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Pridržavanje preporuka novih europskih smjernica za liječenje dislipidemija primjenom "jačih" statina

Meet the requirements of the new European recommendations for the treatment of dyslipidemias by using potent statins

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SAŽETAK: U nedavno objavljenim europskim smjernicama uvedena je nova klasifikacija bolesnika u četiri kategorije rizika te su preporučene čak i niže ciljne razine lipida za pacijente s vrlo visokim rizikom. U svjetlu činjenice da oko polovice europskih pacijenata koji su liječeni hipolipemicima ne postižu ciljne razine lipida prema smjernicama Europskog kardiološkog društva iz 2007. godine, nove ciljne razine lipida se mogu shvatiti kao veći izazov. Uporabom "jačih" statina, poput rosuvastatina ili atorvastatina, u primjerenim dozama, može se udovoljiti zahtjevima novih europskih preporuka.

KLJUČNE RIJEČI: smjernice, LDL kolesterol, regresija ateroskleroze, rosuvastatin.

SUMMARY: Recently issued European guidelines introduced new classification of patients into 4 risk categories and mandated even lower target lipid levels for patients at very high risk. In the light of the fact that about half of patients in Europe receiving lipid-lowering therapy were not reaching target lipid levels as set in the 2007 European Society of Cardiology guidelines, new target lipid levels may be seen as an even greater challenge. However by using potent statins such as rosuvastatin or atorvastatin and in appropriate doses, the requirements of the new European recommendations can be met.

KEYWORDS: guidelines, LDL cholesterol, regression of atherosclerosis, rosuvastatin.

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Iako mnoge osobe na kardiovaskularnu bolest (KVB) ne gledaju kao na nešto strašno poput karcinoma, to je još uvijek zasigurno najčešći uzrok smrtnosti u svijetu.[1] Mnogi su iznenađeni činjenicom da se KVB mogu spriječiti ili barem odgoditi do puno starije životne dobi primjenom zdravog načina života. U slučajevima kada zdrav način života nije dovoljan, na raspolaganju je cijeli niz lijekova za zbrinjavanje čimbenika rizika, poput arterijske hipertenzije, hiperlipidemije, hiperglikemije, itd. Također, velike međunarodne epidemiološke studije kao npr. EUROASPIRE III ukazuju da je primjena lijekova za adekvatno zbrinjavanje čimbenika rizika nedovoljna, čak i kod bolesnika s već utvrđenom KVB.[2] To je zbog prekratkog razdoblja liječenja, korištenja premalih doza i/ili korištenja starijih, manje "jakih" lijekova.[3]

Nedavno je objavljeno nekoliko novih europskih smjernica za zbrinjavanje KVB. U kolovozu 2011. godine, Europsko kardiološko društvo (ESC) i Europsko društvo za aterosklerozu (EAS) su zajednički objavili nove smjernice za zbrinjavanje bolesnika s dislipidemijom[4], a u svibnju 2012. ESC je objavilo nove smjernice za sprječavanje KVB u kliničkoj praksi[5]. Glavna promjena koju donose ove smjernice je nova

Although for many people cardiovascular disease (CVD) may not be as scary as cancer it is still by far the most common cause of death in the world[1]. Many find this surprising as CVD can be prevented or at least postponed to a much older age just by living a healthy lifestyle. In cases where a healthy lifestyle just is not enough, there is a wide range of drugs available to manage the risk factors such as hypertension, hyperlipidemia, hyperglycemia etc. However big international epidemiologic studies such as EUROASPIRE III show that use of drugs is insufficient to manage these risk factors appropriately even in patients with already established CVD.[2] This is either due to too short time of treatment, use of too low doses and/or use of older, less potent drugs.[3]

Recently a few new European guidelines regarding CVD have been released. In August 2011, ESC/EAS released new guidelines for the management of patients with dyslipidemias[4] and in May 2012, ESC released new guidelines on CVD prevention in clinical practice[5]. The main change these guidelines brought was the new classification of patients into 4 risk categories (very high risk, high risk, moderate risk and low risk patients) and introduction of even lower target

klasifikacija bolesnika u 4 kategorije rizika (bolesnici s vrlo visokim rizikom, visokim rizikom, umjerenim rizikom i niskim rizikom) kao i uvođenje i nižih ciljnih razina lipida za visokorizične bolesnike, a LDL kolesterol treba smanjiti na ispod 1.8 mmol/l ili za najmanje 50%.

Postizanje ovih ciljnih razina lipida se može promatrati i kao još veći izazov, no raspoložive su i odgovarajuće mogućnosti liječenja. Koristeći vrlo "jake" statine kao što su rosuvastatin ili atorvastatin u primjerenim dozama razine kolesterola u krvi se mogu smanjiti na željenu razinu te se mogu postići maksimalne koristi od ovih preventivnih strategija.[3] Velika studija kojom se uspoređuje učinkovitost i sigurnost rosuvastatina, atorvastatina, simvastatina i pravastatina diljem doza je pokazala da je primjenom početne doze od 10 mg rosuvastatina oko 80% bolesnika postiglo ciljne razine lipida niže od 2.5 mmol/l kako je bilo preporučeno za visokorizične bolesnike od KVB ili 3 mmol/l kako je bilo preporučeno za bolesnike s umjerenm rizikom KVB.[6] Učestalost pacijenata koji su postigli ciljne razine lipida veći je s povećanjem doze rosuvastatina.

Glavni cilj smanjenja razina lipida je osigurati kliničku dobrobit kod pacijenata. Statini dokazano smanjuju pobolijevanje i smrtnost od KVB u primarnoj i sekundarnoj prevenciji KVB, pri čemu imaju i dodatne učinke koji nisu povezani sa lipidima, tzv. plejotropne učinke.[7] Još jedno važno istraživanje rosuvastatina čiji je cilj analiza primjene statina u prevenciji ukazalo je na 44% smanjenje svih vaskularnih događaja kao primarnog cilja istraživanja, 54% smanjenje infarkta miokarda, 48% smanjenje moždanog udara, 46% smanjenje potrebe za arterijskom revaskularizacijom i 20% smanjenje ukupne smrtnosti. Sve prethodno specificirane podskupine u okviru istraživanja imale su značajne dobrobiti od rosuvastatina, uključujući i one koje su se prethodno smatrale niskog rizika, kao što su žene, osobe s indeksom tjelesne mase nižim od 25 kg/m^2, osobe bez metaboličkog sindroma, nepušači, osobe koje nemaju arterijsku hipertenziju, kao i osobe s rizikom nižim od 10% prema Framinghamskoj ljestvici. Ova studija je imala značajan utjecaj na kliničku praksu jer je na temelju nje kao nova indikacija rosuvastatina uvedena prevencija, a ne samo liječenje KVB.

Snižavanjem vrijednosti LDL kolesterola smanjuje se rizik od glavnih kardiovaskularnih događaja zbog progresije ateroskleroze.[4] Posljednjih godina nekoliko studija dokazalo je da "jači" statini ne samo usporavaju progresiju, nego čak i potiču regresiju ateroskleroze, osobito u visokim dozama.[8-13] Rezultati studije iz prosinca 2011. god. ukazali su da je primjena visokih doza statina, atorvastatinom ili rosuvastatinom, rezultirala značajnom regresijom koronarne ateroskleroze, unatoč različitim učincima na vrijednosti LDL i HDL kolesterola. Iako je liječenje rosuvastatinom 40 mg za rezultat imalo niže razine LDL kolesterola od atorvastatina 80 mg (1,62 vs.1,82 mmol/l), učinak na postotni volumen ateroma mjerenog intravaskularnim ultrazvukom se nije značajno promijenio. U pogledu učinka na normalizaciju ukupnog volumena ateroma, postoji statističko značajno smanjenje u skupini na rosuvastatinu u odnosu na skupinu na atorvastatinu. Oba statina su imala prihvatljive profile nuspojava, uz malu pojavu laboratorijskih nepravilnosti i kardiovaskularnih događaja.[12]

Studije su pokazale da se za svakih 1% smanjenja razina LDL kolesterola relativni rizik za veliki događaj povezan s koronarnom bolesti srca (KBS) smanjuje za približno 1%.[14] Europske smjernice potiču početak uzimanja i povećanje doze lijeka sukladno cilju liječenja te potiču pridržavanje terapije tijekom dužeg razdoblja s ciljem poboljšanja preživlja-

lipid levels for patients at very high risk, bellow 1.8 mmol/l or at least 50% reduction of LDL cholesterol.

Reaching these target lipid levels may be seen as an even greater challenge, however, appropriate treatment options are available. By using high potent statins such as rosuvastatin or atorvastatin in appropriate doses blood cholesterol levels can be reduced to the required level and maximum benefits of these preventive strategies achieved.[3] A large study comparing the efficacy and safety of rosuvastatin, atorvastatin, simvastatin and pravastatin across doses, showed that by using starting dose of 10 mg rosuvastatin around 80% of patients reached target lipid levels below 2.5 mmol/l as set for patients at high CVD risk or 3 mmol/l as set for patients at medium CVD risk.[6] The percentage of patients reaching target lipid levels only increased with increasing dose of rosuvastatin.

The main aim of reducing lipid levels is to bring the patients the clinical benefits. Statins have been proven to reduce 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.[7] Another large rosuvastatin trial aimed to justify the use of statin in prevention showed a 44% reduction in the trial primary end point of all vascular events, a 54% reduction in myocardial infarction, a 48% reduction in stroke, a 46% reduction in need for arterial revascularization and a 20% reduction in all-cause mortality. Importantly all prespecified subgroups within the trial significantly benefitted from rosuvastatin including those previously considered to be at "low risk" such as women, those with body mass index less than 25 kg/m^2, those without metabolic syndrome, nonsmokers, nonhypertensives, and those with Framingham Risk Scores less than 10%. This study had a major impact on clinical practice. Based on it prevention of CVD, not just treatment of CVD, was introduced as new indication to rosuvastatin.

Lowering LDL cholesterol reduces the risk for major cardiovascular events due to progressive atherosclerosis.[4] In recent years several studies proved that potent statins not only slow progression but may even promote regression of atherosclerosis especially when used in high doses.[8-13] The results of a study published in December 2011 showed that high-dose statin therapy with atorvastatin or rosuvastatin resulted in a significant regression of coronary atherosclerosis, despite differential effects on LDL- and HDL cholesterol levels. Although treatment with rosuvastatin 40 mg resulted in lower LDL cholesterol levels than atorvastatin 80 mg (1.62 vs 1.82 mmol/l), the effect on percent atheroma volume measured by intravascular ultrasound did not differ significantly. In terms of effect on normalized total atheroma volume, there was a statistically significant reduction in the rosuvastatin arm compared with a reduction in the atorvastatin arm. Both statins had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.[12]

Studies have shown that for every 1% reduction in LDL cholesterol levels, relative risk for major coronary heart disease (CHD) events is reduced by approximately 1%.[14] European guidelines have been encouraging initiating and up-titrating drug therapies, achieving the treatment goals, and adhering over the long-term to improve event-free survival for quite some time.[4,5] However one of the main challenges in hyperlipidemia treatment today is that still about half of patients in Europe receiving lipid-lowering therapy don't reach target lipid levels; in some countries the percentage is even greater.[2] This is either due to too short time of treatment, use of

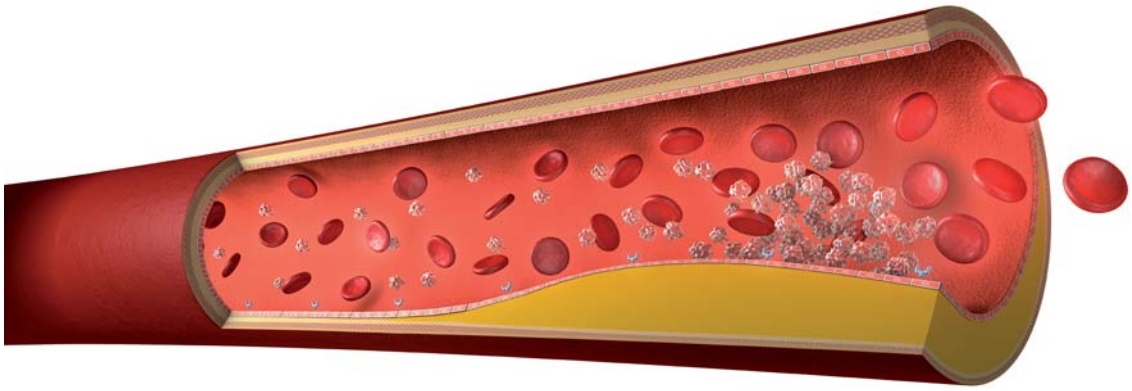

Figure 1. *Cross-section of an artery with developing atherosclerotic plaque and reduced blood flow.*

vanja bez neželjenog događaja.[4,5] No, jedan od glavnih izazova u liječenju hiperlipidemije danas je da još uvijek polovica bolesnika u Europi koja prima hipolipemik ne postiže ciljne razine lipida, a u nekim zemljama je taj postotak još i veći.[2] To je zbog prekratke primjene liječenja, uporabe premalih doza i/ili korištenja starijih, manje "jakih" lijekova. Za ove bolesnike, usprkos terapiji, postoji povećan rizik od razvoja i/ili progresije KVB.

Nove smjernice su također preporučile niže ciljne razine lipida što znači da bi kod mnogo više bolesnika trebalo obaviti reviziju liječenja radi postizanja potrebnih, ciljnih razina lipida. Kako bi premostila ovaj problem, Krka je kao proizvođač prva ponudila dva snažna statina s dvije dodatne doze, atorvastatin 30 i 60 mg te rosuvastatin 15 i 30 mg te tako omogućila liječnicima pristup svim opcijama liječenja koje se baziraju na statinima.[15,16]

Do sada su četiri doze atorvastatina (10, 20, 40 i 80 mg) ili rosuvastatina (5, 10, 20 i 40 mg) bile dostupne na tržištu. No, liječnici su smatrali da su u većini slučajeva samo dvije srednje doze bile primjenjive kod liječenja. Početne doze su se koristile samo kao prvi korak u titriranju ili su bile potpuno preskočene, dok su visoke doze čuvane u rezervi za najteže slučajeve. No, dvije srednje doze često ne zadovoljavaju potrebe liječenja pojedinih bolesnika. Uz Krkin Atoris® i Roswera® liječnici sada mogu istinski prilagoditi liječenje potrebama svakog bolesnika pri tome omogućavajući jednostavnije postizanje cilja uz primjenu prave doze.

too low doses and/or use of older, less potent drugs. Those patients despite receiving treatment are still at an increased risk for development and/or progression of CVD.

The new guidelines also mandated lower target lipid levels which meant that many more patients would need revision of their treatment to reach target lipid levels. In order to bridge this widening gap, Krka is the first producer to offer the two potent statins with 2 additional doses, atorvastatin 30 and 60 mg and rosuvastatin 15 and 30 mg, thus giving doctors access to the fullest range of statin-based treatment options on the market.[15,16]

So far four doses of atorvastatin (10, 20, 40 and 80 mg) or rosuvastatin (5, 10, 20 and 40 mg) were available on the market. However, physicians found that in majority of cases only the two middle doses were applicable to their therapeutic needs. The initial doses have been used only as a first step in titration or may have even been entirely skipped, while the highest doses have been kept in reserve for the most severe cases. However the two middle doses often didn't meet the treatment requirements of individual patients. With Krka's Atoris® and Roswera® physicians can now truly adjust treatment to each patient's needs making it possible to reach the target with just the right dose.

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"Netitriranje, odnosno ne povećavanje doze statina uz loše pridržavanje terapije predstavljaju glavne razloge zašto više od polovice svih koronarnih bolesnika i četiri od pet svih visokorizičnih pacijenata ne postižu ciljne vrijednosti lipida i kao posljedica toga, ne postižu maksimalnu dobrobot od ove preventivne strategije."

ESC/EAS Smjernice za liječenje dislipidemija[4]

"Not up-titrating the dose of statin, and poor adherence to this therapy, are the main reasons why over half of all coronary patients, and four out of five of all high risk patients, are not achieving the lipid goals and, as a consequence, are not achieving the maximum benefits of these preventive strategies."

ESVC/EAS Guidelines for the management of dyslipidaemias[4]

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