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Stručni rad / Professional article

Rosuvastatin kao dio strategije primarne prevencije kardiovaskularnih bolesti

Rosuvastatin as part of the primary prevention strategy against cardiovascular disease

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SAŽETAK: Bolesnici s dokazanom kardiovaskularnom bolesti (KVB) najčešći su kandidati za farmakološko liječenje radi sprječavanja napredovanja bolesti. No, bolesnici bez manifestirane KVB i s povećanim rizikom često se ne liječe, iako bi oni imali najveće koristi od ranog smanjenja rizika u smislu prevencije KVB. Prema nedavno objavljenim europskim smjernicama o prevenciji KVB, smanjenje vrijednosti LDL kolesterola mora biti od primarne važnosti u prevenciji KVB. Uz potentne statine, poput rosuvastatina, možemo postići značajno smanjenje vrijednosti LDL kolesterola, a time i smanjenje ukupnog rizika od KVB nekog pojedinca. Rosuvastatin je također dobio indikaciju za prevenciju značajnih kardiovaskularnih događaja kod visokorizičnih bolesnika temeljem rezultata velikog kliničkog ispitivanja. Post hoc analiza ove kliničke studije koja je uključivala samo visokorizične bolesnike dokazala je da su bolesnici s vrijednostima 10-godišnje procjene rizika prema Framinghamskoj ljestvici >20% ili procijenjenim SCORE rizikom >5% imali statistički značajno smanjenje rizika od 50% i 43% od infarkta miokarda, moždanog udara ili kardiovaskularne smrti kada se liječe rosuvastatinom u usporedbi s pacijentima liječenim placebom. Rosuvastatin također ima prednosti kod drugih visokorizičnih bolesnika, poput onih s dijabetesom i hipertenzijom. Dugoročna podnošljivost terapije statinima je presudna za njihovu učinkovitost u visokorizičnih bolesnika. Dugoročnim liječenjem statinima možemo postići veće smanjenje rizika od KVB i još izraženiju regresiju aterosklerotskih plakova.

KLJUČNE RIJEČI: kardiovaskularna bolest, primarna prevencija, rosuvastatin.

SUMMARY: Patients with established cardiovascular disease (CVD) are the ones that are most commonly considered for therapeutic intervention in order to prevent progression of the disease. In contrast, patients without manifested CVD and at increased risk are often left untreated, even though they would have the greatest benefits from early risk reduction in terms of CVD prevention. According to the recently published European CVD prevention guidelines, the reduction of LDL cholesterol must be of prime concern in the prevention of CVD. With potent statins, such as rosuvastatin, we can achieve meaningful reductions of LDL cholesterol levels and, consequently, reduce an individual's total CVD risk. On the basis of a large clinical study with rosuvastatin, prevention of major cardiovascular events in patients who are estimated to have a high risk was added to statin labels. A post hoc analysis of this clinical study which included only patients considered to be at high risk, showed that patients with a 10-year Framingham risk score of >20% or an estimated SCORE risk of >5% had statistically significant reductions, 50% and 43%, respectively, in the risk of MI, stroke, or cardiovascular death when treated with rosuvastatin compared with patients treated with placebo. Rosuvastatin also has established benefits in other high-risk patients, such as patients with diabetes and hypertension. Long-term compliance with statin therapy is critical for its efficacy in patients at high risk. With long-term statin treatment we can achieve greater reductions of the CVD risk and an even more pronounced regression of atherosclerotic plaques.

KEYWORDS: cardiovascular disease, primary prevention, rosuvastatin.

CITATION: Cardiol Croat. 2013;8(3-4):142-145.

Kardiovaskularne bolesti (KVB) predstavljaju najveću epidemiju čovječanstva. To je najvažniji uzrok smrti muškaraca i žena, usprkos činjenici da se primjenom modernih lijekova može spriječiti ili barem odgoditi.[1] Smatra se da je ukupni trošak KVB za europsku ekonomiju gotovo 196 milijarda eura godišnje. Ovi troškovi predstavljaju zbroj

Cardiovascular disease (CVD) is the greatest epidemic of mankind. It is the single most important cause of death for both men and women, despite the fact that with the use of modern medicine it can often be prevented or at least postponed.[1] Overall, CVD is estimated to cost the EU economy almost 196 billion euros a year. These costs

troškova zdravstvene skrbi, troškova zbog gubitka produktivnosti i troškova zbog neformalnog zbrinjavanja osoba s KVB.[2] Prevencija KVB stoga ostaje i dalje vodeći izazov za opću populaciju. Srećom, tijekom proteklih godina bili smo svjedoci smanjenja smrtnosti od KVB u mnogim europskim zemljama, uglavnom radi poboljšanja strategija prevencije. Procjenjuje se da je 50% smanjenja smrtnosti od koronarne bolesti srca (KBS) povezano s promjenama u čimbenicima rizika, a 40% povezano s poboljšanim liječenjem. Prevencija je obično kategorizirana kao primarna ili sekundarna, iako je kod KVB razlika između njih proizvoljna u pogledu temeljnog aterosklerotskog procesa koji se postupno razvija. Rizik od KVB je najčešće rezultat više međusobno povezanih čimbenika rizika. Ozbiljni kardiovaskularni (KV) događaji se često javljaju u osoba bez prethodne manifestacija bolesti. Stoga je važno djelovati preventivno prije nego bolest uznapreduje do točke gdje klinički simptomi uzrokuju oštećenje KV sustava ili smrtni ishod.[1]

Alat za procjenu rizika, kao što je SCORE, može pomoći u donošenju odluke kada asimptomatska odrasla osoba, bez dokazane KVB zahtijeva liječničku intervenciju. Ovaj alat procjenjuje 10-godišnji rizik za prvi fatalni aterosklerotski događaj, bilo da se radi o srčanom udaru, moždanom udaru, aneurizmi aorte, ili dr. Osobe s rizikom od kardiovaskularne smrti ≥5% su klasificirani u skupinu visokog rizika od KVB, a zahtjevaju uvođenja terapije statinima, kada promjene načina života nisu dovoljne. Određene osobe visokog ili vrlo visokog rizika od KVB (bolesnici s dokazanim KVB, dijabetesom, umjerenom do teškom bubrežnom bolesti i vrlo visokim razinama pojedinih čimbenika rizika) ne trebaju procjenu rizika nego zahtijevaju hitnu intervenciju za sve čimbenike rizika.[1]

are the sum of health care costs, costs due to productivity losses, and costs due to the informal care of people with CVD.[2] CVD prevention is therefore remaining a major challenge for the general population. Fortunately, over the past years we have been witnessing a reduction of CVD mortality in many European countries, which is mainly the result of increasing preventive strategies. It is estimated that 50% of the reductions seen in coronary heart disease (CHD) mortality are related to changes in risk factors, and 40% to improved treatments. Prevention is typically categorised as primary or secondary prevention, although in CVD the distinction between the two is arbitrary in view of the underlying, gradually developing atherosclerotic process. CVD risk is most frequently the result of multiple interacting risk factors. Serious cardiovascular (CV) events often occur in persons with no prior manifestation of the disease. Therefore, it is important to act preventively before disease has progressed up to a point where clinical symptoms cause damage to the CV system or even death.[1]

A risk estimation system, such as SCORE, can assist in making decisions which asymptomatic adults without evidence of CVD require medical intervention. It estimates the 10-year risk for a first fatal atherosclerotic event, whether heart attack, stroke, aneurysm of the aorta, or other. In general, individuals at a risk of CVD death of ≥5% are classified into the high CV risk category and they qualify for the consideration of introducing statin therapy, when lifestyle changes do not suffice. Certain individuals who are at high or very high CVD risk (patients with established CVD, diabetes, moderate to severe renal disease and very high levels of individual risk factors) do not need risk scoring and require immediate intervention for all risk factors.[1]

Table 1. *Intervention strategies as a function of total cardiovascular risk and LDL cholesterol level.*

Total cardiovascular risk (SCORE) %	LDL cholesterol level			
	1.8-2.5 mmol/l	***2.5-4.0 mmol/l***	***4.0-4.9 mmol/l***	***>4.9 mmol/l***
SCORE ≥5 to <10 or high risk	Lifestyle intervention, consider medication*	Lifestyle intervention and immediate medication intervention	Lifestyle intervention and immediate medication intervention	Lifestyle intervention and immediate medication intervention
SCORE ≥10 or very high risk	Lifestyle intervention and immediate medication intervention	Lifestyle intervention and immediate medication intervention	Lifestyle intervention and immediate medication intervention	Lifestyle intervention and immediate medication intervention

*in patients with myocardial infarction, statin therapy should be considered irrespective of LDL cholesterol levels

Visoka razina kolesterola je jedna od glavnih promjenjivih rizičnih čimbenika za razvoj KVB. Prema nedavno objavljenim europskim smjernicama za prevenciju KVB smanjenje vrijednosti LDL kolesterola predstavlja primarni cilj u prevenciji KVB. Ovdje statini — kao prva linija liječenja za smanjenje LDL kolesterola — imaju ključnu ulogu. Naravno, temelj liječenja bolesnika s povišenim razinama kolesterola moraju biti primjerena dijeta i druge nefarmakološke mjere (tjelovježba, smanjenje težine). Međutim, ove intervencije mogu biti nedostatne, osobito u bolesnika s visokim razinama kolesterola ili u visokorizičnih bolesnika.[1] S modernim potent-

A high cholesterol level is one of the major modifiable risk factors for developing CVD. Consequently, recently published European CVD prevention guidelines recommend that the reduction of LDL cholesterol must be of prime concern in the prevention of CVD. This is where statins — as a first-line treatment for the reduction of LDL cholesterol levels — play a critical role. Of course, the cornerstones of the treatment of patients with elevated cholesterol levels have to be appropriate diet and other non-pharmacological measures (exercise, reduction of weight). However, these interventions can be inadequate, especially in patients with high cholesterol

nim statinima, kao što je rosuvastatin, možemo smanjiti razine LDL kolesterola do 55%, i tako eliminacijom jednog od glavnih čimbenika rizika za razvoj KVB možemo smanjiti ukupni kardiovaskularni rizik pojedinca.[1,3] Utvrđeno je da se smanjenjem LDL kolesterola od 1% smanjuje rizik od KBS za 1%.[4]

Brojna velika klinička ispitivanja dokazala su da statini značajno smanjuju pobol i smrtnost od kardiovaskularnih bolesti u bolesnika u primarnoj i sekundarnoj prevenciji.[5-7] Na temelju velikog kliničkog ispitivanja rosuvastatina, koje je za cilj imalo da opravda primjenu terapije statinima u primarnoj prevenciji, dodana je nove indikacija statina koja je odobrena od strane europskih zdravstvenih tijela: prevencija značajnih KV događaja u bolesnika za koje se procjenjuje da imaju visoki rizik od prvog KV događaja, kao dodatak korekciji drugih čimbenika rizika. Učinjena je post hoc analiza ovog kliničke studije koja je uključivala samo visokorizične bolesnike, kao što je definirano bilo Framinghamskom ljestvicom rizika od 20% ili Europskom sistematskom procjenom koronarnog rizika (SCORE) od ≥5%. U usporedbi s cjelokupnom kohortom, bolesnici s višim stupnjem rizika su bili stariji, češće muškarci koji su vjerojatnije pušili, imali hipertenziju i niske razine HDL kolesterola. Rezultati subanalize su pokazali da su bolesnici s vrijednostima procjene rizika Framinghamskom ljestvicom >20% ili SCORE rizikom od >5% imali statistički značajno smanjenje, 50% i 43% rizika infarkta miokarda, moždanog udara, ili kardiovaskularne smrti kada su bili liječeni rosuvastatinom u odnosu na liječene placebom.[8]

Posljednjih godina u nekoliko studija je dokazano da rosuvastatin ne samo usporava napredovanje, nego čak i potiče regresiju ateroskleroze, osobito kada se koristi u visokim dozama.[9,10] Rosuvastatin također može spriječiti razvoj i napredovanje ateroskleroze u bolesnika s dijabetesom, koji inače imaju dva do tri puta veći rizik od kardiovaskularnih događaja — ne samo smanjenjem razine koncentracije kolesterola, nego i poboljšanjem efluksa kolesterola iz pjenastih stanica stijenke arterije blokiranjem štetnih učinaka krajnjih produkata uznapredovale glikacije na makrofage.[11,12]

Hiperkolesteremija često koegzistira s arterijskom hipertenzijom, glavnim čimbenikom rizika za razvoj moždanog i srčanog udara, kao i zatajivanja srca, oštećenja bubrega, periferne vaskularne bolesti i sljepoće.[11] Dodatak hipolipemika može biti koristan kod hipertenzivnih bolesnika. Utvrđeno je da 10% smanjenje kolesterola i arterijskog tlaka možu smanjiti pojavu značajnog KVB događaja za 45%.[13] Terapija rosuvastatinom dodana konvencionalnoj antihipertenzivnoj terapiji je poboljšala dijastoličku funkciju lijeve klijetke i donijela povoljne učinke na aterosklerotske plakove u tih bolesnika.[14]

Ateroskleroza je progresivna bolest, stoga prevencija KVB i kontrola glavnih čimbenika rizika za njezin razvoj treba biti doživotan pristup.[1] Dugoročno pridržavanje terapije statinima je presudno za učinkovitost u visokorizičnih bolesnika kada je pored intervencije životnog stila indicirana i farmakološka terapija.[8] Smanjenje KV rizika se povećava sa svakom dodatnom godinom liječenja statinima.[15] Nedavno objavljeno istraživanje pomoću intravaskularnog ultrazvuka je pokazalo da četverogodišnje liječenje statinima naspram 8-mjesečnog liječenja statinima smanjuje za više od 4 puta volumen vanjske elastične membrane (-1,1% u razdoblju od 8 mjeseci i -5,9% u razdoblju od 4 godine).[16]

Krka ima dugogodišnje iskustvo u području liječenja KVB i zbrinjavanja hiperkolesterolemije od 1996. godine, kada je odobren njezin prvi statin — lovastatin.[17] Od tada, Krka kon-

levels or in patients at higher risk.[1] With modern, potent statins, such as rosuvastatin, we can reduce LDL cholesterol levels by up to 55%, and so, by eliminating one of the main risk factors for developing CVD, we can reduce the individuals total CV risk.[1,3] It has been established that an LDL cholesterol reduction of 1% reduces the risk for CHD by 1%.[4]

A number of large-scale clinical trials have demonstrated that statins substantially reduce CV morbidity and mortality in patients in primary and secondary prevention.[5-7] On the basis of a large clinical study with rosuvastatin, which was aimed to justify the use of statin therapy in primary prevention, an addition of a new indication to statin labels was approved by European health authorities: prevention of major CV events in patients who are estimated to have a high risk for a first CV event, as an adjunct to correction of other risk factors. A post hoc analysis of this clinical study which included only patients considered at high risk, as defined either by a Framingham risk score of 20% or a European systematic coronary risk evaluation (SCORE) score of ≥5% was made. When compared with the entire study cohort, the higher-risk patients were older, more often male and more likely to smoke, had hypertension and low levels of HDL cholesterol. The results of the sub-analysis showed that patients with a 10-year Framingham risk score of >20% or an estimated SCORE risk of >5% had statistically significant reductions, 50% and 43%, respectively, in the risk of myocardial infarction, stroke, or cardiovascular death when treated with rosuvastatin compared with patients treated with placebo.[8]

In recent years, several studies have proved that rosuvastatin not only slows progression but may even promote regression of atherosclerosis, especially when used in high doses.[9,10] Rosuvastatin may also prevent the development and progression of atherosclerosis in diabetic patients, who normally have a two to threefold higher risk of CV events — not only by reducing the serum cholesterol level but also by improving cholesterol efflux from foam cells of the arterial wall via blocking the harmful effects of advanced glycation end products on macrophages.[11,12]

Hypercholesterolemia frequently co-exists with hypertension, a major risk factor for strokes and heart attacks as well as heart failure, renal impairment, peripheral vascular disease and blindness.[11] Adding lipid lowering therapy can be beneficial to hypertensive patients. It has been established that a 10% reduction in blood cholesterol and blood pressure could reduce major CVD events by 45%.[13] Moreover, rosuvastatin therapy added to conventional anti-hypertensive treatment, improved the left ventricular diastolic function and produced favourable effects on arteriosclerotic plaques in these patients.[14]

Atherosclerosis is a progressive disease, therefore prevention of CVD and control over the main risk factors for its development should be a lifelong approach.[1] Long-term compliance with statin therapy is critical for its efficacy in patients at high risk where pharmacologic therapy is indicated in addition to lifestyle interventions.[8] The CV risk reduction increases with every additional year of statin treatment.[15] Furthermore, a recently published trial using intravascular ultrasound examination has shown that a 4-year vs 8-month statin treatment by more than 4-times decreases the external elastic membrane volume (-1.1% at 8 months and -5.9% at 4 years).[16]

Krka has a long-standing experience in the area of treating CVD and has been engaged in the management of hypercholesterolemia since 1996, when its first statin, lovastatin,

tinuirano širi svoj portfelj hipolipemika koji je danas jedan od najširih na tržištu. Krkin rosuvastatin, Roswera®, najaktualniji je dodatak ovog portfelja, a uskoro će biti dostupan u dodatnim dozama od 15 mg i 30 mg koje će omogućiti najširu paletu mogućnosti liječenja rosuvastatinom na tržištu.[18] Rosuvastatin, najpotentniji statin za sniženje razina LDL kolesterola, predstavlja i prvi statin za kojeg su dokazane koristi u primarnoj prevenciji.[3,7] Zbog visoke kvalitete vertikalno integriranih proizvoda i proizvodnje koja ispunjava najstrože europske i međunarodne proizvodne i farmaceutske standarde, Krkini statini su najčešće propisivani statini na tržištima srednje, istočne i jugoistočne Europe. Od kraja 2012. godine Krkin rosuvastatin drži vodeću poziciju među generičkim rosuvastatinima na ovim tržištima.[19] Širok raspon jačina rosuvastatina od 5, 10, 20 i 40 mg omogućava prilagođavanje liječenja potrebama svakog bolesnika u sekundarnoj i primarnoj prevenciji KVB. S novom listom lijekova bit će dostupne nove doze od 15 mg i 30 mg za još bolju prilagodbu liječenja dislipidemije.

Received: 6th Mar 2013

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was approved.[17] Since then, Krka has been continually extending its hypolipemic portfolio, which is today one of the widest on the market. Krka's rosuvastatin, Roswera®, is a most current addition to this portfolio, and by being soon available in additional doses of 15 mg and 30 mg it will offer the fullest range of rosuvastatin-based treatment options on the market.[18] Rosuvastatin, the most potent statin for reducing LDL cholesterol levels, is the statin for which the benefits in primary preventive strategy were first proven.[3,7] Due to the high-quality of vertically integrated products and production complying with the strictest European and international production and pharmaceutical standards, Krka's statins are the most commonly prescribed statins on the markets of Central, Eastern and South-Eastern Europe. Krka's rosuvastatin has been holding the leading position among generic rosuvastatins on these markets since the end of 2012.[19] The wide range of rosuvastatin strengths, 5, 10, 20 and 40 mg enables adjusting the treatment to every patient's needs in both secondary and primary prevention of CVD. With new list of drugs additional doses of 15 mg and 30 mg will be available for even better tailoring of dyslipidemia treatment.

Ne idi poznatim putem. Idi tamo gdje nema staze i ostavi trag.

Do not follow where the path may lead. Go instead where there is no path and leave a trail.

(R. W. Emerson)

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