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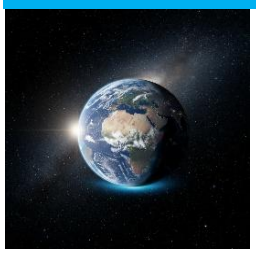

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Targeting lipoprotein(a) in premature atherosclerotic cardiovascular disease: from pathophysiology to RNA-based therapeutics - a narrative review

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Abstract

Background. Elevated lipoprotein(a) [Lp(a)] is an independent, genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD). In young patients presenting with premature atherosclerotic cardiovascular disease (pASCVD), Lp(a) often emerges as the primary driver of residual cardiovascular risk, persisting despite aggressive low-density lipoprotein cholesterol reduction.

Aim. This review aims to summarize the pathophysiology of Lp(a) in the context of plaque vulnerability, evaluate the limitations of current lipid-lowering therapies, and analyze emerging pharmacological interventions including new RNA-targeted therapies.

Material and methods. A comprehensive search of PubMed-MEDLINE and ClinicalTrials.gov was conducted for articles published in English up to March 2026. Keywords included: lipoprotein(a), Lp(a), Lp(a) lowering, premature ASCVD, siRNA, pelacarsen, and olpasiran. We prioritized randomized controlled trials, meta-analyses, and current societal guidelines.

Results. Traditional lipid-lowering agents, including statins, show no significant effect on Lp(a) levels. Conversely, a novel class of RNA-targeted therapeutics - comprising antisense oligonucleotides (pelacarsen) and small interfering RNAs (olpasiran, zerlasiran, lepodisiran) - demonstrates high efficacy in Phase 1 and 2 trials, achieving near-total (up to 98%) and sustained suppression of Lp(a) concentrations.

Conclusions: The advent of RNA-based therapies represents a significant therapeutic advance in preventive cardiology, transforming Lp(a) from an unmodifiable risk marker into a therapeutic target. While ongoing Phase 3 cardiovascular outcomes trials predominantly enroll older cohorts, Mendelian randomization studies suggest that early initiation of Lp(a) lowering in the pASCVD population may yield the greatest long-term clinical benefits.

Keywords: lipoprotein(a); premature atherosclerotic cardiovascular disease; RNA-targeted therapies; residual cardiovascular risk.

1 Introduction and purpose

Despite significant advancements in lipid-lowering therapies and the widespread use of statins, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of global mortality [1]. A substantial proportion of patients, particularly young adults presenting with premature atherosclerotic cardiovascular disease (pASCVD) – most notably premature coronary artery disease (pCAD) – continue to experience recurrent ischemic events despite achieving target low-density lipoprotein cholesterol (LDL-C) levels [2]. This residual cardiovascular risk has

driven the search for novel therapeutic targets, bringing lipoprotein(a) [Lp(a)] to the forefront of preventive cardiology.

Lp(a) is a highly atherogenic, genetically determined circulating lipoprotein particle consisting of an LDL-like particle covalently bound to a unique glycoprotein, apolipoprotein(a) [apo(a)]. Due to its structural homology with plasminogen, Lp(a) exerts pleiotropic pathogenic effects: it is simultaneously pro-atherogenic, pro-inflammatory, and may be pro-thrombotic. Elevated Lp(a) levels – affecting an estimated 20% of the global population – are now recognized as an independent, causal risk factor for myocardial infarction, ischemic stroke, and calcific aortic valve stenosis [3,4]. Circulating Lp(a) concentrations are almost entirely dictated by the *LPA* gene, rendering lifestyle modifications and traditional lipid-lowering agents, such as statins, largely ineffective. In fact, evidence suggests that statin therapy may even paradoxically increase Lp(a) levels in some patients, but reports are heterogenous [5,6].

To this day, the lack of targeted pharmacological interventions has relegated Lp(a) to the status of an unmodifiable risk factor [7]. However, the landscape of cardiovascular pharmacotherapy is currently evolving with the advent of RNA-targeted therapies. Innovative approaches, including antisense oligonucleotides (ASOs) such as pelacarsen, and small interfering RNAs (siRNAs) like olpasiran and lepodisiran, are designed to inhibit the hepatic synthesis of apo(a) at the mRNA level. Early-phase clinical trials have demonstrated strong efficacy, achieving up to a 90% reduction in circulating Lp(a) concentrations with favorable safety profiles.

The aim of this narrative review is to summarize the current understanding of Lp(a) pathophysiology and to critically evaluate the most recent clinical evidence regarding emerging RNA-based therapies. Furthermore, this paper highlights the clinical implications of high Lp(a) reduction, with a specific focus on mitigating residual cardiovascular risk in patients with premature atherosclerotic cardiovascular disease.

2 Search strategy and selection criteria

References for this narrative review were identified through systematic searches of PubMed-MEDLINE and clinical trial registry ClinicalTrials.gov for articles published in English from database inception up to March 2026. The search string incorporated combinations of the following primary keywords: “lipoprotein(a)”, “Lp(a)”, “premature atherosclerotic cardiovascular disease”, “premature ASCVD”, “premature CAD”, “Lp(a) targeted”, “Lp(a) lowering”, “siRNA”, “pelacarsen”, “olpasiran”, “zerlasiran”, “lepodisiran”, and “muvalaplin”. We prioritized recent randomized controlled trials (Phase 1, 2, and design papers for Phase 3), meta-analyses, Mendelian randomization studies, and current societal guidelines (ESC/EAS, AHA/ACC). Older foundational publications were included selectively when establishing core pathophysiological mechanisms or historical context. The final reference selection was based on direct relevance to Lp(a) lowering and mitigating residual cardiovascular risk in younger adults and as in all narrative reviews, selection bias cannot be excluded.

3 Description of the state of knowledge

3.1 Pathophysiology of Lp(a) and premature atherosclerotic cardiovascular disease

3.1.1 Genetic determinants and structure

The pathogenicity of lipoprotein(a) is related to its complex and polymorphic molecular structure. The Lp(a) particle consists of a central low-density lipoprotein (LDL)-like core containing a single molecule of apolipoprotein B-100 (apoB-100). This core is covalently

linked via a single disulfide bond to the defining characteristic of the particle: apolipoprotein(a) [apo(a)], a highly glycosylated hydrophilic protein [8].
The synthesis and circulating levels of Lp(a) are highly heritable, with the *LPA* gene located on the long arm of chromosome 6 accounting for over 90% of the variance in plasma concentrations [9]. The most critical genetic determinant is the variable number of kringle IV type 2 (KIV-2) repeats within the *LPA* gene, which can range from 2 to over 40 copies. This copy number variation dictates the size of the synthesized apo(a) isoform. [10,11] There is an inverse, non-linear relationship between the apo(a) isoform size and plasma Lp(a) concentration. Smaller isoforms are synthesized and secreted by hepatocytes much more efficiently than larger ones. Consequently, individuals harboring alleles for low-molecular-weight apo(a) isoforms typically present with the highest, most atherogenic plasma Lp(a) levels [12].

3.1.2 Mechanisms of atherogenesis and inflammation

Lp(a) drives cardiovascular disease through several concurrent pathways, primarily atherogenic and pro-inflammatory. Because of its LDL-like core, Lp(a) can readily traverse the dysfunctional endothelium and enter the arterial intima. Factors contributing to lipoprotein accumulation include arterial wall permeability, blood pressure and lipoprotein concentration [13]. Once trapped in the subendothelial space, it undergoes oxidative modification, is phagocytosed by macrophages via scavenger receptors, and accelerates the formation of lipid-laden foam cells, the hallmark of early atherosclerotic plaques [14].
Furthermore, Lp(a) is recognized as the preferential carrier of oxidized phospholipids (OxPLs) in human plasma, binding them covalently via its apo(a) moiety. These OxPLs are highly bioreactive and pro-inflammatory. Upon delivery to the arterial wall, OxPL-Lp(a) complexes stimulate endothelial cells to express adhesion molecules (such as VCAM-1) and secrete chemoattractants (like MCP-1) [15], promoting monocyte recruitment. This cascade subsequently triggers the local release of potent pro-inflammatory cytokines, including interleukin-1 β (IL-1 β) and interleukin-6 (IL-6), perpetuating a chronic inflammatory environment within the vascular wall [16].

3.1.3 Pro-thrombotic potential

In addition to driving atherosclerosis, Lp(a) possesses a unique, albeit debated, pro-thrombotic potential. The apo(a) protein shares structural homology with plasminogen, the zymogen of the primary fibrinolytic enzyme, plasmin, because the *LPA* gene is believed to have evolved from a duplicated plasminogen gene (*PLG*) [17]. Due to this mimicry, Lp(a) can competitively inhibit the binding of plasminogen to fibrin and endothelial cell surfaces. This competition potentially impairs tissue plasminogen activator (tPA)-mediated fibrinolysis, shifting the hemostatic balance toward thrombosis [18]. Consequently, a ruptured atherosclerotic plaque in a patient with severely elevated Lp(a) may be significantly more likely to result in a rapid, occlusive thrombus and a subsequent acute ischemic event. However, although Lp(a) exhibits prothrombotic properties *in vitro*, clinical studies have failed to demonstrate a clear correlation between elevated Lp(a) levels and thrombotic events [19].

3.1.4 Lp(a) and plaque vulnerability

The clinical presentation of premature CAD is frequently characterized by acute plaque rupture rather than chronic exertional ischemia. This suggests a unique impact of Lp(a) on plaque stability. Experimental evidence indicates that Lp(a) and its associated OxPLs promote the apoptosis of vascular smooth muscle cells (VSMCs) [20] and increase the expression of matrix metalloproteinases (MMPs) [21]. The degradation of the extracellular matrix combined with a

depleted VSMC population results in a significantly thinner fibrous cap. For a young adult with a lifelong elevation of Lp(a), the coronary arteries often harbor these "vulnerable plaques". Those *in vitro* effects were confirmed in clinical studies, where elevated serum Lp(a) (but not LDL-C or total cholesterol) was associated with the presence of coronary vulnerable plaques [22]. Additionally, patients with elevated Lp(a) had a significantly higher proportion of thin-cap plaques as well as thinner minimal fibrous cap thickness [23]. Moreover, Lp(a) was associated with a higher risk of a vulnerable plaque producing a serious cardiovascular event [24]

3.2 The clinical phenotype of premature ASCVD and cumulative burden

The intersection of elevated lipoprotein(a) and premature atherosclerotic cardiovascular disease (pASCVD) remains a significant clinical challenge in preventive cardiology. pASCVD, traditionally defined as a heart attack, stroke, or peripheral artery disease occurring before age 55 in men or 65 in women, carries significant socioeconomic and psychological consequences. While familial hypercholesterolemia (FH) and lifestyle-driven metabolic syndrome account for a significant proportion of pASCVD, a substantial cohort of young patients presents with acute myocardial infarction in the complete absence of traditional risk factors, such as hypertension, diabetes, smoking, or drastically elevated LDL-C [25,26]. In this specific phenotype, elevated Lp(a) frequently acts as a key pathophysiological driver [27].

The disproportionate impact of Lp(a) on younger individuals is best understood through the concept of "cumulative burden," originally popularized in the context of LDL-C to describe the lifelong integrated exposure to lipoproteins [28]. In this model, the total cardiovascular risk is not just a function of a single measurement, but combines plasma concentration and the duration of exposure (concentration × time). Unlike LDL-C, which typically takes decades to reach highly atherogenic levels as a result of progressive metabolic changes related to lifestyle and aging, Lp(a) concentrations are largely genetically determined and established early in life. Plasma levels reach their lifelong plateau by the age of two and remain relatively stable thereafter [29]. Consequently, an individual born with an *LPA* genotype resulting in high Lp(a) production is subjected to constant, long-lasting atherogenic and pro-inflammatory exposure from early childhood.

Clinically and angiographically, this translates to a more aggressive disease trajectory. Young patients with elevated Lp(a) not only experience their first ischemic event significantly earlier in life, but they also frequently present with a more advanced atherosclerotic phenotype, including a higher incidence of multi-vessel coronary artery disease and accelerated progression of coronary artery calcification (CAC) [4]. In rare cases, it manifests as cardiovascular events not typically seen in this population such as ischemic stroke [30].

The clinical challenge of pASCVD, however, extends far beyond the first myocardial infarction; it is characterized by a high rate of recurrent events despite optimal medical therapy. Young patients with elevated Lp(a) exhibit a persistent residual risk even when their traditional lipid profiles are well controlled. For instance, recent analyses focusing on young patients following a first myocardial infarction confirmed that elevated Lp(a) independently predicts long-term major adverse cardiovascular events (MACE). High Lp(a) operates independently of the patient's LDL-C levels, systemic inflammation (hs-CRP), or the use of dual antiplatelet therapy [31,32].

Clinically, this presents a significant management challenge. A 40-year-old post-MI patient with an Lp(a) of 100 mg/dL may have their LDL-C aggressively lowered to target levels (e.g., < 55 mg/dL) using high-intensity statins and ezetimibe. Yet, because their Lp(a) remains unaddressed – and continues to carry bioactive oxidized phospholipids – their arterial wall

continues to be subjected to high atherogenic stress [33]. This high recurrence rate highlights the unmet clinical need for targeted Lp(a) reduction specifically in the pASCVD demographic. Recognizing this specific clinical phenotype underscores a critical gap in historical management. While screening for Lp(a) is now recommended at least once in an adult's lifetime by major cardiovascular guidelines [7,34], the lack of targeted therapies has historically rendered this knowledge actionable only through the aggressive control of concomitant risk factors – which is just as important in low Lp(a) population. Comprehensive cardiovascular prevention strategies, including physical activity and long-term health monitoring, are essential for reducing global ASCVD risk [35,36], they do not significantly lower genetically determined Lp(a) levels. The cumulative atherogenic burden of Lp(a) in pASCVD highlights the necessity of early, targeted interventions to halt disease progression and slow the occurrence of major cardiovascular events.

3.3 Current lipid-lowering therapies and Lp(a)

The management of patients with significantly elevated Lp(a), particularly those presenting with premature coronary artery disease (pCAD), remains a clinical challenge. Currently, there are no approved pharmacological therapies specifically indicated for the direct lowering of Lp(a) concentrations. Consequently, standard clinical practice relies heavily on the aggressive reduction of apolipoprotein B-containing lipoproteins (primarily LDL-C) to mitigate overall cardiovascular risk.

However, traditional and novel lipid-lowering agents exhibit highly variable effects on Lp(a) levels. A recent, comprehensive meta-analysis encompassing over 145,000 patients from 147 randomized controlled trials mapped the impact of currently available lipid-lowering therapies on Lp(a) concentrations [37]. The study confirmed that foundational therapies, including statins, ezetimibe, and bempedoic acid, have no clinically significant impact on Lp(a). While new non-statin therapies like bempedoic acid represent a significant advancement in managing general dyslipidemia and safely reducing overall cardiovascular risk, particularly in statin-intolerant patients [38], their specific effect on Lp(a) concentrations remains negligible. Conversely, therapies such as PCSK9 inhibitors, inclisiran, and CETP inhibitors demonstrate moderate Lp(a)-lowering capabilities, though these reductions are often insufficient to normalize levels in patients with severe baseline elevations.

The effects of currently available lipid-lowering therapies on Lp(a) are summarized in Table 1.

Effect of current lipid-lowering therapies on lipoprotein(a) levels (based on a comprehensive meta-analysis of 147 RCTs) [37].

Drug class	Effect on Lp(a) levels	Clinical utility in severe Lp(a) elevation
Statins	No significant effect	Inadequate for Lp(a) reduction; essential only for concomitant LDL-C management.
Ezetimibe	No significant effect	Ineffective for Lp(a) reduction.
Bempedoic Acid	No significant effect	Ineffective for Lp(a) reduction.
Fibrates, Omega-3	No significant effect	Ineffective for Lp(a) reduction.
PCSK9 Monoclonal Antibodies	Significant reduction (~29% decrease)	Modest benefit; insufficient to normalize Lp(a) in patients with severe baseline elevations (e.g., > 150 nmol/L).
Inclisiran (PCSK9-targeted siRNA)	Significant reduction (~22% decrease)	Modest benefit; similar clinical limitations to PCSK9 monoclonal antibodies.
CETP Inhibitors	Significant reduction (~46% decrease)	Noticeable reduction, but lack of primary indication and historical off-target effects may limit use.

Niacin	Significant reduction (~37% decrease)	Unfavorable side-effect profile limits clinical application, no proven benefit in cardiovascular events.

While therapies like PCSK9 and CETP inhibitors offer secondary reductions in Lp(a), their absolute impact is frequently inadequate for patients presenting with highly elevated Lp(a). In the absence of effective targeted pharmacotherapy, lipoprotein apheresis remains the only currently available intervention capable of acutely reducing Lp(a) levels by 60% to 80%. However, its invasive nature, high cost, and transient effect restrict its use as a routine therapy.

3.4 Emerging Lp(a)-targeting therapies

Given the limitations of conventional lipid-lowering agents, pharmaceutical development has shifted towards the genetic source of elevated Lp(a). Innovative RNA-based therapies, designed to interrupt the translation of the *LPA* gene, can substantially reduce or nearly eliminate circulating Lp(a).

3.4.1 Antisense oligonucleotides (ASOs): Pelacarsen

Antisense oligonucleotides (ASOs) represent the first generation of RNA-targeted therapies successfully advanced into late-stage clinical trials for Lp(a) reduction. ASOs are short, synthetic, single-stranded sequences of modified nucleic acids designed to selectively bind to a specific messenger RNA (mRNA) target via standard base pairing. Once inside the liver cell, the molecule locates the specific messenger RNA (mRNA) that carries the blueprint for the apo(a) protein. It binds to this mRNA and triggers a natural cellular enzyme (RNase H1) to destroy it [39]. Without the mRNA blueprint, the liver simply cannot manufacture or assemble the Lp(a) particle.

The first ASO with demonstrated efficacy in clinical trials was APO(a)Rx developed by Ionis Pharmaceuticals. In Phase 1 trials it showed a dose-dependent effect on lowering Lp(a) resulting in ca. 78% reduction in Lp(a) with no reported serious adverse effects. [39] However, the primary pharmacological challenge for nucleotide-based therapies is achieving targeted intracellular delivery while minimizing systemic exposure. In the case of APO(a)Rx, this was achieved through conjugation with a GalNAc complex targeting liver-specific receptors, resulting in a molecule roughly 30 times more potent [40].

This new molecule, named pelacarsen, demonstrated efficacy in a Phase 2 trial enrolling 286 patients with established cardiovascular disease and elevated baseline Lp(a) levels. The study demonstrated a significant, dose-dependent reduction in circulating Lp(a). The optimal dosing regimen of 60 mg administered subcutaneously once monthly (or 20 mg weekly) achieved a mean reduction of 72% - 80% ($P = 0.003$ to ≤ 0.001) in 6 months, effectively lowering Lp(a) below the widely recognized risk threshold of 50 mg/dL in up to 98% of participants in the weekly dose group [41]. The medication exhibited a favorable safety profile, with mild injection-site reactions being the most frequently reported adverse events.

To determine whether this biomarker reduction translates into overt clinical benefits, the global Phase 3 Lp(a)HORIZON cardiovascular outcomes trial is currently underway [42]. This large-scale Phase 3 trial has fully enrolled 8323 high-risk patients with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral artery disease, coupled with baseline Lp(a) levels $\geq$ 70 mg/dL, to evaluate a monthly subcutaneous dose of 80 mg. The primary endpoint is the incidence of major adverse cardiovascular events (MACE). The highly anticipated results of Lp(a)HORIZON will definitively answer whether specific Lp(a) lowering can successfully mitigate residual cardiovascular risk in this vulnerable population. This study (NCT04023552) is estimated to finish mid-2026.

3.4.2 Small interfering RNAs (siRNAs)

Small interfering RNAs (siRNAs) represent a subsequent class of RNA-targeted therapeutics designed to inhibit apolipoprotein(a) synthesis. Unlike ASOs, which primarily act within the nucleus, siRNAs exert their effects in the cytoplasm by harnessing the endogenous RNA-induced silencing complex (RISC). Once incorporated into RISC, the siRNA guide strand facilitates the targeted, catalytic degradation of mRNA. The primary pharmacological advantage of this mechanism is its catalytic nature: a single siRNA-RISC complex can sequentially degrade multiple mRNA transcripts, allowing for infrequent dosing every 3 to 6 months [43]. Currently, the clinical landscape of Lp(a)-lowering siRNAs is dominated by three agents: olpasiran, zerlasiran, and lepodisiran. All three of these siRNA molecules utilize GalNAc conjugation to ensure highly specific, receptor-mediated delivery to hepatocytes, thereby minimizing systemic exposure.
While they share the same fundamental RISC-dependent mechanism, these agents are currently in different stages of clinical development. Olpasiran is the most advanced candidate within this class, having successfully completed Phase 2 dose-finding studies and progressed to a large-scale Phase 3 cardiovascular outcomes trial.

3.4.2.1 Olpasiran

The clinical efficacy and safety of olpasiran were evaluated in the Phase 2 OCEAN(a)-DOSE trial. This randomized, double-blind, placebo-controlled study enrolled 281 patients with established atherosclerotic cardiovascular disease and baseline Lp(a) concentrations exceeding 150 nmol/L. Patients were assigned to receive various doses of olpasiran administered subcutaneously every 12 or 24 weeks [44].
The trial revealed a significant, dose-dependent suppression of Lp(a) concentrations among patients receiving the active treatment. Specifically, at week 36, the placebo-adjusted mean percentage reductions from baseline were 70.5% for the 10-mg dose, 97.4% for the 75-mg dose, and 101.1% for the 225-mg dose, all administered on a 12-week dosing schedule. Extending the administration interval to 24 weeks for the 225-mg cohort still yielded a near-complete reduction of 100.5%. All of these dose-dependent decreases were highly statistically significant ($P < 0.001$) [44]. Furthermore, the medication exhibited a highly favorable safety profile; the incidence of adverse events was similar to that of placebo, with mild injection-site reactions being the most frequently reported issue, and no significant hepatotoxicity or renal impairment was observed.
Following these definitive results, the clinical development of olpasiran advanced to the ongoing Phase 3 OCEAN(a)-Outcomes trial (NCT05581303), which is estimated to end in early 2028. This global cardiovascular outcomes study enrolled 7297 patients with Lp(a) levels $\geq$ 200 nmol/L with a history of prior cardiovascular events to determine whether the near-total pharmacological elimination of Lp(a) significantly reduces the risk of the primary composite outcomes of this study: coronary heart disease death, myocardial infarction, or urgent coronary revascularization.

3.4.2.2 Zerlasiran

Zerlasiran is another GalNAc-conjugated siRNA targeting the hepatic synthesis of apolipoprotein(a). Its safety, tolerability, and efficacy were evaluated in a combined single- and multiple-dose randomized clinical Phase 1 trial enrolling patients with stable atherosclerotic cardiovascular disease (ASCVD) and baseline Lp(a) concentrations $\geq$ 150 nmol/L [45].
The multiple-dose arm of the study demonstrated a significant reduction in Lp(a) levels. Patients receiving two doses of zerlasiran achieved maximal median percentage reductions in

Lp(a) of 97%, 98%, and 99% for the 200-mg, 300-mg, and 450-mg cohorts, respectively. This reduction was sustained over time. At 201 days following administration, the biological effect was sustained, maintaining median Lp(a) reductions of 90% in the 300-mg group and 89% in the 450-mg group. The medication was well tolerated throughout the trial, with no serious adverse events reported, strongly supporting its continued clinical development for infrequent administration regimens.

Building upon these early-phase findings, zerlasiran was evaluated in the Phase 2 ALPACAR-360 trial. This multicenter, randomized, double-blind study enrolled 178 patients with stable ASCVD and baseline Lp(a) concentrations ≥ 125 nmol/L. Patients were randomized to receive subcutaneous zerlasiran at doses of 300 mg (every 16 or 24 weeks) or 450 mg (every 24 weeks), compared to placebo [46]. A unique primary endpoint of this trial was the time-averaged percent change in Lp(a) concentration from baseline to 36 weeks, which provides a clinically highly relevant measure of the drug's sustained effect between infrequent doses. The trial demonstrated robust, placebo-adjusted time-averaged reductions of 81.3% for the 300-mg dose every 24 weeks, 82.8% for the 300-mg dose every 16 weeks, and 85.6% for the 450-mg dose every 24 weeks. Furthermore, the absolute median percentage reductions in Lp(a) at week 36 were even greater, reaching 90.0%, 96.4%, and 94.5% for the respective dosing cohorts. The safety profile remained highly favorable, with mild injection site reactions being the most common adverse effect. Phase 2 results establish zerlasiran's viability as a highly potent, twice-yearly therapy. However, Phase 3 trials were postponed due to business decisions.

3.4.2.3 Lepodisiran

Another advanced GalNAc-conjugated siRNA in clinical development is lepodisiran. While its mechanism of action mirrors that of olpasiran and zerlasiran, its extended release formulation results in longer duration of pharmacological effect. The safety, tolerability, and initial efficacy of lepodisiran were evaluated in a randomized, placebo-controlled Phase 1 ascending-dose trial involving 48 participants with baseline Lp(a) concentrations ≥ 75 nmol/L [47]. Participants received a single subcutaneous injection of lepodisiran at doses ranging from 4 mg to 608 mg, or placebo. The results demonstrated significant, dose-dependent reductions in circulating Lp(a). At the maximal dose of 608 mg, lepodisiran achieved a marked reduction of Lp(a), with a maximal median reduction of 97% from baseline. This substantial reduction was sustained over an extended follow-up period. At 337 days (approximately 48 weeks) post-injection, the median reduction in Lp(a) concentration for the 608 mg cohort was still maintained at an 94% below baseline [47]. The medication was well-tolerated, with mild injection-site reactions being the primary reported adverse events.

Following these initial findings, the efficacy and safety of lepodisiran were rigorously evaluated in the Phase 2 ALPACA trial [48]. This randomized, placebo-controlled study enrolled 320 participants with elevated baseline Lp(a) (median 254 nmol/L). The trial tested multiple subcutaneous dosing regimens (16 mg, 96 mg, and 400 mg). To assess both short- and long-term durability, participants were assigned to receive either two active doses (at baseline and day 180) or a single active baseline dose followed by a placebo at day 180. The study demonstrated a dose-dependent pharmacological response. For the primary endpoint – the time-averaged percent change in Lp(a) between days 60 and 180 – patients in the pooled 400 mg cohorts achieved a placebo-adjusted reduction of 93.9%. Furthermore, long-term observation showed that participants receiving the 400 mg dose twice maintained a time-averaged Lp(a) reduction of 94.8% over a full year (measured from day 30 to day 360), as compared with 88.5% in the single-dose group. The medication was generally well-tolerated, with dose-dependent, mild injection-site reactions being the primary reported adverse effect.

Building on these results, lepodisiran has progressed to the ongoing Phase 3 ACCLAIM-Lp(a) cardiovascular outcomes trial (NCT06292013). This study is designed to investigate the effect of lepodisiran on the reduction of major adverse cardiovascular events (MACE) in adult patients with elevated Lp(a) concentrations ≥ 175 nmol/L and ASCVD or documented high-risk factors. The trial is estimated to end in early 2029.

3.4.3 Small-molecule oral therapy: Muvalaplin

While RNA-targeted injectables dominate the advanced clinical pipeline, alternative pharmacological approaches are being developed for patients who may prefer oral administration. Muvalaplin is a first-in-class, orally administered small molecule designed to inhibit Lp(a) formation. Rather than degrading mRNA, muvalaplin acts by physically disrupting the initial non-covalent interaction between apolipoprotein(a) and apolipoprotein B100, thereby preventing the intrahepatic assembly of the intact Lp(a) particle [49].
The efficacy of muvalaplin was evaluated in a Phase 2, randomized, double-blind, placebo-controlled trial (KRAKEN) enrolling 233 patients with elevated baseline Lp(a) (≥ 175 nmol/L) and established ASCVD, diabetes, or familial hypercholesterolemia [50]. Participants received daily oral doses of muvalaplin (10 mg, 60 mg, or 240 mg) or placebo for 12 weeks. The trial demonstrated significant, dose-dependent reductions in circulating Lp(a). At the 12-week primary endpoint, placebo-adjusted reductions in lipoprotein(a) were 47.6% for the 10 mg dose, 81.7% for 60 mg, and 85.8% for the 240 mg/d dose. The medication was generally well-tolerated, with no serious safety concerns reported. These findings establish muvalaplin as a highly promising, once-daily oral alternative to injectable therapies, warranting further investigation in large-scale, long-term cardiovascular outcomes trials. A Phase 3 cardiovascular outcomes trial (MOVE-Lp(a), NCT07157774) is currently ongoing and is estimated to conclude in 2031. This trial includes patients with Lp(a) ≥ 175 nmol/L who either have a documented ASCVD event or are at high risk for one (artery disease, high artery calcium score, diabetic CKD, combination of risk factors) and primary outcome is the occurence of a MACE endpoint.
The characteristics and primary efficacy outcomes of the pivotal Phase 2 trials for advanced Lp(a)-targeted therapies are summarized in Table 2. This overview details the study populations, optimal dosing regimens, and the maximum Lp(a) reduction achieved by each agent. These biomarker reductions provide the direct rationale for the ongoing Phase 3 trials, which are currently evaluating the clinical impact of these therapies on major adverse cardiovascular events (MACE).
Overview of advanced lipoprotein(a)-targeted therapies: Phase 2 trial characteristics, optimal efficacy, and Phase 3 clinical status.

Drug (Phase 2 Trial)	**Phase 2 population**	**Intervention (Highest reduction)**	**Phase 2 primary outcome & efficacy**	**Phase 3 status (Est. completion)**
Pelacarsen Dose-finding [41]	Established CVD. Baseline Lp(a) ≥ 60 mg/dL (~150 nmol/L). **N = 286**	20 mg SC weekly or 60 mg SC monthly vs. Placebo	**Outcome:** % change in Lp(a) at week 25–27. **Efficacy:** ~ 80% mean reduction.	*Lp(a)* - *HORIZON* Ongoing (Mid-2026)
Olpasiran OCEAN(a)-DOSE [44]	Established ASCVD. Baseline Lp(a)	225 mg SC every 12 weeks *or* 225 mg every 24 weeks vs. Placebo	**Outcome:** % change in Lp(a) at week 36. **Efficacy:** 97.5% mean	*OCEAN(a)*-*Outcomes* Ongoing (Early 2028)

	> 150 nmol/L. **N = 281**		reduction for once/12 weeks, 96.9% for once/24 weeks.	
Zerlasiran ALPACAR-360 [46]	Stable ASCVD. Baseline Lp(a) ≥ 125 nmol/L. **N = 178**	450 mg SC every 24 weeks or 300 mg SC every 16 weeks vs. Placebo	**Outcome:** Time-averaged % change in Lp(a) to week 36. **Efficacy:** 85.6% time-averaged reduction (450 mg arm); up to 96.4% median reduction (300 mg arm).	*Postponed*
Lepodisiran ALPACA [48]	Baseline Lp(a) ≥ 175 nmol/L. Median baseline Lp(a) ~254 nmol/L. **N = 320**	400 mg SC (single or two doses) vs. Placebo	**Outcome:** Time-averaged % change in Lp(a) between days 60–180. **Efficacy:** 93.9% time-averaged reduction (primary endpoint); 94.8% time-averaged reduction over 48 weeks (two-dose group).	*ACCLAIM-Lp(a)* Ongoing (Early 2029)
Muvalaplin KRAKEN [50]	High ASCVD risk. Baseline Lp(a) ≥ 175 nmol/L. **N = 233**	240 mg Oral daily vs. Placebo	**Outcome:** % change in intact Lp(a) at week 12. **Efficacy:** 85.8% placebo-adj. reduction.	*MOVE-Lp(a)* Ongoing (2031)

3.5 Bridging the evidence gap: translating trial data to pASCVD

While the pharmacological potency of emerging RNA-targeted therapies and muvalaplin is well-documented in early and mid-stage trials, a significant evidence gap remains regarding their specific application in the premature ASCVD population. A critical appraisal of the currently ongoing Phase 3 cardiovascular outcomes trials – including Lp(a)HORIZON, OCEAN(a)-Outcomes, and ACCLAIM-Lp(a) – reveals that the enrolled cohorts consist predominantly of older adults with established ASCVD, with mean ages typically ranging between 60 and 65 years [41,42,44]. Currently, there are no large-scale, randomized controlled trials exclusively dedicated to evaluating these novel agents in young adults presenting with premature ischemic events.

This lack of direct, premature ASCVD-specific prospective data poses a clinical challenge. However, the rationale for considering this younger demographic as a primary target for future Lp(a)-lowering interventions is strongly supported by Mendelian randomization studies and the concept of cumulative exposure [28]. These genetic analyses demonstrate that individuals with lifelong, genetically determined lower Lp(a) concentrations exhibit a proportional, dose-dependent reduction in their lifetime ASCVD risk [51].

Extrapolating from these genetic models and age-specific risk profiles reveals a clear quantitative threshold regarding the magnitude of therapeutic reduction required. A landmark Mendelian randomization analysis demonstrated that the cardiovascular benefit of lowering Lp(a) is strictly proportional to the absolute mass reduction, not the percentage reduction. Researchers calculated that a lifelong exposure to a roughly 100 mg/dL lower Lp(a) mass concentration is required to provide the exact same coronary heart disease risk reduction as a lifelong exposure to a 38.67 mg/dL (1 mmol/L) lower LDL-C level [51].

This substantial absolute reduction requirement explains why non-specific lipid-lowering drugs – such as PCSK9 inhibitors, which lower Lp(a) by a modest 20% to 30% – often fail to demonstrate an Lp(a)-specific cardiovascular benefit. If a pASCVD patient starts with a baseline Lp(a) of 150 mg/dL, a 25% reduction removes only 37.5 mg/dL of atherogenic mass,

which is biologically insufficient to alter the disease trajectory. However, the emerging class of RNA therapeutics achieves near-total suppression (80% to 98%), easily achieving this 100 mg/dL threshold, and resulting in Lp(a) levels below 30 mg/dL. Therefore, initiating Lp(a) lowering therapy earlier in life may offer the potential to alter their clinical prognosis, stabilizing the arterial wall before cumulative exposure results in advanced, calcified atherosclerosis and vulnerable plaques.

In older populations, the atherosclerotic architecture is typically highly complex, heavily calcified, and driven by decades of combined, multifactorial risk exposure. Conversely, in a younger patient where isolated Lp(a) elevation is a dominant driver of plaque vulnerability, effectively neutralizing this specific factor could potentially attenuate the progression of the disease more effectively than initiating therapy in later decades. This concept strongly parallels the well-established paradigm in familial hypercholesterolemia (FH), where twenty-year follow-up data have definitively proven that early initiation of targeted lipid-lowering therapy is crucial to mitigate cumulative risk and halt atherosclerosis progression [52].

Nevertheless, until prospective data are available, this remains a theoretical advantage. While awaiting the primary MACE outcomes from the ongoing Phase 3 mega-trials, the scientific community must prioritize pre-specified sub-analyses focused on the younger patient cohorts within these studies. Dedicated prospective trials and registry-based studies focusing on the premature ASCVD demographic are now essential to confirm whether the biomarker reduction achieved by these therapies translates into clinical benefit.

4 Summary (conclusions) and discussion

Elevated Lipoprotein(a) is established as a highly prevalent, causal driver of atherothrombosis, exerting its most aggressive clinical impact on young adults presenting with premature ASCVD. Driven by lifelong, genetically determined exposure, the cumulative atherogenic burden of Lp(a) frequently bypasses traditional risk factors, resulting in early plaque vulnerability and higher rates of recurrent ischemic events despite optimal secondary prevention. Until recently, the absence of specific pharmacological interventions restricted clinical management to the aggressive control of concomitant risk factors.

The successful development of RNA-targeted therapeutics (antisense oligonucleotides and siRNAs) and oral small-molecule inhibitors has effectively resolved the biochemical challenge of Lp(a) reduction. Phase 2 trials demonstrate that agents such as pelacarsen, olpasiran, zerlasiran, lepodisiran, and muvalaplin achieve substantial, long-lasting, and safe suppression of circulating Lp(a).

As clinical cardiology awaits the primary outcomes of the ongoing Phase 3 trials, the research agenda must now expand beyond these initial secondary prevention cohorts. Future research should prioritize several critical domains. First, there is an urgent need for pre-specified sub-analyses of the younger demographic within the current Phase 3 trials to evaluate age-dependent treatment interactions. Second, the scientific community must design dedicated prospective trials focusing specifically on the pASCVD population. These studies are necessary to test the hypothesis derived from Mendelian randomization: that early pharmacological intervention yields a greater absolute risk reduction by arresting atherogenesis before the development of complex, calcified plaque architectures.

Furthermore, future investigations must address the health economic implications of lifelong advanced pharmacotherapy. Establishing cost-effective, universal pediatric or young-adult screening protocols for Lp(a) will be necessary to identify asymptomatic individuals who stand to benefit from early primary prevention. Ultimately, transitioning Lp(a) from a passive risk marker to a routinely modified therapeutic target will require a concerted effort to bridge the

remaining evidence gaps between biomarker reduction and long-term cardiovascular outcomes in the most vulnerable patient populations.

Disclosure

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