TERAPIJSKI PRISTUP U LEČENJU DISLIPIDEMIJA: NOVINE I IZAZOVI

THERAPEUTIC APPROACH IN THE TREATMENT OF DYSLIPIDEMIA: NOVELTIES AND CHALLENGES

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Sažetak

Kardiovaskularne bolesti predstavljaju vodeći uzrok morbiditeta i mortaliteta širom sveta. Dislipidemija predstavlja značajan faktor rizika za nastanak kardiovaskularnih bolesti. Snižavanjem nivoa serumskih lipida dolazi do smanjenja kardiovaskularnog morbiditeta i mortaliteta. Primarni terapijski cilj je sniženje vrednosti LDL holesterola (h). Terapija statinima često nije dovoljna za postizanje ciljnih vrednosti LDL-h, pa ih je neophodno kombinovati sa drugim lekovima za snižavanje lipida. Međutim, nakon što je primećeno da do nastanka neželjenih kardiovaskularnih događaja dolazi i pored postignutih ciljnih vrednosti LDL-h, pažnja se pridaje rezidualnom kardiovaskularnom riziku. Stoga je došlo do razvoja novih terapijskih strategija u cilju moduliranja lipoproteina bogatih trigliceridima, lipoproteina (a), apolipoproteina C-III i B. Rezultati ranih faza randomizovanih kliničkih studija ukazali su na značajan efekat novih lekova na smanjenje kardiovaskularnog rizika. Cilj ovog preglednog članka je da predstavi postojeće terapijske opcije za lečenje dislipidemije, ali i nove terapijske agense i buduće perspektive za lečenje ovih poremećaja.

Ključne reči: dislipidemija, terapija, LDL-h

Uvod

Brojna epidemiološka i populaciona istraživanja poslednjih decenija jasno ukazuju da kardiovaskularne bolesti (*Cardiovascular Diseases*, CVD) predstavljaju vodeći uzrok morbiditeta i mortaliteta širom sveta. Čak trećina svih uzroka smrtnosti na globalnom nivou je posledica CVD[1]. U tom smislu veliki napori se ulažu u identifikovanje i modulaciju faktora rizika koji su povezani sa nastankom CVD, od kojih su najčešći poremećaji metabolizma lipida[2]. Dislipidemija predstavlja spektar poremećaja metabolizma lipida koji se manifestuju u vidu povećanja ukupnog holesterola (h), holesterola sadržanog u lipoproteinima male gustine (*Low density lipoprotein*, LDL) i triglicerida (*Triglyceride*, TG), sniženja holesterola sadržanog u lipoproteinima velike gustine (*High density lipoprotein,* HDL) ili kombinacije navedenih poremećaja[3]. Prema istraživanjima u adultnoj populaciji u SAD, povišene vrednosti ukupnog i LDL-h holesterola ima i preko 30% osoba, dok povišene vrednosti triglicerida ima oko 20% odrasle populacije[4].

Prema etiologiji, dislipidemije mogu biti primarne (nasledne) i sekundarne. Primarne dislipidemije su posledica mutacija gena zbog čega dolazi do prekomerne proizvodnje ili defektnog klirensa lipidnih frakcija[3, 5, 6]. Familijarna hiperholesterolemija (*Familial Hypercholesterolemia*, FH) (homozigotna ili heterozigotna) je autozomno dominantni nasledni poremećaj koji karakterišu povišene vrednosti ukupnog i LDL-h, kao i nastanak prematurne CVD[3, 5]. Sekundarne dislipidemije čine više od jedne trećine svih uzroka dislipidemija, a u njihovoj osnovi su najčešće dijabetes, hipotireoza, gojaznost, nepravilna ishrana, nefrotski sindrom i hronična bubrežna insuficijencija, bolesti jetre, prekomerna upotreba alkohola, druge endokrinološke bolesti, ali i lekovi (tiazidi, beta blokatori, glukokortikoidi, estrogen, progesteron, steroidi itd.)[3, 5-7]. Prema podacima iz 2019. godine, povišene vrednosti LDL-h bile su u osnovi 44% mortaliteta od ishemijske bolesti srca i 22% mortaliteta od ishemijskog moždanog udara na globalnom nivou[6].

Prema smernicama EAS/ESC (*European Atherosclerosis Society /European Society of Cardiology*, EAS/ESC) i AHA/ACC (*American Heart Association/American College of Cardiology*, AHA/ACC) skrining test na dislipidemije uključuje određivanje lipidnog profila (ukupni holesterol, LDL-h, TG, HDL-h, non-HDL-h). Pored standardnog profila lipida, prema EAS/ESC smernicama, preporučuje se merenje apolipoproteina B (*Apolipoprotein B*, Apo B) kao markera aterogenih lipoproteina kod svih pacijenata sa visokim nivoom TG, dijabetesom i gojaznošću[8, 9].

Primarni terapijski cilj za lečenje dislipidemija je snižavanje LDL-h. Međutim, danas postoje jasni dokazi da snižavanje lipoproteina (a), Lp (a), kao novi terapijski cilj, značajno doprinosi sniženju kardiovaskularnog (*Cardiovascular*, CV) rizika[8-10]. Uprkos postizanja ciljnih vrednosti LDL-h postoje dokazi da se CVD i dalje javljaju, te je postalo neophodno staviti u fokus rezidualni CV rizik[11, 12].

Poslednjih godina izneto je više dokaza da trajanje izloženosti povišenom LDL holesterolu određuje rizik za aterosklerozu CVD i njegove komplikacije, možda i više od samog nivoa LDL-h. Dakle, veće i što ranije smanjenje LDL-h daje bolju prevenciju CVD. Ovakvi nalazi naglašavaju hitnost identifikacije i rano lečenje visokog LDL-h. Na osnovu akumulacije dokaza, smernice i praksa kliničkih ispitivanja su evoluirali ka postizanju strožih ciljeva LDL-h, posebno kod pacijenata sa visokim rizikom[9]. Nedavne studije primene kombinovane terapije, sa značajnim sniženjem LDL-h, nisu pokazale prag za kliničku korist i otklonili su mnoge brige o bezbednosti, čime su ojačali koncept „niže je bolje"[13, 14].

Nedavni uspesi ispitivanja sa nestatinskim agensima za snižavanje lipida u opadanju CV događaja su pokazali da sniženje LDL-h različitim mehanizmima, uključujući povećanu ekspresiju LDL receptora ili smanjenje apsorpcije holesterola, značajno smanjuje CV događaje[15]. Fokus je stoga, proširen sa „terapije statinima visokog intenziteta" na „terapiju visokog intenziteta" za snižavanje LDL-h. Ovo saznanje, zajedno sa često viđenim značajnim preostalim rizikom za CVD, čak i kod osoba lečenih statinima, ubrzalo je potragu za terapijama koje smanjuju visoko aterogene lipoproteine koje sadrže Apo B (pre svega LDL).

Upravo, cilj ovog preglednog članka je da istakne savremene terapijske pristupe u lečenju dislipidemija sa osvrtom na nove agense i perspektivu budućeg lečenja ovih poremećaja.

Terapijski pristupi lečenju dislipidemija

Najnovije zajedničke preporuke Evropskog udruženja kardiologa (*European Society of Cardiology*, ESC) i Evropskog udruženja za aterosklerozu (*European Atherosclerosis Society*, EAS) za lečenje dislipidemija preporučuju najpre stratifikaciju CV rizika i, prema nivou rizika, dalje lečenje statinima, ezetimibom i inhibitorima enzima proprotein konvertaza subtilizin/keksin tip 9 (*Proprotein convertase subtilisin/kexin type-9*, PCSK9)[9]. U smernicama se visoko intenzivni statini preporučuju kao prva terapijska linija u primarnoj i sekundarnoj prevenciji pacijenata sa hiperholesterolemijom. Ukoliko se ne postignu ciljne vrednosti LDL-h prema stepenu CV rizika, preporučuje se dodavanje ezetimiba. Kod pacijenata koji na navedenoj kombinovanoj terapiji (statin + ezetimib) ne postignu terapijski cilj, u terapiju treba uvesti PCSK9 inhibitore. Smernice ESC/EAS dalje navode da se PCSK9 inhibitori mogu razmotriti i za primarnu CV prevenciju kod veoma rizičnih pacijenata koji ne postignu ciljnu vrednost LDL-h na maksimalno tolerabilnoj dozi statina u kombinaciji sa ezetimibom (tabela 1, slika 1).

U tekstu koji sledi predstavljen je prikaz postojećih terapijskih opcija za snižavanje nivoa lipida, novih agenasa, ali i budućih perspektiva u lečenju dislipidemija (tabela 2, slika 2).

Statini

Statini su lekovi koji se koriste za snižavanje holesterola u primarnoj i sekundarnoj prevenciji CVD poslednje četiri decenije. Korist primene statina u sniženju LDL-h i prevenciji CVD dokazana je u velikom broju randomizovanih kliničkih studija, a metaanaliza koja je obuhvatila 170 hiljada pacijenata ukazala je da smanjenje LDL-h za samo 1 mmol/L smanjuje rizik od glavnih neželjenih CV događaja za čak 22%[16].

Statini su kompetitivni inhibitori 3-hidroksi 3-metilglutaril koenzim A (*3-hydroxy-3-methyl Glutaryl Coenzyme A*, HMG-CoA) reduktaze. Inhibicijom enzima koji reguliše proces sinteze holesterola statini smanjuju intracelularnu sintezu holesterola zbog čega dolazi do povećane ekspresije receptora lipoproteina niske gustine (*Low Density Lipoprotein Receptor*, LDL-R). Na tržištu postoji više različitih vrsta statina: atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, lovastatin i pravastatin.

Efikasnost statina zavisi od doze u kojoj se primenjuju u svakodnevnoj kliničkoj praksi. Statini niske ili srednje efikasnosti smanjuju LDL-h za 30% i trigliceride za 20%, statini visoke efikasnosti smanjuju nivo LDL-h za više od 50%, a nivo triglicerida do 40%. Statini podižu nivo HDL-h do 10% u zavisnosti od doze[13]. Studije pokazuju da nema uticaja statina na Lp (a)[9, 16, 17]. *In vitro* i *in vivo* studije su pokazale da pored modifikacije nivoa lipida u krvi, statini imaju plejotropne efekte kao što su poboljšanje endotelne disfunkcije, antioksidativna svojstva, inhibicija inflamatornog odgovora i stabilizacija aterosklerotičnog plaka[16]. Međutim, kod određenog broja pacijenata i pored terapije statinima vrednosti lipidnih parametara ostaju iznad ciljnih vrednosti[9, 17].

Veliki problem u kliničkoj praksi predstavlja potencijalno „nepodnošenje" statina, dominantno prisustvo bolova u mišićima, zbog čega postoji neadekvatno doziranje statina, ili prekidanje ove vrste terapije. Međutim, metaanalizom kojom je obuhvaćeno 176 studija i ukupno 4,1 miliona pacijenata pokazano je da oko 9% pacijenata ne podnosi

Tabela 1. Kriterijumi za procenu kardiovaskularnog rizika i terapijske ciljne vrednosti LDL-h

Kategorija CV rizika	Terapijska ciljna vrednost LDL-h	Kriterijumi
Nizak rizik	3,0 mmol/L	• SCORE < 1%
Umeren rizik	2,6 mmol/L	• SCORE ≥ 1% i < 5% • Mlađe osobe (T1DM < 35 godina; T2DM < 50 godina) sa trajanjem DM < 10 godina, bez drugih RF.
Visok rizik	1,8 mmol/L	• SCORE ≥ 5% i < 10% • 1 veliki FR (UH > 8 mmol/L, LDL-h > 4,9 mmol/L ili AP ≥ 180/110 mmHg. • FH bez drugih velikih RF. • DM bez oštećenja ciljnih organa, sa trajanjem DM ≥ 10 godina ili drugim RF • Umerena CKD (eGFR 30-59 mL/min/1,73 m²).
Veoma visok rizik	1,4 mmol/L	• ACVD (klinički/imidžing) • SCORE ≥ 10% • FH sa ACVD ili sa drugim izraženim RF • Ozbiljna CKD (eGFR < 30 mL/min/1,73 m²). • DM sa oštećenjem ciljnih organa, ili ≥ 3 velika FR, ili rana pojava T1DM sa trajanjem > 20 godina.

Legenda: CV (*Cardiovascular*) - kardiovaskularni; **LDL-h** (*Low density lipoprotein*) - lipoprotein niske gustine; **SCORE** (*Systematic Coronary Risk Estimation*) - sistemsko izračunavanje koronarnog rizika; **T1DM** (*Type 1 Diabetes Mellitus*) - tip 1 dijabetes melitus; **T2DM** (*Type 2 Diabetes Mellitus*) - tip 2 dijabetes melitus; **RF** (*Risk Factor*) - faktor rizika; **TC** (*Total cholesterol*) - ukupni holesterol; **AP** (*Arterial Pressure*) - arterijski pritisak; **FH** (*Familial Hypercholesterolemia*) - familijarna hiperholesterolemija; **CKD** (*Chronic Kidney Disease*) - hronična bolest bubrega; **ACVD** (*Atherosclerotic Cardiovascular Disease*) - aterosklerotska kardiovaskularna bolest. Modifikovano prema ref. 9.

Slika 1. Procena CV rizika i određivanje nivoa LDL-h

Legenda: CV (*Cardiovascular*) - kardiovaskularni; **LDL-h** (*Low density lipoprotein*) - lipoprotein niske gustine; **PCSK9** (*Proprotein Convertase Subtilisin Kexin-9*) - proprotein konvertaza subtilizin/keksin tip 9; Visokointenzivni statin - rosuvastatin u dozi 20-40 mg ili atorvastatin u dozi 40-80 mg. Modifikovano prema ref. 9.

statine. Najznačajniji neželjeni efekti terapije statinima su miopatija (11 na 100.000 pacijenata/godina), rabdomioliza (3 na 100.000 pacijenata/godina), povišenje enzima jetre i hiperglikemija[17].

Ezetimib

Ezetimib je relativno stari lek koji inhibira intestinalnu apsorpciju holesterola vezujući se za NPCIL1 (*Niemann-Pick C1-like 1 protein*). Ezetimib se može koristiti kao monoterapija u dozi od 10 mg jednom dnevno, međutim efikasnost monoterapije ezetimiba je relativno slaba, kod pacijenata sa heterozigotnom formom FH redukuje ukupni holesterol za 13,5% i LDL-h za 18,6% u poređenju sa placebom[18]. Stoga se ovaj lek najčešće primenjuje u kombinaciji sa statinima, bempedoičnom kiselinom i fibratima. Obzirom da su neželjeni efekti blagi, ezetimib je terapija izbora kod pacijenata koji ne tolerišu statine[19]. Rezultati randomizovane studije IMPROVE-IT koja je uključila preko 18.000 pacijenata nakon akutnog koronarnog događaja, sa periodom praćenja od 6 godina, pokazali su da kombinacija simvastatina i ezetimiba značajno smanjuje rizik od novih CV događaja, zbog čega je ovaj lek ponovo našao svoje mesto u novim preporukama, u kombinovanoj terapiji[20].

Bempedoična kiselina

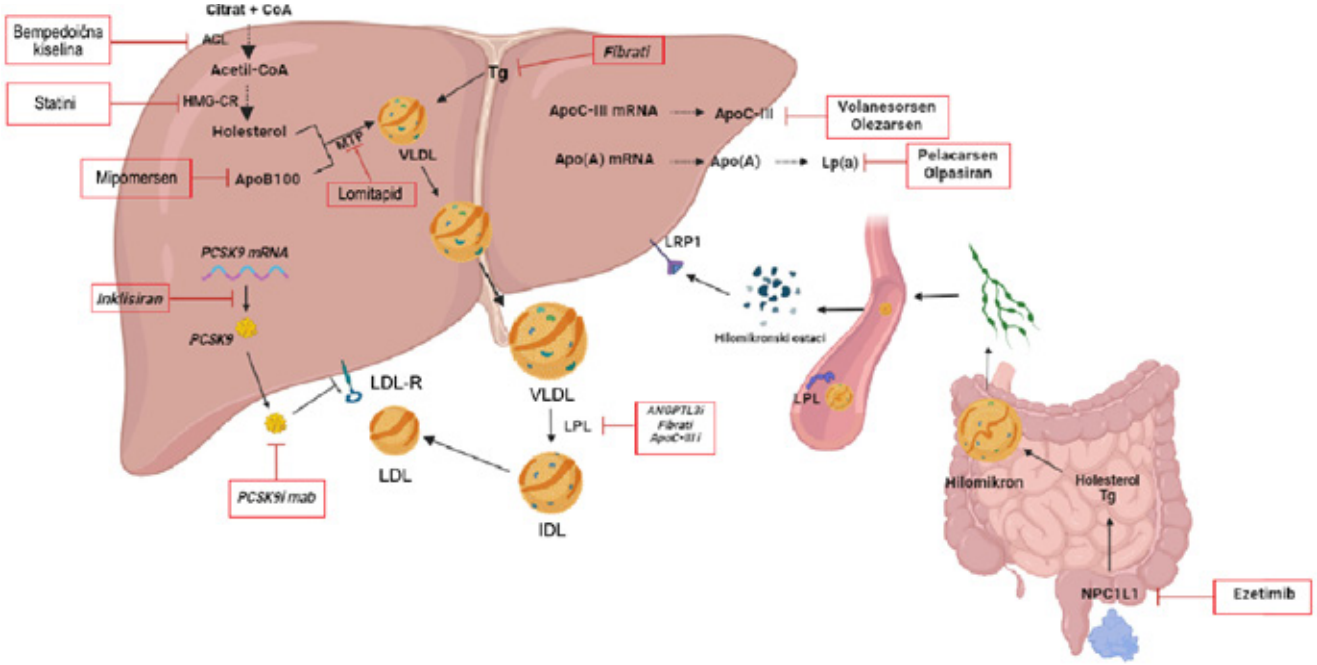
Bempedoična kiselina inhibira enzim adenozin trifosfat citrat liazu koji katalizuje sintezu acetil koenzima A, te na taj način sprečava sintezu holesterola[21]. Za razliku od statina, primena bempedoične kiseline nosi značajno manji rizik za pojavu miopatije i rabdomiolize, te je terapijski izbor kod pacijenata koji ne tolerišu statine. Interesantno, bempedoična kiselina ima blagotvorno dejstvo na glikemiju, za razliku od statina koji, posebno u velikim dozama, mogu povećati

Tabela 2. Terapijske strategije za lečenje dislipidemija i mehanizam dejstva lekova za snižavanje lipida

Naziv leka	Mehanizam dejstva	Ciljni lipoproteini	Indikacije	Režim doziranja i način primene
Statini	HMG-3-CoA reduktaza antagonist	TC; LDL-h; Apo B; TG	Primarne i sekundarne dislipidemije	1 x dnevno p.o.
Fibrati	PPARα agonist	TG; VLDL; LDL-h	Hipertrigliceridemija; Familijarna kombinovana hiperlipidemija	1 x dnevno p.o.
Bempedoična kiselina	ACL inhibitor	LDL-h; Apo B; Non-HDL-h	FH; Familijarna kombinovana hiperlipidemija	1 x dnevno p.o
Ezetimib	NPC1L1 transporter inhibitor	TC; LDL-h; TG	FH; Familijarna kombinovana hiperlipidemija	1 x dnevno p.o
Evolokumab Alirokumab	PCSK9 inhibitor-monoklonsko antitelo	LDL-h;Apo B; Non-HDL-h; Lp (a)	Primarna hiperholesterolemija; Familijarna kombinovana hiperlipidemija HeFH; HoFH	1-2 x mesečno s.c.
Inklisiran	PCSK9 siRNA-mala interferirajuća ribonukleinska kiselina	LDL-h; Apo B; Non-HDL-h; Lp (a); TG	Primarna hiperholesterolemija; Familijarna kombinovana hiperlipidemija;-HeFH; HoFH	1 x u 6 meseci s.c.
Evinakumab	ANGPTL3 inibitor-monoklonsko antitelo	LDL-h; Apo B; Non-HDL-h; TG	HoFH	1 x mesečno i.v.
Pelakarsen	Blokator Apo (A) translacije	LDL-h; Lp (a); Apo B	Nije odobren	1 x mesečno s.c.
Olpasiran	Inhibitor translacije iRNK Lp (a)	Lp (a)	Nije odobren	1 x u 3 meseca s.c.
Volanesorsen	Inhibitor Apo C-III	Apo C-III; TG; Hilomikroni	Hipertrigliceridemija; Hiperhilomikronemija	1 x nedeljno s.c.
Olezarsen	Inhibitor Apo C-III	Apo C-III; TG; Hilomikroni	Nije odobren	1 x nedeljno s.c.

Legenda: TC (*Total Cholesterol*) - ukupni holesterol; **LDL-h** (*Low density lipoprotein*) - lipoprotein niske gustine; **TG** (*Triglycerides*) - trigliceridi; **Apo** (*Apolipoprotein*) - apolipoprotein; **Lp (a)** – lipoprotein (a); **Non-HDL-h** (*Non-HDL-holesterol*); **ACL** (*Adenosine triphosphate-Citrate Lyase*) - adenozin trifosfat citrat liaza; **HMG-CR-3** (*Reductase 3-hydroxy-3-methyl-glutaryl-coenzyme A Reductase*) - hidroksi-3-metil-glutaril koenzim A reduktaza; **NPC1L1** (*Niemann-Pick C1-like 1 protein*); **PPARα** (*Peroxisome Proliferator-activated Receptor-α*) - peroksizomalni proliferativni aktivirajući receptor tipa alfa; **VLDL** (*Very Low Density Lipoprotein*) - lipoproteini veoma niske gustine; **HeFH** (*Heterozygous Familial Hypercholesterolemia*) - heterozigotna familijarna hiperholesterolemija; **HoFH** (*Homozygous Familial Hypercholesterolemia*) - homozigotna familijarna hiperholesterolemija.

Slika 2. Šematski prikaz mehanizma dejstva lekova za snižavanje lipida



Legenda: ACL (*Adenosine triphosphate-Citrate Lyase*) - adenozin trifosfat citrat liaza; **HMG-CR-3** (*Reductase 3-hydroxy-3-methyl-glutaryl-coenzyme A Reductase*) - hidroksi-3-metil-glutaril koenzim A reduktaza; **Apo** (*Apolipoprotein*) - apolipoprotein; **MTP** (*Mitochondrial Trifunctional Protein*) - protein mikrozomalnog trigliceridnog transfera; **TG** (*Triglycerides*) - trigliceridi; **VLDL** (*Very Low Density Lipoprotein*) - lipoprotein veoma niske gustine; **LDL** (*Low Density Lipoprotein*) - holesterol male molekulske mase; **LDL-R** (*Low Density Lipoprotein Receptor*) - receptor lipoproteina male molekulske mase; **IDL** (*Intermediate Density Lipoprotein*) - lipoprotein srednje gustine; **Lp (a)** - lipoprotein (a); **LPL** (*Lipoprotein Lipase*) - lipoproteinska lipaza; **NPC1L1** (*Niemann-Pick C1-like 1 protein*); **LRP1** (*Low-density Receptor-related Protein 1*) - protein povezan sa lipoproteinima niske gustine; **PCSK9 mRNA** - PCSK9 informaciona RNK; **PCSK9 mab** (PCSK9 monoclonal antibodies) - PCSK9 monoklonska antitela.

rizik od novonastalog dijabetesa[22]. Najčešći neželjeni efekti nakon primene bempedoične kiseline su povećanje jetrinih enzima i koncentracije mokraćne kiseline[22, 23].

Efikasnost i sigurnost primene bempedoične kiseline kod pacijenata koji ne tolerišu statine je ispitivana u nekoliko studija od kojih je najznačajnija CLEAR studija. Nakon sprovedenih kliničkih ispitivanja, bempedoična kiselina je indikovana za korišćenje u cilju snižavanja koncentracije

LDL-h kod pacijenata sa FH, kombinovanom sa hipertrigliceridemijom i kod pacijenata sa ateroskleroznom CVD[21-23].

PCSK9 inhibitori

Proprotein konvertaza subtilizin/keksin tip 9 je enzim koji se predominantno stvara u jetri, čija se funkcija ogleda u degradaciji LDL-R u hepatocitima i smanjenju recikliranja ovih receptora, tj. dolazi do nishodne („*down*“) regulacije receptora. Posledično dolazi do povećanja serumske koncentracije LDL-h (smanjenje dostupnih LDL-R za preuzimanje LDL iz cirkulacije). Stoga, inhibicijom PCSK9 monoklonskim antitelima povećava se broj raspoloživih LDL-R („*up*“ regulacija receptora) za preuzimanje LDL-h, odnosno značajno se povećava klirens LDL-h i njegovo sniženje u cirkulaciji[24].

PCSK9 inhibitori su injektabilni agensi (monoklonska antitela) i primenjuju se supkutano jednom do dva puta mesečno, uz izuzetno mali broj neželjenih efekata. Međutim, ograničavajući faktor za njihovu širu primenu je visoka cena[25]. Najčešći neželjeni efekti povezani sa direktnom primenom PCSK9 inhibitora su niži nivoi vitamina E.

Evolokumab i alirokumab su monoklonska antitela koja inhibiraju PCSK9 i odobrena su za kliničku upotrebu kao monoterapija ili u kombinaciji sa statinima i ezetimibom. Evolokumab smanjuje nivoe LDL-h u plazmi za 53% do 75% u zavisnosti da li se primenjuje kao monoterapija ili u kombinaciji sa statinima kod pacijenata sa heterozigotnom formom FH (*Heterozygous Familial Hypercholesterolemia*, HeFH), dok kod homozigotne forme FH (*Homozygous Familial Hypercholesterolemia,* HoFH) sa defektnim LDL-R taj procenat je niži i iznosi oko 31%. Alirokumab redukuje nivoe LDL-h u plazmi za 39% do 58% kod pacijenata sa HeFH i za 11,9% do 34,3% kod pacijenata sa HoFH u zavisnosti da li se primenjuje kao monoterapija ili se koristi zajedno sa statinima[26].

Rezultati dve velike randomizovane kontrolisane kliničke studije (FOURIER i ODYSSEY) pokazali su da primena evolokumaba i alirokumaba kod pacijenata sa visokim CV rizikom na prethodnoj terapiji statinima smanjuju rizik novih CV događaja za 15%[27]. Pomenute studije pokazale su da primena evolokumaba dovodi do smanjenja ukupnog holesterola, TG, non-HDL holesterola, Apo B, ali i blagog povećanja HDL-h. Za razliku od statina, primena PCSK9 inhibitora nedvosmisleno snižava serumske koncentracije Lp (a). Osim toga, pokazano je da primena alirokumaba ima povoljne efekte na smanjenje oksidativnog stresa, smanjenje produkcije inflamatornih citokina, smanjenje aktivnosti metaloproteinaze 2, osteopontina i osteoprotegerina koji su ključni patofiziološki procesi u osnovi ateroskleroze[28].

Trenutne smernice preporučuju primenu PCSK9 inhibitora kod pacijenata sa visokim i vrlo visokim CV rizikom koji na terapiji maksimalno tolerabilnim dozama statinima i ezetimibom ne postižu preporučene ciljne vrednosti LDL-h[9, 26].

Inklisiran

Inklisiran je mala interferirajuća ribonukleinska kiselina (*Small Interfering Ribonucleic Acid,* siRNA) koja blokira sintezu PCSK9 u hepatocitima[26, 29]. Stoga dolazi do ushodne („*up*“) regulacije LDL-R i boljeg preuzimanja LDL-h iz cirkulacije sa posledičnim značajnim sniženjen nivoa LDL-h. Inklisiran je odobren za lečenje pacijenata sa HeFH, familijarnom kombinovanom hiperlipidemijom i potvrđenom aterosklerotskom CVD. Primenjuje se kao supkutana injekcija u dozi od 284 mg. Posle inicijalne primene leka, druga doza se dobija nakon tri meseca, a svaka sledeća na 6 meseci[29]. Glavna prednost inklisirana u odnosu na PCSK9 monoklonska antitela je režim doziranja i dugotrajniji efekat koji obezbeđuje bolju komplijansu[30].

Efikasnost i sigurnost leka su ispitivani u okviru ORION studija kod pacijenata koji su primali maksimalne tolerabilne doze statina i druge lekove za snižavanje lipida. Rezultati jednogodišnjeg praćenja ukazali su da inklisiran snižava LDL-h za 50% u odnosu na placebo[31]. Osim toga, inklisiran ima povoljne efekte na snižavanje ukupnog holesterola, TG, non-HDL-h, Lp (a) i povećanje HDL-h[31]. Trenutno su u toku studije ORION-4, VICTORION-2 i PREVENT koje analiziraju efekte inklisirana na pojavu novih CVD kod pacijenata sa potvrđenom aterosklerotskom CVD na prethodnoj terapiji statinima u odnosu na placebo.

Omega-3 masne kiseline

Omega-3 masne kiseline, kao što su eikozapentaenska kiselina (*Eicosapentaenoic Acid*, EPA) i dokozaheksaenska kiselina (*Docosahexaenoic Acid*, DHA) mogu smanjiti rizik od nastanka novih CV događaja različitim mehanizmima, poput snižavanja nivoa triglicerida, antitrombotskim, antiinflamatornim ili antiaritmijskim dejstvom[32]. Rezultati metaanalize koja je uključila randomizovane kliničke studije, pokazala je superiornost monoterapije EPA, u odnosu na EPA + DHA u redukciji kardiovaskularnog mortaliteta, učestalosti nefatalnog oblika infarkta miokarda, novih CV događaja kao i revaskularizacije, ali je neophodna visoka doza leka (2-4 gr, EPA na dan)[33].

Fibrati

Mehanizam dejstva fibrata se vezuje za aktivaciju peroksizmalnog proliferativnog aktivirajućeg receptora tipa alfa (*Peroxisome Proliferator-Activated Receptor-α,* PPAR-α) koji, aktivacijom lipoproteinske lipaze stimuliše lipolizu i eliminaciju aterogenih čestica bogatih TG iz plazme. Aktivacija PPAR-α indukuje smanjenje produkcije Apo C-III na nivou jetre, zbog čega se smanjuje frakcija lipida sadržanih u VLDL (*Very Low Density Lipoprotein*), i LDL-h[34]. Dodatno, aktivacija navedenih nuklearnih receptora dovodi do povećane produkcije Apo A-I i A-II sa poželjnim povišenjem nivoa HDL-h.

Rezultati metaanalize koja je objedinila nekoliko studija su pokazali da fibrati smanjuju incidencu CV događaja za oko 10%[35]. Fibrati se mogu bezbedno kombinovati sa statinima kod pacijenata kod kojih su isključeni uzroci sekundarne hipertrigliceridemije i koji, uprkos dijetetskom režimu, održavaju visoke nivoe TG[34].

ANGPTL3 inhibitori

ANGPLT3 (*Angiopoietin-like protein 3*) je polipeptid koji ima značajnu ulogu u metabolizmu lipida time što inhibira lipoproteinsku i endotelnu lipazu, čime se povećava nivo TG i LDL-h[36]. Stoga, inhibicijom ANGPTL3 dolazi do smanjenja TG i LDL-h, što je mehanizam dejstva ove grupe lekova koji je nezavisan od LDL receptora[37]. Evinakumab je monoklonsko antitelo iz grupe ANGPTL3 inhibitora odobreno za lečenje HoFH sa značajnim efektom na snižavanje LDL-h[37]. Način administracije evinakumaba je intravenski u dozi od 15 mg/kg, na svake četiri nedelje. U trećoj fazi kliničkog ispitivanja potvrđena je efikasnost evinakumaba sa smanjenjem nivoa LDL-h od 47,1% u poređenju sa placebom[38]. Dobri rezultati upotrebe evinakumaba postignuti su i kod mešovite dislipidemije snižavanjem triglicerida. Ovo bi moglo da implicira da se u budućnosti uspešno primenjuju kod ovih pacijenata. Neželjeni efekti povezani sa primenom evinakumaba su „*flu-like*" simptomi, blago povećanje kreatin kinaze i enzima jetre[38].

Volanesorsen i olezarsen

Volanesorsen i olezarsen zaustavljaju produkciju Apo C-III u jetri i u tankom crevu, a koji se nalazi u sastavu lipoproteina bogatih trigliceridima. Volanesorsen primenjen kod pacijenata sa familijarnom hipertrigliceridemijom ima povoljan efekat na sniženje triglicerida, a time i na smanjenje incidence akutnog pankreatitisa[39]. Metaanalizom je pokazano da tretman volanesorsenom dovodi do smanjenja TG za oko 72%, VLDL za 74%, Apo B-48 za 60%, Apo C-III za 80%, dok je povećanje HDL-h bilo 46% i LDL-h oko 67%[40].

Volanesorsen se primenjuje supkutano u dozi od 285 mg, jednom nedeljno prva tri meseca, a kasnije na svake dve nedelje. Povoljniji bezbednosni profil u smislu manjeg rizika od trombocitopenije ima olezarsen[41]. U prvoj fazi kliničkih ispitivanja nalazi se i ARO-APOC31001 siRNA koja degradira mRNA (*Messenger Ribonucleic Acid*, mRNA) za Apo C-III[42].

Pelakarsen, olpasiran i SLN360

Pelakarsen je antisens oligonukleotid koji se vezuje za Apo mRNA tako da nastali kompleks sprečava sintezu Lp (a) u hepatocitima što smanjuje njegovu produkciju, a time i nivo Lp (a) u serumu[43]. Ujedno, to su jedini lekovi koji mogu modulirati nivo Lp (a) za koji do sada nije postojala nikakva terapijska opcija. Pelakarsen ima značajan uticaj na snižavanje ukupnog holesterola, LDL-h i TG, a primenjuje se supkutano jednom mesečno. Aktuelno, ovaj lek je u trećoj fazi kliničke studije HORIZON koja ima cilj da ispita protektivni uticaj pelakarsena na neželjene kardiovaskularne događaje. Sličan mehanizam dejstva imaju i olpasiran i SLN360 koji su takođe u fazi kliničkih ispitivanja[44, 45].

Mipomersen

Mipomersen ometa proizvodnju Apo B koji se nalazi u sastavu LDL-h, VLDL i Lp (a)[46]. Mipomersen značajno snižava LDL-h, non-HDL-h, Lp (a), TG i Apo B. U Americi je 2012. godine bila odobrena supkutana primena leka u dozi od 200 mg kod pacijenata sa HoFH. Zbog ozbiljnih neželjenih efekata, kao što su hepatotoksičnost i steatoza jetre, lek je povučen sa tržišta 2019. godine[46].

Lomitapid

Lomitapid je inhibitor proteina mikrozomalnog triglyceridnog transfera (*Microsomal Transfer Protein*, MTP) koji je lokalizovan u endoplazmatskom retikulumu hepatocita. Uloga MTP je da transportuje TG, fosfolipide i estre holesterola do Apo B, te inhibicijom istog smanjuje se hepatična produkcija VLDL, a posledično i nivoi ukupnog holesterola, serumskog LDL-h, non-HDL-h i Apo B. Lomitapid je odobren za primenu kod pacijenta sa HoFH, samostalno ili u kombinaciji sa drugim lekovima za snižavanje nivoa lipida, a način administracije je oralni u jednoj dnevnoj dozi od 5-10 mg[47].

Lerodalcibep

Lerodalcibep inhibira PCSK9 preko CRISPR-Cas9 (*Clustered Regularly Interspaced Short Palindromic Repeat-Cas9*) - grupisani kratki palindromski ponovci na jednakim rastojanjima tehnologije. Cas9 je dvolančana DNK nukleaza koja je usmerena na svoju metu pomoću RNK vodiča (*CRISPR RNA*, crRNA)[48]. Lerodalcibep predstavlja rekombinantni fuzioni protein koji se sastoji od PCSK9 - vezujućeg domena i humanog serumskog albumina. Rezultati treće faze kliničkog ispitivanja ukazuju da je lerodalcibep, primenjen supkutano jednom mesečno u dozi od 300 mg kod pacijenata sa HeFH, na terapiji maksimalno tolerabilnim dozama statina i ezetmiba, nakon praćenja od 24 nedelje, pokazao efikasno smanjenje LDL-h za približno 60%, pri čemu je oko 70% pacijenata postiglo redukciju LDL-h ≥ 50% i preporučene ciljne vrednosti prema ESC/EAS vodiču iz 2019. godine u odnosu na placebo[48].

MK-0616

MK-0616 je oralni makrociklični PCSK9 inhibitor u fazi kliničkih ispitivanja. Druga faza kliničkih ispitivanja pokazala je da su oralno primenjeni PCSK9 inhibitori sa dnevnim dozama u rasponu od 6 do 30 mg doveli do redukcije LDL-h i

do 60,9% u odnosu na placebo nakon perioda praćenja od 8 nedelja kod pacijenata sa hiperholesterolemijom i aterosklerozom CVD na prethodnoj terapiji statinima[49].

PCSK9 vakcine

PCSK9 vakcine predstavljaju novu terapijsku strategiju koja bi omogućila intrinzičnu proizvodnju antitela protiv PCKS9[50]. Lipozomalni imunogenetski spoj PCSK9-tetanus peptida sa aluminijumskim adjuvantom je nova formulacija PCSK9 vakcine koja je na animalnom modelu pokazala dugotrajnu sintezu PCSK9 antitela i redukciju LDL-h i VLDL-h kod laboratorijskih miševa za 51,7% kod BALB/c i 19,2% kod C57BL/6[50].

Genska terapija povišenog holesterola

Ohrabrujuća istraživanja na animalnim modelima su pokazala mogućnost genske terapije povišenog holesterola. Naime, sintetisana je mRNK koja kodira gen za PCSK9 (preparat pod imenom VERVE-101), upakovana u lipidne nanočestice. Prekliničke studije na miševima i nehumanim primatima (*Non-Human Primate*, NHP) pokazale su da jednokratna intravenska primena VERVE-101 može inaktivirati gen PCSK9 u jetri[51]. NHP lečeni sa VERVE-101 imali su značajno smanjenje LDL-h koji je ostao trajno snižen tokom više od dve godine praćenja, podržavajući potencijal za trajni efekat lečenja. Nedavno su na kongresu Američkog kardiološkog udruženja (novembra 2023.) predstavljeni i prvi rezultati primene ove terapije kod ljudi (klinička studija faze Ib) sa dobrim i obećavajućim rezultatima[52].

Zaključak

Imajući u vidu da dislipidemija predstavlja značajan faktor rizika za nastanak kardiovaskularnih bolesti, lekovi za snižavanje lipida imaju značaja ne samo u primarnoj, već i u sekundarnoj prevenciji ovih bolesti. Iako prema svim važećim smernicama vrednosti LDL-h predstavljaju i dalje primarni terapijski cilj, sve više pažnje se pridaje i rezidualnom kardiovaskularnom riziku. Statini su najčešće propisivani lekovi širom sveta, mada uprkos njihovoj primeni veliki broj pacijenata ne postiže preporučene ciljne vrednosti LDL-h. Stoga, statini se mogu kombinovati sa ezetimibom i sa PCSK9 inhibitorima. Bempedoična kiselina je odobrena terapijska alternativa za pacijente koji ne tolerišu statine. Inklisiran je pandan PCSK9 inhibitorima, međutim, primena inklisirana mogla bi poboljšati komplijansu pacijenta zbog svog doznog režima. Pelakarsen i olpasiran su buduće terapijske strategije usmerene na snižavanje Lp (a) koji predstavlja nezavisni faktor rizika za kardiovaskularne bolesti. Evinakumab, lomitapid, mipomersen, volanesorsen i olezarsen su lekovi koji prvenstveno utiču na različite korake u metabolizmu aterogenih lipoproteina, te na taj način predstavljaju značajan novi pristup u prevenciji kardiovaskularnih bolesti. U perspektivi se očekuje da će rezultati randomizovanih kontrolisanih studija koje su u toku, definitivno pokazati kolika je efikasnost ovih novih terapijskih opcija za snižavanje nivoa lipida u prevenciji kardiovaskularnih bolesti.

Abstract

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. Dyslipidemia is a significant risk factor for the development of cardiovascular diseases, and lowering the level of serum lipids leads to a reduction in cardiovascular morbidity and mortality. The primary therapeutic target is LDL-cholesterol (c). Statin therapy is often not sufficient to achieve LDL-c target values, so it is necessary to combine them with other lipid-lowering drugs. However, after it was noticed that unwanted cardiovascular events occurred despite the achieved target values of LDL-c, attention was paid to the residual cardiovascular risk. Therefore, there was the development of new therapeutic strategies targeting triglyceride-rich lipoproteins, lipoprotein (a), and apolipoproteins CIII and B. The results of early phases of randomized clinical studies indicated a significant effect of new drugs on reducing cardiovascular risk. This review article aims to present existing therapeutic options for the treatment of dyslipidemia, as well as new therapeutic agents and future perspectives for the treatment of these disorders.

Keywords: dyslipidemia, treatment, LDL-c

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Konflikt interesa: Nema

Primljeno: 26. 01. 2024.
Prihvaćeno: 19. 02. 2024.
Onlajn: 31. 03. 2024.

THERAPEUTIC APPROACH IN THE TREATMENT OF DYSLIPIDEMIA: NOVELTIES AND CHALLENGES

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Abstract

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. Dyslipidemia is a significant risk factor for the development of cardiovascular diseases, and lowering the level of serum lipids leads to a reduction in cardiovascular morbidity and mortality. The primary therapeutic target is LDL-cholesterol (c). Statin therapy is often not sufficient to achieve LDL-c target values, so it is necessary to combine them with other lipid-lowering drugs. However, after it was noticed that unwanted cardiovascular events occurred despite the achieved target values of LDL-c, attention was paid to the residual cardiovascular risk. Therefore, there was the development of new therapeutic strategies targeting triglyceride-rich lipoproteins, lipoprotein (a), and apolipoproteins CIII and B. The results of early phases of randomized clinical studies indicated a significant effect of new drugs on reducing cardiovascular risk. This review article aims to present existing therapeutic options for the treatment of dyslipidemia, as well as new therapeutic agents and future perspectives for the treatment of these disorders.

Keywords: dyslipidemia, treatment, LDL-c

Introduction

Numerous epidemiological and population studies in recent decades indicate that cardiovascular diseases (CVD) represent the leading cause of morbidity and mortality worldwide. As much as a third of all causes of mortality at the global level are the result of CVD[1]. In that regard, significant efforts are being invested in identifying and modulating risk factors associated with the onset of CVD, with lipid metabolism disorders being the most common among them[2]. Dyslipidemia represents a spectrum of lipid metabolism disorders characterized by an increase in total cholesterol (TC), cholesterol contained in low-density lipoproteins (LDL), and triglycerides (TG), as well as a decrease in cholesterol contained in high-density lipoproteins (HDL), or a combination of these disorders[3]. According to research in the adult population in the United States, over 30% of individuals have elevated levels of total and LDL cholesterol, while around 20% of the adult population has elevated triglyceride levels[4].

According to etiology, dyslipidemias can be primary (inherited) or secondary. Primary dyslipidemias result from gene mutations, leading to excessive production or defective clearance of lipid fractions[3, 5, 6]. Familial hypercholesterolemia (FH) (homozygous or heterozygous) is an autosomal dominant inherited disorder characterized by elevated levels of total and LDL cholesterol, as well as the development of premature cardiovascular disease (CVD)[3, 5]. Secondary dyslipidemias account for more than one-third of all causes of dyslipidemias, and they are most commonly associated with diabetes, hypothyroidism, obesity, unhealthy diet, nephrotic syndrome, chronic kidney disease, liver diseases, excessive alcohol consumption, other endocrine disorders, as well as medications such as thiazides, beta-blockers, glucocorticoids, estrogen, progesterone, steroids, etc[3, 5-7]. According to data from 2019, elevated LDL cholesterol levels accounted for essentially 44% of mortality from ischemic heart disease and 22% of mortality from ischemic stroke globally[6].

According to the guidelines of the European Atherosclerosis Society/European Society of Cardiology (EAS/ESC) and the American Heart Association/American College of Cardiology (AHA/ACC), screening for dyslipidemias includes determining the lipid profile (total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, non-HDL cholesterol). In addition to the standard lipid profile, according to the EAS/ESC guidelines, measuring apolipoprotein B (Apo B) as a marker of atherogenic lipoproteins is recommended for all patients with high levels of triglycerides, diabetes, and obesity[8, 9].

DOI: 10.5937/Galmed2409031L

The primary therapeutic goal for treating dyslipidemia is lowering LDL cholesterol. However, there is clear evidence today that lowering lipoprotein(a), as a new therapeutic target, significantly contributes to reducing cardiovascular (CV) risk[8-10]. Despite achieving target LDL cholesterol levels, there is evidence that CVD still occurs, highlighting the need to focus on residual cardiovascular (CV) risk[11, 12]. In recent years, there has been increasing evidence suggesting that the duration of exposure to elevated LDL cholesterol determines the risk for atherosclerotic CVD and its complications, perhaps even more so than the actual level of LDL cholesterol. Therefore, greater and earlier reduction of LDL cholesterol provides better CVD prevention. Such findings emphasize the urgency of identifying and treating high LDL cholesterol early. Based on the accumulation of evidence, guidelines, and clinical trial practices have evolved towards achieving stricter LDL cholesterol targets, especially in patients at high risk[9]. Recent studies on the use of combination therapy, with significant lowering of LDL cholesterol, have not shown a threshold for clinical benefit and have alleviated many safety concerns, thus reinforcing the concept of "lower is better"[13, 14].

Recent successes in trials with non-statin lipid-lowering agents in reducing cardiovascular events have shown that lowering LDL cholesterol through different mechanisms, including increased expression of LDL receptors or decreased cholesterol absorption, significantly reduces cardiovascular events[15]. Therefore, the focus has expanded from "high-intensity statin therapy" to "high-intensity therapy" for lowering LDL cholesterol. This understanding, along with the often observed significant residual risk for CVD, even in individuals treated with statins, has accelerated the search for therapies that reduce highly atherogenic lipoproteins containing Apo B (primarily LDL).

Exactly, this review article aimes to highlight contemporary therapeutic approaches in the treatment of dyslipidemias, with a focus on new agents and the perspective of future treatment of these disorders.

Therapeutic approaches to the treatment of dyslipidemia

The latest joint recommendations from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) for the treatment of dyslipidemias recommend firstly stratifying cardiovascular risk and then, based on the level of risk, further treatment with statins, ezetimibe, and proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibitors[9]. In the guidelines, high-intensity statins are recommended as the first-line therapy in the primary and secondary prevention of patients with hypercholesterolemia. If target LDL cholesterol levels are not achieved based on the level of cardiovascular risk, adding ezetimibe is recommended. For patients who do not achieve the therapeutic goal of this combined therapy (statin + ezetimibe), PCSK9 inhibitors should be introduced into the treatment. ESC/EAS guidelines further state that PCSK9 inhibitors may also be considered for primary cardiovascular prevention in very high-risk patients who do not achieve target LDL cholesterol levels on the maximum tolerable dose of statin in combination with ezetimibe (Table 1, Image 1).

The following text provides an overview of existing therapeutic options for lowering lipid levels, new agents, as well as future perspectives in the treatment of dyslipidemias (Table 2, Image 2).

Statins

Statins are medications used for lowering cholesterol in both primary and secondary prevention of cardiovascular disease (CVD) over the past four decades. The benefit of statin use in lowering LDL cholesterol and preventing CVD has been demonstrated in a large number of randomized clinical trials, and a meta-analysis involving 170,000 patients indicated that reducing LDL cholesterol by just 1 mmol/L reduces the risk of major adverse cardiovascular events by as much as 22%[16].

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. By inhibiting the enzyme that regulates the synthesis of cholesterol, statins reduce intracellular cholesterol synthesis, leading to increased expression of low-density lipoprotein receptors (LDL-R). There are several types of statins available on the market, including atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, lovastatin, and pravastatin.

The efficacy of statins depends on the dosage used in everyday clinical practice. Low or moderate-intensity statins reduce LDL cholesterol by 30% and triglycerides by 20%, while high-intensity statins reduce LDL cholesterol levels by more than 50% and triglyceride levels by up to 40%. Statins can raise HDL cholesterol levels by up to 10%, depending on the dosage[13]. Studies show that statins do not affect on Lp(a) levels[9, 16, 17]. *In vitro* and *in vivo* studies have shown that besides modifying lipid levels in the blood, statins have pleiotropic effects such as improving endothelial dysfunction, antioxidant properties, inhibition of inflammatory response, and stabilization of atherosclerotic plaque[16]. However, in a certain number of patients, despite statin therapy, lipid parameter levels remain above target values[9, 17].

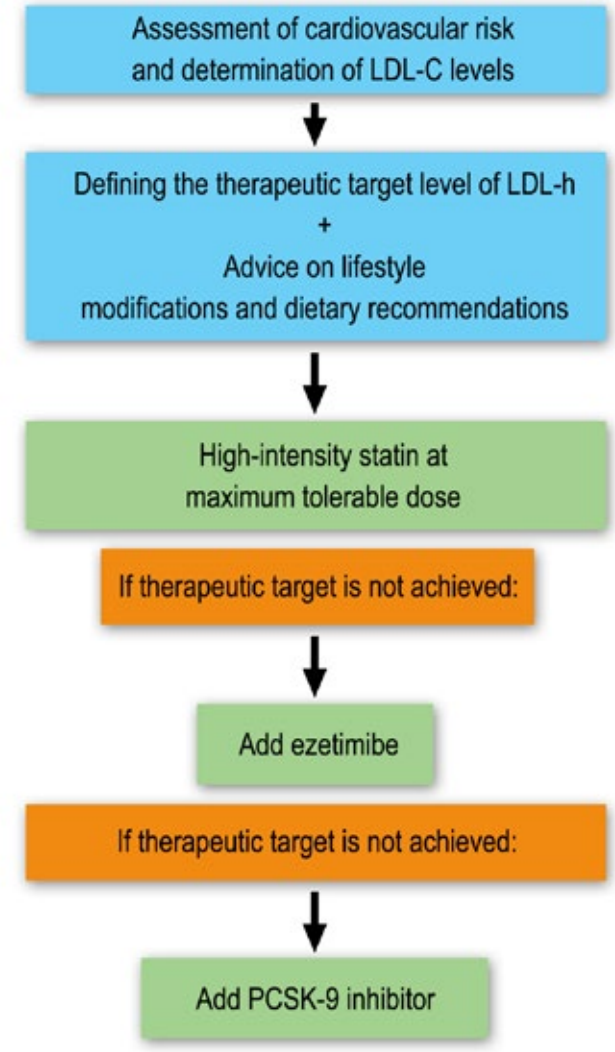
A major problem in clinical practice is the potential "intolerance" to statins, predominantly characterized by the presence of muscle pain, leading to inadequate dosing of statins or discontinuation of this type of therapy. However, a meta-analysis covering 176 studies and a total of 4.1 million patients showed that about 9% of patients do not tolerate statins. The most significant adverse effects of statin therapy are myopathy (11 per 100,000 patients/year), rhabdomyolysis (3 per 100,000 patients/year), elevation of liver enzymes, and hyperglycemia[17].

Table 1. Criteria for assessing cardiovascular risk and therapeutic target values for LDL cholesterol

Category of CV risk	Therapeutic target LDL-cholesterol level	Criteria
Low risk	3.0 mmol/L	• SCORE < 1%
Moderate risk	2.6 mmol/L	• SCORE ≥ 1% i < 5% • Younger individuals (T1DM < 35 years; T2DM < 50 years) with duration of DM < 10 years, without other RF.
High risk	1.8 mmol/L	• SCORE ≥ 5% i < 10% • 1 major RF (fasting plasma glucose > 8 mmol/L, LDL-h > 4.9 mmol/L or blood pressure ≥ 180/110 mmHg. • FH without other major risk factors. • DM without target organ damage, with DM duration ≥ 10 years or other RF • Moderate CKD (eGFR 30-59 mL/min/1.73 m²).
Very high risk	1.4 mmol/L	• ACVD (clinical/imaging) • SCORE ≥ 10% • FH with ACVD or other significant RF • Severe CKD (eGFR < 30 mL/min/1.73 m²). • DM with target organ damage, or ≥ 3 major risk factors, or early onset T1DM with duration > 20 years.

Legend: CV - Cardiovascular; **LDL-h** - Low density lipoprotein; **SCORE** - Systematic Coronary Risk Estimation; **T1DM** - Type 1 Diabetes Mellitus; **T2DM** - Type 2 Diabetes Mellitus; **RF** - Risk Factor; **TC** - Total cholesterol; **AP** - Arterial Pressure; **FH** - Familial Hypercholesterolemia; **CKD** - Chronic Kidney Disease; **ACVD** - Atherosclerotic Cardiovascular Disease. Modified according to ref. 9.

Image 1. Assessment of cardiovascular risk and determination of LDL cholesterol levels



Legend: CV - Cardiovascular; **LDL-h** - Low density lipoprotein; **PCSK9** - Proprotein Convertase Subtilisin Kexin-9; High-intensity statin - rosuvastatin at a dose of 20-40 mg or atorvastatin at a dose of 40-80 mg. Modified according to ref. 9.

Ezetimibe

Ezetimibe is a relatively older drug that inhibits the intestinal absorption of cholesterol by binding to NPC1L1 (Niemann-Pick C1-like 1 protein). Ezetimibe can be used as monotherapy at a dose of 10 mg once daily; however, the efficacy of ezetimibe monotherapy is relatively weak. In patients with heterozygous familial hypercholesterolemia (FH), it reduces total cholesterol by 13.5% and LDL cholesterol by 18.6% compared to placebo[18]. Therefore, this drug is most commonly used in combination with statins, bempedoic acid, and fibrates. Considering its mild side effects, ezetimibe is the treatment of choice for patients who do not tolerate statins[19]. The results of the randomized IMPROVE-IT study, which included over 18,000 patients after an acute coronary event, with a follow-up period of 6 years, showed that the combination of simvastatin and ezetimibe significantly reduces the risk of new cardiovascular events. This finding has reinstated the importance of ezetimibe in new recommendations, particularly in combined therapy[20].

Bempedoic acid

Bempedoic acid inhibits the enzyme adenosine triphosphate citrate lyase, which catalyzes the synthesis of acetyl coenzyme A, thus preventing the synthesis of cholesterol[21]. Unlike statins, the use of bempedoic acid carries a significantly lower risk of myopathy and rhabdomyolysis, making it a therapeutic choice for patients who do not tolerate statins. Interestingly, bempedoic acid has a beneficial effect on glycemia, unlike statins which, especially at high doses, can increase the risk of new-onset diabetes[22]. The most common adverse effects after the administration of bempedoic acid are elevated liver enzymes and concentrations of uric acid[22, 23].

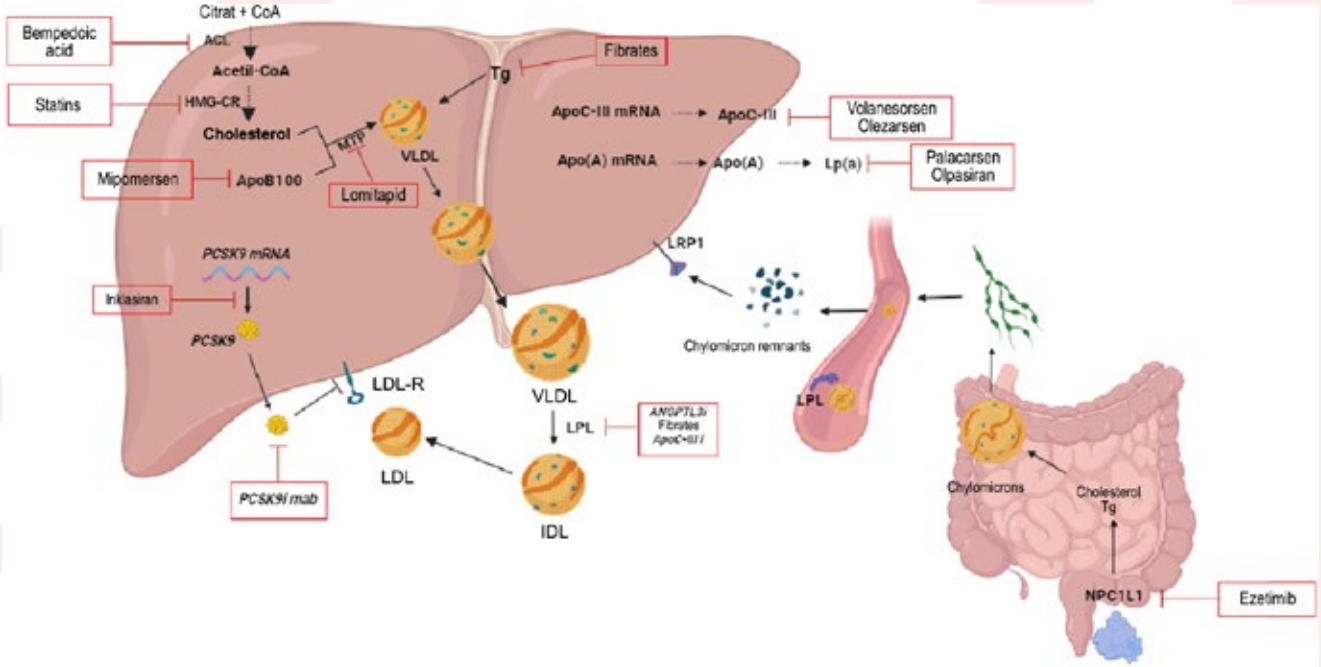
DOI: 10.5937/Galmed2409031L

Table 2. Therapeutic strategies for treating dyslipidemia and mechanism of action of lipid-lowering drugs

The name of the medication	Mechanism of action	Target lipoproteins	Indications	Dosage regimen and mode of administration
Statins	HMG-3-CoA reductase inhibitor	TC; LDL-h; Apo B; TG	Primary and secondary dyslipidemias	1 x daily p.o.
Fibrates	PPARα agonist	TG; VLDL; LDL-h	Hypertriglyceridemia; Familial combined hyperlipidemia	1 x daily p.o.
Bempedoic acid	ACL inhibitor	LDL-h; Apo B; Non-HDL-h	FH; Familial combined hyperlipidemia	1 x daily p.o.
Ezetimibe	NPC1L1 transporter inhibitor	TC; LDL-h; TG	FH; Familial combined hyperlipidemia	1 x daily p.o.
Evolocumab Alirocumab	PCSK9 monoclonal antibody inhibitor	LDL-h;Apo B; Non-HDL-h; Lp (a)	Primary hypercholesterolemia; Familial combined hyperlipidemia HeFH; HoFH	1-2 x monthly s.c.
Inclisiran	PCSK9 siRNA- small interfering ribonucleic acid	LDL-h; Apo B; Non-HDL-h; Lp (a); TG	Primary hypercholesterolemia; Familial combined hyperlipidemia; HeFH; HoFH	1 x in 6 month s.c.
Evinacumab	ANGPTL3 monoclonal antibody inhibitor	LDL-h; Apo B; Non-HDL-h; TG	HoFH	1 x a month i.v.
Pelacarsen	Apo (A) translation blocker	LDL-h; Lp (a); Apo B	Not approved	1 x a month s.c.
Olpasiran	Inhibitor of iRNK translation for Lp(a)	Lp (a)	Not approved	1 x in 3 months s.c.
Volanesorsen	Apo C-III inhibitor	Apo C-III; TG; Chylomicrons	Hypertriglyceridemia; Hyperchylomicronemia	1 x weekly s.c.
Olezarsen	Apo C-III inhibitor	Apo C-III; TG; Chylomicrons	Not approved	1 x a week s.c.

Legend: TC - Total Cholesterol; **LDL-h** - Low density lipoprotein; **TG** - Triglycerides; **Apo** - Apolipoprotein; **Lp (a)** – lipoprotein (a); **Non-HDL-h** - Non-HDL-holesterol; **ACL** - Adenosine triphosphate-Citrate Lyase; **HMG-CR-3** - Reductase 3-hydroxy-3-methyl-glutaryl-coenzyme A Reductase; **NPC1L1** - Niemann-Pick C1-like 1 protein; **PPARα** - Peroxisome Proliferator-activated Receptor-α; **VLDL** - Very Low Density Lipoprotein; **HeFH**- Heterozygous Familial Hypercholesterolemia; **HoFH** - Homozygous Familial Hypercholesterolemia.

Image 2. Schematic presentation of the mechanism of action of lipid-lowering drugs



Legend: ACL - Adenosine triphosphate-Citrate Lyase; **HMG-CR-3** - Reductase 3-hydroxy-3-methyl-glutaryl-coenzyme A Reductase; **Apo** - Apolipoprotein; **MTP** - Mitochondrial Trifunctional Protein; **TG** - Triglycerides; **VLDL** - Very Low Density Lipoprotein; **LDL** - Low Density Lipoprotein; **LDL-R** - Low Density Lipoprotein Receptor; **IDL** - Intermediate Density Lipoprotein; **Lp (a)** - lipoprotein (a); **LPL** - Lipoprotein Lipase; **NPC1L1** - Niemann-Pick C1-like 1 protein; **LRP1** - Low-density Receptor-related Protein 1; **PCSK9 mRNA** - PCSK9 informational RNK; **PCSK9 mab** - PCSK9 monoclonal antibodies.

The effectiveness and safety of bempedoic acid in patients who do not tolerate statins have been investigated in several studies, with the most significant being the CLEAR study. After conducting clinical trials, bempedoic acid is indicated for use in lowering LDL cholesterol levels in patients with familial hypercholesterolemia, combined with hypertriglyceridemia, and in patients with atherosclerotic cardiovascular disease[21-23].

PCSK9 inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme predominantly produced in the liver. Its function involves the degradation of LDL receptors (LDL-R) in hepatocytes, reducing the recycling of these receptors,and down-regulating them. Consequently, this leads to an increase in serum LDL cholesterol levels (reducing available LDL-R for LDL clearance from circulation). Therefore, by inhibiting PCSK9 with monoclonal antibodies, the number of available LDL receptors is increased (up-regulation of receptors), leading to enhanced clearance of LDL cholesterol and significant reduction in its circulation[24]. PCSK9 inhibitors are injectable agents (monoclonal antibodies) administered subcutaneously once or twice a month, with an extremely low number of adverse effects. However, a limiting factor for their wider use is their high cost[25]. The most common adverse effects associated with direct use of PCSK9 inhibitors are lower levels of vitamin E.

Evolocumab and alirocumab are monoclonal antibodies that inhibit PCSK9 and are approved for clinical use as monotherapy or in combination with statins and ezetimibe. Evolocumab reduces plasma LDL cholesterol levels by 53% to 75%, depending on whether it is used as monotherapy or in combination with statins, in patients with heterozygous familial hypercholesterolemia (HeFH). However, in patients with homozygous FH (HoFH) with defective LDL receptors, this percentage is lower, around 31%. Alirocumab reduces plasma LDL cholesterol levels by 39% to 58% in patients with HeFH and by 11.9% to 34.3% in patients with HoFH, depending on whether it is used as monotherapy or in combination with statins[26].

Results from two large randomized controlled clinical trials (FOURIER and ODYSSEY) have shown that the use of evolocumab and alirocumab in patients with high cardiovascular risk who were previously on statin therapy reduces the risk of new cardiovascular events by 15%[27]. The mentioned studies have shown that the use of evolocumab leads to a reduction in total cholesterol, triglycerides, non-HDL cholesterol, Apo B, and a mild increase in HDL cholesterol. Unlike statins, the use of PCSK9 inhibitors unequivocally lowers serum concentrations of Lp(a). Additionally, it has been shown that the use of alirocumab has favorable effects on reducing oxidative stress, decreasing the production of inflammatory cytokines, and reducing the activity of metalloproteinase 2, osteopontin, and osteoprotegerin, which are key pathophysiological processes underlying atherosclerosis[28]. Current guidelines recommend the use of PCSK9 inhibitors in patients with high and very high cardiovascular risk who, despite being on maximum tolerated doses of statins and ezetimibe therapy, do not achieve the recommended target LDL cholesterol levels[9, 26].

Inclisiran

Inclisiran is a small interfering ribonucleic acid (siRNA) that blocks the synthesis of PCSK9 in hepatocytes[26, 29]. As a result, there is an up-regulation of LDL receptors (LDL-R) and better uptake of LDL cholesterol from circulation, leading to significant lowering of LDL cholesterol levels. Inclisiran is approved for the treatment of patients with heterozygous familial hypercholesterolemia (HeFH), familial combined hyperlipidemia, and confirmed atherosclerotic cardiovascular disease (CVD). It is administered as a subcutaneous injection at a dose of 284 mg. After the initial administration of the drug, the second dose is given after three months, and each subsequent dose is administered every six months[29]. The main advantage of inclisiran compared to PCSK9 monoclonal antibodies is the dosing regimen and the longer-lasting effect, which ensures better compliance[30].

The efficacy and safety of the drug were investigated in the ORION studies involving patients receiving maximum tolerated doses of statins and other lipid-lowering medications. Results from one year of follow-up indicated that inclisiran lowers LDL cholesterol by 50% compared to placebo[31]. Additionally, inclisiran has favorable effects on lowering total cholesterol, triglycerides, non-HDL cholesterol, Lp(a), and increasing HDL cholesterol[31]. Currently, studies such as ORION-4, VICTORION-2, and PREVENT are underway to analyze the effects of inclisiran on the occurrence of new cardiovascular disease (CVD) in patients with confirmed atherosclerotic CVD who were previously on statin therapy compared to placebo.

Omega-3 fatty acids

Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can reduce the risk of new cardiovascular events through various mechanisms, including lowering triglyceride levels and exerting antithrombotic, anti-inflammatory, or antiarrhythmic effects[32]. The results of a meta-analysis that included randomized clinical trials have shown the superiority of EPA monotherapy over EPA + DHA in reducing cardiovascular mortality, the frequency of non-fatal myocardial infarction, new cardiovascular events, and revascularization. However, a high dose of the drug (2-4 grams of EPA per day) is necessary[33].

Fibrates

The mechanism of action of fibrates involves the activation of peroxisome proliferator-activated receptor-alpha (PPAR-α), which, upon activation, stimulates lipolysis and the elimination of atherogenic particles rich in triglycerides from the plasma by activating lipoprotein lipase. Activation of PPAR-α induces a reduction in the production of Apo C-III in the liver, leading to a decrease in the lipid fraction contained in very low-density lipoprotein (VLDL) and LDL

cholesterol[34]. Additionally, activation of these nuclear receptors leads to increased production of Apo A-I and A-II, resulting in desirable elevation of HDL cholesterol levels.

The results of a meta-analysis that combined several studies have shown that fibrates reduce the incidence of cardiovascular events by approximately 10%[35]. Fibrates can be safely combined with statins in patients where secondary causes of hypertriglyceridemia are excluded and who, despite dietary management, maintain high levels of triglycerides[34].

ANGPTL3 inhibitors

ANGPLT3 (Angiopoietin-like protein 3) is a polypeptide that plays a significant role in lipid metabolism by inhibiting lipoprotein and endothelial lipase, thereby increasing levels of triglycerides and LDL cholesterol[36]. Therefore, by inhibiting ANGPTL3, there is a reduction in triglycerides and LDL cholesterol, which is the mechanism of action of this group of drugs that is independent of LDL receptors[37]. Evinacumab is a monoclonal antibody from the group of ANGPTL3 inhibitors approved for the treatment of homozygous familial hypercholesterolemia (HoFH) with a significant effect on lowering LDL cholesterol[37]. The administration of evinacumab is intravenous at a dose of 15 mg/kg every four weeks. In the third phase of clinical trials, the efficacy of evinacumab was confirmed with a reduction in LDL cholesterol levels by 47.1% compared to placebo[38]. Good results have been achieved with the use of evinacumab in mixed dyslipidemia by lowering triglyceride levels. This could imply successful future applications for these patients. Adverse effects associated with the use of evinacumab include "flu-like" symptoms, mild elevation in creatine kinase, and liver enzymes[38].

Volanesorsen and olezarsen

Volanesorsen and olezarsen inhibit the production of Apo C-III in the liver and small intestine, which is found in triglyceride-rich lipoproteins. Volanesorsen, when administered to patients with familial hypertriglyceridemia, has a favorable effect on reducing triglyceride levels, thereby reducing the incidence of acute pancreatitis[39]. A meta-analysis has shown that treatment with volanesorsen leads to a reduction in triglycerides by approximately 72%, VLDL by 74%, Apo B-48 by 60%, Apo C-III by 80%, with an increase in HDL by 46% and LDL by around 67%[40].

Volanesorsen is administered subcutaneously at a dose of 285 mg once weekly for the first three months, and later every two weeks. Olezarsen has a more favorable safety profile in terms of a lower risk of thrombocytopenia[41]. In the early phase of clinical trials, ARO-APOC31001 siRNA, which degrades Messenger Ribonucleic Acid (mRNA) for Apo C-III, is also being investigated[42].

Pelacarsen, olpasiran, and SLN360

Pelacarsen is an antisense oligonucleotide that binds to Apo mRNA, forming a complex that prevents the synthesis of Lp(a) in hepatocytes, thereby reducing its production and consequently the level of Lp(a) in the serum[43]. Moreover, these are the only drugs capable of modulating the level of Lp(a) for which there has been no therapeutic option until now. Pelacarsen has a significant impact on reducing total cholesterol, LDL-C, and triglycerides, and it is administered subcutaneously once a month. Currently, this drug is in Phase III of the HORIZON clinical trial, which aims to investigate the protective effect of pelacarsen on adverse cardiovascular events. Similar mechanisms of action are also exhibited by olpasiran and SLN360, which are also in clinical trial phases[44, 45].

Mipomersen

Mipomersen inhibits the production of Apo B found in LDL-C, VLDL, and Lp(a)[46]. It significantly lowers LDL-C, non-HDL-C, Lp(a), triglycerides, and Apo B. In the United States, its subcutaneous administration at a dose of 200 mg was approved in 2012 for patients with HoFH. However, due to serious adverse effects such as hepatotoxicity and liver steatosis, the drug was withdrawn from the market in 2019[46].

Lomitapide

Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), which is localized in the endoplasmic reticulum of hepatocytes. The role of MTP is to transport triglycerides, phospholipids, and cholesterol esters to Apo B, and its inhibition reduces hepatic production of VLDL, consequently lowering levels of total cholesterol, serum LDL-C, non-HDL-C, and Apo B. Lomitapide is approved for use in patients with HoFH, either alone or in combination with other lipid-lowering drugs, and it is administered orally once daily at a dose of 5-10 mg[47].

Lerodalcibep

Lerodalcibep inhibits PCSK9 via CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeat-Cas9) technology. Cas9 is a double-stranded DNA nuclease directed to its target using guide RNA (CRISPR RNA, crRNA)[48]. Lerodalcibep is a recombinant fusion protein consisting of the PCSK9-binding domain and human serum albumin. Results from the third phase of clinical trials indicate that lerodalcibep, administered subcutaneously once monthly at a dose of 300 mg in patients with HeFH, on maximum tolerable doses of statins and ezetimibe, after 24 weeks of follow-up, showed effective reduction of LDL-C by approximately 60%, with about 70% of patients achieving LDL-C reduction ≥ 50% and recommended target values according to the 2019 ESC/EAS guidelines compared to placebo[48].

MK-0616

MK-0616 is an oral macrocyclic PCSK9 inhibitor currently in clinical trial phase. The second phase of clinical trials has shown that orally administered PCSK9 inhibitors at daily doses ranging from 6 to 30 mg resulted in a reduction of LDL cholesterol by up to 60.9% compared to placebo after an 8-week follow-up period in patients with hypercholesterolemia and atherosclerotic cardiovascular disease previously treated with statins[49].

PCSK9 vaccines represent a new therapeutic strategy that would enable the intrinsic production of antibodies against PCSK9[50]. A liposomal immunogenetic compound consisting of PCSK9-tetanus peptide with an aluminum adjuvant is a new formulation of PCSK9 vaccine that has demonstrated long-lasting synthesis of PCSK9 antibodies and reduction in LDL and VLDL cholesterol levels in laboratory mice by 51.7% in BALB/c and 19.2% in C57BL/6 animal models[50].

Gene therapy for high cholesterol

Encouraging research in animal models has demonstrated the potential for gene therapy for high cholesterol. Specifically, mRNA encoding the PCSK9 gene (known as VERVE-101) has been synthesized and packaged into lipid nanoparticles. Preclinical studies in mice and non-human primates (NHP) have shown that a single intravenous administration of VERVE-101 can inactivate the PCSK9 gene in the liver[51]. NHP treated with VERVE-101 experienced a significant reduction in LDL levels, which remained permanently lowered during more than two years of follow-up, supporting the potential for a lasting treatment effect. Recently, at the American Heart Association conference (November 2023), the first results of this therapy in humans (phase Ib clinical trial) were presented, showing good and promising outcomes[52].

Conclusion

Considering that dyslipidemia is a significant risk factor for cardiovascular diseases, lipid-lowering drugs are important not only in primary but also in secondary prevention of these diseases. Although according to all current guidelines, LDL levels remain the primary therapeutic target, increasing attention is being paid to residual cardiovascular risk. Statins are the most commonly prescribed drugs worldwide, although, despite their use, a large number of patients do not achieve the recommended LDL target levels. Therefore, statins can be combined with ezetimibe and PCSK9 inhibitors. Bempedoic acid is an approved therapeutic alternative for patients who do not tolerate statins. Inclisiran is a PCSK9 inhibitor counterpart, however, the use of inclisiran could improve patient compliance due to its dosing regimen. Pelacarsen and olpasiran are future therapeutic strategies aimed at lowering Lp(a), which is an independent risk factor for cardiovascular diseases. Evinacumab, lomitapide, mipomersen, volanesorsen, and olezarsen are drugs that primarily affect various steps in the metabolism of atherogenic lipoproteins, thus representing a significant new approach in cardiovascular disease prevention. In the future, the results of ongoing randomized controlled trials are expected to definitively demonstrate the effectiveness of these new therapeutic options for lowering lipid levels in the prevention of cardiovascular diseases.

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Declaration of interest statement: None

Received: 26. 01. 2024.
Accepted: 19. 02. 2024.
Online: 31. 03. 2024.