Neintervencijsko ispitivanje djelotvornosti i sigurnosti liječenja rosuvastatinom i uvođenja dodatnih jačina lijeka u kliničku praksu u liječenju bolesnika s hiperlipidemijom

Non-Interventional Study of Efficacy and Safety of Rosuvastatin Therapy and Introduction of Additional Doses to Clinical Practice in Patients with Hyperlipidemia

Borut Jug^{1*},
Breda Barbič-Žagar²,
Mateja Grošel²,
Darja Milovanović Jarh²,
Tjaša Lipušček²

¹Univerzitetni klinični center Ljubljana, Ljubljana, Slovenija

²Krka, d. d., Novo mesto, Slovenija

¹University Medical Centre Ljubljana, Ljubljana, Slovenia

²Krka, d. d., Novo mesto, Slovenia

SAŽETAK: Kardiovaskularne (KV) bolesti i dalje su vodeći uzrok morbiditeta i mortaliteta u svijetu i u Sloveniji. Prema preporukama *Europskih smjernica za prevenciju kardiovaskularnih bolesti u kliničkoj praksi*, smanjenje razine LDL kolesterola primjenom statina ključno je za prevenciju KV događaja. Brojna klinička ispitivanja i godine iskustva dokazuju djelotvornost terapije statinima. Unatoč tomu, oni se još uvijek premalo uporabljaju u kliničkoj praksi ili se primjenjuju u neadekvatnim dozama. U tromjesečnome neintervencijskom ispitivanju FROZEN praćena je klinička djelotvornost svih doza Krkina rosuvastatina (Roswera®). Rezultati su pokazali da su bolesnici s visokim ili vrlo visokim rizikom od KV događaja nedovoljno liječeni te su imali manje izgleda za postizanje ciljnih razina LDL kolesterola nego oni s umjerenim rizikom. Liječenje je ocijenjeno sigurnim i učinkovitim tijekom razdoblja praćenja u bolesnika s umjerenim, visokim i vrlo visokim rizikom od KV-a.

SUMMARY: Cardiovascular (CV) diseases remain the leading cause of morbidity and mortality in the world and in Slovenia. According to the recommendations of the *European Guidelines on Cardiovascular Disease Prevention in Clinical Practice*, reducing LDL-cholesterol levels, especially with statins, is essential for prevention of CV events. A number of clinical studies and years of experience demonstrate the efficacy of statin therapy. Nevertheless, they are still rarely used in clinical practice or are used at insufficient doses. The clinical efficacy of all doses of Krka's rosuvastatin (Roswera®) was monitored in FROZEN, a three-month non-interventional study. The results showed that patients at high or very high risk of a cardiovascular event were undertreated and were less likely to reach target LDL-C levels than moderate-risk patients. Treatment was evaluated as safe and effective during the follow-up period in patients at a moderate, high, and very high CV risk.

KLJUČNE RIJEČI: rosuvastatin, hiperlipidemija, LDL kolesterol, djelotvornost, sigurnost.

KEYWORDS: rosuvastatin, hyperlipidemia, low-density lipoprotein cholesterol, efficacy, safety.

CITATION: *Cardiol Croat.* 2020;15(3-4):75-9. | <https://doi.org/10.15836/ccar2020.75>

***ADDRESS FOR CORRESPONDENCE:** Borut Jug, Interna klinika, Univerzitetni klinični center Ljubljana, Zaloška 7, 1000 Ljubljana, Slovenia. / E-mail: borut.jug@kclj.si

ORCID: Borut Jug, <https://orcid.org/0000-0001-6015-2127> • Breda Barbič-Žagar, <https://orcid.org/0000-0002-1173-7361> • Mateja Grošel, <https://orcid.org/0000-0002-4035-7691> • Darja Milovanović Jarh, <https://orcid.org/0000-0001-5085-9823> • Tjaša Lipušček, <https://orcid.org/0000-0002-4522-4409>

TO CITE THIS ARTICLE: Jug B, Barbič-Žagar B, Grošel M, Milovanović-Jarh D, Lipušček T. Non-Interventional Study of Efficacy and Safety of Rosuvastatin Therapy and Introduction of Additional Doses to Clinical Practice in Patients with Hyperlipidemia. *Cardiol Croat.* 2020;15(3-4):75-9. <https://doi.org/10.15836/ccar2020.75>

TO LINK TO THIS ARTICLE: <https://doi.org/10.15836/ccar2020.75>

RECEIVED:

January 29, 2020

UPDATED:

February 20, 2020

ACCEPTED:

February 28, 2020

Uvod

Kardiovaskularne (KV) bolesti i dalje su vodeći uzrok morbiditeta i mortaliteta u svijetu i u Sloveniji.¹ Najčešće su uzrokovane aterosklerozom. Nekoliko čimbenika ubrzava ovaj proces, a među najvažnijima je hiperlipidemija.² Prema najnovijim *Europskim smjernicama za prevenciju kardiovaskularnih bolesti u kliničkoj praksi*, smanjenje razine LDL kolesterola primjenom statina ključno je za prevenciju KV događaja. Rizik od

Introduction

Cardiovascular (CV) diseases remain the leading cause of morbidity and mortality in the world and in Slovenia.¹ They are most often caused by atherosclerosis. Several factors, of which hyperlipidemia is an important one, accelerate the process.² According to the latest *European Guidelines on Cardiovascular Disease prevention in Clinical Practice*, reducing LDL-cholesterol (LDL-C), in particular by statins, is essential for

većih KV događaja dodatno se smanjuje u slučaju znatnijeg smanjenja razina LDL kolesterola.³⁻⁵

Iako je liječenje statinima djelotvorno i dostupno u kliničkoj praksi godinama, incidencija KV događaja i dalje ostaje visoka.⁶⁻⁸ Nažalost, adhezencija za statine daleko je od optimalne, pa čak i do 80 % bolesnika s visokim rizikom od KV-a ne uspijeva postići preporučene razine LDL kolesterola.² Rezultati istraživanja utvrdili su da se adhezencija smanjuje trajanjem liječenja, pa tako čak 77 % bolesnika na terapiji statinima prekida liječenje nakon dvije godine.⁴ Osim toga, podatci iz kliničkih ispitivanja upućuju na to da se terapija statinima često propisuje u niskoj, suboptimalnoj dozi, koja se vrlo rijetko titrira na više do preporučene doze. Stoga su mnogi bolesnici još uvijek pod rizikom od progresije KV bolesti unatoč liječenju.^{4,9}

U članku se prikazuju rezultati neintervencijskog ispitivanja FROZEN kojemu je svrha bila procijeniti djelotvornost i sigurnost terapije Krkinim rosuvastatinom (Roswera®; na tržištu različitih zemalja nalazi se pod različitim nazivom lijeka) u bolesnika s hiperlipidemijom.¹⁰

Bolesnici i metode

Ispitivanje FROZEN provedeno je u razdoblju od listopada 2016. do kraja studenoga 2017. godine u ordinacijama obiteljske medicine u Sloveniji. Ukupno je bilo uključeno 1627 bolesnika s hiperlipidemijom te prisutnim umjerenim, visokim ili vrlo visokim rizikom od nastupa KV događaja. Razdoblje praćenja trajalo je tri mjeseca. Bila su predviđena dva posjeta. Na prvom posjetu, tijekom kojeg je bolesnik uključen u ispitivanje, određena je početna doza rosuvastatina s obzirom na početnu vrijednost lipida i kategoriju KV rizika. Pri drugom su posjetu ispitane razine lipida u krvi, nuspojave i postizanje ciljnih vrijednosti LDL kolesterola.

Uspjeh liječenja rosuvastatinom procijenjen je s obzirom na učestalost bolesnika koji su postigli ciljne razine LDL kolesterola, koje su određene prema smjernicama ESC-a/EAS-a iz 2011. koje su bile na snazi u vrijeme istraživanja: (i) 2,99 mmol/L ili manje za bolesnike s umjerenim rizikom; (ii) 2,49 mmol/L ili manje za bolesnike s visokim rizikom, te (iii) 1,79 mmol/L ili manje i/ili smanjenje za ≥ 50 % za bolesnike s vrlo visokim rizikom.

Rezultati

Prosječna dob uključenih bolesnika bila je $62,7 \pm 10,2$ godina, 50 % je bilo muškaraca i 50 % žene. Ispitivanje je uključivalo 407 (25 %) bolesnika s vrlo visokim rizikom, 780 (48 %) s visokim rizikom i 420 (26 %) s umjerenim rizikom. Za 20 bolesnika (1 %) nisu bili raspoloživi podatci o kategorijama KV rizika. Prije uključivanja u ispitivanje 24 % bolesnika nije bilo prethodno liječeno zbog hiperlipidemije.

Roswera® je bila propisana u šest različitih doza (5 mg, 10 mg, 15 mg, 20 mg, 30 mg i 40 mg). Na početku je ukupna srednja doza rosuvastatina bila $17,8 \pm 9,1$ mg. Nakon tri mjeseca ukupno su 1543 bolesnika (94,8 %) nastavila je liječenje, 41 (2,5 %) ga je prekinuo, a za 43 bolesnika (2,6 %) nisu bili raspoloživi podatci. Ukupna srednja doza primijenjena u terapiji održavanja bila je $19,0 \pm 9,6$ mg.

Rezultati ispitivanja utvrdili su statistički značajno ($p < 0,0001$) smanjenje vrijednosti ukupnog kolesterola (UK), LDL kolesterola i triglicerida (TG). Nakon tri mjeseca, srednji apsolutni UK smanjen je za $2,1 \pm 1,2$ mmol/L, a relativni za $29,3 \pm 14,7$ %; srednji apsolutni LDL kolesterol za

prevention of cardiovascular events. The risk of major cardiovascular events decreases further if the reduction of LDL-C is more significant.³⁻⁵

The efficacy of statin therapy is clearly evident and it has been employed in clinical practice for years, but even so the incidence of cardiovascular events remains high.⁶⁻⁸ Unfortunately, adherence has been far from optimal with 80% of high-risk patients failing to achieve the recommended LDL-C levels.² Adherence decreases during the course of treatment, and according to reports, 77% of patients on statin therapy discontinue the treatment after two years.⁴ Data from clinical trials show that physicians most often prescribe statin therapy at the low dose and very rarely titrate it up to the recommended dose. This is why patients are still at risk of cardiovascular disease development and progression despite the treatment.^{4,9}

Herein we describe the results of FROZEN, a non-interventional study aimed to assess the efficacy and safety of Krka's rosuvastatin (Roswera®; other brand names are used for the medication in different countries) in patients with hyperlipidaemia.¹⁰

Patients and Methods

The study was conducted from October, 2016 to the end of November, 2017 in family medicine clinics in Slovenia. A total of 1,627 patients with hyperlipidemia at moderate, high, or very high risk of a CV event were included. The monitoring period lasted for three months and included two scheduled visits. At visit 1, when a patient was enrolled in the study, the initial dose of rosuvastatin was determined in consideration of the patient's baseline lipid levels and CV risk category. At visit 2, blood lipid levels, adverse reactions, and achievement of target LDL-C levels were assessed.

The successfulness of rosuvastatin therapy was assessed based on the frequency of patients who achieved target LDL-C levels, which were determined according to the ESC/EAS 2011 Guidelines valid at the time: (i) 2.99 mmol/L or lower for moderate-risk patients; (ii) 2.49 mmol/L or lower for high-risk patients; and (iii) 1.79 mmol/L or lower and/or ≥ 50 % reduction for very high-risk patients.

Results

Average patient age was 62.7 ± 10.2 years, and 50% were men and 50% women. The study included 407 (25%) very high-risk, 780 (48%) high-risk, and 420 (26%) moderate-risk patients. No data on risk categories were available for 20 patients (1%). Before inclusion in the study, 24% of patients had not been treated for hyperlipidemia.

Roswera® was prescribed at six different doses (5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg). At initiation, the overall mean dose of rosuvastatin was 17.8 ± 9.1 mg. After three months, 1,543 patients (94.8%) continued therapy, 41 (2.5%) discontinued it, and no data were available for 43 (2.6%) patients. The overall mean dose used in maintenance therapy was 19.0 ± 9.6 mg.

During the study, total cholesterol (TC), LDL-C, and triglycerides (TG) showed statistically significant reductions ($p < 0.0001$). After three months, the mean absolute TC was reduced by 2.1 ± 1.2 mmol/L and relative TC was reduced by 29.3 ± 14.7 %; the mean absolute LDL-C was reduced by 1.8 ± 1.1 mmol/L and relative LDL-C was reduced by 37.2 ± 22.7 %; the

1,8 ± 1,1 mmol/L, a relativni za 37,2 ± 22,7%; srednji apsolutni TG za 0,6 ± 1,4 mmol/L, a relativni za 18,7 ± 34,7 %. Vrijednost HDL kolesterola nije se znatno mijenjala trajanjem liječenja (**slika 1**).

mean absolute TG was reduced by 0.6±1.4 mmol/L and relative TG was reduced by 18.7±34.7%. There was no statistically significant change in HDL-cholesterol (**Figure 1**).

Vrijednost LDL kolesterola bila je statistički značajno smanjena ($p < 0,0001$) neovisno o kategoriji KV rizika. U bolesnika s umjerenim rizikom LDL je smanjen za 1,7 ± 1,1 mmol/L ili 35,1 ± 22,7%, u bolesnika s visokim rizikom za 1,9 ± 1,1 mmol/L ili 37,8 ± 22,5%, a u bolesnika s vrlo visokim rizikom za 1,7 ± 1,1 mmol/L ili 38,1 ± 23,4%. (**tablica 1**). U 685 bolesnika (42,1 %) terapija lijekom Roswera® ocijenjena je vrlo uspješnom, odnosno postignuta je ciljna razina LDL kolesterola (**tablica 2**).

During the study, LDL-C was statistically significantly reduced ($p < 0.0001$) regardless of the cardiovascular risk category. In moderate-risk patients it was reduced by 1.7±1.1 mmol/L or 35.1±22.7%, in high-risk patients by 1.9±1.1 mmol/L or 37.8±22.5%, and in very high-risk patients by 1.7±1.1 mmol/L or 38.1±23.4% (**Table 1**). In 685 patients (42.1%) Roswera® therapy was assessed as very successful (target LDL-C levels were achieved) (**Table 2**).

TABLE 1. LDL-C reduction with respect to a cardiovascular risk category. LDL-C – low-density lipoprotein cholesterol.

	Visit 1	Visit 2	Absolute difference	Relative difference	P
LDL-C	mmol/l	mmol/l	mmol/l	%	
Moderate risk	4.6±0.1	2.9±0.8	-1.7±1.1	-35.1±22.7	$p < 0.0001$
High risk	4.6±1.1	2.8±0.9	-1.9±1.1	-37.8±22.5	$p < 0.0001$
Very high risk	4.1±1.2	2.4±0.8	-1.7±1.1	-38.1±23.4	$p < 0.0001$

TABLE 2. Successfulness of therapy with respect to cardiovascular risk categories.

	Moderate risk	High risk	Very high risk
Very successful	238 (56.7%)	295 (37.8%)	152 (37.4%)
Successful	130 (30.9%)	371 (47.5%)	206 (50.6%)
Unsuccessful	29 (6.9%)	54 (6.9%)	27 (6.6%)
No data	23 (5.5%)	61 (7.8%)	22 (5.4%)

Bolesnici su dobro podnosili lijek te u 1481 bolesnika (91,0 %) nisu zabilježene nuspojave. Devedeset četiri bolesnika (5,8 %) prijavila su nuspojave, a za 52 bolesnika (3,2 %) podatci nisu bili dostupni. U 86 bolesnika (5,3 %) nuspojave na lijek bile su uzročno povezane s terapijom, a u preostalih 8 bolesnika (0,5%) nije zabilježena uzročna povezanost. Najčešće zabilježena nuspojava bila je mialgija, koja je zabilježena u 24 bolesnika (1,5 %). Ostale su nuspojave bile manje učestale (<1 %). Rezultati dokazuju sigurnost terapije rosuvastatinom.

Rasprava

Hiperlipidemija je kronična KV bolest koja zahtijeva pažljivu kontrolu i liječenje. Važno je da se tijekom liječenja postignu i dugoročno održavaju ciljane razine LDL kolesterola. To je jedini način za pružanje optimalne KV zaštite.

Ovo neintervencijsko ispitivanje uključivalo je ambulantne bolesnike iz Slovenije s hiperlipidemijom, od kojih je 76 % već bilo na hipolipemicima, a samo je 24 % oboljelih prvi put započelo terapiju statinima. Nakon tromjesečnog liječenja Krkinim rosuvastatinom dokazano je statistički značajno ($p < 0,0001$) smanjenje vrijednosti UK-a, LDL kolesterola i TG-a, čime je dokazana djelotvornost liječenja. Nakon tri mjeseca 1543 bolesnika (94,8 %) nastavila su primati lijek Roswera®.

Rosuvastatin je bio učinkovit kod svih skupina bolesnika jer je za većinu njih liječenje ocijenjeno vrlo uspješnim ili uspješnim. Ako se ishodi analiziraju prema kategoriji KV rizika, može se zaključiti da je liječenje bolesnika s umjerenim rizikom bilo vrlo uspješno za više bolesnika (56,7 %) nego za one s visokim i vrlo visokim rizikom (37,8 %, odnosno 37,4 %). To znači da bolesnici s umjerenim rizikom postižu ciljane razine LDL kolesterola lakše nego oni s visokim ili vrlo visokim rizikom. I mnoga druga istraživanja pokazuju da je postizanje ciljnih razina značajan izazov za kliničku praksu. U nekim ispitivanjima 80 % bolesnika s visokim rizikom nije uspjelo postići ciljane razine. To pokazuje da su unatoč terapiji bolesnici još uvijek pod rizikom od progresije KV bolesti.^{8,9}

Podatci iz nekih kliničkih ispitivanja upućuju na sklonost liječnika prema propisivanju doza koje nisu dovoljne, a samo ih u rijetkim slučajevima titriraju na više do preporučenih doza, što je pokazalo i ovo ispitivanje.⁹

Liječenje rosuvastatinom sigurno je i dobro podnošljivo. Tijekom tri mjeseca liječenja u 91 % bolesnika nisu zabilježene nuspojave. Nuspojave povezane s ovim lijekom zabilježene su tek u 5,3 % bolesnika. Rezultati sigurnosti bili su usporedivi s rezultatima mnogih velikih kliničkih ispitivanja.⁹

Zaključci

Primaran dugoročni cilj liječenja hiperlipidemije bio je spriječiti KV događaje. Zbog toga je vrlo važno da bolesnici s povišenim razinama LDL kolesterola postignu preporučene ciljane razine s obzirom na svoju kategoriju KV rizika te da ih dugoročno održe. Unatoč vrlo jasnim smjernicama za liječenje hiperlipidemije, bolesnici su u kliničkoj praksi često nedovoljno liječeni ili su neprikladno liječeni. Ovo ispitivanje također je pokazalo da terapija statinima često nije dovoljno intenzivna u bolesnika s visokim i vrlo visokim rizikom od KV događaja jer su oni manje često postizali ciljane razine LDL kolesterola nego bolesnici s umjerenim rizikom. Na temelju prikazanih rezultata može se zaključiti da je Roswera® siguran i učinko-

Patients tolerated Roswera® well and no adverse drug reactions (ADR) were recorded in 1,481 patients (91.0%). Adverse drug reactions were reported by 94 patients (5.8%), and no data were available for 52 patients (3.2%). In 86 patients (5.3%) ADRs were in causal association with the treatment and no causal association was recorded in the remaining 8 patients (0.5%). Myalgia was reported in 24 patients (1.5%) and was the most common ADRs. Other ADRs were less common (<1%). These results demonstrated the safety of rosuvastatin therapy.

Discussion

Hyperlipidemia is a chronic CV disease that requires careful control and management. It is important that target LDL-C levels are achieved in the treatment and maintained in the long term. This is the only way to provide optimal protection.

This non-interventional study included Slovenian outpatients with hyperlipidemia, of which 76% had already been on cholesterol-lowering therapy and only 24% received into statin therapy for the first time. After the three-month course of treatment, TC, LDL-C, and TG were statistically significantly decreased ($p < 0.0001$), demonstrating the efficacy of rosuvastatin therapy. After three months, 1,543 patients (94.8%) continued receiving Roswera®.

Rosuvastatin was effective for all groups of patients, because the treatment was assessed as very successful or successful for most of them. If outcomes are analyzed by risk categories, it can be established that the treatment of moderate-risk patients was very successful for more patients (56.7%) than for high-risk and very high-risk patients (37.8% and 37.4% respectively). This means that patients at moderate risk achieved target LDL-C levels more easily than high-risk or very high-risk patients. Additionally, many other trials showed that achieving target levels poses a significant challenge for clinical practice. In certain trials, 80% of high-risk patients failed to achieve target levels. This indicates that despite therapy patients are still at risk of CV disease development and progression.^{8,9}

Data from certain clinical trials indicate that physicians tend to prescribe doses that are insufficient and only rarely titrate them up to the recommended doses, which was also shown by this study.⁹

The results also show that rosuvastatin therapy is safe and well-tolerated by patients. In the three-month course of the study, 91% of patients reported no adverse drug reactions. Adverse drug reactions associated with the medication were recorded in a mere 5.3% of patients. Safety results were comparable to the results of many large clinical trials.⁹

Conclusions

The primary long-term objective of hyperlipidemia treatment is to prevent CV events. This is why it is very important that patients with increased LDL-C levels achieve target levels recommended based on their CV risk categories and maintain them in the long term. Despite the very clear guidelines for the treatment of hyperlipidemias, patients in clinical practice are often left untreated or are inappropriately treated. Additionally, our study showed that therapy was often not sufficiently intensive for patients at high risk and very high risk of cardiovascular events, as they reached target LDL-C levels less often than patients at moderate risk. According to the results, we can conclude Roswera® is a safe and effective medi-

vit lijek za liječenje hiperlipidemije u bolesnika s umjerenim, visokim te čak i vrlo visokim rizikom od KV događaja.

cation for the treatment of hyperlipidemia in patients at moderate, high, and even very high risk of a cardiovascular event.

LITERATURE

1. World Heart Organization. Fact sheets. Cardiovascular diseases (CVD). [cited 2019 September 3]. Available from: <https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-cvds>
2. Lansberg P, Lee A, Lee ZV, Subramaniam K, Setia S. Nonadherence to statins: individualized intervention strategies outside the pill box. *Vasc Health Risk Manag.* 2018 May 24;14:91-102. <https://doi.org/10.2147/VHRM.S158641>
3. Hanžel J, Šabovič M. Novosti v zdravljenju hiperholesterolemije in arterijske hipertenzije. *Farm. vestn.* 2016;67:134-40. Available from: <http://www.sfd.si/uploads/datoteke/abovi.pdf> (January 15, 2020).
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al; ESC Scientific Document Group. 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):2315-2381. <https://doi.org/10.1093/eurheartj/ehw106>
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J.* 2020 Jan 1;41(1):111-188. <https://doi.org/10.1093/eurheartj/ehz455>
6. Zoungas S, Curtis AJ, McNeil JJ, Tonkin AM. Treatment of dyslipidemia 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>
7. Mendis S, Puska P, 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 September 3]. Available from: <https://apps.who.int/iris/handle/10665/44701>
8. Vonbank A, Agewall S, Kjeldsen KP, Lewis BS, Torp-Pedersen C, Ceconi C, et al. Comprehensive efforts to increase adherence to statin therapy. *Eur Heart J.* 2017 Aug 21;38(32):2473-2479. <https://doi.org/10.1093/eurheartj/ehw628>
9. Milovanović Jarh D, Grošelj M, Barbič-Žagar B. Evidence-based therapy with Krka's rosuvastatin in primary and secondary prevention of cardiovascular disease. *Cardiol Croat.* 2017;12(4):161-5. <https://doi.org/10.15836/ccar2017.161>
10. Zaključno poročilo. Neintervencijsko spremljanje učinkovitosti in varnosti zdravljenja z rosuvastatinom (Sorvasta®) in upoštevanje dodatnih jakosti v klinično prakso pri bolnikih s hiperlipidemijo - FROZEN. Podatki iz dokumentacije. Krka, d. d., Novo mesto, Slovenija, 2019.