

Emerging Pharmacological Therapies in the Treatment of Atherosclerosis: A Review

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REVIEW ARTICLE

Abstract

Despite decades of progress made with statins and proven lipid-lowering strategies, atherosclerotic cardiovascular disease (ASCVD) is still the primary driver of morbidity and mortality worldwide. Even with treatment to the guideline-recommended low-density lipoprotein cholesterol (LDL-C) target, a significant residual risk remains that has driven the development of additional drug classes that target other complementary pathways of atherogenesis, such as hepatic PCSK9 synthesis, ATP-citrate lyase, cholesteryl ester transfer protein (CETP), lipoprotein(a) [Lp(a)] production, and vascular inflammation. The review highlights the latest evidence on emerging drugs for atherosclerosis, such as small interfering RNA (siRNA) therapy (inclisiran); ATP-citrate lyase inhibitors (bempedoic acid); CETP inhibitors (obicetrapib); Lp(a) directed antisense oligonucleotides and siRNAs (pelacarsen, olpasiran, lepodisiran, zerlasiran); and the oral small molecule muvalaplin; in addition to anti-inflammatory drugs such as colchicine and agents that block the IL-1 β and IL-6 pathways. Results so far are consistent with meaningful and durable decreases in atherogenic lipoproteins across multiple novel classes of drugs, with cardiovascular outcome benefit already established for bempedoic acid and colchicine, and outcome trials for Lp(a)-lowering agents and the CETP inhibitor obicetrapib ongoing. However, the recently reported ZEUS trial showed that although IL-6 inhibition with ziltivekimab was associated with powerful suppression of inflammatory biomarkers, it did not translate into a clinical benefit in terms of major adverse cardiovascular events. Taken together, these findings point toward a shift in treatment directions for atherosclerosis toward mechanism-diverse, precision-guided pharmacotherapy, and emphasize the need for large, well-powered outcome trials before biomarker-driven therapies can become part of routine care.

Keywords: Atherosclerosis, Cardiovascular Risk, Inflammation, Novel Therapies, Precision Treatment

1. Introduction

Atherosclerosis is a chronic, progressive disorder that involves the deposition of lipids, infiltration by immune system cells, endothelial dysfunction, and long-term low-grade inflammation of the arterial wall, which eventually results in the formation, growth, instability, and rupture of plaques. It is the most important pathological substrate of myocardial infarction, ischemic stroke, and peripheral arterial disease and is associated with significant cardiovascular morbidity and mortality around the world. Genetic, epidemiological, and randomized clinical trial data strongly support the central importance of atherogenic lipoproteins in disease pathogenesis, and LDL-C is the most important modifiable lipid target currently used to prevent ASCVD. Intensive LDL-C lowering by statins, ezetimibe, and monoclonal antibody PCSK9 inhibitors has significantly lowered rates of cardiovascular events. Clinical trials have shown that a consistent reduction of LDL-C correlates with reduced cardiovascular risk. PCSK9 inhibition can offer additional benefit for patients with established ASCVD receiving background statin therapy. However, a

significant number of treated patients still have recurrent cardiovascular events, suggesting that there is also significant residual cardiovascular risk even after reaching conventional lipid targets. This residual risk is multifactorial and could be due to ongoing atherogenic lipoprotein exposure, genetically determined lipoproteins such as lipoprotein(a) [Lp(a)], remnant cholesterol, abnormal metabolism, and chronic vascular inflammation not adequately controlled by statins. Because it is genetically determined and relatively unaffected by lifestyle changes and the lipid-lowering drugs currently available, Lp(a) has been the subject of special interest. High Lp(a) is an independent risk factor for coronary artery disease, myocardial infarction, stroke, and aortic valve disease. Concurrently, there is growing evidence that inflammation is a key part of the atherosclerotic process, from the earliest phase of endothelial activation to the initial stages of plaque formation, macrophage accumulation, necrotic core formation, plaque destabilization, and thrombosis. In response, there has been an expanding pipeline of novel treatments, such as small interfering RNA therapies against hepatic PCSK9 synthesis, ATP-citrate lyase inhibition, CETP inhibition, and novel drugs that try to decrease the production of Lp(a) or disrupt its assembly. At the same time, anti-inflammatory drug development targeting other pathways such as interleukin-1 β and interleukin-6 is ongoing to see if selective inhibition of vascular inflammation can decrease cardiovascular events without lipid-lowering effects. Importantly, there is considerable variation in the degree of clinical evidence for these therapeutic classes. Bempedoic acid and colchicine have been found to have cardiovascular outcome benefits in randomized trials; several newer Lp(a)-targeted and inflammatory therapies have thus far found promising effects in biological biomarker trials, pending definitive outcome data. In this review, therefore, the pharmacology, mechanisms of action, clinical trial evidence, efficacy, safety, and cardiovascular outcomes of the most clinically advanced emerging pharmacological therapies for atherosclerosis will be summarized. The discussion is divided into three major groups: novel agents for lowering LDL-C and atherogenic lipoproteins, anti-Lp(a) agents and anti-inflammatory agents, focusing particularly on the difference between efficacy of changing surrogate biomarkers and efficacy of reducing major adverse cardiovascular events.

2. Lipid-Lowering Therapies Beyond Statins

In patients who are unable to achieve sufficient LDL reduction with statins or for those who cannot tolerate statins, it is important to consider non-statin lipid-lowering therapies. Inclisiran and bempedoic acid are newer agents that have shown clinically meaningful LDL-C reductions; the level of cardiovascular-outcome evidence is different for the two therapies. Inclisiran is a small interfering RNA (siRNA) therapy that binds to proprotein convertase subtilisin/kexin type 9 (PCSK9) in the liver, increasing the number of LDL receptors in the liver and improving LDL-C clearance from the bloodstream. Inclisiran, when administered on day 1 and day 90 and every 6 months after that, demonstrated reductions of LDL-C of 52.3% and 49.9% at day 510 in phase III ORION-10 and ORION-11 trials, respectively, after adjustment for placebo (Ray et al., 2020). The ORION-10 and

ORION-11 trials enrolled 1,561 and 1,617 patients, respectively, who had elevated LDL-C levels despite taking the highest possible dose of statins. In Orion-10, 4.7% of participants had an injection-site reaction with inclisiran compared with 0.5% who received placebo and in Orion-11, 2.6% had an injection-site reaction with inclisiran versus 0.9% who received placebo, most of which were mild and transient (Ray et al., 2020).

2.1 PCSK9-Directed siRNA Therapy

Inclisiran is a chemically synthesized small interfering RNA (siRNA) therapeutic, which targets the hepatic messenger (m)RNA encoding proprotein convertase subtilisin and kexin type 9 (PCSK9) and is designed to silence the mRNA selectively. This mechanism of action of inclisiran makes it possible to increase the number of LDL-C that can be removed and recycled from the liver, leading to a decrease in the amount of atherogenic lipoproteins in the plasma. The other treatments are usually administered once a week or once every 2-4 weeks, and inclisiran is given subcutaneously at baseline, 3 months, and then every 6 months. The less frequent dosing may be a positive factor for adherence over the longer term, particularly for those who have difficulty with taking oral lipid-lowering drugs daily (Ray et al., 2020). The effectiveness of inclisiran has been proven in the clinical-trial program called ORION phase 3. For patients with known ASCVD or ASCVD risk equivalents on maximally tolerated statin-based therapy (ORION-10 and ORION-11), the mean LDL-C reductions were ~50% lower with inclisiran than with placebo at 17–18 months. This reduction in circulating PCSK9 levels was also accompanied by large reductions, providing evidence of significant and sustained hepatic targeting. This was observed to be the case in heterozygous familial hypercholesterolemia patients as well. In ORION-9, inclisiran was found to be very effective at reducing LDL-C levels compared to placebo in patients with persistently elevated LDL-C levels on top of maximally tolerated lipid-lowering therapy (Raal et al., 2020). A major advantage of inclisiran is that it will not make the liver resistant to the medication. An appealing aspect of inclisiran is its prolonged suppression of PCSK9 synthesis. PCSK9 synthesis may be suppressed for a longer period after administration of siRNA because the siRNA is directed toward hepatocytes and is incorporated into the RNA-induced silencing complex. This drug property allows for only 2 doses per year after the first and third ones. However, in daily clinical practice, the amount of LDL-C reduction may vary between patients, depending on the baseline LDL-C level, previous lipid-lowering treatment, willingness to receive regular injections, and patient characteristics. A major limitation of the ORION program is the distinction between surrogate lipid effects and proven cardiovascular benefit. The key studies of inclisiran were mostly powered to measure LDL-C or PCSK9 reduction, instead of the ultimate measure of major adverse cardiovascular events (MACE). Therefore, long-term cardiovascular outcome studies are needed to determine if the approximately 50% decrease in LDL-C that occurs with inclisiran corresponds to a proportional decrease in MI, ischemic stroke, cardiovascular death, and coronary revascularization. This is particularly important to consider, as a biomarker is a biologically convincing metric that cannot be used to demonstrate clinical benefit without its improvement, even if improvement is seen. To conclude, inclisiran is an important new molecule in the exciting world of lipid-lowering drug therapy leveraging RNA interference technology to target the PCSK9 pathway. The potent and durable LDL-C lowering effect and the relatively infrequent twice-a-year maintenance therapy could be an important management option for those patients who require additional LDL-C lowering beyond standard therapy. The use of inclisiran for long-term treatment of ASCVD will, however, rely on definitive cardiovascular outcome evidence from the drug.

2.2 ATP-Citrate Lyase Inhibition

Kaneka Pharma's Bempedoic acid is a novel oral lipid-lowering medication that acts by inhibiting ATP-citrate lyase (ACL), an enzyme in the early stages of cholesterol biosynthesis. ACL inhibition reduces cholesterol synthesis in the liver and causes up-regulation of liver LDL-receptor, which increases removal of LDL-C from the blood (Pinkosky et al., 2016; Ray et al., 2019). The mechanism of action may be advantageous to those who have had muscle side

effects with statins, as the activating enzyme is present in higher concentrations in the liver than in skeletal muscle (Pinkosky et al., 2016). The clinical efficacy of bempedoic acid over placebo was shown in CLEAR Outcomes. This trial included 13,970 patients who could not tolerate or failed to take guideline-recommended statins and were randomized to receive bempedoic acid 180 mg once daily or placebo (Nissen et al., 2023). The LDL-C effect of bempedoic acid was statistically highly significant during the median follow-up (approximately 40 months). The risk of the main composite endpoint of death from cardiovascular disease, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization was 13% lower with it than with placebo (HR, 0.87; 95% CI, 0.79–0.96) (Nissen et al., 2023). The significant decreases in nonfatal myocardial infarction and coronary revascularization were among the key findings from the trial, highlighting that inhibiting ACL can provide clinically relevant cardiovascular benefits, beyond just impacting a lipid-based biomarker (Nissen et al., 2023). CLEAR Outcomes are particularly relevant to patients who can't take statins and might not be able to get to target LDL-C. Bempedoic acid achieved about a 21% reduction in LDL-C during the trial, relative to placebo, at week 24 and had a modest reduction in high-sensitivity C-reactive protein (hs-CRP) (Nissen et al., 2023). To highlight one point, the results were subsequently comprehensively analyzed, which showed that the cardiovascular advantage of bempedoic acid was similar between diabetics and nondiabetics. At the same time, it did not seem to harm glycemic control or increase the risk of new-onset diabetes, as some intensive statin-treatment approaches have (Nissen et al., 2023; Ray et al., 2024). Additionally, Bempedoic acid showed potential beyond lowering LDL-C – the results were also linked to reductions in LDL-C and hs-CRP in patients with obesity enrolled in CLEAR Outcomes, with results being approximately 22% and 23% greater than the placebo responses, respectively, at 6 months (Nissen et al., 2023). Although there is a reduction in hs-CRP suggesting these data may relate to inflammatory status, cardiovascular outcome data must be considered in the context of the drug's mechanism of action (LDL-C lowering) and not as an independent effect on inflammatory status. Bempedoic acid's safety profile is different than statins, which should be considered when treating patients. There have been reports of serum uric acid levels increasing during treatment and an increased risk of gout, and some other adverse events have been reported as having increased slightly (Nissen et al., 2023). The results are especially important in the context of treatment in patients with a history of gout or hyperuricemia. However, the clinical picture of bempedoic acid is favorable, and it should be considered as an important oral non-statin treatment option for individuals who need further reductions in LDL-C. Bempedoic acid is, overall, one of the most clinically validated novel strategies for residual cardiovascular risk. It uniquely acts on the ACL, has low skeletal muscle activation, is administered orally, and has been shown to lower major cardiovascular events, particularly beneficial in statin-intolerant patients (Nissen et al., 2023). One of several drugs that have shown beneficial effects on some lipid or inflammatory markers, but not yet cardiovascular outcomes, Bempedoic acid is at the top of the new generation of non-statin drugs for ASCVD, having already shown cardiovascular benefit in a large randomized outcome trial.

2.3 CETP Inhibition

Cholesteryl ester transfer protein inhibitors (CETP) have a complicated track record in cardiovascular drug development. Previous agents like torcetrapib, evacetrapib, and dalcetrapib have not produced the expected cardiovascular benefit, and some have led to increases in blood pressure and mortality due to important off-target effects (Barter et al., 2007; Schwartz et al., 2012; HPS3/TIMI55-REVEAL Collaborative Group, 2017). Anacetrapib was then shown to provide a small benefit in terms of major coronary events in the REVEAL trial. The benefit from its clinical development was terminated, though improvement in non-HDL-C levels seemed to be the basis for the benefits strongly (Bowman et al., 2017). The results of this study raised concerns about the ability of CETP inhibition to offer clinically relevant cardiovascular protection when used with modern lipid-lowering drugs. It is a new, CETP-specific oral CETP

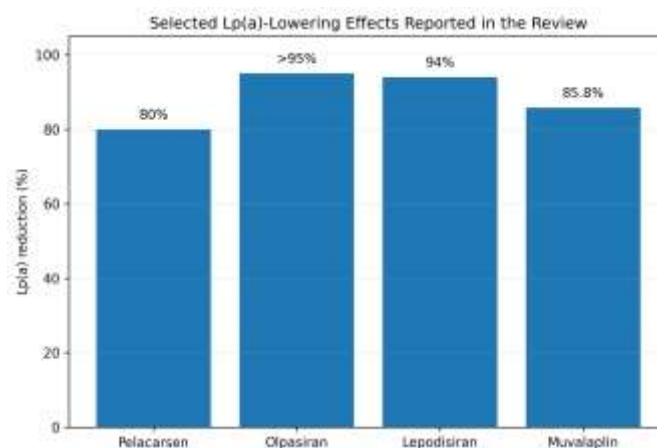
inhibitor that is highly selective, compared to other CETP inhibitors, therefore avoiding off-target effects (Maalizadeh et al., 2025). obicetrapib increases HDL-C levels significantly while decreasing levels of LDL-C, non-HDL-C, and apolipoprotein B (apoB); it works by blocking the transfer of cholesteryl esters from HDL to apoB-containing lipoproteins. The combined effect is why obicetrapib was not used in earlier CETP inhibitors, and it has sparked renewed interest in CETP inhibition as a method for lowering residual atherogenic risk (Maalizadeh et al., 2025). The phase 3 BROADWAY trial included patients with established ASCVD or heterozygous familial hypercholesterolemia who were not well controlled despite maximally tolerated lipid-lowering therapy. At 84 days, treatment with obicetrapib resulted in a placebo-adjusted mean percentage decrease in LDL-C of around 30%, and fulfilled the prespecified primary efficacy endpoint (NewAmsterdam Pharma, 2024). This was achieved against the backdrop of contemporary background lipid-lowering therapy, indicating that CETP inhibition could further lower LDL-C and atherogenic lipoproteins in a patient population not on target even with contemporary background lipid-lowering therapy. The exploratory analysis additionally indicated that fewer major adverse cardiovascular events occurred during the follow-up period, but this was not the purpose of the analysis to provide definitive cardiovascular outcome evidence (NewAmsterdam Pharma, 2024). Further insight has come on the heels of a “pooled” analysis of the phase 3 BROOKLYN and BROADWAY trials. In these trials, obicetrapib resulted in significant decreases in various atherogenic lipid measures, on average, by about 38% in LDL-C and by about 22% in apoB. Conversely, Lp(a) levels were lowered by ~33% (Maalizadeh et al., 2025). Concurrently, there was a significant rise in the level of HDL-C associated with obicetrapib, characteristic of the dual lipid-modifying properties of powerful CETP inhibitors. The importance of an increase in HDL-C alone is unclear. Still, the concurrent decrease in LDL-C, apoB, non-HDL-C, and Lp(a) has a biologically plausible basis for potential cardiovascular benefit (Maalizadeh et al., 2025). Safety is also a concern, especially with other CETP inhibitors, since obicetrapib has not yet been used in patients. Unlike torcetrapib, obicetrapib has not been seen to have the same mineralocorticoid-related, off-target effects, including large increases in blood pressure which hindered the success of torcetrapib (Barter et al., 2007; Maalizadeh et al., 2025). However, durable safety and whether or not the marked shifts in multiple lipoprotein fractions have any clinically relevant adverse implications remain to be determined with longer-term exposures in larger numbers of people. Cardiovascular outcome evidence is the best basis for the definitive evaluation of obicetrapib. The event-driven PREVAIL trial includes over 9,000 patients with established ASCVD on maximally tolerated background lipid-lowering therapy to evaluate the effect of the treatment on MACE (Maalizadeh et al., 2025). This is a key distinction since earlier CETP inhibitors were shown to have marked efficacy on HDL-C and other lipid markers but did not reliably decrease CV events. Thus, while the lipid-lowering effects of obicetrapib are encouraging, the extent to which it is capable of lowering myocardial infarction, stroke, cardiovascular death, and other major adverse cardiovascular events is unknown. Until the results of adequately powered cardiovascular outcome trials are available, however, obicetrapib should be considered a promising emerging therapy, not a proven alternative to therapies with proven cardiovascular outcome benefits.

Key quantitative findings for selected novel lipid-lowering therapies.

Therapy	Primary target/pathway	Key quantitative finding reported
Inclisiran	PCSK9-directed siRNA	LDL-C reduction 52.3% (ORION-10) and 49.9% (ORION-11)
Bempedoic acid	ATP-citrate lyase (ACL) inhibition	LDL-C reduction about 21%; primary composite CV endpoint 13% lower vs placebo
Obicetrapib	CETP inhibition	Placebo-adjusted LDL-C reduction around 30% at 84 days in BROADWAY

3. Lipoprotein(a)-Lowering Therapies

Lipoprotein(a) [Lp(a)] consists of a covalently bound lipoprotein particle to an apo-B-containing particle, apolipoprotein(a) [apo(a)], which is similar to LDL. It has been known to be an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD), myocardial infarction, ischemic stroke, and calcific aortic valve disease (Tsimikas, 2017; Kronenberg et al., 2022). The most frequently used method to measure Lp(a) concentrations is genetic variation in the LPA gene, particularly the apo(a) kringle IV type 2 repeat polymorphism, which results in considerable interindividual and ethnic differences in the levels of Lp(a) in circulation (Clarke et al., 2009; Kronenberg et al., 2022). Lp(a) is one of the most common cardiovascular risk factors among the world's populations, with approximately 20% of the population having elevated levels (Kronenberg et al., 2022). It is thought to exert an atherogenic effect on Lp(a) in multiple ways. The LDL-like component has been shown to stimulate deposition of cholesterol in the arterial wall, and apo(a) shares structural features with plasminogen and has been suggested to play a role in prothrombotic and antifibrinolytic activity (Tsimikas, 2017). In addition, oxidized phospholipids are present in Lp(a). They may enhance endothelial dysfunction and inflammatory signaling through the vascular wall, and promote progression and instability of plaque (Tsimikas et al., 2018). Such biological properties offer a mechanistic understanding of the high epidemiological and genetic linkages between high Lp(a) and cardiovascular disease. There are challenges in treating high Lp(a), as traditional interventions are less effective. In contrast to LDL-C, Lp(a) levels are relatively unresponsive to lifestyle changes, such as diet and exercise, because its circulating level is largely genetically programmed (Kronenberg et al., 2022). Statins continue to be required to lower overall ASCVD risk, but do not appear to lower Lp(a) levels and may actually lead to a modest increase in Lp(a) in some patients (Tsimikas et al., 2018). Ezetimibe and PCSK9-directed treatments can yield small decreases in Lp(a), yet their impacts are not adequate to achieve selective and deep Lp(a) decreases (Raal et al., 2017; Sabatine et al., 2017). As a result, individuals with significantly high Lp(a) can still have significant residual cardiovascular risk despite reaching desirable levels of LDL-C. Such restrictions have provoked the development of therapies that are directly aimed at the inhibition of apo(a) synthesis or Lp(a) assembly. The most developed ones are antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) therapy targeting the production of hepatic apo(a). In clinical trials, agents targeting apo(a) (such as pelacarsen) and siRNA agents (such as zerlasiran, lepodisiran and olpasiran) have shown significant reductions in plasma levels of Lp(a) (Tsimikas et al., 2020; O'Donoghue et al., 2022; Nissen et al., 2023). At the same time, muvalaplin is also a pharmacological strategy as it is a small molecule, orally available, that is designed to interfere with the assembly of apo(a) and apoB-100 into mature Lp(a) particles (Nicholls et al., 2024).



The magnitude and durability of Lp(a) reduction induced by these novel therapies are significantly greater than those achieved with currently available cardiovascular drugs. Such large (80–90% or greater) reductions of exposure to Lp(a) have already been seen in

clinical trials with RNA-based agents, and indicate that genetically mediated deep suppression of Lp(a) may be associated with significantly lower rates of cardiovascular events (O'Donoghue et al., 2022; Nissen et al., 2023). But how strong and sustained a reduction in Lp(a) values is necessary to provide clinically relevant cardiovascular protection is unknown. The outcome trials, all of which are large and event-driven, are thus essential to determine if these remarkable biomarker effects do indeed result in myocardial infarction, stroke, cardiovascular death, and other large cardiovascular outcomes. These findings provide an opportunity to directly target one of the most important inherited cardiovascular risk factors using potent nucleic acid-derived compounds and orally available small molecules. However, these agents are still under investigation, and strict control over known modifiable risk factors, especially LDL-C and blood pressure, is still necessary in patients with high Lp(a) until conclusive cardiovascular outcome evidence is obtained (Kronenberg et al., 2022).

Selected Lp(a)-lowering effects reported for emerging therapies.

Therapy	Study / evidence cited in the review	Lp(a)-lowering result reported
Pelacarsen	Phase 2 dose-ranging study	Largest reductions around 80% versus placebo
Olpasiran	OCEAN(a)-DOSE phase 2	Placebo-corrected changes consistently >95%
Lepodisiran	Early-phase clinical trial	Approximately 94% reduction at the highest dose studied
Muvalaplin	KRAKEN phase 2	85.8% reduction at 240 mg/day with intact Lp(a) assay
Zerlasiran	Early clinical trials	Significant decreases reported; exact percentage not specified in the review

3.1 Antisense Oligonucleotide Therapy

Pelacarsen is a hepatocyte-specific, N-acetylgalactosamine (GalNAc) conjugated antisense oligonucleotide (ASO) with specific activity against apolipoprotein(a) (apo(a) protein) production in the liver. Pelacarsen binds to apo(a) messenger RNA in the liver (hepatocytes) and enhances the degradation of the target RNA, which in turn reduces the synthesis and release of Lp(a) particles in the blood (Tsimikas et al., 2020). GalNAc-conjugation facilitates selective delivery of ASO to hepatocytes through the asialoglycoprotein receptor, translating to potent pharmacological activity, which is much lower than that required with previous non-targeted methods of ASO delivery (Tsimikas et al., 2020). Pelacarsen demonstrated lipid-lowering efficacy in a phase 2 dose-ranging study on patients with known cardiovascular disease and high Lp(a). Lp(a) levels were seen to decrease in a dose-dependent manner across all monthly and higher dosing frequencies, with the largest reductions around 80% versus placebo (Tsimikas et al., 2020). The effect of the dosing period persisted, with most in the higher dose groups achieving levels of Lp(a) associated with a decreased risk of cardiovascular events (Tsimikas et al., 2020). Importantly, no significant differences were observed between pelacarsen and placebo with respect to platelet counts or liver and renal laboratory values. Nevertheless, active treatment had more frequent injection-site reactions (Tsimikas et al., 2020). Furthermore, phase 2 program testing has demonstrated that pelacarsen also significantly lowered total Lp(a) concentration, while also reducing Lp(a)-associated cholesterol, highlighting the specificity of the treatment effect (Yeang et al., 2022). These results presented valuable conceptual evidence that pharmacological inhibition of apo(a) production can result in radical decreases in the circulation of Lp(a). Traditional cardiovascular therapies have been hard to modify this lipoprotein. Pelacarsen is currently being evaluated in the final stage of the Lp(a)HORIZON cardiovascular outcomes trial. The study included a total of 8,323 patients with preexisting ASCVD who had high Lp(a) levels. They were randomized to monthly subcutaneous pelacarsen 80 mg versus placebo, and its primary objective was to demonstrate whether intensive Lp(a) lowering reduces major adverse cardiovascular events (MACE) (Novartis, 2025). Unlike the previous pelacarsen studies, which have primarily estimated the modification of

Lp(a) levels, Lp(a)HORIZON is the first study characterizing the effect on cardiovascular events of reducing the level of this genetically defined lipoprotein. No definitive overall findings from the Lp(a)HORIZON were published by August 2026. Recent reports indicate that the outcome of the trial is expected in the second half of 2026 (Reuters, 2026). Thus, while the phase 2 trials have shown strong and persistent Lp(a) lowering with pelacarsen, it is still too early to define it as a proven cardiovascular outcome-reducing treatment. The outcome of Lp(a)HORIZON will specifically be of interest since it will deliver one of the first direct studies on whether pharmacological reduction of Lp(a), independent of LDL-C reduction, would result in a reduction of cardiovascular events. In sum, the pelacarsen study is the most sophisticated specific approach to down-regulation of Lp(a) and provided good evidence that it is possible to successfully down-regulate hepatic apo(a) production through the use of antisense technology. However, evidence of clinical relevance crucially depends on whether these substantial decreases in Lp(a) levels in previous trials can be translated into decreases in myocardial infarction, stroke, cardiovascular mortality, and other relevant cardiovascular outcome events. The success of Lp(a)HORIZON will thus define the future of Lp(a)-directed therapy as a key routine preventive therapy for ASCVD.

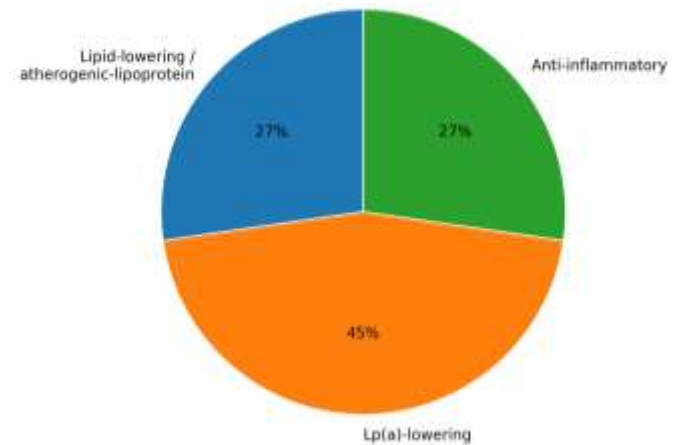
3.2 Small Interfering RNA Therapies

Small interfering RNA (siRNA) therapies will be a major new advance in the field of Lp(a) lowering pharmacology, as these drugs directly target the liver to inhibit the production of apolipoprotein(a) [apo(a)] at the messenger RNA (mRNA) level. They are generally linked to the sugar N-acetylgalactosamine (GalNAc) and thus are taken up by the hepatocyte through the asialoglycoprotein receptor. Upon intracellular delivery, siRNA becomes part of the RNA-induced silencing complex and the synthesis of apo(a) is inhibited, while its mRNA is destroyed in a sequence-specific fashion (O'Donoghue et al., 2022; Nissen et al., 2023). The mechanism can induce much more potent and durable reductions in Lp(a) than any other currently available conventional lipid-lowering therapies. Olpasiran is one of the newest Lp(a)-targeted siRNA therapies. Olpasiran resulted in dose-dependent and significant decreases in the levels of Lp(a) in patients with ASCVD and elevated Lp(a) in the phase 2 OCEAN(a)-DOSE trial. The placebo-corrected changes were consistently >95% in the treatment period, suggesting the potential for RNA interference to achieve virtually complete suppression of circulating Lp(a) (O'Donoghue et al., 2022). Notably, high levels of suppression were maintained between injections, justifying reduced dosing schedules, and the long-lasting pharmacodynamic effects of the siRNA platform (O'Donoghue et al., 2022). Olpasiran is currently in Phase 3 in the phase 3 OCEAN(a)-Outcomes trial, which will compare intensive Lp(a) lowering to standard Lp(a) lowering in patients with already diagnosed ASCVD and high Lp(a) (ClinicalTrials.gov, 2026). The report involves over 7,000 individuals and cardiovascular outcomes (not Lp(a) concentration) as its key efficacy outcome. This difference is important because highly significant decreases in phase 2 were observed. Still, it remains to be determined whether the reductions in Lp(a) seen with the > 90 percent drop in the study will translate to a corresponding decrease in myocardial infarction, stroke, and other clinically relevant adverse cardiovascular events. OCEAN(a)-Outcomes results should thus yield valuable data on the clinical value of pharmacological reduction of Lp(a). A second long-acting GalNAc-conjugated siRNA to block hepatic apo(a) development is called Lepodisiran. Of particular interest is its pharmacological properties, as the molecule has been engineered for longer suppression after a single dose, which may allow annual or even reduced dosing (Nissen et al., 2023). In an early-phase clinical trial, a single dose of lepodisiran led to significant and sustained reductions in Lp(a) by approximately 94% over follow-up, with the highest dose studied (Nissen et al., 2023). The extended duration of effect may be beneficial for long-term therapy, since less frequent dosing may decrease treatment burden and increase adherence compared with more frequent dosing of injectable medications. The phase 3 ACCLAIM-Lp(a) outcomes program aims to provide evidence on whether sustained Lp(a) reduction is associated with a reduced incidence of major cardiovascular events

(Nissen et al., 2023). Just as in the case of olpasiran, the scientific question of interest is no longer: Can the drug significantly reduce Lp(a) - this has already been proven - but: Can such deep and long-lasting suppression result in any clinical benefit? The results will consequently be important in understanding the required reductions in Lp(a) to impact cardiovascular risk and whether long-acting RNA-based therapy is a viable option for those with greatly elevated Lp(a). Another experimental siRNA therapy that targets production of apo(a) in the liver is called Zerlasiran. Early clinical trials have shown that there are significant decreases in Lp(a) levels in the blood, which in turn testify to the overall possibility of RNA interference as a therapy option to address this lipoprotein, which has been hard to target previously (Nissen et al., 2022). Though zerlasiran has shown promising pharmacodynamic effects, it is not as far along in clinical development as pelacarsen, olpasiran and lepodisiran. This means that more extensive studies and cardiovascular outcome trials will be needed to establish its ultimate therapeutic niche. In combination, the three agents, olpasiran, lepodisiran and zerlasiran, demonstrate that large and sustained reductions in Lp(a) are achievable using siRNA technology. The main advantages for hepatocyte targeting, long-term pharmacodynamic effects, and potential reduction in dosing are thought to be the advantages of these novel products (O'Donoghue et al., 2022; Nissen et al., 2023). Nonetheless, the existing data is still mostly based on decreases in the Lp(a) biomarker rather than a concrete cardiovascular outcome advantage. The question of whether the impressive biochemical effectiveness of these agents can translate to clinically significant reductions in ASCVD events will therefore be answered by ongoing phase 3 outcome studies, and whether lowering Lp(a) can be a new pillar of cardiovascular prevention will be addressed.

3.3 Oral Small-Molecule Therapy

Muvalaplin is an oral small-molecule therapy that is mechanistically different from all other classes of LDL-cholesterol-lowering therapies to date, which target lowering of lipoprotein(a) [Lp(a)]. Unlike antisense oligonucleotides and small interfering RNA (siRNA) therapies that target hepatic apolipoprotein(a) [apo(a)] synthesis at the messenger RNA (mRNA) level, muvalaplin blocks the production of Lp(a) particles by disrupting the noncovalent interaction between apolipoprotein(a) and apolipoprotein B-100 (apoB-100) (Nicholls et al., 2023). This mechanism helps to prevent the formation of mature Lp(a) particles. It may serve as an important therapeutic approach that is not based on the direct inhibition of LPA gene expression. Early evidence came from a phase 1 randomized clinical trial (RCT) that assessed the safety, tolerability, pharmacokinetics, and pharmacodynamic effects of muvalaplin in healthy individuals. In this study, oral muvalaplin showed dose-dependent reduction in circulating Lp(a), with up to ~65% reduction after repeated dosing at the highest dose studied (Nicholls et al., 2023). apo(a) shares structural homology with plasminogen (Nicholls et al., 2023), which is an important factor to consider because the treatment did not have clinically important effects on plasminogen concentration or activity. The results were a first indication that the pharmacological inhibition of Lp(a) particle formation might be possible without significant impact on the physiological fibrinolytic pathway. The effectiveness of muvalaplin was then tested in the phase 2 KRAKEN randomized clinical trial in 233 patients with cardiovascular disease (CVD), diabetes or familial hypercholesterolemia (FH) and serum Lp(a) levels of ≥ 175 nmol/L (Nicholls et al., 2024).



Patients were assigned randomly to receive oral muvalaplin 10, 60 or 240 mg daily or placebo for 12 weeks. When tested with the intact Lp(a) assay, the reduction in Lp(a) level was 85.8% (95% CI, 83.1%–88.0%) with muvalaplin at the highest dose of 240 mg once a day (Nicholls et al., 2024). The reduction in circulating Lp(a) was assay-dependent and was 68.9% in the corresponding placebo group (95% CI, 63.8%–73.3%), indicating significant suppression of Lp(a) in plasma (Nicholls et al., 2024). Another lipid parameter was also shown to be dose-dependent in the KRAKEN trial. There was a reduction in LDL-C and apolipoprotein B by 21.3% and 16.1%, respectively, compared to placebo, at 240 mg/day (Nicholls et al., 2024). The main pharmacological action of interest, however, was the substantial decrease in Lp(a). Concurrently, there was no clinically significant difference between treatment groups in the change in high-sensitivity C-reactive protein (Nicholls et al., 2024). Importantly, during the 12-week treatment duration, no significant safety or tolerability concerns were seen with muvalaplin, indicating good tolerability at all dose levels (Nicholls et al., 2024). The oral delivery of muvalaplin is a potentially significant benefit over the injectable RNA-based Lp(a) lowering drugs being developed. While subcutaneous injection for Pelacarsen, olpasiran and lepodisiran is necessary for their administration, an effective oral small molecule could offer a less-invasive alternative for long-term treatment of patients with substantially elevated Lp(a) (Nicholls et al., 2023; Nicholls et al., 2024). However, whether this convenience will lead to increased adherence/persistence and clinical effectiveness in daily practice is still to be determined and will need additional studies over longer periods of time. The existing data with muvalaplin are limited to biomarker modification and not cardiovascular outcomes despite the significant changes seen in phase 1 and phase 2 studies. The KRAKEN investigators specifically found a lack of evidence to support the effect of muvalaplin on cardiovascular events, and recommended further investigation (Nicholls et al., 2024). Therefore, it is not known if lowering Lp(a) by inhibiting the assembly of the particles will lower myocardial infarction, ischemic stroke, cardiovascular death, or other major adverse cardiovascular events. To answer the big question of whether the promising biochemical results seen with muvalaplin result in meaningful cardiovascular benefits, a large, well-powered cardiovascular outcomes trial will be needed. In Phase 2, daily oral treatment appeared to lower Lp(a) significantly by more than 80% at the highest dose studied, as measured by an intact Lp(a) assay, and had an acceptable short-term safety profile (Nicholls et al., 2024). Ultimately, however, its role in ASCVD prevention will depend on longer-term cardiovascular outcome and safety data. In the absence of such data, muvalaplin can be regarded as a potential investigational therapy for elevated Lp(a) until further data are available.

4. Anti-Inflammatory Therapies

Inflammation has been confirmed as a primary and independent risk factor in atherosclerosis, in addition to lipid deposition, in the pathogenesis, progression, and destabilization of atherosclerotic plaques. Retention or modification of atherogenic lipoproteins in the

arterial wall stimulates the activation of the endothelial cell and monocyte and other immune cell recruitment, which subsequently leads to the accumulation of macrophages, the release of cytokines, the formation of a necrotic core, and the weakening of the fibrous cap (Libby, 2021). Consequently, the biological justification is the complementary role of anti-inflammatory therapy as an adjunct to ASCVD prevention, even in individuals on effective lipid-lowering therapy who still have chronic inflammation. The CANTOS trial served to validate the hypothesis that inflammation was a degree of cardiovascular risk that could be modified. But in patients with a history of a myocardial infarction (MI) and high levels of high-sensitivity C-reactive protein (hs-CRP), the use of canakinumab, a monoclonal antibody against IL-1, showed significant reductions in the recurrence of cardiovascular events without any effects on LDL-C, the first direct clinical evidence indicating that selective targeting of inflammation could alter cardiovascular outcomes independent of the conventional lipid lowering (Ridker et al., 2017). But treatment was also found to be a risk factor for deadly infection, which restricted its use as a regular cardiovascular therapy (Ridker et al., 2017). More research has focused on colchicine, a cheap anti-inflammatory agent, which has been demonstrated to prevent polymerization of microtubules and mediate multiple inflammatory pathways that are known to mediate leukocyte activation and NLRP3 inflammasome signaling (Tardif et al., 2019). COLCOT trial showed that low-dose colchicine was effective at preventing cardiovascular events in patients receiving it early after myocardial infarction (MI) (Tardif et al., 2019), and in patients with chronic coronary disease (LoDoCo2 trial) (Nidorf et al., 2020). These results further support the idea that reducing inflammation would reduce cardiovascular risk without depending on LDL-C levels. The downstream inflammatory cytokine of interest, interleukin-6 (IL-6), has recently been of interest and has a role in the hepatic acute-phase responses and systemic inflammatory signaling. Ziltivekimab is a monoclonal antibody against IL-6 ligand, which is specifically used in the treatment of atherosclerotic cardiovascular disease patients with high inflammatory risk. Original studies demonstrated that hs-CRP and other inflammatory biomarkers were significantly reduced, and there was considerable interest in using IL-6 as a more specific anti-inflammatory strategy (Ridker et al., 2021). However, the development of IL-6-guided therapy has also highlighted the importance of the gap between inhibition of inflammatory biomarkers and clinical effects. Ziltivekimab showed significant decreases in inflammatory biomarkers in the phase 3 ZEUS trial, but failed to show significant differences for the primary major adverse cardiovascular event endpoint compared to placebo (ZEUS Investigators, 2026). The finding shows that successful biological target engagement is not always associated with cardiovascular benefit, and that the association of systemic inflammatory markers with plaque inflammatory activity is complex. The contradictory results of the recent trials underscore the importance of adequately sized cardiovascular outcome trials, not only in terms of modification in hs-CRP or any other surrogate inflammatory predictors. Additional identification of patients at risk of inflammation will still be needed, and more knowledge of the inflammatory pathways in terms of plaque progression and clinical instability will be needed in future therapies against inflammation.

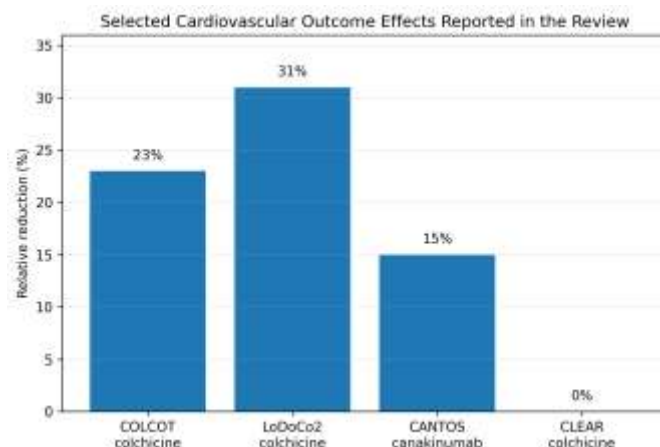
Selected anti-inflammatory cardiovascular outcome findings reported in the review.

Therapy / trial	Population / setting	Outcome reported in the review
Colchicine / COLCOT	4,745 patients after myocardial infarction	Primary composite endpoint 5.5% vs 7.1%; approximately 23% relative reduction
Colchicine / LoDoCo2	5,522 patients with chronic coronary disease	Primary composite endpoint 6.8% vs 9.6%; approximately 31% relative reduction
Canakinumab / CANTOS	10,061 patients with previous MI and elevated hs-CRP	Primary composite endpoint reduced by about 15% at 150 mg

Colchicine / CLEAR	7,062 patients with acute MI	No significant reduction; HR 0.99, P=0.93
Ziltivekimab / ZEUS	6,376 patients with ASCVD, CKD and high hs-CRP	Inflammatory biomarkers decreased, but no significant primary MACE reduction

4.1 Colchicine

Colchicine is an inexpensive, orally active anti-inflammatory alkaloid that prevents microtubule polymerization and disrupts several inflammatory mechanisms involved in atherosclerotic plaque development. Colchicine may inhibit NLRP3 inflammasome activation and downstream effects of proinflammatory cytokines, such as interleukin-18 and interleukin-1 β , in monocytes and macrophages at low doses (Martínez et al., 2018). These pathways have also been implicated in vascular inflammation and plaque instability, so colchicine has been investigated as a potential adjunctive therapy to conventional lipid-lowering treatment to lower or eliminate residual inflammatory cardiovascular risk. The clinical data on colchicine were first provided through the COLCOT trial, which was a randomized trial of 4,745 patients who had suffered myocardial infarction within 30 days, randomized to receive colchicine 0.5 mg daily or placebo (Tardif et al., 2019). The primary composite endpoint of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization because of angina resulting in coronary revascularization was observed in 5.5% of the patients taking colchicine versus 7.1% taking placebo (HR, 0.77; 95% CI, 0.610.96; P=0.02), indicating a relative reduction in the primary endpoint of approximately 23%. The decrease was especially due to fewer strokes and emergency hospitalization cases due to angina that resulted in coronary revascularization, and cardiovascular mortality did not decrease significantly (Tardif et al., 2019). The trial LoDoCo2 then considered the extension of the benefit of low-dose colchicine to stable chronic patients with coronary disease. In 5,522 patients randomly selected to receive either colchicine 0.5 mg daily or placebo, the primary composite endpoint of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization, 6.8% of patients taking colchicine and 9.6% taking placebo experienced the primary outcome over a median of 28.6 months (HR, 0.69; 95% CI, 0.570.83; P<0.001) (Nidorf et al., 2020). This amounted to a relative decrease of about 31% in the primary cardiovascular outcome and also presented valuable independent data that low-dose anti-inflammatory therapy could decrease the incidence of cardiovascular events in patients already undergoing modern secondary-prevention interventions, such as lipid-lowering treatment (Nidorf et al., 2020). However, the level of benefit should be viewed in the context of the diverse populations and endpoints used in the two trials. Both studies showed no statistically significant decrease in all-cause mortality, and LoDoCo2 had a numerically higher incidence of noncardiovascular death with colchicine. Nonetheless, the risk difference was within the confidence interval (Nidorf et al., 2020).



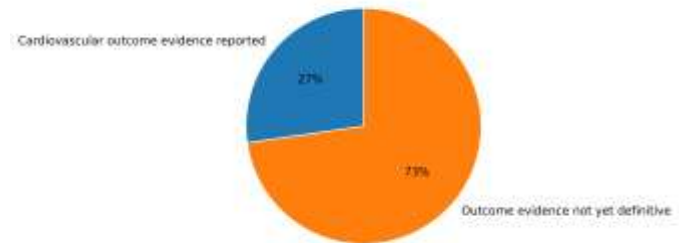
The most common tolerability problem is gastrointestinal, with diarrhea being the most common gastrointestinal problem. Clinicians also should be aware of potential drug interactions and toxicity in

patients with severe renal or hepatic impairment (Tardif et al., 2019). Notably, later evidence has shown that the cardiovascular effects of colchicine can be conditional on the clinical setting and timing of treatment. The CLEAR trial randomized 7,062 patients with acute myocardial infarction (AMI) and initiated colchicine treatment shortly after AMI and found that colchicine did not significantly reduce the primary composite outcome of cardiovascular death, recurrent AMI, stroke, or unplanned ischemia-driven coronary revascularization after approximately three years' follow-up (HR, 0.99; 95% CI, 0.851.16; $P=0.93$) (CLEAR Investigators, 2025). The reduction in C-reactive protein was substantial. Still, it was not possible to translate that effect into a reduction of clinical cardiovascular outcomes, further highlighting the concept of a difference between inflammatory target engagement and clinical outcome. In turn, low-dose colchicine was the first colchicine formulation to be approved by the U.S. Food and Drug Administration to decrease the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adults with known atherosclerotic disease or multiple cardiovascular risk factors (U.S. Food and Drug Administration, 2023). Regulatory approval reflects positive results from COLCOT, LoDoCo2, and the literature, but the varying results across clinical settings highlight the importance of patient selection. In general, colchicine offers significant evidence that pharmacological adjustment of inflammation can decrease cardiovascular events without further lowering in patients with ASCVD who are selected; it is one of the most clinically mature anti-inflammatory strategies in cardiovascular medicine, is low cost and oral, has proven pharmacology, and reduces events in COLCOT and LoDoCo2 (Tardif et al., 2019; Nidorf et al., 2020). However, the more recent CLEAR trial has neutral findings, which suggest that its benefits are not always applicable to all post-MI populations and treatment strategies (CLEAR Investigators, 2025).

4.2 Interleukin-1 β and Interleukin-6 Pathway Inhibition

The CANTOS trial was the first large clinical study to support the inflammatory hypothesis of atherosclerosis by showing that the selective IL-1 β inhibitor had a cardiovascular effect independent of LDL-C reduction. In the CANTOS trial, 10,061 patients with a previous myocardial infarction who had elevated levels of hs-CRP were randomly assigned to receive canakinumab, a monoclonal antibody to IL-1 β , or placebo (Ridker et al., 2017). Despite its lack of significant LDL-C reduction, at the 150 mg dose, canakinumab was able to reduce the primary composite endpoint of nonfatal MI, nonfatal stroke, or cardiovascular death by about 15% compared with placebo (HR, 0.85; 95% CI, 0.74–0.98; $P=0.021$) (Ridker et al., 2017). The cardiovascular benefit also correlated with the extent of the decreases in inflammatory markers, further evidence that inflammation may be a therapeutically targetable component of cardiovascular risk. Even with this proof of concept, canakinumab was never adopted for routine cardiovascular use. There was also a higher likelihood of fatal infections with treatment, and no significant decreases in all-cause mortality (Ridker et al., 2017). However, because it was too expensive and required repeated subcutaneous administration, it was much too limited to be a general cardiovascular-prevention therapy. However, the results of the CANTOS trial created a biological paradigm: It was possible to reduce cardiovascular events through targeted anti-inflammatory treatment without directly reducing circulating LDL-C levels (Ridker et al., 2017). This then led to a focus on other components in the inflammatory cascade of IL-1 β and IL-6 in the downstream pathways that may be more selective or clinically relevant targets. Interleukin-6 (IL-6) is a particularly interesting target due to its downstream role from IL-1 β and its role in the acute-phase response in the liver, such as C-reactive protein (CRP) production.

Clinical Evidence Status of Named Emerging Therapies



Consistently higher levels of IL-6 have been independently linked to cardiovascular events and mortality, and analysis of CANTOS indicated that those who had the most significant reduction in IL-6 and hs-CRP had the most cardiovascular benefit (Ridker et al., 2018). This observation led to the hypothesis that direct inhibition of IL-6 would be a therapeutic approach to decrease residual inflammatory cardiovascular risk. Ziltivekimab is a fully human monoclonal antibody that targets the IL-6 ligand, developed specifically for patients with atherosclerotic cardiovascular disease, chronic kidney disease (CKD), and chronic systemic inflammation. In earlier phase 2 studies, significant decreases in hs-CRP and other inflammatory markers were observed with relatively modest effects on conventional lipid markers, suggesting that its effects may be more as an anti-inflammatory agent than a lipid-lowering agent (Ridker et al., 2021). The next ZEUS trial, phase 3, included 6,376 patients with known ASCVD and CKD and high levels of hs-CRP (at least 2 mg/L), a population with high cardiovascular risk and residual inflammatory activity (ZEUS Investigators, 2026). However, the results of ZEUS did not confirm the anticipated cardiovascular benefit. The expected pharmacodynamic effects were also seen, such as significantly lower levels of inflammatory markers, but not the prespecified reduction in the primary three-point major adverse cardiovascular event (MACE) endpoint (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) after 12 months of treatment with ziltivekimab (ZEUS Investigators, 2026). An additional safety parameter of long-term systemic cytokine inhibition noted in the trial was an increased incidence of serious infections with ziltivekimab (Reuters, 2026). Despite the apparent engagement and IL-6 suppression, there was no apparent reduction in major cardiovascular events when IL-6 was inhibited in the ZEUS population. There is evidence that targeting IL-1 β can reduce cardiovascular events in a specific inflammatory-risk population, but direct IL-6 inhibition with ziltivekimab did not have a similar effect, although both drugs showed strong suppression of the IL-6 biomarker (Ridker et al., 2017; ZEUS Investigators, 2026). These conclusions suggest that the timing of intervention in the inflammatory process, patient selection, disease stage, treatment duration and systemic and plaque-specific inflammation may all impact the clinical efficacy of anti-inflammatory therapy. Importantly, the neutral ZEUS result does not rule out inflammation as a therapeutic target for cardiovascular disease. Instead, it is important to note that a decrease in hs-CRP or IL-6 may not necessarily correspond directly to a decrease in cardiovascular events. The findings also underscore the need for randomized cardiovascular outcome trials to differentiate true disease-modifying versus surrogate biomarker responses. Other ongoing trials are evaluating ziltivekimab in different cardiovascular populations (ACA, 2026): These studies will be valuable for defining the clinical impact of IL-6 inhibition in different disease contexts and inflammatory phenotypes. Taken together, the lessons learned from canakinumab and ziltivekimab illustrate both the promise and the caveats of cytokine-directed therapy in atherosclerosis. Although canakinumab proved a proof of concept for IL-1 β inhibition, it lacked the benefit of mortality reduction, was associated with high infection risk, and was costly; ziltivekimab showed strong IL-6 pathway inhibition without MACE reduction in ZEUS (Ridker et al., 2017; ZEUS Investigators, 2026).

5. Discussion

The treatments listed above reflect a spectrum of pharmacological treatment of atherosclerosis, from a predominantly LDL-C-centric approach to a multi-target approach that addresses multiple aspects of residual cardiovascular disease risk. Genetic, epidemiological and randomized clinical-trial data strongly support a causal association between atherogenic lipoproteins and cardiovascular disease, making intensive LDL-C lowering the mainstay of ASCVD prevention (Ference et al., 2017). Although lipid lowering is achieved, however, there remains a residual risk for cardiovascular events, which indicates that other pathways are associated with the remaining risk: Lp(a), remnant lipoproteins, metabolic abnormalities and vascular inflammation (Libby, 2021; Kronenberg et al., 2022). Collectively, the newer therapies, including inclisiran, bempedoic acid, obicetrapib, anti-inflammatory drugs and Lp(a)-directed drugs are a welcome addition to the therapeutic picture. First, there is a wide variation in the level of clinical proof for the novel LDL-C and atherogenic-lipoprotein-lowering drugs. Inclisiran could be a useful tool for improving adherence and chronic lipid management, thanks to its potent, long-lasting PCSK9 inhibition and LDL-C reduction of approximately 50%, and twice-yearly maintenance therapy. (Ray et al., 2020) But conclusive cardiovascular outcome data are still needed to determine if its tremendous LDL-C lowering effect is matched by a decrease in large cardiovascular events. Bempedoic acid has, however, been demonstrated to have cardiovascular outcome benefit. Among statin-intolerant patients, treatment reduced the primary composite cardiovascular events by 13%, and ATP-citrate lyase inhibition is a clinically proven non-statin treatment (Nissen et al., 2023). Obicetrapib has delivered significant decreases in LDL-C, apoB, non-HDL-C and Lp(a) levels. However, the final clinical utilization of this will rely on the results of the continuing cardiovascular outcomes trial (PREVAIL; Maalizadeh et al., 2025). Secondly, the field of emerging lipid pharmacology, specifically drugs that target Lp(a), is one of the most exciting. However, RNA-based therapies such as pelacarsen, olpasiran, lepdisiran, and others have provided levels of Lp(a) reduction that are significantly higher than those seen with conventional lipid-lowering drugs (Tsimikas et al., 2020; O'Donoghue et al., 2022; Nissen et al., 2023). Muvalaplin has also demonstrated the ability to potentially decrease Lp(a) levels by interfering with the assembly of particles, but not the production of apo(a) (Nicholls et al., 2024). The results are especially significant because high Lp(a) is a largely genetic trait that is relatively unresponsive to lifestyle change and conventional lipid-lowering agents (Kronenberg et al., 2022). But current data are still mostly on decreases in biomarkers. Whether dramatic and lasting Lp(a) reductions will result in fewer myocardial infarctions, strokes, and cardiovascular deaths remains the key question. If Lp(a) proves to be an effective therapeutic target on its own merits in the results of the large cardiovascular outcomes trials such as Lp(a)HORIZON and OCEAN(a)-Outcomes, then it will be a goal of routine ASCVD management. Thirdly, the anti-inflammatory pathway has generated a clinically very diverse picture. CANTOS established a proof-of-concept study showing a beneficial effect of selective inhibition of IL-1 β on reducing recurrent cardiovascular events, indicating inflammation as a causal and potentially therapeutic modifiable factor of ASCVD (Ridker et al., 2017). In both COLCOT and LoDoCo2, low-dose colchicine was demonstrated to have cardiovascular benefits. However, the more recent CLEAR trial, when treatment was administered shortly after myocardial infarction, had a neutral result, indicating potential influences of treatment timing and/or patient selection on treatment outcomes (Tardif et al., 2019; Nidorf et al., 2020; CLEAR Investigators, 2025). In contrast, the ZEUS phase 3 trial showed that ziltivekimab significantly decreased inflammatory biomarkers but not major cardiovascular events (ZEUS Investigators, 2026). The conflicting data show that inflammation is a non-uniform therapeutic target, and that therapeutic outcomes vary according to the type of the mediator, the stage of the disease, the inflammatory phenotype, and the context of the disease. An important finding of this study is that improved biomarkers do not necessarily translate into clinical effectiveness. LDL-C reduction is best supported by the evidence, with LDL-C and apoB-containing lipoproteins shown to

consistently have proportional cardiovascular event reductions in randomized trials, as demonstrated previously (Baigent et al., 2010; Ference et al., 2017). In contrast, the relationship between Lp(a) reduction and cardiovascular benefit has yet to be established in prospective studies, and reductions in inflammatory markers like hs-CRP have not been consistently associated with clinical benefit in all anti-inflammatory approaches (Ridker et al., 2017; ZEUS Investigators, 2026). This translates to the continued need for large, well-powered, and event-driven cardiovascular outcome trials before the new treatments enter mainstream clinical practice. Thus, future treatment strategies to manage residual cardiovascular risk will probably be more personalized and mechanistic, rather than the one-size-fits-all pharmacologic therapy. Combinations of statins with ezetimibe, PCSK9-directed therapies, or bempedoic acid may be appropriate for patients with LDL-C levels that are not sufficiently low; CETP inhibition may also be considered in selected patients. However, those having very high levels of Lp(a) may need targeted Lp(a)-lowering therapy someday (Kronenberg et al., 2022). Conversely, anti-inflammatory therapy might be the best option for those carefully selected patients who continue to have persistent inflammatory activity despite best control of conventional risk factors. This would allow for more appropriate intensity and type of treatment to be used with the most important biological cause of residual risk. However, several practical questions remain unanswered. More recent injectables and RNA therapies may be limited in their widespread uptake, as they are generally more expensive than other therapies and less available, particularly for smaller health systems. Further, long-term safety information is required because many of the new therapies will be prescribed to relatively asymptomatic patients over many years, because of their long-term risk of cardiovascular disease. The order in which these agents are used in combination with other established therapy, such as statins and/or ezetimibe, or PCSK9 monoclonal antibody therapy, is also not known. Comparative-effectiveness studies and real-world evidence will thus need to be conducted to determine the best possible cost/burden on treatment and adverse-event risk combinations. The data are still not compelling enough to consider these therapies as alternatives to intensive LDL-C-lowering treatment; new treatments should be used in addition to, and not as a replacement for, guideline-directed LDL-C lowering therapies in patients with high residual risk. One major concern in drug development will continue to be whether or not there is biological activity or a proven cardiovascular benefit. Achievement of patient-important cardiovascular outcomes over time, long-term safety, identification of the populations that are likely to benefit from the therapies, and understanding how such therapies can be effectively combined with current best practices will be critical requirements for future successful integration of Lp(a)-lowering, novel lipid-lowering and anti-inflammatory therapies into clinical practice.

6. Conclusion

There is now considerable diversity in the pharmacologic management of atherosclerosis, which goes well beyond a statin-only strategy for lowering LDL-C. While intensive LDL-C lowering continues to be the backbone of ASCVD prevention, therapies targeting other pathways, such as hepatic PCSK9 synthesis, ATP-citrate lyase, CETP, lipoprotein(a) [Lp(a)], and vascular inflammation, have been gaining increased attention. Two newer drugs, bempedoic acid and colchicine, have already shown cardiovascular outcome benefits in the right indication and in the appropriate population. In a selected group of patients with coronary disease, low-dose colchicine has also been shown to have cardiovascular benefits. But variations between clinical trials suggest that it may be more or less effective in different patients, with different clinical characteristics and at different stages of treatment. Another significant development is inclisiran, which can achieve long-lasting PCSK9 suppression along with significant LDL-C lowering effects and is administered only twice a year as a maintenance dose. Similarly, obicetrapib has shown very significant effects on LDL-C and other atherogenic lipoproteins. However, it remains to be seen whether it will have a place in routine cardiovascular prevention, pending confirmation of cardiovascular benefit in dedicated outcome studies. The emergence of Lp(a)-

targeted therapy may be one of the biggest breakthroughs in preventive cardiology, as it is a largely genetically determined condition and has historically not had a targeted treatment. Efforts to directly target an important element of genetically determined residual cardiovascular risk have shown remarkably large reductions in circulating Lp(a) levels with Pelacarsen, olpasiran, lepodisiran, zerlasiran, and muvalaplin. The big unknown, though, is whether the significant decreases in Lp(a) levels will lead to a decrease in the number of myocardial infarctions, strokes, cardiovascular deaths, and other big adverse cardiovascular events. Selected inflammatory pathways are modifiable therapeutically to decrease cardiovascular events with the use of canakinumab and colchicine. By comparison, the ZEUS trial in patients with ziltivekimab showed that a significant reduction in inflammatory markers does not always lead to cardiovascular benefits. This study highlights that biological plausibility and successful modulation of the biomarker does not necessarily mean that outcomes for patients will improve, and that the effects of modulation in different inflammatory pathways may be very different. In general, the future of atherothrombotic drug therapy will be more personalized and mechanism-based, with treatment directed towards the primary drivers of cardiovascular risk that remain after pharmacotherapy. However, new therapies should be used in addition to existing evidence-based therapy, especially high-intensity LDL-C lowering therapy. All new therapies must be shown to provide a cardiovascular benefit with good safety, treatment burden, accessibility, and cost-effectiveness in well-powered randomized controlled outcome studies before they can be widely used in the clinic. In sum, this integration of novel classes of therapies—lipid-lowering, Lp(a)-directed, and anti-inflammatory—has the potential to significantly broaden the scope for prevention of recurrent ASCVD events and the global burden of atherosclerotic cardiovascular disease.

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