NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS
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MSc: Cardiometabolic Medicine

MSc Thesis:
Lipoprotein(a) and Vascular Health: A Comprehensive Review of Its Role in Inflammation and Atherosclerosis

Vaios-Dionysios Antoniou

Supervisor: Evangelos Oikonomou

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1 Introduction

Lipoprotein(a) [Lp(a)] is a unique lipoprotein particle that plays a significant role in cardiovascular health and disease. Structurally, Lp(a) consists of a low-density lipoprotein (LDL)-like core particle covalently bound to a glycoprotein called apolipoprotein(a) [apo(a)] via a disulfide bond (1). The LDL-like core contains cholesterol esters, triglycerides, and apolipoprotein B-100 (apoB-100), while apo(a) is characterized by multiple kringle domains that exhibit high homology to plasminogen (2). These kringle domains, particularly kringle IV type 2 (KIV-2), are present in varying numbers due to genetic polymorphisms, leading to significant heterogeneity in Lp(a) particle size and molecular weight (3) (Figure1).

The production of Lp(a) is largely regulated by the LPA gene, located on chromosome 6q26-27, with plasma levels varying over 1,000-fold between individuals due to genetic variations in the number of KIV-2 repeats (4). Unlike other lipoproteins, Lp(a) levels are minimally influenced by diet, exercise, or environmental factors, making it a highly heritable trait (5).

Physiologically, the role of Lp(a) remains incompletely understood, but it is hypothesized to play a dual role in wound healing and lipid transport. The structural similarity between apo(a) and plasminogen suggests that Lp(a) may modulate fibrinolysis and thrombosis, potentially serving as a bridge between lipid metabolism and hemostasis (6). However, this same property may contribute to its pathogenicity, as Lp(a) can competitively inhibit plasminogen activation, leading to impaired clot lysis and a pro-thrombotic state (7). Additionally, Lp(a) is involved in the transport of oxidized phospholipids (OxPLs), which are pro-inflammatory and contribute to the development of atherosclerosis (8).

Therefore, in this article we review the role of Lp(a) on inflammation and atherosclerosis.

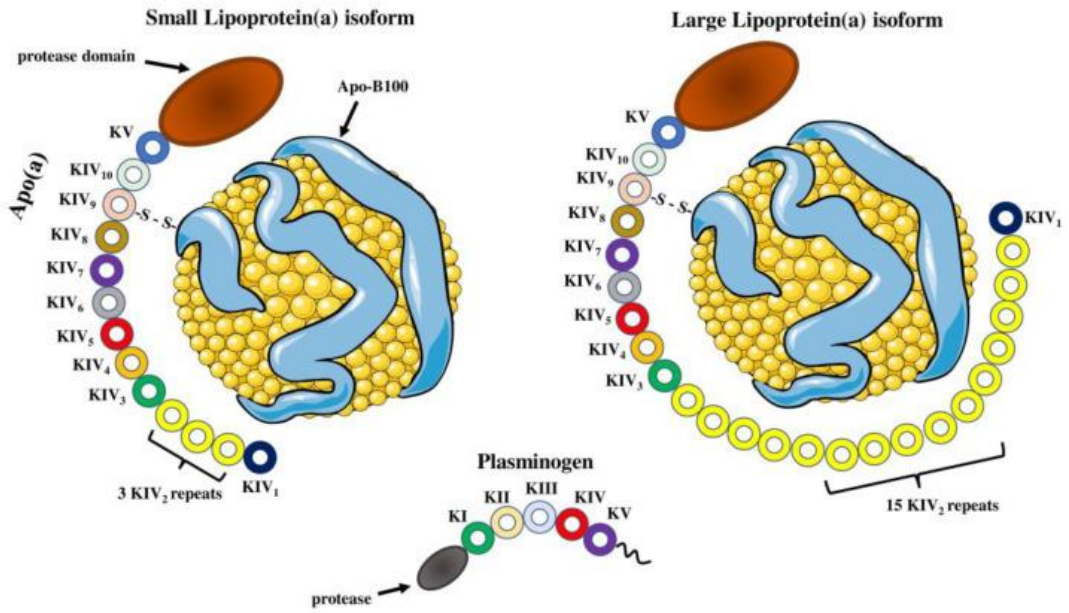

Figure-1: Structure of lipoprotein(a) and plasminogen. Human Lp(a) consists of an LDL-like particle and an apoB-100 particle, in which glycoprotein apo(a) is disulfide-linked. Apo(a) contains 10 different types of plasminogen-like kringle IV domains (KIVs), composed of 1 copy of KIV1, multiple copies of KIV2 and 1 copy of KIV3-10 as well as a single kringle V domain followed by an inactive protease domain. KIV2 repeats of apo(a) determine the size of different Lp(a) isoforms. Apo(a) and plasminogen share high amino acid sequence similarity, including the protease domain and kringles type IV and type V. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported Licence (https://creativecommons.org/licenses/by/3.0/) (accessed on 4 November 2022).(9)

2 Pathophysiological Role of Lp(a) in vascular disease

Lp(a) is a key mediator of vascular inflammation, primarily through its ability to carry oxidized phospholipids (OxPLs) and promote endothelial activation (8). OxPLs on Lp(a) trigger the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), via the activation of nuclear factor-kappa B (NF-κB) signaling (10). These cytokines amplify the inflammatory response, leading to the recruitment of monocytes and their differentiation into macrophages, which ingest oxidized LDL to form foam cells—a critical step in early atherosclerosis (11). In this regard, the most important mechanisms of how lp(a) affects vascular disease is by vascular inflammation and plaque formation.

2.1 Lp(a) and Vascular Inflammation

Lipoprotein(a) [Lp(a)] serves as a potent mediator of vascular inflammation through several interconnected mechanisms that collectively promote atherosclerotic progression. The oxidized phospholipids (OxPL) carried by Lp(a) initiate endothelial activation by upregulating adhesion molecules (VCAM-1, ICAM-1) and promoting monocyte adhesion through NF-κB signaling(12). Simultaneously, Lp(a) triggers NLRP3 inflammasome activation in macrophages, leading to caspase-1-dependent maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18 (11). The lipoprotein further modulates immune cell behavior by promoting monocyte differentiation into pro-inflammatory M1 macrophages and enhancing Th1 lymphocyte polarization (13, 14). Additionally, Lp(a) interacts with the complement system by activating C3 and C5 convertases, generating anaphylatoxins C3a and C5a that amplify vascular inflammation.These synergistic mechanisms establish Lp(a) as a critical orchestrator of chronic vascular inflammation, bridging lipid metabolism with innate and adaptive immune responses in atherosclerosis pathogenesis.(15)

2.1.1 Oxidized Phospholipids and Endothelial Activation

One of the primary mechanisms by which Lp(a) promotes inflammation is through the transport of oxidized phospholipids (OxPLs). Lp(a) is a major carrier of OxPLs in human plasma, and these OxPLs induce the endothelial cell activation (16). OxPLs on Lp(a) trigger the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on the endothelial surface, facilitating the recruitment of monocytes and other immune cells to the arterial wall (12). This process is mediated by the activation of nuclear factor-kappa B (NF-κB), a key transcriptional regulator of inflammation (8).

Endothelial cells exposed to Lp(a) also secrete chemokines such as monocyte chemoattractant protein-1 (MCP-1), which further enhance monocyte migration and infiltration (17).

The interaction between Lp(a) and endothelial cells results in the production of reactive oxygen species (ROS), which degrade nitric oxide (NO) and impair endothelial function (18).

Lp(a) impairs endothelial function by reducing the bioavailability of nitric oxide (NO), a critical regulator of vascular tone and inflammation. This occurs through multiple mechanisms, including the generation of reactive oxygen species (ROS) and the upregulation of endothelin-1, a potent vasoconstrictor (18). ROS produced in response to Lp(a) degrade NO, leading to

endothelial dysfunction and increased vascular permeability, which facilitates the infiltration of inflammatory cells into the arterial wall (19).

The impairment of endothelial function by Lp(a) is further exacerbated by its ability to induce endothelial cell apoptosis, a process mediated by the activation of caspase-3 and the mitochondrial pathway (13). Endothelial cell apoptosis contributes to the denudation of the endothelial layer, exposing the underlying subendothelial matrix to circulating inflammatory cells and lipids, thereby promoting plaque formation (20).

This endothelial dysfunction contributes to the pro-inflammatory environment by increasing vascular permeability and promoting the infiltration of immune cells and lipids into the arterial wall.

When examined in human endothelial cells it was found that the binding of OxPLs also promotes the release of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) (21). These cytokines amplify the inflammatory response, leading to the migration and differentiation of monocytes into macrophages, which subsequently ingest oxidized LDL particles to form foam cells—a hallmark of early atherosclerotic lesions (22).

2.1.2 Activation of the NLRP3 Inflammasome

Lp(a) has been shown to activate the NLRP3 inflammasome, a multiprotein complex that plays a critical role in the innate immune response. The NLRP3 inflammasome is activated by various danger signals, including cholesterol crystals and OxPLs, both of which are associated with Lp(a) (23). Activation of the NLRP3 inflammasome leads to the cleavage and release of interleukin-1β (IL-1β) and interleukin-18 (IL-18), two potent pro-inflammatory cytokines that drive vascular inflammation and contribute to plaque formation (11).

The activation of the NLRP3 inflammasome by Lp(a) is further enhanced by its ability to induce lysosomal destabilization and the release of cathepsins, which are proteolytic enzymes that trigger inflammasome assembly (24).The lysosomal damage leads to potassium efflux and mitochondrial reactive oxygen species (mtROS) production, both of which are critical signals for NLRP3 inflammasome assembly and subsequent caspase-1 activation (25). The activated inflammasome then cleaves pro-IL-1β into its mature form, driving vascular inflammation and promoting plaque progression (26). This process creates a positive feedback loop, amplifying the inflammatory response and further promoting the progression of atherosclerosis. The role of the NLRP3 inflammasome in Lp(a)-mediated inflammation highlights the complex interplay between lipid metabolism and innate immunity in vascular disease (27).

2.1.3 Modulation of Immune Cell Behavior

Lp(a) modulates the behavior of immune cells, particularly monocytes and macrophages, which are key players in vascular inflammation. OxPLs on Lp(a) promote the differentiation of monocytes into macrophages and enhance their uptake of oxidized LDL, leading to the formation of foam cells (28). It does so by promoting monocyte activation and differentiation into pro-inflammatory macrophages through its oxidized phospholipid (OxPL) content, which upregulates scavenger receptors (CD36, LOX-1) and enhances uptake of modified lipoproteins.

The OxPL components of Lp(a) also trigger NLRP3 inflammasome activation in macrophages, increasing secretion of interleukin-1β (IL-1β) and other pro-inflammatory cytokines that amplify vascular inflammation and atherosclerotic plaque progression (12). Additionally, Lp(a) impairs macrophage cholesterol efflux capacity by downregulating ABCA1 transporters, promoting foam cell formation and plaque instability. Foam cells are a major component of atherosclerotic plaques and contribute to plaque instability by secreting pro-inflammatory cytokines and matrix metalloproteinases (MMPs), which degrade the extracellular matrix and weaken the fibrous cap (29).

Moreover, Lp(a) influences adaptive immunity by modulating T cell behavior. Lp(a) has been shown to promote the differentiation of naïve T cells into pro-inflammatory T helper 1 (Th1) cells, which secrete interferon-gamma (IFN-γ) and further exacerbate vascular inflammation (14). Lp(a) promotes Th1 differentiation through its oxidized phospholipid components, which stimulate dendritic cell maturation and enhance their production of interleukin-12 (IL-12), a key cytokine driving Th1 polarization (14).

The OxPL content of Lp(a) also upregulates co-stimulatory molecules (CD80/CD86) on antigen-presenting cells, creating an inflammatory milieu that favors T-bet expression and interferon-gamma (IFN-γ) production in naive T cells (30). This Th1-skewed immune response exacerbates vascular inflammation by activating macrophages and promoting endothelial dysfunction, thereby accelerating atherosclerosis progression (31).

Th1 cells play a critical role in atherosclerosis by promoting macrophage activation and foam cell formation, as well as by enhancing the expression of adhesion molecules on endothelial cells (23).

Lp(a) also impairs the function of regulatory T cells (Tregs), which are responsible for maintaining immune tolerance and suppressing inflammation. Reduced Treg activity in the presence of elevated Lp(a) levels leads to unchecked inflammation and accelerated plaque progression (32). This imbalance between pro-inflammatory Th1 cells and anti-inflammatory Tregs highlights the role of Lp(a) in disrupting immune homeostasis in the vascular wall.

In addition to promoting foam cell formation, Lp(a) enhances the polarization of macrophages toward a pro-inflammatory M1 phenotype, characterized by the secretion of cytokines such as IL-6, TNF-α, and IL-1β (33). This M1 polarization is driven by the activation of Toll-like receptors (TLRs) on macrophages, which recognize OxPLs and other danger signals associated with Lp(a) (34). The pro-inflammatory effects of Lp(a) on immune cells further exacerbate vascular inflammation and contribute to the development of atherosclerosis (35).

2.1.4 Interaction with Complement System

Emerging evidence suggests that Lp(a) may also interact with the complement system, a key component of the innate immune response. Lp(a) has been shown to activate the complement cascade, leading to the generation of pro-inflammatory mediators such as C3a and C5a (36). These mediators promote the recruitment and activation of immune cells, further amplifying the inflammatory response in the vascular wall (37).

Lp(a) activates the complement cascade by binding to and cleaving complement component C3, generating C3a anaphylatoxin, while its oxidized phospholipid (OxPL) content promotes C5 convertase assembly leading to C5a production (15).These anaphylatoxins (C3a, C5a) exert potent pro-inflammatory effects on vascular cells by binding to their respective receptors (C3aR, C5aR1), triggering endothelial activation, monocyte recruitment, and cytokine release (IL-6, IL-1β) through NF-κB signaling (38). The resulting chronic vascular inflammation promotes atherosclerotic plaque progression and instability by enhancing leukocyte infiltration, smooth muscle cell apoptosis, and extracellular matrix degradation (39). The interaction between Lp(a) and the complement system represents a novel mechanism by which Lp(a) contributes to vascular inflammation and atherosclerosis.

2.1.5 Synergistic Effects with Other Lipoproteins

LP(a) interacts synergistically with other lipoproteins, such as LDL and HDL, to modulate immune responses and cytokine production. For example, Lp(a) enhances the pro-inflammatory effects of oxidized LDL by increasing its uptake by macrophages and promoting foam cell formation (40).

In contrast, Lp(a) impairs the anti-inflammatory properties of HDL by reducing its ability to promote cholesterol efflux and inhibit cytokine production (41). Lp(a) impairs HDL function by competitively binding to scavenger receptor class B type 1 (SR-B1), thereby reducing HDL's ability to mediate cholesterol efflux from macrophages (42). Additionally, Lp(a)'s oxidized phospholipids (OxPL) promote HDL dysfunction by modifying apolipoprotein A-I (apoA-I)

structure, decreasing paraoxonase-1 (PON1) activity and impairing HDL's anti-inflammatory and antioxidant properties (26). These mechanisms collectively transform HDL from atheroprotective to pro-inflammatory particles, exacerbating vascular disease progression (43). (Figure 2)

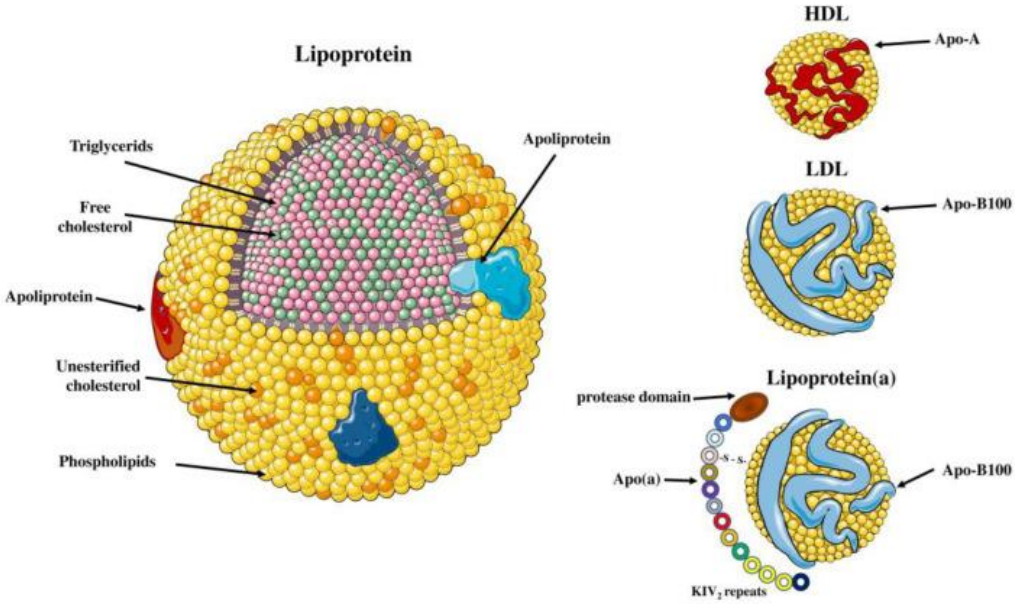

Figure 2: Differences between Lp(a), LDL and HDL. Lipoprotein(a) is composed of one LDL particle containing apo-B100 and apo(a). HDL is composed of a high-density lipid core, and the most common apolipoproteins found on its surface are apo A-I and apo A-II. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/) (accessed on 4 November 2022).(9)

2.2 Contribution of Lipoprotein(a) to Plaque Formation and Progression

Lipoprotein(a) [Lp(a)] has a significant role in the formation and progression of atherosclerotic plaque. Its structure and pro-inflammatory properties make it capable of promoting lipid deposition, foam cell formation, and thinned fibrous cap—critical processes that result in plaque instability and cardiovascular disease (CVD). Overall the studies on the role of Lp(a) in atherosclerosis are shown in the table.

Study	Study Design	Population Characteristics	Key Findings

Atherosclerosis			
Brown et al., 1993 (53)	Case-control	171 cases with preclinical extracranial carotid atherosclerosis and 274 control subjects free of carotid atherosclerosis.	Median levels of Lp(a) were higher in subjects with extracranial carotid atherosclerosis. An inverse correlation between apo(a) size and Lp(a) level was observed in both groups. Apo(a) phenotype distributions were similar in subjects with and without extracranial carotid atherosclerosis.
Maher et al., 1995 (54)	Randomized controlled trial	146 men aged 62 years or younger with CAD and apo B-100 levels ≥125 mg/dL. Step II Diet and lovastatin (40 mg daily) plus colestipol (30 g daily), niacin (4 g daily) plus colestipol or placebo (plus colestipol if LDL > 90th percentile) for 2.5 years.	Lp(a) was the best marker for baseline CAD severity. In patients with minimal LDL reduction (<10%), CAD progression correlated only with in-treatment Lp(a) levels, but, in patients with substantial LDL reduction (≥10%), the regression of disease correlated with LDL but not with Lp(a). Lp(a) levels were not significantly changed in either group.

			Patients with elevated Lp(a) (≥90th percentile) demonstrated more cardiac events (39%) under minimal LDL reduction as compared to events (9%) after substantial reduction.
Dangas et al., 1997 (55)	Cross-sectional	Coronary atheroma removed from 72 patients with stable or unstable angina.	All coronary atheroma specimens exhibited Lp(a) staining. 90% of the macrophage areas colocalized with Lp(a) positive areas, whereas 31.3% of the smooth muscle cell areas colocalized with Lp(a) positive areas. Patients with unstable angina (n = 46) had specimens with larger mean plaque Lp(a) areas than specimens from stable angina patients.
Gazzaruso et al., 1998 (56)	Cross-sectional	267 patients with CAD.	Lp(a) levels did not show any differences among subgroups of patients (one-vessel disease, two-vessel disease and three-or-more-vessel disease (multi-vessel).

			The percentage of apo(a) isoforms of low molecular weight (655 kDa) and the percentage of subjects with at least one apo(a) isoform of low molecular weight were significantly correlated with increasing number of coronary vessels stenosed.
Kronenberg et al., 1999 (57)	Prospective cohort	826 individuals (500 without carotid atherosclerosis and 326 with preexisting carotid artery disease).	Lp(a) plasma levels were significantly associated with early atherogenesis in subjects with LDL cholesterol levels above the population median (3.3 mmol/L). Apo(a) phenotype did not differ in subjects with and without early carotid atherosclerosis. Apo(a) phenotype was found a strong risk predictor of advanced atherogenesis (carotid stenosis >40%), especially LMW apo(a) phenotypes when associated with high Lp(a) plasma concentrations.

Paultre et al., 2002 (58)	Cross-sectional	Randomly selected elderly multiethnic population (173 men and 253 women, consisting of 135 African Americans, 146 Hispanics and 145 whites; mean age 70.5 ± 11.4 years).	Lp(a) levels were not associated with maximum internal carotid artery plaque thickness (MPT). In all men and white women, the amount of Lp(a) carrying the small apo(a) size was associated with carotid atherosclerosis.
Tsimikas et al., 2006 (59)	Prospective cohort	Sample from the Bruneck study (recruitment in 1990 and follow-up in 1995 and 2000 and 2005). 826 subjects had ultrasonographic follow-up of the carotid and femoral arteries in 1995 and 684 in 2000, respectively. Assessment of OxPL/apo B-100 was achieved in 765/826 subjects in 1995 and 671/684 subjects in 2000.	The OxPL/apoB and Lp(a) levels were highly correlated, and this correlation was stable through years of follow-up. The number of apo(a) KIV-2 repeats was inversely related to Lp(a) and OxPL/apoB levels. In multivariable analysis, OxPL/apoB levels were strongly and significantly associated with the presence, extent (assessed by the carotid and femoral atherosclerosis scores) and development between 1995 and 2000 of carotid and femoral atherosclerosis.

			OxPL/apoB were also correlated with progression of vessel stenosis >40% in the carotid arteries between 1995 and 2000 and with the presence of femoral artery stenosis. OxPL/apoB predicted the presence of symptomatic cardiovascular disease during the 10-year follow-up (ischemic stroke and transient ischemic attack, myocardial infarction and symptomatic peripheral artery disease).
Kiechl et al., 2007 (35)	Prospective cohort	Sample from the Bruneck study: 765 subjects with assessment of oxPL/apoB in 1995.	The effects of OxPL/apoB and Lp(a) were not independent of each other. OxPL/apoB levels predict 10-year CVD event rates independent of traditional risk factors, hsCRP and Framingham Risk Score.
Van der Valk et al., 2016 (60)	Cross-sectional	30 subjects with elevated Lp(a) levels (50–195 mg/dL) and 30 subjects with normal Lp(a) (2–28 mg/dL)	Subjects with elevated Lp(a) have increased arterial inflammation and increased peripheral

		matched for age, sex and body mass index.	blood mononuclear cells trafficking to the arterial wall.
Atherothrombosis			
Szczeklik et al., 1992 (61)	Cross-sectional	50 healthy men aged 22–55 years divided into 2 groups: (a) with Lp(a) level > 30 mg/dL and (b) with Lp(a) < 5 mg/dL.	No relationship between serum Lp(a) with t-PA antigen and t-PA activity with PAI-1 activity was reported.
Testa et al., 1999 (62)	Cross-sectional	45 healthy subjects, 27 males and 18 females (mean age 37.54 ± 11.02 years). Intervention: different amounts of purified Lp(a) were added to a plasma with very low Lp(a) concentration (<1 mg/dL). Equal amounts of LDL were added to the plasma sample.	There was an inverse relationship between plasmin formation and the amount of added Lp(a), while no changes in plasmin formation were observed upon inclusion of LDL. Lp(a) level was negatively related to rate of plasmin formation, while plasminogen, PAI-1, t-PA and fibrinogen did not contribute significantly to this relationship.
Von Depka et al., 2000 (63)	Case-control	A total of 685 consecutive patients with at least one episode of VTE and 266 sex- and age-matched healthy controls.	Elevated Lp(a) levels (≥30 mg/dL) were found in 20% of all patients as compared to 7% among healthy controls. The coexistence of FV G1691A mutation and elevated Lp(a) was significantly more

			prevalent among patients with VTE than in the control group. No other established prothrombotic risk factor was found to be significantly combined with increased Lp(a).
Bilgen et al., 2005 (64)	Case-control	167 individuals: 136 CAD cases (37 with no vascular disease, 36 subjects with single vessel, 29 with double vessel and 34 with triple vessel disease) and 31 controls.	Serum Lp(a), oxidized LDL antibody (oLAB) and plasma total TFPI in patients with CAD were found to be significantly higher than in the control group. A significant positive correlation between serum Lp(a) and plasma total TFPI levels in CAD was found.
Di Nisio et al., 2005 (65)	Cross-sectional	62 outpatients (51 males, 11 females) of a clinic were included in the study with CAD history, VTE history, family history of CAD and CAD risk factors comparable among 2 groups: patients with Lp(a) above or below the median (300 mg/L).	Patients with higher Lp(a) concentrations had reduced TFPI antigen levels, whereas the TFPI activity was similar. Patients with Lp(a) below the median had statistically significant higher levels of free protein S as compared with those with higher Lp(a) values.
Undas et al., 2006 (66)	Cross-sectional	52 apparently healthy men, aged 38–63 years	The median Lp(a) concentration was

		and 24 male survivors of MI, aged 42–65 years.	higher in patients than in healthy subjects. Participants with Lp(a) levels < 30 mg/dL had greater fibrin clot permeability than that observed in subjects with Lp(a) ≥ 30 mg/dL; either they were healthy or patients. Haplotypes with ≤22 KIV repeats and ≤8 pentanucleotide repeats were associated with high median Lp(a) levels. Subjects with ≤22 KIV repeats had lower clot permeability as compared to that observed in individuals >22 KIV repeats. These changes were detected in both patients and healthy subjects.
Pineda et al., 2009 (67)	Case-control	142 subjects presenting with MI at a young age (≤45 years) and 95 controls.	Cases had significantly higher Lp(a) levels.
Liu et al., 2022 (68)	Cross-sectional	92 subjects without statins or antiplatelet agents.	Significant correlation was found between arachidonic acid-induced average aggregation rate and ApoB, ApoA1, Lp(a),

			Lp-PLA2 and platelet counts.
Inflammation and Endothelial Dysfunction			
Wu et al., 2004 (69)	Cross-sectional	Multiethnic study of 89 healthy subjects (age 42 ± 9 years; 50 men, 39 women) free of other cardiac risk factors.	Lp(a) levels were found to correlate inversely to FMD ($r = -0.33$, $p < 0.005$) but not to nitrate-induced dilation. Subjects with small apo(a) size of ≤ 22 kringle IV repeats had significantly lower FMD than those with large apo(a) independent of Lp(a) levels.
Anuurad et al., 2008 (70)	Cross-sectional	167 African Americans and 259 Caucasians.	Lp(a) levels were increased among African Americans with higher vs. lower levels of hsCRP. Allele-specific apo(a) levels for medium apo(a) sizes (22–30 kringle IV repeats) were significantly higher among African Americans, with high levels of CRP or fibrinogen compared with those with low levels. No difference was found for Caucasians.

			No differences among African Americans or Caucasians for small apo(a) sizes.
Volpato et al., 2010 (71)	Prospective cohort	Sample from InCHIANTI study (1002 Italian subjects, 60 to 96 years of age over a 6-year follow-up with an ankle–brachial index (ABI) < 1.5. Longitudinal analysis was limited to 686 participants.	At baseline, Lp(a) level was directly related to the number of increased inflammatory markers (IL-6, IL-1 receptor antagonist, fibrinogen and CRP). Participants with elevated Lp(a) levels (≥32.9 mg/dL) demonstrated increased prevalence of lower limbs-peripheral arterial disease compared with subjects in the lowest Lp(a) quartile.
Nemati et al., 2013 (72)	Case-control	90 patients with psoriasis and 90 age-matched controls.	The levels of total cholesterol, LDL, apo B-100 and vascular adhesion protein-1 (VAP-1) in patients with psoriasis were found to be significantly higher than those of healthy subjects. In psoriatic patients, elevation of VAP-1 correlates with Lp(a) levels.

Nishino et al., 2014 (73)	Cross-sectional	441 patients with suspected vasospastic angina (VSA).	hs-CRP and Lp(a) are significantly higher in the VSA group (showed coronary spasm by the ACh test) than in the atypical chest pain group, who showed negative ACh test. Multivariate analyses identified Lp(a) as independent marker for VSA.
Mu et al., 2015 (74)	Cross-sectional	42 patients undergoing CABG (26 males and 8 females aged 48–76 years) and 12 renal artery specimens from kidney transplant donors served as controls.	Increased VCAM-1 expression in atherosclerotic patients compared with controls. In atherosclerotic patients, aortic VCAM-1 expression was positively correlated with Lp(a) (r = 0.507).
Topçiu-Shufta et al., 2016 (75)	Cross-sectional	78 patients undergoing hemodialysis treatment for a period longer than 6 months with no evidence of CVD history.	Lp(a) levels exhibit a significant positive correlation with levels of CRP, IL-6, D-dimer, fibrinogen and vWF.

Lp(a): lipoprotein (a); apo(a): apolipoprotein(a); LDL: low-density lipoprotein; CAD: coronary artery disease; apo B-100: apolipoprotein B-100; Ab: antibodies; LMW: low molecular weight; MPT: maximum internal carotid artery plaque thickness; OxPL: oxidized phospholipids; KIV-2: kringle-IV type 2; hsCRP: high-sensitivity C-reactive protein; Lp-PLA2: phospholipase A2; CVD: cardiovascular disease; t-PA: tissue plasminogen activator; PAI-1: plasminogen activator inhibitor 1; VTE: venous thromboembolism; FV: factor V; TFPI: tissue factor pathway inhibitor; MI: myocardial infarction; vWf: Von Willebrand factor; HDL: high-density lipoprotein; ApoA1: apolipoprotein A1; AMI: acute myocardial infarction; SO: surgical operations; FMD: flow-mediated dilation; IL-6: Interleukin-6; Intereukin-1; CRP: C-

reactive protein; VAP-1: vascular adhesion protein-1; heFH: heterozygous familial hypercholesterolemia; VSA: vasospastic angina; Ach: acetylcholine; VCAM-1: vascular cell adhesion molecule 1.

2.2.1 Lipid accumulation in the arterial wall

Lp(a) has a significant role in lipid deposition within the intima of the arteries, a fundamental early event in the plaque development process.

Lp(a) has cholesterol esters and triglycerides in its LDL-core, which deposit in the arterial wall upon entry of Lp(a) particles through the endothelial barrier (12). This is facilitated by enhanced endothelial permeability induced by the pro-inflammatory effect of Lp(a), including the generation of reactive oxygen species (ROS) and the activation of adhesion molecules (44). Once Lp(a) enters the intima, it becomes oxidatively modified and results in the production of Ox-Lp(a). Ox-Lp(a) is more readily taken up by macrophages compared to native Lp(a), resulting in lipid accumulation and the formation of fatty streaks (45). The OxPLs carried by Lp(a) also enhance this process by stimulating the expression of scavenger receptors, such as CD36 and LOX-1, on macrophages, which facilitate the ingestion of oxidized lipids (33).

2.2.2 Foam Cell Formation

Foam cells are lipid-laden macrophages that are a feature of atherosclerotic plaques. Lp(a) facilitates foam cell formation by promoting the ingestion of oxidized lipids by macrophages. Ox-Lp(a) is engulfed by macrophages via scavenger receptors, leading to cholesterol ester storage and macrophage conversion into foam cells (10). The mechanism is exacerbated by the pro-inflammatory cytokines produced due to Lp(a), such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which stimulate macrophage activation and lipid incorporation (23).

The foam cell formation process is also promoted by the ability of Lp(a) to suppress cholesterol efflux from macrophages. Lp(a) suppresses the function of ATP-binding cassette transporters (ABCA1 and ABCG1), which mediate the export of cholesterol from macrophages to high-density lipoprotein (HDL) particles (41). Inhibition of cholesterol efflux leads to lipid retention in macrophages, inducing foam cell formation and plaque development.

2.2.3 Fibrous Cap Thinning and Plaque Instability

The stability of atherosclerotic plaques is primarily based on the integrity and thickness of the fibrous cap, a layer of connective tissue that encapsulates the lipid core of the plaque. Lp(a) facilitates thinning of the fibrous cap and induction of plaque instability by various mechanisms.

First, Lp(a) promotes the secretion of matrix metalloproteinases (MMPs), proteolytic enzymes responsible for degrading the extracellular matrix constituents of the fibrous cap, such as collagen and elastin (46). Pro-inflammatory cytokines (IL-1β and TNF-α) as mentioned above, enchance the expression of MMPs (11).

Second, Lp(a) interferes with collagen synthesis by vascular smooth muscle cells (VSMCs), the cells that keep the fibrous cap intact. Lp(a) induces apoptosis and inhibits proliferation of VSMCs, reducing their ability to heal and reinforce the fibrous cap (47). The effect is mediated through the generation of ROS and induction of pro-apoptotic signaling cascades in VSMCs (13).

Finally, Lp(a) promotes the infiltration of inflammatory cells, such as macrophages and T cells, into the plaque. These cells secrete additional pro-inflammatory cytokines and MMPs, further destabilizing the fibrous cap and increasing the likelihood of plaque rupture (14). Plaque rupture releases the thrombogenic lipid core into the bloodstream, inducing thrombi formation and acute cardiovascular events, such as myocardial infarction and stroke (48).

2.2.4 Role in Calcification and Plaque Progression

Lp(a) also contributes to plaque progression by promoting vascular calcification, a process that involves the deposition of calcium within the arterial wall. Lp(a) enhances the expression of osteogenic factors, such as bone morphogenetic protein-2 (BMP-2), in vascular smooth muscle cells, promoting their differentiation into osteoblast-like cells and facilitating calcium deposition (49). This calcification process increases plaque stiffness and contributes to the progression of atherosclerosis (50). (Figure 3)

The OxPL components also enhance calcium deposition in atherosclerotic plaques by binding to extracellular matrix proteins and activating pro-calcific signaling pathways involving Wnt/β-catenin and RUNX2 (51). Furthermore, Lp(a)-derived OxPL and reduces collagen synthesis, leading to thin-cap fibroatheroma formation and plaque vulnerability (49).

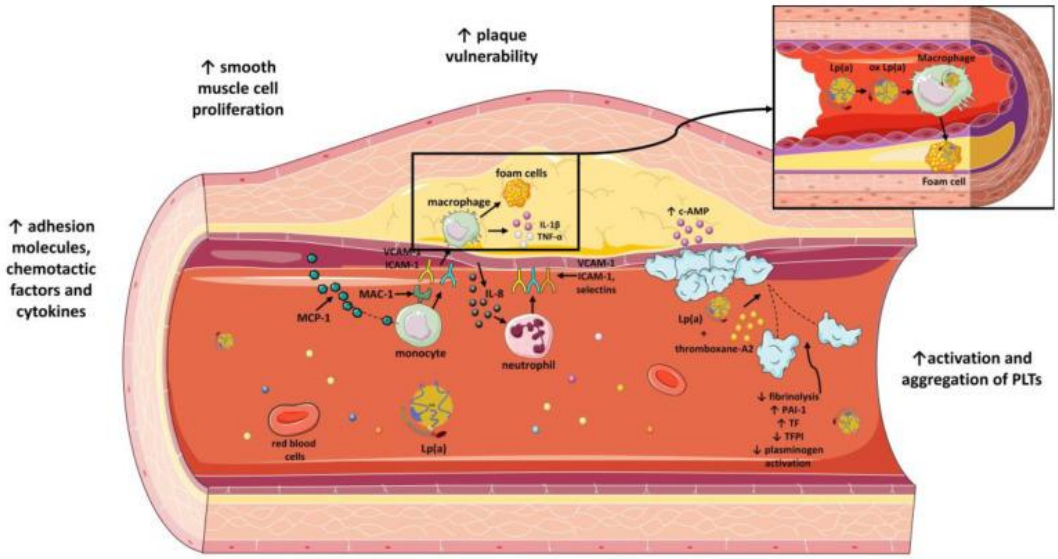

Figure 3: The impact of lipoprotein(a) on atherosclerotic process and atherothrombosis. Lp(a) increases atherosclerotic plaque vulnerability, vascular smooth muscle cell proliferation and adhesion of molecules, chemotactic factors and plasma cytokines. Moreover, Lp(a) enhances platelet activation and aggregation and inhibits fibrinolysis by inhibiting plasminogen activation. Lp(a) inhibits TFPI and enhances expression of TF. Moreover, Lp(a) induces increased expression of PAI-1. Lipoprotein(a): Lp(a); TFPI: tissue factor pathway inhibitor; PAI-1: plasminogen activator inhibitor-1; TF: tissue factor; ICAM-1: intercellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule 1; MAC-1: macrophage-1 antigen; MCP-1: monocyte chemoattractant protein-1; PLTs: platelets; IL-1β: interleukin 1 beta; TNF-α: tumor necrosis factor alpha; c-AMP: cyclic adenosine monophosphate; ox Lp(a): oxidized lipoprotein(a); IL-8: interleukin-8; ↓: downregulation; ↑: upregulation. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported Licence (https://creativecommons.org/licenses/by/3.0/) (accessed on 4 November 2022).(52)

3 Current Therapeutic Landscape for Lp(a) Management

3.1 Conventional Therapies and Their Limitations

Despite the well-established role of Lipoprotein(a) [Lp(a)] as an independent risk factor for cardiovascular diseases (CVD), managing elevated Lp(a) levels remains challenging due to the limited efficacy of conventional therapies.

1.Statins and their partial effect in Reducing Lp(a)

Statins are a cornerstone of lipid-lowering therapies, showing great efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels and significantly lowering the rate of cardiovascular events (76). However their efficacy in lowering Lp(a) levels is limited. While statins can reduce LDL-C by about 50-60%, their effect on Lp(a) levels is null or even absent, with possible rises in Lp(a) levels noted in some patients (42).

Mechanisms of Statin-Induced Lp(a) Increase:

- Enhanced Apo(a) Synthesis: Statins stimulate the transcription of the Lp(a) gene encoding apolipoprotein(a) [apo(a)] and lead to increased Lp(a) synthesis (77).

- Reduced Activity of LDL Receptors: They also enhance the clearance of LDL particles by inducing the expression of LDL receptors; however, Lp(a) is not effectively cleared by this pathway because of its size and peculiar structure (78).

Clinical Implications: The ineffectiveness of statins in reducing Lp(a) concentrations is a notable limitation, especially in individuals with high Lp(a) levels who continue to be at a high cardiovascular risk despite having achieved the targeted LDL-C levels as per prescription (79).

This highlights the necessity for additional treatments aimed specifically at Lp(a).

2. PCSK9 Inhibitors and Partial Lp(a)-Lowering Effects

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab and alirocumab, have emerged as a significant class of lipid-lowering therapies. These monoclonal antibodies work by inhibiting PCSK9, a protein that degrades LDL receptors, leading to an increase in LDL receptor activity and enhanced removal of LDL particles from the circulation (80). In addition to their profound LDL-C-lowering effect, PCSK9 inhibitors have been shown to decrease Lp(a) levels by approximately 20-30% (81).

Mechanisms of Lp(a) Reduction by PCSK9 Inhibitors:

- Augmented LDL Receptor Functionality: PCSK9 inhibitors enable the clearance of LDL particles from the circulation, which may have the potential to reduce Lp(a) levels due to the structural similarity between Lp(a) and LDL (25).
- Reduced Apo(a) Production: PCSK9 inhibitors can reduce the expression of the LPA gene, leading to a decrease in the production of both apo(a) and Lp(a) (22).

Limitations of PCSK9 Inhibitors:

Inhibition of PCSK9 has shown to reduce levels of Lp(a); nevertheless, this reduction is relatively insignificant compared with that of LDL-C. Such a level of partial efficacy is probably too limited to entirely counteract the cardiovascular risk associated with increased levels of Lp(a) (82).

The increased cost and reduced availability of PCSK9 inhibitors highly limit their utility in clinical practice (83).

To conclude, conventional therapeutic options, such as statins and PCSK9 inhibitors, have limited efficacy in reducing elevated levels of lipoprotein(a) (Lp(a)). Statins have not been found to significantly reduce Lp(a) and can increase its levels, while PCSK9 inhibitors yield only a modest reduction in Lp(a). These limitations highlight the need for novel therapeutic approaches with specific targeting of Lp(a) to effectively reduce cardiovascular risk in patients with high Lp(a) levels.

3.2 Emerging Therapies Targeting Lp(a)

The limitations of conventional therapies in managing elevated Lp(a) levels have spurred the development of novel treatments specifically targeting Lp(a). Among these, antisense

oligonucleotides (ASOs) and small interfering RNA (siRNA)-based therapies have shown significant promise in reducing Lp(a) levels and potentially mitigating cardiovascular risk. This section explores the mechanisms, clinical trial outcomes, and safety profiles of these emerging therapies.

1. Antisense Oligonucleotides, e.g., Pelacarsen.

Mechanism of action: Antisense oligonucleotides (ASOs) are short strands of manufactured genetic material. They bind to messenger RNA (mRNA), resulting in the degradation of the mRNA molecules. As a result, the protein encoded by the mRNA is not produced. Pelacarsen, presently named IONIS-APO(a)-LRx, is an ASO designed to target specifically the messenger RNA (mRNA) of apolipoprotein(a), a molecule solely in lipoprotein(a). ASO binding to the mRNA stops the production of the apo(a) molecule (25) (Figure 4).

Clinical Trial Outcomes: In phase 2 studies of subjects with elevated levels of Lp(a), Pelacarsen showed a dose-dependent decrease in Lp(a) levels, with reductions of up to 80%. In addition, the treatment was well tolerated and was not associated with any notable safety issues. From June 25, 2014, to Nov 18, 2015, 64 participants were enrolled to the phase 2 trial. 35 were randomly assigned to IONIS-APO(a)$_{Rx}$ and 29 to placebo. From April 15, 2015, to Jan 11, 2016, they enrolled 58 healthy volunteers to the phase 1/2a trial of IONIS-APO(a)-L$_{Rx}$. Of 28 participants in the single-ascending-dose phase, three were randomly assigned to 10 mg, three to 20 mg, three to 40 mg, six to 80 mg, six to 120 mg, and seven to placebo. Of 30 participants in the multiple-ascending-dose phase, eight were randomly assigned to 10 mg, eight to 20 mg, eight to 40 mg, and six to placebo. Significant dose-dependent reductions in mean Lp(a) concentrations were noted in all single-dose IONIS-APO(a)-L$_{Rx}$ groups at day 30. In the multidose groups, IONIS-APO(a)-L$_{Rx}$ resulted in mean reductions in Lp(a) of 66% (SD 21·8) in the 10 mg group, 80% (SD 13·7%) in the 20 mg group, and 92% (6·5) in the 40 mg group (p=0·0007 for all vs placebo) at day 36 (84).

Phase 3 Trial: Currently, the Lp(a) HORIZON study is examining the safety and effectiveness of Pelacarsen in lowering cardiovascular events in patients with elevated levels of Lp(a) and with prior cardiovascular history. The initial results are eagerly expected and have great potential to position Pelacarsen as a groundbreaking remedy for lowering Lp(a) (31).

Safety Profile:_Pelacarsen has been shown to have a positive tolerance profile in clinical trials, the most common side effect being pain at the site of administration, described as mild to moderate in severity. With careful monitoring of long-term safety, the treatment is well tolerated overall (22).

2. si-RNA based Therapies

Mechanism of Action: Gene-silencing therapeutics, like olpasiran (earlier known as AMG 890), utilize the mechanism of RNA interference to silence specific genes, Olpasiran targets specifically the apo(a)mRNAs, which are degraded and hence decrease the level of Lp(a). As they have longer duration of action, the frequency of administration of siRNA therapeutics is lower than with antisense oligonucleotides(ASOs)(82).(Figure4)

Progress and Investigative Activity

Phase 1 Trials: Phase 1 of the trial showed that olpasiran has the potential to significantly lower levels of Lp(a). Some patients achieved reductions of over 90% in Lp(a), marking a significant achievement that reflects on the effectiveness of siRNA therapies in lowering levels of Lp(a) (85).

Phase II trials: The OCEAN(a) study is currently assessing the safety and efficacy of olpasiran in patients with elevated levels of Lp(a) and confirmed cardiovascular history.

The Olpasiran trials of Cardiovascular Events And lipoprotein(a) reduction-DOSE finding study is a multicenter, randomized, double-blind, placebo-controlled dose-finding study in 281 subjects with established ASCVD and Lp(a) > 150 nmol/L. Patients were randomly allocated to one of 4 active subcutaneous doses of olpasiran (10 mg q12 weeks, 75 mg q12 weeks, 225 mg q 12 weeks, or 225 mg q24 weeks) or matched placebo. The primary objective is to evaluate the effects of olpasiran dosed every 12 weeks compared with placebo on the percent change in Lp(a) from baseline at 36 weeks.

Initial data indicate olpasiran to have significant efficacy in lowering Lp(a) levels, and it has a good safety profile (86).

SafetyProfile: siRNA therapeutics have exhibited positive safety profiles in early studies, with no unacceptable side effects noted. Side effects have been seen as reactions at the site of administration, like those seen with ASOs, and are typically mild in nature. Although long-term safety and efficacy remain to be studied, the early data are encouraging (87).

As it is shown from the trial above there are emerging therapies targeting Lp(a), such as antisense oligonucleotides (e.g., Pelacarsen) and siRNA-based therapies (e.g., olpasiran), represent a significant advancement in the management of elevated Lp(a) levels. These therapies have demonstrated potent Lp(a)-lowering effects in clinical trials, with favorable safety profiles. The ongoing phase 3 trials of Pelacarsen and phase 2 trials of olpasiran are expected to provide further insights into their efficacy in reducing cardiovascular events and their long-term safety(88). If proven effective, these therapies could revolutionize the treatment of patients with elevated Lp(a) and high cardiovascular risk.

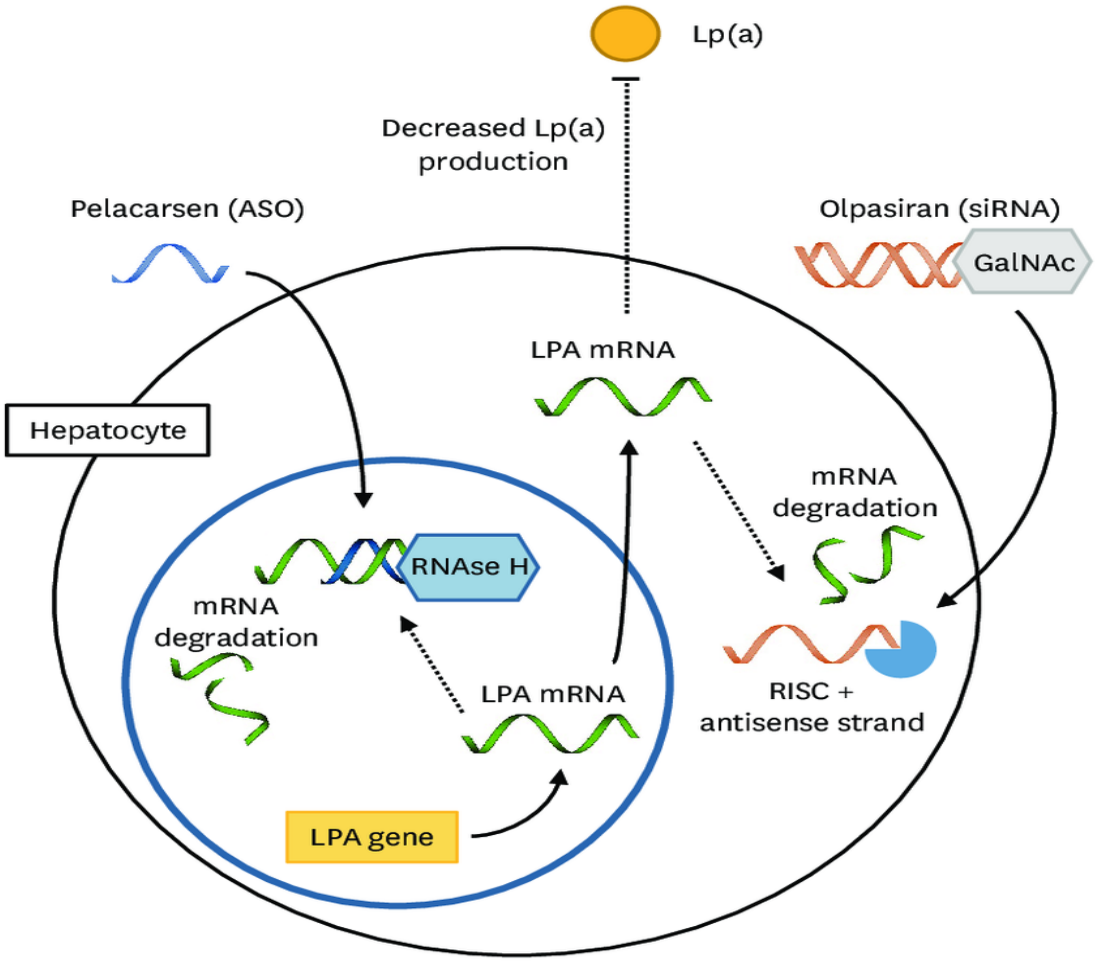

Figure 4: Pelacarsen is an ASO targeting the mRNA of the LPA gene. Binding of the ASO results in mRNA degradation through RNAse H. Olpasiran is a siRNA. The antisense strand combines with RISC and targets LPA mRNA for degradation. The inhibition of LPA mRNA translation by pelacarsen and olpasiran results in decreased production of Apo(a) and Lp(a). ASO, antisense oligonucleotide; siRNA, small interfering RNA; RISC, RNA-induced silencing complex; Apo, apolipoprotein; Lp(a), lipoprotein (a); GalNAc, N-acetylgalactosamine. (88)

3.3 Lifestyle and Adjunctive Interventions

While Lipoprotein(a) levels are genetically determined and minimally influenced by lifestyle factors, certain interventions may help mitigate the cardiovascular risks associated with elevated Lp(a). These include dietary modifications, exercise, and the use of anti-inflammatory agents and antioxidants. This section explores the evidence supporting these interventions and their potential role in managing Lp(a)-related risks.

1. Dietary Modifications and Exercise

Diet has no significant impact on the level of Lp(a). However, certain diet and nutrients can lower the overall cardiovascular risk linked with elevated Lp(a).

- Mediterranean diet: Rich in fruits, vegetables, whole grains, nuts, and olive oil, the Mediterranean diet has been shown to improve lipid profiles and decrease inflammation and has even been shown to decrease cardiovascular risk from high Lp(a).(89) It has no net effect on Lp(a), but it will increase endothelial function and decrease oxidative stress (90).

- Low-fat diets have also been shown to reduce Lp(a) levels somewhat in certain people, although the effect is variable and generally small (22).

- Omega-3 Fatty Acids: Omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduce triglyceride levels and inflammation.Eicosapentoic acid (EPA) reduces triglycerides primarily by inhibiting hepatic lipogenesis through suppression of sterol regulatory element-binding protein-1c (SREBP-1c), a key transcription factor that regulates fatty acid and triglyceride synthesis (91). Additionally, EPA enhances triglyceride clearance by upregulating lipoprotein lipase activity and promoting β-oxidation of fatty acids in the liver and skeletal muscle. These combined effects lead to decreased very-low-density lipoprotein (VLDL) production and increased catabolism of triglyceride-rich lipoproteins High triglycerides cause Lp(a) to rise (92).

Exercise is a crucial element of cardiovascular risk control but is not quantitatively associated with a lowering of Lp(a) levels. Physical activity may, however, optimize cardiovascular health by lowering blood pressure, improving body sensitivity to insulin, and improving the condition of the endothelium (93).

- Aerobic exercise: Aerobic exercise such as running, cycling, and swimming has been shown to improve lipid profiles and reduce inflammation, which counteracts the risks associated with high Lp(a) (94).

- Resistance Training: Resistance training has been said to build muscle and promote metabolic improvement, but its effect on levels of Lp(a) is not definitively established (95).

2. Role of Anti-Inflammatory Agents and Antioxidants

Since Lp(a) is known to be pro-inflammatory, the most effective strategy for lowering the cardiovascular risks associated with an increased concentration of the molecule may be the administration of pharmacological anti-inflammatory agents.

- Colchicine: This gout medication has been shown to reduce the risk of certain heart problems. It might aid the heart, even though it does not lower Lp(a) itself (96). Colchicine exerts cardioprotective effects primarily through its potent anti-inflammatory action by inhibiting microtubule polymerization in neutrophils, thereby reducing their adhesion, migration, and release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) (96). This mechanism helps stabilize atherosclerotic plaques by decreasing neutrophil extracellular trap (NET) formation and suppressing NLRP3 inflammasome activation, which are key drivers of plaque inflammation and vulnerability (97). Clinical trials have demonstrated that low-dose colchicine (0.5 mg daily) significantly reduces cardiovascular events in patients with coronary artery disease, particularly by lowering the risk of recurrent myocardial infarction and stroke. (96)

- IL-1β Inhibitors: IL-1β inhibitors, such as canakinumab, have been shown to reduce cardiovascular events in high-risk patients. These agents target the inflammatory pathways activated by Lp(a), potentially reducing plaque instability and cardiovascular risk. More specifically CANTOS Study, a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter, showed that antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (98).

- Antioxidants: Oxidation is linked with the advancement of vascular disorders mainly because of the effects imparted by Lp(a) on them. Antioxidants are capable of neutralizing oxidative agents, thus lowering oxidative stress levels (99).

- Vitamin E: Vitamin E is a powerful antioxidant that can help reduce oxidative stress and improve the function of the endothelium. However, the effects of vitamin E on Lp(a) and cardiovascular outcomes are not always consistent. Although the HOPE trial was the first of many randomized controlled intervention studies to show that vitamin E supplements given to high-risk patients did not decrease heart disease incidence , it is also the first example of vitamin E supplements having benefit in subjects with increased oxidative stress. Specifically, vitamin E supplementation

decreased heart attack risk in subjects with demonstrable inadequate antioxidant protection due to impaired haptoglobin function. Sub-group analysis of diabetic patients in the HOPE trial who have the haptoglobin 2-2 (Hp 2-2) genotype had a "statistically significant reduction in the risk of CV death (0.45 [0.23–0.90]) and nonfatal myocardial infarction (0.57 [0.33–0.97])", when they were given vitamin E supplements.(100).

- Coenzyme Q10 is an antioxidant that plays a key role in energy metabolism promotion as well as in supporting mitochondrial functions. The use of this substance is likely to improve endothelial function and also reduce oxidative stress levels (101).

- N-Acetylcysteine (NAC) is a precursor of glutathione, an important antioxidant in the human body. It has been shown to reduce oxidative stress and inflammation, with potential benefits for those with elevated levels of Lp(a) (102).

While lifestyle changes and ancillary treatments have a minimal direct effect on lipoprotein(a) levels, they have the potential to appreciably reduce cardiovascular risks associated with raised levels of lipoprotein(a). Dietary changes, along with the adoption of the Mediterranean dietary regimen and omega-3 fatty acid supplements, when combined with regular physical exercise, may maximize overall cardiovascular well-being and reduce inflammatory reactions. The use of anti-inflammatory drugs and antioxidants may abate the lipoprotein(a)-associated pro-inflammatory and pro-oxidative effects and reduce the risk for cardiovascular events. More research is needed to fully evaluate the potential benefits of those interventions for patients with raised levels of lipoprotein(a).

4 Lp(a)-Directed Therapies in Clinical Practice

4.1 Patient Stratification and Risk Assessment

Elevated Lp(a) is a significant independent risk factor for cardiovascular diseases (CVD), including atherosclerosis, myocardial infarction, and stroke. Effective risk stratification and monitoring are essential for identifying high-risk individuals and guiding therapeutic decisions. This section explores the criteria for identifying high-risk individuals and the role of biomarkers and imaging in monitoring disease progression.

1. Identifying High-Risk Individuals Based on Levels and Cardiovascular History

Lp(a) Levels: High Lp(a) levels are a critical determinant for cardiovascular disease risk and are linked to higher chances of contracting CVD (103).

The following are mostly accepted cut-points for the identification of high-risk individuals:

Medium Level of Risk: If the level of Lp(a) is more than 30 mg/dL (approximately 75 nmol/L), the potential risk of cardiovascular diseases is average (79).

High Risk: If the level of Lp(a) is higher than or equal to 50 mg/dL, it is considered a high risk especially in those individuals who have other cardiovascular risk factors (79).

Very High Risk: Lp(a) levels with a concentration of 100 mg/dL (~250 nmol/L) have a hugely increased risk for CVD even in the absence of other risk factors (79).

Cardiovascular History: People who come from a line with cases of early CVD (any history of myocardial infarction (MI) or stroke involving an occlusive vascular disease in a first-degree male relative aged <55 years or in a first-degree female relative aged <65 years) should be screened for the presence of elevated levels of Lp(a) because they are at higher risk (104).

Moreover, patients with familial hypercholesterolemia (FH) commonly have elevated levels of Lipoprotein A as well, which contributes to a higher risk of cardiovascular problems (1).

Lp(a) Should be Measured Once Over a Lifespan in Individuals with:
(1) premature CVD
(2) familial hypercholesterolemia, or other genetic forms of dyslipidemia
(3) recurrent CVD despite optimal lipid-lowering treatment
(4) ≥5% 10-year risk of fatal CVD according to ESC SCORE Guidelines
(5) family history of premature CVD and/or elevated Lp(a) (≥50 mg/dL)
(6) ≥10% 10-year risk of fetal CVD according to US Guidelines
(7) calcific aortic valve stenosis
(8) 10–19% Framingham risk according to the 2012 Canadian Cardiovascular Society recommendations

This table took data from:(9, 105-108)

Risk estimation tools, such as Pooled Cohort Equations (PCE) and SCORE2, can be used for 10-year cardiovascular risk estimates, but current tools do not include Lp(a) levels, necessitating need for further risk stratification. (109)

2. Role of Biomarkers in Monitoring Disease Progression

1. Lipid Biomarkers:

- Lp(a): Multiple measurements of Lp(a) levels can assist in tracking the advancement of the ailment and analyzing the effectiveness of medicines that reduce Lp(a). However, Lp(a) levels don't fluctuate significantly with time, so there is no requirement for persistent monitoring (22).

- Low-Density Lipoprotein Cholesterol (LDL-C): The LDL-C is still a major biomarker for measuring the risk of heart diseases. In case of high Lp(a) level patients, immediate lowering of LDL-C is recommended to reduce the overall (76).

- Apolipoprotein B (ApoB): ApoB is a measure of the total number of atherogenic lipoprotein particles, including LDL and Lp(a). It gives additional risk stratification in presence of elevated Lp(a) (110). Apolipoprotein B (apoB) provides enhanced risk stratification when combined with lipoprotein(a) [Lp(a)] measurements because it reflects the total burden of atherogenic particles, including those containing Lp(a) (110). Since each Lp(a) particle contains one apoB molecule, elevated Lp(a) levels contribute to the total apoB count, thereby improving the estimation of cardiovascular risk beyond LDL cholesterol measurements (106). This combined approach is particularly valuable in patients with discordant lipid profiles, where high Lp(a) may be the primary driver of elevated apoB and associated atherosclerotic risk (111).

2. Inflammatory Biomarkers:

- High-Sensitivity C-Reactive Protein (hs-CRP): hs-CRP is a systemic inflammation marker and relates to raised cardiovascular risk. It might be possible that the elevated hs-CRP levels in patients with high levels of Lp(a) are related to the greater inflammatory load and increased risk of plaque instability (112).

- Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-α) are the two most common types of inflammatory cytokines that are present in the body of patients who have high amounts of Lp(a) and may provide additional information about the disease progression (113).

3. Oxidative Stress Biomarkers:

- Oxidized LDL (Ox-LDL): Ox-LDL is a marker of oxidative stress and is associated with plaque formation and instability. High levels of Ox-LDL in individuals with elevated Lp(a) can suggest a more advanced abrasive process and an increased risk of cardiovascular problems (45).

3. Role of Imaging in Monitoring Disease Progression

- Coronary Artery Calcium (CAC) Scoring: CAC scoring is a non-invasive imaging technique that quantifies the amount of calcium in the coronary arteries, providing a measure of atherosclerotic burden. Patients with elevated Lp(a) and high CAC scores are at significantly increased risk of cardiovascular events (114). Given the pro-inflammatory properties of Lp(a) and the vulnerable nature of calcified plaques, low-dose colchicine (0.5 mg daily) has emerged as a valuable therapeutic option. Recent trials demonstrate significant cardiovascular event reduction with this approach in patients with established coronary disease. The anti-inflammatory mechanism of colchicine complements the atherosclerotic stabilization achieved through lipid-lowering.(25, 96)

- Carotid Intima-Media Thickness (CIMT): CIMT is a measure of the thickness of the inner layers of the carotid artery and is used to assess subclinical atherosclerosis. Elevated Lp(a) levels are associated with increased CIMT, making it a useful tool for monitoring disease progression (115) (Figure 5).

- Plaque Imaging: Advanced imaging techniques, such as coronary computed tomography angiography (CCTA) and magnetic resonance imaging (MRI), can assess plaque characteristics, including size, composition, and vulnerability. Patients with elevated Lp(a) are more likely to have vulnerable plaques, which are prone to rupture and cause acute cardiovascular events (116).

- Positron Emission Tomography (PET): PET imaging can assess vascular inflammation and plaque activity using radiotracers such as 18F-fluorodeoxyglucose (FDG). This technique may provide additional insights into the inflammatory burden in patients with elevated Lp(a) (117).

Effective patient stratification and risk assessment are critical for managing individuals with elevated Lp(a) levels. Identifying high-risk individuals based on Lp(a) levels and cardiovascular history, combined with the use of biomarkers and imaging, can help guide

therapeutic decisions and monitor disease progression. Further research is needed to refine risk stratification tools and incorporate Lp(a) into routine clinical practice.

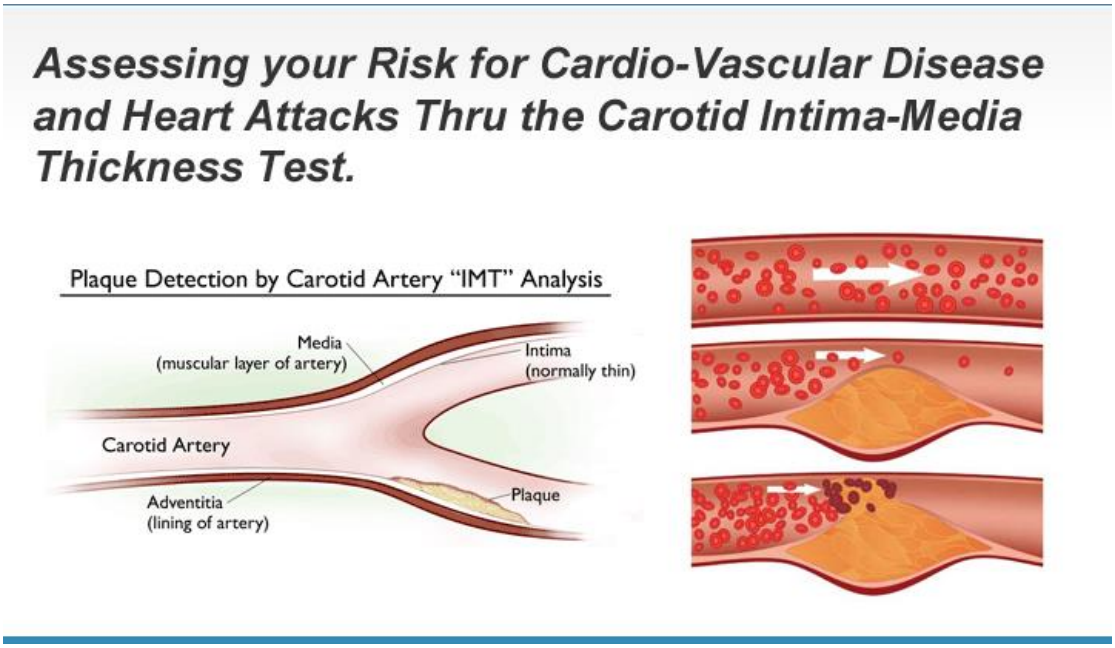

Figure 5: Carotid IMT is a strong predictor of future vascular events. The relative risk per IMT difference is slightly higher for the end point stroke than for myocardial infarction. (115)

4.2 Treatment Guidelines and Recommendations

Elevated Lipoprotein(a) [Lp(a)] is increasingly recognized as a significant independent risk factor for cardiovascular diseases (CVD). However, managing elevated Lp(a) remains challenging due to its strong genetic regulation and limited therapeutic options. This section explores current clinical guidelines and the potential integration of novel therapies into standard practice.

1. Current Clinical Guidelines on Managing Elevated Lp(a)

Screening and Risk Assessment:

- European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines: These guidelines recommend measuring Lp(a) levels at least once in a lifetime to identify individuals with genetically elevated levels (≥ 50 mg/dL or ≥

125 nmol/L), particularly those with a family history of premature CVD or familial hypercholesterolemia (FH) (118).

- American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines: While these guidelines do not specifically recommend routine Lp(a) screening, they acknowledge its role as a risk-enhancing factor that may influence treatment decisions, particularly in patients with borderline or intermediate cardiovascular risk (119).

Lifestyle Modifications:

- Diet and Exercise: Although lifestyle modifications have limited effects on Lp(a) levels, guidelines emphasize the importance of a heart-healthy diet (e.g., Mediterranean diet) and regular physical activity to reduce overall cardiovascular risk (89).

- Smoking Cessation: Smoking cessation is strongly recommended, as smoking exacerbates the pro-inflammatory and pro-thrombotic effects of elevated Lp(a) (120).

Pharmacological Therapies:

- Statins: Statins are the first-line therapy for lowering LDL cholesterol (LDL-C) but have minimal effects on Lp(a) levels. Guidelines recommend aggressive LDL-C lowering in patients with elevated Lp(a) to mitigate overall cardiovascular risk (76).

- PCSK9 Inhibitors: PCSK9 inhibitors (e.g., evolocumab, alirocumab) are recommended for patients with elevated Lp(a) and high cardiovascular risk, as they lower both LDL-C and Lp(a) levels by approximately 20-30% (80).

- Lipoprotein Apheresis: Lipoprotein apheresis is reserved for patients with extremely high Lp(a) levels (≥ 60 mg/dL or ≥ 150 nmol/L) and progressive CVD despite maximal medical therapy (121). Lipoprotein apheresis reduces circulating atherogenic lipoproteins through extracorporeal blood filtration that selectively

removes apolipoprotein B (apoB)-containing particles, including low-density lipoprotein (LDL), lipoprotein(a) [Lp(a)], and very-low-density lipoprotein (VLDL) (121). The procedure typically employs dextran sulfate adsorption columns or heparin-induced extracorporeal LDL precipitation to bind and eliminate these lipoproteins from plasma, resulting in acute reductions of 50-75% in LDL-C and 60-70% in Lp(a) levels (122). Regular apheresis (weekly or biweekly) provides cumulative vascular benefits by improving endothelial function, reducing inflammatory markers, and potentially inducing plaque regression in patients with severe hypercholesterolemia or elevated Lp(a) (123).

- Pelacarsen: Pelacarsen (IONIS-APO(a)-LRx) is an ASO that specifically targets apolipoprotein(a) [apo(a)] mRNA, reducing Lp(a) levels by up to 80% in clinical trials. The ongoing Lp(a) HORIZON trial is evaluating its efficacy in reducing cardiovascular events, and if successful, Pelacarsen could become a first-in-class therapy for Lp(a) reduction (25).

If approved, Pelacarsen could be integrated into standard practice for patients with elevated Lp(a) and high cardiovascular risk, particularly those with Lp(a) levels ≥ 50 mg/dL (125 nmol/L) and a history of CVD (22).

- Olpasiran: Olpasiran (AMG 890) is a siRNA therapy that targets apo(a) mRNA, achieving reductions in Lp(a) levels of over 90% in early-phase trials. The OCEAN(a) trial is currently evaluating its efficacy and safety in patients with elevated Lp(a) and CVD (82).

Furthermore, Olpasiran could be used as a highly effective therapy for patients with very high Lp(a) levels (≥ 100 mg/dL or ≥ 250 nmol/L) and a history of recurrent cardiovascular events (85).

- Colchicine: Colchicine has been shown to reduce cardiovascular events in patients with coronary artery disease, potentially benefiting those with elevated Lp(a) due to

its anti-inflammatory effects. Guidelines may consider recommending colchicine for secondary prevention in high-risk patients with elevated Lp(a) (96).

- Interleukin-1β (IL-1β) Inhibitors: IL-1β inhibitors (e.g., canakinumab) have demonstrated cardiovascular benefits in high-risk patients and may be considered for patients with elevated Lp(a) and persistent inflammation (98).

Current clinical guidelines emphasize the importance of identifying and managing elevated Lp(a) levels, particularly in high-risk individuals. While lifestyle modifications and conventional therapies (e.g., statins, PCSK9 inhibitors) remain the cornerstone of treatment, emerging therapies such as antisense oligonucleotides (e.g., Pelacarsen) and siRNA-based therapies (e.g., olpasiran) hold promises for significantly reducing Lp(a) levels and cardiovascular risk. The integration of these novel therapies into standard practice will require further evidence from ongoing clinical trials and updates to clinical guidelines.

5 Challenges and Future Directions

5.1 Addressing Critical Gaps in Lipoprotein(a) Research: A Comprehensive

Academic Perspective

The growing recognition of Lp(a) as a significant independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis has been well-documented in recent epidemiological and genetic studies (79, 124). This recognition has brought into focus several critical knowledge gaps that must be addressed to advance both scientific understanding and clinical management (1, 125).Two particularly areas of investigation include:

(1) the need for robust long-term outcomes data from Lp(a)-lowering clinical trials

(2) the complex genetic and epigenetic regulation of Lp(a) metabolism (22).

These gaps represent substantial barriers to the development of evidence-based therapeutic strategies and personalized approaches to cardiovascular risk reduction (104).

The Imperative for Long-Term Outcomes Data:

Recent years have witnessed remarkable progress in the development of targeted Lp(a)-lowering therapies, particularly antisense oligonucleotides (ASOs) and small interfering RNA (siRNA) agents (42). Phase II clinical trials with pelacarsen (IONIS-APO(a)-LRx) have demonstrated up to 80% reductions in Lp(a) levels with weekly 20 mg dosing (84), while olpasiran (AMG 890) has shown even more dramatic reductions exceeding 90% with quarterly subcutaneous administration (86). The siRNA agent SLN360 has achieved near-complete Lp(a) suppression (98% reduction) at its highest tested dose (82). While these pharmacodynamic effects are undeniably impressive, they raise several fundamental clinical questions that remain unresolved (126).

The dose-response relationship and establishment of therapeutic thresholds represent a crucial knowledge gap (25). It remains uncertain what degree of Lp(a) reduction is necessary to achieve meaningful clinical benefit, and whether this threshold varies based on baseline Lp(a) levels or other patient characteristics (127). Furthermore, the impact of these therapies on atherosclerotic plaque biology requires thorough investigation (23). Specifically, researchers must determine whether Lp(a) reduction leads to actual plaque regression or merely stabilizes existing lesions, and how these therapies affect critical plaque characteristics such as necrotic core size and fibrous cap thickness (128).

Long-term safety considerations present another significant area of uncertainty (22). The potential consequences of prolonged apolipoprotein(a) suppression on wound healing, thrombotic risk, and immune function remain poorly understood (78). Additionally, population-specific responses to therapy require careful examination, particularly given the well-documented ethnic variations in Lp(a) levels and associated cardiovascular risk (129).The so-called "African paradox," where individuals of African descent typically exhibit higher Lp(a) levels but lower CAD risk compared to other populations, highlights the need for targeted investigations into potential protective genetic modifiers (70).

Several landmark clinical trials are currently addressing these questions. The Lp(a)HORIZON trial (NCT04023552) is evaluating pelacarsen in patients with established

cardiovascular disease and Lp(a) levels ≥70 mg/dL, with major adverse cardiovascular events (MACE) as the primary endpoint(25). Similarly, the OCEAN(a)-Outcomes trial (NCT05581303) is investigating olpasiran in patients with ASCVD and very high Lp(a) levels (≥200 nmol/L), focusing on a composite endpoint of cardiovascular death, myocardial infarction, and urgent revascularization. These studies, along with others in development, will provide critical insights into the clinical benefits of Lp(a) reduction (79).

Trial Name	Intervention	Population	Primary Endpoint	Estimated Completion
Lp(a)HORIZON (NCT04023552) (82, 85)	Pelacarsen	CVD + Lp(a)≥70 mg/dL	MACE reduction	2025
OCEAN(a)-Outcomes (NCT05581303) (85, 86)	Olpasiran	ASCVD + Lp(a)≥200 nmol/L	CV death/MI/urgent revasc	2026
SLN360 Phase II (NCT04606602) (130)	SLN360	High Lp(a)	Safety/efficacy	2024

5.2 Innovations in Treatment Development for Lipoprotein(a)-Associated Cardiovascular Disease

1. Combination Therapies Targeting Multiple Pathways

The complex pathophysiology of Lp(a)-mediated vascular disease necessitates innovative therapeutic strategies that simultaneously target multiple pathological pathways (131). Current research focuses on several promising combination approaches:

a) Lp(a) Reduction with Anti-Inflammatory Agents

Emerging evidence suggests synergistic benefits when combining Lp(a)-lowering therapies with anti-inflammatory agents (79). The rationale stems from Lp(a)'s dual role in lipid deposition and vascular inflammation:

- PCSK9 inhibitors +Colchicine: Preliminary data show enhanced plaque stabilization when combining evolocumab (Lp(a) reduction ~25%) with low-dose colchicine (anti-inflammatory) in high-risk patients. The ongoing CLEAR Outcomes trial (NCT02898610) is evaluating this combination in post-MI patients (1, 35).

- siRNA therapies + IL-1β inhibition: Preclinical models demonstrate that olpasiran (siRNA) combined with canakinumab (anti-IL1β antibody) may more effectively reduce vascular inflammation than either therapy alone (82).

b) Lp(a) and LDL-C Dual Targeting

Given the additive cardiovascular risk from elevated Lp(a) and LDL-C, combination approaches are being investigated:

- Pelacarsen + statins: Phase II data show additive effects on atherogenic lipoprotein burden when combining the ASO pelacarsen with high-intensity statins (132).

- Lipoprotein apheresis + pharmacotherapy: For patients with extreme elevations (Lp(a) >150 mg/dL), monthly apheresis combined with PCSK9 inhibitors provides more sustained lipoprotein reduction than either modality alone (121).

Mechanistic Considerations:

These combinations target distinct aspects of Lp(a) pathogenicity:

I. Reduced Lp(a) particle number (ASO/siRNA)

II. Decreased oxidized phospholipid delivery (antioxidants)

III. Attenuated vascular inflammation (anti-cytokine therapies) (133).

2. Personalized Medicine Approaches for Lp(a)-Driven Vascular Disease

Advances in genetic testing and biomarker profiling are enabling precision medicine strategies for Lp(a)-associated risk:

a) Genotype-Guided Therapy Selection

Emerging pharmacogenomic data suggest differential treatment responses based on LPA genotype (133):

- KIV-2 repeat variants: Patients with low repeat number (<22) show better response to ASO therapies (103).
- rs10455872 carriers: This SNP predicts greater cardiovascular benefit from Lp(a) reduction independent of absolute Lp(a) levels (86).

b) Phenotype-Specific Treatment Algorithms

Novel stratification approaches consider both Lp(a) levels and phenotypic manifestations:

Phenotype	Therapeutic Approach	Rationale
Isolated elevated Lp(a)	Monotherapy (e.g., pelacarsen)	Target primary abnormality
Lp(a) + inflammation	Combination with anti-IL6 agents	Address inflammatory component
Lp(a) + thrombotic tendency	Additive antithrombotic therapy	Counteract prothrombotic effects

c) Advanced Biomarker Integration

Cutting-edge approaches incorporate dynamic biomarkers beyond static Lp(a) measurements:

- OxPL-apoB levels: May better predict treatment response than Lp(a) concentration alone (21).
- Coronary calcium progression: Serial CT angiography to guide therapy intensity (50, 134, 135).
- 18F-FDG PET imaging: Quantifies vascular inflammation reduction post-therapy (117).

3.Implementation Challenges and Future Directions:

Despite these promising developments, significant barriers remain to widespread implementation. The cost-effectiveness of comprehensive genetic testing and advanced biomarker monitoring requires further evaluation, as does the development of validated clinical decision algorithms. Ongoing research efforts are focused on developing polygenic risk scores that incorporate multiple LPA variants, validating non-invasive imaging biomarkers, and establishing cost-effective screening protocols (136).

As these innovations mature, they promise to transform the management of Lp(a)-associated cardiovascular disease from reactive to proactive, from generalized to personalized, and from treatment-focused to prevention-oriented.

The convergence of mechanistic insights, therapeutic innovation, and precision medicine approaches represents a paradigm shift in addressing this long-neglected cardiovascular risk factor. Continued progress along these complementary fronts offers the potential to significantly reduce the global burden of Lp(a)-associated cardiovascular disease (125).

5.3 Public Health and Preventive Strategies for Lipoprotein(a)-Associated Cardiovascular Risk

Despite robust evidence establishing lipoprotein(a) [Lp(a)] as an independent, genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD), awareness remains critically low among both healthcare providers and the general public (118). Epidemiological studies demonstrate that elevated Lp(a) levels (>50 mg/dL or >125 nmol/L) affect approximately 20% of the global population, conferring a 2-3-fold increased risk of coronary artery disease and aortic valve stenosis. However, surveys indicate fewer than 1% of at-risk individuals have undergone Lp(a) testing, highlighting a substantial implementation gap in preventive cardiology (129).

Modern societies have begun addressing this knowledge deficit through updated clinical guidelines. The 2022 European Atherosclerosis Society consensus statement recommends Lp(a) measurement at least once in every adult's lifetime, with particular emphasis on testing individuals with premature ASCVD, familial hypercholesterolemia, or a family history of elevated Lp(a) (21). Similarly, the National Lipid Association's scientific statement advocates for incorporating Lp(a) into routine cardiovascular risk assessment algorithms. These recommendations are supported by Mendelian randomization studies confirming the causal relationship between Lp(a) and ASCVD across diverse populations (109).

Educational initiatives targeting primary care providers represent a crucial intervention point, as most cardiovascular risk assessment occurs in general practice settings. Innovative programs integrating Lp(a) education into electronic health record decision-support tools have demonstrated success in increasing test ordering rates by 40-60% in pilot studies. Parallel public health campaigns emphasizing the hereditary nature of Lp(a) and its independence from traditional risk factors like diet and exercise are needed to drive patient-initiated testing requests (79).

Population-Level Screening and Early Intervention Programs

The development of cost-effective screening strategies for elevated Lp(a) presents both challenges and opportunities for public health implementation (137). Current evidence supports a tiered screening approach:

- Universal testing at age 18-20: Early identification allows for prolonged risk stratification and implementation of preventive measures. Economic modeling suggests this strategy may be cost-effective when considering lifetime ASCVD risk reduction (133).

- Cascade family screening: First-degree relatives of individuals with Lp(a) >90th percentile should undergo testing, as familial clustering accounts for 70-90% of Lp(a) level variability. This approach has proven effective in European lipid clinics, identifying at-risk relatives in >80% of screened families (138).

Targeted testing in high-risk populations: Including Lp(a) measurement in:

A. Patients with premature ASCVD (<55 years men, <65 years women)
B. Those with familial hypercholesterolemia
C. Individuals with low-density lipoprotein cholesterol (LDL-C) discordance (high LDL-C but no other risk factors) (136)

Emerging screening technologies may enhance program feasibility. Genetic screening for LPA risk variants shows promise for identifying high-risk individuals, though cost and interpretation challenges remain (138).

Early intervention programs for identified high-risk individuals should emphasize:

- Aggressive LDL-C management: Despite neutral effects on Lp(a) itself, intensive statin therapy reduces composite ASCVD risk in high Lp(a) individuals (77).

- Lifestyle optimization: While Lp(a) levels are genetically determined, smoking cessation and blood pressure control mitigate associated cardiovascular risk.

- Emerging therapies: Antisense oligonucleotide trials suggest potential for 80-90% Lp(a) reduction, though outcomes data are pending (84).

Implementation barriers include inconsistent insurance coverage for Lp(a) testing in asymptomatic individuals and lack of FDA-approved therapies specifically targeting Lp(a).

Successful models from European countries with national lipid screening programs demonstrate that integrating Lp(a) into existing cardiovascular prevention frameworks can achieve testing rates >60% in target populations (79, 133).

6 CONCLUSION

Lipoprotein(a) [Lp(a)] has emerged as a major independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis, with approximately 20% of the global population having elevated levels (>50 mg/dL) that confer a 2-4-fold increased risk of coronary artery disease.

The pathophysiology of Lp(a)-mediated vascular damage involves dual mechanisms: atherogenic effects through LDL-like particle deposition and oxidized phospholipid transport, combined with thrombotic potential due to its structural homology with plasminogen. This unique biology explains the particularly strong associations observed between elevated Lp(a) and clinical outcomes, including premature ASCVD and progressive disease despite optimal management of conventional risk factors like LDL cholesterol.

Recent therapeutic advances have transformed the landscape of Lp(a) management, with antisense oligonucleotides (pelacarsen) and siRNA-based therapies (olpasiran) demonstrating unprecedented efficacy in clinical trials by achieving 80-90% reductions in Lp(a) levels while maintaining favorable safety profiles. These breakthroughs are being complemented by innovative combination approaches that pair Lp(a) reduction with anti-inflammatory agents, as well as personalized treatment algorithms based on LPA genotype and specific phenotypic manifestations of disease.

However, several critical challenges must still be addressed to realize the full potential of these advances. Most importantly, while phase 2 trials have clearly established the pharmacodynamic efficacy of these novel agents, the ongoing Lp(a)HORIZON and OCEAN(a)-Outcomes trials must confirm that substantial Lp(a) reduction translates to reduced ASCVD events in clinical practice. Current evidence suggests that achieving Lp(a) levels below 50 mg/dL may be required for meaningful cardiovascular risk reduction, though this threshold requires further validation across diverse populations.

The translation of these scientific advances into clinical practice faces significant implementation barriers, as current data indicate that fewer than 5% of eligible patients undergo Lp(a) testing, with even lower rates of subsequent risk stratification and targeted management.

To address this gap, comprehensive implementation strategies are needed that incorporate standardized testing protocols for primary prevention, integrated risk assessment tools that properly account for Lp(a), and specialized referral pathways for high-risk individuals identified through screening. These efforts must also consider important health equity dimensions, as the genetic determinants of Lp(a) create unique disparities - particularly the observation that individuals of African ancestry tend to have higher median Lp(a) levels but may experience different risk relationships compared to other populations.

Moving forward, a coordinated "call to action" across multiple stakeholders will be essential to capitalize on these scientific advances. Researchers must prioritize the completion of outcomes trials for Lp(a)-lowering therapies while also developing validated, cost-effective screening algorithms and investigating population-specific risk thresholds. Clinicians should implement universal once-in-lifetime Lp(a) testing per current guideline recommendations, while simultaneously adopting aggressive management of concomitant risk factors in high Lp(a) patients and participating in registry studies to characterize real-world treatment effects. Policy makers play a crucial role in supporting insurance coverage for Lp(a) testing in preventive care, accelerating regulatory pathways for promising therapies, and funding public health initiatives to increase awareness. Finally, patient engagement through advocacy for appropriate testing and participation in clinical trials will be vital for advancing the field.

The convergence of basic science, therapeutic innovation, and precision medicine approaches has positioned the cardiovascular community at a watershed moment in addressing Lp(a)-associated risk. Realizing the full potential of these advances will require sustained collaboration across the research-clinical-policy continuum to transform our growing scientific understanding into tangible reductions in the global burden of cardiovascular disease. By addressing the remaining knowledge gaps and implementation challenges through this multidisciplinary approach, we can fundamentally improve the prevention and management of Lp(a)-mediated vascular disease for populations worldwide.

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