LIPOPROTEIN(A) AS A THERAPEUTIC TARGET: ARE WE ENTERING A NEW ERA IN CARDIOVASCULAR PREVENTION?

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Abstract

Background: Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein associated with increased risk of atherosclerotic cardiovascular disease and calcific aortic valve stenosis. Conventional lipid-lowering therapies have minimal effect on Lp(a), leaving a significant component of residual risk untreated.

Aim: To evaluate the role of Lp(a) as a causal cardiovascular risk factor and assess whether emerging targeted therapies can establish Lp(a) as a therapeutic target.

Methods: A narrative review was conducted using PubMed, Scopus, and Web of Science. Studies published between 2015 and 2025 were screened using the terms "lipoprotein(a)", "Lp(a)", "cardiovascular risk", "atherosclerosis", "PCSK9 inhibitors", "pelacarsen", and "olpasiran". Randomized trials, large observational studies, and guideline documents were prioritized. The final analysis included 20 key sources.

Results: Elevated Lp(a) is independently associated with increased cardiovascular risk. Statins do not reduce Lp(a), while PCSK9 inhibitors achieve modest reductions. Novel therapies based on antisense oligonucleotides and small interfering RNA demonstrate substantial Lp(a) lowering in phase 2 studies.

Conclusion: Lp(a) is shifting from a risk marker to a potential therapeutic target. Ongoing outcome trials will determine its role in cardiovascular prevention.

Keywords: *lipoprotein(a), Lp(a), cardiovascular risk, residual risk, antisense therapy, siRNA*

METHODS

Aim

To assess the clinical relevance of Lp(a) and its potential as a therapeutic target in cardiovascular prevention.

Design: Narrative review focused on clinically relevant evidence.

Data sources: PubMed, Scopus, Web of Science

Timeframe: 2015–2025.

Search terms: "lipoprotein(a)", "Lp(a)", "cardiovascular disease", "atherosclerosis", "aortic stenosis", "PCSK9 inhibitors", "pelacarsen", "olpasiran".

Inclusion criteria: Randomized controlled trials; Meta-analyses; Large observational studies; Guideline documents; Exclusion criteria; Case reports; Small cohorts without clinical endpoints.

Scope

Identified: over 180 studies, of which: 20 key publications are included.

1. Introduction

Lipoprotein(a) is an inherited lipoprotein that has emerged as a significant and independent determinant of cardiovascular risk. Its plasma concentration is primarily genetically controlled through the LPA gene and remains relatively constant throughout life, with minimal influence from lifestyle or environmental factors [1].

Epidemiological and genetic evidence consistently links elevated Lp(a) levels with an increased risk of atherosclerotic cardiovascular disease, including coronary artery disease, ischemic stroke, and peripheral arterial disease [2]. In addition, Lp(a) has a unique and strong association with calcific aortic valve stenosis, which distinguishes it from other lipid fractions and expands its clinical relevance beyond atherosclerosis.

The pathophysiological role of Lp(a) is multifactorial. Structurally, it consists of an LDL-like particle bound to apolipoprotein(a), which confers both atherogenic and prothrombotic properties. Lp(a) promotes cholesterol deposition within the arterial wall, carries oxidized phospholipids that

enhance vascular inflammation, and interferes with fibrinolysis due to structural homology between apolipoprotein(a) and plasminogen. These combined effects contribute to plaque formation, progression, and instability. Despite this strong biological and clinical evidence, Lp(a) has historically remained underrecognized in routine clinical practice. One of the main reasons is the lack of effective therapies capable of selectively reducing its levels. Conventional lipid-lowering treatments, including statins, have little or no effect on Lp(a), while their widespread use has shifted attention primarily toward LDL cholesterol control.

This paradigm is now changing. Advances in molecular therapies, particularly antisense oligonucleotides and small interfering RNA, have demonstrated the ability to reduce Lp(a) levels by more than 80–90% in early-phase clinical trials [3]. These developments have repositioned Lp(a) from a passive risk marker to an active therapeutic target. Current clinical guidelines recommend at least one lifetime measurement of Lp(a), especially in individuals with premature cardiovascular disease, a family history of early events, or unexplained residual risk. However, implementation remains inconsistent, and many high-risk patients are not screened.

The central issue is no longer whether Lp(a) is clinically relevant, but whether targeted reduction will translate into meaningful reductions in cardiovascular events. This question defines the transition from observational evidence to interventional cardiology and frames the emerging role of Lp(a) in modern cardiovascular prevention.

2. Structure and Biological Properties of Lipoprotein(a)

Lipoprotein(a) is a complex lipoprotein particle structurally similar to low-density lipoprotein (LDL), with one key distinction: the presence of apolipoprotein(a) [apo(a)], which is covalently bound to apolipoprotein B-100 via a disulfide bond [1].

The defining feature of Lp(a) is apo(a), a highly polymorphic glycoprotein encoded by the LPA gene. Apo(a) consists of multiple kringle IV (KIV) repeats, particularly the KIV type 2 domain, the number of which varies significantly between individuals. This genetic variability determines both the size of the apo(a) isoform and the plasma concentration of Lp(a). Smaller isoforms are associated with higher circulating levels and greater cardiovascular risk [1, 2].

Lp(a) levels are almost entirely genetically determined and reach adult concentrations early in life. Unlike LDL cholesterol, they are minimally affected by diet, physical activity, or most pharmacological interventions. This stability makes Lp(a) a consistent lifelong risk factor rather than a dynamic biomarker [2].

From a biochemical perspective, Lp(a) carries a high content of oxidized phospholipids (OxPL), which are key mediators of vascular inflammation. These OxPLs bind preferentially to apo(a), making Lp(a) one of the main carriers of pro-inflammatory lipids in circulation. This property links Lp(a) directly to endothelial dysfunction and progression of atherosclerotic plaques [3].

Apo(a) shares structural homology with plasminogen, particularly in its kringle domains. However, unlike plasminogen, it lacks fibrinolytic activity. Instead, Lp(a) competes with plasminogen for binding sites on fibrin and endothelial surfaces. This inhibits plasmin generation and impairs fibrinolysis, promoting a prothrombotic state [1]. Lp(a) also plays a role in vascular calcification. It is actively involved in the pathogenesis of calcific aortic valve disease through the delivery of oxidized phospholipids to valvular interstitial cells. These lipids stimulate osteogenic signaling pathways, leading to progressive valve calcification. This mechanism explains the strong and specific association between Lp(a) and aortic stenosis [3]. In addition to its vascular effects, Lp(a) interacts with macrophages, smooth muscle cells, and endothelial cells. It enhances foam cell formation, increases expression of adhesion molecules, and promotes inflammatory cytokine release. These actions accelerate plaque formation and instability. An important clinical implication is that Lp(a) acts independently of LDL cholesterol. Patients with well-controlled LDL-C may still have

high Lp(a)-driven risk. This explains why a subset of patients continues to experience cardiovascular events despite optimal lipid-lowering therapy.

In summary, Lp(a) combines three key pathological pathways: lipid deposition, inflammation, and thrombosis. This unique combination distinguishes it from other lipoproteins and supports its role as a causal and independent driver of cardiovascular disease.

3. Pathophysiological Mechanisms and Clinical Impact

Lipoprotein(a) contributes to cardiovascular disease through a combination of atherogenic, inflammatory, and prothrombotic mechanisms. These pathways act in parallel and explain its independent association with cardiovascular events.

The atherogenic component of Lp(a) is related to its LDL-like structure. It promotes cholesterol accumulation within the arterial wall and contributes to foam cell formation. However, unlike LDL cholesterol, Lp(a) carries a high burden of oxidized phospholipids, which amplify vascular inflammation and accelerate plaque progression. The inflammatory effect of Lp(a) is driven by these oxidized phospholipids. They stimulate endothelial dysfunction, increase expression of adhesion molecules, and promote recruitment of inflammatory cells into the vascular wall. This leads to the formation of unstable atherosclerotic plaques with a higher likelihood of rupture [4].

The prothrombotic properties of Lp(a) are mediated by apolipoprotein(a), which shares structural homology with plasminogen. This similarity allows Lp(a) to compete with plasminogen for binding sites, reducing plasmin generation and impairing fibrinolysis. As a result, Lp(a) promotes thrombus formation and persistence, particularly in the setting of plaque rupture [5].

These combined mechanisms explain why Lp(a) is associated not only with atherosclerotic disease but also with acute cardiovascular events. Elevated Lp(a) levels have been linked to increased risk of myocardial infarction, stroke, and peripheral arterial disease, independent of traditional risk factors [6].

An additional and distinct clinical effect of Lp(a) is its role in calcific aortic valve disease. Lp(a)-associated oxidized phospholipids trigger osteogenic differentiation of valvular interstitial cells, leading to progressive valve calcification. This mechanism is unique among lipoproteins and explains the strong association between elevated Lp(a) and aortic stenosis [6]. Importantly, Lp(a) contributes to residual cardiovascular risk. Even in patients who achieve target LDL cholesterol levels with statins or other therapies, elevated Lp(a) remains a driver of ongoing risk. This highlights the limitation of current lipid-lowering strategies and the need for therapies specifically targeting Lp(a).

The clinical implication is clear: Lp(a) is not only a biomarker but a causal factor in cardiovascular disease. Its effects are mediated through distinct biological pathways that are not adequately addressed by conventional therapies.

4. Lipoprotein(a) and Cardiovascular Risk

The clinical relevance of lipoprotein(a) is supported by a large body of epidemiological, genetic, and observational evidence. Elevated Lp(a) is consistently associated with a higher risk of atherosclerotic cardiovascular disease across different populations and clinical settings.

One of the strongest arguments for its clinical importance is the concordance between observational studies and Mendelian randomization analyses. Observational data show that individuals with elevated Lp(a) have a significantly higher incidence of myocardial infarction and other major cardiovascular events. Mendelian randomization strengthens this association by supporting a causal relationship rather than a simple correlation [7].

The risk associated with Lp(a) is particularly relevant in premature cardiovascular disease. Patients with early myocardial infarction, recurrent events despite standard therapy, or a strong family history of coronary disease often have elevated Lp(a) levels. In such cases, Lp(a) may explain part of the residual risk that remains insufficiently captured by traditional lipid markers [8]. Lp(a) also has

prognostic value in secondary prevention. In patients with established atherosclerotic cardiovascular disease, elevated Lp(a) identifies a subgroup at persistently high risk even when LDL cholesterol is well controlled. This is clinically important because such patients may appear optimally treated on standard lipid profiles while remaining exposed to substantial ongoing risk [8].

Another important aspect is the distribution of risk across Lp(a) levels. Cardiovascular risk does not suddenly appear above a single threshold, but increases progressively with rising concentrations. However, markedly elevated levels are associated with the greatest absolute risk and are most relevant in clinical decision-making. This is why many consensus documents emphasize the identification of patients with clearly elevated Lp(a), especially in the setting of unexplained or disproportionate cardiovascular burden [9].

The effect of Lp(a) extends beyond coronary artery disease. Elevated levels have also been associated with ischemic stroke and peripheral arterial disease, further supporting its role as a generalized vascular risk factor [7]. This broad clinical impact reinforces the view that Lp(a) should be considered within the overall framework of cardiovascular prevention, rather than as a niche lipid abnormality. From a practical perspective, Lp(a) is most informative when it explains discordance between apparent lipid control and actual clinical outcome. A patient with recurrent events, controlled LDL-C, and few obvious residual risk factors may still have significant Lp(a)-related risk. In this context, measurement of Lp(a) adds prognostic depth and can improve risk stratification.

Taken together, the available evidence supports the position that elevated Lp(a) is not merely associated with cardiovascular disease, but is a clinically meaningful, independent, and likely causal contributor to both first and recurrent vascular events.

5. Lipoprotein(a) and Calcific Aortic Valve Disease

Lipoprotein(a) has a distinct and clinically important association with calcific aortic valve disease. Unlike most lipid fractions, which are primarily linked to atherosclerosis, Lp(a) plays a direct role in the development and progression of aortic valve calcification. Epidemiological studies show that elevated Lp(a) levels are strongly associated with an increased risk of aortic valve stenosis. This relationship is supported by genetic data, where variants in the LPA gene correlate with both higher Lp(a) concentrations and a higher incidence of calcific aortic valve disease, reinforcing a causal link [10].

The underlying mechanism differs from classical atherosclerosis. Lp(a) carries oxidized phospholipids that accumulate in the aortic valve. These lipids trigger inflammatory and osteogenic pathways within valvular interstitial cells. As a result, these cells undergo phenotypic transformation into osteoblast-like cells, promoting calcium deposition and progressive stiffening of the valve [11]. This process is not passive degeneration but an active, regulated pathway driven by lipid-mediated signaling. Lp(a) acts as a carrier of pro-calcific stimuli, making it a central mediator in the initiation and progression of valve calcification.

Clinical data support this mechanistic link. Higher Lp(a) levels are associated not only with the presence of aortic stenosis but also with faster disease progression. Patients with elevated Lp(a) tend to develop valve disease earlier and progress more rapidly toward clinically significant stenosis [10].

Importantly, current medical therapies have no proven effect on slowing the progression of calcific aortic stenosis. Standard lipid-lowering treatments, including statins, do not alter the course of the disease. This makes Lp(a) an attractive therapeutic target, as it represents one of the few modifiable pathways identified in the pathogenesis of aortic valve calcification. The potential clinical impact is significant. If targeted Lp(a)-lowering therapies can slow or prevent valve calcification, this could change the management of aortic stenosis, which is currently limited to surgical or transcatheter valve replacement in advanced stages.

In this context, Lp(a) is not only a marker of vascular risk but also a key factor in a specific structural heart disease. This expands its relevance beyond traditional cardiovascular prevention and supports the rationale for targeted intervention.

6. Screening and Clinical Interpretation of Lipoprotein(a)

Measurement of lipoprotein(a) is now recommended as part of cardiovascular risk assessment, yet it remains underused in routine practice. Current guidelines support at least one lifetime measurement of Lp(a), particularly in individuals at increased cardiovascular risk [12]. Screening is most informative in specific clinical settings. These include patients with premature atherosclerotic cardiovascular disease, a family history of early cardiovascular events, recurrent events despite optimal lipid-lowering therapy, and individuals with unexplained high cardiovascular risk. In such cases, Lp(a) can identify a genetically driven component of risk that is not captured by standard lipid parameters [12]. Lp(a) measurement is also relevant in patients with calcific aortic valve disease, given its established role in valve calcification. In addition, testing may be considered in patients with borderline or intermediate risk to refine risk stratification and guide intensity of preventive strategies.

A key practical issue is the interpretation of Lp(a) levels. Unlike LDL cholesterol, Lp(a) does not have universally standardized thresholds. However, consensus documents commonly define levels above 50 mg/dL (or approximately 125 nmol/L) as elevated and associated with increased cardiovascular risk [13]. Very high levels confer a substantially greater lifetime risk. It is important to recognize that Lp(a) exists in different isoforms, which vary in size and influence assay results. This has led to variability between measurement methods, particularly when values are reported in mass units (mg/dL) rather than particle concentration (nmol/L). For clinical practice, consistency in the assay used is more important than the unit itself. Unlike other lipid parameters, Lp(a) typically requires only a single measurement. Because levels are genetically determined and stable over time, repeated testing is generally unnecessary unless specific therapies targeting Lp(a) are initiated. Another important aspect is the integration of Lp(a) into overall cardiovascular risk assessment. Elevated Lp(a) should not be interpreted in isolation but rather as a risk enhancer. In patients with borderline or intermediate risk, high Lp(a) may justify more aggressive management of modifiable risk factors, including LDL cholesterol reduction. At present, the main clinical utility of Lp(a) testing lies in risk stratification rather than direct therapeutic decision-making. However, this is expected to change as targeted therapies become available.

In summary, Lp(a) measurement provides valuable information in selected patients and helps identify individuals with increased inherited cardiovascular risk. Wider implementation of screening may improve early detection of high-risk patients and support more individualized prevention strategies.

7. Current Therapeutic Options

Management of elevated lipoprotein(a) remains limited. Most conventional lipid-lowering therapies have little or no direct effect on Lp(a), which explains why it has long been considered a non-modifiable risk factor. Lifestyle interventions, including diet, physical activity, and weight reduction, have minimal impact on Lp(a) levels. This contrasts with LDL cholesterol and reinforces the genetic determination of Lp(a) [14]. Statins, the cornerstone of lipid-lowering therapy, do not reduce Lp(a). In some cases, a modest increase in Lp(a) has been observed. Despite this, statins remain essential because they reduce overall cardiovascular risk through LDL-C lowering and should not be withheld in patients with elevated Lp(a) [14]. Ezetimibe has a neutral or minimal effect on Lp(a). Its role remains focused on additional LDL-C reduction rather than modification of Lp(a)-related risk.

PCSK9 inhibitors represent the first widely available pharmacological class with a measurable effect on Lp(a). Agents such as evolocumab and alirocumab reduce Lp(a) levels by approximately

20–30%. This effect is consistent across clinical trials and is independent of their LDL-C lowering action [15]. Importantly, secondary analyses suggest that part of the cardiovascular benefit observed with PCSK9 inhibitors may be related to Lp(a) reduction, although this relationship is not yet fully defined.

Lipoprotein apheresis is currently the most effective method for lowering Lp(a) in clinical practice. It can achieve acute reductions of 60–70% per session. However, its use is limited by cost, availability, and the need for repeated procedures. It is generally reserved for patients with very high Lp(a) levels and progressive cardiovascular disease despite optimal medical therapy [16].

Niacin has been shown to reduce Lp(a) levels by up to 20–30%. However, its use has declined due to lack of demonstrated outcome benefit in contemporary trials and a higher incidence of adverse effects. As a result, it is no longer recommended for routine management of elevated Lp(a). Overall, current therapeutic options do not provide a targeted and sustained reduction of Lp(a). Management is therefore focused on aggressive control of modifiable risk factors, particularly LDL cholesterol, blood pressure, and lifestyle factors.

This limitation highlights the unmet clinical need that has driven the development of novel therapies specifically designed to lower Lp(a).

8. Emerging Targeted Therapies

The development of therapies that directly target lipoprotein(a) marks a major shift in cardiovascular prevention. Unlike conventional treatments, these agents act at the level of apolipoprotein(a) synthesis, leading to substantial and sustained reductions in Lp(a) concentrations.

Two main approaches have emerged: antisense oligonucleotides (ASO) and small interfering RNA (siRNA). Both strategies reduce hepatic production of apolipoprotein(a) by targeting LPA messenger RNA, but they differ in mechanism and dosing frequency.

Antisense oligonucleotides, such as pelacarsen, bind to LPA mRNA and promote its degradation, thereby reducing apo(a) synthesis. In phase 2 studies, pelacarsen achieved dose-dependent reductions in Lp(a) of up to 80%. These reductions were consistent across different baseline levels and were associated with parallel decreases in oxidized phospholipids [17]. The ongoing HORIZON trial is designed to determine whether this reduction translates into fewer cardiovascular events.

Small interfering RNA therapies offer a complementary approach. Agents such as olpasiran act through RNA interference, leading to sustained suppression of LPA expression. In the OCEAN(a)-DOSE trial, olpasiran reduced Lp(a) levels by more than 90%, with effects maintained for several months after dosing [18]. This prolonged action allows for less frequent administration and may improve long-term adherence.

Another siRNA agent, SLN360, has also demonstrated substantial Lp(a) reductions in early-phase studies, confirming that RNA-based targeting of Lp(a) is a reproducible and scalable strategy [19]. A key advantage of these therapies is their specificity. Unlike traditional lipid-lowering drugs, which have broad metabolic effects, ASO and siRNA therapies selectively reduce Lp(a) with minimal impact on other lipid fractions. This allows for targeted intervention in patients with elevated Lp(a) despite optimal LDL-C control.

Safety profiles in early trials have been generally favorable, with most adverse events limited to injection-site reactions. However, long-term safety and tolerability remain to be fully established. The central unanswered question is whether large reductions in Lp(a) will translate into meaningful reductions in cardiovascular events. While genetic and epidemiological data strongly support causality, definitive evidence requires outcome trials.

If these therapies demonstrate clinical benefit, they may redefine cardiovascular prevention by introducing Lp(a) as a modifiable and treatable risk factor. This would represent a shift comparable to the introduction of statins for LDL cholesterol.

9. Clinical Challenges and Unanswered Questions

Despite strong biological plausibility and impressive reductions in Lp(a) with novel therapies, several key clinical questions remain unresolved. These uncertainties currently limit the integration of Lp(a)-targeted treatment into routine practice.

The most important issue is whether lowering Lp(a) will lead to a reduction in cardiovascular events. While Mendelian randomization studies support a causal relationship, interventional outcome data are still lacking. Ongoing trials, such as those evaluating pelacarsen, are expected to provide definitive evidence on whether Lp(a) reduction translates into clinical benefit [20].

Another challenge is defining the threshold for treatment. Although levels above 50 mg/dL (or approximately 125 nmol/L) are generally considered elevated, it remains unclear at what level intervention becomes clinically justified. The relationship between Lp(a) and risk appears continuous, which complicates the establishment of strict cut-off values for therapy initiation. Patient selection is also an open question. Not all individuals with elevated Lp(a) have the same absolute risk. The greatest benefit from targeted therapies is likely to occur in patients with established cardiovascular disease or those with multiple risk factors. Identifying these high-risk subgroups is essential for efficient and cost-effective use of emerging treatments. The interaction between Lp(a) and other lipid fractions adds further complexity. It is not yet fully understood how aggressive LDL-C lowering modifies Lp(a)-related risk. Some data suggest that even with optimal LDL-C control, elevated Lp(a) remains clinically relevant, but the magnitude of residual risk varies across patient populations [18]. Cost and accessibility represent additional barriers. RNA-based therapies are expected to be expensive, which raises questions about their implementation in large populations. Health systems will need to determine whether targeted Lp(a) reduction provides sufficient benefit to justify widespread use.

Long-term safety is another consideration. Although early-phase trials show favorable safety profiles, the effects of prolonged and profound Lp(a) suppression are not fully known. Given the physiological role of Lp(a) is not completely understood, long-term data will be critical.

There are also practical challenges related to measurement. Variability between assays and differences in reporting units can complicate interpretation and clinical decision-making. Standardization of Lp(a) measurement remains an important unmet need.

Finally, integration into clinical guidelines will depend on the results of outcome trials. At present, Lp(a) is considered a risk enhancer rather than a primary treatment target. A shift toward targeted therapy will require strong evidence demonstrating not only biomarker reduction but also meaningful improvements in patient outcomes.

In summary, Lp(a)-targeted therapy is a promising but still evolving field. The transition from mechanistic insight to clinical application depends on resolving these key uncertainties.

10. Conclusion

Lipoprotein(a) has moved from a neglected lipid parameter to a clinically relevant and potentially modifiable cardiovascular risk factor. Strong epidemiological and genetic evidence supports its causal role in atherosclerotic cardiovascular disease and calcific aortic valve stenosis.

Current clinical practice is limited by the absence of therapies that specifically and effectively reduce Lp(a). Conventional lipid-lowering treatments do not address this pathway, leaving a component of residual cardiovascular risk untreated. As a result, management has focused on aggressive control of modifiable risk factors, particularly LDL cholesterol.

The development of targeted therapies based on antisense oligonucleotides and small interfering RNA represents a major advance. These agents achieve substantial reductions in Lp(a) levels, far beyond what has been possible with existing treatments. This has shifted the clinical perspective from risk identification to potential intervention.

The key issue is whether Lp(a) reduction will translate into improved clinical outcomes. Ongoing large-scale trials are expected to determine whether targeting Lp(a) reduces cardiovascular events and modifies disease progression, including aortic valve calcification.

If these trials confirm clinical benefit, Lp(a) will become a therapeutic target alongside LDL cholesterol. This would introduce a new dimension in cardiovascular prevention, particularly for patients with persistent risk despite optimal standard therapy.

At present, Lp(a) should be recognized as an important risk enhancer that refines cardiovascular risk assessment and supports more intensive preventive strategies. The coming years will determine whether it becomes a central target in routine clinical practice.

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