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

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SAŽETAK: Posljednje smjernice o liječenju dislipidemija Europskoga kardiološkog društva i Europskoga društva za aterosklerozu došle su nakon dvaju velikih istraživanja koja su dokazala učinkovitost inhibitora proprotein konvertaze subtilizin/keksin tipa 9 (PCSK9i), ali i ključnu činjenicu da svako dodatno sniženje LDL kolesterola smanjuje povišeni kardiovaskularni rizik, odnosno da ne postoji preniska ciljna koncentracija LDL kolesterola u krvi. Navedeno se odrazilo na preporuku o mnogo nižim ciljnim vrijednostima LDL kolesterola, napose za osobe s visokim i vrlo visokim kardiovaskularnim rizikom, zbog čega je prepoznata potreba za kombiniranjem statina s drugim hipolipemicima, prije svega ezetimiba, a zatim i PCSK9i. U liječenju osoba s visokim rizikom s hipertrigliceridemijom usprkos primjeni statina preporučene su omega-3 masne kiseline. Došlo je do nekih preinaka u kategorizaciji kardiovaskularnog rizika, prije svega u osoba sa šećernom bolešću i s obiteljskom hiperkolesterolemijom, a pridana je i veća važnost određivanju apolipoproteina B i lipoproteina(a) u preciznijoj procjeni kardiovaskularnog rizika. Sada nam preostaje uložiti znatan trud u to da navedene preporuke implementiramo u svakodnevnu kliničku praksu i tako dodatno smanjimo teret zbog kardiovaskularnih bolesti u populaciji.

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 every 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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Europsko kardiološko društvo (ESC) u suradnji s Europskim društvom za aterosklerozu (EAS) u kolovozu 2019. g. objavilo je *Smjernice za liječenje dislipidemija* koje donose važne novosti u kardiovaskularnoj prevenciji i liječenju.[1] Glavna je promjena nastala kao posljedica rezultata dvaju velikih kliničkih istraživanja koja su u bolesnika s dokazanom aterosklerotskom kardiovaskularnom bolesti (ASKVB) i akutnim koronarnim sindromom (AKS) čvrsto dokazala korist od još izrazitijeg snizivanja vrijednosti

In August 2019, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) published their joint *Guidelines for the Management of Dyslipidemias* that introduced important novelties in cardiovascular prevention and management.[1] The main change introduced was based on the results of two large clinical studies that demonstrated robust benefits in patients with confirmed atherosclerotic cardiovascular disease (ASCVD) and acute coronary syndrome (ACS) when LDL cholesterol

LDL kolesterola (LDL-K) dodatkom inhibitora proprotein konvertaze subtilizin/keksin tipa 9 (PCSK9i) intenzivnoj statinskoj terapiji. Pokazalo se da nema preniske koncentracije LDL-K, odnosno da svako sniženje LDL-K donosi kliničku korist[2,3].

Smjernice poklanjaju osobit interes prevenciji ASKVB-a kroz: 1) promociju zdravih životnih navika u zajednici, 2) procjenu ukupnoga kardiovaskularnog rizika (KVR) pojedinca analizirajući njegove čimbenike rizika, osobito koncentraciju LDL-K, 3) poduzimanje preventivnih i terapijskih mjera prema pojedincu čiji će opseg biti razmjeran njegovu ukupnom KVR-u.

Nove su smjernice ponešto izmijenile klasifikaciju bolesnika prema težini KVR-a. Dio je osoba sa šećernom bolešću (DM) reklasificiran u niže kategorije rizika, tako da je u kategoriji vrlo visokog rizika ostao dio bolesnika iz prethodnih smjernica, a dio je premješten u kategoriju visokog rizika[4]. Osim toga, dio bolesnika iz kategorije visokog rizika, prema starim smjernicama, sada je premješten u kategoriju umjerenog rizika koja prije nije uključivala osobe sa šećernom bolesti. Nove su smjernice u kategoriju vrlo visokog rizika dodale osobe s obiteljskom hiperkolesterolemijom (OH) i dodatnim čimbenikom rizika ili s već razvijenim ASKVB-om.

Prema novim smjernicama, u kategoriji osoba s **vrlo visokim rizikom** jesu bolesnici s: 1) ASKVB koja je dokazana klinički ili slikovnom metodom (nove su smjernice uključile CT koronarografiju[5]); 2) šećernom bolešću dugoga trajanja (>20 godina) ili opterećenoj s još ≥3 dodatna velika čimbenika rizika, ili pak kompliciranoj oštećenjem ciljnih organa; 3) teškom kroničnom bolesti bubrega (eGFR <30 mL/min/1,73 m^2); 4) obiteljskom hiperkolesterolemijom s dodatnim velikim čimbenikom rizika ili kompliciranom ASKVB.

U kategoriji osoba **visokog rizika** jesu bolesnici s: 1) izrazito povišenim barem jednim čimbenikom rizika (npr. ukupni kolesterol (UK) >8 mmol/L, LDL-K >4,9 mmol/L, arterijski tlak ≥180/110 mmHg); 2) šećernom bolesti trajanja ≥10 godina ili s dodatnim čimbenikom rizika; 3) kroničnom bolešću bubrega (eGFR 30 – 59 mL/min/1,73 m^2); 4) obiteljskom hiperkolesterolemijom bez dodatnog čimbenika rizika ili dokazane ASKVB.

U kategoriji osoba **umjerenog rizika** mlađi su bolesnici sa šećernom bolesti (DM tip 1 <35 godina, DM tip 2 < 50 godina) trajanja <10 godina i bez dodatnih čimbenika rizika.

Kategoriju KV rizika naizgled zdravih osoba (muškaraca u dobi >40 i žena >50 godina ili u postmenopauzi) treba procijeniti s pomoću SCORE bodovnog sustava, koji na temelju podataka o dobi, spolu, pušenju, vrijednostima sistoličkoga tlaka i UK-a izračunava 10-godišnji kumulativni rizik za prvi fatalni kardiovaskularni događaj. Osobe s vrijednostima rizika ≥10 % ulaze u kategoriju vrlo visokog rizika, one s 5 – 9 % u kategoriju visokog rizika, s 1 – 4 % u kategoriju umjerenog rizika, a s <1 % u kategoriju niskog rizika. Ako su dostupni, trebamo se koristiti podatcima o sistoličkom tlaku i UK-u prije početka liječenja. Za izračunavanje rizika stanovnika Republike Hrvatske i dalje se koristimo SCORE tablicom za zemlje s visokim rizikom. Za razliku od smjernica iz 2016., novi SCORE sustav uključuje osobe dobi do 70 godina. Novost je i uklanjanje stupca koji se odnosi na koncentraciju UK od 8 mmol/L, jer takve osobe automatski svrstavamo pod visoki rizik. Kako bismo povećali preciznost procjene rizika, možemo se koristiti i tablicama koje uključuju podatak o vrijednostima HDL kolesterola (HDL-K), osim ako je HDL-K >2,3 mmol/L, jer se u tom slučaju povećava rizik.

(LDL-C) was reduced even further by adding a proprotein 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.[2,3]

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.[4] 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 coronarography[5]); 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 m^2); 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 m^2); 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 mlađih se osoba predlaže procjena relativnog KVR-a i tzv. dobi prema izračunanom riziku sa svrhom bolje predodžbe KV rizika, a time i motiviranja pojedinca 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[6]. Nove smjernice preporučuju uporabu rezultata neinvazivnih slikovnih metoda, tj. nalaza aterosklerotskih plakova na ultrazvuku karotida i/ili femoralnih arterija i/ili pak koronarnoga kalcijskog zbroja >100 na CT koronarografiji) za podizanje kategorije rizika u pojedinaca s niskim ili umjerenim KV 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 predviđanje učinka redukcije nekog čimbenika rizika na ukupni KVR. Primjerice, prestanak pušenja prepolovit će KVR. Osim prepoznavanja i liječenja osoba s visokim i vrlo visokim rizikom, i osobama s umjerenim KVR-om važno je pružiti profesionalan savjet o koristima od modifikacije životnih navika, a u nekim slučajevima čak i preporučiti medikamentno liječenje.

Lipidi i lipoproteini

Smjernice ističu aterogenost lipoproteinskih čestica koje sadržavaju apolipoprotein B (ApoB), tj. LDL-a, VLDL-a i ostatnih čestica[7]. I dalje se preporučuje rutinsko mjerenje UK-a i HDL-K-a koji su nam potrebni za računanje rizika primjenom SCORE bodovnog sustava, LDL-K-a koji je primaran lipidni cilj za probir, dijagnozu i liječenje i na kraju triglicerida. Nove smjernice veću važnost pridaju mjerenju non-HDL-K-a i ApoB-a radi procjene rizika u osoba s visokim trigliceridima, šećernom bolesti, pretilih 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 anamnezom prerane KVB (muškarci <55 godine, žene <60 godina); 3) u osoba na granici umjerenog i visokog KV rizika. Američka Nacionalna udruga za lipide dodatno je preporučila mjerenje Lp(a) u osoba s preranom ASKVB, te u osoba s obiteljskom hiperkolesterolemijom, vrlo visokim LDL-K (≥4,9 mmol/L), graničnom indikacijom za propisivanje hipolipemika, progresivnom ASKVB usprkos uzimanju hipolipemika i u slučaju neočekivano slabog odgovora LDL-K na lijekove.[8] Lp(a) je vrsta LDL čestice čija je molekula apolipoproteina B povezana s molekulom apolipoproteina(a). Lp(a) lako prodire kroz endotel i zadržava se u arterijskoj stijenci uzrokujući aterosklerozu. Štetni učinak ove čestice dodatno je pojačan njezinim prokoagulantnim i proupalnim svojstvima. Smatra se da Lp(a) >430 nmol/L podiže rizik od ASKVB-a jednak riziku u osoba s heterozigotnom obiteljskom hiperkolesterolemijom.[9] Nema jasnih preporuka o liječenju osoba s visokim Lp(a), ali se, unatroč intenzivnoj terapiji statinom i ezetimibom, preporučuje PCSK9i, a pojedini se bolesnici mogu liječiti aferezom.[1,8]

Uzimajući u obzir snažne dokaze o kontinuiranom smanjenju KVR-a razmjerno smanjenju serumske razine LDL-K, ESC

gested for young people for a better idea of their CV risk and also to motivate individuals to change their lifestyle habits. Namely, even if a young person has a low absolute CVR, the SCORE relative risk chart may indicate that their relative risk is actually significantly high. The risk age of a person corresponds to the age of a person with the same CVR but with an ideal risk profile, meaning that they are a non-smoker, with a TC of <4 mmol/L and systolic blood pressure of <120 mmHg.[6] The new guidelines recommend using the results of non-invasive imaging methods, i.e. findings of atherosclerotic plaque on ultrasound of the carotid and/or femoral arteries and/or of a coronary artery calcium score >100 in CT coronarography, to raise the risk category in individuals with low or moderate CV risk, which can, for example, be important in making a decision on introducing statins into therapy.

The approach to prevention and treatment allows flexibility, and if optimal control of one risk factor is not achieved, total risk should be reduced by strong action against the other factors. The SCORE chart can be used to predict the impact of reducing one risk factor on total CVR. For example, giving up smoking reduces CVR by half. In addition to recognizing and treating persons with high and very high risk, it is also essential to provide professional advice to persons with moderate CVR regarding the benefits of modifying their lifestyle habits and even recommend drug treatment in some cases.

Lipids and lipoproteins

The guidelines emphasize the atherogenic properties of lipoprotein particles containing apolipoprotein B (ApoB), i.e. LDL, VLDL, and residual particles.[7] Routine measurement of TC and HDL-C, required to calculate the risk using the SCORE system, is still recommended, as well as LDL-C measurement, which is the primary lipid target for screening, diagnosis, and treatment, and finally triglyceride measurement. The new guidelines attribute more importance to measuring non-HDL-C and ApoB in order to evaluate the risk in people with high triglycerides, diabetes mellitus, obesity, and very low values of LDL-C.

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 unexpectedly poor response of LDL-C to drugs.[8] 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 nmol/L is considered to increase the risk of ASCVD to a level equal to that in people with heterozygous familial hypercholesterolaemia.[9] 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.[1,8]

Taking into consideration the strong evidence for the continued reduction of CVR proportionate to the reduction of serum

smjernice predlažu terapijske strategije temeljene na visini rizika i koncentraciji LDL-K svakog pojedinca. Međutim, savjetuje se izbjegavanje pretjeranoga 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 lijekovi 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 (**tablica 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-K <3,4 mmol/L i ApoB <100 mg/dL za osobe umjerenog rizika.

levels of LDL-C, the ESC Guidelines suggest therapeutic strategies based on the level of risk and LDL-C concentration in each individual. However, it is advised to avoid overtreatment in elderly persons based on their high SCORE risk just because of their high age, when their other risk factors are relatively low.

Treatment goals, lifestyle modifications, 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.

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

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% and < 1.4 mmol/L	• in secondary prevention: I A • in primary prevention without FH: I C • in primary prevention with FH: IIa C
High	reduction ≥50% and < 1.8 mmol/L	I A
Moderate	<2.6 mmol/L	IIa A
Low	<3.0 mmol/L	IIb A

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

Smjernice iz 2019. već u samom uvodu ističu kliničku važnost snizivanja LDL-K po principu što niže, to bolje, tj. bez definiranja donje granice LDL-K, te nepostojanja dokaza za pojavu komplikacija zbog „preniskog" LDL-K. Smanjenjem LDL-K za svaki 1 mmol/L smanjit ćemo relativan rizik od kardiovaskularnih komplikacija za oko 20 %.[10]

Ovako visoko postavljeni terapijski ciljevi zahtijevaju intenzivnije terapijske mjere, a time i čestu potrebu kombiniranja hipolipemika. Zbog navedenog su u smjernicama predloženi algoritmi i tablice s praktičnim preporukama, ovisno o kategoriji rizika za bolesnika, o početnoj razini LDL-K i o njegovoj očekivanoj redukciji uz određene vrste lijekova. Učinak liječenja hipolipemicima treba se provjeriti nakon 1 – 3 mjeseca, odnosno u istom razmaku nakon intenziviranja liječenja sve dok ne postignemo terapijski cilj.

Velika se važnost pridaje promjenama životnoga stila, mediteranskoj prehrani, osobito uporabi ekstradjevičanskoga maslinova ulja, svakodnevnoj tjelesnoj aktivnosti ≥30 min,

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%.[10]

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,

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

Osnovni lijekovi za liječenje dislipidemija jesu statini, inhibitori apsorpcije kolesterola, inhibitori proprotein konvertaze subtilizin/keksin tipa 9 (PCSK9i) i fibrati. Smjernice savjetuju kaskadnu terapijsku strategiju koju počinjemo statinom visokog intenziteta. Ako nismo postigli ciljni LDL-K, pojačavamo je dodavanjem ezetimiba 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 KV događaja za 22 %, koronarnih incidenata za 23 % i ukupne petogodišnje smrtnosti od 10 %. Statini su učinkoviti i u osoba starijih od 75 godina. Statini se nisu pokazali korisnima u bolesnika na hemodijalizi ili sa srčanim popuštanjem. Iako pokazuju učinak klase, izbor statina ovisi o visini željenoga terapijskog cilja, ali treba uzeti u obzir moguće interakcije s ostalim lijekovima i pratećim bolestima. Prema intenzitetu snizivanja 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 postignutom sniženju LDL-K. Statini neznatno snizuju Lp(a), blago podižu HDL-K (za 1-10%) i tek nešto bolje sniuju trigliceride uz intenzivnu terapiju (za 10 – 20 %).[11]

Rabdomioliza je najvažnija nuspojava liječenja. Preporučuje se mjerenje kreatin kinazu (CK) prije uvođenja lijeka. Rutinsko praćenje CK nije nužno, osim pri pojavi mijalgije. Ako je porast CK <4 puta, nije potrebno prekinuti terapiju statinom, čak i ako bolesnik ima mišićne simptome. U tom slučaju savjetuju se redovito praćenje simptoma 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 drugi 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 pojava bolova i osjetljivosti mišića, ali bez pratećeg porasta CK-a ili funkcijskog poremećaja.[12] U slučaju porasta CK >10 puta, potreban je prekid terapije statinom, uz praćenje kreatinina i CK svaka 2 tjedna. Ako bolesnik nema simptoma, ali je CK porastao za <10 puta, može se nastaviti s uzimanjem lijeka uz novu kontrolu CK za 2 – 6 tjedana. Prije uvođenja statina preporučuje se rutinski izmjeriti vrijednost ALT-a. Ovo ćemo ponoviti 8 – 12 tjedana nakon uvođenja lijeka ili povećanja doze. Ako ALT poraste za ≥3 puta, treba smanjiti dozu statina ili ga prekinuti i ponoviti mjerenje ALT-a nakon 4 – 6 tjedana. Novi pokušaj liječenja statinom moguć je nakon normalizacije ALT-a.

Smjernice ističu mnogo veću korist od smanjenja KVR-a s obzirom na blago povećani rizik od pojave dijabetesa uz liječenje statinima.[13] Zbog navedenog preporučuje se redovito kontrolirati sadržaj HbA1c ili glukoze u serumu u slučaju propisivanja visoke doze statina ili u osoba s povišenom rizikom među koje se ubrajaju starije osobe, pretili i osobe s drugim znakovima inzulinske rezistencije.

daily physical activity for ≥30 min, reduced intake of saturated fats and food and beverages with added sugar, and completely avoiding trans fats in one's diet, although the latter measure lowers TC and LDL-C and increases HDL-C by a mere 5-10%. The expected effect of weight loss on the reduction of serum triglycerides in obese persons has been reduced.

The basic medicinal products for the treatment of dyslipidemias are statins, cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), and fibrates. The guidelines advise a cascade therapeutic strategy starting with a high-intensity statin. If target LDL-C is not achieved, we enhance it by adding ezetimibe and finally a PCSK9 inhibitor.

STATINS

Statins have the capacity to lower LDL-C by up to 50%. A reduction of LDL-C concentration by 1 mmol/L with statin therapy reduces the risk of major adverse CV events by 22%, coronary incidents by 23%, and the total 5-year mortality by 10%. Statins are effective even in people older than 75. Statins have not demonstrated benefits in patients on hemodialysis or patients with heart failure. Although they show class effect, the choice of statins depends on the desired therapeutic target; however, the potential interactions with other drugs and associated diseases should also be considered. According to the intensity of LDL-C reduction, we can differentiate between high-intensity statin therapy (atorvastatin 40-80 mg, rosuvastatin 20-40 mg), which achieves a reduction by approximately 50%, and moderate intensity therapy, which achieves a reduction by approximately 30%. Although statins demonstrate pleiotropic effects, the benefit of their use depends primarily on the achieved LDL-C reduction. Statins slightly reduce Lp(a), mildly increase HDL-C (by 1-10%), and lower triglycerides only slightly more in the case of intensive therapy (by 10-20%).[11]

The most important adverse reaction to treatment is rhabdomyolysis. Measuring creatine kinase (CK) before introducing the drug is recommended. Routine monitoring of CK is not necessary, except in myalgia. If CK increases by <4 times, statin therapy does not have to be discontinued, even if the patient is experiencing muscle symptoms. In such cases, regular monitoring of symptoms and CK control are advised. If the complaints persist, statin therapy should be discontinued and the patient should be re-evaluated in 6 weeks. At that point, another statin can be introduced or the previous statin can be reintroduced at a lower dosage or taken every two days or one to two times a week. This is the first time the new guidelines emphasize the existence of the so-called nocebo effect of statins, i.e. statin-associated muscle symptoms, characterized by painful and sore muscles without an associated increase in CK or functional impairment.[12] In case of an increase in CK by >10 times, statin therapy should be discontinued and creatinine and CK should be monitored every two weeks. Drug treatment can continue if the patient shows no symptoms but CK has increased by <10 times, and CK should be measured again in 2-6 weeks. It is recommended to routinely measure ALT before starting statin treatment. This should be repeated again 8-12 weeks after introducing treatment or increasing the dose. If ALT increases by ≥3 times, the statin dose should be lowered or the treatment should be discontinued and ALT re-evaluated after 4-6 weeks. Re-attempting statin treatment is possible after ALT normalizes.

The new guidelines highlight a significantly larger benefit of reducing CVR vs. mildly increased risk of diabetes with sta-

INHIBITORI APSORPCIJE KOLESTEROLA

Jedini lijek iz ove skupine i dalje je ezetimib. Naglašena je korist od sinergističkog učinka ezetimiba sa statinima, sekvestrantima žučnih 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 konvertaze subtilizin/keksin tipa 9 (PCSK9i) pokazali su se vrlo učinkovitima u redukciji KV događaja u bolesnika vrlo visokog rizika. Osim toga što snizuju koncentraciju LDL-K za čak 60 %, djeluju i na smanjenje serumskog Lp(a) za 25 – 30 %.[2,3] Nove su 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 čimbenikom koji usprkos maksimalno podnošljivoj dozi statina i ezetimibu 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 nabrojene studije koje su izvijestile o redukciji KVR-a proporcionalnoj postignutoj redukciji non-HDL-K. Nove smjernice umanjuju važnost nuspojava fibrata, 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 triglyceride >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] Komentiran je rezultat istraživanja REDUCE-IT koje je dokazalo korist od ove terapije na smanjenje učestalosti KV događaja u visokorizičnih bolesnika s povišenim trigliceridima usprkos liječenju statinom.[15] S obzirom na fibrate, primjena etileikozapentaenske kiseline u dozi 2 x 2 g na dan dobila je višu klasu preporuke (II. a) u liječenju hipertrigliceridemije u osoba s visokim ili vrlo visokim rizikom koje usprkos liječenju statinom imaju koncentraciju triglicerida 1,5 – 5,6 mmol/L.

Liječenje dislipidemija u različitim kliničkim okolnostima

OBITELJSKA HIPERKOLESTEROLEMIJA

Heterozigotna obiteljska hiperkolesterolemija (OH) opisuje se kao relativno čest uzrok prerane aterosklerotske bolesti. Na OH treba posumnjati pri dijagnosticiranju KVB-a u muškaraca dobi <55 godina ili u žena dobi <60 godina, odraslih 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 ksantome tetiva. Za dijagnosticiranje se primjenjuju kriteriji Nizozemske mreže lipidnih klinika

tin treatment.[13] Because of the above, regular monitoring of serum HbA1c 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 sequestrants, 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%.[2,3] The new guidelines assigned a higher class of recommendation (I A) to PCSK9i for secondary prevention 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 disease. 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-K prije liječenja i eventualno dostupnog rezultata genske analize. Dobiveni zbroj bodova daje vjerojatnost ovakve dijagnoze. Ako je moguće, dijagnozu treba potvrditi genskim testiranjem jer potvrđenu mutaciju možemo iskoristiti za kaskadni probir ostalih članova obitelji. Rani probir na OH u djece se preporučuje 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 „izoliranom" 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 hipolipemičkom terapijom i aferezama. Dodatak lomitapida može smanjiti LDL-K do 50 % i time smanjiti potrebnu učestalost afereza.[16]

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 dobre pokazatelje opterećenja trigliceridima bogatih lipoproteina i ostatnih čestica. Statini su prvi izbor u liječenju, ali se ezetimib pokazao vrlo učinkovitim, uzrokujući veću redukciju KV rizika u osoba vrlo visokog KV rizika sa šećernom bolešću u usporedbi s onima bez šećerne bolesti.[17] PCSK9i u osoba sa šećernom bolesti također uzrokuju dodatnu redukciju apsolutnog rizika za trogodišnje velike KV događaje za 2,7 % u usporedbi s osobama bez šećerne bolesti. Sve je ovo posljedica većega apsolutnog rizika od ovakve populacije bolesnika. Osobe sa šećernom bolesti tipa 1 i dobrom kontrolom glikemije pokatkad imaju „supernormalni" lipidni profil s niskim trigliceridima i LDL-K, te HDL-K koji je na gornjoj granici normale ili je čak lagano povišen. Ovo je posljedica potkožnih injekcija inzulina koje potiču aktivnost lipoprotein lipaze u masnome tkivu i mišićima i time ubrzavaju obrtaj VLDL čestica. Međutim, izmijenjeni sastav nastalih HDL i LDL čestica može povisiti njihov aterogeni potencijal.[18] Liječenje statinom može se propisati mladim osobama sa šećernom bolešću tipa 1 i 2 (≤30 godina) ako postoje znakovi oštećenja ciljnih organa i/ili je LDL-K >2,5 mmol/L, osim ženama koje planiraju trudnoću.

OSOBE S AKUTNIM KORONARNIM SINDROMOM

Smjernice ističu važnost intenzivnog i produljenog liječenja statinima visokog intenziteta u bolesnika s akutnim koronarnim sindromom (AKS) sa svrhom brze relativne redukcije LDL-K za minimalno 50 % i apsolutne redukcije LDL-K <1,4 mmol/L. Ako maksimalno podnošljivom dozom statina ovo ne postignemo nakon 4 – 6 tjedana, statinu treba dodati ezetimib. Ne postigne li se zadani cilj ni nakon idućih 4 – 6 tjedana, treba razmotriti dodavanje PCSK9i. Ako je bolesnik na maksimalno podnošljivoj dozi statina i ezetimiba još od prije AKS-a, uvođenje PCSK9i treba razmotriti tijekom hospitalizacije.

U slučaju da se u bolesnika tijekom iduće dvije godine ponovi vaskularni događaj (nije nužno da je riječ o ponovljenom AKS-u!), savjetuje se spustiti vrijednost LDL-K na <1,0 mmol/L. Nakon hospitalne faze bolesnike s AKS-om treba uputiti na kardiovaskularnu rehabilitaciju koja kroz cjeloviti

<55 or women aged <60 years, adults with LDL-C >5 mmol/L, children with LDL-C >4 mmol/L, persons with tendinous xanthomata, or persons with relatives suffering from FH, premature CVD, or tendinous xanthomata. Diagnosis is established using the Dutch Lipid Clinic Network criteria, which take into consideration data from familial and personal medical history, physical examination, pre-treatment LDL-C values, and the potentially available results of genetic analysis. The score sum reflects the probability of this diagnosis. If possible, diagnosis should be confirmed by genetic testing because a confirmed mutation can be used for a cascade screening of other family members. Early screening for FH in children is recommended at the age of ≥5 years. In persons with FH and another additional major risk factor, and especially if they have already developed ASCVD, it is useful to introduce PCSK9i treatment if target LDL-C was not achieved with intensive statin and ezetimibe therapy. Persons with "isolated" FH are treated like any other persons with high CV risk.

Homozygous FH is a rare, but very severe form of the disease, characterized by very high LDL-C concentration (>13 mmol/L), early and progressive ASCVD, and often ending with death at the age of <30 years. It is treated with intense hypolipemic therapy and apheresis. Addition of lomitapide can reduce LDL-C by up to 50%, reducing the frequency of the need for apheresis.[16]

PERSONS WITH DIABETES MELLITUS

The new guidelines reclassified persons with diabetes mellitus according to CV risk categories and made their target LDL-C values stricter. Non-HDL-C and ApoB are recommended as secondary therapeutic goals in these patients as good indicators of burden with triglyceride-rich lipoproteins and residual particles. Statins are the first choice of treatment, but ezetimibe has been shown as very effective, causing a greater reduction in CV risk in persons with very high CV risk with diabetes mellitus vs. those without diabetes mellitus.[17] 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.[18] 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

pristup redukciji ukupnoga kardiovaskularnog rizika s pomoću tjelovježbe te edukacije bolesnika o KVB-u, promjenama nezdravih životnih navika i pravilnoj prehrani, postiže bolju kontrolu čimbenika rizika i znatno smanjuje smrtnost.[19]

ISHEMIJSKI MOŽDANI UDAR

Bolesnici nakon preboljenoga ishemijskog moždanog udara ili tranzitornoga ishemijskog napadaja 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 smrti za 12 %.[20]

BOLEST PERIFERNIH ARTERIJA

Na temelju rezultata istraživanja FOURIER nove su smjernice u terapijske preporuke uvele PCSK9i.[21] Kratko je navedena korist od primjene fenofibrata na smanjenje broja amputacija u spomenutoj populaciji, kao i na progresiju dijabetičke retinopatije.[22]

OSOBE STARIJE ŽIVOTNE DOBI

Liječenje statinima bolesnika s ASKVB-om u dobi >65 godina jednako je preporučeno kao i za mlađe 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, ezetimiba i PCSK9 inhibitora. Preostaje nam uložiti dodatni napor za implementaciju ovih preporuka u svakodnevnom kliničkom radu i za postizanje dobre adherencije bolesnika uz propisanu terapiju kako bismo sjajne rezultate kliničkih ispitivanja preslikali u stvarni život.

considered. If the patient was on the maximum tolerable dose of statin and ezetimibe even before ACS, PCSK9i introduction should be considered during hospital stay.

In case of vascular event recurrence in the patient during the next two years (not necessarily ACS recurrence!), it is advisable to reduce LDL-C to <1.0 mmol/L. After hospitalization, patients with ACS should be referred to cardiovascular rehabilitation, which achieves better control of risk factors and significantly reduces mortality through a wholesome approach to reduction of total cardiovascular risk by exercising and educating patients on CVD, changing unhealthy lifestyle habits, and appropriate diet.[19]

ISCHEMIC STROKE

After suffering an ischemic stroke or transitory ischemic attack, patients have the same therapeutic goals as people with very high CV risk. With each reduction of LDL-C by 1 mmol/L, we reduce the risk of recurrent neurological events, myocardial infarction, and CV death by 12%.[20]

PERIPHERAL ARTERY DISEASE

Based on the results of the FOURIER study, the new guidelines introduced PCSK9i into the therapeutic recommendations.[21] The benefits of using fenofibrate for the reduction of amputations in this population as well as for diabetic retinopathy progression are briefly mentioned.[22]

ELDERLY PERSONS

Statin treatment of patients with ASCVD aged >65 is equally recommended as in young people. There is insufficient evidence to confirm the benefits of using statins in primary prevention in people older than 75, although the guidelines allow for that possibility in people with high or very high risk (IIb).[23] In case of kidney insufficiency or risk of interactions with other medicinal products, we should start with a low dose of statins and titrate it carefully.

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, ezetimibe, 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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