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Važnost intenzivnog snižavanja LDL kolesterola — uloga "jačih" statina

The importance of intensive lowering of LDL cholesterol — the role of potent statins

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SAŽETAK: Povećani LDL kolesterol glavni je čimbenik rizika za kardiovaskularne bolesti (KVB), poglavito koronarnu bolest srca i infarkt miokarda. Lijekovi izbora za smanjenje LDL kolesterola su statini. Velika su istraživanja pokazala da je za prevenciju KVB važno postići što je moguće nižu koncentraciju LDL kolesterola u krvi. To je posebno važno u sekundarnoj prevenciji, dakle u bolesnika s dokazanom koronarnom bolešću, preživjelim infarktom miokarda, tranzitornom ishemijskom atakom ili moždanim udarom, onih s dokazanim ateroskleroznim suženjem karotidnih ili perifernih arterija te dijabetičara. Međutim, oko 50% bolesnika s dokazanom KVB, unatoč liječenja statinima, ne postižu ciljne vrijednosti lipida koje bi sukladno smjernicama trebali imati. Možda bi rješenje tog problema mogla biti šira uporaba "jačih" statina koji snažnije smanjuju LDL kolesterol. Rosuvastatin, koji je "najjači" statin na hrvatskom tržištu, osim najsnažnijeg smanjivanja LDL kolesterola ima i neka druga dodatna korisna svojstva kao što su povećanje zaštitnog HDL kolesterola i smanjenje triglicerida, smanjenje hsCRP te smanjenje rizika venskih tromboembolija i renoprotektivne učinke. Intenzivno liječenje "jačim" statinima značajno smanjuje lipidni sadržaj ateroskleroznih nakupina što upućuje da bi oni mogli imati i učinke u smislu stabiliziranja tih nakupina. To bi moglo dodatno objasniti njihovu veliku djelotvornost u smanjenju smrtonosnih i nesmrtonosnih kardiovaskularnih događaja.

KLJUČNE RIJEČI: LDL kolesterol, HDL kolesterol, triglyceridi, infarkt miokarda, koronarna bolest srca, statini.

SUMMARY: Increased LDL cholesterol is the main risk factor for cardiovascular (CVD) diseases, particularly coronary heart disease (CHD) and myocardial infarction (MI). The treatment of choice for elevated LDL cholesterol are statins. Large clinical trials have shown that lowering of LDL cholesterol is crucial for prevention of CVD and that there is no lower threshold for benefits of such lowering. This is particularly important in secondary prevention, i.e. in patients with CHD, MI, transitory ischaemic attacks (TIA), stroke, in those with atherosclerotic changes of carotic or periphery ateries and in diabetic patients. However, approximately 50% of patients with CVD still do not attain LDL cholesterol goals according to the guidelines despite the use of statin therapy. Therefore, the use of more potent statins which produce greater reductions of LDL cholesterol when compared with other agents in this class might be a solution. Rosuvastatin, being the most potent statin on the Croatian market, provides additional benefits in the lipid profile apart from strongest LDL cholesterol lowering such as increasing HDL cholesterol and decreasing triglycerides, decreasing hsCRP, as well as reducing the risk of venous thromboembolism and preserving renal function. Aggressive lipid-lowering therapy with more potent statins can significantly reduce the lipid content of the atherosclerotic plaques which implies that they may be able to stabilize plaques. This can additionally explain their efficacy in reducing fatal and nonfatal cardiovascular events.

KEYWORDS: LDL cholesterol, HDL cholesterol, triglycerides, myocardial infarction, coronary heart disease, statins.

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Dobro je poznato da je dislipidemija, posebno hiperkolesterolemija, uz arterijsku hipertenziju, pušenje, dijabetes i debljinu, nedvojbeno najvažniji čimbenik rizika za kardiovaskularne bolesti (KVB), navlastito koronarnu bolest srca (KBS) i infarkt miokarda. Kako su te bolesti već godinama glavni razlog smrtnosti u Hrvatskoj i od njih umire gotovo polovica pučanstva (u 2010. godini umrlo je od njih 49,2% svih stanovnika Hrvatske), one bitno doprinose znatno kraćem očekivanom trajanju života u Hrvatskoj nego u, primjerice, zemljama Europske unije — svega 73,5 godina

It is well known that dyslipidemia, especially hypercholesterolemia with arterial hypertension, smoking, diabetes and obesity is undisputedly the most important risk factor for cardiovascular diseases (CVD), particularly coronary heart disease (CHD) and myocardial infarction. Since these diseases have been the main cause of mortality in Croatia for many years and almost half of the population die of them (in 2010 49.2% of all Croatian citizens died of them), they significantly contribute to much shorter life expectancy in Croatia than for example in the countries of the European Union — only 73.5 years of age for males and 79.6 years of

za muškarce i 79,6 godine za žene u nas 2010. godine[1]. Posebno brine što povećani pobol i pomor od tih bolesti sve više pogađaju mlađe skupine bolesnika oba spola koji su u najproduktivnijoj životnoj dobi. Stoga je jasno ogromno javno zdravstveno značenje borbe protiv čimbenika rizika koji ih uzrokuju, posebno hiperkolesterolemije[2,3].

Ciljne vrijednosti LDL kolesterola i ostalih lipidnih pokazatelja

Glavni lipidni pokazatelj koji se liječenjem dislipidemija pokušava sniziti je LDL kolesterol[4]. Sukladno novim smjernicama o liječenju dislipidemija koje su zajednički načinili Europsko kardiološko društvo i Europsko društvo za aterosklerozu u bolesnika s vrlo visokim rizikom KVB, a to su svi oni sa dokazanom KVB (invazivnim ili neinvazivnim dijagnostičkim metodama, oni s preboljelim infarktom miokarda, akutnim koronarnim sindromom, ishemijskim moždanim udarom ili pak nakon koronarne revaskularizacije) ili s dijabetesom tipa 2 stariji od 40 godina odnosno koji imaju jedan ili više drugih čimbenika rizika za KVB kao i oni s dijabetesom tipa 1 i oštećenjima ciljnih organa (primjerice mikroalbuminurijom) te oni s umjerenim ili teškim zatajenjem bubrega (glomerulska filtracija <60 ml/min/1,73m^2) odnosno oni s razinom SCORE ≥10%, LDL-kolesterol treba smanjiti na ispod 1,8 mmol/l odnosno za najmanje 50% ako se ova ciljna vrijednost nikako ne može postići[4].

U osoba s visokim rizikom za KVB, a to su one s izraženim jednim čimbenikom rizika (primjerice jako povećanim kolesterolom ili pak s dijabetesom tipa 2), odnosno s razinom SCORE ≥5 do <10%, valja postići LDL-kolesterol manji od 2,5 mmol/l.

Osobe s umjerenim rizikom za KVB, kojih ima mnogo među onima srednje životne dobi, a to su osobe sa SCORE >1 do ≤5%, trebaju imati LDL-kolesterol manji od 3,0 mmol/l dok oni s niskim rizikom (SCORE <1%) ne zahtijevaju nikakvu intervenciju ili, ako im je LDL-kolesterol veći od 2,5 mmol/l, trebaju samo promijeniti način života u onaj zdraviji.

Smatra se da visoki, odnosno vrlo visoki rizik imaju i bolesnici koji imaju neku od prirođenih, genski uzrokovanih dislipidemija. Najvažnija iz te skupine poremećaja je obiteljska hiperkolesterolemija kod koje dolazi do izrazitog povećanja količine LDL kolesterola u krvi (>8,5 mmol/l ali i manje ako imaju preuranjenu KVB, ksantome ili pak anamnestički podatak o preuranjenoj KVB u obitelji)[5]. Smatra se da je rizik KBS također povećan ako je HDL-kolesterol manji od 1,0 u muškaraca ili manji od 1,2 mmol/l u žena, odnosno ako su trigliceridi veći od 1,7 mmol/l[4].

Prema tome, koncentracije LDL kolesterola veće od navedenih valjalo bi u osoba koje nemaju nikakvih kliničkih znakova koronarne, cerebrovaskularne ili periferne bolesti (primarna prevencija) kao i u onih koji su u velikom riziku jer su im dokazana aterosklerozna suženja koronarnih, moždanih ili perifernih krvnih žila odnosno dijabetes (sekundarna prevencija), smanjiti na spomenute ciljne vrijednosti. To se u onih s umjerenim rizikom i LDL kolesterolom manjim od 2,5 mmol/l te u onih s vrlo malim rizikom može u pravilu postići samo dijetom i pojačanom fizičkom aktivnošću. Međutim, u svih ostalih, ako se promjenom načina života ne uspije normalizirati vrijednosti lipida, odnosno postići spomenute ciljne vrijednosti, primjenjuju se lijekovi. Lijekove valja, uz savjete o promjeni načina života, bez odgađanja odmah početi davati svima koji imaju visoki ili vrlo visoki rizik te LDL kolesterol veći od 2,5 odnosno 1,8 mmol/l.

age for women in Croatia in 2010[1]. We are particularly concerned with the fact that younger groups of patients of the both genders in the most productive age are more and more affected by ever higher morbidity and mortality from these diseases. Therefore we become aware of the enormous public health importance of combating the risk factors that cause them, especially hypercholesterolemia[2,3].

Target values of LDL cholesterol and other lipid indicators

The main lipid indicator which we by treating dyslipidemia try to lower is the LDL cholesterol[4]. According to the new guidelines on the treatment of dyslipidemia, which have been jointly created by the European Society of Cardiology and European Society of Atherosclerosis in patients with very high CVD risk, and these are all those with proven CVD (by invasive or noninvasive diagnostic methods, those with a history of myocardial infarction, acute coronary syndrome, ischemic stroke, or after coronary revascularization) or with type 2 diabetes aged over 40 or who have one or more other risk factors for CVD and those with type 1 diabetes and damaged target organs (e.g. microalbuminuria) and those with moderate or severe renal failure (glomerular filtration <60 ml/min/1.73m^2) or those with level SCORE ≥10%, LDL-cholesterol should be lowered to below 1.8 mmol/l or by at least 50% if this target value cannot be achieved[4].

In persons with high CVD risk, these are those persons with emphasized one risk factor (such as strongly elevated cholesterol or type 2 diabetes), or with level SCORE ≥5 to <10%, LDL-cholesterol lower than 2.5 mmol/l needs to be achieved.

Persons with moderate risk of CVD whose number is great among middle aged people, these are the persons with SCORE >1 to ≤5%, need to have LDL-cholesterol lower than 3.0 mmol/l while those with low risk (SCORE <1%) are not required to undergo any intervention or if their LDL-cholesterol exceeds 2.5 mmol/l, they just need to change their way of life in the way to lead healthier way of life.

It is believed that patients who have some of the congenital or genetically caused dyslipidemia have a high or a very high risk. The most important disorder from this group of disorders is the familial hypercholesterolemia, which causes a pronounced elevation in the amount of LDL cholesterol in blood (>8.5 mmol/l but even less if they have premature CVD, xanthoma, or a family history of premature CVD in the family).[5] It is believed that the CHD risk is also higher if the HDL-cholesterol is lower than 1.0 in men or lower than 1.2 mmol/l in women, or if triglycerides are higher than 1.7 mmol/l[4].

Thus, LDL cholesterol concentrations higher than those above mentioned should be lowered to the above target values in persons who have no clinical signs of coronary, cerebrovascular or peripheral diseases (primary prevention) as well as in those who are at high risk because atherosclerotic narrowing of the coronary, cerebral, or peripheral blood vessels or diabetes (secondary prevention) were proved for them. This can be achieved only by diet and increased physical activity in those with moderate risk and LDL cholesterol lower than 2.5 mmol/l and in those with very low risk. However, in all others the drugs will be used if they fail to normalize lipid values or achieve the above mentioned target values by changing their way of life. In addition to giving advice on changes to the lifestyle, drugs are to be administered immediately to all those who have high or very high risk and whose LDL cholesterol is higher than 2.5 or 1.8 mmol/l.

Kakvo je stvarno stanje u Europi i u nas?

Procjene srednje vrijednosti ukupnog kolesterola u pučanstvu različitih europskih zemalja kreću se za muškarce starije od 15 godina od 4,5 do 6,2 mmol/l, a za žene starije od 15 godina od 4,6 do 6,1 mmol/l. Za Hrvatsku je ta procjena za muškarce 5,5, a za žene 5,3 mmol/l, dakle prosječno više od poželjnog[6]. Još je veći problem što mnogi bolesnici s KVB imaju previsoke koncentracije ukupnog i LDL kolesterola, a njih obvezatno treba liječiti. Na takvo nezadovoljavajuće stanje upućuju i podaci velikih istraživanja provedenih u Hrvatskoj, ali i u Europi. Tako nešto stariji podaci istraživanja TASPIC-CRO ukazuju da je 2003. godine u Hrvatskoj čak 68% bolesnika s dokazanom KBS imalo vrijednosti LDL kolesterola veće od onih koje su tadašnjim smjernicama bile smatrane prihvatljivim (a one su bile značajno više nego što savjetuju najnovije smjernice)[7]. U ispitivanju EUROASPIRE III je 2007. godine ustanovljeno da je čak 55,9% bolesnika s dokazanom KBS u Hrvatskoj imalo LDL kolesterol ≥2,5 mmol/l[8]. Prema tome, daleko preveliki broj osoba koje imaju rizik za KVB imaju previsoke koncentracije LDL kolesterola i svakako bi ih trebalo jače sniziti. Zašto se to ipak ne događa? Dio odgovora zacijelo leži i u nedovoljnom prepoznavanju dislipidemije kao najvažnijeg čimbenika rizika za KVB od strane bolesnika, ali i liječnika[9,10].

Međutim, niti koncentracije protuaterogenog HDL kolesterola, osobito u bolesnika s KVB odnosno s visokim i jako visokim rizikom, u prosjeku nikako nisu zadovoljavajuće. Tako je u EUROASPIRE III istraživanju čak 34,1% bolesnika s dokazanom KBS u Hrvatskoj imalo preniski HDL kolesterol, a valja naglasiti da je u Europi prosječno još više takvih bolesnika — čak 36,7%[8]. Dakle, i preniski HDL kolesterol bi u velikog broja osoba trebalo povećati daleko uspješnije nego što se to čini.

Statini i liječenje hiperkolestrolemije — postoji li donja granica?

Od početka njihove šire kliničke uporabe 1984. godine, terapijom prvog izbora za liječenje hiperkolesterolemije smatraju se inhibitori HMG-CoA reduktaze ili statini. Statini prve generacije bili su lovastatin, simvastatin i pravastatin nakon kojih su na tržište došli fluvastatin i atorvastatin, a zadnji je na naše tržište došao rosuvastatin. Oni se daju jednom navečer ili podijeljeno u 2 doze od kojih jedna obvezatno mora biti večernja. Uvijek se mora početi s najmanjom dozom koja se onda postupno povećava dok se ne postigne ciljna vrijednost kolesterola u krvi i na toj se dozi ostaje trajno uz povremene kontrole[11]. Dok se ne postignu željene ciljne vrijednosti lipida u krvi, lipidi u krvi se kontroliraju svaka 2-3 mjeseca, a kasnije svakih godinu dana.

Od spomenutih se statina rosuvastatin i atorvastatin smatraju "jačim" statinima. Naime, uz ostale manje razlike koje postoje među pojedinim statinima, najvažnija je ta da miligram jednog statina nije po svojoj učinkovitosti u smanjivanju LDL kolesterola jednak miligramu drugog statina. Tako će, primjerice, doza od 5 mg rosuvastatina smanjiti LDL kolesterol za otprilike slični postotak kao i 20 mg atorvastatina ili 40 mg simvastatina ili pak 80 mg lovastatina, dok čak ni 80 mg fluvastatina neće uspjeti postići takvo smanjenje LDL kolesterola. Sukladno tome, dozom od 40 mg rosuvastatina postići će se nešto jače smanjenje LDL kolesterola nego sa 80 mg atorvastatina dok niti najveće doze drugih statina tj. 80 mg, neće ni približno postići takav učinak[12].

What is the real situation in Europe and our country like?

Estimates of the mean values of total cholesterol in the population of different European countries vary for men over 15 years of age from 4.5 to 6.2 mmol/l, and for women over 15 years of age from 4.6 to 6.1 mmol/l. For Croatia, this estimate for men is 5.5 and women 5.3 mmol/l, so, on the average, higher than what is desired[6]. Another even greater problem is that many patients with CVD have too high concentrations of total and LDL cholesterol which must be treated. This unsatisfactory state is indicated by the data of large studies conducted not only in Croatia, but in Europe as well. So, some older data of the study TASPIC-CRO shows that in 2003 in Croatia even 68% of patients with proved CHD had higher LDL cholesterol values than those that were considered acceptable according to the previous guidelines (and they were significantly higher than those suggested by the most recent guidelines)[7]. In EUROASPIRE III study in 2007 it was found that as many as 55.9% of patients with proved KBS in Croatia had LDL cholesterol ≥2.5 mmol/l[8]. Accordingly, far too many persons who are at risk for CVD have too high LDL cholesterol concentrations and they certainly should lower them significantly. Why does not it happen anyway? A part of the answer surely lies in the inadequate recognition of dyslipidemia as a major risk factor of CVD not only by a patient but also a physician as well[9,10].

However, even antiatherogenic HDL cholesterol concentrations, especially in patients with CVD or with high and very high risk, are on the average by no means satisfactory. So in the EUROASPIRE III study even 34.1% of patients with proven CHD in Croatia had too low HDL cholesterol, and it should be noted that in Europe on the average there are even more such patients — even 36.7%.[8] So, too low HDL cholesterol should be elevated in a large number of people far more successfully than it seems.

Statins and treatment of hypercholesterolemia — is there a lower limit?

Since the beginning of their wider clinical use in 1984, HMG-CoA reductase inhibitors or statins are considered to be the first choice therapy for the treatment of hypercholesterolemia. First generation statins were lovastatin, simvastatin and pravastatin, followed by fluvastatin and atorvastatin that were launched on the market, and the last one to be launched on the market was rosuvastatin. They are administered once in the evening or are divided into 2 doses, of which one must be administered in the evening. We must always begin with the lowest dose which is then gradually increased until the target value of cholesterol in the blood is achieved and such dose is to be maintained permanently with occasional follow-ups[11]. Lipid levels are to be followed-up every 2-3 months until the desired target lipid levels are achieved and later they are followed-up every year.

Out of these statins, rosuvastatin and atorvastatin are considered to be "more potent" statins. Actually, apart from some other minor differences that exist among specific statins, the most important is that one milligram of one statin does not equal one milligram of some other statin in its efficacy in lowering LDL cholesterol levels. Thus, for example, a dose of 5 mg of rosuvastatin will reduce LDL cholesterol by approximately similar percentage as 20 mg of atorvastatin or 40 mg of simvastatin or 80 mg of lovastatin, while even 80 mg of fluvastatin will not manage to achieve such a reduction in LDL cholesterol. Accordingly, a dose of 40 mg of rosuvastatin will achieve some greater lowering in LDL cholesterol than a dose with 80 mg of atorvastatin while even

Već su rezultati najvećeg ispitivanja sa statinima, tzv. *Heart Protection Study*, objavljeni prije šest godina, ukazali da snižavanje koncentracije LDL kolesterola u krvi statinima na vrijednosti niže od onih koje su tada bile smatrane 'normalnim', tj. za LDL kolesterol od 3,0 do 2,0 mmol/l, bez obzira na početnu koncentraciju LDL kolesterola donose dodatnu korist bolesnicima koji su u velikom riziku[13]. Sukladni tome bili su i rezultati velikog istraživanja ASCOT-LLA, u kojem je rabljen atorvastatin, koji su također upućivali da snižavanje LDL kolesterola s početnih 'svega' 3,4 mmol/l na 1,2 mmol/l donosi dodatnu korist u smislu manjeg broja kardiovaskularnih zbivanja i preživljenja bolesnika[14]. Na to su upućivali i rezultati novijih ispitivanja TNT, PROVE IT-TIMI 22, ASTEROID, IDEAL i REVERSAL[15-20]. Gotovo su sva ta istraživanja provedena s tzv. "jačim" statinima — rosuvastatinom i atorvastatinom. Ona su pokazala da intenzivno snižavanje LDL kolesterola pomoću tih statina s ne baš jako povećanih vrijednosti na koncentracije od svega oko 1,55 do 1,8 mmol/l uzrokuje značajno smanjenje ponovne pojave infarkta miokarda, smrtnosti, potrebe za revaskularizacijom pa i pojave moždanog udara u bolesnika s velikim rizikom, primjerice zbog preživljenog akutnog koronarnog sindroma, odnosno značajno ultrazvučno dokazano smanjenje aterosklerotičkih suženja arterija.

Upravo je istraživanje REVERSAL još prije desetak godina pokazalo da treba znatno jače nego se to ranije smatralo smanjiti LDL kolesterol u krvi jer se tek s 45% smanjenjem LDL kolesterola uspjelo postići zaustavljanje napredovanja aterosklerotskih nakupina u arterijama, odnosno njihova regresija, dok se uz svega 25% smanjenja LDL kolesterola progresija aterosklerotičkih nakupina nastavljala[20]. Dapače, nedavno objavljeni rezultati istraživanja provedenog na 1.054 bolesnika sa akutnim infarktom miokarda koji su imali LDL kolesterol manji od 1,8 mmol/l pokazali su da je čak i u njih davanje statina nakon jedne godine dovelo do značajnog smanjenja velikih koronarnih događaja, osobito koronarne smrtnosti i potrebe za revaskularizacijom[21].

Sva su ta istraživanja ukazala da je, izgleda, točna postavka koja, kada je riječ o ukupnom i LDL kolesterolu, glasi: što niže — to bolje, tj. da zapravo ne postoji donja granica kolesterola ispod koje njegovo snižavanje, osobito u izrazito ugroženih bolesnika, ne smanjuje rizik. Pritom je dokazano da takvo jako snižavanje ukupnog i LDL kolesterola nedvojbeno nije vezano uz veću pojavu zloćudnih bolesti ili ne-kardiovaskularne smrtnosti, što se ranije pretpostavljalo. Međutim, ne smiju se zanemariti nedavno objavljeni rezultati metaanalize koja je obuhvatila pet velikih ispitivanja načinjenih kod 32.752 bolesnika, a koja je pokazala da intenzivno liječenje statinima nosi i nešto veći rizik nastanka dijabetesa nego li liječenje manjim dozama statina[22]. Doduše, prethodno je i metaanaliza 13 velikih ispitivanja sa statinima načinjenih na 91.140 bolesnika pokazala da statini općenito malo povećavaju rizik nastanka dijabetesa[23]. Ipak, u ovom trenutku postoji opći konsenzus da korist jačeg sniženja LDL kolesterola uvelike nadmašuje spomenuti rizik.

Prednosti "jačih" statina

Budući da su već navedeni rezultati nekoliko EUROASPIRE istraživanja jasno pokazali da oko 50% bolesnika s dokazanom KBS ne postiže ciljne vrijednosti LDL kolesterola usprkos uzimanju statina (u EUROASPIRE III je prosječno oko 80% bolesnika u Europi uzimalo statine, u Hrvatskoj 83,1%), očito je da bolesnici ne uzimaju statine u odgovarajućoj dozi, odnosno da uzimaju "preslabe" statine[24]. Upravo

the highest doses of some other statins, i.e. 80 mg will not even closely achieve such an effect[12].

The results of the largest study with statins, the *Heart Protection Study*, published six years ago, showed that lowering the LDL cholesterol concentrations in blood with statins to values lower than those which were then considered 'normal', i.e. for LDL cholesterol from 3.0 to 2.0 mmol/l, regardless of the initial LDL cholesterol concentration yield additional benefit to patients who are at great risk[13]. Similar results were obtained from the large study ASCOT-LLA, where atorvastatin was used, and the results also showed that lowering of LDL cholesterol from the initial 'only' 3.4 mmol/l to 1.2 mmol/l yields additional benefits in terms of reduced number of cardiovascular events and survival of patients[14]. This was indicated even by the results of recent studies TNT, PROVE IT-TIMI 22, ASTEROID, IDEAL and REVERSAL[15-20]. Almost all those studies were conducted with the so called potent statins — rosuvastatin and atorvastatin. They showed that great lowering of LDL cholesterol by applying such statins from not so very elevated values to concentrations of only around 1.55 to 1.8 mmol/l results in a significant lowering of recurrence of myocardial infarction, mortality, need for revascularization and the occurrence of stroke in high risk patients, as for example due to the history of acute coronary syndrome, or significant lowering of atherosclerotic narrowing of the arteries proved by ultrasound.

It is the REVERSAL study that some ten years ago showed that the LDL cholesterol in blood should be much more significantly lowered than what was thought earlier, because we managed to stop the progression of atherosclerotic accumulation in the arteries or its regression by lowering LDL cholesterol to 45%, while the progression of atherosclerotic accumulations continued when the LDL cholesterol was lowered to only 25%[20]. As a matter of fact, the recently published results of the study conducted on 1,054 patients with acute myocardial infarction who had LDL cholesterol lower than 1.8 mmol/l showed that even administering statins to them after one year led to a significant reduction in major coronary events, especially coronary mortality and the need for revascularization[21].

All these studies showed that the assumption regarding total and LDL cholesterol seems to be true and it says: the lower cholesterol we achieve, the better it is, that is, in fact there is no lower limit below which cholesterol lowering will not reduce the risk especially when high risk patients are concerned. It has been proven that such a strong lowering of total and LDL cholesterol is certainly not related to an increased occurrence of malignant diseases or non-cardiovascular mortality, as it was previously assumed. However, we should not ignore the recently published results of the meta-analysis which included five major tests conducted on 32,752 patients, which showed that intensive treatment by using statins is connected with a slightly higher risk of developing diabetes than the treatment with lower doses of statin[22]. However, the meta-analysis which included 13 major trials with statins previously conducted on 91,140 patients showed that statins generally slightly increase the risk of diabetes[23]. However, at this point there is general consensus that the benefit of a higher reduction of LDL cholesterol greatly outweighs this risk.

Advantage of more potent statins

Since the above results of several EUROASPIRE studies clearly showed that about 50% of patients with proven CHD does not achieve target LDL cholesterol levels despite taking statins (in the EUROASPIRE III there was around 80% of patients in Europe who took statins, 83.1% in Croatia), it

to naglašava važnost onih statina koji snažnije smanjuju LDL kolesterol i time omogućuju intenzivniju terapiju dislipidemija. "Najjači" statin na tržištu — rosuvastatin je ujedno i prvi statin koji je službeno dobio indikaciju da se daje u primarnoj prevenciji KVB. Naime, u velikom istraživanju JUPITER provedenom na 17,802 ispitanika dokazano je da primjena 20 mg rosuvastatina klinički zdravim osobama koje nisu imale visoki rizik za KVB već su imale prosječne koncentracije LDL kolesterola (LDL kolesterol <3,4 mmol/l) ali povišenu visoko specifičnu C reaktivnu bjelančevinu (hsCRP) kao važni biljeg upale (a već se odavno zna da je ateroskleroza dijelomice uzrokovana i kroničnom upalom slabog intenziteta), nakon prosječno 1,9 godine značajno smanjuje pojavu velikih kardiovaskularnih događaja[25]. Rosuvastatin je pritom ne samo dodatno bitno smanjio LDL kolesterol već je i značajno povećao HDL kolesterol (povećava ga jače nego atorvastatin) i smanjio trigliceride. Pritom su učinci na smanjenje hsCRP i LDL kolesterola bili međusobno neovisni, a najveću korist imali su ispitanici u kojih je postignut LDL kolesterol manji od 1,8 mmol/l i hsCRP manji od 2 mg/l, dok je učinak bio još bolji onih u kojih je postignut hsCRP manji od 1 mg/l.

Osobito je važno obilježje rosuvastatina da uz smanjenje LDL kolesterola značajno smanjuje i trigliceride te povećava HDL kolesterol. To je pokazano još u ispitivanju ASTEROID u kojem je 40 mg rosuvastatina povećavalo HDL kolesterol za prosječno 14,7%[18]. Naime, budući da je niz istraživanja nedvojbeno pokazao da su osim povećane koncentracije LDL kolesterola i povećani trigliceridi te sniženi HDL kolesterol važan čimbenik rizika za nastanak ateroskleroze i njome uzrokovanih KVB, vrlo je važno osim smanjenja LDL kolesterola smanjiti trigliceride i povećati smanjeni HDL kolesterol, osobito u bolesnika s dijabetesom tipa 2 i metaboličkim sindromom[26-28].

Zanimljivo je i neočekivano opažanje u ispitivanju JUPITER vezano uz značajno smanjenje pojave venskih tromoembolija[25]. Pritom, iako se radilo o snižavanju LDL kolesterola na tako niske razine, nuspojave rosuvastatina (mijalgija, artralgija, opstipacija, mučnina) nisu bile ništa češće nego pri davanju drugih, znatno slabijih statina, odnosno nije bilo bitnijih razlika u odnosu na skupinu ispitanika koja je umjesto rosuvastatina dobivala placebo. To su potvrdili i rezultati velike metaanalize koja je izravno uspoređivala nuspojave na različite statine u 16.876 ispitanika iz 33 kliničkih istraživanja[29]. Kada je učestalost nuspojava na rosuvastatin provjerena u jednom drugom velikom ispitivanju koje je obuhvatilo 200.000 osoba/godina, potvrđeno je da usprkos svojem jačem djelovanju na snižavanje LDL kolesterola, vjerojatno zato što mu katabolizam ne ovisi o detoksifikaciji u jetri putem citokroma P450 3A4, ne uzrokuje veće nuspojave vezane uz jetru, mišiće ni bubrege u usporedbi s ostalim statinima[30].

Budući da je u ranim ispitivanjima uočeno da davanje izrazito visokih doza rosuvastatina, tj. 80 mg može uzrokovati proteinuriju zbog djelovanja na proksimalne bubrežne tubule (tako se visoke doze rosuvastatina stoga i ne preporučuju), vrlo su značajni rezultati metaanalize koja je ispitivala učinke intenzivnog snižavanja LDL kolesterola s 40 mg rosuvastatina na 40.600 ispitanika koji prethodno nisu imali nikakvu bolest bubrega, a bili su sudionici 36 velikih ispitivanja. Dokazano je da intenzivno liječenje nije utjecalo na rizik nastanka zatajenja bubrega u tih bolesnika[31].

is obvious that patients do not take statins in appropriate doses, or they take the last powerful statins[24]. It emphasizes the importance of those statins that reduce LDL cholesterol more strongly and thus allow more intensive treatment of dyslipidemia. The most potent statin on the market — rosuvastatin is also the first statins which was officially prescribed for administration in the primary prevention of CVD. Specifically, the large JUPITER study conducted on 17.802 patients was proved that administering of 20 mg of rosuvastatin to clinically healthy persons who did not have a high CVD risk but had average LDL cholesterol concentrations (LDL cholesterol <3.4 mmol/l) but who had elevated high specific C reactive protein (hsCRP) as an important marker of inflammation (and we have long known that atherosclerosis is partly caused by low intensity chronic inflammation), after an average of 1.9 years significantly reduces the occurrence of major cardiovascular events[25]. Rosuvastatin did not only additionally and substantially lowered LDL cholesterol, but it also significantly elevated HDL cholesterol (it elevated it by more than atorvastatin) and lowered triglycerides. The effects on lowering LDL cholesterol and hsCRP were independent of each other, and had the greatest benefit in patients who had LDL cholesterol lower than 1.8 mmol/l and hsCRP lower than 2 mg/l achieved, while the effect was even greater in those who had hsCRP achieved lower than 1 mg/l.

A particularly important characteristic of rosuvastatin is that lowering LDL cholesterol is accompanied by significant lowering of triglycerides and elevation of HDL cholesterol. This was shown in the ASTEROID study where 40 mg of rosuvastatin elevated the HDL cholesterol by the average value of 14.7%[18]. Namely, since a great number of studies have clearly demonstrated that apart from elevated LDL cholesterol concentration even the elevated triglycerides and lowered HDL cholesterol are an important risk factor for occurrence of atherosclerosis and related CVD, it is very important not only to lower LDL cholesterol, but also to lower triglycerides and elevate the lower HDL cholesterol, especially in patients with type 2 diabetes and metabolic syndrome[26-28].

An interesting and unexpected observation in the JUPITER study is related to a significant reduction of occurrence of venous thromoembolism[25]. Although lowering of LDL cholesterol to such low levels was concerned, the rosuvastatin side effects (myalgia, arthralgia, constipation, nausea) were no more frequent than when other, less powerful statins were administered, and there were no more significant differences recorded compared to the group of subjects that instead of rosuvastatin was administered placebo. This was confirmed by the results of the large meta-analysis that directly compared the side effects of different statins in 16,876 subjects from 33 clinical trials[29]. When the frequency of side effects of rosuvastatin was checked in another large study that included 200.000 persons/years, it was confirmed that despite its stronger effect on lowering the LDL cholesterol, probably because the catabolism does not depend on detoxification in the liver by cytochrome P450 3A4, it does not cause greater side effects associated with the liver, muscles or kidneys when compared to the other statins[30].

Since the early studies revealed that administering very high doses of rosuvastatin, or 80 mg can cause proteinuria due to the effects on renal proximal tubule (therefore, such high doses of rosuvastatin are not recommended), the results of meta-analysis proved to be very important which tested the effects of intensive lowering of LDL cholesterol from 40 mg of rosuvastatin in 40,600 patients who previously did not have any kidney disease, and were participants in 36 large

U suglasju s time su i rezultati ispitivanja AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[32]. Naime, to je ispitivanje prvenstveno učinjeno da se ispitaju učinci rosuvastatina na bolesnike sa terminalnim zatajenjem bubrega koji su bili na kroničnoj hemodijalizi. Iako se ovim ispitivanjem nije uspjelo dokazati da takvo liječenje uzrokuje statistički značajne korisne učinke na smanjenje kardiovaskularnih događaja u tih bolesnika (smanjenje je bilo 16,2%), ono je ipak vrlo važno. Naime, tim je ispitivanjem bilo obuhvaćen 731 bolesnik s dijabetesom i u njih je dokazano značajno smanjenje (za 32%) kardiovaskularnih događaja. Stoga je zaključeno da bi liječenje rosuvastatinom bolesnika s dijabetesom na hemodijalizi moglo smanjiti rizik smrtonosnih i nesmrtonosnih koronarnih događaja u tih bolesnika. Dapače, izgleda da u bolesnika s dijabetičkom nefropatijom rosuvastatin smanjuje albuminuriju i oksidacijski stres mehanizmima neovisnim od smanjenja LDL kolesterola[33].

Još je jedna važna spoznaja proistekla iz već spomenutog ispitivanja JUPITER. Naime, u tom je ispitivanju bilo 5.695 ispitanika starijih od 70 godina koji nisu imali hiperkolesterolemiju ali su imali povećani hsCRP. Naknadnom analizom pokazano je da i u njih davanje rosuvastatina smanjuje incidenciju velikih kardiovaskularnih događaja pa se slijedom toga i starijima može preporučiti uzimanje jačih statina[34].

Učinci "jačih" statina na strukturu ateroma i njihova ostala pleiotropna djelovanja

Osim uobičajenih pleiotropnih učinaka koji su dokazani i za ostale statine u uobičajenim dozama, uočeno je da intenzivno liječenje "jačim" statinima može značajno smanjiti lipidnu jezgru ateroma već za nekoliko tjedana te stabilizirati nestabilne aterome. To je dokazano u nedavno završenom istraživanju u kojem je uz pomoć intravaskularnog ultrazvuka (IVUS) evaluiran učinak 40 mg rosuvastatina nakon šest do osam tjedana u usporedbi s dvojnim antiagregacijskim liječenjem i statinom kojeg su ti bolesnici od ranije dobivali nazvanom YELLOW (Reduction in YELlow Plaque by Aggressive Lipid LOWering Therapy). Pokazano je značajno smanjenje lipidne jezgre ateroma u bolesnika koji su intenzivno liječeni rosuvastatinom[35]. Slični su rezultati postignuti i u netom objavljenom istraživanju u kojem je uz pomoć IVUS-a uspoređivan učinak dva "jaka" statina — 20 mg atorvastatina i 10 mg rosuvastatina, dakle u uobičajenim i usporedivim dozama. Oba su lijeka nakon šest mjeseci uzimanja pokazala značajnu učinkovitost u postizanju regresije koronarne ateroskleroze u bolesnika koji ranije nisu dobivali statine, ali je učinak bio jači u onih koji su dobivali rosuvastatin[36]. Već se otprije na temelju rezultata istraživanja COSMOS, u kojem je također rabljen IVUS, zna da rousvastatin smanjuje aterome u bolesnika sa stabilnom KBS[37]. Može se očekivati da će slični biti i rezultati velikog istraživanja nazvanog SATURN (Study of coronary Atheroma by inTravascular Ultrasound: effect of Rosuvastatin versus atorvastatiN) koje se upravo provodi na 1385 bolesnika sa dokazanom KBS koji će tijekom 24 mjeseci dobivati 40 mg rosuvastatina ili 80 mg atorvastatina. Provjeravati će se učinak na aterome uz pomoć IVUS-a, ali i učinak na kardiovaskularne događaje[38].

U suglasju sa spomenutim su i rezultati istraživanja nazvanog METEOR (Measuring Effects on Intima-Media Thickness) koje je provedeno na 984 ispitanika s umjereno povećanim rizikom KVB te umjereno povećanom debljinom intistudies. It is proved that intensive treatment did not affect the risk of occurrence of kidney failure in these patients[31].

This was confirmed by the results of the AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)[32]. This study was namely primarily done to test the effects of rosuvastatin in patients with end-stage renal failure who were undergoing chronic hemodialysis. Although this study failed to prove that such treatment causes statistically significant beneficial effects on reducing cardiovascular events in these patients (reduction was 16.2%), it is nevertheless very important. Specifically, this study included 731 patients with diabetes and a significant reduction (32%) of cardiovascular events was proved for them. It was therefore concluded that the rosuvastatin treatment of patients with diabetes who underwent hemodialysis could reduce the risk of fatal and non-fetal coronary events in such patients. Indeed, it seems that in patients with diabetic nephropathy, rosuvastatin reduces albuminuria and oxidative stress by mechanisms that are independent of lowering LDL cholesterol[33].

There is another important information obtained from the already mentioned JUPITER. Specifically, this study included 5.695 patients over 70 years of age who did not have hypercholesterolemia, but they had elevated hsCRP. The subsequent analysis showed that administering rosuvastatin to them reduces the incidence of major cardiovascular events and consequently we can recommend administration of more potent statins to elderly patients.

The effects of more potent statins on the structure of atheroma and their other pleiotropic effects

Besides the usual pleiotropic effects that are proven even for some other statins in usual doses, it was observed that intensive treatment by more potent statins may significantly reduce the atheromatous lipid core within a couple of weeks and stabilize unstable atheromas. It has been proved in the recently completed study in which the effect of 40 mg rosuvastatin was evaluated by using intravascular ultrasound (IVUS) after six to eight weeks compared with dual antiaggregation treatment and with statin that these patients were previously administered called YELLOW (Reduction in Yellow Plaque by Aggressive Lipid LOWering Therapy). The significant lowering of atheromatous lipid core in patients who were intensively treated by rosuvastatin was shown[35]. Similar results were obtained in the recently published study where by using IVUS we compared the effect of two more potent statins — 20 mg of atorvastatin and 10 mg of rosuvastatin, it means, in usual and comparable doses. The both drugs after six months of their administration showed a significant efficacy in achieving the regression of coronary atherosclerosis in patients who were not previously administered statins, but the effect was better than in those who were administered rosuvastatin[36]. It has been long known that according to the results of the COSMOS study, where IVUS was also applied, rousvastatin reduces atheromas in patients with stable CHD[37]. We can expect similar results of the large study called SATURN (Study of coronary Atheroma by in Travascular Ultrasound: effect of Rosuvastatin versus atorvastatin), which is being conducted on 1,385 patients with proven CHD who will during a 24 months' period receive 40 mg of rosuvastatin or 80 mg of atorvastatin. The effect

ma-medija karotida — CIMT (taj je pokazatelj važan surogatni biljeg ateroskleroze i korelira s aterosklerotskim promjenama na koronarnim arterijama). Prosječni LDL kolesterol im je bio oko 4 mmol/l, a dobivali su ili 40 mg rosuvastatina ili placebo. Rezultat istraživanja je jasno pokazao da rosuvastatin uzrokuje značajno smanjenje progresije CIMT[39]. Liječenje rosuvastatinom je u usporedbi s pravastatinom značajno usporilo povećanje debljine intima-medija nakon dvanaest mjeseci i u netom završenom ispitivanju pod nazivom JART (Justification for Atherosclerosis Regression Treatment)[40].

Kada je, pak, riječ o pleiotropnim učincima "jačih" statina valja spomenuti vrlo iznenađujuće upravo objavljeno opažanje da liječenje rosuvastatinom može donekle smanjiti incidenciju pneumonije[41]. Podjednako su iznenađujući bili i rezultati također nedavno objavljene naknadne analize bolesnika iz istraživanja JUPITER koji su pokazali da su povećane količine hsCRP povezane s većim rizikom pojave fibrilacije atrija, a da liječenje rosuvastatinom značajno smanjuje taj rizik[42].

Zaključak

Usprkos velikom napretku u sprječavanju pobola i smrtnosti od KVB, a osobito KBS i infarkta miokarda, postignutom statinima, još uvijek mnogi bolesnici ne dosižu ciljne vrijednosti lipida u krvi. Budući je nedvojbeno pokazano da, osobito u sekundarnoj prevenciji, odnosno u izrazito ugroženih bolesnika, treba postići što je moguće nižu koncentraciju LDL kolesterola, da bi se to postiglo nerijetko treba davati tzv. "jače" statine koji postižu snažnije smanjenje LDL kolesterola. Dokazano je, osobito za rosuvastatin, da su za smanjenje velikih kardiovaskularnih događaja važni i pleiotropni učinci, posebice oni protuupalni (što pokazuje značajno smanjenje hsCRP) te učinci na stabilizaciju ateroma.

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on atheromas by using IVUS and effect on cardiovascular events will be tested[38].

This is also confirmed by the results of the study entitled METEOR (Measuring Effects on Intima-Media Thickness), which was conducted on 984 patients with moderately increased CVD risk and moderately increased carotid intima-media thickness CIMT (this is an important indicator of a surrogate marker of atherosclerosis and correlates with atherosclerotic changes made to the coronary arteries). The average LDL cholesterol was approximately 4 mmol/l, and they received either 40 mg of rosuvastatin or placebo. The result of the study has clearly shown that rosuvastatin results in a significant reduction of progression of CIMT[39]. The treatment by rosuvastatin has in comparison to pravastatin significantly slowed down the increase in intima-media thickness after 12 months even according to the recently completed study entitled JART (Justification for Treatment Atherosclerosis Regression)[40].

When, however, pleiotropnic effects of "more potent" statins are concerned, we must mention a very surprising recently publicized observation that the treatment by rosuvastatin may to a certain degree reduce the incidence of pneumonia[41]. The results of the recently publicized subsequent analysis of patients from the JUPITER study were equally surprising which showed that the elevated amounts of hsCRP are associated with greater risk for incidence of atrial fibrillation, and that rosuvastatin treatment significantly reduces this risk[42].

Conclusion

Despite great progress in preventing morbidity and mortality from CVD, especially coronary heart disease and myocardial infarction achieved with statins, many patients still do not reach target levels of lipids in blood. Since it has been undisputedly shown that the lowest possible LDL cholesterol concentrations should be achieved particularly in secondary prevention or in high risk patients, in order to achieve this we often have to administer the so-called more potent statins which lead to more intensive lowering of LDL cholesterol. It has been proved, especially for rosuvastatin, that pleiotropnic effects, especially anti-inflammatory effects and the effects on the stabilization of atheroma are especially important for the reduction of major cardiovascular events (which shows a significant reduction in hsCRP).

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