REVIEW

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Lipoprotein (a) in the context of atherosclerosis: pathological implications and therapeutic perspectives in myocardial infarction. A narrative review

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Abstract

Lipoprotein (a) [Lp(a)] is a recognized independent cardiovascular (CV) risk factor with significant implications in the morphopathology of atherosclerotic plaques, particularly in the context of myocardial infarction (MI). Structurally, Lp(a) consists of a low-density lipoprotein (LDL) particle covalently bound to apolipoprotein A (ApoA), and its resemblance to plasminogen (PLG) underpins its dual proatherogenic and prothrombotic effects. Elevated Lp(a) levels disrupt endothelial repair mechanisms, enhance the deposition of oxidized LDL, and promote foam cell formation, which are critical for the initiation and progression of atherosclerosis. Pathologically, atherosclerotic plaques associated with Lp(a) display hallmark features of instability, including thin fibrous caps, increased macrophage infiltration, calcification, and fragile neovascularization. These features contribute to plaque ruptures and thrombotic complications. Additionally, the structural similarity of Lp(a) to PLG interferes with fibrinolysis, creating a prothrombotic environment that exacerbates the risk of acute ischemic events. Genetic and non-genetic factors influence plasma Lp(a) concentrations, with significant inter-individual and ethnic variability contributing to varying CV risk profiles. Despite advancements in the understanding of the pathophysiological role of Lp(a), effective therapeutic options remain limited. Current management focuses on mitigating traditional CV risk factors, while emerging therapies, such as antisense oligonucleotides and short interfering ribonucleic acid (siRNA) targeting hepatic ApoA production, offer promising avenues for reducing Lp(a) levels. Further clinical validation of these therapies is warranted. This review underscores the importance of incorporating Lp(a) measurement into routine CV risk assessment and emphasizes the need for continued research on its morphopathological impacts and therapeutic modulation, with the aim of reducing the burden of atherosclerosis and MI.

Keywords: lipoprotein (a), myocardial infarction, atheroma plaque, cardiovascular disease, cardiovascular risk factors.

Historical context and relevance

Analyzing the natural progression of acute coronary syndromes, we observed that risk factors are the progenitors of structural and functional changes underlying the pathophysiological processes involved in their development [1]. The likelihood of non-fatal or fatal events, thus defining cardiovascular (CV) risk, is represented through various studies such as the Framingham Heart Study and INTERHEART, which have highlighted several CV risk factors including hypertension, diabetes mellitus, obesity, smoking, psychosocial stress, and dyslipidemia [2, 3].

Dyslipidemia is characterized by classical parameters such as low-density lipoprotein–cholesterol (LDL-C), high-density lipoprotein–cholesterol (HDL-C), triglycerides, and total lipids. However, in recent years, new molecules such as apolipoprotein B (ApoB), apolipoprotein A1 (ApoA1), low-density lipid particles, and lipoprotein (a) [Lp(a)] have emerged on the central panel of the lipid profile, demonstrating their significant involvement in the onset and development of acute coronary events [4].

Among them, Lp(a) has become a scientific subject of interest in the medical community [5]. Numerous prospective and retrospective studies have supported its involvement in the development of coronary atherosclerotic pathologies. Starting from Kare Berg's description of Lp(a) as an antigen, in 1963 [6], genetic determinism data published by Sandholzer in 1992, and large randomized studies by researchers such as Kramstrup, Kronenberg, and Tsimikas on Lp(a)'s involvement in CV pathology, all have introduced this new CV risk factor into the scientific agenda [5]. These studies have shown that high levels of this lipid formation can increase CV risk by up to four times. Therefore, Lp(a) is not only an emerging biomarker but also an independent CV risk factor that requires special attention in clinical practice. In this context, reviewing the current literature

regarding the structure, function, and impact of Lp(a) on acute coronary syndromes is essential to reduce the burden of CV diseases.

Structure of Lp(a)

Lp(a) (Figure 1) is formed from an LDL molecule covalently linked to an ApoA [7]. Evolutionarily, ApoA is similar to plasminogen (PLG) in biological structure, containing copies of PLG Kringle IV (KIV), one copy of PLG Kringle V (KV), and an inactive protease domain, without containing PLG KI, KII, KIII or KIV [8].

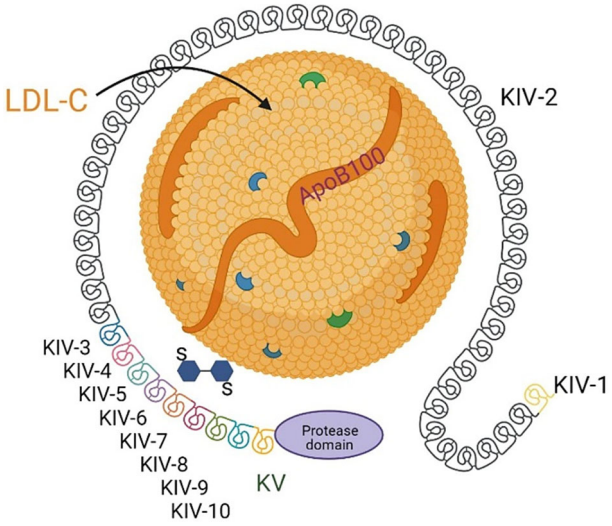

Figure 1 – ***The components of lipoprotein (a) molecule. KIV: Kringle IV; KV: Kringle V; LDL-C: Low-density lipoprotein–cholesterol.***

Through reducing agents, the LDL molecule dissociates from ApoA by breaking the disulfide bond, rich in oxidative phospholipids, between ApoA and apolipoprotein B100 (ApoB100), which is a part of the LDL molecule [9]. While mutagenesis and hydrodynamic studies have described the presence of a single disulfide bond between ApoA Cys4057 and ApoB Cys4326, electron microscopy provides new insights, suggesting multiple bonds, supporting the hypothesis that ApoA wraps around the LDL molecule with multiple non-covalent interactions between ApoA and ApoB [10, 11].

Another important aspect of Lp(a)'s structure is the ester core of cholesterol and triglycerides, which can cause a synergism between increased Lp(a) and LDL-C values, as the free LDL molecule cannot be distinguished from the one bound to Lp(a) [12, 13].

Lp(a) metabolism

Although clear evidence regarding the exact cellular site of Lp(a) assembly is not currently available, with various studies proposing different hypotheses, the liver is certainly the organ that produces Lp(a) [14]. Most studies indicate that the surface of hepatocytes is the assembly site for ApoA and ApoB components through a covalent disulfide bond, forming the Lp(a) molecule [14]. Other authors suggest that the extracellular space is a more feasible site for this molecule's formation [15].

According to most large studies, the two constituent molecules assemble as follows: ApoB100, an essential element of LDL, is synthesized in the liver, with its *APOB* precursor gene located on chromosome 2, resulting from protein folding and glycosylation processes [16]. This preprotein undergoes cleavage and post-translational modifications, adding an essential disulfide residue for binding to ApoB100 and forming the Lp(a) molecule [17]. After the incorporation of ApoB100 into LDL and the formation of ApoA with Kringle domains similar to PLG, the effective assembly of Lp(a) occurs, mediated by terminal Cys ends [18].

Assembled Lp(a) molecules are transported from the endoplasmic reticulum to the Golgi apparatus, where they may undergo additional modifications such as phosphorylation, sulfation, or glycosylation, which are crucial for molecular stability and functionality [19]. Glycosylation is the most significant process for Lp(a), as it induces structural changes that increase the molecule's affinity for cholesterol receptors, leading to increased LDL uptake and endocytosis and thus greater cholesterol accumulation in cells [20]. Additionally, glycosylated Lp(a) can influence thrombosis through its similarity to PLG. From the Golgi apparatus, Lp(a) vesicles are transported to specific locations on the hepatocyte plasma membrane through a network of motor proteins and a cytoskeletal filament network [21]. Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) complex proteins, specifically v-SNAREs and t-SNAREs, facilitate the fusion between Lp(a)-transporting vesicle membranes and the hepatocyte membrane, creating a continuous channel through which the Lp(a) content is excreted into the extracellular space. Once in the extracellular space, Lp(a) can freely diffuse through hepatic capillaries passively or actively through transporter proteins [22].

The plasma level of Lp(a) results from the intense genetic activity of two *LPA* alleles, producing isoforms of varying sizes, with the smallest being the most abundant. Another process could be the uptake of the molecule by macrophages, thus playing a role in atherogenesis through foam cells [23].

Distribution and variability

In a recent statement on CV diseases by the *American College of Cardiology* (ACC), it was estimated that the percentage of individuals with elevated Lp(a) levels is approximately 20–25% [24, 25].

Approximately 10 000 patients enrolled in various studies, including the INTERHEART study, have shown ethnic differences in Lp(a) levels, with higher values in Sub-Saharan Africans and South Asians than in Hispanics and Europeans [26]. Additionally, statistical analyses of different isoforms suggest that smaller ApoA isoforms predict major adverse cardiac events (MACEs) risk in these ethnic groups [27, 28].

Additionally, data published in "Circulation", corroborated with those from a UK cohort, indicate that women have slightly higher levels than men, with hormonal roles being implicated, and these levels equalizing with the onset of menopause [29].

CV risk observed in obese children is linked to elevated levels of Lp(a), a marker with a strong genetic component [30].

The *European Society of Cardiology* (ESC) highlights that, alongside the genetic component, several non-genetic factors can influence up to 20% changes in Lp(a) levels.

Among these, sedentarism, a diet high in saturated fats [31], hypothyroidism [32], growth hormone therapy, pregnancy [33], chronic kidney disease, hemodialysis, and chronic inflammatory conditions can increase levels by up to 20% [34, 35]. Protective factors reducing Lp(a) levels include a low-carbohydrate diet [31], hyperthyroidism [32], post-menopausal therapy [33], and the interleukin (IL)-6 inhibitor Tocilizumab [36].

Lp(a) and the morphopathology of atherosclerotic plaque

Lp(a) is a complex lipoprotein consisting of ApoB100, covalently bound to ApoA. This unique structure imparts significant pathogenic properties, making Lp(a) an independent CV risk factor, as thoroughly documented in scientific literature [5]. Studies have established a strong correlation between elevated Lp(a) levels and an increased risk of major CV events, including coronary artery disease, myocardial infarction (MI), and strokes [5, 37].

The formation of atherosclerotic plaques (Table 1) begins with subtle dysfunction at the endothelial level, the protective layer of the vascular walls. Lp(a) plays a crucial role in exacerbating this dysfunction by interfering with natural endothelial repair processes and facilitating the infiltration of oxidized LDL lipoproteins into the arterial wall. These oxidized LDL particles are recognized by the immune system as harmful, prompting the recruitment of macrophages that engulf lipoproteins and transform them into foam cells. These foam cells (Figure 2) are a central component of atherosclerotic plaque, contributing to the buildup of an unstable lipid mass within the arterial wall [38, 39].

Table 1 – ***The prothrombotic and proatherogenic effects of lipoprotein (a)***

Lp(a) and atheromatous plaque	Lp(a) and prothrombotic effect
• increased oxidative phospholipids	• inhibits plasminogen activation
• foam cell formation	• reduces the fibrinolysis process
• endothelial dysfunction	• decreases tissue factor activity
• smooth muscle cell proliferation	• intensifies platelet aggregation [41]
• monocyte chemoattraction	
• progression of arterial wall inflammation [40]	

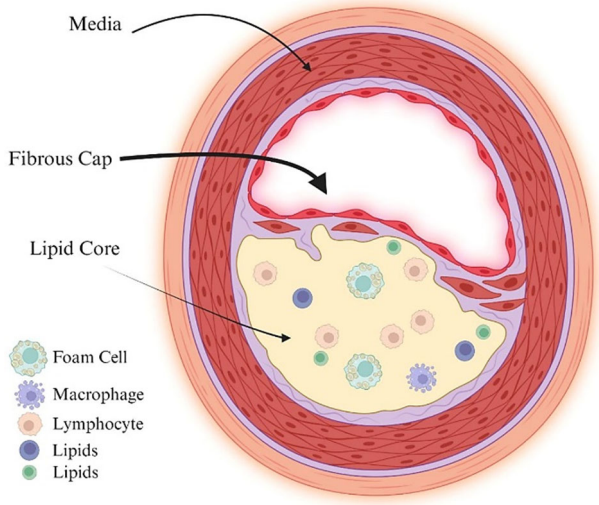

Figure 2 – ***Morphology of atherosclerotic plate.***

The proatherogenic contribution of Lp(a) extends beyond that of lipid accumulation [42]. The ApoA component has sequences resembling PLG, which interfere with fibrinolysis – the natural process of thrombus dissolution. This interference creates a prothrombotic environment, significantly increasing the risk of thrombus formation, particularly in the event of plaque rupture. Consequently, Lp(a) not only fosters plaque development but also amplifies the risk of severe thrombotic complications [40, 41].

Inflammation plays a critical role in plaque progression, and Lp(a) intensifies this process by stimulating the recruitment and activation of inflammatory cells such as macrophages and lymphocytes [40, 43]. These cells release a series of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6, which contribute to the degradation of the extracellular matrix (ECM) [44–46]. This degradation weakens the fibrous cap of the plaque, making it more susceptible to rupture. A ruptured plaque exposes necrotic lipid material to the bloodstream, triggering thrombus formation, which can block blood flow, leading to acute events like MI or stroke [39, 40, 47].

Another critical aspect of Lp(a) involvement in atherosclerosis is its role in promoting plaque calcification. Calcification is a marker of disease severity and is associated with arterial stiffening and loss of elasticity. In patients with elevated Lp(a) levels, the calcification process is accelerated, contributing to progressive narrowing of the arterial lumen and compromised blood flow. This not only exacerbates the disease but also leads to the formation of vulnerable plaques that are more prone to rupture [48, 49].

In the later stages of atherosclerotic plaque development, muscle cells migrate into the arterial intima, proliferate, and synthesize collagen to form the fibrous cap of the plaque [50, 51]. This fibrous structure stabilizes the plaque by isolating the necrotic lipid content from the bloodstream. However, Lp(a) disrupts this process by inhibiting smooth muscle cell proliferation and reducing collagen production. The result is a thin and unstable fibrous cap, significantly increasing the likelihood of plaque rupture and subsequent thrombus formation, heightening the risk of acute CV events [47, 51].

In addition to these mechanisms, Lp(a) influences the formation of new fragile blood vessels and neovessels within the atherosclerotic plaque. These neovessels are essential for nutrient delivery to the avascular regions of the plaque but are prone to rupture, leading to intraplaque hemorrhages. Lp(a), through its proinflammatory and pro-thrombotic properties, promotes microthrombus formation within these fragile neovessels, amplifying the risk of intraplaque hemorrhage and plaque instability [52, 53].

Histologically, atherosclerotic plaques are characterized by complex structures comprising foam cells, macrophages, smooth muscle cells, and components of the ECM. The presence of inflammatory markers and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) reflects a persistent inflammatory environment that contributes to disease progression [43, 44]. Lp(a) plays a key role in maintaining this inflammatory milieu, accelerating arterial wall degradation, and promoting plaque instability.

Thus, Lp(a) is a critical factor in the development and progression of atherosclerotic plaques (Figure 2) through

complex mechanisms involving endothelial dysfunction, lipid accumulation, chronic inflammation, interference with fibrinolysis, and promotion of calcification [37, 54]. These processes contribute to the formation of unstable plaques and an increased risk of acute CV events, underscoring the need for innovative therapeutic strategies to manage elevated Lp(a) levels and reduce CV risk [42, 55].

Prothrombotic impact

Boffa & Koschinsky (2016) suggested the prothrombotic effect of Lp(a), which describes the molecular mimicry between ApoA–Lp(a) and PLG [54, 56]. The structural homology in the amino acid sequence of the Kringle domains of ApoA and PLG (KIV) allows ApoA to competitively bind to fibrin, thus inhibiting the formation of plasmin and its breakdown (of fibrin) [57]. Additionally, the structural similarity enables Lp(a) to bind to tissue-type plasminogen activator (t-PA), forming molecular complexes that catalyze the inhibition of fibrinolysis [58]. This effect is also found with other factors like urokinase-type plasminogen activator (u-PA; urokinase), coagulation factor XII [41], Nexim-1 protease, plasminogen activator inhibitor-1 (PAI-1) and some complement system factors [59].

Endothelial dysfunction is a cumulation of processes with both proatherogenic and prothrombotic roles [60]. The integrity of the endothelial barrier is influenced by high plasma concentrations of Lp(a), which modulates the expression of junctional proteins such as occludins, claudins, and cadherins through various inflammatory pathways or oxidative stress induction [60, 61]. The two processes influenced by Lp(a), proatherogenicity and prothrombotic effect, are essential elements in the onset and progression of ischemic coronary disease, coronary syndromes, and especially in the pathogenesis of acute MI. A meta-analysis of 7382 cases of coronary heart disease identified a 2.08-fold higher risk of carriers of the *ApoA* gene isoform [62]. This idea was studied inversely, demonstrating that genetic variants associated with low Lp(a) concentrations are CV disease producers [63, 64]. The same studies highlighted structural differences in Lp(a) across different ethnicities and races (Black, Caucasian) [65]. In context, the coronavirus disease 2019 (COVID-19) pandemic has had profound impact, contributing to the development of numerous comorbidities in the general population [66]. Concurrently, the prothrombotic and proinflammatory properties of Lp(a) have been notably intensified in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [67]. Kronenberg supports this hypothesis, demonstrating that Lp(a) is a CV risk factor independent of other factors and argues the involvement of different isoforms and genetic variants in the proatherogenic, prothrombotic, and proinflammatory effect [38, 68, 69].

Diagnosis and measurement of Lp(a)

Epidemiological studies have shown large variations in median concentrations of Lp(a), influenced by racial/ethnic differences and the use of various testing methods [65]. Historically, Lp(a) concentrations have been reported in mg/dL through immunoassays, predominantly immuno-turbidimetric [70, 71]. Recently, an increasing number of studies have reported the number of particles in nmol/L [72]. The main issue is the lack of traceability of the common calibrator, which is essential for comparing measurements and establishing common risk thresholds [71, 70]. Measurement errors are influenced by the use of frozen *versus* fresh samples as well as the variable size of the ApoA isoform [71]. Tests based on polyclonal antibodies are prone to significant errors, while tests with monoclonal antibodies are preferable but difficult to implement on a large scale [73]. For precise and comparable measurements, the use of fresh samples and validated tests, with traceability to a recognized international calibrator, is recommended [74]. The current consensus is that reporting the number of particles (nmol/L) is preferable for reporting the total mass (mg/dL) [71]. However, all tests based on polyclonal antibodies are affected by measurement errors and can only approximate the number of particles. Clinical studies, such as Lp(a) HORIZON, have investigated whether reducing Lp(a) can decrease CV events, which could significantly change CV risk management [75]. The HERITAGE study provides valuable information regarding the necessity of measuring Lp(a) in patients in the CV risk category. 48 992 patients with an average age of 62.6 years were grouped based on Lp(a) levels: below 30 mg/dL, 30–50 mg/dL, and above 50 mg/dL, with an average value of 18 mg/dL [76]. All data suggest that young patients with simultaneously high Lp(a) and LDL-C levels are at risk of developing premature CV diseases [75, 76] According to the Guidelines of the *ESC* and the *European Atherosclerosis Society* (EAS), establishing concentration thresholds for Lp(a) is crucial for assessing CV risk [77]. An Lp(a) level of ≥50 mg/dL (≥125 nmol/L) is often used to identify an increased risk of major CV events, including MI and stroke. Research has shown that patients with Lp(a) levels above this threshold have a significantly higher risk of developing CV diseases than those with lower levels. Lp(a) levels ≥70 mg/dL (≥175 nmol/L) are used in certain clinical studies to select high-risk CV patients and include them in intervention studies [78]. At this level, the CV risk is significantly increased, justifying close monitoring and potential therapeutic interventions. Additionally, Lp(a) levels ≥90 mg/dL (≥225 nmol/L) are associated with an extremely high risk of CV events, often requiring more aggressive therapeutic interventions to prevent severe complications. Another study emphasizing the importance of testing for Lp(a) demonstrated a link between elevated levels (>30 mg/dL) and the severity of coronary damage in patients with MI [79]. These thresholds are essential for risk stratification and adequate management of patients with high Lp(a) levels [80]. The recommendations formulated by the ESC [81] and the *ACC* [82] emphasize the critical importance of assessing Lp(a) levels to identify individuals at high risk of major CV events. Both Guidelines recommend a single measurement of Lp(a) in all adults, paying particular attention to patients with a family or personal history of premature CV disease [81–83].

Treatment strategies

The challenges currently posed by Lp(a) and for future research horizons are represented by therapeutic solutions and the management of pathologies in which this molecule is a converging point in their pathophysiology. The existing limitations of therapies stem from the lack of molecules with a direct action on lowering plasma concentrations of Lp(a). As mentioned above, managing conventional risk

factors and optimizing lifestyle can bring reductions of up to 20% in plasma concentrations [84], with a reduction of coronary events by up to 8% in patients undergoing apheresis [85]. This technique is used at Lp(a) values above 60 mg/dL and in the presence of CV disease [86]. Statins, the lethal weapons available to practitioners for lowering LDL-C and treating dyslipidemia, do not demonstrate the same effect in lowering Lp(a). Meta-analyses [87–89] present contradictory data, reporting an increase in Lp(a) based on three studies and a decrease in Lp(a) concentrations (four studies). Administration of Rosuvastatin in the Jupiter study results in increased plasma Lp(a) compared to placebo [90]. Results from the evaluation of approximately 44 000 patients in the FOURIER and ODYSSEY outcomes trials (2019), regarding the action of Evolocumab and Alirocumab [proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors] on MACEs risk, especially in patients with high Lp(a) values, demonstrate a moderate effect of these substances [91, 92]. Therapy with antisense oligonucleotides and short interfering ribonucleic acid (siRNA) solutions with a direct action on ApoA production in the liver [93] or combined therapy, represents a field of research and future treatment options for pathological effects and diseases caused by Lp(a).

Conclusions and perspectives

Lp(a), first discovered by Kare Berg in 1963, has evolved from a scientific curiosity to a major CV risk factor recognized in international clinical guidelines. Epidemiological and clinical studies have demonstrated its significant role in the pathogenesis of atherosclerotic CV diseases, particularly through its contribution to endothelial dysfunction, lipid accumulation, chronic inflammation, and thrombus formation. Histologically, atherosclerotic plaques associated with elevated Lp(a) levels exhibit distinctive features, including activated macrophages, advanced calcifications, and unstable fibrous caps, making them prone to rupture and acute major events. Although significant progress has been made in understanding the structure and metabolism of Lp(a), standardizing plasma measurements and developing specific therapies remain critical challenges. Currently, CV risk management for patients with elevated Lp(a) focuses on controlling conventional risk factors and optimizing lifestyle, which can modestly reduce plasma levels. However, emerging therapies such as antisense oligonucleotides and siRNA molecules targeting hepatic ApoA production offer promising prospects for targeted treatments, though they require further validation through rigorous clinical trials. Integrating Lp(a) measurements into routine clinical practice, particularly for patients with a family or personal history of premature CV disease and educating physicians and patients about the significance of this biomarker are crucial steps. In the field of morphopathology, an in-depth analysis of atherosclerotic plaques associated with Lp(a) provides opportunities to better understand the underlying mechanisms and guide future therapeutic strategies. Continuous research and multidisciplinary collaboration will contribute to reducing the burden of CV diseases and improving patient outcomes.

Conflict of interests

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Authors' contribution

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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