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Terapija atorvastatinom i nove europske preporuke za liječenje dislipidemije

Atorvastatin treatment meets new European recommendations for the treatment of dyslipidemias

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SAŽETAK: Kardiovaskularne bolesti (KVB) su i dalje vodeći uzrok globalnog mortaliteta te uzrokuju gotovo polovicu smrti u Europi. Istraživanja pokazuju da dislipidemija predstavlja jedan od najznačajnijih čimbenika rizika koji doprinose razvoju KVB. U kolovozu 2011. god. Europsko kardiološko društvo i Europsko društvo za aterosklerozu objavili su nove smjernice za liječenje pacijenata s dislipidemijama, koje snižene razine LDL kolesterola i dalje smatraju primarnim ciljem liječenja. Smjernice preporučaju propisivanje terapije statinima do najviše moguće doze ili najviše podnošljive doze kako bi se dosegla ciljna razina LDL kolesterola. Nekoliko kliničkih studija potvrdilo je učinkovitost i sigurnost atorvastatina u kliničkoj praksi kod širokog spektra bolesnika. Studija Anglo Scandinavian Cardiac Outcomes Trial - Lipid-Lowering Arm (ASCOT-LLA) je ukazala da smanjenje velikih kardiovaskularnih događaja primjenom atorvastatina može omogućiti dugoročnu dobrobit na ukupnu smrtnost. Krka je posvećena kontinuiranoj procjeni učinkovitosti i sigurnosti svojih proizvoda.

KLJUČNE RIJEČI: LDL kolesterol, smjernice, atorvastatin.

SUMMARY: Cardiovascular disease (CVD) still remains the leading cause of global mortality and causes nearly half of all deaths in Europe. Research shows that among many risk factors contributing to the development of CVD, dyslipidemia is one of the most significant. In August 2011, the European Society of Cardiology and the European Atherosclerosis Society released new guidelines for the management of patients with dyslipidemias, which consider low LDL cholesterol levels still as the primary treatment target. The guidelines recommend physicians prescribe statin therapy up to the highest dose possible or the highest tolerable dose to reach the target LDL cholesterol level. Several clinical studies confirmed the efficacy and safety of atorvastatin in clinical practice in a wide range of patients. The Anglo Scandinavian Cardiac Outcomes Trial - Lipid-Lowering Arm (ASCOT-LLA) has demonstrated that reductions in major cardiovascular events with atorvastatin may contribute to long-term benefits on all-cause mortality. Krka is dedicated to continuously evaluate the efficacy and safety of its products.

KEWYORDS: LDL cholesterol, guidelines, atorvastatin.

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Kardiovaskularne bolesti (KVB) i dalje predstavljaju vodeći uzrok globalnog mortaliteta i uzrokom su gotovo 17 milijuna smrti godišnje[1] te gotovo pola smrti u Europi (više od 4,3 milijuna smrtnih slučajeva godišnje).[2] Više čimbenika uzrokom je KVB.[3] Istraživanja pokazuju da je između mnogih čimbenika rizika koji doprinose razvoju KVB dislipidemija, zajedno s arterijskom hipertenzijom, jedna od najznačajnijih.[4]

U kolovozu 2011. god. Europsko kardiološko društvo (ESC) i Europsko društvo za aterosklerozu (EAS) izdali su nove smjernice za liječenje pacijenata s dislipidemijama. Kako su triglyceridi i HDL kolesterol (HDL-c) također značajni čimbenici rizika za KVB, smjernice preporučuju da se iste koriste i za procjenu rizika. Međutim, za razliku od prethodnih smjernica, one za njih ne predlažu specifične ciljne razine. Umjesto toga se fokusiraju na mjerila čimbenika rizika, ukupnom kolesterolu i LDL-c, koja su robustna i podupire ih velika baza dokaza. Na temelju kardiovaskularnog (KV) rizi-

Cardiovascular disease (CVD) still remains the leading cause of global mortality, accounting for almost 17 million deaths annually[1] and nearly half of all deaths in Europe, i.e. for over 4.3 million deaths each year.[2] The causes of CVD are multifactorial.[3] Research shows that among many risk factors contributing to the development of CVD, dyslipidemia, along with hypertension, plays one of the most significant roles.[4]

In August 2011, the European Society of Cardiology and the European Atherosclerosis Society released new guidelines for the management of patients with dyslipidemias. Since triglycerides and HDL-cholesterol (HDL-c) also are strong risk factors for CVD, guidelines recommend clinicians use them when estimating the risk. However, unlike previous guidelines, they do no suggest specific target levels for either of them. Instead, they focus on measures of risk factors, total cholesterol and LDL-c, as they are robust and supported by a major evidence base. Based on cardovascu-

ka (izračunatog pomoću ljestvice *Systemic Coronary Risk Estimation* — SCORE), pacijenti se mogu podijeliti u sljedeće skupine: pacijenti s vrlo visokim rizikom, visokim rizikom, umjerenim rizikom i niskim rizikom. Za pacijente koji imaju vrlo visok rizik, ciljne razine LDL-c bi trebale biti čak i niže od ranijih preporuka.[3]

Preporuke za terapijske ciljeve za LDL-c su prikazane u **Tablici 1**.

lar (CV) risk (calculated by using the *Systemic Coronary Risk Estimation* — SCORE), patients can be divided into the following groups: very high risk, high risk, moderate risk and low risk patients. For patients at very high risk, the target levels of LDL-c should be even lower as recommended earlier.[3]

The recommendations for treatment targets for LDL-c are presented in **Table 1**.

Table 1. *Recommendations for treatment targets for LDL-c (adapted from Eur Heart J. 2011;32:1769-818.).*

Cardiovascular risk level	*LDL-c treatment target*
Very high risk (established CVD, type 2 diabetes, type 1 diabetes, with target organ damage, moderate to severe CKD or a SCORE level of ≥10%)	**<1.8 mmol/l** or at least 50% reduction
High risk (markedly elevated single risk factors, a SCORE level of ≥5 to <10%)	**<2.5 mmol/l**
Moderate risk (SCORE ≥1% and <5%)	**<3.0 mmol/l**

CVD — cardiovascular disease; CKD — chronic kidney disease; SCORE — Systematic Coronary Risk Evaluation.

Već poznati princip "što je niže to bolje" se i dalje primjenjuje na razine LDL-c. Svako smanjenje vrijednosti LDL-c za 1,0 mmol/l (40 mg/dl) se povezuje s odgovarajućim smanjenjem KV mortaliteta i morbiditeta za 22%.[5] Prema europskim smjernicama za liječenje, statini su primarna terapija za snižavanje LDL-c, zbog svoje visoke učinkovitosti i dobro dokumentiranog učinka smanjenja kardiovaskularnog i ukupnog mortaliteta. Niz velikih kliničkih studija je pokazao da statini značajno smanjuju KV morbiditet i mortalitet i kod primarne i kod sekundarne prevencije. Također se pokazalo da statini usporavaju progresiju ili čak omogućuju regresiju koronarne ateroskleroze. Vodstvo EAS preporuča propisivanje terapije statinima do najviše moguće doze ili najviše podnošljive doze, kako bi se dosegla ciljna razina LDL-c.[3]

Rješenje postizanja ciljne niske razine lipida koje preporučaju nedavne smjernice leži u uporabi visokopotentnih statina, poput atorvastatina. Snižavanjem razine kolesterola u krvi, atorvastatin smanjuje KV morbiditet i mortalitet kod primarne i također sekundarne prevencije KVB, zajedno s dodatnim nelipidnim učincima, takozvanim plejotropnim učincima.[6]

Nekoliko kliničkih studija je potvrdilo učinkovitost i sigurnost atorvastatina u kliničkoj praksi na širokom rasponu pacijenata s displipidemijom te kod širokih raspona doza — od minimalne do maksimalne doze atorvastatina. Među njima je bila i studija ASCOT-LLA, jedna od poznatijih kliničkih studija koja se usredotočila na smanjenje razine kolesterola kod hipertenzivnih pacijenata uz još bar tri ostala KV čimbenika rizika. Dokazano je 36% smanjenje primarnih ishoda (nefatalni infarkt miokrda, uključujući nijemi infarkt miokarda i fatalni ishod koronarne bolesti srca) kod pacijenata liječenih s 10 mg atorvastatina u odnosu na placebo.[7] Relativno smanjenje rizika za koronarne bolesti srcca (KBS) je bilo najviše unutar prvih nekoliko mjeseci od terapije atorvastatinom te se nakon toga stabiliziralo. Obavljene su dodatne analize kako bi se nadalje razjasnio vremenski interval u svrhu koristi za pacijente s KBS i moždanim udarom. Nakon 2-godišnjeg praćenja su bile evidentne dobrobiti u usporedbi s placebo skupinom[8], a 11 godina nakon početne randomizacije mortalitet od svih uzroka je ostao značajno niži kod onih koji-

The already known principle "the lower the better" still applies for LDL-c levels. Every 1.0 mmol/l (40 mg/dl) reduction in LDL-c is associated with a corresponding 22% reduction in CV mortality and morbidity.[5] According to the European treatment guidelines, statins are the first-line therapy for lowering LDL-c, due to their high efficacy and well documented effect in reducing cardiovascular and all-cause mortality. A number of large-scale clinical trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and secondary prevention. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis. EAS task force chair recommends physicians prescribe statin therapy up to the highest dose possible or the highest tolerable dose to reach the target LDL-c level.[3]

A solution of how to achieve low lipid targets recommended in recent guidelines, lies in the use of high potency statins such as for example atorvastatin. By lowering blood cholesterol levels, atorvastatin reduces CV morbidity and mortality in primary as well as in secondary prevention of CVD, along with exerting additional non-lipid effects, the so called pleiotropic effects.[6]

Several clinical studies confirmed the efficacy and safety of atorvastatin in clinical practice in a wide range of patients with dyslipidemias and for a wide dose range — from the minimum to the maximum atorvastatin dose. Among them, one of the better known clinical studies, which focused on reducing cholesterol levels in hypertensive patients with at least three other CV risk factors, was ASCOT-LLA which demonstrated a 36% reduction in the primary endpoint (non-fatal MI, including silent MI and fatal CHD) in patients treated with atorvastatin 10 mg compared to placebo.[7] Relative risk reductions for coronary arterial disease (CAD) were greatest within the first few months of treatment with atorvastatin and stabilised thereafter. Additional analyses were undertaken to shed further light on the time interval to benefit for both CAD and stroke. Significant benefits compared with placebo were evident at 2-year follow-up[8], and 11 years[9] after initial randomisation all-cause mortality remai-

ma je originalno dodijeljen atorvastatin. "Nasljedni" učinci kod onih kojima je originalno dodijeljen atorvastatin mogu doprinijeti dugoročnoj koristi za ukupni mortalitet[9] što se podudara s preporukama novih smjernica prema kojima je liječenje dislipidemije ključan i sastavni dio prevencije KVB.[3]

Pošto je liječenje dislipidemije i prevencija kardiovaskularnih bolesti jedno od najvažnijih područja moderne medicine, Krka je odlučila ući na područje dislipidemije već 1996. godine sa svojim vlastitim asortimanom proizvoda za liječenje hiperlipidemije. Danas se taj asortiman proizvoda sastoji od tri statina: simvastatin (Vasilip®), atorvastatin (Atoris®) i rosuvastatin(Roswera®).[10]

ned significantly lower in those originally assigned to atorvastatin. "Legacy" effects in those originally assigned to atorvastatin may contribute to long-term benefits on all-cause mortality[9] which is coincident with the new guideline recommendations according to which the management of dyslipidemias is an essential and integral part of CVD prevention.[3]

As treatment of dyslipidemias and prevention of cardiovascular diseases is being one of the most important fields of modern medicine, Krka decided to enter the field of dyslipidemias already in 1996 with its own range of products for treating hyperlipidemia. Today, this range of products includes three statins: simvastatin (Vasilip®), atorvastatin (Atoris®) and rosuvastatin(Roswera®).[10]

Table 2. *Studies with Krka's atorvastatin and their results.*

Study	*Patient profiles*	*No. of patients*	*Duration of treatment*	*Results*	*Safety and tolerability of Krka's atorvastatin during the study*
INTER-ARS study[12]	High-risk patients with hyperlipidemia and increased absolute coronary risk[12]	117	16 weeks	Fully **comparable efficacy** of Krka's atorvastatin (decrease of LDL-c: - **37.8%**) and the originator's atorvastatin[12]	Fully comparable safety of Krka's atorvastatin and the originator's atorvastatin[12]
FARVATER study[13]	Patients with ishemic heart disease and primary hyperlipidemia[13]	50	24 weeks	Krka's atorvastatin (10-20 mg/d) increased endothelium-dependent vasodilatation by **40-51%**, common carotid artery distensibility by **43-45%**, reduced vascular wall stiffness by **23-26%**[13]	During the study, only 2 adverse events (4%), linked to atorvastatin therapy, were registered[13]
OSCAR study[14]	High-risk patients[14]	7,098	8 weeks	Lipid and blood pressure reduction resulted in total cardiovascular risk **decrease by 33%**[14]	During the study, only 195 (2.7%) adverse events were registered[14]
ATOP study[15]	Patients with primary high-risk (SCORE), metabolic syndrome, coronary heart disease, occlusive disease of noncoronary arteries and diabetes mellitus[15]	334	12 weeks (first phase - 6 weeks, second phase - 6 weeks)	After 12 weeks of treatment, the average total cholesterol and LDL- c **reductions** were **26%** and **36%**, respectively[15]	Only 3.3% of the patients discontinued the treatment due to adverse events[15]
ATLANTICA study[16]	Patients with primary hypercholesterole-mia and mixed hyperlipidemia[16]	632	24 weeks	The best LDL-c reduction was seen in patients with Krka's atorvastatin dose titration — from **10 mg to 80 mg (-38.6%)**[16]	Only 2.1% of the patients had adverse reactions[16]

Krkin atorvastatin je vodeći statin u središnjoj, istočnoj i jugoistočnoj Europi te se u njega već 10 godina pouzdaju mnogi liječnici i pacijenti.11 U tom razdoblju je Krka obavila nekoliko vlastitih kliničkih studija, kao što su studije INTER-ARS, FARVATER, OSCAR, ATOP i ATLANTICA. Ove studije su obavljene na širokom rasponu pacijenata u primarnoj i sekundarnoj prevenciji KVB.12-16 Rezultati njihovih rezultata sažeti su u Tablici 2.12-16 Objavljeni rezultati Krkinih vlastitih studija sa svojim atorvastatinom potvrdili su njegovu učinkovitost i sigurnost te predstavljaju važan doprinos boljem liječenju hiperlipidemije kod različitih skupina pacijenata i stvaranje povjerenja prema Krkinim proizvodima.

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Krka's atorvastatin is the leading statin in Central, Eastern and South-Eastern Europe and has been trusted by many doctors and patients for 10 years now.11 In this period, Krka has performed several own clinical studies which include INTER-ARS, FARVATER, OSCAR, ATOP and the ATLANTICA study. These studies were performed in a wide range of patients in primary and secondary prevention of CVD.12-16 The results of their findings are summed up in Table 2.12-16 The presented results of Krka's own studies with its atorvastatin confirmed its efficacy and safety and represent an important contribution to better management of hyperlipidemia in different groups of patients and the foundation of trust in Krka's products.

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