the whole range of strengths, including 15 mg and 30 mg, is the ROSU-PATH study (**Table 3**). This is an on-going study, so we are here presenting the first interim results that include 329 patients from 5 countries. Two different titration schemes are compared – the standard (10 mg – 20 mg – 40 mg) and the alternative titration scheme, including two additional strengths (15 mg – 30 mg – 40 mg). The results have shown that rosuvastatin improves the whole lipid profile and reduces LDL-C in a dose dependent manner.

ma u prosjeku trebalo manje titracija do najviše doze, što znači da su brže postigli ciljne razne te stoga dobili veći pozitivni učinak od liječenja.[20,21]

FIGURE 1.



Comparison in relative reduction of LDL-cholesterol after first 4 weeks of the treatment between the 10 mg and 15 mg of rosuvastatin.

Sigurnost je važan dio kliničkih studija s Krkinim statinima. Dokazano je da se oba istražena statina dobro toleriraju jer su neželjene reakcije primijećene samo u vrlo malom postotku pacijenata. Sigurnost je potvrđena na širokom rasponu pacijenata i u punom rasponu doza lijeka. Nadalje, dokazano je da je sigurnosni profil atorvastatina usporediv s izvornim atorvastatinom, bez ikakvih razlika u sigurnosnim varijablama među skupinama. Podatci o sigurnosti rosuvastatina procijenjeni na temelju kliničke studije ROSU-PATH ne pokazuju nikakvu značajnu razliku u neželjenim reakcijama između skupina sa standardnom i alternativnom titracijom lijeka.[7-9,11,12,16,18-22]

Zaključak

Farmaceutska tvrtka Krka se uvijek trudi biti korak bliže potrebama liječnika i pacijenata. Naši se proizvodi redovito testiraju u kliničkoj praksi u sklopu različitih kliničkih istraživanja. Proveli smo više od 120 kliničkih studija kod više od 270 000 pacijenata u 27 zemalja, uključujući kliničke studije sa statinima. Te su studije pokazale učinke liječenja statinima utemeljene na dokazima te su važan doprinos boljem liječenju hiperlipidemije u različitim skupinama pacijenata te čine osnovu povjerenja u Krkine proizvode.

Furthermore, the study has demonstrated that patients who start treatment with 15 mg of rosuvastatin are on a faster way to their goal. After the first four weeks of the treatment, their LDL-C was significantly more reduced when compared to patients receiving rosuvastatin 10 mg (**Figure 1**). Greater reductions at the beginning of the treatment possibly resulted in more patients in the alternative titration scheme reaching the target lipid levels. These patients needed, on average, a lower number of titrations to the highest dose, meaning they reached target levels faster and thus received greater benefits from the treatment.[20,21]

An important aspect of clinical studies with Krka's statins is safety. It was proven that both studied statins are well tolerated, since adverse reactions were observed only in a few percentages of the patients. Their safety was confirmed in a wide range of patients and across the whole range of strengths. Furthermore, it was proven that the safety profile of atorvastatin is comparable to that of the originator's atorvastatin, while no differences in any of the safety parameters between the groups were found. In addition, the safety data on rosuvastatin evaluated in the ROSU-PATH clinical study showed no significant difference in the occurrence of adverse reactions between the standard and alternative titration arm.[7-9,11,12,16,18-22]

Conclusion

Krka is always trying to go one step closer to the physicians' and patients' needs. Our products are regularly tested in clinical practice by different clinical studies. We have carried out more than 120 different clinical studies in more than 270,000 patients in 27 countries, including clinical studies with statins. These latter studies have demonstrated evidence-based benefits of statin therapy and represent an important contribution to a better management of hyperlipidemia in different groups of patients, as well the foundation of trust in Krka's products.

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