



Lipoprotein(a): from the complex metabolism to the optimal lowering drug

Francesco Di Giacomo Barbagallo^{1,2} · Martina Berteotti³ · Giosiana Bosco^{1,2} · Leandro Cosco³ · Antonino Di Pino¹ · Francesco Alfano³ · Salvatore Piro¹ · Roberto Scicali¹  · Luis Masana⁴ · Rossella Marcucci³

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Abstract

Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein particle associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, ischemic stroke, peripheral artery disease, and calcific aortic valve stenosis. Structurally, Lp(a) consists of an LDL-like particle covalently bound to apolipoprotein(a), a plasminogen-like glycoprotein that confers distinct biological properties. In particular, Lp(a) is the main circulating carrier of oxidized phospholipids, which promote endothelial dysfunction and vascular inflammation. Lp(a) contributes to vascular injury through multiple mechanisms, including lipid retention within the arterial wall, inflammatory activation, impairment of fibrinolysis, and vascular calcification. These processes contribute to plaque development and progression. Circulating Lp(a) levels are largely determined by genetic variability within the *LPA* gene, particularly by kringle IV type 2 copy number variation, which influences apolipoprotein(a) isoform size and secretion. Despite its clinical relevance, therapeutic options specifically targeting Lp(a) remain limited. Lipoprotein apheresis is the main available strategy for a substantial reduction in selected high-risk patients, while conventional lipid-lowering therapies have minimal effects and PCSK9 inhibitors provide only partial reductions. However, several targeted therapies are currently under investigation. Antisense oligonucleotides and small interfering RNAs reduce hepatic *LPA* expression and achieve marked reductions in circulating Lp(a) levels, and novel small molecule agents interfere with Lp(a) particle formation. Gene-editing strategies are a potential future approach for long-term Lp(a) reduction. In conclusion, Lp(a) is a key determinant of residual cardiovascular risk. A better understanding of its pathophysiology and the development of targeted therapies may improve cardiovascular risk stratification and prevention strategies.

Keywords Lipoprotein(a) · Cardiovascular risk · Atherosclerosis · Inflammation · *LPA* gene · Targeted Lp(a) lowering · Emerging therapies

Introduction

Lipoprotein(a) (Lp(a)) is a plasma lipoprotein particle that is largely determined genetically and remains relatively stable throughout life [1]. Several epidemiological studies, genome-wide association analyses, and Mendelian randomization studies have consistently shown that elevated Lp(a) concentrations are associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, ischemic stroke, peripheral artery disease, and calcific aortic valve stenosis [2–4]. These findings indicate that Lp(a) should be considered a distinct lipoprotein particle involved in cardiovascular risk, independently of traditional lipid parameters.

✉ Roberto Scicali
roberto.scicali@unict.it

¹ Department of Clinical and Experimental Medicine, Internal Medicine, Garibaldi Hospital, University of Catania, Via Palermo 636, 95122 Catania, Italy

² Department of Medicine and Surgery, “Kore” University of Enna, Enna, Italy

³ Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy

⁴ Reus Lipid RDI Cluster (LIRIC), IISPV, CIBERDEM, Universitat Rovira i Virgili, Reus, Spain

From a structural perspective, Lp(a) consists of an LDL-like particle containing apolipoprotein B-100 (apoB-100) covalently bound to apolipoprotein(a) (apo(a)) [5]. This peculiar molecular organization gives Lp(a) biological properties that differ from other circulating lipoproteins. In particular, the presence of apo(a), a glycoprotein similar to plasminogen, introduces functional domains involved in inflammatory activation, oxidative pathways, and interference with fibrinolysis [6]. In addition, Lp(a) is the main circulating carrier of oxidized phospholipids (OxPL), which are potent mediators of vascular inflammation and endothelial dysfunction [7]. In this context, experimental and clinical evidence indicates that Lp(a) contributes to cardiovascular disease through multiple complementary pathways involving lipid deposition within the arterial wall, inflammatory activation, and pro-thrombotic mechanisms [8, 9]. These processes do not act separately, but may converge within the vascular wall, promoting endothelial dysfunction, monocyte recruitment, foam cell formation, and plaque progression. A better understanding of the structural characteristics, genetic regulation, and pathophysiological effects of Lp(a) is, therefore, needed to clarify its role in ASCVD and to support the development of targeted therapeutic strategies aimed at reducing Lp(a)-mediated cardiovascular risk.

Structural and molecular features of lipoprotein(a)

The Lp(a) particle is characterized by a unique molecular structure consisting of an LDL-like core containing apoB-100 covalently bound to apo(a) by a single disulfide bridge [10]. This structural organization is a key feature of Lp(a) and contributes to its specific biological properties.

Apo(a) is a highly glycosylated protein encoded by the *LPA* gene and exhibits marked structural homology with plasminogen, a central component of the fibrinolytic system [11]. This homology is mainly related to the presence of multiple kringle domains, which are looped protein structures stabilized by internal disulfide bonds [11]. In contrast to plasminogen, apo(a) lacks kringle I–III domains, but contains ten distinct kringle IV (KIV) subtypes, followed by a kringle V domain and an inactive protease-like domain, which does not exhibit enzymatic activity [12]. Among these domains, kringle IV type 2 (KIV-2) is characterized by a high level of copy number variability across subjects. The number of KIV-2 repeats may range widely, from a few units to more than 40 repeats leading to substantial heterogeneity in apo(a) isoform size [13]. The extensive repetition of KIV-2 domains leads to high conformational complexity in the apo(a) form, influencing its folding, stability and interaction with other molecular components. Specific kringle domains, particularly those containing lysine-binding sites, mediate interactions with fibrin, fibrinogen, and proteoglycan-rich structures within the vascular wall [14]. This

property enables Lp(a) to localize preferentially at sites of endothelial dysfunction and to promote vascular injury.

Another relevant molecular feature of Lp(a) is its ability to transport oxidized phospholipids (OxPL), which are mainly bound to apo(a). These bioactive lipid molecules are involved in endothelial dysfunction, inflammatory activation, and atherosclerotic plaque progression [15]. The preferential association of OxPL with Lp(a) is not merely a compositional characteristic, but reflects a selective binding process that contributes to the unique biochemical identity of this lipoprotein.

Overall, the coexistence of an LDL-like core, a plasminogen-like apolipoprotein component, and oxidized phospholipids defines the complex molecular architecture of Lp(a) and provides the basis for its involvement in multiple biological pathways related to vascular injury.

Genetic determinants and isoform variability of lipoprotein(a)

Circulating Lp(a) levels show a wide interindividual variability that is largely explained by genetic determinants located within the *LPA* gene, with heritability estimates ranging from approximately 70% to over 90% [13]. In contrast to other lipid parameters, Lp(a) concentrations are minimally influenced by environmental or lifestyle factors and are primarily determined by inherited genetic variability [16]. The most relevant genetic determinant of Lp(a) levels is the variability in the number of KIV-2 repeats within the *LPA* gene [13]. This copy number variation leads to the production of apo(a) isoforms with different molecular sizes, which directly modulate circulating Lp(a) concentrations. An inverse relationship exists between apo(a) isoform size and Lp(a) levels; subjects carrying smaller apo(a) isoforms, characterized by a lower number of KIV-2 repeats, exhibit higher plasma Lp(a) concentrations, whereas larger isoforms are associated with lower circulating levels [17]. This relationship is one of the most distinctive biological features of Lp(a) and reflects differences in apo(a) synthesis and secretion. In addition to KIV-2 copy number variation, several single nucleotide polymorphisms (SNPs) within the *LPA* locus have been associated with circulating Lp(a) levels [18, 19]. Genome-wide association studies have consistently identified genetic variants strongly linked to elevated Lp(a) concentrations and increased risk of atherosclerotic cardiovascular disease [20, 21]. Overall, the genetic regulation of Lp(a) is primarily driven by isoform-dependent mechanisms influencing hepatic production of apo(a), with additional contributions from genetic variants within and beyond the *LPA* locus. This genetic framework explains the marked interindividual variability of Lp(a) levels and underlies the heterogeneity in Lp(a)-associated cardiovascular risk.

Metabolism and assembly of lipoprotein(a)

Lp(a) is primarily synthesized in the liver, where apo(a) is produced by hepatocytes and then released into the bloodstream [22]. Once secreted, apo(a) binds to circulating LDL particles containing apoB-100, leading to the formation of the Lp(a) particle through a covalent disulfide bond [5]. These early interactions are mediated by lysine-binding sites located within specific kringle domains of apo(a), which recognize complementary lysine residues on apoB, facilitating particle formation [23]. The assembly of Lp(a) occurs predominantly in the extracellular compartment after apo(a) secretion [24]. Unlike other lipoproteins, which are formed in the cell prior to secretion, Lp(a) is formed in the extracellular compartment [22].

As previously discussed, apo(a) isoform size plays a central role in regulating its intracellular processing and secretion.

Apo(a) is synthesized on ribosomes associated with the rough endoplasmic reticulum, where the extensive KIV-2 domain imposes a significant structural burden on protein folding [25]. Larger apo(a) isoforms, characterized by a higher number of KIV-2 repeats, require a more complex and prolonged folding process and are more dependent on chaperone-mediated quality control within the endoplasmic reticulum [26]. As a result, these isoforms show prolonged intracellular retention and are more susceptible to misfolding. Misfolded or incompletely folded apo(a) molecules are preferentially targeted to intracellular degradation pathways, including endoplasmic reticulum-associated degradation, thereby reducing the amount of apo(a) available for secretion. In contrast, smaller apo(a) isoforms undergo more efficient folding and processing, resulting in higher secretion [26]. These differences in intracellular handling provide an explanation for the higher production rates observed in subjects carrying smaller apo(a) isoforms.

In contrast to LDL particles, the mechanisms responsible for Lp(a) clearance remain less clearly defined. It has been suggested that Lp(a) has a limited interaction with the classical LDL receptor (LDLR) pathway, indicating that LDLR-mediated uptake is not the primary mechanism of Lp(a) catabolism [27]. This aspect has relevant clinical implications, as therapies that increase LDL receptor activity, such as statins, have minimal effects on circulating Lp(a) levels [28]. These observations support the concept that Lp(a) metabolism is largely independent from classical LDL pathways. Other mechanisms have been proposed to contribute to Lp(a) clearance, including receptor-mediated uptake by hepatic and extrahepatic tissues [29]; however, the relative contribution of these pathways is not completely understood.

Overall, current evidence indicates that circulating Lp(a) levels are primarily determined by hepatic production of

apo(a), whereas the pathways regulating its clearance are still only partially characterized.

Lp(a) measurement and clinical implementation

The clinical interpretation of Lp(a) levels is influenced by methodological issues relating to the standardization of tests and the units of measurement used. Lp(a) can be expressed either as a mass concentration (mg/dL) or as a particle concentration (nmol/L) [10]. However, direct conversion between these units is not recommended, as the molecular weight of Lp(a) varies substantially depending on the size of the apo(a) isoform, which is determined primarily by the number of type 2 repeats in kringle IV [30]. Therefore, the same mass concentration may correspond to a different number of particles from one individual to another. Current guidelines and consensus documents recommend measuring Lp(a) at least once in adulthood to identify individuals with genetically elevated levels and to improve cardiovascular risk stratification. Lp(a) values ≥ 50 mg/dL, corresponding approximately to ≥ 125 nmol/L, are generally considered elevated and associated with increased cardiovascular risk, although fixed conversion between mg/dL and nmol/L should be avoided [10, 31]. Testing is particularly relevant in subjects with premature ASCVD, recurrent cardiovascular events despite optimal LDL-C lowering, familial hypercholesterolemia, calcific aortic valve stenosis, or a family history of premature ASCVD or elevated Lp(a). In the absence of specific treatments for Lp(a), the detection of elevated Lp(a) levels should prompt more intensive management of all modifiable cardiovascular risk factors and optimization of LDL-C lowering, particularly in selected patients with very high Lp(a) levels and progressive ASCVD.

Pathophysiological mechanisms of lipoprotein(a)

Lipoprotein(a) contributes to vascular injury through multiple mechanisms involving lipid retention, inflammatory activation, and impairment of fibrinolytic pathways [32]. This integrated pathogenic profile provides the biological basis for the consistent association between elevated Lp(a) levels, atherosclerotic cardiovascular disease and calcific aortic valve disease (Fig. 1).

Pro-atherogenic effects

A first central aspect is the pro-atherogenic activity of Lp(a). Similar to other apoB-containing lipoproteins, Lp(a) can cross the endothelial barrier and accumulate within the arterial intima, where it contributes to cholesterol deposition and plaque growth [33]. However, compared with LDL, Lp(a) may be retained more strongly within the vascular wall, as it interacts not only via its apoB component, but also

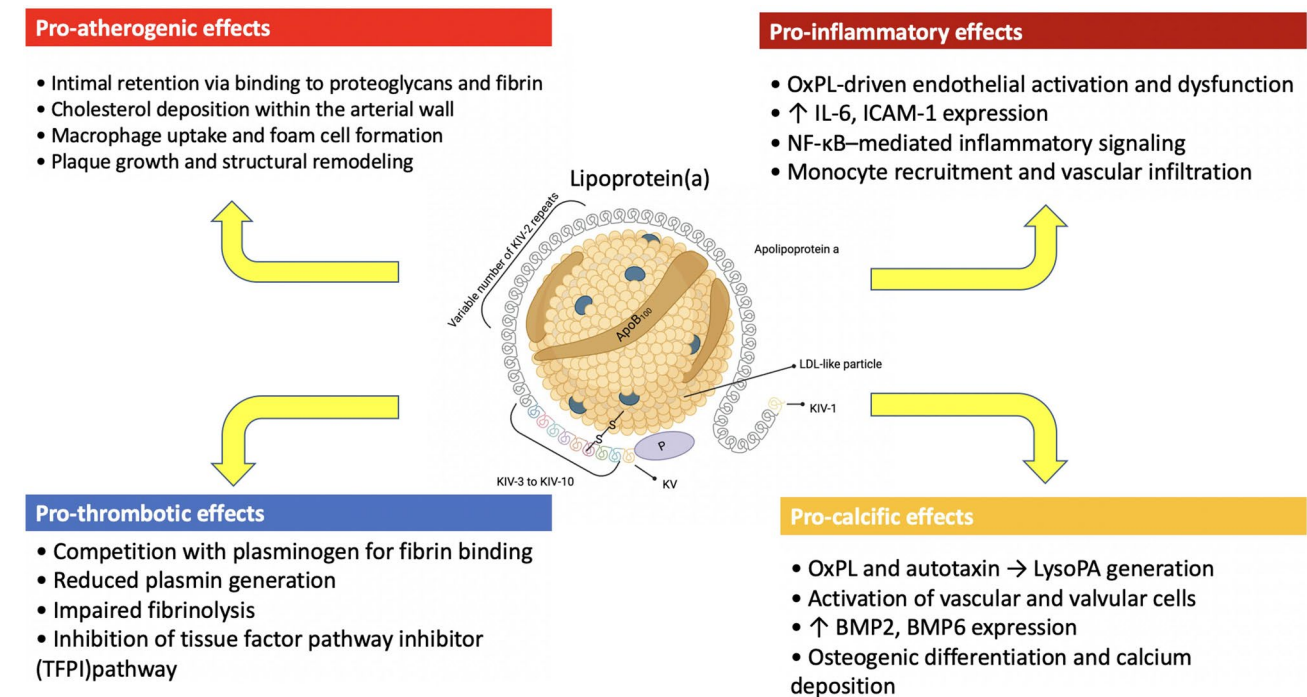


Fig. 1 Biological properties of lipoprotein(a). *OxPL* oxidized phospholipids, *IL-6* interleukin-6, *ICAM-1* Intercellular adhesion molecule-1, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated

B cells, *TFPI* tissue factor pathway inhibitor, *LysoPA* lysophosphatidic acids, *BMP* bone morphogenetic protein

via apo(a), which binds extracellular matrix components, including fibrin and proteoglycan-rich structures [6]. Once inside the arterial wall, Lp(a) contributes not only to lipid accumulation, but also to the transition from simple lipid deposition to an active inflammatory lesion characterized by monocyte recruitment, macrophage infiltration, and progressive plaque remodeling [34]. In this context, the LDL-like fraction of Lp(a) acts as a source of cholesterol accumulation, while apo(a) and the oxidized lipids associated with it significantly amplify the biological consequences of this retention.

Pro-inflammatory effects

A central feature of Lp(a) is its pro-inflammatory activity, largely driven by its high content of oxidized phospholipids (OxPL), which are mainly associated with apo(a) and act as potent bioactive mediators within the vascular wall [35]. These oxidized phospholipids are not passive markers of oxidative stress, but active signals that promote endothelial activation, leukocyte recruitment, and amplification of innate immune responses [36]. Several studies have shown that Lp(a) induces the upregulation of adhesion molecules, such as ICAM-1, and promotes metabolic and transcriptional changes in endothelial cells that facilitate monocyte migration [37, 38]. Moreover, apo(a) can

interact with the β 2-integrin Mac-1 on inflammatory cells, thereby activating NF-κB-dependent pathways and promoting the adhesion and trans-endothelial migration of monocytes [39]. This is highly relevant because it indicates that Lp(a) does not simply deposit within the intima, but actively recruits inflammatory cells into the plaque. After migration into the vascular wall, monocytes differentiate into macrophages and internalize modified lipoproteins through scavenger receptor-mediated pathways, contributing to foam cell formation and progression of the lesion toward a more complex phenotype [40]. Moreover, oxidized phospholipids carried by Lp(a) have been implicated in macrophage apoptosis and in the transition toward unstable plaque morphology, thus linking oxidative stress to plaque vulnerability [41]. These data indicate that the inflammatory effect of Lp(a) is relevant and largely depends on its ability to concentrate oxidized phospholipids within the vascular microenvironment.

In addition, Lp(a) transports lipoprotein-associated phospholipase A2, which contributes to the further processing of oxidized phospholipids and to the generation of bioactive lysophospholipid mediators, thereby sustaining endothelial dysfunction and local inflammatory activation [42]. Overall, the pathogenic role of Lp(a) extends beyond its structural similarity to LDL and reflects its ability to amplify oxidative and inflammatory signaling within the atherosclerotic plaque.

Pro-thrombotic and anti-fibrinolytic effects

In addition to its atherogenic and inflammatory properties, Lp(a) also has prothrombotic and antifibrinolytic effects, which are primarily associated with the structural homology between apo(a) and plasminogen [10].

Although apo(a) is similar to plasminogen, it does not have fibrinolytic activity and can, therefore, inhibit plasminogen-dependent fibrinolysis. Evidence suggests that Lp(a) may compete with plasminogen for binding sites on fibrin and cell surfaces, thereby reducing tissue plasminogen activator-mediated plasmin production and impairing fibrinolysis [10]. These mechanisms are combined with the ability of Lp(a) to bind to and inhibit the tissue factor pathway inhibitor, thereby promoting coagulation [43]. However, current evidence does not support a consistent association between Lp(a) levels and venous thromboembolism, suggesting that its prothrombotic effects are predominantly relevant in the arterial rather than the venous circulation [44].

Thus, the coexistence of local fibrin deposition and inflammatory activation suggests that Lp(a) promotes a prothrombotic microenvironment at sites of atherosclerotic plaque, favoring its rupture.

Pro-calcific effects

Another important characteristic of Lp(a) biology is its pro-calcific activity, which extends its pathogenic relevance beyond classical atherosclerosis [5]. Lp(a) is associated not only with coronary and cerebrovascular disease, but also with valvular and vascular calcification, particularly calcific aortic valve disease [45, 46]. Mechanistically, Lp(a) acts as a carrier of oxidized phospholipids and autotaxin, which promote the generation of lysophosphatidic acid (LysoPA), a bioactive lipid mediator that activates intracellular signaling pathways in vascular smooth muscle cells and valvular interstitial cells. This signaling cascade enhances the expression of osteogenic factors, such as bone morphogenetic proteins (BMPs), particularly BMP2 and BMP6, key regulators of osteoblastic differentiation, as well as the activation of inflammatory and apoptosis processes, ultimately leading to calcium deposition and progressive tissue mineralization [47]. Thus, the pathogenic action of Lp(a) is not confined to intimal lipid accumulation and thrombosis, but also includes the ability to promote fibro-calcific transformation of cardiovascular tissues.

For these reasons, Lp(a) should be considered a multifunctional atherothrombotic particle rather than a simple quantitative lipid biomarker.

Its pathogenic role derives from the convergence of pro-atherogenic, pro-inflammatory, pro-thrombotic, and pro-calcific pathways, which together promote plaque development and contribute to its vulnerability (Fig. 2.)

Current clinical management and future therapeutic perspectives

According to the recent American guidelines, Lp(a) levels ≥ 50 mg/dL (105 nmol/L) are associated with a 1.4-fold increase in cardiovascular risk, whereas levels ≥ 100 mg/dL (250 nmol/L) approximately double this risk [48, 49]. Accordingly, a once-in-a-lifetime measurement of Lp(a) is recommended [48, 50]. Elevated Lp(a) levels are observed in approximately 20% of the general population, with concentrations above 50 mg/dL [51].

Given that Lp(a) levels are largely genetically determined, screening is particularly indicated in patients with a personal or family history of premature ASCVD [50].

Despite the clear and compelling need to reduce Lp(a) levels, lipoprotein apheresis remains the only currently available therapeutic option [52], capable of achieving acute reductions of 70–75% [53, 54]. In the absence of targeted therapies, particular attention should, therefore, be paid to the aggressive management of all other cardiovascular risk factors [50].

Some evidence is available regarding the indirect effects of lipid-lowering therapies on Lp(a). Statins, ezetimibe and bempedoic acid do not significantly affect Lp(a) levels [53], whereas PCSK9 inhibitors reduce Lp(a) concentrations by about 30% [55, 56]. While these reductions contribute to lowering major adverse cardiovascular events (MACE) in high-risk patients, they are often insufficient in individuals with markedly elevated Lp(a) levels as the major determinant of residual risk [52]. Niacin has been associated with a reduction in Lp(a) levels of approximately 25–35% [53]; however, its clinical use has been limited by the lack of demonstrated cardiovascular benefit and an unfavorable side-effect profile. More recently, obicetrapib, a cholesteryl ester transfer protein (CETP) inhibitor developed primarily to increase HDL cholesterol levels, was shown to reduce Lp(a) by 33.7% in the phase 3 BROADWAY trial [57]. However, CETP inhibitors remain under investigation and are not yet available in routine clinical practice. Encouragingly, several novel therapeutic strategies specifically targeting Lp(a) are currently under investigation (Fig. 3).

The main completed and ongoing clinical studies evaluating current and emerging Lp(a)-lowering strategies are summarized in Table 1 [55, 56, 58–64]. This table includes both non-Lp(a)-specific lipid-lowering therapies with secondary effects on Lp(a), such as PCSK9 inhibitors, inclisiran and CETP inhibitors, as well as targeted approaches, including antisense oligonucleotides, small interfering RNAs, oral small molecules and gene-editing strategies. For each study, the therapeutic class, mechanism of action, phase of development, study population, sample size, magnitude of Lp(a) reduction, cardiovascular outcomes assessed, study status and expected completion timeline are reported.

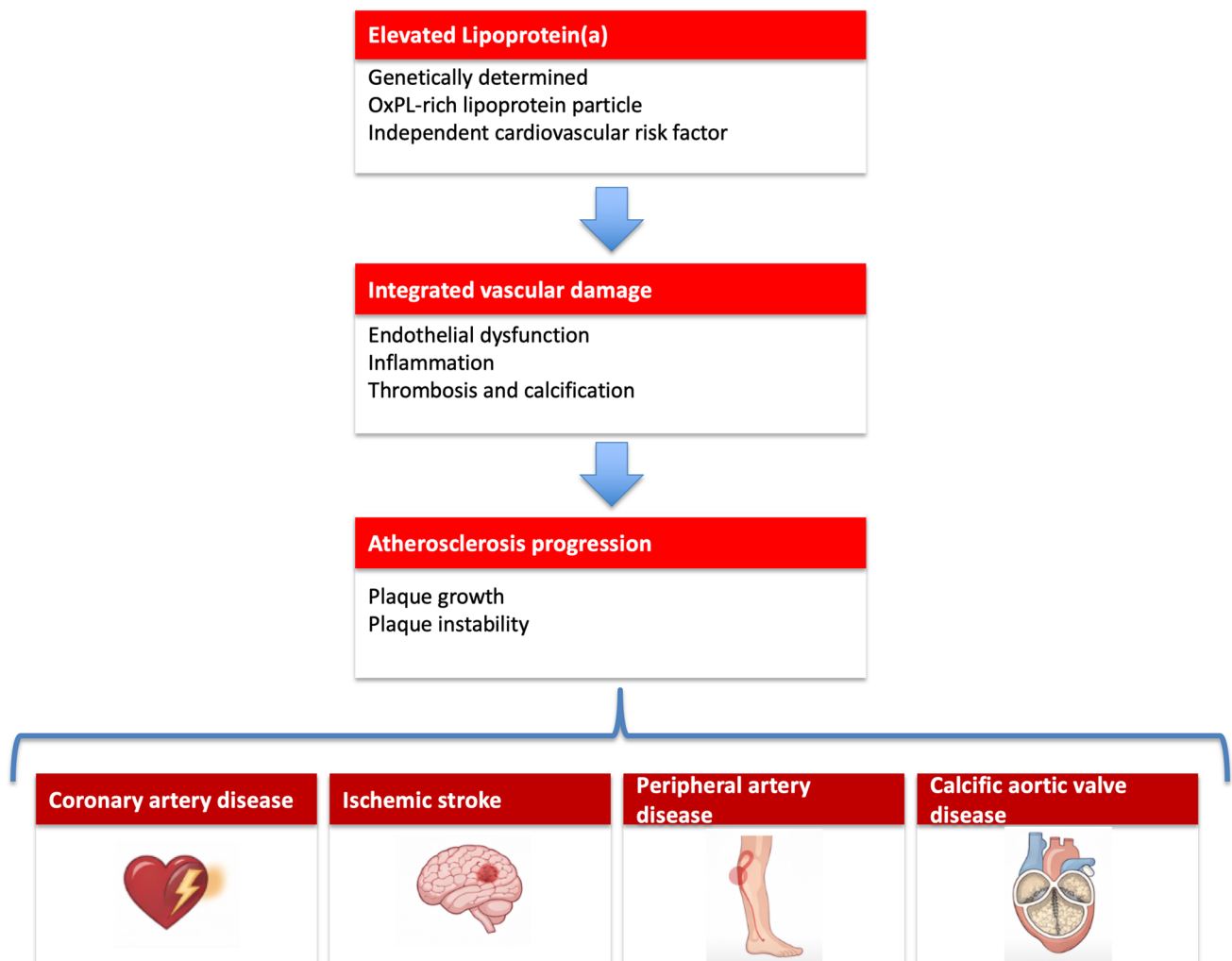


Fig. 2 Lp(a) and vascular injury. *OxPL* oxidized phospholipids

However, although these therapies have shown marked pharmacodynamic effects and promising short-term safety profiles, no Lp(a)-lowering therapy has yet demonstrated a definitive benefit in terms of cardiovascular outcomes that can be specifically attributed to the reduction of Lp(a)[65]. Therefore, the causal link between pharmacological Lp(a)-lowering and event reduction remains to be established by ongoing phase 3 outcome trials.

Antisense oligonucleotides (ASOs): pelacarsen

One of the most promising approaches involves antisense oligonucleotides, particularly pelacarsen. After subcutaneous administration, pelacarsen is taken up by hepatocytes via the asialoglycoprotein receptor through its triantennary N-acetylgalactosamine conjugation. Within hepatocytes, pelacarsen sterically inhibits LPA mRNA, which encodes apolipoprotein(a), thereby preventing its translation into protein. In addition, LPA mRNA is degraded

through RNase H1-mediated cleavage. These combined mechanisms result in reduced apo(a) availability and, consequently, decreased Lp(a) production.

Two major trials are currently ongoing:

- HORIZON trial: a phase 3, double-blind, placebo-controlled RCT designed to determine whether monthly 80 mg administration reduces MACE in patients with established cardiovascular disease and elevated Lp(a) (≥ 70 mg/dL). The study includes over 8000 patients and is expected to conclude by June 2026 (NCT04023552) [66].
- CAVS trial: a phase 2 RCT evaluating whether pelacarsen can slow the progression of aortic stenosis compared with placebo in patients with mild-to-moderate disease and Lp(a) ≥ 70 mg/dL. Approximately 500 patients will be enrolled, with study completion expected in 2029 (NCT05646381).

STRATEGIES TO LOWER LIPOPROTEIN(a) [Lp(a)]

OVERVIEW OF AVAILABLE, EMERGING AND FUTURE THERAPIES

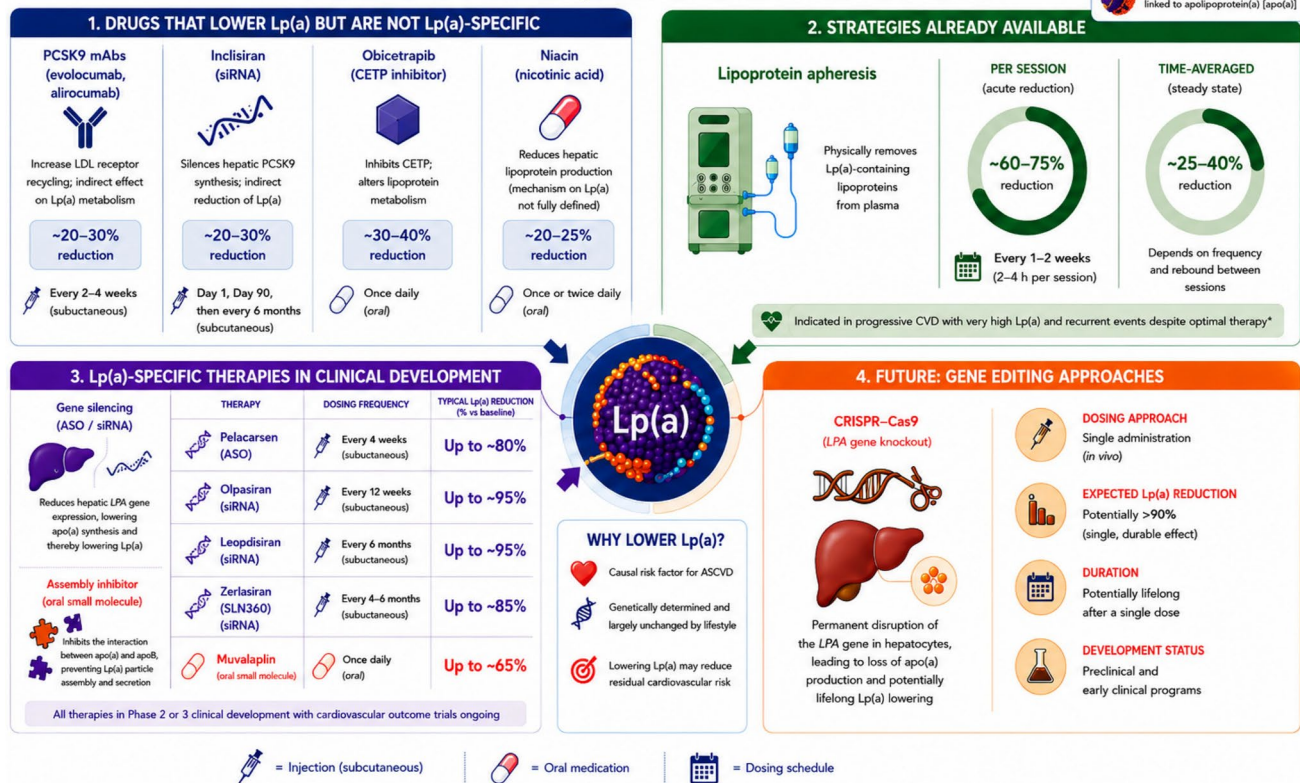


Fig. 3 Strategies to Lower Lp(a). Summary of current and emerging strategies to reduce Lp(a). Non-Lp(a)-specific therapies, including PCSK9 inhibitors, inclisiran, CETP inhibitors, and niacin, provide modest reductions (~20–40%). Lipoprotein apheresis remains the only available intervention specifically indicated for severe Lp(a) elevation, achieving acute reductions of ~60–75% per session. Lp(a)-targeted therapies in clinical development, including pelacarsen and

siRNA agents (olpasiran, lepodisiran, zerlasiran), reduce hepatic LPA expression and achieve substantial reductions (up to ~80–95%). Muvalaplin, an oral agent, inhibits Lp(a) particle assembly. Gene editing approaches represent potential future strategies for durable Lp(a) reduction. The impact on cardiovascular outcomes is under investigation

Small interfering RNAs (siRNAs): olpasiran, lepodisiran, zerlasiran

In contrast to ASOs, siRNAs are double-stranded RNA molecules composed of a guide (antisense) strand and a passenger (sense) strand, which are delivered intracellularly. Once inside the cell, the guide strand incorporates into the RNA-induced silencing complex (RISC) and binds complementary LPA mRNA, promoting its degradation and resulting in gene silencing.

Notably, siRNAs exert a more sustained effect than ASOs, as the guide strand is recycled after mRNA cleavage and can repeatedly target additional mRNA molecules, thereby prolonging the silencing effect.

Several subcutaneously administered siRNA-based therapies are currently under investigation:

- OCEAN(a) trial: the phase 2 OCEAN(a)-DOSE trial enrolled 281 patients and demonstrated significant Lp(a) reductions across different olpasiran dosing regimens [61]. The ongoing phase 3 trial aims to enroll approximately 7000 patients to evaluate whether olpasiran given by subcutaneous injection once every 12 weeks reduces MACE in individuals with established ASCVD and Lp(a) ≥ 200 nmol/L. Completion is expected in 2028 (NCT05581303).
- Acclaim Lp(a): the phase 2 ALPACA trial demonstrated substantial and sustained reductions in Lp(a) levels from 60 to 180 days following lepodisiran administration [67]. The ongoing phase 3 AcclaimLp(a) trial is evaluating the impact on cardiovascular outcomes of a 400 mg dose administered every six months in patients with elevated Lp(a) and established ASCVD, as well as in individuals

Table 1 Completed and ongoing studies evaluating Lp(a)-lowering strategies

A. Non Lp(a) specific lipid lowering therapies with secondary effects on Lp(a)				
Study/trial (phase/status/timeline)	Therapy/class and mechanism	Population (sample size)	Lp(a) reduction	CV outcomes/current evidence
Fourier Phase 3 completed	Evolocumab/PCSK9 inhibitor. PCSK9 inhibition with indirect Lp(a) reduction	ASCVD with elevated LDL-C on optimized therapy ($n = 27,564$)	Median 26.9%	MACE reduction; post hoc analyses explored Lp(a)-related residual risk
Odyssey outcomes Phase 3 completed	Alirocumab/PCSK9 inhibitor. PCSK9 inhibition with indirect Lp(a) reduction	Recent acute coronary syndrome on intensive or maximally tolerated statin therapy ($n = 18,924$)	23–30%	MACE reduction; post hoc analyses explored the contribution of Lp(a) lowering
Orion program Phase 2/3 completed; extension data available	Inclisiran/anti-PCSK9 siRNA. RISC-mediated degradation of PCSK9 mRNA with indirect Lp(a) reduction	ASCVD, ASCVD risk equivalent, or familial hypercholesterolemia; sample size variable across studies	15–25%	LDL-C lowering trials; outcome benefit not specifically attributable to Lp(a) lowering
Rose/broadway program Phase 2/3 completed or ongoing development	Obicetrapib/CETP inhibitor. CETP inhibition with indirect Lp(a) reduction	Hypercholesterolemia or high cardiovascular risk on lipid-lowering therapy; sample size variable across studies	33–57%	LDL-C lowering; cardiovascular outcome benefit specifically related to Lp(a) not established
B. Lp(a) targeted and emerging therapeutic strategies				
Study/trial (phase/status/timeline)	Therapy/class and mechanism	Population (sample size)	Lp(a) reduction	CV outcomes/current evidence
AKCEA-APO(a)-LRx Phase 2 completed	Pelacarsen/ASO. GalNAc-conjugated ASO; RNase H1-mediated degradation of LPA mRNA	Established cardiovascular disease and elevated Lp(a) ($n = 286$)	Up to 80%	Lp(a) lowering; no definitive cardiovascular outcome data
Lp(a)HORIZON Phase 3 ongoing	Pelacarsen/ASO. Hepatic LPA mRNA inhibition and reduced apo(a) synthesis	Established cardiovascular disease and elevated Lp(a) ($n > 8,000$)	Under evaluation; prior phase 2 reductions up to 80%	MACE: cardiovascular death, nonfatal MI, nonfatal stroke, urgent coronary revascularization
OCEAN(a)-DOSE Phase 2 completed	Olpasiran/siRNA. RISC-mediated degradation of LPA mRNA	ASCVD and Lp(a) > 150 nmol/L ($n = 281$)	70% to $> 95\%$, dose-dependent	Lp(a) lowering; no definitive cardiovascular outcome data
OCEAN(a)-Outcomes Phase 3 ongoing	Olpasiran/siRNA. Sustained LPA silencing	ASCVD and Lp(a) > 200 nmol/L (approximately $n = 7000-7300$)	Under evaluation	CHD death, MI, urgent coronary revascularization
Lepodisiran phase 1/ALPACA Phase 1/2 completed or ongoing development	Lepodisiran/siRNA. Long-duration RISC-mediated degradation of LPA mRNA	Elevated Lp(a), with or without established ASCVD depending on study	Sustained reductions up to 90–97% in early studies	Lp(a) lowering; no definitive cardiovascular outcome data
ACCLAIM-Lp(a) Phase 3 ongoing; expected 2029	Lepodisiran/siRNA. Long-duration LPA silencing	Established ASCVD or high-risk primary prevention with elevated Lp(a) ($n \sim 12,500$)	Under evaluation	MACE: cardiovascular death, MI, stroke, urgent coronary revascularization
SLN360/ALPACAR Phase 1/2 completed or ongoing development	Zerlasiran/siRNA. RISC-mediated degradation of LPA mRNA	Elevated Lp(a), stable ASCVD or high ASCVD risk depending on study (phase 2 $n \sim 178$)	$> 80-90\%$, depending on regimen	Lp(a) lowering; no phase 3 cardiovascular outcome data yet
KRAKEN Phase 2 completed	Muvalaplin/oral small molecule. Inhibits apo(a)-apoB interaction and Lp(a) particle assembly	Lp(a) > 175 nmol/L and ASCVD, diabetes, or heart failure ($n = 233$)	47.6%, 81.7%, and 85.8% with 10, 60, and 240 mg/day using intact Lp(a) assay	Lp(a) lowering; no definitive cardiovascular outcome data

Table 1 (continued)

Study/trial (phase/status/timeline)	Therapy/class and mechanism	Population (sample size)	Lp(a) reduction	CV outcomes/current evidence
MOVE-Lp(a) Phase 3 ongoing	Muvalaplin/oral small molecule. Inhibition of Lp(a) particle assembly	Elevated Lp(a) and high cardiovascular risk	Under evaluation	Major cardiovascular events
Gene-editing approaches Preclinical/early clinical development	CRISPR/Cas9 or base-editing strategies. Targeted modification of <i>LPA</i> or related pathways for durable Lp(a) reduction	Markedly elevated Lp(a) or experimental models; human outcome data unavailable	Under evaluation	Safety, durability of Lp(a) lowering; no cardiovascular outcome data

ASO antisense oligonucleotide, *ASCVD* atherosclerotic cardiovascular disease, *CETP* cholesteryl ester transfer protein, *CV* cardiovascular, *LDL-C* low-density lipoprotein cholesterol, *Lp(a)* lipoprotein(a), *MACE* major adverse cardiovascular events, *MI* myocardial infarction, *PCSK9* proprotein convertase subtilisin/kexin type 9, *RISC* RNA-induced silencing complex, *siRNA* small interfering RNA

over 55 years of age who are at high risk of experiencing a first ASCVD event. The trial aims to enroll approximately 12,500 patients and is expected to conclude in 2029 (NCT06292013). Notably, this is the largest siRNA trial to date and the only one to include patients without prior cardiovascular events, but with a high-risk profile [68]. Fare clic o toccare qui per immettere il testo.

- ALPACAR trial: a phase 2 study in which zerlasiran demonstrated Lp(a)-lowering efficacy comparable to other siRNAs (>96% reduction), with a favorable safety profile and infrequent dosing. Reductions in Lp(a) from baseline to week 36 were −85.6% (95% CI −90.9 to −80.3%), −82.8% (95% CI −88.2 to −77.4%), and −81.3% (95% CI −86.7 to −76.0%) for dosing regimens of 450 mg every 24 weeks, 300 mg every 16 weeks, and 300 mg every 24 weeks, respectively. However, zerlasiran is currently the only siRNA targeting Lp(a) that has not yet entered a phase 3 cardiovascular outcome trial (NCT05537571) [69, 70].

Small molecules: muvalaplin

Muvalaplin is the only oral agent currently under investigation. It inhibits Lp(a) formation by disrupting the interaction between apoB-100 and apo(a), a critical step for the formation of the disulfide bond required to generate functional Lp(a). In parallel, additional oral small molecules targeting Lp(a), including YS2302018, currently in preclinical development, are emerging as promising therapeutic strategies [71].

In the phase 2 KRAKEN trial, 233 patients with Lp(a) ≥ 175 nmol/L and ASCVD, diabetes, or heart failure were enrolled. Muvalaplin achieved placebo-adjusted reductions in Lp(a) of 47.6% (95% CI 35.1–57.7%), 81.7% (95% CI 78.1–84.6%), and 85.8% (95% CI 83.1–88.0%) at doses of 10 mg/day, 60 mg/day, and 240 mg/day, respectively [64].

The ongoing phase 3 MOVE Lp(a) trial (NCT07157774) will evaluate cardiovascular outcomes in high-risk patients with elevated Lp(a) and is expected to provide the first outcome data for an oral Lp(a)-lowering therapy [72].

Unlike pelacarsen and olpasiran, which inhibit Lp(a) production at the transcriptional level, muvalaplin does not directly reduce apo(a) or apoB-100 synthesis. As such, it remains unclear whether these components, if still present in the circulation, may continue to accumulate within the arterial wall, potentially limiting its effectiveness in preventing ASCVD events [52].

Although most current phase 3 outcome trials are focused on secondary prevention, it is anticipated that, should these therapies demonstrate cardiovascular benefit, future studies will extend their use to primary prevention populations [48].

Finally, an emerging yet still early-stage therapeutic approach with considerable potential is CRISPR-Cas9 gene

editing for Lp(a) including more precise base-editing strategies, which enable targeted nucleotide modifications without double-strand DNA breaks, which offers the promise of a permanent, one-time treatment for individuals with markedly elevated Lp(a) [73]. A phase I clinical trial is currently enrolling participants. As with all gene-editing therapies, careful evaluation of potential off-target effects and immune responses remains essential. Furthermore, robust data on cardiovascular outcomes following Lp(a) reduction will be crucial to determine the true clinical benefit of a permanent intervention, such as gene editing [74].

Unresolved issues and future perspectives

Despite strong genetic, epidemiological and mechanistic evidence supporting the role of Lp(a) as a causal risk factor for ASCVD, several clinically relevant questions remain unresolved. First, although elevated Lp(a) levels are consistently associated with increased cardiovascular risk, the amount of pharmacological reduction in Lp(a) required to achieve a clinically significant reduction in cardiovascular events has not yet been definitively established [28]. Mendelian randomization studies suggest that significant reductions may be required, particularly in individuals with markedly elevated baseline Lp(a) levels, but this hypothesis requires confirmation in clinical trials focused on cardiovascular outcomes [75]. Furthermore, it is not yet clear whether the clinical benefit of Lp(a)-lowering therapies will depend only on the quantitative reduction in circulating Lp(a) or also on additional biological effects, such as the reduction of oxidized phospholipids, vascular inflammation, endothelial activation and plaque instability [76]. Third, the optimal target population for Lp(a)-lowering therapies has yet to be precisely defined. Most of the phase 3 trials currently underway focus on patients with established ASCVD and markedly elevated Lp(a) levels, while the potential role of these therapies in primary prevention, in individuals with a family predisposition or in patients with calcified aortic valve disease requires further investigation [58]. Finally, although early-phase studies have shown marked reductions in Lp(a) and reassuring short-term safety profiles, long-term data are still required.

Conclusions

In conclusion, Lp(a) is an established cardiovascular risk factor, largely genetically determined, and associated with an increased risk of premature ASCVD. Beyond its role as an independent risk factor, Lp(a) may also act as a risk modifier depending on the individual clinical profile and is a key contributor to residual cardiovascular risk even in patients achieving optimal LDL-C levels. At present, lipoprotein apheresis remains the most effective targeted strategy

for reducing Lp(a) levels in clinical practice. Therefore, although specific therapies for Lp(a) represent significant therapeutic progress, their definitive role in cardiovascular prevention will depend on the results of ongoing clinical trials, which will need to demonstrate whether a reduction in Lp(a) leads to a decrease in cardiovascular events.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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Human and animal rights statement and informed consent This article does not contain any studies with human participants or animals performed by any of the authors. Informed consent was not required for this study, as it is a review article and does not involve individual patient data.

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