Stručni rad / Professional article

Nove doze — nove mogućnosti liječenja

New doses — new treatment options

Jasna Meško, Sanja Brus, Mateja Grošelj, Breda Barbič-Žagar*

Krka, d. d., Novo mesto, Slovenija

Krka, d. d., Novo mesto, Slovenia

SAŽETAK: Dislipidemija je jedan od najvažnijih i najčešćih promjenjivih čimbenika rizika za kardiovaskularne bolesti (KVB). Postoji mnogo različitih hipolipemika, ali do današnjeg dana statini su i dalje ostali jedini lijekovi koji dokazano smanjuju kardiovaskularnu smrtnost i morbiditet u bolesnika sa i bez utvrđene KVB. To je razlog zašto su oni postali temeljna terapija u smjernicama. U posljednjih nekoliko godina, smjernice za zbrinjavanje dislipidemije i prevenciju KVB predlažu još više smanjenje ciljnih vrijednosti razine lipida. Bile su prihvaćene na temelju rezultata iz kliničkih studija, uključujući i rezultate iz meta-analiza, što pokazuje da je daljnje sniženje LDL kolesterola rezultiralo dobrobitima, bez novih ili neočekivanih neželjenih nuspojava. Nadalje, kliničke studije su pokazale da čak i malo smanjenje LDL kolesterola ima značajan klinički učinak i da svakim 1% smanjenjem razine LDL kolesterola smanjuje i relativan rizik od velikih manifestacija koronarne bolesti srca za oko 1%. Unatoč poznatim prednostima postizanja ciljnih razina lipida, većina bolesnika, posebice u sekundarnoj prevenciji, ih ne postiže. Statini se obično propisuju u manjim dozama, a često se ne titriraju porastom doze do postizanja terapijskih ciljeva. Posjedovanje cjelovitog asortimana doza može biti jedan od pristupa za poboljšanje uspješnosti u postizanju ciljnih razina lipida u zbrinjavanju hiperlipidemije. To bi moglo pomoći u poboljšanju kliničkih ishoda i pružanju maksimalnih koristi za bolesnike od liječenja statinima za bolesnike.

KLJUČNE RIJEČI: LDL kolesterol, smjernice, ciljne vrijednosti lipida, statini, kardiovaskularni rizik.

SUMMARY: Dyslipidemia is one of the most important and common modifiable risk factors for cardiovascular disease (CVD). There are many different types of lipid lowering medicines, but till this date statins have remained the only medicines proven to reduce cardiovascular mortality and morbidity in patients with and without established CVD. This is why they have become the mainstay of therapeutic guidelines. In recent years, guidelines for the management of dyslipidemia and on CVD prevention have mandated even lower target lipid levels. These were accepted based on the results from clinical studies, including the results of meta-analyses, which demonstrated that further lowering of LDL cholesterol produced additional benefits, without new or unexpected safety issues. Moreover, clinical studies have shown that even a small reduction of LDL cholesterol has a significant clinical effect and that every 1% reduction in the LDL cholesterol level reduces the relative risk for major coronary heart disease events by approximately 1%. Despite the known benefits of reaching target lipid levels, the majority of patients, especially in secondary prevention, are not reaching them. Statins are usually prescribed at lower doses and often not up-titrated to achieve the therapeutic goals. Having a complete range of doses can be one of the approaches to improve the success rate in reaching target lipid levels in the management of hyperlipidemia. It could help improve clinical outcomes and provide maximum benefits of statin treatment for the patients.

KEYWORDS: LDL cholesterol, guidelines, target lipid levels, statins, cardiovascular risk.

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Dislipidemija je jedan od najvažnijih i najčešćih promjenjivih čimbenika rizika za kardiovaskularne bolesti (KVB). Terapija hipolipemicima jedan je od sastavnih dijelova intervencijske strategije u prevenciji KVB. Statini su i dalje jedini hipolipemici koji dokazano smanjuju kardiovaskularnu smrtnost i pobol u bolesnika sa i bez utvrđene KVB. To je razlog zašto su postali temeljna terapija u smjernicama za zbrinjavanje KVB.[1,2]

U posljednjih nekoliko godina, smjernice za zbrinjavanje dislipidemije i prevenciju KVB su stavile veći naglasak na postizanje ciljnih razina lipida i uvele niže ciljeve kod visokorizič-

Dyslipidemia is one of the most important and common modifiable risk factors for cardiovascular disease (CVD). Lipid-lowering therapy is an integral part of intervention strategies in the prevention of CVD. Till this date, statins have remained the only hypolipidemics proven to reduce cardiovascular mortality and morbidity in patients with and without established CVD. This is why they have become the mainstay of therapeutic guidelines for the CVD management.[1,2]

In recent years, guidelines for the management of dyslipidemia and on CVD prevention have placed greater emphasis

nih bolesnika. U tih bolesnika LDL kolesterol bi se trebao smanjiti na vrijednost nižu od 1,8 mmol/L ili ako je taj cilj neostvariv, LDL kolesterol bi se trebao smaniti najmanje za 50%. Smanjenje LDL kolesterola za više od 50% se može postići atorvastatinom ili rosuvastatinom, koji su dva najučinkovitija statina na tržištu.[1-3] Novi ciljevi liječenja u dislipidemiji su utvrđeni na temelju rezultata iz kliničkih studija, uključujući i dvije meta-analize od strane Cholesterol Treatment Trialists' (CTT) Collaboration. Rezultati upućuju na to da snižavanje LDL kolesterola na niže vrijednosti može proizvesti dodatne dobrobiti, bez novih ili neočekivanih neželjenih nuspojava.[4,5] Prva meta-analiza je pokazala da je svako smanjenje za 1 mmol/l vrijednosti LDL kolesterola povezano s odgovarajućim 20-25% smanjenjem smrtnosti od KVB i nefatalnog infarkta miokarda.[4] Druga analiza je pokazala da je smanjenje velikih kardiovaskularnih događaja izravno proporcionalno s postignutim apsolutnim smanjenjem vrijednosti LDL te da se daljnja prednost dobiva intenzivnijom terapijom statinima čak i ako je LDL kolesterol niži od 2.0 mmol/l.[5] Druge kliničke studije su pokazale da čak i malo smanjenje LDL kolesterola ima značajan klinički učinak. Svako 1% smanjenja razine LDL kolesterola smanjuje relativni rizik značajnog događaja koronarne bolesti srca (KBS) za približno 1%. Dakle, svakih 1% smanjenja je važno i dovodi do veće dobrobiti za bolesnika.[6] Rosuvastatin i atorvastatin su dva najsnažnija statina na tržištu koji omogućuju smanjenje više od 50% vrijednosti LDL kolesterola te bi mogli prepoloviti petogodišnji rizik od KBS.[3,6] Načelo "što je niža vrijednost LDL kolesterola, to je veće smanjenje rizika" je također utvrđen u primarnoj i sekundarnoj prevenciji moždanog udara. Meta-analiza randomiziranih ispitivanja statina u kombinaciji s drugim strategijama prevencije je pokazala da svako smanjenje LDL kolesterola za 1mmol/l odgovara smanjenju relativnog rizika od moždanog udara za 21%.[7]

on reaching target lipid levels and have introduced lower targets for patients at very high risk. In these patients, LDL cholesterol should be lowered to below 1.8 mmol/l or, if this target is unachievable, LDL cholesterol should be reduced at least by 50%. LDL cholesterol reduction by over 50% can be achieved with atorvastatin or rosuvastatin, the two most effective statins on the market.[1-3] New treatment targets in dyslipidemia were established based on the results from clinical studies, including two meta-analyses by the Cholesterol Treatment Trialists' (CTT) Collaboration. Findings suggested that lowering of LDL cholesterol to lower therapeutic targets could produce additional benefits, without new or unexpected safety issues.[4,5] The first meta-analysis has shown that every 1 mmol/l reduction in LDL cholesterol is associated with a corresponding 20-25% reduction in CVD mortality and non-fatal myocardial infarction.[4] The second cycle of analyses has shown that the reduction in major cardiovascular events is directly proportional to the absolute LDL reduction that is achieved, and that further benefit is gained from more intensive statin therapy even if LDL cholesterol is already lower than 2.0 mmol/l.[5] Moreover, other clinical studies have indicated that even a small reduction of LDL cholesterol has a significant clinical effect. Every 1% reduction in the LDL cholesterol level reduces the relative risk for major coronary heart disease (CHD) events by approximately 1%. Therefore, every 1% reduction counts and leads to a greater clinical benefit for the patient.[6] Rosuvastatin and atorvastatin, the two most potent statins on the market, which can produce a greater than 50% reduction in LDL cholesterol levels, could therefore halve the CHD risk over a 5-year period.[3,6] The finding 'the lower the LDL cholesterol concentration, the greater the risk reduction' was also established in primary and secondary prevention of stroke. A meta-analysis of randomised trials of statins in combination with other preventive strategies has shown that each 1 mmol/l decrease in LDL cholesterol equates to a reduction in the relative risk for stroke of 21%.[7]

Table 1. *Cardiovascular risk groups and recommended LDL cholesterol goals.*[2]

Very high risk: LDL-C <1.8 mmol/l or at least 50% reduction
• known cardiovascular disease • diabetes (type 1 or type 2) with 1 or more cardiovascular risk factors and/or target organ damage • severe chronic kidney disease • asymptomatic patients with SCORE ≥ 10%
High risk: LDL-C <2.5 mmol/l
• very high levels of individual risk factor (dyslipidemia and hypertension) • diabetes (type 1 or type 2) without cardiovascular risk factors or target organ damage • moderate chronic kidney disease • asymptomatic patients with SCORE ≥ 5% and 10%
Moderate risk: LDL-C <3.0 mmol/l
• asymptomatic patients with SCORE ≥ 1% and 5%
Low risk: LDL-C <3.0 mmol/l
• asymptomatic patients with SCORE < 1%

Paralelno s ispitivanjima kliničkih ishoda provedene su studije metodama oslikavanja radi ispitivanja učinaka terapije statinima na napredak ateroskleroze. Rezultati studija s visokom dozom atorvastatina ili rosuvastatina su pokazali značajnu regresiju koronarne ateroskleroze.[8,9] Osim toga,

Parallel to clinical outcome trials, imaging studies have been conducted to examine the effects of statin therapy on the progression of atherosclerosis. The results of studies with high-dose atorvastatin or rosuvastatin therapy demonstrated a significant regression of coronary atherosclerosis.[8,9]

studija koja je uspoređivala utjecaj na ukupni volumen ateroma (PAV) mjerenog intravaskularnim ultrazvukom između liječenja rosuvastatinom 40 mg i atorvastatinom 80 mg je pokazala da se učinci tih dvaju terapija ne razlikuju značajno.[9] Studije pokazuju da postoji potencijal za optimističniju strategiju u kojoj bi agresivne lipidno modularne terapije zapravo mogle preokrenuti proces aterosklerotske bolesti.[8,9]

Dokazi o prednostima snižavanja LDL kolesterola do određenih ciljnih vrijednosti i primjeni dovoljnih doza za postizanje ovih ciljeva su jači nego ikad. Međutim, mnogi visokorizični bolesnici, posebno u sekundarnoj prevenciji, ne postignu ciljnu vrijednost LDL kolesterola kao što je definirano u smjernicama. Prema nedavno predstavljenim podacima iz studije EUROASPIRE IV, većina koronarnih bolesnika s dislipidemijom uzimaju hipolipemike (gotovo isključivo statine), ali su još uvijek neadekvatno liječeni. Više od 40% tih bolesnika ne postigne razinu LDL kolesterola <2,5 mmol/l. Prema novim smjernicama, cilj bi trebao biti još niži, što za posljedicu ima još veći broj bolesnika koji ne postižu ciljne razine lipida.[10] Ti bolesnici, unatoč liječenju, imaju povišen rizik od KV događaja.

I dalje ostaje suočavanje s izazovima za kliničku praksu. Unatoč dobro utvrđenim prednostima i obilju kliničkih smjernica o zbrinjavanju koje snažno zagovaraju uporabu statina kod bolesnika s visokim rizikom od KV bolesti, statini se obično propisuju u nižim dozama i često se titriranjem doze ne povećavaju do postizanja ciljnih vrijednosti lipida. Obzirom na činjenicu da je glavna svrha smanjenja razine lipida postići maksimalnu kliničku dobrobit, u smjernicama se govori o potrebi za uvođenjem liječenja, a zatim za titriranjem na višu dozu radi postizanja ciljeva liječenja i poboljšanja preživljavanja bez neželjenih događaja.[1]

Krka je prepoznala ovu potrebu i nudi, kao prvi proizvođač u svijetu, kako snažne statine u dvije dodatne doze, Atoris® (atorvastatin) 30 i 60 mg tako i Roswera® (rosuvastatin) 15 i 30 mg. Krkin najširi spektar dostupnih jačina statina na tržištu, omogućuje prilagođavanje doze osobinama i potrebama svakog bolesnika. Mnogi bolesnici s povećanim rizikom od KV bolesti koji ne postižu ciljne razine lipida trenutnom terapijama bi imali veće šanse da ih postignu s atorvastatinom 30 mg ili rosuvastatinom 15 mg. Atorvastatin 60 mg ili 30 mg rosuvastatina mogu biti posebno pogodni kao doza održavanja u bolesnika u sekundarnoj prevenciji, npr. nakon kardiovaskularnog događaja te u bolesnika kod kojih je potrebno intenzivnije zbrinjavanje lipida.

Učinkovitost i sigurnost Krkinih statina dokazana je u više od 35.000 bolesnika. Najnovija neintervencijska klinička studija s Krkinim rosuvastatinom u kojoj su se također istraživale dodatne prednosti, potvrdila je učinkovitost i sigurnost Krkinog rosuvastatina i njegovog linearnog odnosa doze i terapijskog učinka.[11] Opsežna klinička ispitivanja, zajedno s vertikalno integriranom proizvodnjom u skladu s najstrožim europskim i međunarodnim proizvodnim i farmaceutskim standardima odigrali su ključnu ulogu u izgradnji povjerenja u Krkine lijekove te su učinili Krku vodećim proizvođačem statina na tržištima srednje, istočne i jugoistočne Europe. Krkin atorvastatin je najpropisivaniji statin na ovim tržištima.[12]

Širok sepktar dostupnih jačina može biti jedan od pristupa za poboljšanje uspješnosti u postizanju ciljnih razina lipida u zbrinjavanju hiperlipidemije. To bi moglo pomoći u poboljšanju kliničkih ishoda i pružanju maksimalne dobrobiti za bolesnike liječene statinima. Bolje pridržavanje liječenja koje se zasniva na smjernicama moglo bi potencijalno smanjiti javnozdravstveni i gospodarski teret kojeg su nametnule KVB.

Additionally, a study which compared the effect on percent atheroma volume (PAV) measured by intravascular ultrasound between the treatment with rosuvastatin 40 mg and atorvastatin 80 mg has found that the effects of these two treatments do not differ significantly.[9] The studies suggest that there is potential for a more optimistic strategy, in which aggressive lipid-modulating therapies could actually reverse the atherosclerotic disease process.[8,9]

The evidence about the benefits of lowering LDL cholesterol to specific targets and of using sufficient doses to reach these targets is stronger than ever. However, many high-risk patients, particularly in secondary prevention, do not reach LDL cholesterol goals as defined in guidelines. According to the recently presented data from the EUROASPIRE IV study, a majority of coronary patients with dyslipidemia are taking lipid lowering drugs (almost exclusively statins) but are still inadequately treated. More than 40% of these patients do not reach LDL cholesterol levels <2.5 mmol/l. According to new guidelines, the target should be even lower, which results in even greater percentage of patients not reaching target lipid levels.[10] These patients are, despite treatment, at an increased risk for CV events.

The challenges for clinical practice remain to be confronted. Despite the well-established benefits and abundance of clinical management guidelines strongly advocating statin use in patients at higher CV risk, statins are usually prescribed at their lower doses and often not up-titrated to achieve lipid goals. Given the fact that the main purpose of reducing lipid levels is to gain the maximum clinical benefits, the guidelines address the need to initiate and then up-titrate drug therapies to achieve the treatment goals and improve event-free survival.[1]

Krka has recognised this need and offers, as the first producer in the world, both potent statins in two additional doses, Atoris® (atorvastatin) 30 and 60 mg and Roswera® (rosuvastatin) 15 and 30 mg. Its broadest range of statin dosage options on the market allows adjusting the dose to every patient's characteristics and needs. Many patients at an increased CV risk who are not reaching target lipid levels with currently available treatments, would have better chances of reaching them with atorvastatin 30 mg or rosuvastatin 15 mg. Atorvastatin 60 mg or rosuvastatin 30 mg can be particularly suitable as maintenance doses in patients in secondary prevention, e.g. after a CVD event, and in patients who need more intensive lipid management.

The efficacy and safety of Krka's statins have been demonstrated in over 35,000 patients. A most recent non-interventional clinical study with Krka's rosuvastatin, which also investigated additional strengths, confirmed the efficacy and safety of Krka's rosuvastatin and its linear dose-response relationship.[11] Extensive clinical trials, together with vertically integrated production complying with the strictest European and international production and pharmaceutical standards, have played a crucial role in building trust in Krka's medicines and have made Krka a leading producer of statins on the markets of Central, Eastern and South-Eastern Europe. Krka's atorvastatin is the most prescribed statin on these markets.[12]

Having a complete range of doses can be one of the approaches to improve the success rate in reaching target lipid levels in the management of hyperlipidemia. It might help improve clinical outcomes and provide maximum benefits of statin treatment for the patients. A better adherence to guidelines-based therapies could potentially reduce the public health and economic burden imposed by CVD.

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*Address for correspondence: Krka d. d., Dunajska 65, SLO-1000 Ljubljana, Slovenija.

Phone: +386-1-4571-339;

E-mail: breda.zagar@krka.biz

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Za nakladnika: mr. sc. Jasna Ninčević, dr. med., spec. epidemiologije
Urednica: dr. sc. Ivana Marasović Šušnjara, dr. med, spec. javnog zdravstva
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