American Journal of Preventive Cardiology 19 (2024) 100701

Contents lists available at ScienceDirect

American Journal of Preventive Cardiology

journal homepage: www.journals.elsevier.com/american-journal-of-preventive-cardiology

Advances in targeting LDL cholesterol: PCSK9 inhibitors and beyond

Maya Safarova [a,1], Tia Bimal [b,1], Daniel E. Soffer [c], Benjamin Hirsh [d,e], Michael D. Shapiro [f], Guy Mintz [d,e], Agnes Cha [g], Eugenia Gianos [b,d,*]

[a] Division of Cardiovascular Medicine, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI USA
[b] Northwell, New Hyde Park, NY, Cardiovascular Institute, Lenox Hill Hospital, USA
[c] Department of Internal Medicine, University of Pennsylvania, Philadelphia, PA USA
[d] Department of Cardiology, Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY, USA
[e] Northwell, New Hyde Park, NY, Cardiovascular Institute, Sandra Atlas Bass Heart Hospital, USA
[f] Center for the Prevention of Cardiovascular Disease, Section on Cardiovascular Medicine, Wake Forest University School of Medicine, Winston Salem, NC, USA
[g] Northwell/Vivo Health Pharmacy, Ambulatory Pharmacy Services, Lake Success, NY, USA

ARTICLE INFO

Keywords:
Lipid-lowering
Advanced therapies
Non-statins
Precision lipidology

ABSTRACT

There is a direct relationship between the duration and level of exposure to low density lipoprotein cholesterol (LDL-C) levels over one's lifespan and cardiovascular events. Early treatment to lower elevated LDL-C is crucial for better outcomes with multiple therapies currently available to reduce atherogenic lipoproteins. Statins remain the foundation of LDL-C lowering therapy as one of the most cost-effective drugs to reduce atherosclerotic events (ASCVD) and mortality. Nonetheless, LDL-driven goal attainment remains suboptimal globally, highlighting a considerable need for non-statin therapies to address residual risk related to statin intolerance, non-adherence, and inherited lipoprotein disorders. LDL-C lowering interventions beyond statins include ezetimibe, PCSK9 monoclonal antibodies, inclisiran and bempedoic acid with specific guideline recommendations as to when to consider each. For patients with homozygous familial hypercholesterolemia requiring more advanced therapy, lomitapide and evinacumab are available, providing mechanisms that are not LDL receptor dependent. Lipoprotein apheresis remains an effective option for clinical familial hypercholesterolemia as well as elevated lipoprotein (a). There are investigational therapies being explored to add to our current armamentarium including CETP inhibitors, a third-generation PCSK9 inhibitor (small recombinant fusion protein oral PCSK9 inhibitor) and gene editing which aims to directly restore or disrupt genes of interest at the DNA level. This article is a brief review of the pharmacotherapy options beyond statins for lowering LDL-C and their impact on ASCVD risk reduction. Our primary aim is to guide physicians on the role these therapies play in achieving appropriate LDL-C goals, with an algorithm of when to consider each based on efficacy, safety and outcomes.

1. Introduction

Over the last several decades, clinical trials examining statin and non-statin therapies consistently demonstrate significant outcomes benefit from a reduction in atherogenic lipoproteins [1]. In fact, there is a direct relationship between the duration and level of exposure to low density lipoprotein cholesterol (LDL-C) levels over one's lifespan and cardiovascular events [2]. The earlier patients receive treatment for elevated LDL-C, the better the outcomes. In addition, patients with higher baseline risk for atherosclerotic cardiovascular disease (ASCVD) derive the greatest benefit from LDL-C lowering proportional to the degree of LDL-C reduction from baseline.

Since their Food and Drug Administration (FDA) approval, statin therapy has become one of the most impactful interventions to reduce ASCVD events and mortality [1]. As the foundation of therapy for ASCVD risk reduction, they are inexpensive and highly effective, providing cost-effective therapy in the primary and secondary prevention setting. While mean age-adjusted total cholesterol levels decreased

Abbreviations: LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ASCVD, Atherosclerotic cardiovascular disease; PCSK9, Proprotein convertase subtilisin/kexin type 9; Lp(a), Lipoprotein (a); hoHF, homozygous familial hypercholesterolemia.

* Corresponding author at: Northwell, 2000 Marcus Avenue, Suite 300, New Hyde Park, NY 11042-1069.
E-mail address: egianos@northwell.edu (E. Gianos).

[1] The two co-first authors contributed equally to this manuscript.

https://doi.org/10.1016/j.ajpc.2024.100701
Received 17 January 2024; Received in revised form 7 June 2024; Accepted 22 June 2024
Available online 25 June 2024
2666-6677/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

in the US population from 197 mg/dL in 2007–2008 to 189 mg/dL in 2017–2018 for men and women, cholesterol screening rates remain suboptimal. As such, only 66 % of Hispanic adults, 75 % of Asian adults, 71 % of Black adults, and 74 % of White adults have been reported to receive lipid screening over the past decade [3]. In men and women at an equivalent ASCVD risk, statin therapy was shown to have similar effectiveness for the prevention of major vascular events [4]. However, national trends demonstrate low uptake of lipid-lowering therapies, especially in women [3]. Further, across the globe, LDL-driven goal attainment remains suboptimal [5], introducing a significant need for non-statin therapies to address residual ASCVD risk related to statin intolerance, non-adherence, and heritable lipid disorders. Approximately 50 % of patients with established ASCVD have inadequate LDL-C reduction and poor adherence rates even as soon as 12 months after initiation of therapy [6]. Novel treatments may further extend individualized care to patients with varying needs and phenotypes.

The following is a brief review of the pharmacotherapy options for LDL-lowering and evidence for ASCVD risk reduction. It is meant to be a resource that supports the role of therapy based upon evidence of efficacy, safety, tolerability, convenience, and patient acceptance. The issues of cost and value are beyond the scope of this review and differ based upon region and individual characteristics, but obviously are important determinants of utilization. Clinicians are encouraged to follow accepted guidelines with an individualized approach, and advocate for broader access when guideline-based therapies are not authorized or affordable for their patients.

2. Atherogenic lipoproteins and the need for advanced therapies

It is well-established that apolipoprotein B (apoB)-containing lipoproteins are the building blocks for atherosclerosis. They include chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, lipoprotein(a) (Lp(a)), and remnant particles [7]. With a few exceptions, even at low concentrations, the predominant circulating atherogenic lipoprotein is LDL [8]. Therefore, the predominant goal in the management of ASCVD is to reduce available circulating LDL and its incorporation into developing atheroma, thus enabling the stabilization and remodeling processes mediated by high-density lipoprotein (HDL). LDL-C represents the cholesterol content in LDL and its concentration in serum correlates directly with the progression of atherosclerotic lesions. As a result, treatment strategies have been directed toward lowering LDL-C [1]. Despite the consistent benefit seen with LDL-C lowering treatments and observational, epidemiologic, genetic, and randomized controlled data supporting lower levels for longer durations, there continues to be residual ASCVD risk in treated individuals attributed, in part, to incomplete reduction in LDL-C, non-HDL-C, apoB, triglyceride-rich lipoproteins (TRL), small dense LDL (sdLDL), and Lp(a) [9].

ApoB is a large protein containing >4500 amino acids in its primary structure. Thus, atherogenic lipoproteins can accommodate only a single apoB particle on their surface. The lipoproteins vary based upon their origin (hepatic or intestinal), lipid content (cholesterol to triglyceride ratio), exchangeable apolipoproteins (apo) (e.g., apoCIII, apoCII, apoE, apoA), and in the case of Lp(a), the presence of apo(a) and oxidized phospholipid content. Shared circulatory residence enables lipoprotein interaction with each other, subsequent remodeling (especially mediated by cholesteryl ester transfer protein [CETP]) by lipid and protein exchange. This results in a range of atherogenic potential (Lp(a) > TRL-remnant > LDL), and lipid content within each class, which affects the ability to reproducibly measure and assess atherogenic potential with a single measurement. Therefore, the total atherogenic lipoprotein burden is not completely captured by the measurement of LDL-C alone. Consideration of additional atherogenic particles and assessment of apoB and non-HDL-C [10] is worthwhile when choosing therapies for cardiovascular risk reduction. The number of LDL and VLDL particles in plasma is a function of the rate at which they are produced and the rate at which they are removed and cleared from plasma. VLDL secretion rates are increased in patients with familial combined hyperlipidemia and hypertriglyceridemia, abdominal obesity, insulin resistance, and diabetes [11]. The rate at which VLDL particles can be cleared is limited and VLDL apoB particle numbers increase, as a result apoB provides incremental improvement in risk prediction in these patients.

LDL-C lowering can be achieved by reducing available cholesterol in LDL, or by enhancing clearance of LDL from circulation (Fig. 1) [12]. Dietary modification (decrease in saturated fat and increase in fiber content) [13], regular physical activity [14], often weight reduction, attention to optimal sleep and stress management are first line treatments for ASCVD risk reduction [15]. In addition to the ability to lower LDL-C, there are additional cardiovascular benefits that healthy diet and lifestyle choices can provide. Pharmacologic therapeutics can impact lipid and lipoprotein synthesis and clearance. Clearance of the LDL particles via LDL-receptor upregulation is the common mechanistic pathway for statins, cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants, proprotein convertase subtilisin-kexin 9 inhibitors (PCSK9i), and the cholesterol synthesis inhibitor, bempedoic acid.

3. Need for accurate lab measurement

Another source of residual risk conveyed by atherogenic lipoproteins may be attributed to the incomplete measurement of total atherogenic burden by LDL-C measurement alone. As described in the 2018 Multisociety Guideline on the Management of Blood Cholesterol, apoB and non-HDL-C are stronger indicators of atherogenicity than LDL-C alone [16]. When LDL-C < 100 mg/dL and/or when triglycerides are elevated, the most commonly used LDL-C calculation (Friedewald formula) underestimates atherogenic risk compared to other measurement techniques due to the errors in estimating VLDL-C. When triglycerides are in the range 150 to 400 mg/dL or 150–800 mg/dL, the Martin-Hopkins method and NIH equation 2, respectively, provide greater accuracy than Friedewald equation [17]. Appropriate use and reporting of lipid test results should improve their utility and precision in the management of individuals at risk for ASCVD events [18].

4. Statin therapy as first line

Since the sentinel work by Akira Endo [19] and subsequent FDA approval of lovastatin (Mevacor®) in 1987, there have been numerous randomized clinical trials (RCTs) reproducibly demonstrating improvement in ASCVD prognosis and outcomes in individuals treated with statins compared to placebo. Efficacy and safety of more intensive lowering of LDL-C was comprehensively reported in the meta-analyses conducted by the Cholesterol Treatment Trialists' Collaboration (CTT). Based on these data, for every 38.7 mg/dL lowering in LDL-C there is a 22 % reduction in major adverse event (MACE) rate, including coronary events, strokes, need for coronary revascularization and vascular mortality, as well as a reduction in all-cause mortality by ~10 % [1,20]. Further reductions in LDL-C produce additional reductions in the incidence of major vascular events in people of all ages, including those over the age of 75. Statin therapy is effective in a wide range of populations, including women and men, in people with diabetes, and in those at lower risk for ASCVD. **Supplemental Table 1** summarizes expected LDL-C lowering effects for each statin enabling every dose of statin to be characterized as either high, moderate, or low intensity therapy [21–62].

5. LDL-C: lower for longer

Mendelian randomization is an effective approach to evaluate causal relationship between a biological factor and a disease of interest. Using data from the genome-wide association studies (GWAS) in the Global Lipids Genetics Consortium, a 1-standard deviation increase in the LDL-C levels mediated by the *HMGCR, NPC1L1*, and *PCSK9* genes was

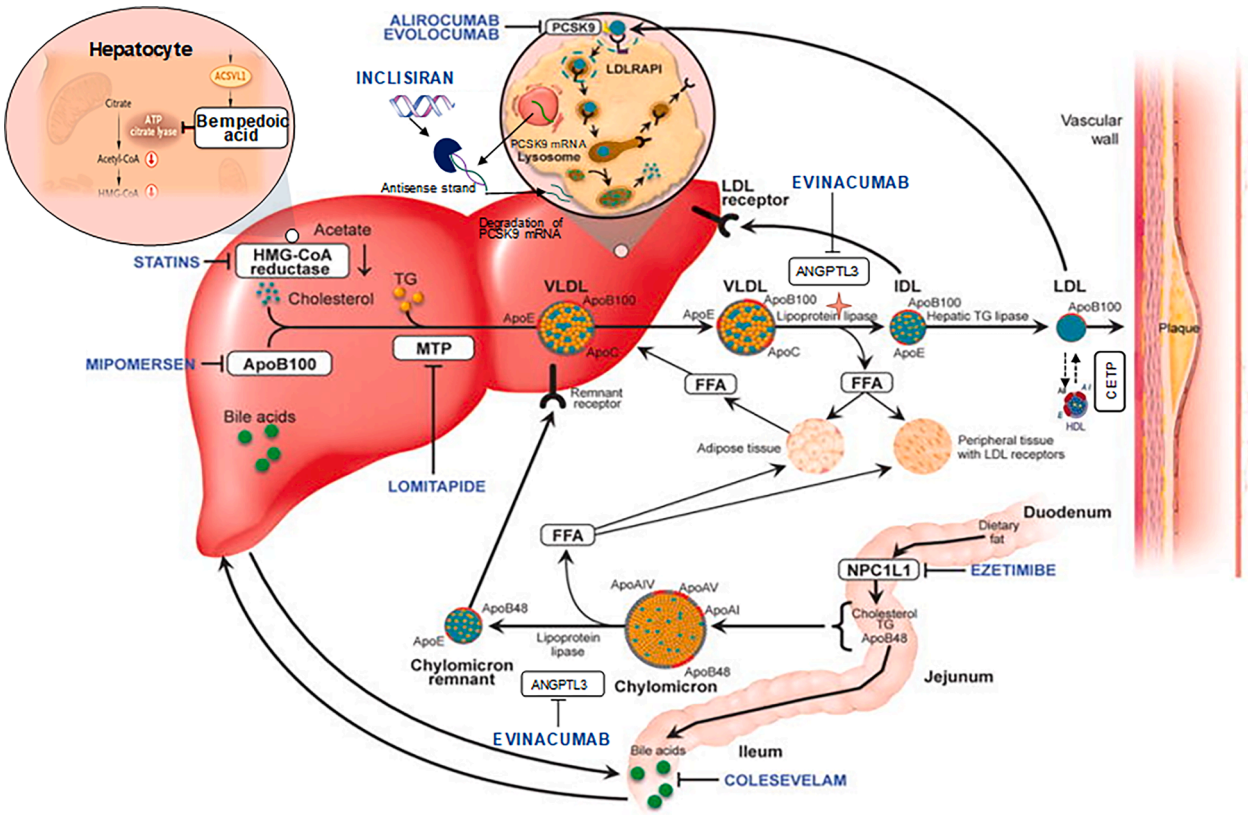

Fig. 1. Current therapeutic armamentarium of approved lipid-modifying agents. Schematic diagram of the site and mechanism of action, affecting various steps in the LDL synthesis and clearance pathway. With permission and modifications from Safarova et al. [12]. Abbreviations: LDL-C: low density lipoprotein cholesterol; NPC1L1: Niemann-Pick C1-Like 1; LDL-R: low density lipoprotein receptor; ACL: ATP citrate lyase inhibitor; PCSK9: Proprotein convertase subtilisin/kexin type 9; siRNA: Small interfering ribonucleic acid; ANGPTL3: Angiopoietin-like 3; ApoB: Apolipoprotein B; FFA: free fatty acids, CETP cholesteryl ester transfer protein; MTP Microsomal Triglyceride Transfer Protein; HDL high-density lipoprotein.

associated with 1.2 years lower lifespan [63]. In a series of meta-analyses, Ference et al. [64] used 6 lipid-related genes (*SORT1, PCSK9, LDLR, HMGCR, ABCG8, APOE*) to demonstrate consistent 3-fold risk reduction in coronary events per 38.7 mg/dL lower LDL-C, as compared to a statin started later in life. Early prolonged exposure to lower LDL-C due to inherited predisposition is associated with a reduction in the lifetime risk of ASCVD. This supports the notion that earlier intervention with LDL-lowering therapy may result in better ASCVD outcomes [64]. Further, observational data suggest safety of early long-term use of statin therapy initiated in childhood in patients with familial hypercholesterolemia (FH) [65,66]. The PESA (Progression of Early Subclinical Atherosclerosis) trial with 3471 individuals (baseline age 40–55 years; 36 % female) who underwent structured assessment of peripheral subclinical atherosclerosis using 3D-vascular ultrasound, revealed the following findings: (i) atherosclerosis regression was possible in early stages of the disease, as regression was observed in 8 % with baseline disease, (ii) higher LDL-C showed the strongest association with disease progression in individuals free of disease at enrollment, (iii) with increasing age for every 10-unit increase in LDL-C and blood pressure there was an attenuation in the odds of subclinical atherosclerosis progression at 6 years, highlighting their marked impact in younger individuals and emphasizing importance of early detection and control [67].

This has led to the contemporary refrain summarizing the LDL-C approach as “lower for longer, and earlier, is better for ASCVD management.” Further, to test this practice in the clinical trial setting, the PRECAD (Prevent Coronary Artery Disease) trial will randomize young volunteers, aged 20–39 with atherosclerosis, to either receive aggressive therapy with LDL <70 mg/dL or undergo watchful waiting for assessment of total atherosclerosis burden as a surrogate of ASCVD [68]. To capture the transition to symptomatic disease, the PESA-CNIC-SANTANDER study which is an ongoing prospective cohort study examining imaging, biological, and behavioral parameters of early subclinical atherosclerosis, will assess natural course of atherosclerotic and related trains until at least 2029 [69].

6. Safety of very low LDL levels

PCSK9 inhibitor trials provided the first opportunity to observe the benefits and safety of achieving very low LDL-C levels with pharmacotherapy. In addition, the safety of low LDL-C levels complements the findings observed from individuals with genetically determined low levels of the PCSK9 protein and LDL-C levels. Loss-of-function mutations in *PCSK9* are associated with markedly low LDL-C, reduced risk of coronary heart disease, and no measurable adverse effects [70–72]. Similarly, persons with loss-of-function mutations in *ANGPTL3* exhibit decreased plasma lipid levels and a significantly reduced prevalence of ASCVD without any apparent adverse effects [73,74]. Using a phenome-wide association (PheWAS) approach, no association was found between LDL-C-related variants in *PCSK9, APOB,* and *LDLR* and non-lipid-related phenotypes including diabetes, neurocognitive disorders, or cataracts, suggesting that major off-target side effects would be less likely with pharmacologic manipulation of the examined genes [75].

Interventional data with the open label extension of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial included 6635 patients with a median follow-up of 4.8 years and a median LDL-C level of 32 mg/dL [76]. In addition to evolocumab, patients were on maximally tolerated high intensity statin therapy with or without ezetimibe. There was an early and

consistent separation of the survival curves with the risk of the primary and secondary efficacy endpoint being 18 % and 21 % lower per each 38.7 mg/dL of LDL-C, respectively. Individuals with LDL-C below 10 mg/dL demonstrated the lowest risk of adverse cardiovascular outcomes.

The ODYSSEY OUTCOMES trial examined the ASCVD outcomes in acute coronary syndrome (ACS) patients treated with alirocumab or placebo, with the PCSK9 inhibitor dose adjusted to achieve LDL-C 25–50 mg/dL. This RCT showed both efficacy and safety at very low LDL levels, albeit for a short duration because those with LDL-C < 15 mg/dL on alirocumab were converted to placebo in a blinded fashion [77]. Those with the LDL-C levels below 70 mg/dL on average demonstrated greater incremental clinical benefit with monoclonal antibodies (mAb) to PCSK9 with higher Lp(a) levels [78–80], suggesting benefit from a further personalized approach to lipid-lowering therapies. Analysis of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) with data on almost 15,281 individuals showed a 21 % reduction in the risk of cardiovascular death, major coronary events, or stroke in patients achieving an LDL-C level less than 30 mg/dL with ezetimibe as compared with 70 mg/dL or greater [81].

No causal relationship between statins and cancer, cataracts, cognitive dysfunction, peripheral neuropathy, erectile dysfunction, or tendonitis has been observed to date [82]. Given prior concerns that low LDL-C alters cognitive function, to examine the potential effect on neurocognitive implications the EBBINGHAUS study assessed subjects treated with evolocumab or placebo with a battery of well-validated, comprehensive cognitive tests amongst patients who had achieved very low LDL-C levels <85 mg/dL with high intensity statin and PCSK9 inhibitors with or without ezetimibe, including those with LDL <25 mg/dL. No significant difference in cognitive performance scores was reported in this analysis [83]. In FOURIER-OLE (open-label extension) in patients with LDL-C as low as <20 mg/dL, including LDL-C < 10 mg/dL there was no significant safety concerns over a follow-up of 8.6 years [76]. The legacy effect was observed in those achieving very low LDL-C levels demonstrating the lowest cumulative incidence of the composite cardiovascular death, myocardial infarction, stroke, unstable angina, or coronary revascularization very early in treatment. There were further reductions in cardiovascular events when compared with delayed treatment initiation [84]. Data on safety of the newer lipid-modifying therapeutics continued beyond 8 years is not known, therefore, ongoing surveillance is necessary to further inform providers and clinicians.

This paradigm prompted a 2023 Scientific Statement from the American Heart Association, which reviewed the data for LDL lowering and brain function and largely refuted concerns about heightened risk for cognitive impairment, dementia, and hemorrhagic stroke [85]. The brain produces its own supply of cholesterol via astrocytes and oligodentrocytes and therefore is not dependent on the transport of the cholesterol across the blood brain barrier. Although the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial showed an increase in hemorrhagic stroke in patients taking atorvastatin 80 mg oral daily, a subsequent secondary analysis of this data identified that hemorrhagic stroke risk was highest in statin-treated patients with existing cerebral small vessel disease [86]. The Treat Stroke to Target (TST) trial showed that patients who had LDL-C < 70 mg/dL had better outcomes such as lower primary composite outcome of ischemic stroke, myocardial infarction, new symptoms leading to urgent coronary or carotid revascularization, or death from cardiovascular causes [87].

7. When to consider intensification of lipid-modifying strategies

While individual clinicians and patients may consider any order and combination of cholesterol-lowering pharmacotherapies, the 2018 cholesterol guidelines and the 2022 ACC ECDP (Expert Consensus Decision Pathway) suggest an evidence-based practical approach [16,21]. Given the weight of the recommendations, payors tend to follow this advice, which means that use of high-cost therapies beyond statins and ezetimibe has limited access for most patients except in prescribed circumstances. Ultimately, these guiding documents also stress the importance of shared clinician-patient decision-making that prioritizes evidence of benefit, safety, tolerability, potency (outlined in **Supplemental Table 2**) [16], ease of use, affordability, availability, and patient acceptance. With few exceptions, pharmacologic LDL-C lowering should begin with statins, followed by ezetimibe, PCSK9 mAb, then bempedoic acid. Inclisiran is an alternative to the PCSK9 mAb when available and preferred. Use of non-statin and non-ezetimibe therapeutics is limited to approved circumstances. Bile acid sequestrants are rarely used because of modest potency, poor tolerability, and lack of cardiovascular outcomes benefit in patients already treated with a statin. Treatment with lomitapide and evinacumab is reserved for individuals with homozygous FH.

Addition of non-statin pharmacotherapy is determined by specific LDL-C thresholds. The highest risk conditions have the lowest LDL-C threshold, promoting intensive treatment for those with the highest burden of atherosclerosis most likely to benefit from the additional pharmacotherapy. Fig. 2 provides a phenotype-driven approach to shared-decision making adapted and modified from the 2022 ACC ECDP, using recently published data. The current FDA approved indications for bempedoic acid include adults with heterozygous FH, patients with existing ASCVD, and since March 22, 2024, individuals at high risk for ASCVD who are unable to take recommended statin therapy, including those not taking a statin [88].

8. Beyond statin therapies

8.1. Ezetimibe (FDA approval: 2002)

Ezetimibe reduces cholesterol absorption, by inhibiting Niemann-Pick C1-like 1 (NPC1L1) at the brush border of the small intestine [21,70]. This mechanism reduces chylomicron-cholesterol delivery to the liver, thereby reducing hepatic cholesterol levels, resulting in upregulation of LDL-receptors, and effectively increasing cholesterol clearance from the blood stream. It also effects hepato-biliary sterol transport, but its enterocyte effect seems to predominate the impact on serum LDL-C. Ezetimibe is available in a fixed dose of 10 mg oral daily. It reduces LDL-C by a mean 18 % as monotherapy and by 25 % when added to statins [21,70], though individual results may vary considerably. Moreover, it can modestly reduce hs-CRP levels when used in combination with statins [89,90]. The IMPROVE IT trial, which studied ezetimibe in conjunction with a moderate-intensity statin in patients who had recent (within ten days) acute coronary syndrome, showed a 2 % decrease in ASCVD over a 7-year follow-up period [22]. The Study of Heart and Renal Protection (SHARP study) showed the safety of combining ezetimibe and statins in patients with chronic kidney disease [21,91]. Evidence regarding the primary prevention of ASCVD with ezetimibe is summarized in **Suppl Table 3** [91–96]. However, hard-outcome placebo-controlled data remain limited in the primary prevention setting. The common side effects include upper respiratory tract infection (4 %) and sinusitis and arthralgia (3 %). In rare cases, the addition of ezetimibe to statin therapy required discontinuation due to adverse events, such as myalgias, rhabdomyolysis, transaminase increases, and gastrointestinal adverse events [97].

8.2. Bile acid sequestrants (1973)

Bile acid sequestrants like colesevelam, cholestyramine, and colestipol are non-absorbed polymers which absorbs bile acids in the intestines and impede their reabsorption. As the bile acid pool is decreased, the hepatic enzyme 7-alpha-hydroxylase is up-regulated which can increase the conversion of cholesterol to bile acids, depleting intra-hepatic cholesterol. This results in increased transcription and activity of the cholesterol biosynthetic enzyme HMG-CoA

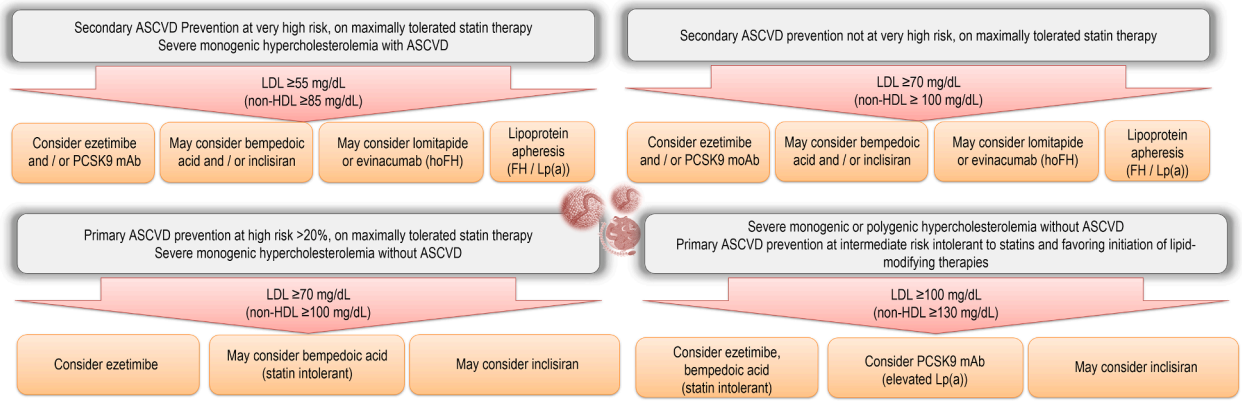

Fig. 2. Therapeutic thresholds in primary and secondary prevention of ASCVD. Individualized approach to the reduction of the lipoprotein-driven risk of ASCVD should be based on the: 1) preferred route of administration, 2) preferred frequency of administration, 3) medication-specific side effects, 4) clinical profile of the patient, 5) LDL-lowering potential, 6) Lp(a)-lowering potential. **As of 2024, bempedoic acid is FDA-approved for primary prevention of ASCVD and FH with or without maximally tolerated statin therapy. No data on safety and efficacy exists on combining monoclonal antibodies to PCSK9 and siRNA to PCSK9. Therefore, this group does not recommend this combination at this time. Intensification of the lipid-lowering therapy and aggressive LDL-C lowering should be considered in individuals without a prior index event but severe coronary artery calcification, such CAC score ≥1000 [124] or left main coronary artery involvement [125] The presence of any degree of coronary calcification should warrant at least a moderate potency statin.

reductase and greater numbers of hepatic LDL-receptors with increased clearance of LDL from the blood. Colesevelam, cholestyramine, and colestipol are indicated for reduction of LDL-C in patients with primary dyslipidemia. Colesevelam may be used for glycemic control in adults with type 2 diabetes, as it enhances glucose-stimulated glucagon-like peptide 1, and to decrease LDL-C in boys and post-menarchal girls with heterozygous FH. Bile resins should be avoided in individuals with baseline TG above 250 mg/dL since they may raise the TG levels via decreased activation of the farnesoid X receptor (FXR receptor). In individuals with thyrotoxicosis cholestyramine decreases reabsorption of thyroid hormone from enterohepatic circulation. The NHLBI's Lipid Research Clinic's (LRC) Coronary Primary Prevention Trial with cholestyramine in middle-aged men lowered LDL-C by 11 %, resulting in a 19 % reduction in nonfatal and a 24 % reduction in fatal myocardial infarction with no change in all-cause mortality [28]. The LDL-C lowering with cholestyramine is dose-dependent with 12 gs of the resin associated with an 18 % reduction in LDL-C. The effects of colesevelam and colestipol on cardiovascular outcomes have not been determined. This class is the only cholesterol-lowering class considered to be safe during pregnancy. Dosing of bile acid sequestrants can be challenging as it requires separation from other medications and the typical side effects include bloating, constipation, and hypertriglyceridemia. The main side effect of all three bile acid sequestrants is constipation and dyspepsia. These symptoms can be mitigated if cholestyramine is completely suspended in liquid several hours before intake as well as if diet is enriched with high fiber consumption. To reduce drug-drug interactions, it is recommended to administer other medications one hour before or four hours after taking cholestyramine.

8.3. Bempedoic acid (2020)

Bempedoic acid is a prodrug that requires conversion by the hepatic-specific very-long-chain acyl-CoA synthetase 1 (ASCVL1) into its active metabolite [34]. Thus, it is not activated outside the hepatocyte and may have a significant advantage for patients with statin intolerance. It inhibits cholesterol biosynthesis within the same pathway targeted by statins. Upregulation of LDL-receptor density results in increased clearance of LDL from the bloodstream. Bempedoic acid comes in a fixed dose of 180 mg, which is administered orally once daily. It has a half-life of 9 h, and it offers additional mean 15 %−25 % LDL lowering. A significant lowering in hs-CRP (average 33 %) has been observed. The combination of bempedoic acid and ezetimibe lowers LDL-C by an average of 35 % [98]. Bempedoic acid has been studied in individuals with statin intolerance, ASCVD, heterozygous FH on statin therapy, and in those not achieving adequate response to lipid-lowering therapy, with cardiovascular outcomes proportional to the degree of LDL-C lowering. Main side effects include hyperuricemia (26 %) and gout (11 %) in patients with prior gout history. Bempedoic acid treatment in the phase 3 trials was associated with small but reversible low-grade increases in serum creatinine, blood urea nitrogen, and uric acid in some individuals. No adjustments in bempedoic acid dosage are currently recommended for patients with renal impairment, except for end-stage renal disease due to lack of data. Small decreases in eGFR are secondary to drug-induced reduction in tubular secretion of creatinine due to inhibition of the tubular transporter of type 2 organic acids (OAT2) in the proximal tubular cells. Numerically a higher incidence of cholelithiasis in patients treated with bempedoic acid was observed in the CLEAR OUTCOMES trial [34].

8.4. PCSK9 inhibitors

PCSK9 (proprotein convertase subtilisin/kexin 9) is a hepatically-derived protein that regulates LDL-receptor expression. PCSK9 inhibition leads to an increase in LDL-receptor density on the liver surface, resulting in reduced serum LDL-C levels. There are two FDA-approved approaches: 1) human monoclonal antibodies; and 2) small interfering (si) RNAs.

8.5. Monoclonal antibodies (2015)

The two currently available medications are alirocumab and evolocumab. Alirocumab, given as 75 mg or 150 mg formulations every two weeks, can lower LDL-C by 45–58 % when used in combination with maximally tolerated statins. Evolocumab given 140 mg every 2 weeks can lower LDL-C by an average of 64 % or given 420 mg every 4 weeks can lower LDL-C by 58 %. Both medications have completed cardiovascular outcomes trials, the ODYSSEY Outcomes (alirocumab) and the FOURIER (evolocumab) trials, both showed 15 % relative risk reduction (1.5 % to 1.6 % absolute risk reduction) compared to placebo when added to statin therapy with or without ezetimibe in higher risk patients with pretreatment LDL-C above 70 mg/dL (alternative criteria included: nonHDL-C above 100 mg/dL in FOURIER, or nonHDL-C and apoB above 100 and 80 mg/dL, respectively in ODYSSEY OUTCOMES). A mortality benefit was noted in the ODYSSEY trial with hazard ratio, 0.71; 95 % CI, 0.56 to 0.90; $P_{\text{interaction}}$=0.007. Side effects for the class are rare. Adverse effects for evolocumab include headaches (11 %) and nasopharyngitis

(4–12 %) and for alirocumab include injection side reactions (4–17 %) and hypersensitivity reactions (9 %). PCSK9 inhibitors did not increase the risk of new-onset diabetes, nor did they worsen glycemia [99]. Discontinuation rates of PCSK9 mAb are the same as that for placebo in RCTs.

8.6. Small interfering RNAs (2021)

Inclisiran is a double stranded small interfering ribonucleic acid (siRNA) transported in lipid nanoparticle expressing GalNac (N-acetylgalatcosamine). GalNac enables rapid selective hepatic uptake and clearance of medicine from blood stream within 24 h. The single active strand persists on the RNA-induced silencing complex (RISC) disabling PCSK9 mRNA transcription for more than 6 months, with durable LDL-C reductions associated. It is indicated for lowering LDL-C in adults with primary hyperlipidemia in the primary and secondary prevention settings, in addition to diet and statin therapy. Inclisiran is particularly useful in individuals who would benefit from less frequent dosing: 284 mg subcutaneous on day 1, day 90, and then every 6 months. Inclisiran lowers LDL-C on average by 48–52 %. Adverse reactions reported by patients treated with inclisiran include injection site reaction (8 %) and antibody development (5 %). Other reported side effects included urinary tract infections, diarrhea, and dyspnea. A patient-level, pooled analysis of patients with heterozygous FH, ASCVD, or ASCVD risk equivalent on maximally tolerated statin-therapy demonstrated a 26 % reduction in the likelihood of non-adjudicated cardiovascular death, cardiac arrest, non-fatal myocardial infarction, and fatal and non-fatal stroke. In the pragmatic VICTORION-INITIATE clinical trial, addition of inclisiran immediately upon failure to reach LDL-C $<$ 70 mg/dL despite receiving maximally tolerated statins resulted in significantly higher proportion of individuals reaching LDL-C levels below 70 mg/dL (82% vs. 22 %) and 55 mg/dL (72% vs. 9 %) with no significant increase in the rates of reported serious adverse events, as compared to usual care patients receiving treatment under community standards [100]. The cardiovascular outcomes RCTs are ongoing; the estimated trial completion for the ORION 4 is July 2026 (ClinicalTrials.gov Identifier: NCT03705234) and for the VITORIAN-2P is October 2027 (NCT05030428). Inclisiran in addition to high-intensity statin, ezetimibe, or apheresis did not reduce LDL-C levels in patients with homozygous FH (the ORION-5 trial;, mean age, 43 years, 61 % women, baseline LDL-C 294 mg/dL) [101].

8.7. Evinacumab (2021)

Evinacumab is a human monoclonal antibody which inhibits angiopoietin like 3 (ANGPTL3) administered as a monthly intravenous infusion. Circulating ANGPTL3 inhibits the TG-hydrolytic activity of lipoprotein lipase (LPL), so ANGPTL3 inhibition enables VLDL delipidation and subsequent clearance, which likely reduces downstream LDL particle formation. In addition, in individuals with homozygous FH who have very little or no LDL-receptor expression, evinacumab is shown to reduce LDL-C through an LDL-receptor independent pathway. Thus, it is indicated in patients who are 12 years or older with homozygous FH. The mean reduction in LDL-C is 49 %−52 %. Because of the potential for fetal toxicity and hypersensitivity reactions, pregnancy testing is required prior to starting this medication in female patients and a warning to stop the drug if hypersensitivity reaction occurs. To date, no drug-drug interactions have been identified. The phase 3 trial was focused on the LDL-C changes from the baseline. No CV outcomes trials/program has been initiated for evinacumab to date. Similar to other monoclonal antibodies, some common adverse effects include nasopharyngitis (16 %) and influenza-like symptoms (7 %).

8.8. Lomitapide (2012)

Lomitapide inhibits microsomal triglyceride transfer protein (MTP), which is a cellular protein needed for the assembly and secretion of triglyceride-rich apolipoprotein B-containing lipoproteins, facilitating transport of dietary and endogenous fat by the intestine and liver. It has been FDA approved for patients with homozygous FH aged $\geq$18 years. Lomitapide reduces LDL in a dose-dependent manner by 25–50 %. In patients receiving lipoprotein apheresis, concomitant use of lomitapide can reduce the frequency of the procedures. The most commonly reported adverse events were mild-to-moderate in intensity gastrointestinal symptoms, increased risk of hepatic steatosis, steatohepatitis and liver cirrhosis. In the USA, lomitapide is available through a restricted JUXTAPID REMS program [39]. Adherence to a low-fat diet ($<$20 % of daily total energy from fat) and restriction of alcohol consumption can significantly improve tolerability of the drug. Monitoring of liver function tests (alanine and aspartate aminotransferases, alkaline phosphatase, total bilirubin) before initiating treatment and prior to each increase of dose is recommended. Referral to a hepatologist should be considered if abnormal ($\geq$3 upper limit of norm) ALT and AST testing persists. In patients with end-stage renal disease receiving dialysis or mild hepatic impairment (Child-Pugh A) daily dosing should not exceed 40 mg.

8.9. Lipoprotein apheresis

Six different lipoprotein apheresis systems are commercially available across the world, though only one is used in the U.S. [102]. The FDA indications for the use of lipoprotein apheresis in the U.S. include: 1) homozygous FH with LDL-C $>$=500mgdL, 2) heterozygous FH with LDL-C $>$=300 mg/dL, 3) heterozygous FH with ASCVD with LDL-C $>$=100 mg/dL, 4) clinical FH and established ASCVD with LDL-C $\geq$ 100 mg/dL; Lp(a) $\geq$60 mg/dL (120 nmol/L); all on maximally tolerated lipid-lowering treatment. This represents the only FDA-approved therapeutic option for patients with elevated Lp(a), in the setting of clinical FH and established ASCVD.

On average, greater than 60 % of atherogenic apoB-containing lipoproteins are immediately reduced following a single procedure. The higher the baseline lipid and lipoprotein levels and the greater the quantity of treated plasma/blood, the greater the observed relative reduction in apoB-containing lipoproteins. Lipoprotein apheresis results in an average of 68 % total cholesterol lowering, 85 % LDL-C lowering, 70 % Lp(a) lowering, and 64 % TG lowering per session. Gradual increase in the LDL-C and Lp(a) levels after lipoprotein apheresis session to pre-treatment levels is expected within 2–4 weeks and 1–3 weeks, respectively, depending on the duration of treatment. There is a non-linear rebound of LDL-C between the apheresis sessions with a consistent relationship between regular treatment sessions, resulting in a time-averaged reduction of LDL cholesterol of around 48 % between apheresis intervals [103]. Simultaneous lipid-lowering therapy targeting LDL and Lp(a) enhances the efficacy of lipoprotein apheresis and offers a valuable therapeutic approach in patients with difficult to control LDL-C levels. Treatment sessions acutely reduce the PCSK9 levels by the mean of 51 % including the removal of LDL-bound PCSK9 and apoB-free PCSK9.

Lipoprotein apheresis additionally modulates levels of pro-inflammatory and anti-inflammatory factors, prothrombotic, fibrinolytic, and rheologic markers. It is associated with an increase in expression of endothelium-derived nitric oxide and factors affecting vascular permeability and a decrease in PCSK9. Lipoprotein apheresis alters the proteomics of the lipoprotein particles, including reduction in the concentration of the oxidized-LDL-C and Lp(a) particles, and reduction of proinflammatory apoE4 bound to HDL particles and remnant lipoproteins. Other effects attributed to lipoprotein apheresis include improvement in blood rheology, endothelial function, microvascular flow, myocardial perfusion, reduction in circulating inflammatory markers, however the exact mechanism for the significant outcomes benefit noted in observational data has not fully been elucidated [102].

Lipoprotein apheresis can be successfully initiated as early as age 2 in children with FH. Case-based evidence supports use of various types of selective lipoprotein apheresis in pregnancy. The safety and efficacy of combined long-term lipoprotein apheresis and lipid-lowering therapy for the prevention of ASCVD has been reported since 1998 with multiple observational studies showing substantial improvement in major cardiovascular events on the order of 65–95 % reduction in MACE when treated individuals were compared to their pre-treatment event rates or standard of care [52,104-109]. In a sham-controlled randomized controlled trial of individuals with elevated Lp(a), refractory angina, lipoprotein apheresis improved myocardial perfusion, atheroma burden, exercise capacity and symptoms [53]. The occurrence of adverse events is low and is typical of other extracorporeal procedures. The treatment is usually done on a biweekly basis and is dependent on the inter-apheresis LDL-C levels and patient acceptance. The most common adverse event is hypotension (<2 %). The incidence of all other adverse events, which include flushing and/or blotching, chest pain, anemia, abdominal discomfort, hemolysis, and arrhythmia, is less than 1 %. Difficulty obtaining venous access may require either insertion of a port or surgical creation of an arteriovenous fistula.

9. Investigational lipid-modifying therapies

9.1. Obicetrapib

Trials with obicetrapib offer promise for efficacy and safety. Obecitrapib reduces LDL-C by decreasing the transfer of HDL cholesteryl ester into TG-rich lipoproteins and increased hepatic LDL-C clearance. In a phase 2b ROSE trial obicetrapib showed a 40 % and 50 % reduction in LDL-C levels and 24 % and 40 % reduction in ApoB levels at doses of 5 and 10 mg, respectively [110]. Dose-dependent reduction in Lp(a) of 55 % was reported. There are three ongoing phase 3 clinical trials, including BROADWAY (NCT05142722) and BROOKLYN (NCT05425745) in patients with heterozygous FH, and PREVAIL (NCT05202509) in patients with a history of ASCVD, assessing cardiovascular outcomes with anticipated completion in 2026. Obicetrapib has been studied in combination with high-intensity statins and ezetimibe [111]. The most prevalent adverse events were gastrointestinal disorders (5 %) and nervous system disorders (primarily headache) [110]. Myalgias have not been significantly increased with obicetrapib.

9.2. Lerodalcibep

Lerodalcibep is a third generation PCSK9 inhibitor, a novel small recombinant fusion protein of PCSK9-binding domain and human serum albumin. To date, the phase 3 program continues to enroll patients across the spectrum of ASCVD risk. The LIBerate-HR (High Risk; mean age 65 years, 47 % female) trial demonstrated reduction in the LDL-C, Lp (a), and apoB levels, of 56 %, 33 %, and 43 % using a monthly injection of lerodalcibep in patients with established or at high risk for ASCVD on stable statin therapy (publication in review) [112]. Among patients with genetically confirmed hoFH (mean age 29 years; 55 % female), lerodalcibep reduced LDL-cholesterol levels by 9 % and evolocumab by 11 % after 24 weeks of treatment [113]. The LIBerate-HeFH trial showed an average of 59 % LDL-C lowering at week 24 in patients (mean age 53 years, 52 % female) with heFH as compared to placebo [114]. There was no difference in the incidence of adverse events related to glycemic control. The LIBerate-OLE (Open-Label Extension) study reported effects of continued treatment with subcutaneous lerodalcibep 300 mg beyond 24 weeks until week 48 in patients with heFH, 90 % of whom were on background statins and 51 % on ezetimibe. The intention-to-treat analysis showed a mean reduction of 49 % in LDL-C. ApoB and Lp(a) were reduced by 35 % and 20 %, respectively. No significant safety concerns were identified.

9.3. Macrocyclic Peptide (MK-0616)–PCSK9 Complex is an investigational oral PCSK9 inhibitor

It was tested in the phase 2b trial showing a dose-dependent LDL-C lowering effect up to 60 % with a 30 mg dose. The half-life of MK-0616 after single doses of 10, 35, 100, 200, and 300 mg on average ranges from 35 to 130 h [115]. MK-0616 was shown to be generally well-tolerated. The phase 3 program CORALreef was announced in 2023 and will focus on cardiovascular outcomes in those with 1) established ASCVD or those at intermediate to high risk; 2) heterozygous FH; 3) high ASCVD risk. Approximately 17,000 participants will be recruited across the phase 3 program with an estimated primary completion date in November 2029.

9.4. Gene editing and gene transfer targeting lipid metabolism

Gene editing aims to directly restore or disrupt genes of interest at the DNA level. Somatic non-integration gene therapy can transfer copies of normally functioning genes and coding DNA sequence into dysfunctional cells to tailor treatment of monogenic diseases. Somatic gene-editing therapy induces gene mutation in situ through gene disruption/deletion/insertion/replacement using endonuclease. Gene repair applications are limited to the treatment of monogenic disorders, while the potential applications of gene disruption are broader, including common forms of dyslipidemias. Human fibroblast-derived using pluripotent stem cells (iPSC) technology in homozygous FH were treated with CRISPR/SpCas9 nickase and a repair template aiming at restoring normal *LDLR* structure [116]. The VERVE (VERVE-101, VERVE-102, and VERVE-201) is an in vivo liver base DNA editing intervention targeting the *PCSK9* and *ANGPTL3* genes. The heart-1 phase 1b clinical trial used *PCSK9* target in patients with heterozygous FH and established ASCVD on oral standard-of-care therapy [117]. In this first-in-human study of patients, a 39–48 % LDL-C lowering and 47–84 % reduction in PCSK9 was observed. In the animal study, VERVE-101 lowered PSCK9 levels by 67 %−83 % and LDL-C by 49 %−69 %, depending on the dose and sustained at one year [117]. Off-target effects secondary to CRISPR (short for "clustered regularly interspaced short palindromic repeats") technology have not yet been observed. Further, in December 2023, the FDA granted approval for the world's first CRISPR–Cas9 gene editing therapy in sickle cell disease [118].

10. Impact of system failures

Clinical behaviors can be affected by education, incentives and nudges. Rising demand, process inefficiencies, and structural barriers may result in delayed provider response to clinical guidelines. This challenge can be addressed by the development of simple quality metrics [119]. The Center for Medicare & Medicaid Services (CMS) changed the lipid quality metric utilized by almost all health systems around the country in 2015, after the 2013 ACC/AHA Cholesterol Guideline was published and declared that evidence for dose titration and non-statin therapy was lacking at time of publication. Thus, CMS incentivized clinicians to prescribe statins, but did not offer any incentive for LDL-C goal achievement. Shortly after the 2013 Guideline, clinical trials have been published that support the "lower for longer" hypothesis but CMS has not yet reverted incentives for lowering LDL-C back to pre-2015 accounting. Nonetheless, based upon the evolving science, the updated 2018 AHA/ACC/Multisociety Guideline on the Management of Blood Cholesterol (a.k.a. the 2018 cholesterol guidelines) [16] affirms this relationship. Subsequent approval and recommendation for the use of evinacumab, bempedoic acid, and inclisiran by the 2022 ACC Expert Consensus Decision Pathway (ECDP) on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk further suggests a role for ongoing management and prescription of non-statins to augment foundational care with statins [21]. See Fig. 3 for timeline of events affecting incorporation

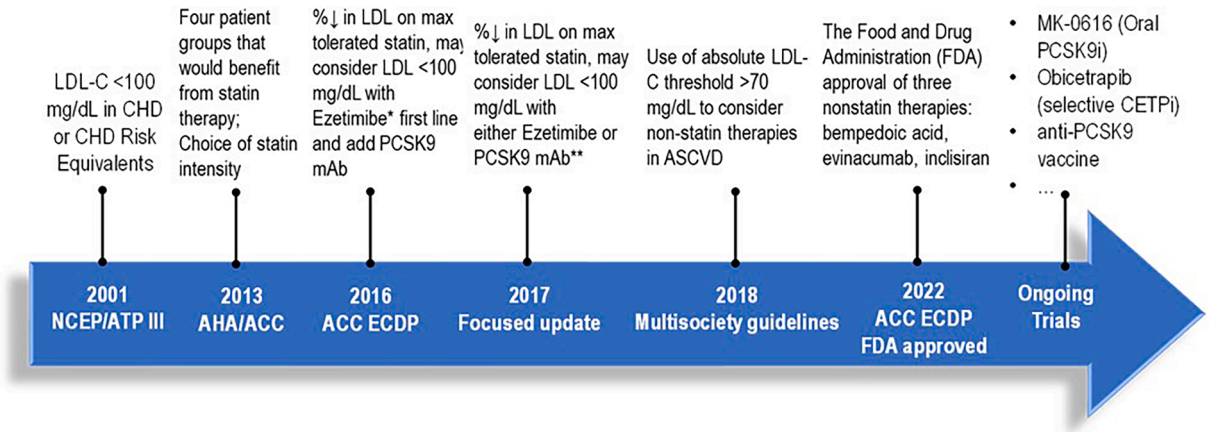

Fig. 3. Milestones in non-statin therapies for LDL-C lowering based on the data supporting the routine use of U.S. Food and Drug Administration (FDA)-approved non-statin drugs combined with statin therapy for LDL-C reduction with the goal of further reducing ASCVD events. Abbreviations: LDL-C: low density lipoprotein cholesterol; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel-III; PCSK9: Proprotein convertase subtilisin/kexin type 9; mAB: monoclonal antibody; ASCVD: Atherosclerotic cardiovascular disease; CETPi: cholesterol ester transfer protein inhibitor.

of evidence for statins and non-statins. **Supplemental Figure 1** provides examples of promising novel targeted therapies, using various drug delivery vehicles.

10.1. Implementation science and disparities of care in lipid management

Despite advanced therapies proven to be both safe and effective for optimal lipid lowering, there remains a substantial gap in use in clinical practice. Underserved populations experience even lower rates of intensive LDL-C lowering compared to general populations [120], as do women [121]. The obstacles to increased uptake are multi-factorial, stemming from lack of physician awareness, patient reluctance and nonadherence, prohibitive drug costs, complex approval processes, and inadequate payor incentives [122]. Resumption of pre-2015 outcome-focused LDL-C CMS metrics, rather than the current statin-based process standard, could go a long way to return the focus on LDL-C goal attainment for clinicians, promoting better care and outcomes for all populations, especially the underserved. Other approaches to improve adherence and access to care include universal provider education in health systems when newer therapies come to the market and electronic health record (EHR) based strategies that take advantage of automated detection by electronic phenotyping algorithms with linkage to best practice alerts, clinical decision support and decision aids [123]. Lastly, although patient assistance programs exist for those meeting requirements, medication cost remains an obstacle for a number of patients who neither qualify for these programs nor can afford the medications. Despite these cost issues, the uptake of advanced therapies remains limited even in those who are fully covered by insurance highlighting the fact that solutions will need to be multi-faceted in overcoming obstacles on the provider, patient and system level.

11. Conclusion

Multiple advanced treatments are currently available to address residual atherogenic lipoprotein risk beyond statin therapy. With every approximately 40 mg/dL reduction in LDL-C level with statins and non-statins, there is an average >20 % reduction in cardiovascular events illustrating the urgency to attain lower LDL-C goals. Guideline-directed care continues to support the role of statins as foundational, however, the evidence strongly supports consideration of LDL-C lowering with non-statins when statins alone are not adequate. An approach that targets residual risk due to LDL-C and other atherogenic particles, in addition to baseline patient risk, will improve outcomes for all. Better outcomes with higher adherence and patient satisfaction may also be achieved with combination therapies for atherogenic particles that are better tolerated and are more likely to achieve optimal lipoprotein levels. Impacting the behavior of prescribers, patients, and health systems through education, recognition of patients not at goal and incentives to optimize outcomes, may enable this process.

Funding

None.

Disclosures

Eugenia Gianos reports a relationship with Kaneka Corporation that includes: non-promotional speaking and lecture fees. Benjamin Hirsh reports a relationship with Kaneka Pharma America LLC that includes: consulting or advisory and with Amarin Pharma Inc that includes: consulting or advisory. Guy Mintz reports a relationship with Kaneka Corporation that includes: consulting or advisory and reports a relationship with Novartis that includes: consulting or advisory and speaking and lecture fees. Michael Shapiro reports a relationship with the following entities: 89bio Inc that includes funding grants, Esperion Therapeutics Inc that includes funding grants, Novartis that includes board membership, consulting or advisory, and funding grants, Ionis Pharmaceuticals Inc that includes board membership, consulting or advisory, and funding grants, a relationship with Merck & Co Inc that includes funding grants, New Amsterdam that includes board membership and funding grants, Amgen Inc that includes consulting or advisory and funding grants, Regeneron Pharmaceuticals Inc that includes consulting or advisory and funding grants, a relationship with Novo Nordisk Inc that includes board membership and consulting or advisory, Aidoc that includes consulting or advisory, Shanghai Pharma Biotherapeutics that includes consulting or advisory, EmendoBio Inc that includes consulting or advisory, Kaneka Corporation that includes consulting or advisory, Agepha that includes board membership, a relationship with Precision Biosciences Inc that includes board membership and a relationship with American Society for Preventive Cardiology that includes board membership. Daniel Soffer reports a relationship with Ionis Pharmaceuticals Inc that includes consulting or advisory, Novartis that includes board membership, a relationship with Amgen Inc that includes board membership and consulting or advisory, Amryt Pharmaceuticals Inc that includes consulting or advisory, GeninCode that includes consulting or advisory, PHAR that includes consulting or advisory, a relationship with Endless Health that includes consulting or advisory, and a relationship with National Lipid Association that includes board membership. If there are other authors, they declare that they have no known competing financial interests or

personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Maya Safarova: Data curation, Investigation, Writing – original draft, Writing – review & editing. **Tia Bimal:** Data curation, Investigation, Writing – original draft. **Daniel E. Soffer:** Conceptualization, Writing – review & editing. **Benjamin Hirsh:** Conceptualization, Writing – review & editing. **Michael D. Shapiro:** Conceptualization, Writing – review & editing. **Guy Mintz:** Writing – review & editing. **Agnes Cha:** Investigation, Writing – original draft. **Eugenia Gianos:** Conceptualization, Data curation, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Eugenia Gianos reports a relationship with Kaneka Corporation that includes: speaking and lecture fees. Benjamin Hirsh reports a relationship with Amarin Pharma Inc that includes: consulting or advisory. Benjamin Hirsh reports a relationship with Kaneka Corporation that includes: consulting or advisory. Guy Mintz reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory and speaking and lecture fees. Guy Mintz reports a relationship with Kaneka Corporation that includes: consulting or advisory. Michael Shapiro reports a relationship with 89bio Inc that includes: funding grants. Michael Shapiro reports a relationship with Esperion Therapeutics Inc that includes: funding grants. Michael Shapiro reports a relationship with Novartis Pharmaceuticals Corporation that includes: board membership, consulting or advisory, and funding grants. Michael Shapiro reports a relationship with Ionis Pharmaceuticals Inc that includes: board membership, consulting or advisory, and funding grants. Michael Shapiro reports a relationship with Merck & Co Inc that includes: funding grants. Michael Shapiro reports a relationship with New Amersterdam that includes: board membership and funding grants. Michael Shapiro reports a relationship with Amgen Inc that includes: board membership, consulting or advisory, and funding grants. Michael Shapiro reports a relationship with Regeneron Pharmaceuticals Inc that includes: consulting or advisory and funding grants. Michael Shapiro reports a relationship with Novo Nordisk Inc that includes: board membership and consulting or advisory. Michael Shapiro reports a relationship with Aidoc that includes: consulting or advisory. Michael Shapiro reports a relationship with Shanghai Pharma Biotherapeutics that includes: consulting or advisory. Michael Shapiro reports a relationship with Emendo Biotherapeutics that includes: consulting or advisory. Michael Shapiro reports a relationship with Kaneka Corporation that includes: consulting or advisory. Michael Shapiro reports a relationship with Agepha that includes: board membership. Michael Shapiro reports a relationship with Precision Biosciences Inc that includes: board membership. Michael Shapiro reports a relationship with American Society for Preventive Cardiology that includes: board membership. Daniel Soffer reports a relationship with Ionis Pharmaceuticals Inc that includes: consulting or advisory. Daniel Soffer reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory. Daniel Soffer reports a relationship with Amgen Inc that includes: board membership and consulting or advisory. Daniel Soffer reports a relationship with Amryt Pharmaceuticals Inc that includes: consulting or advisory. Daniel Soffer reports a relationship with GeninCode that includes: consulting or advisory. Daniel Soffer reports a relationship with PHAR that includes: consulting or advisory. Daniel Soffer reports a relationship with Endless Health that includes: consulting or advisory. Daniel Soffer reports a relationship with National Lipid Association that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Monique Carrero-Tagle for her assistance with coordinating this manuscript. We would also like to acknowledge the help of Gagan Riar in summarizing the data for efficacy and adverse effects.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100701.

References

[1] Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.
[2] Domanski MJ, Tian X, Wu CO, et al. Time course of LDL cholesterol exposure and cardiovascular disease event risk. J Am Coll Cardiol 2020;76:1507–16.
[3] Martin SS, Aday AW, Almarzooq ZI, et al. 2024 heart disease and stroke statistics: a report of us and global data from the american heart association. Circulation 2024;149:e347–913.
[4] Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015;385:1397–405.
[5] Virani SS. Non-HDL cholesterol as a metric of good quality of care: opportunities and challenges. Tex Heart Inst J 2011;38:160–2.
[6] Akyea RK, Kai J, Qureshi N, Iyen B, Weng SF. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. Heart 2019;105:975–81.
[7] Nordestgaard BG, Zilversmit DB. Large lipoproteins are excluded from the arterial wall in diabetic cholesterol-fed rabbits. J Lipid Res 1988;29:1491–500.
[8] Mortensen MB, Dzaye O, Bøtker HE, et al. Low-density lipoprotein cholesterol is predominantly associated with atherosclerotic cardiovascular disease events in patients with evidence of coronary atherosclerosis: the western denmark heart registry. Circulation 2023;147:1053–63.
[9] Hoogeveen RC, Ballantyne CM. Residual cardiovascular risk at Low LDL: remnants, lipoprotein(a), and inflammation. Clin Chem 2021;67:143–53.
[10] Wilkins JT, Li RC, Sniderman A, Chan C, DM Lloyd-Jones. Discordance between apolipoprotein b and ldl-cholesterol in young adults predicts coronary artery calcification: the CARDIA study. J Am Coll Cardiol 2016;67:193–201.
[11] Glavinovic T, Thanassoulis G, de Graaf J, Couture P, Hegele RA, Sniderman AD. Physiological bases for the superiority of apolipoprotein B over low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol as a marker of cardiovascular risk. J Am Heart Assoc 2022;11:e025858.
[12] Safarova MS, Kullo IJ. My approach to the patient with familial hypercholesterolemia. Mayo Clin Proc 2016;91:770–86.
[13] Jovanovski E, Yashpal S, Komishon A, et al. Effect of psyllium (Plantago ovata) fiber on LDL cholesterol and alternative lipid targets, non-HDL cholesterol and apolipoprotein B: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2018;108:922–32.
[14] Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. N Engl J Med 2002;347:1483–92.
[15] Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. Circulation 2022;146:e18–43.
[16] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the american college of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2019;139:e.1082-e143.
[17] Ginsberg HN, Rosenson RS, Hovingh GK, et al. LDL-C calculated by Friedewald, Martin-Hopkins, or NIH equation 2 versus beta-quantification: pooled alirocumab trials. J Lipid Res 2022;63:100148.
[18] Wilson PWF, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: practical recommendations a scientific statement from the national lipid association writing group. J Clin Lipidol 2021;15:629–48.
[19] Endo A, Kuroda M, Tanzawa K. Competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypocholesterolemic activity. FEBS Lett 1976;72:323–6.
[20] Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581–90.
[21] Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC expert consensus decision pathway on the role of Nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a Report of the

American College of cardiology solution set oversight committee. J Am Coll Cardiol 2022;80:1366–418.
[22] Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–97.
[23] Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181–92.
[24] Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1092–7.
[25] Lexidrug. Pediatric and neonatal lexi-drugs online. Waltham, MA: UpToDate, Inc. Accessed January 10, 2024.
[26] Clinical Resource. Non-Statin lipid-lowering agents. pharmacist's letter/prescriber's letter. Therapeutic Research Center; February 2022.
[27] Organon LLC. Zetia [Highlights of Prescribing Information]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021445s042lbl.pdf. Revised 7/2023. Accessed March 21, 2024.
[28] The Lipid Research Clinics. The lipid research clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351–64.
[29] Davidson MH, Dillon MA, Gordon B, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. Arch Intern Med 1999;159:1893–900.
[30] Sprecher DL, Abrams J, Allen JW, et al. Low-dose combined therapy with fluvastatin and cholestyramine in hyperlipidemic patients. Ann Intern Med 1994;120:537–43.
[31] Pan HY, DeVault AR, Swites BJ, et al. Pharmacokinetics and pharmacodynamics of pravastatin alone and with cholestyramine in hypercholesterolemia. Clin Pharmacol Ther 1990;48:201–7.
[32] Simons LA, Simons J, Parfitt A. Successful management of primary hypercholesterolaemia with simvastatin and low-dose colestipol. Med J Aust 1992;157:455–9.
[33] Sankyo. D. Welcol [Highlights of Prescribing Information]. Revised 2011 ed: U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022362s007lbl.pdf Revised 2011. Accessed March 21, 2024.
[34] Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med 2023;388:1353–64.
[35] Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. J Am Heart Assoc 2019;8:e011662.
[36] Esperion. Nexletol [Highlights of Prescribing Information]. U.S. Food and drug administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211616s000lbl.pdf Accessed March 21, 2024.
[37] Giammanco A, Cefalù AB, Noto D, Averna MR. Therapeutic options for homozygous familial hypercholesterolemia: the role of Lomitapide. Curr Med Chem 2020;27:3773–83.
[38] AMRYT Pharma. Juxtapid registries. 2023. Available at: https://juxtapid.com/juxtapid-registries/#:~:text=To%20learn%20more%20about%20the,%2D877%2D902%2D4099. Accessed January 17, 2024.
[39] U.S. Food and Drug Administration, Department of Health and human services. Supplement approval. Rems assessment plan revision. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/203858Orig1s013,s016ltr.pdf Access March 21, 2024.
[40] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–107.
[41] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.
[42] Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531–40.
[43] Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2541–8.
[44] Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014;370:1809–19.
[45] Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase Subtilisin/Kexin Type 9 antibodies in adults with hypercholesterolemia: a systematic review and Meta-analysis. Ann Intern Med 2015;163:40–51.
[46] Amgen Inc. Repatha [Highlights of Prescribing Information]. U.S. Food and Drug administration website https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125522orig2s000lbl.pdf. Revised 02/2021. Accessed March 21, 2024.
[47] Regeneron Pharmaceuticals, Inc. Praulent [Highlights of Prescribing Information]. U.S. Food and Drug Administration website https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125559s029s030lbl.pdf. Revised 04/2021. Accessed March 21, 2024.
[48] Ray KK, Wright RS, Kallend D, et al. Two Phase 3 trials of inclisiran in patients with elevated LDL Cholesterol. N Engl J Med 2020;382:1507–19.
[49] Novartis Pharmaceuticals Corporation. Leqvio [Highlights of Prescribing Information]. U.S. Food and Drug Administration website https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214012lbl.pdf. Accessed March 21, 2024.
[50] Raal FJ, Rosenson RS, Reeskamp LF, et al. Evinacumab for homozygous familial hypercholesterolemia. N Engl J Med 2020;383:711–20.
[51] Regeneron Pharmaceuticals, Inc. Evkeeza [Highlights of Prescribing Information]. U.S. Food and Drug Administration website https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761181s000lbl.pdf. Accessed March 21, 2024.
[52] Kroon AA, Aengevaeren WR, van der Werf T, et al. Effect of aggressive versus conventional lipid lowering treatment on coronary atherosclerosis. Circulation 1996;93:1826–35.
[53] Khan TZ, Hsu LY, Arai AE, et al. Apheresis as novel treatment for refractory angina with raised lipoprotein(a): a randomized controlled cross-over trial. Eur Heart J 2017;38:1561–9.
[54] Safarova MS, Ezhov MV, Afanasieva OI, et al. Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography. Atheroscler Suppl 2013;14:93–9.
[55] McGowan MP. Emerging low-density lipoprotein (LDL) therapies: management of severely elevated LDL cholesterol–the role of LDL-apheresis. J Clin Lipidol 2013;7:S21–6.
[56] NewAmsterdam Pharma. Randomized study to evaluate the effect of Obicetrapib on top of maximum tolerated lipid-modifying therapies (BROADWAY). U.S. National Library of Medicine; 2023.
[57] NewAmsterdam Pharma. Cardiovascular outcome study to evaluate the effect of Obicetrapib in patients with cardiovascular disease (PREVAIL). U.S. National Library of Medicine; 2023.
[58] NewAmsterdam Pharma. Evaluate the effect of obicetrapib in patients with Hefh on top of maximum tolerated lipid-modifying therapies. (BROOKLYN). U.S. National Library of Medicine; 2023.
[59] Merck Sharp & Dohme LLC. A study of MK-0616 (Oral PCSK9 inhibitor) in adults with heterozygous familial hypercholesterolemia (MK-0616-017) CORALreef hefh. U.S. National Library of Medicine; 2023.
[60] Merck Sharp & Dohme LLC. A study of MK-0616 (Oral PCSK9 inhibitor) in adults with hypercholesterolemia (MK-0616-013) CORALreef lipids. U.S. National Library of Medicine; 2023.
[61] Merck Sharp & Dohme LLC. MK-0616 (Oral PCSK9 inhibitor) cardiovascular outcomes study (MK-0616-015) CORALreef outcomes. U.S. National Library of Medicine; 2023.
[62] Jiyan C, Li L, Gao X, et al. PCSK9 monoclonal antibody recaticimab in adult heterozygous familial hypercholesterolemia (REMAIN-3): a multicenter, randomized, double-blind, placebo-controlled phase 3 study. J Am Coll Cardiol 2024;83:1707.
[63] Daghlas I, Gill D. Low-density lipoprotein cholesterol and lifespan: a Mendelian randomization study. Br J Clin Pharmacol 2021;87:3916–24.
[64] Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol 2012;60:2631–9.
[65] Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med 2019;381:1547–56.
[66] Kusters DM, Avis HJ, de Groot E, et al. Ten-year follow-up after initiation of statin therapy in children with familial hypercholesterolemia. JAMA 2014;312:1055–7.
[67] Mendieta G, Pocock S, Mass V, et al. Determinants of progression and regression of subclinical atherosclerosis over 6 years. J Am Coll Cardiol 2023;82:2069–83.
[68] Devesa A, Ibanez B, Malick WA, et al. Primary prevention of subclinical atherosclerosis in young adults: JACC review topic of the week. J Am Coll Cardiol 2023;82:2152–62.
[69] Ibanez B, Fernández-Ortiz A, Fernández-Friera L. Progression of early subclinical atherosclerosis (PESA) study: JACC focus seminar 7/8. J Am Coll Cardiol 2021;78:156–79.
[70] Zhao Z, Tuakli-Wosornu Y, Lagace TA, et al. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet 2006;79:514–23.
[71] Hooper AJ, Marais AD, Tanyanyiwa DM, Burnett JR. The C679X mutation in PCSK9 is present and lowers blood cholesterol in a Southern African population. Atherosclerosis 2007;193:445–8.
[72] Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–72.
[73] Romeo S, Yin W, Kozlitina J, et al. Rare loss-of-function mutations in ANGPTL family members contribute to plasma triglyceride levels in humans. J Clin Invest 2009;119:70–9.
[74] Musunuru K, Pirruccello JP, Do R, et al. Exome sequencing, ANGPTL3 mutations, and familial combined hypolipidemia. N Engl J Med 2010;363:2220–7.
[75] Safarova MS, Satterfield BA, Fan X, et al. A phenome-wide association study to discover pleiotropic effects of. NPJ Genom Med 2019;4:3.
[76] Gaba P, O'Donoghue ML, Park JG, et al. Association between achieved low-density lipoprotein cholesterol levels and long-term cardiovascular and safety outcomes: an analysis of FOURIER-OLE. Circulation 2023;147:1192–203.
[77] Schwartz GG, Szarek M, Bhatt DL, et al. Transiently achieved very low LDL-cholesterol levels by statin and alirocumab after acute coronary syndrome are associated with cardiovascular risk reduction: the ODYSSEY OUTCOMES trial. Eur Heart J 2023;44:1408–17.
[78] Schwartz GG, Szarek M, Bittner VA, et al. Lipoprotein(a) and benefit of PCSK9 inhibition in patients with nominally controlled LDL cholesterol. J Am Coll Cardiol 2021;78:421–33.
[79] Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on Lipoprotein(a) and cardiovascular risk after acute coronary syndrome. J Am Coll Cardiol 2020;75:133–44.

[80] O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. Circulation 2019;139:1483–92.
[81] Giugliano RP, Wiviott SD, Blazing MA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT trial. JAMA Cardiol 2017;2:547–55.
[82] Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the american heart association. Arterioscler Thromb Vasc Biol 2019;39:e38–81.
[83] Giugliano RP, Mach F, Zavitz K, et al. Design and rationale of the EBBINGHAUS trial: a phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy-A cognitive study of patients enrolled in the FOURIER trial. Clin Cardiol 2017;40:59–65.
[84] O'Donoghue ML, Giugliano RP, Wiviott SD, et al. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. Circulation 2022;146:1109–19.
[85] Goldstein LB, Toth PP, Dearborn-Tomazos JL, et al. Aggressive LDL-C lowering and the brain: impact on risk for dementia and hemorrhagic stroke: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2023;43. e404-e42.
[86] Amarenco P, Benavente O, Goldstein LB, et al. Results of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial by stroke subtypes. Stroke 2009;40:1405–9.
[87] Amarenco P, Kim JS, Labreuche J, et al. Benefit of targeting a LDL (Low-Density Lipoprotein) cholesterol <70 mg/dL during 5 years after ischemic stroke. Stroke 2020;51:1231–9.
[88] Esperion. U.S. FDA approves broad new labels for NEXLETOL® and NEXLIZET® to prevent heart attacks and cardiovascular procedures in both primary and secondary prevention patients, regardless of statin use. 2024. Available at: https://www.esperion.com/news-releases/news-release-details/us-fda-approves-broad-new-labels-nexletolr-and-nexlizetr-prevent. Accessed March 22, 2024.
[89] Amarenco P, Bogousslavsky J, Callahan A, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–59.
[90] Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. Atherosclerosis 2018;277:195–203.
[91] Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160:785–94. .e10.
[92] Fleg JL, Mete M, Howard BV, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol 2008;52:2198–205.
[93] Kastelein JJ, Sager PT, de Groot E, Veltri E. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. Am Heart J 2005;149:234–9.
[94] Meaney A, Ceballos G, Asbun J, et al. The VYtorin on Carotid intima-media thickness and overall arterial rigidity (VYCTOR) study. J Clin Pharmacol 2009;49:838–47.
[95] Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343–56.
[96] Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or Older (EWTOPIA 75): a Randomized, controlled trial. Circulation 2019;140:992–1003.
[97] Kashani A, Sallam T, Bheemreddy S, Mann DL, Wang Y, Foody JM. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. Am J Cardiol 2008;101:1606–13.
[98] Ruscica M, Sirtori CR, Carugo S, Banach M, Corsini A. Bempedoic acid: for whom and when. Curr Atheroscler Rep 2022;24:791–801.
[99] Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:941–50.
[100] Koren MJ, Rodriguez F, East C, et al. An "Inclisiran First" strategy vs usual care in patients with atherosclerotic cardiovascular disease. J Am Coll Cardiol 2024;83:1939–52.
[101] Raal F, Durst R, Bi R, et al. Efficacy, safety, and tolerability of Inclisiran in patients with homozygous familial hypercholesterolemia: results from the ORION-5 randomized clinical trial. Circulation 2024;149:354–62.
[102] Safarova MS, Moriarty PM. Lipoprotein apheresis: current recommendations for treating familial hypercholesterolemia and elevated lipoprotein(a). Curr Atheroscler Rep 2023;25:391–404.
[103] Thompson GR, Barbir M, Davies D, et al. Efficacy criteria and cholesterol targets for LDL apheresis. Atherosclerosis 2010;208:317–21.
[104] Thompson GR, Maher VM, Matthews S, et al. Familial Hypercholesterolaemia regression study: a randomised trial of low-density-lipoprotein apheresis. Lancet 1995;345:811–6.
[105] Jaeger BR, Richter Y, Nagel D, et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. Nat Clin Pract Cardiovasc Med 2009;6:229–39.
[106] Leebmann J, Roeseler E, Julius U, et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. Circulation 2013;128:2567–76.
[107] Ezhov MV, Afanasieva OI, Il'ina LN, et al. Association of lipoprotein(a) level with short- and long-term outcomes after CABG: the role of lipoprotein apheresis. Atheroscler Suppl 2017;30:187–92.
[108] Aengevaeren WR, Kroon AA, Stalenhoef AF, Uijen GJ, van der Werf T. Low density lipoprotein apheresis improves regional myocardial perfusion in patients with hypercholesterolemia and extensive coronary artery disease. LDL-Apheresis Atherosclerosis Regression Study (LAARS). J Am Coll Cardiol 1996;28:1696–704.
[109] Kroon AA, van Asten WN, Stalenhoef AF. Effect of apheresis of low-density lipoprotein on peripheral vascular disease in hypercholesterolemic patients with coronary artery disease. Ann Intern Med 1996;125:945–54.
[110] Nicholls SJ, Ditmarsch M, Kastelein JJ, et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. Nat Med 2022;28:1672–8.
[111] Ballantyne CM, Ditmarsch M, Kastelein JJ, et al. Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. J Clin Lipidol 2023;17:491–503.
[112] Klug E. Efficacy and safety of lerodalcibep in patients at very high and high risk for cardiovascular disease - LIBerate-hr. Atlanta, GA: American College of Cardiology Annual Scientific Session; 2024.
[113] Raal F, Mehta V, Kayikcioglu M, et al. Randomized, open-label, cross-over, phase-3 study to evaluate efficacy and safety of LIB003 compared with evolocumab in homozygous familial hypercholesterolaemia patients on stable lipid-lowering therapy (liberate-HOFH). Atherosclerosis 2023;379. S24-S5.
[114] Raal F, Fourie N, Scott R, et al. Long-term efficacy and safety of lerodalcibep in heterozygous familial hypercholesterolaemia: the LIBerate-HeFH trial. Eur Heart J 2023;44:4272–80.
[115] Johns DG, Campeau LC, Banka P, et al. Orally bioavailable macrocyclic peptide that inhibits binding of PCSK9 to the low density lipoprotein receptor. Circulation 2023;148:144–58.
[116] Omer L, Hudson EA, Zheng S, Hoying JB, Shan Y, Boyd NL. CRISPR correction of a homozygous low-density lipoprotein receptor mutation in familial hypercholesterolemia induced pluripotent stem cells. Hepatol Commun 2017;1:886–98.
[117] Lee RG, Mazzola AM, Braun MC, et al. Efficacy and SAFETY OF AN INVESTIGATIONAL SINGLE-COURSE CRISPR base-editing therapy targeting. Circulation 2023;147:242–53.
[118] Sheridan C. The World's first CRISPR therapy is approved: who will receive it? Nat Biotechnol 2024;42(1):3–4.
[119] Virani SS, Aspry K, Dixon DL, et al. The importance of low-density lipoprotein cholesterol measurement and control as performance measures: a joint clinical perspective from the National Lipid Association and the American Society for Preventive Cardiology. Am J Prev Cardiol 2023;13:100472.
[120] Schreuder MM, Hamkour S, Siegers KE, et al. LDL cholesterol targets rarely achieved in familial hypercholesterolemia patients: a sex and gender-specific analysis. Atherosclerosis 2023;384:117117.
[121] Newman JD, Alexander KP, Gu X, et al. Baseline predictors of low-density lipoprotein cholesterol and systolic blood pressure goal attainment after 1 year in the ISCHEMIA trial. Circ Cardiovasc Qual Outcomes 2019;12:e006002.
[122] Desai NR, Farbaniec M, Karalis DG. Nonadherence to lipid-lowering therapy and strategies to improve adherence in patients with atherosclerotic cardiovascular disease. Clin Cardiol 2023;46:13–21.
[123] Hirsh BJ, Hirsch JS, Hmoud H, et al. A system approach to improving guideline-directed therapy for cardio-renal-metabolic conditions: the "beyond diabetes" initiative. Am J Prev Cardiol 2023;16:100608.
[124] Peng AW, Dardari ZA, Blumenthal RS, et al. Very high coronary artery calcium (≥1000) and association with cardiovascular disease events, non-cardiovascular disease outcomes, and mortality: results from MESA. Circulation 2021;143:1571–83.
[125] Razavi AC, Shaw LJ, Berman DS, et al. Left main coronary artery calcium and diabetes confer very-high-risk equivalence in coronary artery calcium >1,000. JACC Cardiovasc Imaging 2024. Feb 12:S1936-878X(24)00026-3.