Advancements in lipid-lowering therapy: the role of proprotein convertase subtilisin/kexin type 9 inhibitors and beyond in cardiovascular risk reduction

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Atherosclerotic cardiovascular disease (ASCVD) is a leading global cause of death. Although statins are the foundation of lipid-lowering therapy, many high-risk patients fail to achieve low-density lipoprotein cholesterol (LDL-C) targets due to intolerance or insufficient response. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have emerged as potent agents that address this residual risk. This review summarizes the clinical efficacy, safety, and mechanistic role of PCSK9 inhibitors in cardiovascular risk reduction. Relevant randomized trials, meta-analyses, and observational studies were analyzed, alongside emerging nonstatin therapies including bempedoic acid, inclisiran, and Angiopietin-like 3 inhibitors. PCSK9 inhibitors, such as alirocumab and evolocumab, have shown LDL-C reductions of up to 62% and significant decreases in major adverse cardiovascular events. Trials like Further cardiovascular outcomes research with PCSK9 inhibition in subjects With elevated risk (FOURIER) and Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab (ODYSSEY OUTCOMES) reported relative risk reductions of 15–24% in select populations. These agents also reduce lipoprotein(a) (Lp(a)) and stabilize atherosclerotic plaques. Additional therapies like inclisiran and bempedoic acid further expand treatment options, particularly for statin-intolerant patients. PCSK9 inhibitors offer a well-tolerated and effective approach to lowering LDL-C and mitigating cardiovascular risk. Their integration, along with emerging therapies, provides a comprehensive strategy to address residual ASCVD risk and improve patient outcomes. This review highlights the pivotal role of PCSK9 inhibitors in achieving significant LDL-C reduction and improving cardiovascular outcomes, especially in high-risk and statin-intolerant populations. By also targeting Lp(a) and promoting plaque stabilization, these agents address multiple contributors to residual ASCVD risk. Incorporating PCSK9 inhibitors and emerging nonstatin therapies into clinical practice offers a powerful strategy to enhance long-term cardiovascular prevention. *Coron Artery Dis* 36: 696–706 Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a chronic condition characterized by the buildup of atheromatous plaques within the walls of arteries, leading to stenosis or thrombosis [1]. ASCVD is the leading cause of death globally, responsible for 17.9 million deaths in 2019—32% of all fatalities worldwide—while in the USA, it remains the primary cause of mortality, with a crude death rate of 210.9 per 100 000 individuals [2]. The average age of all adults with ASCVD in the USA was 65.3 years; men comprised 55.5% of the total, and according to self-reports, 78.5, 12.6, and 8.9% of the population were Hispanic, non-Hispanic White, and non-Hispanic Black, respectively [3]. Despite the fact that women typically have a lower incidence of cardiovascular disease (CVD) than males, they have a worse prognosis and a greater fatality rate following acute cardiovascular events [4]. One study showed that Hispanic women had a higher in-hospital mortality rate (3.7%) than White women (2.5%) for patients under 65 with acute myocardial infarction (AMI), while men had a lower mortality rate in both groups, showing race and ethnicity have also altered cardiovascular outcomes from ASCVD [5]. The pathogenesis of ASCVD-related mortality and events, such as myocardial infarction (MI) and stroke, is driven by the progressive accumulation of atherosclerotic plaque within arterial walls. Lowering low-density lipoprotein cholesterol (LDL-C) remains the cornerstone of ASCVD risk reduction, as elevated LDL-C is a well-established causal factor in atherogenesis [6]. Type 2 diabetes (Odds

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ratio (OR): 7.6, 95% confidence interval (CI): 2.8–25), obesity, and metabolic syndrome are some of the lifestyle variables that have a significant impact on ASCVD, and some of the conventional risk factors include cigarette smoking (OR: 7.0, 95% CI: 2.8–20), physical inactivity, hypertension (OR: 2.54, 95% CI: 1.09–5.89), older age, and dyslipidemia [7,8]. Statins are the first-line therapy for lowering LDL-C by inhibiting 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol biosynthesis, thereby reducing intracellular cholesterol levels and upregulating LDL receptors (LDLRs) to enhance LDL-C clearance from circulation. However, a subset of patients may not attain optimal LDL-C reduction. Statin intolerance, primarily manifested as myalgia or other muscle-related symptoms, has been reported in approximately 5–30% of individuals receiving statin therapy, potentially hindering adherence and achievement of LDL-C targets [9]. Despite statin therapy, many patients fail to achieve sufficient LDL-C reduction, particularly those with elevated baseline LDL-C levels or individuals at very high ASCVD risk who require more aggressive lipid-lowering strategies. Consequently, residual ASCVD risk persists in patients receiving statins. Evidence suggests a proportional relationship between the magnitude and duration of atherogenic lipoprotein reduction and cardiovascular risk mitigation. Therefore, nonstatin pharmacologic agents are frequently utilized as adjunctive or alternative therapies to optimize lipid management and achieve target LDL-C levels [6,9]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, discovered in 2003, offer an alternative approach for patients requiring additional lipid-lowering therapy (LLT). PCSK9 regulates LDLR degradation in response to cellular cholesterol levels. LDLRs not bound to PCSK9 are more likely to be recycled to the cell membrane, leading to increased plasma LDL-C clearance [10]. Currently, evolocumab and alirocumab are the only Food and Drug Administration (FDA)-approved PCSK9 inhibitors, both of which are associated with a significant reduction in LDL-C and other apoB-containing lipoproteins [11]. Historically, the clinical benefit of nonstatin therapies in combination with statins for ASCVD risk reduction was not well established. However, this paradigm shifted in 2015 with the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). This randomized, double-blind, placebo-controlled study enrolled over 18 000 patients who had been hospitalized within the preceding 10 days for acute coronary syndrome (ACS), comparing the efficacy of simvastatin plus ezetimibe vs. simvastatin plus placebo. The addition of ezetimibe to statin therapy resulted in an incremental reduction in LDL-C and a significant improvement in cardiovascular outcomes. Moreover, ezetimibe offers practical advantages, including once-daily oral administration, cost-effectiveness, and a favorable safety profile with a low incidence of adverse effects [12]. In the same year as the IMPROVE-IT trial, the USA FDA approved two fully human monoclonal antibodies, evolocumab and alirocumab, designed for PCSK9. These self-administered injectable therapies emerged as a novel class of lipid-lowering agents, offering an additional strategy for reducing LDL-C levels in patients with persistently elevated cardiovascular risk [13]. PCSK9 inhibitors have been shown to reduce LDL-C levels by up to 60% when used as an adjunct to statin therapy. Furthermore, randomized controlled trials (RCT) have demonstrated their efficacy in lowering ASCVD risk, particularly in high-risk populations requiring intensive lipid-lowering strategies for secondary prevention [14,15]. In 2020, the FDA approved bempedoic acid, a nonstatin lipid-lowering agent shown to effectively reduce LDL-C levels. In 2023, a randomized, placebo-controlled trial involving nearly 14 000 patients with or at high risk for ASCVD who were unable or unwilling to take statins due to adverse effects demonstrated that bempedoic acid significantly reduced cardiovascular events. This agent is administered orally once daily and is generally well tolerated, though it is more expensive than generic ezetimibe. Notably, bempedoic acid is associated with an increased risk of gout and cholelithiasis [16,17]. As ongoing research continues to explore and refine these approaches, a multifaceted strategy for ASCVD risk reduction will be essential in improving patient outcomes and reducing the burden of CVD worldwide. This review will critically assess the evolving landscape of pharmacologic therapies targeting PCSK9, focusing on their efficacy, safety, and clinical integration in the management of ASCVD risk.

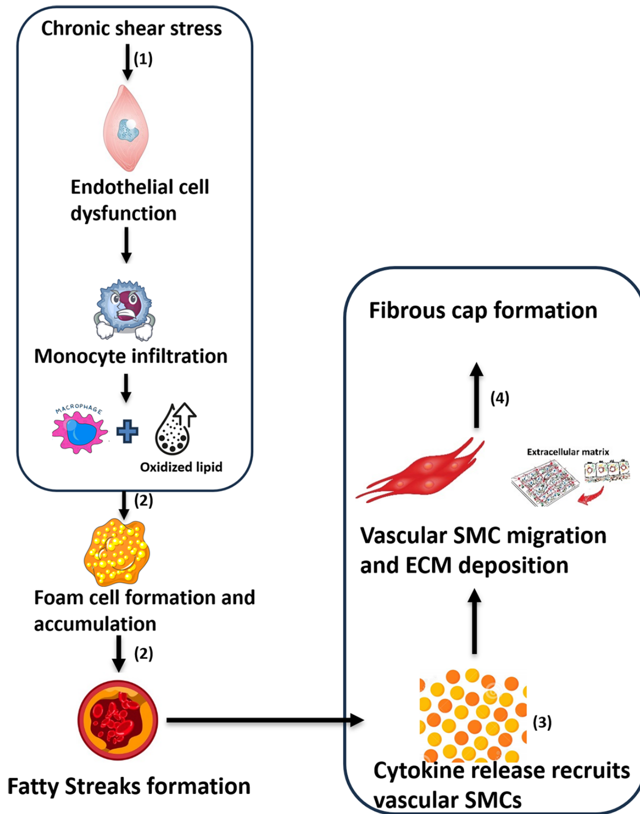
Pathophysiology

Atherosclerosis, a chronic inflammatory disease, is the underlying pathological process responsible for ASCVD, including coronary heart disease (CHD), stroke, and peripheral arterial disease. This condition is driven by the accumulation of LDL-C and residual lipoprotein particles in the arterial intima, particularly at sites of disturbed laminar flow, leading to endothelial dysfunction, inflammation, and plaque formation [18].

Role of low-density lipoprotein and lipoprotein(a) in atherogenesis

LDL, a heterogeneous class of lipoprotein particles, serves as the primary cholesterol carrier to peripheral tissues. Its hydrophilic membrane, composed of phospholipids, free cholesterol, and apolipoproteins (primarily ApoB-100), facilitates receptor-mediated endocytosis. However, the retention and subsequent modification of LDL in the subendothelial space serve as a key initiating event in atherogenesis. Modified LDL disrupts endothelial homeostasis by impairing nitric oxide-mediated vasodilation, stimulating endothelial cells to express adhesion molecules, and promoting monocyte recruitment [19]. Beyond oxidized LDL, at least three distinct forms of modified LDL—small dense,

Fig. 1



Inflammation-mediated atherosclerotic plaque development. Illustration of key stages: (1) Chronic shear stress induces endothelial dysfunction; (2) Monocyte infiltration and uptake of oxidized lipids form foam cells/fatty streaks; (3) Cytokine release recruits vascular smooth muscle cells (SMC); (4) Vascular SMC migration and extracellular matrix (ECM) deposition establish a fibrous cap over the lipid core.

electronegative, and desialylated LDL—have been identified in the bloodstream of atherosclerotic patients, each exhibiting pro-inflammatory and pro-atherogenic properties [20–22]. Similarly, lipoprotein(a) (Lp(a)), a highly atherogenic LDL-like particle bound to apolipoprotein(a), has been implicated in the acceleration of atherosclerosis through its inhibition of fibrinolysis, increased oxidative stress, and promotion of vascular inflammation [22].

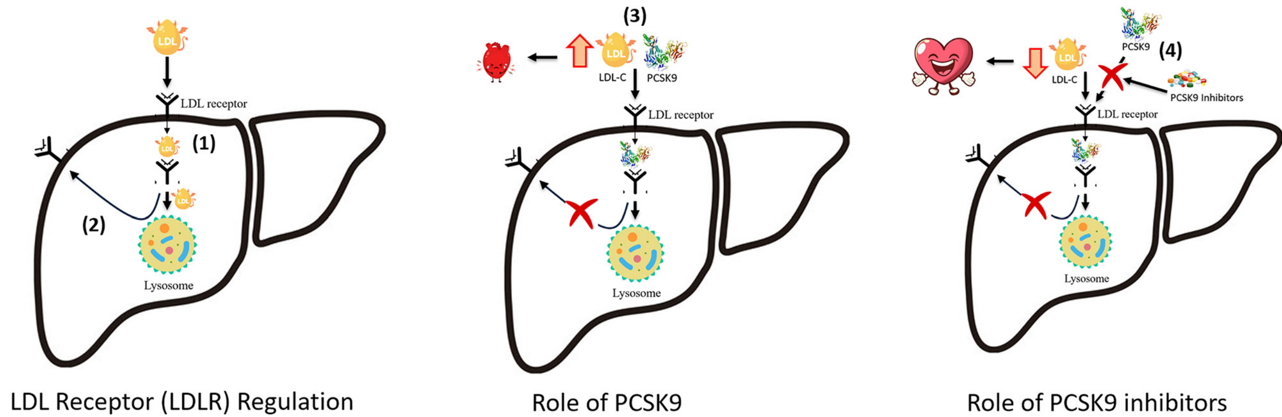
Inflammation and plaque progression

Endothelial dysfunction, characterized by increased permeability and expression of adhesion molecules, facilitates monocyte migration into the arterial intima. These monocytes differentiate into macrophages, engulf modified LDL, and transform into foam cells, forming fatty streaks—the earliest visible lesions of atherosclerosis [23]. This process is further exacerbated by the release of inflammatory cytokines such as interleukin-1 beta and tumor necrosis factor-alpha, which perpetuate vascular inflammation and promote smooth muscle cell migration and proliferation, contributing to fibrous cap formation and lesion progression [24]. This process is visualized in Fig. 1.

Role of proprotein convertase subtilisin/kexin type 9 in regulating plasma low-density lipoprotein cholesterol levels

PCSK9 plays a pivotal role in regulating plasma LDL levels by promoting LDLR degradation. PCSK9 binds to LDLR, preventing its recycling and thereby reducing hepatic LDL clearance, leading to increased circulating LDL-C [25]. This mechanism is visualized in Fig. 2. Mechanistic analyses have identified two distinct pathways of PCSK9-induced LDLR degradation: an intracellular pathway, where PCSK9 binds nascent LDLR and directs it to lysosomal degradation, and an extracellular pathway, where secreted PCSK9 binds to the LDLR epidermal growth factor-like repeat A domain and prevents receptor recycling [26]. Genetic studies have demonstrated that gain-of-function mutations in PCSK9 result in autosomal dominant hypercholesterolemia, characterized by significantly elevated LDL-C levels and increased ASCVD risk [27]. Conversely, loss-of-function mutations in PCSK9 have been associated with markedly lower LDL-C levels and a significant reduction in ASCVD risk, as evidenced in the Dallas Heart Study and Atherosclerosis Risk in Communities study [28,29]. Beyond its role in LDL metabolism, PCSK9 has emerged as a novel biomarker for cardiovascular risk. Elevated plasma PCSK9 levels have been positively correlated with increased fibrinogen levels, suggesting a potential role in thrombosis and heightened cardiovascular event risk [30]. Furthermore, in patients with coronary atherosclerosis, higher circulating PCSK9 levels have been found to correlate with an increased necrotic core fraction, a marker of plaque vulnerability, independent of LDL-C levels and statin use [31]. These findings suggest that PCSK9 may contribute to residual cardiovascular risk beyond its impact on LDL-C. Given the central role of LDL-C, Lp(a), and PCSK9 in atherogenesis, targeted therapies beyond statins have been developed to mitigate ASCVD risk. PCSK9 inhibitors, such as Evolocumab, are fully human monoclonal antibodies that selectively bind PCSK9, preventing its interaction with LDLR and thereby enhancing LDL-C clearance [32]. This mechanism translates into significant LDL-C reductions and potential plaque stabilization, positioning PCSK9 inhibitors as a complementary or superior alternative to statins, particularly in high-risk populations. Moreover, emerging lipid-lowering strategies targeting Lp(a) and inflammatory pathways hold promise in addressing residual cardiovascular risk, underscoring the necessity of a multifaceted approach in ASCVD management. Further research is warranted to determine the long-term efficacy of these novel modalities in clinical settings.

Fig. 2



PCSK9-Mediated LDL receptor degradation and therapeutic inhibition. Illustration of the LDL-R pathway: (1) LDL-R binds and internalizes LDL-C; (2) LDL-R normally recycles to the cell surface; (3) PCSK9 binds LDL-R, directing it to lysosomal degradation; (4) PCSK9 inhibitors block PCSK9 interaction with LDL-R or reduce PCSK9 synthesis, promoting LDL-R recycling and lowering circulating LDL-C. LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; PSCK9, proprotein convertase subtilisin/kexin type 9.

Discussion

Statin monotherapy is a cornerstone of LLT; however, substantial evidence indicates that it frequently fails to achieve optimal LDL-C reduction in high-risk populations, including individuals with familial hypercholesterolemia (FH) or a history of ACS [33]. Recent surveys, such as EUROASPIRE V, DA VINCI, and SANTORINI, have demonstrated that despite the availability of high-intensity statins, a significant proportion of patients do not achieve guideline-recommended LDL-C targets, reinforcing the necessity for adjunctive lipid-lowering therapies [34–36]. This persistent gap between guideline-directed therapy and real-world LDL-C control highlights the need for more aggressive and innovative therapeutic strategies. In favor of combination therapy, evidence suggests that adding ezetimibe to statins provides incremental LDL-C reductions and improved cardiovascular outcomes. The IMPROVE-IT trial demonstrated that ezetimibe combined with statins resulted in superior LDL-C lowering and cardiovascular event reduction compared to statin monotherapy [12]. However, despite these findings, combination therapies remain underutilized in clinical practice, and a substantial proportion of high-risk patients continue to exhibit residual cardiovascular risk. While ezetimibe offers a modest reduction in LDL-C, its efficacy plateaus, necessitating the development of more potent lipid-lowering agents such as PCSK9 inhibitors. Given their ability to achieve robust LDL-C reductions, PCSK9 inhibitors have emerged as a promising therapeutic option for patients who fail to reach LDL-C targets with conventional therapies. The ODYSSEY Alirocumab prolonged surveillance of safety in real-life practice (APPRISE) study evaluated alirocumab in patients with heterozygous FH (HeFH) or persistently elevated LDL-C despite maximally tolerated statin therapy. The results demonstrated that alirocumab reduced LDL-C by more than 50%, reinforcing its role as a critical adjunctive therapy [37]. Similarly, in high-risk FH patients undergoing combination LLT, Pérez De Isla *et al.* [38] found that alirocumab significantly reduced coronary plaque burden and favorably altered plaque composition, supporting its role in atherosclerosis modification. These findings underscore the superior efficacy of PCSK9 inhibitors in patients who remain at high cardiovascular risk despite intensive statin therapy. Their ability to substantially lower LDL-C levels, enhance plaque stability, and potentially reduce atherosclerotic burden positions them as a transformative advancement in lipid management.

Proprotein convertase subtilisin/kexin type 9 inhibitors in cardiovascular risk reduction and low-density lipoprotein cholesterol lowering

PCSK9 inhibitors, particularly evolocumab and alirocumab, have demonstrated substantial efficacy in lowering LDL-C levels and reducing major adverse cardiovascular events (MACE) across multiple large-scale clinical trials. Their benefits extend beyond lipid-lowering, offering meaningful cardiovascular risk reduction for high-risk populations inadequately managed with conventional therapies. The Open-label study of long-term evaluation against LDL cholesterol (OSLER) trials evaluated the long-term effects of evolocumab, showing a 61% reduction in LDL-C and a 56% reduction in cardiovascular events over a median follow-up of 11 months [39]. Similarly, the ODYSSEY Combination therapy of ezetimibe and statins in hypercholesterolemia (COMBO) I and II trials demonstrated that alirocumab, when added to maximally tolerated statin therapy, achieved consistent and sustained

LDL-C reductions—approximately 46% in COMBO I and 49% over 2 years in COMBO II—accompanied by improvements in cardiovascular outcomes [40,41]. The ODYSSEY LONG TERM trial further confirmed the durability of alirocumab's effect, with LDL-C reductions maintained at 62% over 78 weeks and continued cardiovascular event reduction [42]. Collectively, these trials reinforce the role of PCSK9 inhibitors as cornerstone agents in lipid management, particularly for patients with persistently elevated LDL-C despite optimal statin use. Future studies should continue to explore their impact on all-cause mortality and potential cardioprotective mechanisms beyond lipid modulation.

Cardiovascular outcomes and long-term efficacy of proprotein convertase subtilisin/kexin type 9 inhibitors

The cardiovascular benefits of PCSK9 inhibition are best illustrated by three complementary trial programs. In the post-ACS setting, the ODYSSEY OUTCOMES trial randomized 18 924 patients and showed that alirocumab, titrated to an LDL-C target of 25–50 mg/dl, reduced MACE by 15% over 2.8 years; the effect rose to 24% among patients whose baseline LDL-C exceeded 100 mg/dl, underscoring a threshold-dependent benefit [14]. Real-world data from the ODYSSEY APPRISE study confirmed that similar LDL-C reductions can be achieved in routine practice: after 12 weeks, nearly 70% of high-risk or HeFH patients reached guideline targets despite prior statin failure [37].

In stable ASCVD, the FOURIER trial demonstrated that fixed-dose evolocumab reduced LDL-C by approximately 60% at 48 weeks and produced a 15% decline in the primary composite endpoint; reductions in cardiovascular death, MI, and stroke were consistent across baseline LDL-C levels [15]. The FOURIER-OLE extension further confirmed the long-term durability of this effect, showing that after up to 8.4 years of evolocumab exposure, the risk of MACE remained 15–20% lower and cardiovascular mortality was reduced by 23% compared to placebo [43].

A recent meta-analysis by Grover *et al.* [44] involving 57 890 patients across 10 phase three trials corroborated reductions in MI and coronary revascularization but did not demonstrate a statistically significant effect on all-cause mortality—likely due to limited trial duration and the influence of noncardiovascular events. Together, these findings establish PCSK9 inhibitors as a key component of secondary prevention, with sustained LDL-C lowering, consistent cardiovascular event reduction, and a favorable long-term safety and efficacy profile. Future research should aim to clarify their effects on overall mortality and further investigate mechanisms beyond LDL-C reduction, including Lp(a) lowering and plaque stabilization, to enhance risk stratification and long-term outcomes.

Proprotein convertase subtilisin/kexin type 9 inhibitors in very high-risk acute coronary syndrome and peripercutaneous coronary intervention patients

PCSK9 inhibitors are increasingly recognized as valuable adjuncts in managing ACS and percutaneous coronary intervention (PCI) patients, particularly those with suboptimal LDL-C control despite statin and ezetimibe therapy. In post-PCI ACS patients, Hao *et al.* [45] demonstrated that evolocumab markedly reduced LDL-C levels (from 3.54 to 0.57 mmol/l) compared to controls (3.52 to 1.26 mmol/l), and was associated with a 15.8% absolute reduction in MACE over 3 months (8.82 vs. 24.59%), highlighting the potential benefit of early and intensive lipid lowering in high-risk settings. Similarly, Mehta *et al.* [46] reported that STEMI patients receiving alirocumab post-PCI achieved a greater LDL-C reduction (72.9%) than placebo-treated patients (48.1%), further supporting its efficacy in rapidly achieving lipid targets.

However, not all mechanistic endpoints show benefit. In a small trial, Ishihara *et al.* [47] found that although evolocumab significantly reduced LDL-C (25.6 vs. 79.8 mg/dl in controls), it did not improve periprocedural microvascular resistance or reduce biomarkers of myocardial injury post-PCI. These findings suggest that while PCSK9 inhibitors are effective in lipid control, their role in enhancing PCI-specific physiological outcomes—such as microvascular perfusion or myocardial salvage—remains uncertain.

Overall, PCSK9 inhibitors offer robust LDL-C reduction in very high-risk ACS and peri-PCI patients and may contribute to early secondary prevention. Future studies are needed to clarify their effect on procedural recovery metrics and to determine whether their lipid-lowering benefits translate into durable improvements in post-PCI outcomes.

Proprotein convertase subtilisin/kexin type 9 inhibitors' impact on lipoprotein(a)

Lp(a) is a well-established independent risk factor for atherosclerosis, thrombosis, and CVD, driven by its pro-atherogenic, pro-thrombotic, and pro-inflammatory properties. Unlike LDL-C, Lp(a) has a prolonged plasma half-life, exacerbating its pathological effects. Conventional LLTs are largely ineffective at reducing Lp(a) levels and may even paradoxically increase their concentration by up to 30% [48,49]. Consequently, PCSK9 inhibitors have been evaluated for their potential role in Lp(a) modulation. Okada *et al.* investigated the effect of early evolocumab administration on Lp(a) levels in patients with AMI following primary PCI. Participants were randomized to receive either pitavastatin alone or pitavastatin in combination with evolocumab within 24 h and again at 2 weeks post-PCI. The results demonstrated that evolocumab significantly lowered Lp(a) levels across all baseline categories (≤10,

10–20, and >20 mg/dl) compared to the control group. Additionally, evolocumab effectively prevented the expected increase in Lp(a) levels within 4 weeks, highlighting its potential role in mitigating Lp(a)-mediated cardiovascular risk [50]. Similarly, Hao *et al.* [45] found that in post-PCI patients, evolocumab led to a 38.84% reduction in Lp(a), whereas the control group experienced an increase in Lp(a) levels. Supporting these findings, a preliminary analysis from the evolocumab in acute coronary syndrome (EVACS) I and II trials examined the periinfarction and early postinfarction effects of evolocumab in ACS patients. In the placebo group, Lp(a) levels rose significantly from 64 to 80 nmol/l at discharge and to 82 nmol/l at 30 days, while in the evolocumab-treated group, Lp(a) levels remained stable regardless of baseline concentration [51]. These results suggest that early PCSK9 inhibition may prevent the periinfarction Lp(a) surge, potentially mitigating further cardiovascular risk in very high-risk ACS patients.

Proprotein convertase subtilisin/kexin type 9 impact on atherosclerosis and plaque regression

The role of PCSK9 inhibitors in atherosclerotic plaque regression and stabilization has gained increasing attention, especially in high-risk cardiovascular patients. By lowering LDL-C beyond levels achieved with statins alone, PCSK9 inhibitors may drive structural and compositional changes in atherosclerotic plaques that confer greater cardiovascular protection.

In the ODYSSEY Japan Intravascular Ultrasound Study (J-IVUS) trial, Ako *et al.* evaluated alirocumab in Japanese patients with ACS and uncontrolled LDL-C. While both groups saw plaque volume reduction, the alirocumab group showed a numerically greater decline in total atheroma volume (−4.8 vs. −3.1%), though the difference was not statistically significant [52]. Similarly, Lepor *et al.* [53] demonstrated that alirocumab reduced lipid core volume and plaque neovascularization in statin-intolerant patients over 12 months, though plaque calcification and lumen size remained largely unchanged—suggesting stabilization rather than structural regression.

More robust changes were seen in the effects of the PCSK9 antibody alirocumab on coronary atherosclerosis in patients with acute myocardial infarction (PACMAN-AMI) trial, where the addition of alirocumab to high-intensity statins in AMI patients significantly reduced percent atheroma volume (−2.13 vs. −0.92%) and lipid burden, while increasing fibrous cap thickness—hallmarks of favorable plaque remodeling [54]. These effects were mirrored in the high-resolution assessment of coronary plaques in a global evolocumab randomized study (HUYGENS) trial, which showed that evolocumab enhanced fibrous cap thickness (+42.7 vs. +21.5 μm), reduced lipid arc, and promoted plaque regression (−2.29 vs. −0.61%) over 52 weeks [55].

In FH patients, the effect of alirocumab on coronary atherosclerosis evaluated by intravascular ultrasound (ARCHITECT) trial confirmed the long-term impact of alirocumab on coronary plaque burden and composition. Over 78 weeks, alirocumab plus statins reduced plaque burden (from 34.6 to 30.4%) and shifted plaque makeup toward more stable forms—marked by increased calcified and fibrous components and decreased necrotic and fibro-fatty elements [38].

Recent evidence from the reduction in coronary Yellow plaque lipid content after intensive statin therapy (YELLOW) III trial reinforces the plaque-modifying effects of PCSK9 inhibitors. In this prospective imaging study, patients with stable coronary artery disease received evolocumab (140 mg biweekly) alongside statins for 26 weeks. Optical coherence tomography showed fibrous cap thickness increased from ~70.9 to 97.7 μm, while the prevalence of vulnerable thin-cap fibroatheromas dropped from 48 to 13%. Lipid content (maxLCBI$_{4\ mm}$) decreased from 306.8 to 213.1 as assessed by near-infrared spectroscopy, and intravascular ultrasound confirmed appropriate reductions in atheroma volume. Notably, at 6-month follow-up, 20% of patients showed no fibrous cap thickening, and 24% had no LCBI reduction despite LDL-C lowering. Transcriptomic analysis revealed gene expression differences between responders and nonresponders, highlighting the potential for biomarker-guided personalization to detect patients whose plaque morphology would respond best to PCSK9 inhibition therapy. These statistically significant findings underscore the multifaceted role of PCSK9 inhibitors beyond cholesterol lowering [56]. Table 1 further summarizes the notable clinical trials comparing alirocumab and evolocumab with placebo or standard care.

Collectively, these studies suggest that PCSK9 inhibitors, particularly when combined with statins, contribute meaningfully to plaque regression and stabilization. Their ability to enhance fibrous cap integrity and shift plaque composition toward stability may help reduce future cardiovascular events, especially in noninfarct arteries or subclinical disease. Further longitudinal studies are needed to determine whether these imaging-based changes translate into durable clinical benefit.

Novel lipid-lowering agents

Suboptimal LDL-C control necessitates the need for additional nonstatin therapies, especially in patients with statin intolerance and inherited disorders. Bempedoic acid, a prodrug that inhibits adenosine triphosphate (ATP) citrate lyase upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway, received FDA approval in 2020 and has since been evaluated in multiple RCTs to assess its lipid-lowering efficacy. In a multicenter trial by Ballantyne *et al.*, patients were randomized to receive either a

Table 1 Summary of clinical trials comparing alirocumab and evolocumab with placebo or standard care

First author and year	Sample size	Follow-up period	Key outcomes
El Shahawy *et al*., 2017 [40]	720 (2:1)	2 years	At 24 weeks, alirocumab reduced LDL-C by 52% vs. ezetimibe's 22%, sustained at 2 years (49 vs. 17%; $P < 0.0001$). More alirocumab patients achieved LDL-C < 70 mg/dl (73 vs. 40%) and consecutive LDL-C < 25 mg/dl (28 vs. 0.4%)
Robinson *et al*., 2015 [42]	2067	12 weeks	Evolocumab demonstrated significantly greater LDL-C reduction compared to placebo in patients on moderate- and high-intensity statins, with biweekly dosing reducing LDL-C by 66–75% and monthly dosing achieving a 63–75% reduction
Sabatine *et al*., 2017 [15]	27 564	Median follow-up period of 2.2 years	Evolocumab showed better outcomes compared to placebo, reducing LDL-C by 59%. It also lowered the incidence of the primary endpoint (9.8 vs. 11.3%; hazard ratio (HR) 0.85) and the secondary endpoint (5.9 vs. 7.4%; HR 0.80), indicating a significant reduction in cardiovascular events
O'Donoghue *et al*., 2022 [43]	6635 (3355:3280::I:C)	Median follow-up period of 5.0 years	Evolocumab demonstrated better outcomes compared to placebo, with 63.2% of patients achieving LDL-C levels <40 mg/dl at 12 weeks. During the open-label extension follow-up, patients initially randomized to evolocumab experienced a 15–20% lower risk of major adverse cardiovascular events (MACE) and a 23% lower risk of cardiovascular death compared to those originally assigned to placebo
Hao *et al*., 2022 [45]	136 (1:1)	1 and 3 months	Alirocumab demonstrated better outcomes compared to placebo, with a reduction in LDL-C by 114.5 mg/dl, a slight decrease in Lp(a) by 0.11 mg/dl, and a reduced risk of major adverse cardiovascular events (MACE) with a hazard ratio of 0.85
Mehta *et al*., 2022 [46]	68	6 weeks/45 days	At 45 days, alirocumab reduced LDL-C by 72.9 vs. 48.1% (sham control; Δ −22.3%), with 92.1% achieving LDL-C ≤ 1.4 mmol/l (vs. 56.7%)
Ishihara *et al*., 2022 [47]	100 (54:46::I:C)	2–6 weeks	Evolocumab showed better lipid-lowering outcomes compared to placebo when used as pretreatment alongside statin therapy to prevent periprocedural microvascular dysfunction, although the primary endpoint–index of microvascular resistance (IMR) after PCI–was not achieved. Before PCI, the geometric mean LDL-C was significantly lower in the evolocumab group (25.6 mg/dl) compared to the control group (79.8 mg/dl)
Okada *et al*., 2022 [50]	102 (52:50::I:C)	4 weeks	Evolocumab reduced Lp(a) levels vs. control (−2.7% vs. +82.0%; Δ −86.3%). This suppression was significant across all baseline Lp(a) subgroups (≤10, 10–20, and >20 mg/dl)
Ako *et al*., 2019 [52]	206	36 weeks	Alirocumab demonstrated better outcomes compared to standard care, with a reduction in LDL-C by 63.2 mg/dl, Lp(a) by 15.5 mg/dl, and total atheroma volume (TAV) by 4.8%, compared to a 3.1% reduction in TAV in the control group
Räber et *al*., 2022 [54]	300 (148:152::I:C)	52 weeks	At 52 weeks, alirocumab reduced percent atheroma volume (−2.13% vs. placebo −0.92%; Δ −1.21%), decreased lipid core burden index (−79.42 vs. −37.60; Δ −41.24), and increased fibrous cap thickness (+62.67 vs. +33.19 μm; Δ +29.65 μm)
Nicholls *et al*., 2022 [55]	161 (1:1)	52 weeks	Evolocumab improved plaque stability and reduced atheroma burden vs. placebo, achieving lower LDL-C (28.1 vs. 87.2 mg/dl). It increased minimum fibrous cap thickness (+42.7 vs. +21.5 μm), reduced maximum lipid arc (−57.5 vs. −31.4 °), and decreased macrophage index (−3.17 vs. −1.45 mm). Similar benefits were seen in lipid-rich regions. Atheroma volume regressed further with evolocumab (−2.29 vs. −0.61%)
Biccirè *et al*., 2024 [57]	245 (118:127::I:C); 591 lesions were included: 287 lesions in the alirocumab group and 304 lesions in the placebo group	52 weeks	Alirocumab demonstrated better outcomes compared to standard care, with a reduction in LDL-C by 130.4 mg/dl and total atheroma volume (TAV) by 4.86 vs. 2.78% in the control group, although it was associated with an increase in Lp(a) by 8.1 mg/dl
Furtado *et al*., 2022 [58]	27 564	Median follow-up period of 2.2 years	Patients with prior PCI in the placebo arm had higher rates of MACE and major coronary events compared to those without prior PCI, with hazard ratios of 1.61 and 1.72, respectively. Evolocumab provided similar relative risk reductions in MACE and major coronary events regardless of prior PCI status, with no significant interaction between treatment effect and PCI history. The absolute risk reductions with evolocumab were numerically greater in patients with prior PCI for both MACE and major coronary events, reaching statistical significance for major coronary events
Koskinas *et al*., 2019 [59]	308 (1:1)	8 weeks	Evolocumab demonstrated a higher percentage of patients achieving target LDL-C levels, with a reduction in LDL-C by 109.4 mg/dl, although it was associated with an increase in Lp(a) by 49.5 mg/dl
Koskinas *et al*., 2024 [60]	300	52 weeks	Alirocumab outperformed placebo, reducing percent atheroma volume and maxLCBI 4 mm while increasing minimum fibrous cap thickness. maxLCBI 4 mm reduction was smaller with high baseline Lp(a) [−40.2 vs. −91.4 (low Lp(a))], resembling placebo (−37.6). Atheroma volume and cap thickness changes were unaffected by baseline Lp(a)
Nicholls *et al*., 2016 [61]	968	78 weeks	Evolocumab reduced atheroma burden more than placebo, lowering LDL-C (36.6 vs. 93.0 mg/dl; Δ −56.5). It decreased percent atheroma volume (PAV; −0.95 vs. +0.05%, Δ −1.0%) and normalized total atheroma volume (TAV; −5.8 vs. −0.9 mm^3, Δ −4.9). Plaque regression rates were higher with evolocumab (64.3 vs. 47.3% for PAV; 61.5 vs. 48.9% for TAV)

(*Continued*)

Table 1 (*Continued*)

First author and year	Sample size	Follow-up period	Key outcomes
Roe *et al.*, 2019 [62]	18 924	2.8 years	Alirocumab showed nonsignificant but consistent MACE reductions across subgroups: HR = 0.84 [very high-risk (VHR)] and HR = 0.86 (non-VHR). Absolute risk reductions were numerically greater in VHR patients (2.1 vs. 0.8% non-VHR), particularly those with multiple prior ASCVD events (2.4 vs. 1.8% single event)
Schwartz *et al.*, 2021 [63]	18 924	4 months	After propensity matching, MACE reductions were similar for achieved LDL-C < 25 mg/dl (HR = 0.74; ARR = 0.92/100 patient-years) and 25–50 mg/dl (HR = 0.74; ARR = 1.05). Benefit diminished with LDL-C > 50 mg/dl (HR = 0.87; ARR = 0.62), partly due to poorer adherence
Szarek *et al.*, 2019 [64]	18 924 (1:1)	Median follow-up period of 2.8 years	Alirocumab significantly reduced both nonfatal cardiovascular (CV) events (HR = 0.87) and mortality (HR = 0.83) vs. placebo, preventing 190 first and 385 total events (3064 first/5425 total events observed)
Trankle *et al.*, 2019 [65]	20 (1:1)	72 h and 14 days	Alirocumab significantly reduced LDL-C vs. placebo at 14 days (−64 mg/dl vs. +1 mg/dl; $P < 0.001$). No between-group differences were observed in C-Reactive protein (CRP) changes at 72 h or 14 days

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention.

fixed-dose combination of bempedoic acid (180 mg) and ezetimibe (10 mg), bempedoic acid monotherapy, ezetimibe monotherapy, or placebo, all on a background of stable statin therapy. After 12 weeks, the combination therapy yielded the greatest LDL-C reduction—36.2% from baseline—compared to 23.2% with ezetimibe alone and 17.2% with bempedoic acid alone [66]. However, the modest LDL-C reduction achieved with bempedoic acid compared to PCSK9 inhibitors may limit its utility in very high-risk populations. Its role may be best suited for statin-intolerant patients or those requiring mild to moderate LDL-C reduction. Additionally, long-term cardiovascular outcome data remain limited. Another ongoing trial (ES-BempeDACS) evaluates the efficacy of triple oral therapy with bempedoic acid + ezetimibe + high-intensity statin vs. high-intensity statin ± ezetimibe alone in lowering LDL-C to <55 mg/dl in post-PCI patients [67].

Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification Trial deduced the role of cholesteryl ester transfer protein (CETP) inhibitors, including anacetrapib, in reducing LDL-C levels and thus, the incidence of CHD, when given in combination with statins [68]. CETP inhibition prevents the transfer of cholesteryl esters from high-density lipoprotein (HDL) into other lipoproteins, leading to the formation of a larger and increased number of HDL particles, slowing the catabolism of HDL. On the other hand, it leads to decreased conversion to LDL cholesteryl esters and, thus, faster LDL catabolism. In addition, CETP inhibitors have a proven role in decreasing the incidence of new-onset diabetes [69]. Cardiovascular Outcome Study to Evaluate the Effect of Obicetrapib in Patients With Cardiovascular Disease (PREVAIL) study is an ongoing phase III trial that focuses on the effect of anacetrapib along with other lipid-lowering therapies on LDL-C and MACE. (NCT05202509) Preliminary data from Reduction of Cardiovascular Events With Omega-3 Supplementation Evaluation (ROSE) and ROSE2 phase II trials have also shown favorable effects on dyslipidemia and ASCVD risk reduction [68]. Despite favorable lipid changes, CETP inhibitors have a mixed history, with past agents like torcetrapib failing due to off-target effects. The true impact on clinical events—particularly with newer agents like obicetrapib—requires validation in ongoing outcome trials. Moreover, the HDL-raising effects have not yet translated into consistent cardiovascular benefit.

Inclisiran is a double-stranded small interfering RNA molecule, which got FDA approval in 2021 for use as a lipid-lowering agent. A single active strand attached to RNA-induced silencing complex disables PCSK9 mRNA transcription, significantly reducing LDL-C levels to almost half the baseline. It is especially useful when infrequent medication administration is preferable since inclisiran is given on day 90, followed by every 6 months [70]. ORION-10 and ORION-11 trials enrolled a total of 3178 patients and reported a decrease of >50% in baseline LDL-C levels after 540 days of follow-up [35]. While the LDL-C-lowering effect of inclisiran is comparable to PCSK9 monoclonal antibodies, outcome data on MACE are still pending. Its infrequent dosing schedule offers convenience and may improve long-term adherence, but questions remain about its cost-effectiveness and integration into existing care models.

Angiopietin-like 3 (ANGPTL3) inhibitors, including evinacumab, are another class of novel LLT, capable of reducing plasma LDL-C levels independent of action on LDLRs [71]. These are monoclonal antibodies that work by inhibiting lipoprotein lipase, preventing the downstream conversion of Very-Low-Density Lipoprotein (VLDL) to LDL particles [69]. Rosensan *et al.* reported sustained apolipoprotein-B and non-HDL-C reductions with monthly dosing of evinacumab with good tolerability. Zodasiran, an RNA interference therapy that works by targeting ANGPTL3 in the liver, has also proven to significantly reduce the serum triglyceride levels over a span of 24 weeks in the ARCHES-2 trial [72]. Although ANGPTL3 inhibition offers an LDLR–independent pathway to lipid lowering, its clinical role remains niche,

especially in patients with homozygous FH or severe refractory hyperlipidemia. Larger trials are needed to establish its long-term safety, cost-effectiveness, and additive value over existing agents.

Lomitapide is another lipid-lowering drug that works by inhibiting microsomal triglyceride transfer protein, responsible for the secretion of triglyceride-rich apolipoprotein-B, while maintaining hepatic safety, approved recently for FH [73]. Lipoprotein apheresis is another modality approved by the FDA for cases of FH and established ASCVD [70]. However, lomitapide's use is limited by gastrointestinal side effects, elevated liver enzymes, and the need for a strict low-fat diet, which may impair adherence. Lipoprotein apheresis, while effective, is invasive, resource-intensive, and largely reserved for patients with severe, refractory hypercholesterolemia due to its limited accessibility and high cost.

Despite the demonstrated efficacy of PCSK9 inhibitors, their widespread implementation faces significant real-world barriers. High costs associated with mAb therapies often limit accessibility, especially in resource-constrained settings. Insurance coverage may be restrictive, with prior authorization requirements or step therapy protocols that delay initiation. Furthermore, the injectable route of administration may negatively impact patient adherence compared to oral agents. These issues underscore the need for healthcare system adaptations, including value-based pricing, improved formulary inclusion, and patient-centered education strategies to enhance uptake and long-term adherence.

Future directions and author perspectives

While PCSK9 inhibitors and other novel lipid-lowering agents have demonstrated substantial efficacy, future research should focus on several priority areas: (1) long-term impact on all-cause and cardiovascular mortality, particularly in diverse populations; (2) cost-effectiveness and health economic modeling in real-world settings; (3) strategies to improve adherence, including patient education and simplified dosing regimens; and (4) comparative studies of emerging combination regimens involving RNA-based and monoclonal therapies. We hypothesize that combining RNA-based therapies (such as inclisiran) with monoclonal antibodies targeting ANGPTL3 (e.g. evinacumab) may provide synergistic LDL-C and triglyceride reductions in patients with mixed dyslipidemia or polygenic hyperlipidemia. Furthermore, a shift toward algorithm-guided, biomarker-driven personalization of lipid-lowering regimens—incorporating Lp(a), apoB, and inflammatory markers—could help identify patients who derive the greatest marginal benefit from each class of agents. Future trials should evaluate these combinatorial strategies not only for lipid control but also for long-term cardiovascular event reduction and cost-effectiveness in real-world populations.

Conclusion

Over the past three decades, LLT has advanced dramatically, yet ASCVD continues to exact an unacceptably high global toll. Optimized, high-intensity statin therapy remains the foundation of care, but sizable residual risk persists—particularly in patients with FH, recent ACSs, refractory dyslipidaemia, or those undergoing PCI. Robust data now show that adding nonstatin agents such as ezetimibe and, more powerfully, PCSK9 inhibitors can cut LDL-C by 50–60% and meaningfully reduce MACE.

Translating these trial results into population-level benefit requires tackling several real-world barriers. High list prices, stringent prior-authorization policies, and step-therapy mandates restrict access to PCSK9 monoclonal antibodies, while the need for subcutaneous injections may erode long-term adherence. Equitable uptake will therefore depend on (i) value-based pricing negotiations and expanded formulary inclusion; (ii) streamlined insurance pathways that prioritize high-risk phenotypes; and (iii) patient-centered education plus simplified dosing schedules (e.g. twice-yearly inclisiran) to enhance persistence.

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Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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