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LIPOPROTEIN(A) AS AN INDEPENDENT CARDIOVASCULAR RISK FACTOR: CURRENT EVIDENCE AND THERAPEUTIC PERSPECTIVES – A NARRATIVE REVIEW

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ABSTRACT

Cardiovascular diseases remain a major global public health challenge despite substantial advances in diagnosis and treatment. The occurrence of cardiovascular events in patients with well-controlled traditional risk factors highlights the need to identify additional determinants of risk. Lipoprotein(a) [Lp(a)] is a distinct lipoprotein fraction whose plasma concentration is largely genetically determined and remains relatively stable throughout life. An increasing body of evidence indicates that Lp(a) is an independent risk factor for coronary artery disease, ischemic stroke, and calcific aortic valve stenosis, owing to its atherogenic, proinflammatory, and prothrombotic properties. Lp(a) measurement is gaining importance in cardiovascular risk assessment; however, its use in routine clinical practice remains limited. Management of patients with elevated Lp(a) concentrations currently relies primarily on intensive control of other cardiovascular risk factors, particularly low-density lipoprotein (LDL) cholesterol. The development of RNA-based therapies offers the prospect of targeted Lp(a) lowering. This review provides a comprehensive overview of current knowledge on the biology, clinical significance, diagnosis, and therapeutic options related to lipoprotein(a) and discusses its emerging role in cardiovascular risk stratification and precision medicine.

KEYWORDS

Lipoprotein(A), Cardiovascular Risk, Atherosclerosis, Aortic Valve Stenosis, Coronary Artery Disease, RNA-Based Therapies

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1. Introduction

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide despite significant advances in their diagnosis and treatment. Risk assessment is primarily based on traditional risk factors such as low-density lipoprotein (LDL) cholesterol levels, arterial hypertension, and smoking. Nevertheless, the occurrence of cardiovascular events despite adequate control of these factors suggests that additional determinants of risk exist (Yun et al., 2026; Tsimikas, 2024).

Lipoprotein(a) is a distinct lipoprotein particle composed of an LDL-like particle bound to apolipoprotein(a) and exhibiting structural similarity to plasminogen. Plasma Lp(a) concentration is largely genetically determined and shows little variation throughout life, distinguishing it from other lipid parameters (Boffa & Koschinsky, 2024; Schmidt et al., 2016; Saeed et al., 2021).

Current evidence identifies lipoprotein(a) as an independent risk factor for cardiovascular diseases, including coronary artery disease, ischemic stroke, and calcific aortic valve stenosis. Epidemiological studies and genetic analyses confirm its causal involvement in the pathogenesis of these conditions, highlighting the growing importance of this lipoprotein in clinical practice (Verbeek et al., 2018; Volgman et al., 2024; Wambua et al., 2025).

Although the number of studies supporting the clinical significance of lipoprotein(a) continues to increase, this marker is still not fully incorporated into routine cardiovascular risk assessment. A significant challenge also remains the limited availability of therapies directly targeting its reduction. At the same time, the development of new approaches, including RNA-based therapies, offers promising perspectives (Tsimikas, 2024; Alhomoud et al., 2025; Formisano et al., 2025).

The aim of this review is to summarize current knowledge on lipoprotein(a) as an independent cardiovascular risk factor, with particular emphasis on its biology, clinical significance, diagnosis, and therapeutic options.

2. Methodology of The Literature Review

This article is a narrative review. The aim was to collect, systematize, and summarize current knowledge regarding lipoprotein(a) as an independent cardiovascular risk factor. The analysis included epidemiology and genetic determinants, pathophysiology, clinical significance, diagnosis, therapeutic options, and public health implications.

The literature review was conducted using the PubMed (MEDLINE) database, covering the years 2016–2026. Articles available in full text via PubMed Central and other open-access sources were included in the analysis. The search strategy was based on various combinations of keywords using Boolean operators (AND, OR): lipoprotein(a), Lp(a), cardiovascular risk, cardiovascular disease, coronary artery disease, atherosclerosis, aortic valve stenosis, myocardial infarction, ischemic stroke, diagnosis and treatment.

At the initial stage, approximately 100 publications were identified, and studies not available in full text or lacking detailed clinical data were excluded. The next stage involved selecting the most recent and most frequently cited sources to ensure the timeliness and reliability of the presented information. Review articles, clinical studies, meta-analyses, and expert statements were included. Key inclusion criteria were full-text availability and publication in English. The review also incorporates a public health perspective, emphasizing the importance of lipoprotein(a) as a risk factor for cardiovascular diseases.

Following the analysis of available titles, abstracts, and full-text articles, a total of 31 publications consistent with the objectives of this review were ultimately included.

3. Structure and Biological Properties of Lipoprotein(A)

3.1. Structure of Lipoprotein(A)

Lipoprotein(a) is a particle structurally similar to low-density lipoprotein (LDL). It consists of one LDL particle containing apolipoprotein B-100 and one molecule of apolipoprotein(a), a highly polymorphic glycoprotein. Apo(a) is covalently linked to apoB-100 by a single disulfide bond (Schmidt et al., 2016; Jawi et al., 2020; Yun et al., 2026).

Apo(a) contains characteristic kringle domains, which exhibit a high degree of structural similarity to plasminogen (PLG) (Schmidt et al., 2016). This feature implies that lipoprotein(a) may influence processes of coagulation and fibrinolysis. The structure of plasminogen includes five kringle domains (KI–KV) and a serine protease domain, whereas apolipoprotein(a) contains 10 subtypes of KIV (KIV1–KIV10), a KV domain, and an inactive domain exhibiting similarity to a serine protease (Sosnowska et al., 2025).

A distinctive feature of apo(a) is the variable number of kringle IV type 2 (KIV-2) repeats. The number of KIV-2 copies in the LPA gene determines substantial heterogeneity in the size of apo(a) isoforms. Importantly, plasma Lp(a) concentration is inversely correlated with the number of these repeats (Sosnowska et al., 2025; Saeed et al., 2021).

Lp(a) concentration remains relatively stable throughout life, as it is more than 90% genetically determined, while diet and lifestyle have only a minimal influence on its levels (Tsimikas, 2017). This characteristic distinguishes lipoprotein(a) from other lipid fractions.

3.2. Role of Lipoprotein(A)

Although effective and specific methods for lowering lipoprotein(a) levels are currently being developed, its physiological function is still not fully understood. Due to its unique structure, Lp(a) may participate in various biological processes that, depending on the metabolic context, may have both physiological and pathological significance. It has been suggested that Lp(a) may be involved in the regulation of inflammatory processes, immune response, and the transport of oxidized phospholipids (Boffa & Koschinsky, 2024; Saeed et al., 2021; Ghose et al., 2024).

Importantly, lipoprotein(a) is the main carrier of oxidized phospholipids (OxPL) in human plasma. These phospholipids exhibit strong proinflammatory properties and may play a significant role in the development of atherosclerotic lesions (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Yun et al., 2026). It has been demonstrated that the majority of oxidized phospholipids are transported by Lp(a), suggesting its potential role in initiating and promoting inflammatory processes within the vascular wall (Boffa & Koschinsky, 2024).

The structural similarity of apolipoprotein(a) to plasminogen suggests a possible involvement of Lp(a) in the regulation of coagulation and fibrinolysis, tissue repair processes, and the response to vascular injury (Saeed et al., 2021; Boffa & Koschinsky, 2024; Schmidt et al., 2016). However, in the case of elevated Lp(a) levels, these mechanisms may contribute to the development of inflammatory processes and the progression of atherosclerotic changes within the vascular wall (Boffa & Koschinsky, 2024; Lampsas et al., 2023).

3.3. Metabolism of Lipoprotein(A)

Apolipoprotein(a), produced in hepatocytes, is secreted into the extracellular space, where it binds to an LDL particle via a disulfide bond. This mechanism leads to the formation of lipoprotein(a), which subsequently circulates in plasma (Boffa & Koschinsky, 2024; Jawi et al., 2020; Schmidt et al., 2016). Plasma Lp(a) concentration appears to depend largely on the rate of apo(a) synthesis (Boffa & Koschinsky, 2024).

The mechanisms responsible for the catabolism of lipoprotein(a) have not yet been fully elucidated. The processes involved in its clearance from the circulation are also still under investigation (Boffa & Koschinsky, 2024; Jawi et al., 2020; Saeed et al., 2021). However, the liver is often indicated as the primary site of Lp(a) catabolism. Other organs, particularly the kidneys, may also be involved in Lp(a) catabolism (Boffa & Koschinsky, 2024; Kaur et al., 2024; Saeed et al., 2021). It is likely that various lipoprotein receptors are involved in this process, for example, the low-density lipoprotein receptor (LDLR). However, its role in Lp(a) clearance appears to be significantly limited compared to other lipoproteins (Schmidt et al., 2016; Boffa & Koschinsky, 2024).

Despite numerous studies, the mechanisms underlying Lp(a) metabolism, including its synthesis, secretion, and clearance, remain incompletely understood (Boffa & Koschinsky, 2024; Jawi et al., 2020; Saeed et al., 2021). This issue is the subject of ongoing research.

4. Epidemiology and Genetic Determinants of Lipoprotein(A)

4.1. Prevalence of Elevated Lp(a) Levels in The Population

Epidemiological data indicate that elevated lipoprotein(a) levels occur in a significant proportion of the general population. It is estimated that approximately 20–25% of individuals worldwide have Lp(a) concentrations associated with increased cardiovascular risk. In the literature, the most commonly accepted threshold for increased cardiovascular risk is an Lp(a) level above 50 mg/dL (≈125 nmol/L) (Tsimikas, 2017; Verbeek et al., 2018; Yun et al., 2026). The distribution of Lp(a) levels in the general population is wide and shows considerable interindividual variability (Tsimikas, 2017; Yun et al., 2026).

It has been demonstrated that lipoprotein(a) levels differ significantly between populations. The highest Lp(a) concentrations are observed in individuals of African descent, whereas in European and Asian populations these values are generally lower (Verbeek et al., 2018; Kaur et al., 2024; Yun et al., 2026).

Given the high prevalence of elevated lipoprotein(a) levels and their significant association with cardiovascular disease risk, the importance of measuring Lp(a) in the general population is increasingly emphasized (Clair et al., 2025; Fan et al., 2025; Sosnowska et al., 2025).

4.2. Genetic Determinants of Lp(a) Concentration

Studies indicate that lipoprotein(a) concentration is largely genetically determined, while the contribution of environmental factors to its regulation is minimal. It is estimated that genetic factors account for more than 90% of the variability in Lp(a) levels in the population (Schmidt et al., 2016; Saeed et al., 2021). The main gene responsible for regulating Lp(a) concentration is the LPA gene, which encodes apolipoprotein(a) (Schmidt et al., 2016; Saeed et al., 2021; Volgman et al., 2024).

Polymorphism of the LPA gene leads to the formation of multiple variants of apolipoprotein(a). The variability in apo(a) structure primarily results from differences in the number of kringle IV type 2 repeats (Schmidt et al., 2016; Saeed et al., 2021; Volgman et al., 2024; Yun et al., 2026). It has been shown that the variable number of these repeats influences both the size of apo(a) isoforms and plasma Lp(a) concentration. An inverse relationship between the number of KIV-2 repeats and plasma Lp(a) levels has been demonstrated (Schmidt et al., 2016; Saeed et al., 2021). These traits are inherited in an autosomal manner and may therefore determine individual Lp(a) levels in the general population (Schmidt et al., 2016; Saeed et al., 2021; Yun et al., 2026).

Due to the predominant influence of genetic factors, Lp(a) concentration remains relatively stable throughout life (Schmidt et al., 2016; Saeed et al., 2021).

4.3. Factors Influencing Lp(a) Levels

Lipoprotein(a) concentration is primarily genetically determined; however, certain environmental factors may slightly modify its levels. Unlike other lipid fractions, such as LDL or triglycerides, the influence of diet and lifestyle on Lp(a) concentration is limited (Saeed et al., 2021; Kaur et al., 2024).

Studies demonstrate that certain diseases may affect plasma Lp(a) levels. Kidney diseases, particularly chronic kidney disease and nephrotic syndrome, are especially relevant in this context (Saeed et al., 2021; Kaur et al., 2024; Yun et al., 2026).

Lp(a) levels may also be influenced by hormonal factors. Estrogens are associated with a reduction in Lp(a) levels, whereas an increase is often observed during menopause (Saeed et al., 2021; Kaur et al., 2024; Yun et al., 2026). Some studies have also reported an increase in Lp(a) levels during pregnancy (Saeed et al., 2021).

Due to the limited ability to modify Lp(a) levels through environmental factors, increasing attention is being paid to therapies aimed at directly lowering its concentration. This remains a major limitation in cardiovascular prevention (Alhomoud et al., 2025; Hamasaki et al., 2025; Formisano et al., 2025; Tsimikas, 2024).

5. Pathophysiological Mechanisms

5.1. Atherogenic Effects

Lipoprotein(a) plays a significant role in the process of atherogenesis. The atherogenic properties of this lipoprotein result primarily from its structural similarity to low-density lipoprotein (LDL). Lp(a) can penetrate the vascular wall and accumulate in the subendothelial space, initiating the development of atherosclerotic lesions (Lampsas et al., 2023; Boffa & Koschinsky, 2024; Saeed et al., 2021). Moreover, lipoprotein(a) exhibits the ability to bind components of the extracellular matrix, thereby promoting its retention within the vascular wall and further progression of atherosclerotic changes (Boffa & Koschinsky, 2024).

One of the key atherogenic mechanisms of Lp(a) is the transport of oxidized phospholipids (OxPL), which exhibit proinflammatory properties. The presence of these compounds may lead to activation of endothelial cells and amplification of the inflammatory response within the vascular wall (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Yun et al., 2026).

Lipoprotein(a) may also promote the formation of foam cells as a result of increased lipid uptake by macrophages. This process leads to further lipid accumulation within the vascular wall and progression of atherosclerotic lesions (Saeed et al., 2021; Lampsas et al., 2023; Volgman et al., 2024).

Consequently, Lp(a) is involved in both the initiation and progression of atherosclerotic lesions, exhibiting both atherogenic and proinflammatory effects (Boffa & Koschinsky, 2024; Yun et al., 2026).

5.2. Proinflammatory Effects

In addition to its atherogenic properties, lipoprotein(a) also exhibits significant proinflammatory effects. This phenomenon is largely associated with the presence of oxidized phospholipids (OxPL), which may initiate inflammatory processes within the vascular wall (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Yun et al., 2026).

Lp(a) and the oxidized phospholipids (OxPL) it carries may lead to activation of endothelial cells and increased expression of adhesion molecules. This process promotes the recruitment of monocytes into the vascular wall and enhances the inflammatory response (Saeed et al., 2021; Lampsas et al., 2023; Boffa & Koschinsky, 2024). It has also been shown that lipoprotein(a) may induce the production of proinflammatory cytokines, such as IL-6 (interleukin-6) and TNF-α (tumor necrosis factor alpha), further amplifying the inflammatory process within the vascular wall (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Yun et al., 2026).

The presence of lipoprotein(a) also promotes activation of immune system cells, including macrophages. This leads to the persistence of chronic inflammation within the vascular wall and accelerates the development of atherosclerotic lesions (Saeed et al., 2021; Yun et al., 2026; Volgman et al., 2024).

5.3. Prothrombotic Properties

Lipoprotein(a) also exhibits prothrombotic effects. This is primarily due to the structural similarity of apolipoprotein(a) to plasminogen – a key protein involved in the process of fibrinolysis (Schmidt et al., 2016; Saeed et al., 2021; Boffa & Koschinsky, 2024).

Because of its structural similarity to plasminogen, Lp(a) may compete with it for binding sites on cell surfaces and within fibrin. This phenomenon limits plasminogen activation and leads to impairment of fibrinolytic processes (Schmidt et al., 2016; Saeed et al., 2021; Lampsas et al., 2023). Additionally, it has been

shown that Lp(a) may also interact with fibrin molecules, promoting clot stabilization and hindering its dissolution (Schmidt et al., 2016; Boffa & Koschinsky, 2024; Saeed et al., 2021).

Consequently, the prothrombotic properties of lipoprotein(a) may contribute to the persistence of thrombi and thereby increase the risk of thrombosis. The combination of atherogenic, proinflammatory, and prothrombotic properties makes Lp(a) an important factor in the pathogenesis of cardiovascular diseases, such as coronary artery disease and ischemic stroke (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Yun et al., 2026).

5.4. Role in Aortic Valve Stenosis

In recent years, increasing attention has been paid to the role of lipoprotein(a) in valvular disease pathogenesis, including aortic valve stenosis. Numerous studies indicate that Lp(a) may play a significant role in calcific aortic valve disease (CAVD) (Wambua et al., 2025; Maloberti et al., 2022; Boffa & Koschinsky, 2024).

This mechanism is largely associated with the accumulation of Lp(a) within the aortic valve and the presence of oxidized phospholipids (OxPL), which exhibit strong proinflammatory effects. These compounds may stimulate the differentiation of valvular interstitial cells toward an osteoblast-like phenotype, leading to calcium deposition and progressive valve calcification (Wambua et al., 2025; Boffa & Koschinsky, 2024; Yun et al., 2026).

As a result, elevated Lp(a) levels may contribute to faster progression of aortic valve stenosis and increase the risk of developing advanced disease requiring interventional treatment (Maloberti et al., 2022; Wambua et al., 2025; Saeed et al., 2021).

The association of Lp(a) with both atherosclerotic processes and calcific aortic valve disease highlights its importance as a significant risk factor for cardiovascular diseases.

6. Lipoprotein(A) as an Independent Risk Factor for Cardiovascular Diseases

6.1. Coronary Artery Disease and Myocardial Infarction

Lipoprotein(a) is currently recognized as an important, independent risk factor for cardiovascular diseases, particularly coronary artery disease and myocardial infarction. Numerous epidemiological studies have demonstrated a strong association between elevated Lp(a) levels and an increased risk of atherosclerotic cardiovascular disease (ASCVD) events. Importantly, this relationship remains evident even after adjustment for traditional risk factors such as LDL cholesterol levels, arterial hypertension, and smoking. Furthermore, genetic studies, including Mendelian randomization analyses, provide evidence of a causal relationship between elevated Lp(a) levels and the development of atherosclerosis and its complications (Doherty et al., 2025; Verbeek et al., 2018; Yun et al., 2026).

Data from numerous meta-analyses and population-based studies indicate that the risk of coronary artery disease increases with rising Lp(a) levels. This risk is particularly high in individuals with lipoprotein(a) concentrations exceeding 50 mg/dL (≈125 nmol/L). As Lp(a) levels increase, a gradual rise in the risk of myocardial infarction and other cardiovascular events is also observed (Verbeek et al., 2018; Fan et al., 2025; Parcha et al., 2025).

The increased risk appears to result from several mechanisms. Lp(a) transports oxidized phospholipids, which enhance inflammatory responses within the vascular wall and contribute to endothelial dysfunction, thereby accelerating the development of atherosclerotic plaques. In addition, due to its structural similarity to plasminogen, apolipoprotein(a) may impair fibrinolysis, promoting thrombus formation and increasing the risk of acute coronary syndromes (Boffa & Koschinsky, 2024; Volgman et al., 2024; Lampsas et al., 2023).

Strong evidence supports the causal role of lipoprotein(a) in the development of coronary artery disease. Genetic studies demonstrate that variants of the LPA gene associated with elevated Lp(a) levels are linked to an increased risk of myocardial infarction. Results from Mendelian randomization analyses further support the hypothesis that lipoprotein(a) is not merely a biomarker but also directly contributes to the pathogenesis of atherosclerosis (Doherty et al., 2025; Volgman et al., 2024; Yun et al., 2026).

Elevated Lp(a) levels are of particular clinical importance both in patients with premature coronary artery disease and in individuals who experience cardiovascular events despite well-controlled LDL cholesterol levels. Lipoprotein(a) may therefore represent an important component of residual cardiovascular risk. For this reason, increasing emphasis is placed on measuring Lp(a) to enable more precise risk stratification and identification of patients who may benefit from more intensive preventive strategies (Clair et al., 2025; Razavi et al., 2025; Parcha et al., 2025).

6.2. Ischemic Stroke

Accumulating evidence suggests that elevated lipoprotein(a) levels may play a significant role in the pathogenesis of ischemic stroke. It has been shown that individuals with high Lp(a) levels are more likely to experience cerebrovascular events, particularly those of atherosclerotic origin (Verbeek et al., 2018; Yun et al., 2026; Saeed et al., 2021). This association appears to be particularly pronounced in strokes related to large artery disease (Verbeek et al., 2018; Yun et al., 2026).

Population-based studies indicate that elevated Lp(a) levels are associated with an increased risk of ischemic stroke. This risk is particularly high in individuals with very high concentrations of this lipoprotein. These observations suggest the presence of a dose–response relationship between lipoprotein(a) levels and the incidence of cerebrovascular events (Verbeek et al., 2018; Fan et al., 2025; Yun et al., 2026).

This increased stroke risk is likely mediated by pathophysiological mechanisms similar to those observed in coronary artery disease. Lp(a) may promote the development of atherosclerotic changes in the carotid and intracranial arteries, as well as enhance inflammation and increase the propensity for thrombus formation (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Volgman et al., 2024).

Elevated lipoprotein(a) levels are of particular clinical importance in patients with ischemic stroke of undetermined etiology and in individuals who have experienced premature cerebrovascular events. Measurement of Lp(a) in such cases may represent an important component of an extended cardiovascular risk assessment (Clair et al., 2025; Razavi et al., 2025; Yun et al., 2026).

6.3. Aortic Valve Stenosis

Accumulated scientific evidence suggests that elevated lipoprotein(a) levels may also play a significant role in the pathogenesis of calcific aortic valve disease (CAVD). Data suggest that Lp(a) levels are associated with an increased risk of developing this condition as well as with its more rapid progression (Wambua et al., 2025; Maloberti et al., 2022; Boffa & Koschinsky, 2024).

The mechanisms underlying the association between lipoprotein(a) and aortic valve stenosis primarily involve the accumulation of this lipoprotein within the valve and the transport of oxidized phospholipids. These compounds enhance inflammatory processes and promote the differentiation of valvular interstitial cells into osteoblast-like cells, leading to calcium deposition and progressive valve calcification (Boffa & Koschinsky, 2024; Yun et al., 2026; Wambua et al., 2025).

Numerous population-based studies have demonstrated that individuals with elevated Lp(a) levels have a higher risk of developing aortic valve stenosis. Moreover, clinical observations suggest that high levels of this lipoprotein may contribute to faster disease progression and a greater need for interventional treatment (Maloberti et al., 2022; Wambua et al., 2025; Yun et al., 2026).

An increasing body of evidence indicates that lipoprotein(a) may serve as an important biomarker associated with both the risk of development and progression of aortic valve stenosis. Consequently, growing attention is being directed toward therapies aimed at lowering Lp(a) levels, which may play a significant role in slowing disease progression (Yun et al., 2026; Maloberti et al., 2022; Alhomoud et al., 2025). Together, these findings support the view that Lp(a) may become a novel therapeutic target in the management of valvular diseases.

6.4. Premature Atherosclerosis

Available epidemiological data indicate that elevated lipoprotein(a) levels constitute a significant risk factor for the premature development of atherosclerosis. High Lp(a) levels are observed in patients who develop cardiovascular diseases at a younger age. This finding suggests that this lipoprotein plays an important role in accelerating the atherosclerotic process (Tsimikas, 2017; Verbeek et al., 2018; Yun et al., 2026).

Study results highlight the association between high Lp(a) levels and an increased risk of cardiovascular diseases at a younger age. This relationship is particularly evident in patients with premature coronary artery disease and in individuals with a family history of cardiovascular diseases (Verbeek et al., 2018; Parcha et al., 2025; Tsimikas, 2017).

The pathophysiological mechanisms linking Lp(a) with premature atherosclerosis include its atherogenic, proinflammatory, and prothrombotic properties. In addition, the transport of oxidized phospholipids by Lp(a) particles may enhance inflammatory responses within the vascular wall, thereby promoting the development of atherosclerotic lesions (Boffa & Koschinsky, 2024; Lampsas et al., 2023; Saeed et al., 2021).

Measurement of lipoprotein(a) levels is of particular clinical importance both in young patients with cardiovascular diseases and in individuals who experience cardiovascular events despite normal LDL cholesterol levels. In such cases, Lp(a) testing may help identify patients at increased cardiovascular risk and enable earlier implementation of preventive measures (Clair et al., 2025; Razavi et al., 2025; Parcha et al., 2025).

The accumulated evidence confirms the significant role of lipoprotein(a) as an independent risk factor for cardiovascular diseases, highlighting the need for its measurement to allow more precise cardiovascular risk stratification.

7. Diagnostics of Lipoprotein(A)

7.1. Laboratory Methods for Measuring Lp(a)

Due to the growing clinical importance of lipoprotein(a), both its accurate measurement and proper interpretation of laboratory results are essential. In recent years, measurement of Lp(a) has been increasingly incorporated into cardiovascular risk assessment. The level of this lipoprotein is largely genetically determined and remains relatively stable throughout life. Therefore, a single measurement of Lp(a) may provide important information regarding individual cardiovascular risk (Cegla et al., 2021; Razavi et al., 2025; Tsimikas, 2017).

Immunochemical methods are most commonly used to measure lipoprotein(a) levels, including immunoturbidimetry, immunonephelometry, and enzyme-linked immunoassays. These methods use specific antibodies to detect apolipoprotein(a). However, a major challenge in Lp(a) diagnostics remains the high structural variability of apolipoprotein(a), associated with the variable number of kringle IV type 2 repeats. This may affect the reliability of the obtained results (Velilla et al., 2025; Cegla et al., 2021; Razavi et al., 2025).

An important aspect of lipoprotein(a) diagnostics is the way laboratory results are reported. The concentration of this lipoprotein may be expressed in two units – mg/dL or nmol/L. However, due to the significant variability in the size of Lp(a) particles, conversion between these units is unreliable. Therefore, reporting results in nmol/L is recommended, as it better reflects the number of lipoprotein particles in plasma (Velilla et al., 2025; Razavi et al., 2025; Cegla et al., 2021).

The considerable structural variability of apolipoprotein(a), as well as differences between laboratory methods, make the standardization of Lp(a) measurements essential. The use of standardized measurement methods is necessary for proper interpretation of results and facilitates comparison of data across different clinical studies (Velilla et al., 2025; Cegla et al., 2021; Razavi et al., 2025).

7.2. Interpretation of Test Results

Proper interpretation of lipoprotein(a) concentration is an important component of cardiovascular risk assessment. Lp(a) levels, in contrast to many other lipid parameters, are largely genetically determined and show minimal variation throughout life (Cegla et al., 2021; Razavi et al., 2025; Tsimikas, 2017).

Results from numerous studies indicate that an increased risk of cardiovascular events is observed in individuals with lipoprotein(a) levels exceeding approximately 50 mg/dL (≈125 nmol/L) (Tsimikas, 2017; Verbeek et al., 2018; Yun et al., 2026).

Elevated Lp(a) levels are of particular clinical importance in patients who experience cardiovascular events despite adequate control of LDL cholesterol levels (Parcha et al., 2025; Clair et al., 2025; Razavi et al., 2025).

7.3. The Role of Lp(a) Measurement in Cardiovascular Risk Assessment

Measurement of lipoprotein(a) concentration may represent a valuable addition to traditional cardiovascular risk assessment. Incorporating Lp(a) levels into clinical evaluation enables more precise risk stratification, particularly in patients with intermediate cardiovascular risk (Clair et al., 2025; Razavi et al., 2025; Parcha et al., 2025).

Measurement of Lp(a) levels may be of particular clinical value in patients with premature cardiovascular events and in individuals with a family history of cardiovascular diseases (Cegla et al., 2021; Yun et al., 2026; Clair et al., 2025).

Information on elevated lipoprotein(a) levels may have a significant impact on therapeutic management strategies, including intensification of lipid-lowering therapy and more stringent control of other cardiovascular risk factors (Parcha et al., 2025; Razavi et al., 2025).

In clinical practice, a single measurement of Lp(a) concentration is usually sufficient for assessing individual cardiovascular risk, as the level of this lipoprotein remains relatively stable throughout life (Cegla et al., 2021; Saeed et al., 2021). In light of the growing body of scientific evidence, Lp(a) measurement is increasingly being incorporated into the recommendations of scientific societies regarding cardiovascular risk assessment (Yun et al., 2026; Doherty et al., 2025).

8. Current Guidelines and Clinical Recommendations

Accumulated scientific evidence in recent years indicates a significant role of lipoprotein(a) in the development of cardiovascular diseases. Consequently, Lp(a) has been incorporated into the recommendations of numerous scientific societies, which emphasize its importance as an independent cardiovascular risk factor and highlight the rationale for measuring this lipoprotein in specific patient groups (Yun et al., 2026; Doherty et al., 2025; Jang et al., 2026).

According to current recommendations from major scientific societies, Lp(a) should be measured at least once during adulthood. This aims to identify individuals with genetically determined elevated levels of this lipoprotein (Cegla et al., 2021; Yun et al., 2026; Jang et al., 2026).

Current guidelines also highlight the particular importance of Lp(a) measurement in patients with premature cardiovascular disease, a family history of cardiovascular diseases, and in individuals with suspected familial hypercholesterolemia (Cegla et al., 2021; Yun et al., 2026; Clair et al., 2025).

In cases of elevated lipoprotein(a) levels, current recommendations of scientific societies emphasize the importance of strict control of other modifiable cardiovascular risk factors, particularly the reduction of LDL cholesterol levels (Parcha et al., 2025; Yun et al., 2026; Doherty et al., 2025).

These findings highlight the growing role of lipoprotein(a) in cardiovascular disease prevention strategies and support the rationale for its measurement in routine clinical practice.

9. Therapeutic Strategies

9.1. Lifestyle Modification

Lipoprotein(a) concentration is largely genetically determined; therefore, its modification through conventional non-pharmacological approaches remains limited. Unlike other lipid parameters, such as LDL cholesterol or triglycerides, Lp(a) levels are relatively stable throughout life. However, this does not diminish the importance of lifestyle modification, which remains a key component of management due to its beneficial impact on reducing overall cardiovascular risk (Irvine et al., 2026; Sosnowska et al., 2025; Tsimikas, 2024).

Existing studies on the impact of diet on lipoprotein(a) levels provide limited and often inconsistent results. In contrast to other lipid fractions, dietary changes generally do not result in a significant reduction in Lp(a) levels. Some studies suggest a possible association between specific dietary patterns and Lp(a) concentration; however, these findings are insufficient to establish dietary recommendations, and current guidance for patients with elevated lipoprotein(a) levels is primarily based on general principles of a cardioprotective diet (Saeed et al., 2021; Kaur et al., 2024; Manzato et al., 2024).

Similarly, regular physical activity does not have a significant impact on Lp(a) levels. Nevertheless, it has been shown to exert beneficial effects on other cardiovascular risk factors, such as lipid profile, blood pressure, body weight, insulin sensitivity, and other metabolic parameters. For this reason, increasing physical activity, maintaining a healthy body weight, and smoking cessation are important components of comprehensive cardiovascular prevention in individuals with elevated levels of this lipoprotein (Manzato et al., 2024; Schuth et al., 2024; Saeed et al., 2021).

Although lifestyle modification does not usually lead to a significant reduction in lipoprotein(a) levels, it remains an important component of management in patients with elevated Lp(a). In clinical practice, particular emphasis is placed on effective control of other modifiable cardiovascular risk factors, including elevated LDL cholesterol, arterial hypertension, and diabetes. This is of particular importance given the limited ability to directly lower Lp(a) levels using conventional therapeutic approaches (Parcha et al., 2025; Irvine et al., 2026; Formisano et al., 2025).

9.2. Pharmacological Treatment

Despite advances in the treatment of lipid disorders, the possibilities for direct pharmacological reduction of lipoprotein(a) levels remain limited. Most commonly used lipid-lowering drugs have minimal or no effect on Lp(a) levels. Therefore, the management of patients with elevated lipoprotein(a) concentrations is primarily focused on strict control of other cardiovascular risk factors, particularly effective reduction of LDL cholesterol levels (Tsimikas, 2024; Kaur et al., 2024; Formisano et al., 2025; Yun et al., 2026).

For many years, statins have been the cornerstone of lipid-lowering therapy and one of the most important components of cardiovascular disease prevention. However, their effect on Lp(a) levels is limited. Data from clinical studies indicate that statin therapy usually does not lead to a reduction in lipoprotein(a) levels and, in some cases, may even result in a slight increase. Nevertheless, statins remain an important

component of therapy in patients with elevated Lp(a), as they effectively reduce LDL cholesterol levels and decrease the risk of cardiovascular events (Tsimikas, 2024; Schuth et al., 2024; Manzato et al., 2024).

In recent years, increasing attention has been paid to PCSK9 inhibitors. In addition to their potent LDL cholesterol-lowering effects, they also demonstrate the ability to moderately reduce lipoprotein(a) levels. Clinical studies indicate that treatment with these agents can reduce Lp(a) levels by approximately 20–30% on average. The exact mechanism of this effect has not yet been fully elucidated; however, it is thought to be related to increased uptake of lipoprotein(a) particles via LDL receptors. The most widely used PCSK9 inhibitors include the monoclonal antibodies alirocumab and evolocumab (Schuth et al., 2024; Saeed et al., 2021; Tsimikas, 2024).

Effective reduction of lipoprotein(a) levels remains one of the greatest challenges in modern pharmacotherapy of lipid disorders. Currently, there are no widely available pharmacological therapies that enable direct and selective reduction of Lp(a) levels. Consequently, current therapeutic strategies focus primarily on more intensive lowering of LDL cholesterol and optimal control of other modifiable cardiovascular risk factors. At the same time, the development of new therapies targeting lipoprotein(a) remains one of the most promising and rapidly evolving areas of research in cardiology (Tsimikas, 2024; Yun et al., 2026; Alhomoud et al., 2025; Hamasaki et al., 2025).

9.3. Lipoprotein Apheresis

Lipoprotein apheresis is an extracorporeal blood purification method that involves the selective removal of atherogenic lipoproteins from a patient's blood. This procedure enables a significant reduction in both LDL cholesterol and lipoprotein(a) levels. In clinical practice, apheresis is primarily used in patients at very high cardiovascular risk, particularly in cases of inadequate response to pharmacological treatment or persistently elevated Lp(a) levels despite intensive lipid-lowering therapy (Greco et al., 2020; Schuth et al., 2024; Maloberti et al., 2022; Tsimikas, 2017).

Available studies indicate that lipoprotein apheresis allows for a substantial reduction in lipoprotein(a) levels, which may reach approximately 60–70% immediately after the procedure. A similar effect is observed for LDL cholesterol. Importantly, the procedures must be performed regularly, usually every 1–2 weeks, as the achieved reduction is short-lived. Despite these limitations, apheresis remains an effective treatment option in patients with very high cardiovascular risk (Greco et al., 2020; Schuth et al., 2024; Maloberti et al., 2022; Tsimikas, 2017).

However, it should be emphasized that lipoprotein apheresis is associated with additional limitations. The procedure is costly and time-consuming, and its performance requires specialized medical infrastructure. This limits its widespread use in clinical practice. Consequently, this method is usually reserved for selected patients at very high cardiovascular risk, particularly when other forms of treatment do not achieve the desired effects (Greco et al., 2020; Schuth et al., 2024; Maloberti et al., 2022).

Despite its high effectiveness, lipoprotein apheresis remains a method with limited clinical applicability. Therefore, increasing attention has recently been directed toward new therapies aimed at directly reducing lipoprotein(a) levels, particularly therapeutic strategies based on RNA technology (Alhomoud et al., 2025; Hamasaki et al., 2025; Tsimikas, 2024).

9.4. RNA-Based Therapies

RNA-based therapies represent one of the newest approaches to the treatment of elevated lipoprotein(a) levels. They enable direct modulation of molecular mechanisms responsible for Lp(a) synthesis. These therapies reduce the hepatic production of apolipoprotein(a) by inhibiting the expression of the LPA gene. Unlike conventional lipid-lowering drugs, RNA-based therapies allow for selective and substantial reduction of lipoprotein(a) levels. Therefore, they are considered among the most promising therapeutic strategies (Alhomoud et al., 2025; Hamasaki et al., 2025; Tsimikas, 2024; Yun et al., 2026).

Among the most promising and extensively studied approaches are antisense oligonucleotides (ASOs), which inhibit apolipoprotein(a) synthesis through degradation of its mRNA. The most important representative of this class is pelacarsen, which has demonstrated the ability to reduce lipoprotein(a) levels by up to approximately 80% in clinical studies. Its impact on cardiovascular event risk is currently being evaluated in multiple clinical trials (Graham et al., 2016; Tsimikas, 2024; Alhomoud et al., 2025).

Another group of innovative therapies includes agents based on small interfering RNA (siRNA) technology. These therapies act by inhibiting LPA gene expression, leading to degradation of the corresponding mRNA in hepatocytes. The most promising agents include olpasiran and SLN360, which have

demonstrated the ability to reduce Lp(a) levels by up to 80–90% in clinical studies. In some studies, this effect has been observed to persist for several months after administration. These findings suggest that such therapies may become an important component of treatment for patients with elevated lipoprotein(a) levels in the future (Alhomoud et al., 2025; Kaur et al., 2024; Tsimikas, 2024).

Available data indicate that RNA-based therapies may significantly change the management of patients with elevated lipoprotein(a) levels in the future. Compared with existing therapeutic approaches, they enable substantially greater reductions in Lp(a) levels due to their direct effect on apolipoprotein(a) synthesis. However, further clinical studies are required to evaluate their long-term efficacy and safety (Tsimikas, 2024; Yun et al., 2026; Alhomoud et al., 2025).

9.5. Future Therapeutic Perspectives

In recent years, significant progress has been observed in the development of new treatment approaches aimed at reducing lipoprotein(a) levels. Improved understanding of the mechanisms responsible for its synthesis has enabled the development of targeted therapies. In the future, these approaches may significantly change the management of patients with elevated Lp(a) levels. Of particular importance are RNA-based therapies, which are classified as molecularly targeted therapies (Tsimikas, 2024; Yun et al., 2026; Alhomoud et al., 2025).

Ongoing studies on RNA-based therapies, including pelacarsen and olpasiran, are focused on evaluating their effects on both lipoprotein(a) levels and cardiovascular event risk. Confirmation of their efficacy and safety may lead to their incorporation into routine clinical practice. This may result in significant changes in current guidelines as well as in the management of patients with elevated Lp(a) levels (Tsimikas, 2024; Alhomoud et al., 2025; Hamasaki et al., 2025).

In the coming years, further development of therapies targeting lipoprotein(a) reduction can be expected, along with the increasing importance of individualized treatment in patients with elevated Lp(a) levels. Greater availability of effective therapeutic options may contribute to wider use of lipoprotein(a) measurement in clinical practice and improved identification of patients at high cardiovascular risk (Yun et al., 2026; Clair et al., 2025; Parcha et al., 2025).

The development of therapies targeting Lp(a) represents one of the most promising directions in modern cardiology. The introduction of effective methods for lowering its levels may significantly reduce cardiovascular risk and contribute to a shift in current approaches to the prevention and treatment of cardiovascular diseases (Tsimikas, 2024; Yun et al., 2026).

10. Discussion and Clinical Implications

Based on the analyzed literature, lipoprotein(a) can be considered a significant, independent, and largely genetically determined risk factor for cardiovascular diseases. Its clinical relevance extends beyond its association with coronary artery disease and includes its role in the pathogenesis of ischemic stroke and calcific aortic valve stenosis. Elevated Lp(a) levels may be of particular clinical importance in patients with a normal lipid profile, supporting the inclusion of this parameter in a more comprehensive cardiovascular risk assessment (Boffa & Koschinsky, 2024; Tsimikas, 2024; Doherty et al., 2025; Yun et al., 2026; Volgman et al., 2024).

Growing evidence supports broader incorporation of lipoprotein(a) measurement into clinical practice. It is particularly important in patients with premature cardiovascular events, a positive family history, suspected or confirmed familial hypercholesterolemia, and in individuals who experience cardiovascular events despite adequate control of LDL cholesterol levels. In these patient groups, measurement of this lipoprotein enables more precise risk assessment and may influence therapeutic decisions (Cegla et al., 2021; Razavi et al., 2025; Parcha et al., 2025; Jang et al., 2026). Consequently, Lp(a) should be regarded as an important component of cardiovascular risk assessment rather than merely an additional laboratory parameter.

Despite the growing importance of lipoprotein(a), its use in clinical practice remains limited. One of the main challenges is the standardization of measurement methods and result reporting, which is related to the structural variability of apolipoprotein(a) and affects measurement accuracy. Additional difficulties arise from the use of different units and inconsistencies in threshold values across guidelines. These factors complicate result interpretation and limit clinical applicability (Cegla et al., 2021; Velilla et al., 2025; Razavi et al., 2025). Therefore, the main challenge is not the lack of scientific evidence, but the difficulty in implementing it in routine clinical practice.

Identification of elevated Lp(a) levels should lead to intensified control of other modifiable cardiovascular risk factors. In clinical practice, optimization of lipid-lowering therapy is crucial, particularly reduction of LDL cholesterol levels, along with control of other components of overall cardiovascular risk. In the future, the development of RNA-based therapies offers the prospect of more precisely targeted treatment for this group of patients (Tsimikas, 2024; Alhomoud et al., 2025; Hamasaki et al., 2025; Schuth et al., 2024; Yun et al., 2026).

The dynamic development of research on lipoprotein(a) does not resolve all uncertainties. It is necessary to determine to what extent pharmacological reduction of Lp(a) levels translates into a reduction in clinically significant outcomes, such as myocardial infarction, ischemic stroke, or the need for intervention due to aortic valve stenosis. It also remains unclear which patient groups derive the greatest benefit from targeted therapies. This indicates a transition from viewing Lp(a) solely as a risk biomarker toward its role as a therapeutic target (Tsimikas, 2024; Alhomoud et al., 2025; Parcha et al., 2025).

Lipoprotein(a) is no longer considered merely an additional lipid parameter but is increasingly recognized as an important component of cardiovascular risk assessment. It can be expected that in the near future its role in both primary and secondary prevention will continue to grow due to its prognostic significance and the development of targeted therapies (Yun et al., 2026; Tsimikas, 2024; Doherty et al., 2025).

11. Conclusions

The analyzed literature confirms that lipoprotein(a) is a significant, independent, and largely genetically determined risk factor for cardiovascular diseases (Boffa & Koschinsky, 2024; Doherty et al., 2025; Yun et al., 2026).

Lp(a) plays a key role in the pathogenesis of coronary artery disease, ischemic stroke, and aortic valve stenosis, and measurement of its concentration may contribute to a more precise assessment of cardiovascular risk.

Measurement of lipoprotein(a) is of particular importance in patients with premature cardiovascular events, a positive family history, and in individuals with persistent risk despite adequate control of LDL cholesterol levels (Cegla et al., 2021; Razavi et al., 2025; Clair et al., 2025).

Currently, the management of patients with elevated Lp(a) levels is primarily based on optimization of other cardiovascular risk factors, including reduction of LDL cholesterol levels. At the same time, the development of RNA-based therapies offers the prospect of more precise and causal treatment in the future (Tsimikas, 2024; Alhomoud et al., 2025; Hamasaki et al., 2025).

In the coming years, the role of lipoprotein(a) in both primary and secondary prevention is likely to increase. Moreover, its role may gradually evolve from a risk biomarker toward a therapeutic target. This may contribute to changes in both cardiovascular risk assessment and treatment strategies. This highlights the need for broader inclusion of Lp(a) in routine cardiovascular risk assessment.

List of abbreviations:

ASCVD – atherosclerotic cardiovascular disease
ASO – antisense oligonucleotides
apo(a) – apolipoprotein(a)
apoB-100 – apolipoprotein B-100
CAVD – calcific aortic valve disease
IL-6 – interleukin-6
LDL – low-density lipoprotein
LDLR – low-density lipoprotein receptor
Lp(a) – lipoprotein(a)
OxPL – oxidized phospholipids
siRNA – small interfering RNA
TNF-α – tumor necrosis factor alpha

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