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SAVREMENA DIJAGNOSTIKA, KLASIFIKACIJA I TERAPIJA DISLIPIDEMIJA PREMA MEĐUNARODNIM SMERNICAMA 2025.–2026. - PREGLEDNI RAD

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Sažetak: Dislipidemije predstavljaju jedan od ključnih, modifikabilnih faktora rizika za aterosklerotsku kardiovaskularnu bolest (ASKVB), uključujući koronarnu bolest srca, cerebrovaskularnu ishemiju i periferne arterijske bolesti. Epidemiološki podaci pokazuju jasnu linearnu vezu između nivoa holesterola lipoproteina niske gustine (LDL-C) i učestalosti kardiovaskularnih događaja, potvrđujući LDL-C kao primarni uzročni faktor aterogeneze. Kod očigledno zdravih osoba, rizik za nastanak ASKVB je najčešće rezultat interakcije višestrukih faktora rizika, što je osnova za procenu i upravljanje ukupnim kardiovaskularnim (KV) rizikom. Skrininga faktora rizika mora da obuhvata i lipidni status kod muškaraca sa više od 40 godina starosti i kod žena sa više od 50 godina starosti ili nakon rane menopauze. Sistem za procenu rizika kao što je SCORE 2 i SCORE 2OP (Izračunavanje desetogodišnjeg rizika od smrtonosnih i nesmrtonosnih kardiovaskularnih događaja a OP je kod starih osoba) može doprineti kod donošenja logičnih odluka u lečenju da bi se izbeglo subdoziranje ili predoziranje leka. Određene osobe prezentovane sa visokim ili veoma visokim rizikom za razvoj KVB ne zahtevaju procenu rizika SCORE, već hitno zbrinjavanje svih faktora rizika. Ovo važi za pacijente sa dokazanom KVB, dijabetom ili hroničnom bubrežnom bolešću (HBB). U poslednjoj dekadi, a naročito u periodu 2023.–2026. godine, došlo je do značajnih promena u međunarodnim smernicama. Prema smernicama i preporukama Evropskog udruženja kardiologa (European Society of Cardiology - ESC), Evropskog društva za aterosklerozu (European Atherosclerosis Society -EAS), Američkog koledža kardiologije (American College of Cardiology - ACC), Američkog udruženja za srce (American Heart Association - AHA) i Američkog udruženja za dijabetes (American Diabetes Association - ADA), javlja se jasan pomak ka agresivnijem snižavanju LDL-holesterola, personalizaciji terapije i široj primeni kombinovanih terapijskih strategija. Rana dijagnostika i agresivna kontrola lipidnog profila ostaju centralne komponente prevencije aterosklerotske kardiovaskularne bolesti. Sve ove smernice ističu potrebu za ranijom, intenzivnijom i kombinovanom terapijom radi postizanja što nižih vrednosti aterogenih lipoproteina, sa posebnim fokusom na LDL-C i non-HDL-C (to je ukupni holesterol minus holesterol lipoproteina visoke gustine-HDL-C; obuhvata sve aterogene frakcije: LDL, VLDL, IDL, lipoprotein(a)) i apolipoprotein B (apoB). Napredak u razumevanju lipidnog metabolizma i dostupnost novih terapija značajno su unapredili mogućnosti lečenja. Ovaj pregledni rad sistematski prikazuje savremene principe dijagnostike, klasifikacije, terapije i prognoze dislipidemija, uz poređenje ključnih preporuka vodećih smernica. Posebno se razmatraju novi terapijski modaliteti, uključujući Proproteinsku konvertazu subtilizin/keksin tip 9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitore. Posebno je dat značaj genskoj terapiji RNK interferencije- ovim mehanizmom ćelija može „utišati“ (silence) određene gene putem male interferirajuće RNK (small interfering RNA - siRNA) što je mehanizam terapijskog dejstva inclisirana.

Ključne reči: dislipidemija, LDL holesterol, PCSK9 inhibitori, ateroskleroza, smernice.

UVOD

Dislipidemije obuhvataju poremećaje metabolizma lipida koji značajno doprinose razvoju aterosklerotske kardiovaskularne bolesti (ASKV). Povišen holesterola lipoproteina niske gustine LDL-C predstavlja glavni uzročni faktor aterogeneze. Dislipidemije predstavljaju heterogenu grupu poremećaja metabolizma lipida koje karakterišu povišene ili snižene koncentracije lipoproteina u plazmi. One su ključni, modifikabilni faktor rizika za aterosklerotsku kardiovaskularnu bolest (ASCVD), uključujući koronarnu bolest srca, cerebrovaskularna oboljenja i periferne vaskularne bolesti. Epidemiološki podaci pokazuju jasnu linearnu vezu između nivoa LDL holesterola (LDL-C) i učestalosti

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CONTEMPORARY DIAGNOSTICS, CLASSIFICATION, AND TREATMENT OF DYSLIPIDEMIAS ACCORDING TO INTERNATIONAL GUIDELINES 2025–2026

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Summary: Dyslipidemias represent one of the key modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, cerebrovascular ischemia, and peripheral arterial disease. Epidemiological data show a clear linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and the incidence of cardiovascular events, confirming LDL-C as the primary causal factor in atherogenesis. In apparently healthy individuals, the risk of developing ASCVD is most often the result of the interaction of multiple risk factors, which forms the basis for assessing and managing overall cardiovascular (CV) risk. Risk factor screening should include lipid profiling in men over 40 years of age and in women over 50 years of age or after early menopause. Risk estimation systems such as SCORE2 and SCORE2-OP (used to calculate the 10-year risk of fatal and non-fatal cardiovascular events, with OP referring to older persons) can contribute to rational therapeutic decisions in order to avoid under- or overtreatment. Certain individuals classified as high or very high cardiovascular risk do not require SCORE risk assessment but instead require immediate management of all risk factors. This applies to patients with established cardiovascular disease, diabetes, or chronic kidney disease (CKD). In the last decade, and particularly in the period 2023–2026, significant changes have occurred in international guidelines. According to recommendations of the European Society of Cardiology (ESC), European Atherosclerosis Society (EAS), American College of Cardiology (ACC), American Heart Association (AHA), and American Diabetes Association (ADA), there has been a clear shift toward more aggressive LDL-cholesterol lowering, personalized therapy, and broader use of combination treatment strategies. Early diagnosis and aggressive lipid control remain central components of ASCVD prevention. All these guidelines emphasize the need for earlier, more intensive, and combination therapy to achieve very low levels of atherogenic lipoproteins, with special focus on LDL-C, non-HDL-C (total cholesterol minus HDL cholesterol; includes all atherogenic fractions: LDL, VLDL, IDL, lipoprotein(a)), and apolipoprotein B (ApoB). Advances in understanding lipid metabolism and the availability of new therapies have significantly improved treatment options. This review systematically presents modern principles of diagnosis, classification, treatment, and prognosis of dyslipidemias, along with a comparison of key guideline recommendations. Special attention is given to novel therapeutic modalities, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Particular emphasis is also placed on RNA interference gene therapy, where cells can “silence” specific genes via small interfering RNA (siRNA), which represents the mechanism of action of inclisiran.

Key words: dyslipidemia, LDL cholesterol, PCSK9 inhibitors, atherosclerosis, guidelines.

INTRODUCTION

Dyslipidemias encompass disorders of lipid metabolism that significantly contribute to the development of atherosclerotic cardiovascular disease (ASCVD). Elevated low-density lipoprotein cholesterol (LDL-C) represents the main causal factor of atherogenesis. Dyslipidemias are a heterogeneous group of lipid metabolism disorders characterized by increased or decreased concentrations of plasma lipoproteins. They are a key modifiable risk factor for ASCVD, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Epidemiological data demonstrate a clear linear relationship between LDL cholesterol (LDL-C) levels and the incidence of cardiovascular events, confirming LDL-C as the primary causal factor in atherogenesis [1–7].

In apparently healthy individuals, the risk of developing ASCVD is most often the result of the interaction of multiple risk factors. This forms the basis for assessment and management of

kardiovaskularnih događaja, potvrđujući LDL-C kao primarni uzročni faktor aterogeneze [1–7].

Kod očigledno zdravih osoba, rizik za nastanak ASKVB je najčešće rezultat interakcije višestrukih faktora rizika. Ovo je osnova za procenu i upravljanje ukupnim KV rizikom. Kod skrininga faktora rizika morali bi obuhvatiti i lipidni status kod muškaraca >40 godina starosti i kod žena >50 godina starosti ili nakon menopauze. Osavremenjeni elektronski internet Sistem za procenu rizika Heart Score (*www.heartscore.org*): **SCORE 2** i **SCORE 2OP** doprinosi kod donošenja logičnih odluka u lečenju da bi se izbeglo subdoziranje ili predoziranje hipolipemicima. Određene osobe prezentovane sa visokim ili veoma visokim ili ekstremnim rizikom za razvoj KVB ne zahtevaju procenu rizika, već hitno zbrinjavanje svih faktora rizika. Ovo važi za pacijente sa dokazanom ASKVB, dijabetes mellitusom (DM) ili hroničnom bubrežnom bolešću (HBB) stadijuma veće od G3b-4 ili manifestnom hroničnom bubrežnom insuficijencijom (HBI). Mora se napomenuti da su svi sistemi za procenu rizika prilično kruti i zahtevaju dodatnu pažnju prilikom kreiranja završnog stava u lečenju. Dodatni faktori koji utiču na procenu rizika svrstani su u elektronskom sistemu za procenu kao što je Heart Score (*www.heartscore.org*). Pristup ukupnoj proceni rizika dozvoljava fleksibilnost, ukoliko se ne može dostići najbolji preventivni rezultat sa jednim faktorom rizika, rizik se svakako može sniziti sa jačim delovanjem na ostale faktore rizika.

Prema aktuelnim svetskim, američkim i evropskim smernicama sve srpske nazive ADA, AHA/ACC, ESC/EAS 2023–2026), rana dijagnostika i agresivna kontrola lipidnog profila ostaju centralne komponente prevencije ASCVD. [3–5].

U periodu 2023.–2026. godine objavljene su nove verzije ključnih međunarodnih smernica za lečenje dislipidemija, uključujući: Evropsko kardiološko i Evropsko aterosklerotsko društvo (ESC/EAS), Američko udruženje za srce(AHA), Američki koledž kardiologa (ACC) i Američko udruženje za dijabetes (ADA).

Sve ove smernice ističu potrebu za ranijom, intenzivnijom i kombinovanom terapijom radi postizanja što nižih vrednosti aterogenih lipoproteina, sa posebnim fokusom na LDL-C, non-HDL-C i apolipoprotein B (apoB) [3–5] (Tabela 1).

Tabela 1. Uporedni prikaz ključnih preporuka ADA vs ESC/EAS (2023–2026)

ADA (2024–2026)	ESC/EAS (2023–2026)
LDL-C ciljevi za dijabetičare: strožiji (često <1,4 mmol/L)	LDL-C ciljevi po riziku: veoma strogi (<1,4 mmol/L za visok rizik; <1,0 mmol/L za ekstremni rizik)
Preporučuje merenje apoB kod većine pacijenata sa DM2	Nivoi apoB i non-HDL-C ravnopravni ciljevi terapije
Inclisiran preporučen kod problema sa adherencijom	Inclisiran uvršten u standardne terapijske algoritme
Favorizuje ranu kombinovanu terapiju	Insistira na „stepwise + combination“ pristupu
Personalizovan pristup terapiji	Matrični pristup po kategorijama rizika

CILJ RADA

Cilj ovog preglednog rada je da sveobuhvatno prikaže savremene principe dijagnostike, klasifikacije ranog skrininga, procene desetogodišnjeg kardiovaskularnog rizika SCORE 2 i SCORE 2OP alatima i terapijskog upravljanja dislipidemijama u skladu sa najnovijim međunarodnim standardima prema aktuelnim smernicama i vodličima (ESC,EAC, ADA, AHA, ACC).

KLASIFIKACIJA DISLIPIDEMIJA

Primarne dislipidemije

- Porodična hiperholesterolemija (FH)
- Familijarna kombinovana hiperlipidemija
- Poligenska hiperlipidemija

Sekundarne dislipidemije

Najčešće uzrokovane:

- dijabetes melitus,
- gojaznost i metabolički sindrom,
- hronična bubrežna bolest,
- hipotireoza,
- bolesti jetre,
- lekovi (kortikosteroidi, antipsihotici, retinoidi, imunokompresivi) [15–17].

DIJAGNOZA DISLIPIDEMIJA

Standardni dijagnostički pristup

Dijagnostika uključuje merenje standardnog lipidnog profila: ukupni holesterol,

overall cardiovascular (CV) risk. Risk factor screening should include lipid profiling in men over 40 years of age and in women over 50 years of age or after menopause. The updated electronic risk assessment system HeartScore (www.heartscore.org
), including SCORE2 and SCORE2-OP, supports clinical decision-making in order to avoid under- or overtreatment with lipid-lowering therapy. Certain individuals presenting with high, very high, or extreme cardiovascular risk do not require formal risk scoring but instead require immediate management of all risk factors. This applies to patients with established ASCVD, diabetes mellitus (DM), or chronic kidney disease (CKD) stage G3b–G4 or overt chronic renal failure. It should be noted that all risk scoring systems are relatively rigid and require additional clinical judgment when making final therapeutic decisions. Additional risk modifiers are included in electronic systems such as HeartScore (www.heartscore.org
). This comprehensive approach allows flexibility, as failure to achieve optimal risk reduction through one factor can be compensated by more intensive control of other risk factors.

According to current global, American, and European guidelines (ADA, AHA/ACC, ESC/EAS 2023–2026), early diagnosis and aggressive lipid control remain central components of ASCVD prevention [3–5].

In the period 2023–2026, new versions of major international dyslipidemia guidelines were published, including those of the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS), the American Heart Association (AHA), the American College of Cardiology (ACC), and the American Diabetes Association (ADA).

All these guidelines emphasize the need for earlier, more intensive, and combination therapy in order to achieve lower levels of atherogenic lipoproteins, with special focus on LDL-C, non-HDL-C, and apolipoprotein B (ApoB) [3–5] (Table 1).

Table 1. Comparative overview of key ADA vs ESC/EAS recommendations (2023–2026)

ADA (2024–2026)	ESC/EAS (2023–2026)
LDL-C targets for diabetic patients: more stringent (often <1.4 mmol/L)	LDL-C targets based on risk: very strict (<1.4 mmol/L for high risk; <1.0 mmol/L for extreme risk)
Recommends measurement of ApoB in most patients with type 2 diabetes	ApoB and non-HDL-C levels are considered equally important therapeutic targets
Inclisiran recommended in cases of poor adherence	Inclisiran included in standard therapeutic algorithms
Favors early combination therapy	Emphasizes a "stepwise + combination" approach
Personalized therapeutic approach	Matrix-based risk stratification approach

AIM OF THE STUDY

The aim of this review article is to comprehensively present contemporary principles of diagnosis, classification, early screening, assessment of 10-year cardiovascular risk using SCORE2 and SCORE2-OP tools, and therapeutic management of dyslipidemias in accordance with the latest international standards and guidelines (ESC/EAS, ADA, AHA, ACC).

CLASSIFICATION OF DYSLIPIDEMIAS

Primary dyslipidemias

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia

Polygenic hyperlipidemia

Secondary dyslipidemias

Most commonly caused by:

Diabetes mellitus

Obesity and metabolic syndrome

Chronic kidney disease

Hypothyroidism

Liver diseases

Medications (corticosteroids, antipsychotics, retinoids, immunosuppressants) [15–17]

DIAGNOSIS OF DYSLIPIDEMIAS

Standard diagnostic approach

Diagnosis includes measurement of the standard lipid profile: total cholesterol, LDL-C, HDL-C, and triglycerides; calculation of non-HDL-C and ApoB; assessment of secondary causes; evaluation of global cardiovascular risk; and review of family history.

Dyslipidemia screening is always indicated in patients with clinical manifestations of cardiovascular disease (CVD), in clinical

LDL-C, HDL-C, trigliceridi; izračunavanje non-HDL-C i apoB; procenu sekundarnih uzroka; procenu globalnog kardiovaskularnog rizika i ispitivanje porodične anamneze.

Skrining za dislipidemiju je uvek indikovan kod pacijenata sa kliničkim manifestacijama KVB, u kliničkim stanjima povećanog KV rizik i kad god se ukaže potreba za skriningom faktora rizika. U nekoliko kliničkih stanja, dislipidemija može doprineti povećanju rizika za razvoj KVB. Autoimuna hronična inflamatorna stanja kao što su reumatoidni artritis, sistemski lupus eritematosus (SLE) i psorijaza se smatraju stanjima u kojima je povećan KV rizik. Pored toga, kod žena, dijabetes i hipertenzija tokom trudnoće su rizični indikatori, a kod muškaraca, erektilna disfunkcija. Pacijenti sa hroničnom bubrežnom bolešću i manifestnom bubrežnom insuficijencijom takođe imaju uvećan KV rizik i kod njih je indikovan skrining za dislipidemiju.

Uvek je potrebno identifikovati kiničke manifestacije genetskih dislipidemija, kao što su ksantomi, ksantelazme i rani arcus cornealis (pre 45 godina), jer su oni indikatori ozbiljne lipoproteinske bolest, pre svega porodične hiperholesterolemije (FH), koja je najčešće uzrok monogenetskih poremećaja i udružena je sa preranom ASKVB. Skrining za dislipidemiju je takođe indikovan kod pacijenata sa perifernom arterijskom bolešću (PAB) ili u prisustvu povećanja debljine intima-medija karotida (IMK) ili karotidnih plakova.

Skrining za dislipidemiju bi trebalo razmotriti kod svih odraslih muškaraca ≥40 godina ili kod žena ≥50 godina ili u ranoj postmenopauzi, posebno u prisustvu ostalih faktora rizika. Takođe, je indikovano za skrining potomaka pacijenata sa ozbiljnom dislipidemijom i njihovo praćenje u specijalizovanim klinikama, ako je potrebno. Takođe, preporučuje se skrining i članova porodica pacijenata sa preuranjenim ASKVB [2].

Evaluacija laboratorijskih parametara lipida i apolipoproteina [2]

Predložene analize koje se koriste za procenu lipida su ukupni holesterol (TC), trigliceridi (TG), HDL-C, LDL-C. Uzorci krvi uzeti nakon gladovanja i oni nakon obroka daju slične rezultate za totalni holesterol (TC), LDL-holesterol i HDL-holesterol. Trigliceridi (TGs) su uslovljeni hranom. Postoji značajna unutar-pojedinačna varijacija kod serumskih lipida. Varijacije od 5-10% za TC i >20% za TG, posebno kod pacijenata sa hipertrigliceridemijom (HTG), nisu retkost. Ovo je donekle zbog analitičke varijacije, ali je takođe i zbog spoljnih faktora poput ishrane, intenziteta fizičke aktivnost, i sezonskih varijacija poput povišenog nivoa TC i HDL-holesterola tokom zime.

LDL holesterol - U većini kliničkih studija LDL-holesterol je izračunat pomoću Friedewald-ove formule [2]:

LDL-C =TC -HDL-C - TG/ 2.2; u mmol/L

LDL-C = TC - HDL-C - TG/5 u mg/dL

Metodološke greške se mogu akumulirati jer se oslanjaju na 3 analize: za ukupni holesterol (TC), trigliceride (TGs) i HDL-holesterol. Direktne metode za određivanje LDL-holesterola su dostupne i one se sada široko koriste**.** Generalno, direktne i indirektne (izračunate) vrednosti LDL-holesterola pokazuje dobro slaganje. Nove formule za izračunavanje LDL-C kao što su Martin/Hopkins, Sampson, posebno su preporučene u ADA i AHA/ACC smernicama [3–4]. Direktne metode za utvrđivanje HDL–holesterola i LDL–holesterola su trenutno široko korišćene i one su pouzdane kod pacijenata sa normalnim vrednostima lipida. Međutim u hipertrigliceridemiji (HTG) mogu biti nepouzdane, i rezultati mogu varirati među komercijalnim testovima.

Lipoprotein(a)-LP(a) u nekoliko studija je pronađen kao dodatni nezavisni faktor rizika; u patofiziologiji aterosklerotskih vaskularnih bolesti i u aortnoj stenozi. LP(a) ima zajednička svojstva sa LDL, ali on sadrži jedinstven protein, apolipoprotein (a)-apo(a), koji je strukturno homolog plazminogenu. Merenja LP(a) su posebno stabilna tokom vremena. Statini ne smanjuju nivo LP(a), ali e smanjenje LP(a) za 30% prikazano upotrebom Proprotein konvertaza subtilizin/keksin tip 9 (PCSK9) inhibitorima i nikotinskom kiselinom. Uticaj na kardiovaskularne (CVD) događaje koji ciljaju LP(a) gen nije dokazan. Lekovi koji utiču na Lp(a) gen snižavaju nivoe ovih cirkulišućih proteina za preko 80%.

Najveći broj sistema za procenu KV rizika koriste TC i LDL-holesterol, i upotreba ostalih mera, poput apoB, i non-HDL-holesterola, mada deluje logično, zasnovani su na post hok analizama. TC i LDL–C ostaju primarni ciljevi lečenja, dok non-HDL-holesterol i apoB su identifikovani kao sekundarni ciljevi. Kod pacijenta sa povišenim nivoom TG, dodatni rizik nose TG bogati lipoproteini koji se moraju uzeti u obzir.

conditions associated with increased cardiovascular risk, and whenever risk factor screening is warranted. In several clinical conditions, dyslipidemia may contribute to an increased risk of developing CVD. Chronic autoimmune inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis are considered conditions associated with increased cardiovascular risk. In addition, in women, gestational diabetes and hypertension during pregnancy are important risk indicators, while in men, erectile dysfunction is considered a risk marker. Patients with chronic kidney disease and overt renal failure also have increased cardiovascular risk, and dyslipidemia screening is indicated in these individuals.

It is always necessary to identify clinical manifestations of genetic dyslipidemias, such as xanthomas, xanthelasmas, and early corneal arcus (before the age of 45), as these are indicators of severe lipoprotein disorders, primarily familial hypercholesterolemia (FH), which is most often a monogenic disorder associated with premature ASCVD. Screening for dyslipidemia is also indicated in patients with peripheral arterial disease (PAD) or in the presence of increased carotid intima-media thickness (IMT) or carotid plaques.

Screening should also be considered in all adult men aged ≥40 years or women aged ≥50 years or in early postmenopause, especially in the presence of additional risk factors. Screening is also indicated in the offspring of patients with severe dyslipidemia, with follow-up in specialized clinics if necessary. Furthermore, screening of family members of patients with premature ASCVD is recommended [2].

Evaluation of Lipid and Apolipoprotein Laboratory Parameters [2]

The proposed lipid analyses used for assessment include total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C. Blood samples collected in the fasting state and those collected after meals provide similar results for total cholesterol (TC), LDL cholesterol, and HDL cholesterol. Triglycerides (TGs), however, are influenced by food intake.

There is significant intra-individual variability in serum lipid levels. Variations of 5–10% for TC and >20% for TG, particularly in patients with hypertriglyceridemia (HTG), are not uncommon. This is partly due to analytical variation, but also to external factors such as diet, physical activity level, and seasonal variation, including higher TC and HDL cholesterol levels during winter.

LDL cholesterol

In most clinical studies, LDL cholesterol is calculated using the Friedewald formula [2]:

LDL-C = TC − HDL-C − TG / 2.2 (mmol/L)
LDL-C = TC − HDL-C − TG / 5 (mg/dL)

Methodological errors may accumulate because this calculation is based on three parameters: total cholesterol (TC), triglycerides (TG), and HDL cholesterol. Direct methods for LDL-C measurement are available and are now widely used. In general, direct and calculated LDL-C values show good agreement.

New LDL-C estimation formulas, such as the Martin/Hopkins and Sampson equations, are particularly recommended in ADA and AHA/ACC guidelines [3–4]. Direct methods for measuring HDL-C and LDL-C are widely used and are reliable in patients with normal lipid profiles. However, in hypertriglyceridemia (HTG), they may be unreliable, and results can vary between commercial assays.

Lipoprotein(a) [Lp(a)]

Lipoprotein(a) [Lp(a)] has been identified in several studies as an independent risk factor in the pathophysiology of atherosclerotic cardiovascular disease and aortic stenosis. Lp(a) shares similarities with LDL but contains a unique protein, apolipoprotein(a) [apo(a)], which is structurally homologous to plasminogen.

Lp(a) measurements are relatively stable over time. Statins do not reduce Lp(a) levels; however, a reduction of approximately 30% has been observed with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors and nicotinic acid. However, a clear reduction in cardiovascular outcomes through direct Lp(a) targeting has not yet been conclusively demonstrated. Emerging therapies targeting the Lp(a) gene can reduce circulating Lp(a) levels by more than 80%.

Lipid parameters in cardiovascular risk estimation

Most cardiovascular risk assessment systems use TC and LDL-C, while other markers such as apoB and non-HDL-C, although physiologically logical, are mainly supported by post-hoc analyses. TC and LDL-C remain primary therapeutic targets, while non-HDL-C and apoB

Totalni holesterol (TC) se preporučuje za procenu totalnog KV rizika uz pomoć starog SCORE sistema. Međutim, u pojedinačnim slučajevima, TC može biti obmanjujući. To se posebno odnosi na žene, koje često imaju povišen nivo HDL-holesterola, i kod osoba obolelih od dijabetesa ili sa povišenim vrednostima TG koji često imaju snižen nivo HDL holesterola. Procena ukupnog rizika nije potrebna kod osoba sa porodičnom hiperlipidemijom (uključujući i FH) ili one sa TC >7.5mmol/l (290mg/ml). Ovi pacijenti su uvek sa visokim rizikom i trebalo bi im ukazati posebnu pažnju.

Non-HDL-holesterol se koristi za procenu totalnog iznosa aterogenih lipoproteina u plazmi: VLDL, VLDL ostataka, holesterola srednje gustine (IDL), LDL, Lp(a) i ima visoku korelaciju sa nivoima apoB. Non-HDL-holesterol je lako izračunati:

non-HDL= TC – HDL-holesterol.

Prema updejtovanom vodiču ESC za dislipidemije [3] SCORE2 i SCORE2OP preporučuju non-HDL-holesterol kao bolji indikator rizika od LDL-holesterola. U nekoliko objavljenih analiza Sistema za procenu rizika, non-HDL-holesterol je u odnosu na druge mere pokazao kao superioran, dok u drugim, LDL-holesterol i non-HDL-holesterol daju slične informacije. U poređenju sa non-HDL-holesterolom, korišćenje LDL-holesterola u određenim situacijama ima prednosti. Non-HDL holesterol se jednostavno izračunava i ne zahteva dodatne analize. Non-HDL–holesterol takođe uključuje aterogene lipoproteine bogate trigliceridima (VLDL, IDL i ostatke), koji su od suštinskog značaja s obzirom na skorašnje informacije iz genetskih studija (GWASs) koje podržavaju zapažanja da TG igraju značajnu ulogu u aterogenezi. Sva dosadašnja istraživanja koriste LDL-holesterol, te je on primarni cilj lečenja. Međutim, non-HDL holesterol bi trebalo koristiti kao sekundarni cilj kada je LDL-ciljana vrednost dostignuta. Ciljana vrednost za non-HDL-holesterol se lako izračunava kao zbir LDL-holesterol ciljane vrednost na koju se doda 0.8 mm/L (30 mg/dL).

Lipoprotein visoke gustine – holesterol (HDL-holesterol)

Nizak HDL-holesterol se pokazao kao veoma značajan i nezavistan faktor rizika u nekoliko studija i koristi se u većini Sistema za procenu rizika, uključujući HeartScore. Veoma visoke vrednosti HDL-holesterola nisu udružene sa ateroprotekcijom. Na osnovu epidemioloških studija, nivo HDL-holesterola koji je asociran sa povećanim rizikom je za muškarce < 1,0mmol/L (40mg/dL) i za žene < 1,2 mmol/L (48 mg/dL). Uloga HDL-holesterola za zaštitu protiv kardiovaskularnih oboljenja (CVD) dovedena je u pitanje u nekoliko studija koristeći Mendelian randomizaciju. Skorašnje studije ukazuju da disfunkcionalni HDL može biti više relevantan za razvoj ateroskleroze od nivoa HDL-holesterola.

Trigliceridi

Vrednosti triglicerida (TG) se određuju preciznim enzimskim tehnikama. Retke greške se dešavaju kod pacijenata sa hiperglicerolemijom, gde su detektovane greške kod veoma visokih vrednosti TG. Visoki nivoi TG su često udruženi sa niskim HDL-holesterolom i visokim nivoima LDL čestica male gustine. U brojnim meta analizama TG mogu se pokazati kao nezavistan faktor rizika. Pored toga, skoriji podaci o genetskim uzrocima podržavaju tvrdnju da visoki nivoi TG direktno uzrokuju kardiovaskularne (CV) bolesti. Skorašnje studije sugerišu da vrednosti TGs prilikom ne-pošćenja mogu da nose informacije u pogledu lipoproteinskih ostataka udruženih sa povećanim rizikom.

APOLIPOPROTEINI

Postoje dobre imunohemijske metode za odredjivanje apolipoproteina u konvencionalnim autoanalizatorima. Analitička performansa je dobra i analize ne zahtevaju uslove pošćenja i nisu osetljive na povišene nivoe triglicerida (TG).

Apolipoprotein B (ApoB) je glavni apolipoprotein iz aterogenetske porodice lipoproteina (VLDL, IDL i LDL). ApoB je dobar za procenu velikog broja ovih čestica u plazmi. Ova karakteristika je veoma važna u slučaju visoke koncentracije lipoproteina male gustine LDL. Nekoliko prospektivnih studija je pokazalo je da apoB jednak LDL-holesterolu i non-HDL-holesterolu prilikom predviđanja rizika. ApoB nije ocenjen kao primarni cilj za lečenje u kliničkim ispitivanjima, ali nekoliko post hok analiza kliničkih ispitivanja predlaže da apoB može da se koristi ne samo kao marker rizika, već i kao cilj lečenja.

Apolipoprotein A1. ApoA1 je glavni protein HDL-holesterola i obezbeđuje zadovoljavajuće procene koncentracije HDL-holesterola. Međutim, svaka čestica HDL može da nosi jednu do pet ApoA1 molekula..

are considered secondary targets. In patients with elevated triglycerides, additional risk is contributed by triglyceride-rich lipoproteins, which must be taken into account.

Total cholesterol (TC) is recommended for cardiovascular risk estimation using the SCORE system. However, in individual cases, TC may be misleading. This is particularly relevant in women, who often have elevated HDL-C levels, and in patients with diabetes or elevated triglycerides, who frequently have reduced HDL-C levels.

Overall risk assessment is not required in individuals with familial hyperlipidemia (including FH) or in those with TC >7.5 mmol/L (290 mg/dL), as these patients are always considered high risk and require special clinical attention.

Non-HDL cholesterol

Non-HDL cholesterol is used to estimate the total amount of atherogenic lipoproteins in plasma, including VLDL, VLDL remnants, intermediate-density lipoproteins (IDL), LDL, and Lp(a), and it shows a strong correlation with ApoB levels. It is easily calculated as:

non-HDL-C = TC − HDL-C

According to the updated ESC dyslipidemia guidelines [3], SCORE2 and SCORE2-OP recommend non-HDL-C as a better risk indicator than LDL-C. In several analyses, non-HDL-C has shown superiority over other measures, while in others it provides similar information to LDL-C. Compared with LDL-C, non-HDL-C has the advantage of simplicity and does not require additional testing. It also includes triglyceride-rich atherogenic lipoproteins (VLDL, IDL, and remnants), which are increasingly recognized as important in atherogenesis based on genetic (GWAS) evidence.

LDL-C remains the primary treatment target; however, non-HDL-C is recommended as a secondary target once LDL-C goals are achieved. The non-HDL-C target can be estimated by adding 0.8 mmol/L (30 mg/dL) to the LDL-C target value.

High-density lipoprotein cholesterol (HDL-C)

Low HDL-C is an important independent cardiovascular risk factor and is included in most risk scoring systems, including HeartScore. Very high HDL-C levels are not necessarily protective. Epidemiological studies define increased risk thresholds as:

Men: HDL-C < 1.0 mmol/L (40 mg/dL)

Women: HDL-C < 1.2 mmol/L (48 mg/dL)

The protective role of HDL-C has been questioned in several Mendelian randomization studies. Recent evidence suggests that dysfunctional HDL particles may be more relevant to atherosclerosis development than absolute HDL-C levels.

Triglycerides (TG)

Triglycerides are measured using enzymatic methods. Rare analytical errors may occur in patients with extreme hypertriglyceridemia, particularly at very high TG levels. Elevated TG levels are often associated with low HDL-C and increased numbers of small dense LDL particles.

Multiple meta-analyses suggest that TG may represent an independent cardiovascular risk factor. Genetic studies further support the role of triglycerides in directly contributing to cardiovascular disease. Recent data also suggest that non-fasting TG levels may provide important information regarding remnant lipoproteins associated with increased cardiovascular risk.

APOLIPOPROTEINS

There are reliable immunochemical methods for the determination of apolipoproteins using conventional autoanalyzers. Analytical performance is generally good, and these assays do not require fasting conditions and are not affected by elevated triglyceride (TG) levels.

Apolipoprotein B (ApoB)

Apolipoprotein B (ApoB) is the main apolipoprotein of the atherogenic lipoprotein family (VLDL, IDL, and LDL). ApoB is useful for estimating the total number of these particles in plasma. This feature is particularly important in cases of elevated low-density lipoprotein (LDL) concentrations. Several prospective studies have shown that ApoB performs similarly to LDL cholesterol and non-HDL cholesterol in predicting cardiovascular risk. Although ApoB has not been established as a primary treatment target in clinical trials, several post-hoc analyses suggest that it may be used not only as a risk marker but also as a potential therapeutic target.

Apolipoprotein A1 (ApoA1)

Apolipoprotein A1 (ApoA1) is the main protein component of HDL cholesterol and provides a reliable estimate of HDL particle concentration. However, each HDL particle may carry between one and five ApoA1 molecules.

Apolipoprotein CIII (ApoCIII)

Apolipoprotein CIII (ApoCIII) is recognized as a potentially important emerging

Apolipoprotein CIII. Apo CIII je prepoznat kao potencijalno važan novi faktor rizika. Apo CIII je ključni regulator za metabolizam TG i visoki nivoi serumskog apo CIII su udruženi sa visokim nivoima serumskih VLDL i serumskih TGs. Pored toga, gubitak funkcije mutacijama je udružen sa niskim nivoima TG kao i sa smanjenim rizikom za kardiovaskularne bolesti

Genetska dijagnostika [4]

Genetska dijagnostika se preporučuje kod sumnje na porodičnu hiperholesterolemiju (FH), izuzetno visokih vrednosti LDL-C (>4,9 mmol/L ili >190 mg/dL) i porodične anamneze rane ishemijske bolesti srca.

TERAPIJSKI PRISTUPI

Terapija dislipidemija zasniva se na kombinaciji nefarmakoloških i farmakoloških strategija, usmerenih prvenstveno na redukciju LDL-holesterola, ali i na kontrolu triglicerida, povećanje HDL-holesterola i redukciju ukupnog aterogenog opterećenja. Savremene smernice saglasne su u ključnom principu: "što niže – to bolje" u odnosu na LDL-C, posebno kod pacijenata sa visokim i veoma visokim kardiovaskularnim rizikom [1–9].

1. Nefarmakološki pristupi

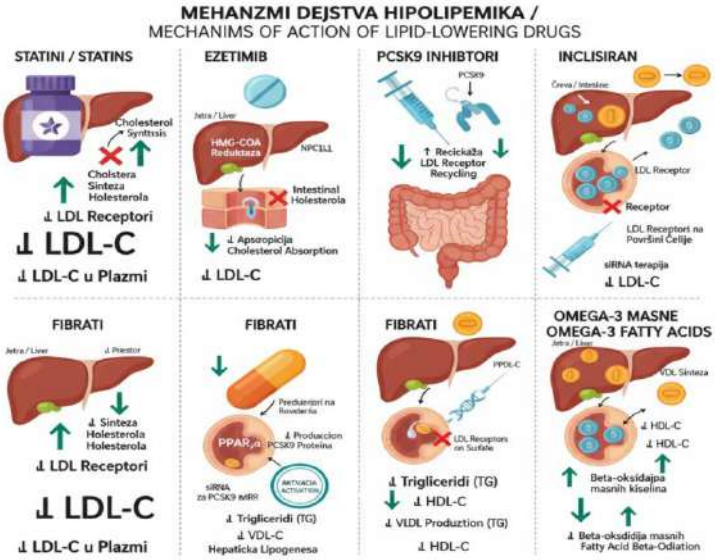
Modifikacija životnog stila - ovi pristupi predstavljaju osnovu terapije kod svih pacijenata sa dislipidemijom, bez obzira na rizik. Najvažnije intervencije obuhvataju redukcija unosa zasićenih i trans masti; mediteranski ili DASH tip ishrane; povećanje unosa vlakana i biljnih sterola; aerobna fizička aktivnost ≥150 min nedeljno; redukcija telesne mase za ≥5–7% kod gojaznih pacijenata; prestanak pušenja; redukcija alkohola kod hipertrigliceridemije. Iako promene životnog stila smanjuju LDL-C za 5–15%, kod pacijenata sa visokim rizikom najčešće nisu dovoljne kao monoterapija [16–22].

2. Farmakološka terapija dislipidemija (Tabela 2 i Shema 1)

Tabela 2. Terapijske klase lekova — poređenje preporuka smernica

Terapija	ADA	AHA/ACC	ESC/EAS
Statini	Osnova terapije; cilj što niži LDL-C	Prva linija	Prva i osnovna linija
Ezetimib	Druga linija ili dodatak	Dodatak statinu	Obavezno u visokom riziku
PCSK9 inhibitori	Kod neispunjavanja ciljeva	Poželjni nakon ACS	Obavezni za visok/vrlo visok rizik
Inclisiran	Kod loše adherencije	Alternativa PCSK9 inhibitorima	Integrisan u algoritme
Fibrati	Kod TG > 5.6 mmol/L	Kod teške HTG	Kod TG > 5.6 mmol/L
Omega-3 (EPA)	Kod rezidualnog rizika	REDUCE-IT populacija	Dodatna opcija

Shema 1. Grafički prikaz mehanizma dejstva hipolipemika



cardiovascular risk factor. ApoCIII is a key regulator of triglyceride metabolism, and elevated serum ApoCIII levels are associated with increased concentrations of VLDL and serum triglycerides. In addition, loss-of-function mutations in ApoCIII are associated with low triglyceride levels and reduced cardiovascular risk.

GENETIC DIAGNOSTICS [4]

Genetic testing is recommended in cases of suspected familial hypercholesterolemia (FH), extremely elevated LDL-C levels (>4.9 mmol/L or >190 mg/dL), and a family history of premature ischemic heart disease.

THERAPEUTIC APPROACHES

The treatment of dyslipidemias is based on a combination of non-pharmacological and pharmacological strategies, primarily aimed at reducing LDL cholesterol, but also at controlling triglycerides, increasing HDL cholesterol, and reducing overall atherogenic burden. Contemporary guidelines are consistent with the key principle: "the lower, the better" for LDL-C, especially in patients at high and very high cardiovascular risk [1–9].

1. Non-pharmacological approaches

Lifestyle modification

These interventions represent the foundation of therapy in all patients with dyslipidemia, regardless of risk level. The most important measures include:

Reduction of saturated fat and trans fat intake

Mediterranean or DASH dietary pattern

Increased intake of dietary fiber and plant sterols

Aerobic physical activity ≥150 minutes per week

Weight reduction of ≥5–7% in overweight and obese patients

Smoking cessation

Reduction of alcohol intake in hypertriglyceridemia

Although lifestyle changes can reduce LDL-C by approximately 5–15%, they are usually insufficient as monotherapy in patients at high cardiovascular risk [16–22].

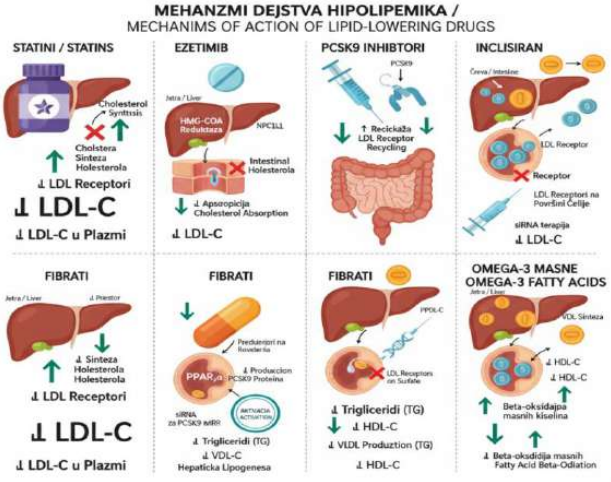
2. Pharmacological treatment of dyslipidemia

(Table 2 and Figure 1)

Table 2. Therapeutic Drug Classes — Comparison of Guideline Recommendations

Therapy	ADA	AHA/ACC	ESC/EAS
Statins	Mainstay of therapy; aim for the lowest possible LDL-C	First-line therapy	First and essential line of therapy
Ezetimibe	Second-line or add-on therapy	Add-on to statins	Mandatory in high-risk patients
PCSK9 inhibitors	Used when targets are not achieved	Preferred after ACS	Required in high and very high risk
Inclisiran	For poor adherence	Alternative to PCSK9 inhibitors	Integrated into treatment algorithms
Fibrates	For TG > 5.6 mmol/L	For severe hypertriglyceridemia	For TG > 5.6 mmol/L
Omega-3 (EPA)	For residual cardiovascular risk	REDUCE-IT population	Additional therapeutic option

Scheme 1. Graphical representation of the mechanism of action of lipid-lowering drugs



Statini (inhibitori HMG-CoA reduktaze)

Statini su i dalje prva linija terapije kod većine pacijenata. Dele se na: visokointenzivne (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) i srednje-intenzivne (simvastatin, pravastatin, lovastatin, pitavastatin). Efekti su redukcija LDL-C: 30–60% u zavisnosti od doze i smanjenje rizika od infarkta miokarda, šloga i kardiovaskularne (CV) smrti za 25–40% [8–10]. Nuspojave su miopatije, povišenje jetrenih enzima, vrlo retko rabdomioliza.

Ezetimib (inhibitor apsorpcije holesterola)

Ezetimib inhibira NPC1L1 transporter u tankom crevu i time smanjuje apsorpciju holesterola. Klinički značaj jeste da je preporučen kao *druga linija* kod bolesnika kod kojih LDL-C ostaje iznad cilja uz maksimalnu dozu statina jer daje dodatnih 20–25% redukcije LDL-C, bezbedan je i dobro podnošljiv [13].

Proproteinska konvertaza subtilizin/keksin tip 9 (Proprotein Convertase Subtilisin/Kexin Type 9) inhibitori ili PCSK9 inhibitori su monoklonska antitela: Evolokumab i Alirokumab. Blokiraju PCSK9 protein, čime povećavaju recikliranje LDL receptora i obaraju LDL-C za 50–65%. Indikacije su pacijenti sa vrlo visokim rizikom (preboleli infarkt, polivaskularna bolest); pacijenti sa FH; bolesnici koji na maksimalnoj terapiji statinom + ezetimibom a ne postižu ciljne vrednosti [10–11]. Velike studije (FOURIER, ODYSSEY Outcomes) pokazale su značajno smanjenje KV-mortaliteta i infarkta miokarda.

Inklisiran (siRNA terapija)

Inklisiran je mala interferirajuća RNK (siRNA) koja blokira sintezu PCSK9 u hepatocitima. Prednosti su da se primenjuje samo dva puta godišnje i postiže se trajna redukcija LDL-C od ~50% i da je idealan za pacijente sa lošom adherencijom. Uključivanje u smernice: ESC/EAS 2023–2026 uključuje inclisiran u standardni algoritam za vrlo visok rizik a ADA ga preporučuje ako terapijska adherencija predstavlja problem [5–7].

Fibrati

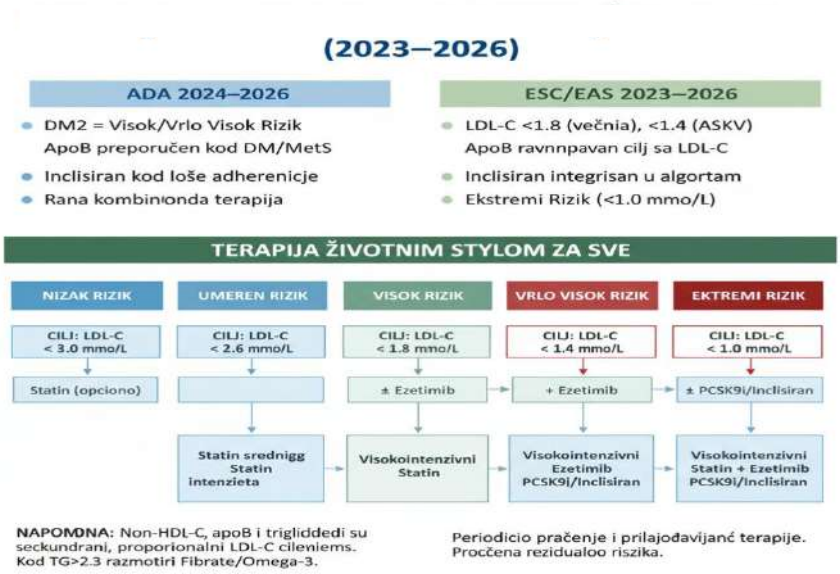
Fenofibrat i Bezafibrat. Indikacije za fibrate: trigliceridi >5,6 mmol/L (>500 mg/dL), prevencija pankreatitisa, rezidualna hipertrigliceridemija kod DM2.

Omega-3 masne kiseline (EPA formulacije) - visoke doze EPA (2–4 g/d) koriste se za smanjenje TG i stabilizaciju plaka. REDUCE-IT studija pokazala je smanjenje KV-ishoda kod pacijenata sa povišenim TG [39].

NOVINE U SMERNICAMA 2023–2026 (ADA, ESC/EAS, AHA/ACC)

U poslednje tri godine došlo je do nekoliko važnih promena koje značajno utiču na svakodnevnu kliničku praksu. (Tabela 3 i Shema 2.)

Shema 2. Grafički prikaz terapiskog algoritma i poređenja smernica



Statins (HMG-CoA reductase inhibitors)

Statins remain the first-line therapy in most patients. They are classified into high-intensity statins (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) and moderate-intensity statins (simvastatin, pravastatin, lovastatin, pitavastatin). Effects include LDL-C reduction of 30–60% depending on dose and a reduction in the risk of myocardial infarction, stroke, and cardiovascular (CV) mortality by 25–40% [8–10].n

Adverse effects include myopathy, elevated liver enzymes, and very rarely rhabdomyolysis.

Ezetimibe (cholesterol absorption inhibitor)

Ezetimibe inhibits the NPC1L1 transporter in the small intestine, thereby reducing cholesterol absorption.

Its clinical importance lies in its recommendation as second-line therapy in patients whose LDL-C remains above target despite maximal statin therapy. It provides an additional LDL-C reduction of 20–25% and is safe and well tolerated [13].

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors

PCSK9 inhibitors are monoclonal antibodies, including evolocumab and alirocumab. They block the PCSK9 protein, thereby increasing LDL receptor recycling and reducing LDL-C levels by 50–65%.

Indications include:

Patients at very high risk (previous myocardial infarction, polyvascular disease)

Patients with familial hypercholesterolemia (FH)

Patients who do not achieve target LDL-C levels despite maximal statin + ezetimibe therapy [10–11]

Major clinical trials (FOURIER, ODYSSEY Outcomes) demonstrated a significant reduction in cardiovascular mortality and myocardial infarction.

Inclisiran (siRNA therapy)

Inclisiran is a small interfering RNA (siRNA) that inhibits hepatic synthesis of PCSK9 in hepatocytes.

Advantages include administration only twice yearly and sustained LDL-C reduction of approximately 50%, making it particularly suitable for patients with poor adherence.

Guideline integration: ESC/EAS 2023–2026 includes inclisiran in standard treatment algorithms for very high-risk patients, while ADA recommends it in cases of poor therapeutic adherence [5–7].

Fibrates

Fenofibrate and bezafibrate are used in specific lipid disorders.

Indications include:

Triglycerides >5.6 mmol/L (>500 mg/dL)

Prevention of pancreatitis

Residual hypertriglyceridemia in type 2 diabetes mellitus (DM2)

Omega-3 fatty acids (EPA formulations)

High-dose EPA (2–4 g/day) is used to reduce triglyceride levels and stabilize atherosclerotic plaque.

The REDUCE-IT trial demonstrated a reduction in cardiovascular outcomes in patients with elevated triglycerides [39].

NEW DEVELOPMENTS IN THE 2023–2026 GUIDELINES (ADA, ESC/EAS, AHA/ACC)

In the past three years, several important changes have occurred that significantly impact everyday clinical practice. (Table 3 and Scheme 2).

Tabela 3. Uporedni LDL-C ciljevi po smernicama (ADA, AHA/ACC, ESC/EAS)

Kategorija rizika	ADA 2024–2026	AHA/ACC 2023–2025	ESC/EAS 2023–2026
Umeren rizik	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L
Visok rizik	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L
Veoma visok rizik	LDL-C < 1.4 mmol/L	LDL-C smanjiti maksimalno (često <1.4 mmol/L)	LDL-C < 1.4 mmol/L
Ekstremni rizik	—	—	LDL-C < 1.0 mmol/L
FH (heterozigotna)	cilj ≥50% redukcije LDL-C	≥50% redukcije LDL-C	<1.8 mmol/L; ako ASKV <1.4 mmol/L
FH (homozigotna)	specijalizovani centri	PCSK9 + lomitapid	PCSK9 + lomitapid/evinacumab

1. ADA 2024–2026 – Dijabetes i dislipidemija
Pacijenti sa DM2 automatski spadaju u kategoriju visokog ili veoma visokog rizika. LDL-C cilj kod većine dijabetičara: <1,8 mmol/L, a kod ASKV<1,4 mmol/L. Preporučeno je merenje apoB kod osoba sa gojaznošću, metaboličkim sindromom i visokim TG a inklisiran je preporučen kod loše adherencije. Naglasak je na ranoj primeni kombinovane terapije.
2. AHA/ACC 2023–2025 - personalizovani pristup terapiji; PCSK9 inhibitori sve češće već nakon prvog infarkta; LDL-C cilj: "što niže, to bolje", ali bez formalnog numeričkog cilja u nekim situacijama; važnost doživotnog praćenja LDL-C kod pacijenata sa FH; snažna uloga ne-HDL-C kod pacijenata sa visokom koncentracijom TG.
3. ESC/EAS 2023–2026 – Najagresivniji pristup LDL-C. Uvedena je kategorija "ekstremni rizik" polivaskularna bolest, ponovljeni ACS). LDL-C ciljevi: visok rizik <1,8 mmol/L, veoma visok rizik <1,4 mmol/L, ekstremni rizik <1,0 mmol/L. LDL-C, non-HDL-C i apoB su ravnopravni ciljni parametri; inclisiran zvanično uključen u terapijski algoritam; snažniji naglasak na redukciji remnantnih lipoproteina i TG.

Terapijski uporedni algoritam po stepenu kardiovaskularnog rizika je prikazan na Tabeli 4 i 5.

Tabela 4. Uporedni terapijski algoritam po stepenu kardiovaskularnog rizika

Rizik	ADA	AHA/ACC	ESC/EAS
Nizak rizik	Životni stil ± statin	Životni stil	Životni stil ± statin
Umeren rizik	Statin srednje jačine	Statin po proceni	Statin srednje jačine
Visok rizik	Visokointenzivni statin	Visokointenzivni statin	Visokointenzivni statin + ezetimib
Veoma visok rizik	Statin + ezetimib; PCSK9 po potrebi	Visokointenzivni statin + ezetimib + PCSK9 rani	Statin + ezetimib + PCSK9 obavezno
Ekstremni rizik	—	—	Statin + ezetimib + PCSK9 ± inclisiran
FH	Maksimalna kombinovana terapija	Statin + ezetimib, PCSK9	Statin + ezetimib + PCSK9

Tabela 5. Preporuke za specifične populacije

Populacija	ADA	AHA/ACC	ESC/EAS
Dijabetes	Automatski visok rizik	Većina u visokom riziku	Strogi ciljevi LDL-C (<1.4 mmol/L)
CKD	LDL-C <1.8 mmol/L	Oprez sa statinima kod GFR <30	FoKUS na apoB i non-HDL-C
Stariji	Korist proporcionalna apsolutnom riziku	Individualizacija	Statini preporučeni do 75 god.
FH	Statin + ezetimib + PCSK9	Rano testiranje članova porodice	Najagresivniji pristup
Nakon ACS	LDL-C <1.4 mmol/L brzo	PCSK9 nakon prvog ACS	PCSK9 u prvoj liniji nakon ACS

1. ***Efekat snižavanja LDL-holesterola na kardiovaskularne ishode***
U velikoj metaanalizi Cholesterol Treatment Trialists' Collaboration, koja je obuhvatila više od 170.000 pacijenata, pokazano je da svako smanjenje LDL-C za 1 mmol/L (~39 mg/dL) redukuje rizik od velikih vaskularnih događaja za oko 22% [23]. Ovaj efekat je prisutan kod

Scheme 2. Graphical representation of the therapeutic algorithm and comparison of guidelines

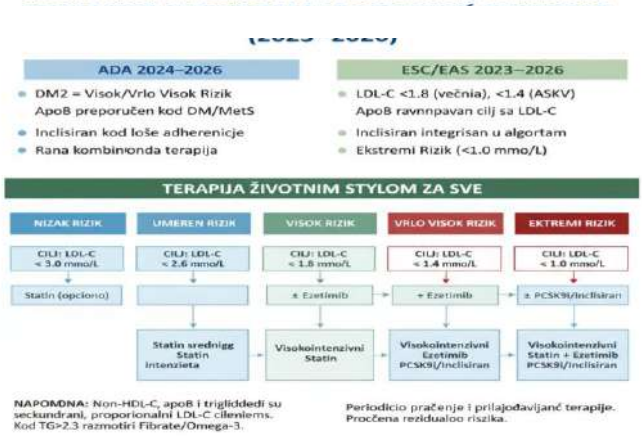


Table 3. Comparative LDL-C targets according to guidelines (ADA, AHA/ACC, ESC/EAS)

Risk category	ADA 2024–2026	AHA/ACC 2023–2025	ESC/EAS 2023–2026
Moderate risk	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L
High risk	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L
Very high risk	LDL-C < 1.4 mmol/L	LDL-C reduction as much as possible (often <1.4 mmol/L)	LDL-C < 1.4 mmol/L
Extreme risk	—	—	LDL-C < 1.0 mmol/L
FH (heterozygous)	≥50% LDL-C reduction target	≥50% LDL-C reduction	<1.8 mmol/L; if ASCVD <1.4 mmol/L
FH (homozygous)	specialized centers	PCSK9 + lomitapide	PCSK9 + lomitapide/evinacumab

1. ADA 2024–2026 – Diabetes and dyslipidemia

Patients with type 2 diabetes mellitus (DM2) are automatically classified as having high or very high cardiovascular risk. The LDL-C target in most diabetic patients is <1.8 mmol/L, while in patients with ASCVD the target is <1.4 mmol/L. Measurement of apoB is recommended in individuals with obesity, metabolic syndrome, and high triglycerides. Inclisiran is recommended in cases of poor adherence. The emphasis is on early initiation of combination therapy.

2. AHA/ACC 2023–2025 – Personalized therapeutic approach

PCSK9 inhibitors are increasingly used even after the first myocardial infarction. The LDL-C goal is "the lower, the better," although in some situations there is no strict numerical target. Lifelong LDL-C monitoring is emphasized in patients with familial hypercholesterolemia (FH). Non–HDL-C has an important role in patients with elevated triglycerides.

3. ESC/EAS 2023–2026 – Most aggressive LDL-C approach

A new "extreme risk" category has been introduced (e.g., polyvascular disease, recurrent ACS). LDL-C targets are: high risk <1.8 mmol/L, very high risk <1.4 mmol/L, extreme risk <1.0 mmol/L. LDL-C, non–HDL-C, and apoB are considered equal target parameters. Inclisiran is formally included in the therapeutic algorithm. There is a stronger focus on reduction of remnant lipoproteins and triglycerides.

The comparative therapeutic algorithm according to cardiovascular risk level is shown in Tables 4 and 5.

Table 4. Comparative therapeutic algorithm according to cardiovascular risk level

Risk	ADA	AHA/ACC	ESC/EAS
Low risk	Lifestyle ± statin	Lifestyle	Lifestyle ± statin
Moderate risk	Moderate-intensity statin	Statin based on clinical judgment	Moderate-intensity statin

muškaraca i žena, kod mlađih i starijih, kod dijabetičara, kod pacijenata sa prethodnim infarktom miokarda i u primarnoj i sekundarnoj prevenciji. Snižavanje LDL-C je korisno u gotovo svim kliničkim populacijama.

2. ***Statini – dokazi iz kliničkih studija***

Visokointenzivni statini dokazano smanjuju infarkt miokarda za 25–35%, ishemijski moždani udar za 20–30%, kardiovaskularnu smrt za 15–20% [6–8]. Pored LDL-redukcije, statini imaju i pleiotropne efekte stabilizaciju plaka, antiinflamatorno dejstvo i poboljšanje endotelne funkcije [24].

3. ***Ezetimib – klinički ishodi***

IMPROVE-IT studija (ezetimib + statin) pokazala je dodatno snižavanje LDL-C za ~23%, 6% relativno smanjenje primarnog KV-ishoda (p=0.016) [11]. Ovo potvrđuje važnost kombinovane terapije.

4. ***PCSK9 inhibitori – najveći benefit kod najrizičnijih pacijenata***

FOURIER studija (evolokumab) pokazuje LDL-C smanjen na ~0,8 mmol/L, 15% redukcija KV događaja, 27% smanjenje rizika od infarkta miokarda [10]. ODYSSEY Outcomes (alirokumab) značajno smanjenje KV mortaliteta nakon akutnog koronarnog sindroma [11]. Ključnoje: što je LDL-C niži – korist je veća.

5. ***Inclisiran – nova era dugotrajne kontrole lipida***

Inclisiran, kao siRNA terapija, smanjuje LDL-C trajno i stabilno. Prednosti su primena na svakih 6 meseci, bolja adherencija i ~50% redukcije LDL-C [12]. Još uvek se očekuju velike studije ishoda, ali dosadašnji podaci su obećavajući.

6**.** ***Trigliceridi i rezidualni rizik***

Povišeni trigliceridi i remnantske čestice lipoproteina značajno povećavaju rizik od KV događaja, naročito kod pacijenata sa dijabetesom i metaboličkim sindromom [19–20]. REDUCE-IT studija (EPA 4 g/dan) pokazala je 25% redukciju velikih KV događaja i 20% smanjenje KV mortaliteta [39]. Ovo potvrđuje da je rezidualni rizik važan i da nije dovoljan samo LDL-C.

NAJNOVIJE AMERIČKE PREPORUKE ZA LEČENJE DISLIPIDEMIJA IZ 2026

Nove američke preporuke preporuke [40] vraćaju fokus na ciljne vrednosti LDL holesterola: kod pacijenata sa graničnim ili intermedijarnim rizikom ciljne vrednosti su <2,6 mmol/L, kod visokorizičnih pacijenata <1,8 mmol/L, a kod pacijenata sa veoma visokim rizikom (tj. u sekundarnoj prevenciji) treba težiti vrednostima LDL <1,4 mmol/L.

Usvojen je **PREVENT-ASCVD kalkulator**, koji predviđa 10-godišnji i 30-godišnji rizik od neželjenih kardiovaskularnihdogađaja (infarkt miokarda, moždani udar ili kardiovaskularni mortalitet). Karakteristike pacijenata koje su važne za procenu ovog rizika su starost, pol, sistolni krvni pritisak, antihipertenzivna terapija, prisustvo dijabetesa, status pušenja, kao i laboratorijski markeri (ukupan i LDL holesterol). Ovo su neophodne varijable za osnovni model. Kod proširenog modela potreban je podatak o indeksu telesne mase (BMI) i bubrežnoj funkciji, dok potpuni model uključuje i albuminuriju i HbA1c [40].

Novost je procena osim 10-godišnji kardiovaskularni rizik i 30-godišnji rizik za osobe starosti između 30 i 59 godina. Nove preporuke osnažuju primenu dodatnih biomarkera za procenu rezidualnog kardiovaskularnog rizika, kao što je **lipoprotein(a)**, čije se određivanje savetuje jednom u životu, kao i **apolipoprotein B**, koji je posebno koristan kod pacijenata sa dijabetesom i hipertrigliceridemijom.

Veća pažnja se pridaje određivanju **koronarnog kalcijumskog skora (CAC) [40]**, naročito u slučajevima neizvesnosti da li započeti terapiju statinima ili ne. To je najčešće slučaj kod pacijenata sa graničnim ili intermedijarnim rizikom. Važan deo novih preporuka odnosi se na ranije i intenzivnije smanjenje LDL holesterola. Ovo se oslanja na koncept da duže izlaganje povišenom LDL holesterolu određuje kardiovaskularni rizik. Stoga je važno ranije uvesti terapiju i tako smanjiti izlaganje visokom LDL holesterolu, što dovodi do izraženije redukcije kardiovaskularnog rizika. S tim u vezi, komplementarna preporuka jeste **univerzalni lipidni skrining** i prevencija tokom života. Ne treba čekati na razvoj kardiovaskularnih događaja, već se savetuje periodična provera lipidnog statusa, uz poseban osvrt na skrining osoba sa dijabetesom, kardio-renalno-metaboličkim sindromom kao i kod dece [40].

PROGNOZA

Dislipidemije, ako se ne dijagnostikuju i ne leče adekvatno, značajno povećavaju rizik od aterosklerotske kardiovaskularne bolesti, prerane invalidnosti i smrtnosti. Međutim,

Risk	ADA	AHA/ACC	ESC/EAS
High risk	High-intensity statin	High-intensity statin	High-intensity statin + ezetimibe
Very high risk	Statin + ezetimibe; PCSK9 if needed	High-intensity statin + early ezetimibe + PCSK9	Statin + ezetimibe + mandatory PCSK9
Extreme risk	—	—	Statin + ezetimibe + PCSK9 ± inclisiran
FH	Maximal combination therapy	Statin + ezetimibe, PCSK9	Statin + ezetimibe + PCSK9

Table 5. Recommendations for specific populations

Population	ADA	AHA/ACC	ESC/EAS
Diabetes	Automatically high risk	Most patients at high risk	Strict LDL-C targets (<1.4 mmol/L)
CKD	LDL-C <1.8 mmol/L	Caution with statins when GFR <30	Focus on apoB and non–HDL-C
Elderly	Benefit proportional to absolute risk	Individualization	Statins recommended up to age 75
FH	Statin + ezetimibe + PCSK9	Early family screening	Most aggressive approach
Post-ACS	Rapid LDL-C reduction <1.4 mmol/L	PCSK9 after first ACS	PCSK9 as first-line after ACS

1. Effect of LDL cholesterol reduction on cardiovascular outcomes

In a large meta-analysis by the Cholesterol Treatment Trialists' Collaboration, including over 170,000 patients, it was shown that each reduction of LDL-C by 1 mmol/L (~39 mg/dL) reduces the risk of major vascular events by approximately 22% [23]. This effect is consistent across men and women, younger and older individuals, patients with diabetes, those with prior myocardial infarction, and in both primary and secondary prevention. LDL-C reduction is beneficial in almost all clinical populations.

2. Statins – evidence from clinical trials

High-intensity statins have been shown to reduce myocardial infarction by 25–35%, ischemic stroke by 20–30%, and cardiovascular mortality by 15–20% [6–8]. In addition to LDL reduction, statins exert pleiotropic effects, including plaque stabilization, anti-inflammatory action, and improvement of endothelial function [24].

3. Ezetimibe – clinical outcomes

The IMPROVE-IT trial (ezetimibe + statin) demonstrated an additional LDL-C reduction of ~23% and a 6% relative reduction in primary cardiovascular outcomes (p=0.016) [11]. This supports the importance of combination therapy.

4. PCSK9 inhibitors – greatest benefit in highest-risk patients

The FOURIER trial (evolocumab) showed LDL-C reduction to ~0.8 mmol/L, a 15% reduction in cardiovascular events, and a 27% reduction in myocardial infarction risk [10]. The ODYSSEY Outcomes trial (alirocumab) demonstrated a significant reduction in cardiovascular mortality after acute coronary syndrome [11]. The key principle is: the lower the LDL-C, the greater the benefit.

5. Inclisiran – a new era of long-term lipid control

Inclisiran, an siRNA-based therapy, provides sustained and stable LDL-C reduction. Its advantages include dosing every 6 months, improved adherence, and approximately 50% LDL-C reduction [12]. Large outcome trials are still ongoing, but current data are promising.

6. Triglycerides and residual risk

Elevated triglycerides and remnant lipoprotein particles significantly increase cardiovascular risk, particularly in patients with diabetes and metabolic syndrome [19–20]. The REDUCE-IT trial (EPA 4 g/day) demonstrated a 25% reduction in major cardiovascular events and a 20% reduction in cardiovascular mortality [39]. This confirms that residual risk is important and that LDL-C reduction alone is not sufficient.

LATEST AMERICAN RECOMMENDATIONS FOR THE MANAGEMENT OF DYSLIPIDEMIA (2026)

The new American recommendations [40] reintroduce a focus on LDL cholesterol target values: for patients with borderline or intermediate risk, the target is <2.6 mmol/L; for high-risk patients <1.8 mmol/L; and for very high-risk patients (i.e., in secondary prevention), LDL-C should be reduced to <1.4 mmol/L.

The PREVENT-ASCVD calculator has been adopted, which estimates both 10-year and 30-year risk of adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular mortality). Key patient characteristics used for risk estimation include age, sex, systolic blood

savremeni terapijski pristupi omogućavaju dramatično poboljšanje prognoze.

1. Prognoza

Prognoza zavisi od početnih vrednosti LDL-C, prisustva komorbiditeta, stepena adherencije, genetskih faktora (posebno kod FH) i pravovremenosti terapije. Kod pacijenata koji postižu ciljne vrednosti LDL-C prema ESC/EAS (<1.4 mmol/L za visok rizik), rizik od novih KV događaja može se smanjiti i do 50% [5].

2. Kliničke implikacije

Savremene smernice 2023–2026 podvlače sledeće principe: LDL-C je glavni terapeutski cilj, Niži LDL-C = bolja prognoza. Kombinovana terapija je pravilo, a ne izuzetak. Statin + ezetimib + PCSK9 inhibitor / inclisiran. ApoB i non-HDL-C su jednako važni kao i LDL-C. Posebno kod pacijenata sa visokim trigliceridima i dijabetesom. Personalizacija terapije. Različiti ciljevi za različite kategorije rizika.

KARDIOVASKULARNI BENEFITI I ISHODI

Snižavanje aterogenih lipoproteina, posebno LDL-holesterola, predstavlja najefikasniju farmakološku strategiju u prevenciji aterosklerotske kardiovaskularne bolesti (ASKV). Brojne randomizovane kliničke studije, genetičke analize i meta-analize pokazuju jasnu uzročnu vezu između redukcije LDL-C i smanjenja rizika od velikih kardiovaskularnih događaja [8–12,25–34].

1. *Efekat snižavanja LDL-holesterola na kardiovaskularne ishode*

U velikoj metaanalizi Cholesterol Treatment Trialists' Collaboration, koja je obuhvatila više od 170.000 pacijenata, pokazano je da svako smanjenje LDL-C za 1 mmol/L (~39 mg/dL) redukuje rizik od velikih vaskularnih događaja za oko 22% [25]. Ovaj efekat je prisutan kod muškaraca i žena, kod mlađih i starijih, kod dijabetičara, kod pacijenata sa prethodnim infarktom miokarda i u primarnoj i sekundarnoj prevenciji. S*nižavanje LDL-C je korisno u gotovo svim kliničkim populacijama.*

2. *Statini – dokazi iz kliničkih studija*

Visokointenzivni statini dokazano smanjuju infarkt miokarda za 25–35%, ishemijski moždani udar za 20–30%, kardiovaskularnu smrt za 15–20% [8–10]. Pored LDL-redukcije, statini imaju i pleiotropne efekte stabilizaciju plaka, antiinflamatorno dejstvo i poboljšanje endotelne funkcije [26].

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Povišeni trigliceridi i remnantske čestice lipoproteina značajno povećavaju rizik od KV događaja, naročito kod pacijenata sa dijabetesom i metaboličkim sindromom [19–20]. REDUCE-IT studija (EPA 4 g/dan) pokazala je 25% redukciju velikih KV događaja i 20% smanjenje KV mortaliteta [39]. Ovo potvrđuje da je rezidualni rizik važan i da nije dovoljan samo LDL-C.

GENSKA TERAPIJA I BUDUĆE PERSPEKTIVE

[41]

In vivo gensko ili bazno uređivanje (GENE OR BASE EDITING) predstavlja novu terapijsku strategiju koja se u poslednje vreme testira za lečenje dislipidemija ciljajući gene PCSK9 i ANGPTL3. VERVE-101 je eksperimentalna terapija zasnovana na CRISPR baznom uređivanju, koja sadrži *mRNA* za adeninski bazni editor usmeren na gen PCSK9, sa ciljem trajnog „utišavanja“ (inaktivacije) tog gena [42].

Kod ne-ljudskih primata, infuzija leka VERVE-101 dovela je do smanjenja LDL-C za 69% uz postojan efekat do 476 dana nakon doziranja, bez značajnih neželjenih događaja. Nakon potvrđene efikasnosti kod primata, prva studija na ljudima obuhvatila je 10 pacijenata sa heterozigotnom porodičnom hiperlipidemijom (HeFH) i prosečnim nivoom LDL-C od 201 mg/dL. Jedna intravenozna infuzija genske terapije zasnovane na CRISPR tehnologiji putem

pressure, antihypertensive therapy, presence of diabetes, smoking status, and laboratory markers (total and LDL cholesterol). These variables are required for the basic model. The expanded model additionally includes body mass index (BMI) and kidney function, while the full model also incorporates albuminuria and HbA1c [40].

A notable innovation is the assessment of both 10-year and 30-year cardiovascular risk in individuals aged 30 to 59 years. The new recommendations also strengthen the use of additional biomarkers for assessing residual cardiovascular risk, such as lipoprotein(a), which is recommended to be measured at least once in a lifetime, and apolipoprotein B, which is particularly useful in patients with diabetes and hypertriglyceridemia.

Greater emphasis is placed on the assessment of coronary artery calcium (CAC) score [40], especially in situations where the decision to initiate statin therapy is uncertain—most commonly in patients with borderline or intermediate risk.

An important aspect of the new recommendations is earlier and more intensive LDL-C reduction. This is based on the concept that cumulative exposure to elevated LDL-C determines cardiovascular risk. Therefore, earlier initiation of therapy reduces lifetime exposure to high LDL-C levels and leads to a greater reduction in cardiovascular risk.

Accordingly, a complementary recommendation is universal lipid screening and lifelong prevention. Rather than waiting for cardiovascular events to occur, periodic assessment of lipid status is advised, with particular attention to screening in patients with diabetes, cardio-renal-metabolic syndrome, and in children [40].

PROGNOSIS

Dyslipidemias, if not properly diagnosed and treated, significantly increase the risk of atherosclerotic cardiovascular disease, premature disability, and mortality. However, contemporary therapeutic approaches allow for a substantial improvement in prognosis.

1. Prognosis

Prognosis depends on baseline LDL-C levels, the presence of comorbidities, degree of adherence, genetic factors (especially in familial hypercholesterolemia), and the timeliness of therapy initiation. In patients who achieve LDL-C target levels according to ESC/EAS guidelines (<1.4 mmol/L for high-risk patients), the risk of new cardiovascular events can be reduced by up to 50% [5].

2. Clinical implications

Recent guidelines (2023–2026) emphasize the following principles: LDL-C is the primary therapeutic target; lower LDL-C equals better prognosis. Combination therapy is the rule rather than the exception (statin + ezetimibe + PCSK9 inhibitor / inclisiran). ApoB and non–HDL-C are equally important as LDL-C, particularly in patients with elevated triglycerides and diabetes. Personalization of therapy is essential, with different targets for different risk categories..

CARDIOVASCULAR BENEFITS AND OUTCOMES

Reduction of atherogenic lipoproteins, particularly LDL cholesterol, represents the most effective pharmacological strategy in the prevention of atherosclerotic cardiovascular disease (ASCVD). Numerous randomized clinical trials, genetic analyses, and meta-analyses demonstrate a clear causal relationship between LDL-C reduction and decreased risk of major cardiovascular events [8–12,25–34].

1. Effect of LDL cholesterol reduction on cardiovascular outcomes

In a large meta-analysis by the Cholesterol Treatment Trialists' Collaboration, including over 170,000 patients, each 1 mmol/L (~39 mg/dL) reduction in LDL-C was associated with approximately a 22% reduction in major vascular events [25]. This effect is consistent across men and women, younger and older individuals, patients with diabetes, those with prior myocardial infarction, and in both primary and secondary prevention. LDL-C lowering is beneficial in nearly all clinical populations.

2. Statins – evidence from clinical trials

High-intensity statins have been shown to reduce myocardial infarction by 25–35%, ischemic stroke by 20–30%, and cardiovascular mortality by 15–20% [8–10]. In addition to LDL-C reduction, statins exert pleiotropic effects, including plaque stabilization, anti-inflammatory action, and improvement of endothelial function [26].

3. Ezetimibe – clinical outcomes

The IMPROVE-IT trial (ezetimibe + statin) demonstrated an additional LDL-C reduction of ~23% and a 6% relative reduction in primary cardiovascular outcomes (p=0.016)

ciljano usmerenih lipidnih nanočestica dovela je do značajnog smanjenja LDL-C do 55% [43]. Naslednik pomenute terapije, Verve-102, predstavlja sredstvo za bazno uređivanje gena PCSK9 sa unapređenim usmeravanjem na jetru i redizajniranim nanočesticama, i trenutno je u fazi kliničkog razvoja. Danas raspolažemo brojnim efikasnim strategijama za suzbijanje lipidnih faktora rizika za kardiovaskularne bolesti (KVB). Još obećavajuće inovacije nagoveštavaju dalji napredak u ovoj oblasti. Međutim, primena dokazanih terapija, prihvatanje od strane pacijenata, doslednost u sprovođenju lečenja i obezbeđivanje pravednog pristupa savremenim terapijskim dostignućima ostaju izazovi koje zajednica mora da prevaziđe [4].

ZAKLJUČAK

Dislipidemije ostaju jedan od najvažnijih faktora rizika za aterosklerozu i kardiovaskularni mortalitet. Snižavanje aterogenih lipoproteina, posebno LDL holesterola, predstavlja najefikasniju farmakološku strategiju u prevenciji aterosklerotske kardiovaskularne bolesti (ASKV). Brojne randomizovane kliničke studije, genetičke analize i meta analize pokazuju jasnu uzročnu vezu između redukcije LDL C i smanjenja rizika od velikih kardiovaskularnih događaja Napredak u razumevanju lipidnog metabolizma i dostupnost novih terapija značajno su unapredili mogućnosti lečenja. Integracija preporuka ADA, AHA/ACC i ESC/EAS omogućava optimalan i individualizovan pristup, posebno kod bolesnika sa visokim i veoma visokim rizikom. Novost američkog vodiča ACC/AHA iz 2026. godine je procena osim 10-godišnjeg kardiovaskularnog nefatalnog i fatalnog rizika i rizik i 30-godišnji rizik za osobe starosti između 30 i 59 godina. Nove preporuke osnažuju primenu dodatnih biomarkera za procenu rezidualnog kardiovaskularnog rizika, kao što je **lipoprotein(a)**, **apolipoprotein B**, ne-HDL holesterol, koronarni kalcijumski skor , indeks telesne mase i A1C kao i **apolipoprotein B**, koji je posebno koristan kod pacijenata sa dijabetesom i hipertrigliceridemijom.Nastavak istraživanja u oblasti lipidologije, razvoj novih lekova i unapređena genetska dijagnostika doprineće još efikasnijoj prevenciji ASKV u budućnosti.

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[11], supporting the importance of combination therapy.

4. PCSK9 inhibitors – greatest benefit in highest-risk patients

The FOURIER trial (evolocumab) showed LDL-C reduction to ~0.8 mmol/L, a 15% reduction in cardiovascular events, and a 27% reduction in myocardial infarction risk [8]. The ODYSSEY Outcomes trial (alirocumab) demonstrated a significant reduction in cardiovascular mortality after acute coronary syndrome [9]. The key principle is: the lower the LDL-C, the greater the benefit.

5. Inclisiran – a new era of long-term lipid control

Inclisiran, as an siRNA-based therapy, provides sustained and stable LDL-C reduction. Its advantages include administration every 6 months, improved adherence, and approximately 50% LDL-C reduction [12]. Large outcome trials are still awaited, but current data are promising.

6. Triglycerides and residual risk

Elevated triglycerides and remnant lipoprotein particles significantly increase cardiovascular risk, particularly in patients with diabetes and metabolic syndrome [19–20]. The REDUCE-IT trial (EPA 4 g/day) demonstrated a 25% reduction in major cardiovascular events and a 20% reduction in cardiovascular mortality [39]. This confirms that residual risk is important and that LDL-C reduction alone is not sufficient.

GENE THERAPY AND FUTURE PERSPECTIVES [41]

In vivo gene or base editing represents a novel therapeutic strategy currently being investigated for the treatment of dyslipidemia, targeting genes such as PCSK9 and ANGPTL3. VERVE-101 is an experimental CRISPR-based therapy that includes mRNA encoding an adenine base editor targeting the PCSK9 gene, with the aim of permanently "silencing" (inactivating) this gene [42].

In non-human primates, a single infusion of VERVE-101 resulted in a 69% reduction in LDL-C, with sustained effects lasting up to 476 days post-dose, without significant adverse events. Following confirmed efficacy in primates, the first human study included 10 patients with heterozygous familial hypercholesterolemia (HeFH) and a mean LDL-C level of 201 mg/dL. A single intravenous infusion of CRISPR-based gene therapy delivered via targeted lipid nanoparticles resulted in up to a 55% reduction in LDL-C [43].

A next-generation therapy, Verve-102, represents an improved PCSK9 base-editing approach with enhanced liver targeting and redesigned lipid nanoparticles, and is currently in clinical development.

Today, numerous effective strategies are available to manage lipid-related cardiovascular risk factors. Even more promising innovations suggest continued progress in this field. However, the implementation of proven therapies, patient acceptance, adherence to treatment, and ensuring equitable access to modern therapeutic advances remain key challenges that must be addressed [4]..

CONCLUSION

Dyslipidemias remain one of the most important risk factors for atherosclerosis and cardiovascular mortality. Reduction of atherogenic lipoproteins, particularly LDL cholesterol, represents the most effective pharmacological strategy for the prevention of atherosclerotic cardiovascular disease (ASCVD). Numerous randomized clinical trials, genetic analyses, and meta-analyses demonstrate a clear causal relationship between LDL-C reduction and a decreased risk of major cardiovascular events.

Advances in the understanding of lipid metabolism and the availability of novel therapies have significantly improved treatment options. The integration of recommendations from ADA, AHA/ACC, and ESC/EAS enables an optimal and individualized approach, particularly in patients at high and very high risk.

A key novelty of the 2026 ACC/AHA guidelines is the assessment not only of 10-year cardiovascular risk (fatal and nonfatal), but also of 30-year risk in individuals aged 30 to 59 years. The new recommendations further emphasize the use of additional biomarkers for assessing residual cardiovascular risk, such as lipoprotein(a), apolipoprotein B, non–HDL cholesterol, coronary artery calcium score, body mass index, and HbA1c. Apolipoprotein B is particularly useful in patients with diabetes and hypertriglyceridemia.

Continued research in lipidology, the development of new therapeutic agents, and

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advances in genetic diagnostics will contribute to even more effective prevention of ASCVD in the future..

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