Što je novo u posljednjim smjernicama o liječenju dislipidemija Europskoga kardiološkog društva i Europskog društva za aterosklerozu?

What is New in the Most Recent Guidelines for the Management of Dyslipidemias of the European Society of Cardiology and the European Atherosclerosis Society?

SUMMARY: The most recent Guidelines for the management of dyslipidemias of the European Society of Cardiology and the European Atherosclerosis Society arrived after two major studies that demonstrated the efficiency of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), as well as the key fact that any additional reduction of LDL cholesterol reduces increased cardiovascular risk, i.e. that there is no lower limit of target blood concentration of LDL cholesterol. The latter was reflected in the recommendation of significantly lower target values of LDL cholesterol, especially for people with high and very high cardiovascular risk, resulting in the recognition of the need to combine statins with other hypolipemic agents, primarily ezetimibe followed by PCSK9i. Omega-3 fatty acids are recommended for the treatment of high-risk patients with hypertriglyceridemia despite statin treatment. Some modifications were made to cardiovascular risk categories, primarily for patients with diabetes mellitus and familial hypercholesterolemia, and more importance has been assigned to determining apolipoprotein B and lipoprotein(a) for more precise assessment of cardiovascular risk. We are now tasked with investing significant efforts into implementing these recommendations in our daily clinical practice in order to further reduce the population burden of cardiovascular diseases.

KLJUČNE RIJEČI: dislipidemije, smjernice, liječenje, kardiovaskularni rizik.

KEYWORDS: dyslipidemias, guidelines, management, cardiovascular risk.

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What is New in the Most Recent Guidelines for the Management of Dyslipidemias of the European Society of Cardiology and the European Atherosclerosis Society?

LDL cholesterol (LDL-C) was reduced even further by adding a propionate convertase subtilisin/kexin type 9 inhibitor (PCSK9i) to intensive statin therapy. It was demonstrated that there is no LDL-C concentration that is too low, i.e. that every reduction in LDL-C has clinical benefits.

The guidelines pay special attention to ASCVD prevention by: 1) promoting healthy lifestyle habits in the community, 2) assessing the total cardiovascular risk (CVR) of an individual by analyzing their risk factors, in particular LDL-C concentration, 3) undertaking individually tailored preventive and therapeutic measures, the intensity of which should be proportional to the patient’s total CVR.

The new guidelines have slightly modified patient classification according to CVR levels. A portion of patients with diabetes mellitus (DM) has been reclassified into categories of less severe risk, leaving some patients in the very high risk category from the previous guidelines, and moving others into the high risk category. Also, a portion of patients categorized as high-risk according to the previous guidelines has now been moved to the moderate-risk category, which did not previously include patients with diabetes. The new guidelines also added patients with familial hypercholesterolemia (FH) and another additional risk factor or already present ASCVD to the very high risk category.

The very high risk category now includes patients with: 1) ASCVD that has been documented either clinically or by imaging (the new guidelines include CT coronaryography); 2) long-term diabetes mellitus (>20 years) or burdened with ≥3 additional major risk factors, or complicated target organ damage; 3) severe chronic kidney disease (eGFR <30 mL/min/1.73 m²); 4) familial hypercholesterolemia with another additional major risk factor or complicated with ASCVD.

The high risk category includes patients with: 1) at least one risk factor markedly elevated (e.g. total cholesterol (TC) >8 mmol/L, LDL-C >4.9 mmol/L, arterial blood pressure ≥180/110 mmHg); 2) diabetes mellitus duration ≥10 years or another additional risk factor; 3) chronic kidney disease (eGFR 30-59 mL/min/1.73 m²); 4) familial hypercholesterolemia without other additional risk factors or without documented ASCVD.

The moderate risk category includes young patients with diabetes mellitus (type 1 DM <35 years; type 2 DM <50 years) duration <10 years, without other risk factors.

The category of CV risk in apparently healthy people (men aged >40 and women >50 years or postmenopausal) should be evaluated using the SCORE system, which calculates the 10-year cumulative risk of the first fatal cardiovascular event based on age, gender, smoking, systolic blood pressure values, and TC. Persons with risk values of ≥10% belong to the very high risk category, 5–9% to the high risk category, 1–4% to the moderate risk category, and <1% to the low risk category. If available, we should use the systolic blood pressure and TC data before starting treatment. To calculate the risk in the Croatian population, we still use the SCORE chart for high-risk countries. Unlike the 2016 Guidelines, the new SCORE system includes persons up to 70 years of age. Another novelty is the removal of the column referring to TC concentration of 8 mmol/L, because we automatically classify such people as having high risk. For more precise risk assessment, we can also use the charts with HDL cholesterol (HDL-C) levels, except if HDL-C is >2.3 mmol/L, since the risk then increased.

Instead of calculating the absolute CVR, an estimate of the relative CVR and the so-called calculated CV risk age is sug-
Umjesto izračuna apsolutnog KVR-a u mladih se osoba predlaže procjena relativnog KVR-a i tvr. dobi prema izračunana riziku sa svrhom bolje predozrbe K VR rizika, a time i motiviranja pojedinačna na promjenu životnih navika. Naime, čak i ako neka mlada osoba ima niski apsolutni KVR, SCORE tablica relativnog rizika može pokazati da mu je relativni rizik zapravo vrlo visok. Dob prema riziku za određenu osobu odgovara dobi neke osobe koja ima isti KVR, ali s idealnim rizičnim profilom, što znači da nije pušač, ima UK <4 mmol/L i sistolički tlak <120 mmHg. Nove smjernice preporučuju uporabu rezultata neinvazivnih slikovnih metoda, tj. nalaza aterosklerotskih plakova na ultrazvuku karotida i/ili femoralnih arterija i/pak koronarnoga kalcijuskog zbroja >100 na CT koronagrafiji za podizanje kategorije rizika u pojedinacima s niskim ili umjerenim rizikom, što primjerice može biti od važnosti pri donošenju odluke o uvođenju statina u terapiju.

U pristupu prevenciji i liječenju dopuštena je prilagodljivost, pa, ako se ne postigne optimalna kontrola jednog čimbenika rizika, ukupni rizik treba reducirati snažnijim djelovanjem na ostale čimbenike. SCORE tablica može se primijeniti za preddijanje učinka smanjenja nekog čimbenika rizika na ukupni KVR. Primjerice, prestanak pušenja preporučuje če KVR. Osim prepoznavanja i liječenja osoba s visokim i vrlo visokim rizikom, i osobama s umjerenim KVR-om, važno je pružiti profesional savjet o koristima od modifikacije životnih navika, a u nekim slučajevima čak i preporučiti medikalno liječenje.

Lipidi i lipoproteini

Smjernice ističu aterogenost lipoproteinskih čestica koje sadržavaju apolipoprotein B (ApoB), tj. LDL-a, VLDL-a i ostalih čestica. I dalje se preporučuje rutinsko mjerenje UK-a i HDL-K-a koji su nam potrebni za računanje rizika primjenom SCORE bodovnog sustava, LD K-a koji je izrađen na temelju UK-a i ApoB-a radi procjene rizika u osoba s visokim trigliceridima, češćom bolesti, pretulih ili u onih s vrlo niskim vrijednostima LDL-K-a.

Novost je preporuka ESC-a za mjerenje Lp(a): 1) u odraslih osoba barem jednom u životu; 2) u osoba s obiteljskom aterogenezom prerane KBV (muškarci <55 god., žene <60 godina); 3) u osoba na granici umjerenog i visokog KBV rizika. Američka Nacionalna udruga za lipide dodatno je preporučila mjerenje Lp(a) u osobama s preranom ASKVB, te u osobama s obiteljskim hiperkolesterolemijom, vrlo visokim LDL-K (>4,9 mmol/L), graničnom indikacijom za propisivanje hipolipemičkarne terapije, gdje je u slučaju nečekivano slabog odgovora LDL-K na lijekove i ApoB-a radi procjene rizika u osoba s visokim trigliceridima, šećerom bolesti, pretulih ili u onih s vrlo niskim vrijednostima LDL-K-a.

A novelty is that ESC now recommends measuring Lp(a): 1) in adults, at least once in their lifetime; 2) in persons with family history of premature CVD (men <55 years, women <60 years); 3) in persons bordering between moderate and high CV risk. The American National Lipid Association has additionally recommended to measure Lp(a) in persons with premature ASCVD, persons with familial hypercholesterolemia, very high LDL-C (≥4.9 mmol/L), borderline indication for prescribing hypolipemic agents, progressive ASCVD despite receiving hypolipemic agents, and in case of an unexpected poor response of LDL-C to drugs. Lp(a) is a type of LDL particle whose apolipoprotein B molecule is connected with an apolipoprotein(a) molecule. Lp(a) easily penetrates the endothelium and stays in the arterial wall, causing atherosclerosis. The detrimental effect of this particle is further increased by its pro-coagulant and pro-inflammatory properties. Lp(a) >430 mmol/L is considered to increase the risk of ASCVD to a level equal to that in people with heterozygous familial hypercholesterolemia. There are no clear recommendations on treating persons with elevated Lp(a), but PCSK9i is recommended in addition to intense statin and ezetimibe therapy, and certain patients can be treated with apheresis. Taking into consideration the strong evidence for the continued reduction of CVD proportionate to the reduction of serum
Smjernice predlažu terapijske strategije temeljene na visini rizika i koncentraciji LDL-K svakog pojedinca. Međutim, savjetuje se izbjegavanje preteranoga medikamentnog liječenja starijih osoba na temelju visokog SCORE rizika samo zbog njihove visoke dobi, dok su im drugi čimbenici relativno niski.

**Ciljevi liječenja, promjena životnih navika i lijevki za liječenje dislipidemija**

Osnovni pristup u prevenciji i liječenju KVB-a uključuje promjene životnih navika, kontrolu arterijskoga tlaka i snizivanje LDL-K zbog njegove ključne uloge u nastanku ateroskleroze. Izuzevši osobe s niskim KVR-om, svim ostalim rizičnim kategorijama znatno su snižene ciljne vrijednosti LDL-K (tabl. 1). Za razliku od smjernica iz 2016., nove smjernice razlikuju preporučene vrijednosti LDL-K za osobe s niskim i umjerenim rizikom. Kao sekundarni terapijski ciljevi lipidnog profila u osoba umjerenog do vrlo visokog rizika preporučeni su non-HDL-K i ApoB: non-HDL-K <2,2 mmol/L i ApoB <65 g/L za osobe s vrlo visokim rizikom; non-HDL-K <2,6 mmol/L i apoB <80 mg/dL za osobe visokog rizika; non-HDL-C <3,4 mmol/L i ApoB <100 mg/dL za osobe umjerenog rizika.

**TABLE 1. LDL-C therapeutic goals from the 2019 ESC/EAS Guidelines for the management of dyslipidemias**

| Risk category | LDL-C goals | Recommendation |
|---------------|-------------|----------------|
| Patients with ASCVD who experience a second vascular event within 2 years while taking maximally tolerated statin therapy | <1.0 mmol/L | Iib B |
| Very high | reduction ≥50% | • in secondary prevention: I A |
| and < 1.4 mmol/L | | • in primary prevention without FH: I C |
| High | reduction ≥50% | I A |
| and < 1.8 mmol/L | | • in primary prevention with FH: IIIa C |
| Moderate | <2.6 mmol/L | IIIa A |
| Low | <3.0 mmol/L | IIIb A |

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

Even the introduction to the 2019 Guidelines already emphasizes the clinical importance of lowering LDL-C according to the principle “the lower, the better”, i.e. without a defined lower limit of LDL-C value, and the non-existence of evidence of any complications caused by LDL-C being “too low”. With each reduction in LDL-C by 1 mmol/L, we reduce the relative risk of cardiovascular complications by approximately 20%.[17] These high-set therapeutic goals require more intense therapeutic measures, and thereby also a frequent need to combine hypolipemic agents. Because of the above, the guidelines suggest algorithms and tables with practical recommendations depending on the patient’s risk category, baseline LDL-C level, and its expected reduction with certain types of hypolipemic drugs. The effect of treatment with hypolipemic drugs should be evaluated after 1-3 months or in the same interval after treatment intensification, until the therapeutic goal is reached. Great importance is attributed to lifestyle modifications, Mediterranean diet, especially using extra virgin olive oil, and drugs for treatment of dyslipidemias

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**Great importance is attributed to lifestyle modifications, Mediterranean diet, especially using extra virgin olive oil, and drugs for treatment of dyslipidemias**

The basic approach for the prevention and treatment of CVD involves lifestyle modifications, arterial pressure control, and reduction of LDL-C due to its key role in the development of atherosclerosis. With the exception of persons with low CVR, target values of LDL-C have been significantly reduced in all other risk categories (Table 1). Unlike the 2016 Guidelines, the new guidelines differentiate between the recommended LDL-C values in persons with low and moderate risk. Non-HDL-C and ApoB are recommended as secondary therapeutic goals for the lipid profiles of people with moderate to very high risk: non-HDL-C <2,2 mmol/L and ApoB <65 g/L for persons with very high risk; non-HDL-C <2,6 mmol/L and ApoB <80 mg/dL for persons with high risk; non-HDL-C <3,4 mmol/L and ApoB <100 mg/dL for persons with moderate risk.

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smanjenom unosu zasićenih masti, hrane i pića s dodanim šećerom, te potpunom izbjegavanju transmastu u prehrani, iako ova, zadnja mjera snizuje UK i LDL-K, odnosno povećava HDL-K za samo 5 – 10 %. Smanjeni je očekivani učinak mršavljenja u pretlih osoba na smanjenje triglicerida u serumu.

Osnovni lijekovi za liječenje dislipidemija jesu statini, inhibitori apsorpcije kolesterola, inhibitori proprotein konvertaze subtilizin/kexin tipa 9 (PCSK9i) i fibrate. Smjernice savjetuju kaskadnu terapijsku strategiju koju počinjemo statinom visokoj intenziteta. Ako nismo postigli ciljni LDL-K, pojačavamo je dodavanjem ezetimibe i na kraju PCSK9 inhibitora.

**STATINI**

Kapacitet statina za smanjenje LDL-K iznosi do 50 %. Smanjenje koncentracije LDL-K za 1 mmol/L uz terapiju statinom smanjuje rizik od velikih nepovoljnih CV događaja za 22 %, koronarnih incidenta za 23 % i ukupne petogodišnje smrtnosti od 10 %. Statini su učinkoviti i u osoba starijih od 75 godina. Statini se nisu pokazali korisni u bolesnicima s bolestima na hešmodijalizi ili sa srčanim popuštanjem. Iako pokazuju učinak klase, izbor statina ovisi o visini željenog terapijskog cilja, ali pratećim bolestima. Prema intenzitetu snizuivanja LDL-K a razlikujemo terapiju statinom visokog intenziteta (atorvastatin 40 – 80 mg, rosuvastatin 20 – 40 mg) koji postižu redukciju od oko 50 % i terapiju umjerenog intenziteta kojom se postiže redukcija od oko 30 %. Iako statini pokazuju pleotropne učinke, korist od njihove primjene prije svega ovisi o postignutoj snizuivanju LDL-K. Statini neznatno snizuju Lp(a), blago podižu HDL-C (od 1-10%) i teko nešto bolje snizuju trigliceride uz intenzivnu terapiju (za 10 – 20%).

Rabdomioliza je najvažnija nuspojava liječenja. Preporučuje se mjerenje kreatin kinaz (CK) prije uvođenja lijeka. Rutinski praćenje CK nije nužno, osim pri pojavi mišićkih simptoma. Ako je porast CK <4 puta, nije potrebno prekinuti terapiju statinom, čak i ako bolesnik ima mišićne simptome. U tom slučaju se redovito praćenje symptoma i kontrola CK-a. Ako tegobe ipak potraju, statin treba prekinuti i bolesnika reevaluirati nakon 6 tjedana. Tada se može uvesti drugi statin ili vratiti prethodni statin u manjoj dozi ili svaki dan ili jednom do dvaput na tjedan. Smjernice prvi put ističu postojanje tzv. nocebo učinka statina, tj. mišićnih simptoma povezanih s uzimanjem statina (engl. statin-associated muscle symptoms) koji karakterizira pojave bolova i osjetljivosti mišića, ali bez pratećeg porasta CK-a ili funkcijskog poremećaja. U slučaju porasta CK >10 puta, potreban je prekid terapije statinom, uz mjerenje kreatinina i CK svaka 2 tjedna. Ako bolesnik nema simptoma, ali je CK porastao za <10 puta, može se nastaviti uz uzimanje lijeka bez kontrolu CK-a, ali bolesnik treba prekinuti i bolesnika reevaluirati nakon 6 tjedana. Ako bolesnik nema simptoma, ali je CK porastao za >10 puta, može se nastaviti uz uzimanje lijeka bez kontrolu CK-a, ali bolesnik treba prekinuti i bolesnika reevaluirati nakon 6 tjedana. Smjernice ističu među koje se ubrajaju starijе osobe, pretli{i osobe s drugim znakovima inzulinske rezistencije.

**STATINS**

Iako pokazuju učinak dina, statini se nisu pokazali korisni u bolesnika na hemodializi ili sa srčanim popuštanjem. Ako porast CK >10 puta, potrebno je prekinuti terapiju statinom, uz praćenje kreatinina i CK svaka 2 tjedna. Ako bolesnik ima mišićne simptome. U tom slučaju, statin treba prekinuti i bolesnika reevaluirati nakon 10 – 12 tjedana. Smjernice ističu mnogo veću korist od smanjenja KVR-a s obzirom na blago povećani rizik od pojave dijabetesa uz liječenje statinom. Zbog navedenog preporučuje se redovito kontrolirati sadržaj HbA1c ili glukozde u serumu u slučaju proispisivanja visoke doze statina ili u osoba s povišenom rizikom među koje se ubrajaju starijе osobe, pretli{i osobe s drugim znakovima inzulinske rezistencije.

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INHIBITORI APSORPCIJE KOLESTEROLA
Jedini lijek iz ove skupine i dalje je ezetimib. Naglašena je korist od sinergističkog učinka ezetimiba sa statinima, se-kvestrantima žućhih kiselina i PCSK9 inhibitorima. Nove su smjernice veću važnost (klasa I. preporuke) pridale ezetimibu u propisivanju nakon što maksimalno podnošljivom dozom statina nije postignut zadani cilj, za razliku od prethodnih smjernica (klase II. a).

INHIBITORI PROPROTEIN KONVERTAZE SUBTILIZIN/KEKSIN TIPA 9
Inhibitori proprotein konverteze subtilizin/keksin tipa 9 (PCSK9i) pokazali su se vrlo učinkovitim u redukciji KV do-gađa u bolesnika vrlo visokog rizika. Osim toga što snizuju koncentraciju LDL-K za čak 60 %, djeluju i na smanjenje se-rumskog Lp(a) za 25 – 30 %.24 Nove smjernice dodijelile PCSK9i višu klasu preporuke (I. a) za sekundarnu prevenciju KVB-a, te za primarnu prevenciju u bolesnika s obiteljskom hiperkolesterolemijom i dodatnim velikim rizičnim čimbeni-kom koji usporedujemo maksimalno podnošljivoj dozi statina i eze-timibu nisu postigli ciljnu vrijednost LDL-K. Primjena PCSK9i u svrhu primarne prevencije u osoba s vrlo visokim rizikom bez obiteljske hiperkolesterolemije dobila je nižu klasu preporuke (II. b).

FIBRATI
Smjernice i dalje propitkuju korist od liječenja fibratima, iako su nabojeću studije koje su izvijestile o redukciji KVR-a pro-portionalno postignutoj redukciji non-HDL-K. Nove smjerni-ce umanjavaju važnost nuspojava fribata, uključujući rizik od porasta kreatinina i homocisteina. Fibrati se mogu propisati (klasa preporuke II. b) osobama visokog KV rizika koji su uz statin postigli ciljni LDL-K, ali i dalje imaju serumske triglice-ride >2,3 mmol/L.

N-3 MASNE KISELINE
Smjernice navode rezultat Cochrane metaanalize koja nije potvrdila učinak n-3 masnih kiselina na KV smrtnost i morbiditet, osim na koronarne događaje.14 Komentari za rezultat istraživanja REDUCE-IT koje je dokazalo korist od ove terapije na smanjenje učestalosti KV KV događaja u visokorizičnih bolesnika s povišenom trigliceridima usporedo liječenju statinom.15 S obzirom na fribate, primjena etileikoaptena-ske kiseline dozi 2 x 2 g na dan dobila je višu klasu preporuke (II. a) u liječenju hipergliceridemije u osoba s visokim ili vrlo visokim rizikom koje usporedo liječenju statinom imaju koncentraciju triglicerida 1,5 – 5,6 mmol/L.

Liječenje dislipidemija u različitim kliničkim okolnostima

OBITELJSKA HIPERKOLESTEROLEMIJA
Heterozigotna obiteljska hiperkolesterolemija (OH) opisu-je se kao relativno čest uzrok prerane atheroslerotlike bole-sti. Na OH treba posmatrati pri dijagnosticiranju KVB-a u muškaraca dobi >55 godina ili u žena dobi >60 godina, odra-slih osoba s LDL-K >5 mmol/L, u djece s LDL-K >4, mmol/L, osoba sa ksantomima tetiva, ili u osoba čiji rođaci boluju od OH, prerane KVB ili imaju ksanome tetiva. Za dijagnosticira-nje se primjenjuju kriteriji Nizozemske mreže lipidih klinika tin treatment.13 Because of the above, regular monitoring of serum HbAlc or glucose is recommended when prescribing high statin doses or in persons with increased risk, including the elderly, persons with obesity, and persons with other evidence of insulin resistance.

CHOLESTEROL ABSORPTION INHIBITORS
Ezetimibe is still the only drug in this class. The benefit of the synergistic effect of ezetimibe with statins, bile acid se-questrants, and PCSK9 inhibitors is emphasized. The new guidelines attribute more importance (class I recommendation) to ezetimibe in prescribing therapy after the maximum tolerable statin dose has failed to achieve the set goal, unlike the previous guidelines (class IIa).

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 INHIBITORS
Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have been shown to be very effective in reducing CV events in patients with very high risk. Other than lowering LDL-C concentration by up to 60%, they also act by reducing serum Lp(a) by 25-30%.23 The new guidelines assigned a higher class of recommendation (I A) to PCSK9i for secondary pre-vention of CVD and for primary prevention in patients with familial hypercholesterolemia and another additional major risk factor who failed to achieve target LDL-C value despite taking the maximum tolerable dose of statins and ezetimibe. The use of PCSK9i for primary prevention in persons with very high risk without familial hypercholesterolemia was assigned a lower class of recommendation (IIb).

FIBRATES
The guidelines still question the benefits of treatment with fibrates, although studies reporting CVR reduction proportionate to the achieved non-HDL-C reduction are mentioned. The new guidelines give less importance to adverse effects of fibrates, including the risk of increased creatinine and homocysteine. Fibrates can be prescribed (recommendation class IIb) to persons with high CV risk who achieved their target LDL-C levels with statins, but still have serum triglycerides at >2.3 mmol/L.

N-3 FATTY ACIDS
The guidelines mention the result of a Cochrane meta-analysis that did not confirm the effect of n-3 fatty acids on CV mortality and morbidity, except in coronary events.14 The guidelines comment on the results of REDUCE-IT, a study showing benefits of this therapy for the reduction of CV events frequency in high-risk patients with elevated triglycerides despite receiving statin treatment.15 In comparison with fibrates, the use of icosapent ethyl at the dosage of 2×2 g per day received a higher class of recommendation (IIa) for the treatment of hypertriglyceridemia in persons with high or very high risk with a triglycerides concentration of 1.5-5.6 mmol/L despite receiving statin therapy.

Treatment of dyslipidemias in different clinical settings

FAMILIAL HYPERCHOLESTEROLEMIA
Heterozygous familial hypercholesterolemia (FH) is described as a relatively frequent cause of premature atherosclerotic dis-ease. FH should be suspected in diagnosing CVD in men aged
(Dutch Lipid Clinic Network) koji uzimaju u obzir podatke iz obiteljske i osobne anamneze, fizikalnoga pregleda, vrijednosti LDL-C prije liječenja i eventualno dostupnog rezultata genetske analize. Dobiveni zbroj bodova daje vjerojatnost ovakve dijagnoze. Ako je moguće, dijagnozu treba potvrditi genskim testiranjem jer potvrđena mutacija možemo iskoristiti za kaskadni probi ostalih članova obitelji. Rani probi na OH u djece se preporučuju u dobi ≥5 godine. Osobama s OH koje imaju dodatni veliki čimbenik rizika, a osobito ako se u njih već razvila ASKVB, korisno je uvesti PCSK9i ako intenzivna terapija statinom i ezetimibom nije postigla ciljni LDL-K. Osobe s „izoliranim“ OH liječe se kao ostale osobe visokog KV rizika.

Homozigotna OH rijedak je, ali vrlo težak oblik bolesti koji karakteriziraju vrlo visoka koncentracija LDL-K (>13 mmol/L), rana i progresivna ASKVB, koja često završava smrću u dobi <30 godina. Liječi se intenzivnom hipolipidemickom terapijom i aferezama. Dodatak lomitapida može smanjiti LDL-K do 50 % i time smanjiti potrebnu učestalost afereza.15

OSOBE SA ŠEĆERNOM BOLESTI

Nove su smjernice reklasificirale osobe sa šećernom bolesti prema kategorijama KV rizika i postrožile njihove ciljne vrijednosti LDL-K. Kao sekundarni terapijski ciljevi u ovih bolesnika preporučuju se non- HDL-K i ApoB kao dobro pokazatelje opterećenja trigliceridima bogatih lipoproteina i ostatnih čestica. Statini su prvi izbor u liječenju, ali se ezetimib pokazao vrlo učinkovitim, uzrokujući veću redukciju LDL-K u osoba sa visokog KV rizika sa šećerom bolešću u usporedbi s onima bez šećerne bolesti.16 PCSK9i u osoba sa šećernom bolesti također uzrokuju dopuna redukciji apsolutnog rizika za trogođišnje velike KV događaje za 2,7 % u usporedbi s osobama bez šećerne bolesti. Sve je ovo posljedica većeg apsolutnog rizika od ovakve populacije bolesnika. Osobe sa šećernom bolesti tipa 1 i 2 u dobi ≥10 godine, osobe sa diabetes mellitus vs. those without diabetes mellitus.16 PCSK9i in persons with diabetes mellitus also cause an additional reduction of absolute risk for 3-year major CV events of 2.7% vs. people without diabetes mellitus. All of this is a consequence of increased absolute risk in this patient population. Persons with type 1 diabetes mellitus and good glycemic control sometimes have a “supernormal” lipid profile with low triglycerides and LDL-C, with HDL-C being at the upper limit of normal values or even slightly elevated. This is a consequence of subcutaneous insulin injections that promote the activity of lipoprotein lipase in adipose tissue and muscles, accelerating the rate of VLDL particle turnover. However, the changed composition of the resulting HDL and LDL particles can increase their atherogenic potential. Statin treatment can be prescribed in young persons with type 1 and 2 diabetes mellitus (≥30 years) if there is evidence of target organ damage and/or LDL-C is ≥2.5 mmol/L, except in women planning to become pregnant.

PERSONS WITH ACUTE CORONARY SYNDROME

The guidelines emphasize the importance of intensive and prolonged high-intensity statin treatment in patients with acute coronary syndrome (ACS), with the goal of a quick relative reduction of LDL-C by at least 50% and an absolute reduction of LDL-C ≤1.4 mmol/L. Ezetimibe should be added to statin treatment if this is not achieved with the maximum tolerable statin dosage within 4-6 weeks. If the set goal is not reached after an additional 4-6 weeks, addition of PCSK9i should be
What is New in the Most Recent Guidelines for the Management of Dyslipidemias of the European Society of Cardiology and the European Atherosclerosis Society?

pristup redukciji ukupnoga kardiovaskularnog rizika s pomoću tjelesne aktivnosti i hranjenja bolesnika o KVB-u, promjenama nezdravih životnih navika i pravilnoj prehrani, poštivanje bolju kontrolu čimbenika rizika i znatno smanjuje smrtnost.19

**ISCHEMIC STROKE**

Bolesnici nakon preboljenja ishemijskog moždanog udara ili transzitornoga ishemijskog napada imaju terapijske ciljeve kao osobe s vrlo visokim KVR-om. Redukcijom LDL-K za svakih 1 mmol/L smanjujemo rizik od ponavljanja neuroloških događaja, ali i infarkta miokarda i KV smrtni za 12%.20

**OVERSE STARIJE ŽIVOTNE DOBI**

Liječenje statinima bolesnika s ASKVB-om u dobi >65 godina jednako je preporučeno kao i za mlade osobe. Nema dovoljno dokaza za korist od statina u primarnoj prevenciji u osoba starijih od 75 godina, iako smjernice ostavljaju tu mogućnost ako je osoba visokog ili vrlo visokog rizika (II b).23 Postoji li bubrežna insuficijencija ili rizik od interakcije s drugim lijekovima, trebamo početi s malom dozom statina i oprezno je titrirati.

**Zaključak**

Nove smjernice za liječenje dislipidemija u prvi plan stavljaju kliničku korist od što bržeg i intenzivnijeg sniženja vrijednosti LDL-K po principu „što niže, to bolje”, i to osobito u osoba s visokim i vrlo visokim kardiovaskularnim rizikom. Uz ovako ambiciozne ciljeve porasla je važnost kombiniranja temeljnih hipolipemijskih lijekova, statina visokog intenziteta, ezetimba i PCSK9 inhibitora. Preostaje nam uložiti dodatni napor za implementaciju ovih preporuka u svakodnevni klinički rad i za postizanje dobre adherencije bolesnika uz propisanu terapiju kako bismo sijajne rezultate kliničkih ispitivanja prelikali u stvarni život.

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**Conclusion**

The new guidelines for the treatment of dyslipidemias give priority to the clinical benefits of reducing LDL-C quickly and intensely, according to the principle of “the lower, the better”, especially in persons with high and very high cardiovascular risk. With such ambitious goals, combining basic hypolipemic drugs, high-intensity statins, ezetimbe, and PCSK9 inhibitors becomes more important. We are now tasked with putting extra effort into implementing these recommendations in our daily clinical practice and achieving good patient adherence with the prescribed therapy, in order to translate these excellent results from clinical trials to the real world.
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