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REVIEW

Lipoprotein(a) and Its Role in Peripheral Arterial Disease: A Narrative Review

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Abstract: Lipoprotein (a) (Lp[a]) is an independent risk factor for cardiovascular disease (CVD). Structurally like low-density lipoprotein, Lp(a) is distinguished by the covalent attachment of apolipoprotein(a) to apolipoprotein B-100. Although its physiological role remains incompletely understood, evidence suggests that Lp(a) may facilitate wound healing and inhibit cancer growth and metastasis. In contrast, Lp(a) exhibits proatherogenic properties; it transports proinflammatory oxidized phospholipids, induces the secretion of proinflammatory cytokines, increases endothelial permeability, promotes smooth muscle cell migration and proliferation, and upregulates adhesion molecules that facilitate monocyte recruitment and retention. In addition, Lp(a) exerts prothrombotic activity by enhancing platelet aggregation, suppressing plasminogen activation, and inhibiting fibrinolysis. Although its clinical relevance in CVD is well established, the role of Lp(a) in peripheral arterial disease (PAD) remains unclear. This narrative review aimed to synthesize and critically examine the current evidence on the biological role of Lp(a) in PAD pathogenesis and identify knowledge gaps in PAD-specific outcomes. This review summarizes the epidemiology, pathophysiology, and management of elevated Lp(a) levels in patients with PAD and examines their association with post-treatment clinical outcomes. Elevated Lp(a) levels are associated with an increased PAD incidence and a higher risk of restenosis post-revascularization. Understanding the mechanisms by which Lp(a) contributes to PAD pathogenesis is essential for developing effective targeted therapeutic approaches and improving the identification and management of high-risk patients.

Plain Language Summary: Peripheral arterial disease occurs when the blood vessels in the legs become narrowed, reducing blood flow. This can cause pain, limit mobility, and increase the risk of serious complications, such as heart attack, stroke, or limb loss.

Lipoprotein may play an important role in this disease. It resembles "bad cholesterol" but is more harmful because it promotes vessel damage, inflammation and clotting. While its role in heart disease and stroke is well known, its association with peripheral arterial disease is less clear.

This review examined current research and found that individuals with higher lipoprotein(a) levels are more likely to develop peripheral arterial disease and have worse results after treatment, including re-narrowing of blood vessels.

These findings suggest that lipoprotein(a) levels could help identify high-risk patients and guide treatment choices. New therapies designed to lower lipoprotein(a) levels are under development and may improve outcomes for patients with peripheral arterial disease.

Keywords: restenosis, atherosclerosis, vascular biomarkers, thrombosis

Introduction

Lipoprotein (a) (Lp[a]) is a distinct lipoprotein particle that has garnered considerable attention in cardiovascular medicine owing to its proatherogenic and prothrombotic roles in the development of atherosclerotic coronary and cerebrovascular

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diseases. However, its association with peripheral arterial disease (PAD) is unclear. PAD, a manifestation of atherosclerosis affecting arteries outside the heart and brain, typically presents with progressive lower extremity discomfort and functional limitations, substantially impairing activities of daily living. In 2019, the global prevalence of PAD among individuals aged ≥ 40 years was estimated at 1.52%, corresponding to approximately 113 million individuals.[1] Notably, 42.6% of these cases occurred in countries with low-to-middle sociodemographic indices, highlighting disparities in disease burden and the influence of socioeconomic determinants.[1] Furthermore, 69.4% of disability-adjusted life years attributed to PAD were linked to modifiable risk factors, underscoring the importance of preventive strategies.[1]

The substantial clinical burden of PAD highlights the potential value of Lp(a) as a biomarker for identifying at-risk individuals and informing treatment strategies.[2,3] Although current pharmacological therapies are limited, recent therapeutic developments targeting Lp(a) appear promising and are likely to be available soon. Elucidating the mechanisms by which Lp(a) contributes to PAD pathogenesis is essential for developing of targeted therapeutic approaches. In addition, examining the interplay between Lp(a) and other contributing factors may inform more precise and individualized interventions in the future.

This narrative review aimed to synthesize and critically examine current evidence on the biological role of Lp(a) in PAD pathogenesis and identify knowledge gaps in PAD-specific outcomes. It also explores therapeutic strategies for patients with PAD and elevated Lp(a) levels, with the goal of improving clinical outcomes.

Materials and Methods

To ensure methodological clarity, we established explicit inclusion and exclusion criteria. We excluded studies that were not published in English, conference abstracts without accompanying peer-reviewed full texts, reports with no original data on Lp(a) and PAD, and case reports or small series with < 10 participants. These restrictions were intended to reduce bias from anecdotal observations and non-validated sources.

The quality of all eligible studies was assessed using validated instruments appropriate for the study design (See Supplementary Tables S1, S2 and S3). Observational studies were evaluated using the Newcastle–Ottawa Scale, which considers the representativeness and selection of study populations, comparability of cohorts based on key confounders (such as age, sex, smoking status, and low-density lipoprotein (LDL)-cholesterol), and the validity and adequacy of outcome assessment. Studies scoring ≥ 7 points (out of 9) were classified as high quality. Randomized and non-randomized clinical trials were assessed using the Cochrane Risk of Bias 2.0 tool, which examines potential bias in the randomization process, adherence to assigned interventions, completeness of outcome data, accuracy of outcome measurements, and selective reporting. Each domain was classified as low risk, some concerns, or high risk. Systematic reviews and meta-analyses were appraised using AMSTAR 2, a 16-item tool that assesses the comprehensiveness of the search strategy, handling of duplicate data, assessment of study bias, appropriateness of synthesis methods, and consideration of publication bias. Reviews with critical methodological flaws were rated as having low confidence. These quality assessments were incorporated into the evidence synthesis, with greater weight accorded to robust studies and a more cautious interpretation applied to lower-quality evidence.

A narrative review of the literature was conducted to examine the association between Lp(a) and PAD. Comprehensive searches were performed in PubMed, Embase, Ovid, and Google Scholar for articles published until May 2024. Search terms and their variants included “lipoprotein(a)”, “peripheral arterial disease”, “atherosclerosis”, “hyperlipidemia treatment”, “statins”, “ezetimibe”, “lipoprotein apheresis”, “PCSK9 inhibitors”, and “diet.” Eligible study designs included clinical trials, observational cohorts, Mendelian randomization studies, systematic reviews, and meta-analyses. Literature reviews were included only if they incorporated a critical synthesis of the primary data.

This strategy ensured a transparent, balanced, and unbiased presentation of the available evidence, capturing both concordant and discordant findings, with conclusions weighted according to study quality.

Key Studies on Lp(a) and Its Relevance in PAD

In 2006, Aboyans, Criqui, Denenberg, Knoke, Ridker, and Fronek[2] conducted a longitudinal study investigating the association between Lp(a) levels and the progression of both large- and small-vessel PAD. They reported that large-vessel PAD progression—defined as a ≥ 0.3 decrease in the ankle–brachial pressure index (ABPI)—was significantly

associated with elevated Lp(a) levels.[2] In contrast, small-vessel PAD progression—defined as a ≥ 0.27 decrease in the toe–brachial index—was not associated with increased Lp(a) concentrations.[2]

The 2012 European Prospective Investigation of Cancer (EPIC)-Norfolk study assessed the relationship between Lp(a) and vascular outcomes, including coronary artery disease (CAD), stroke, and PAD, over 212,981 person–years of follow-up. A 2.7-fold increase in serum Lp(a) concentration (equivalent to one standard deviation) was associated with a hazard ratio of 1.37 (95% confidence interval [CI], 1.25–1.50) for incident PAD.[3] This association was independent of LDL-cholesterol levels. Higher Lp(a) levels were also significantly associated with increased PAD-related hospitalization and mortality, underscoring the clinical relevance of elevated Lp(a) in patients at risk for PAD.[3]

In 2020, Golledge, Rowbotham, Velu, Quigley, Jenkins, Bourke, Bourke, Thanigaimani, Chan, and Watts[4] conducted a multicenter prospective cohort study involving 1,472 patients with documented PAD—including those with claudication, critical limb ischemia, and abdominal aortic aneurysm (AAA)—to examine the relationship between serum Lp(a) levels and the need for surgical intervention (endovascular and open procedures).[4] High Lp(a) concentration was defined as ≥ 30 mg/dL. Kaplan–Meier analysis showed that, at 3 years, lower limb revascularization occurred in 30.4% of patients with elevated Lp(a) versus 25.3% of those with normal levels (P = 0.029 by log–rank test).[4]

A recent study investigated the risk of PAD in patients with type 2 diabetes mellitus (T2DM). Lp(a) was identified as one of the four strongest risk factors in this population.[5] PAD was present in 77% of patients with T2DM, which was substantially higher than that reported in previous studies. Several factors may explain this increased prevalence: PAD is often underdiagnosed owing to its asymptomatic early stages; the study population consisted of hospitalized patients with T2DM, likely representing individuals with more advanced diseases and greater comorbidity burden; the study was conducted at a major hospital in Hainan Province, China, known for treating complex cases; and the average age of participants was 60.3 years, with older age being a recognized risk factor for PAD.

Pathophysiological Effects of Lp(a), Its Role in Atherosclerosis, and Clinical Implications for PAD

Structure and Physiological Function of Lp(a)

Lp(a) structurally resembles LDL,[6] with the key distinction of apolipoprotein (a) (apo[a]), which is covalently linked to apolipoprotein B100 (apo-B100) via a single disulfide bond and is stabilized by noncovalent interactions[7] (Figure 1). The

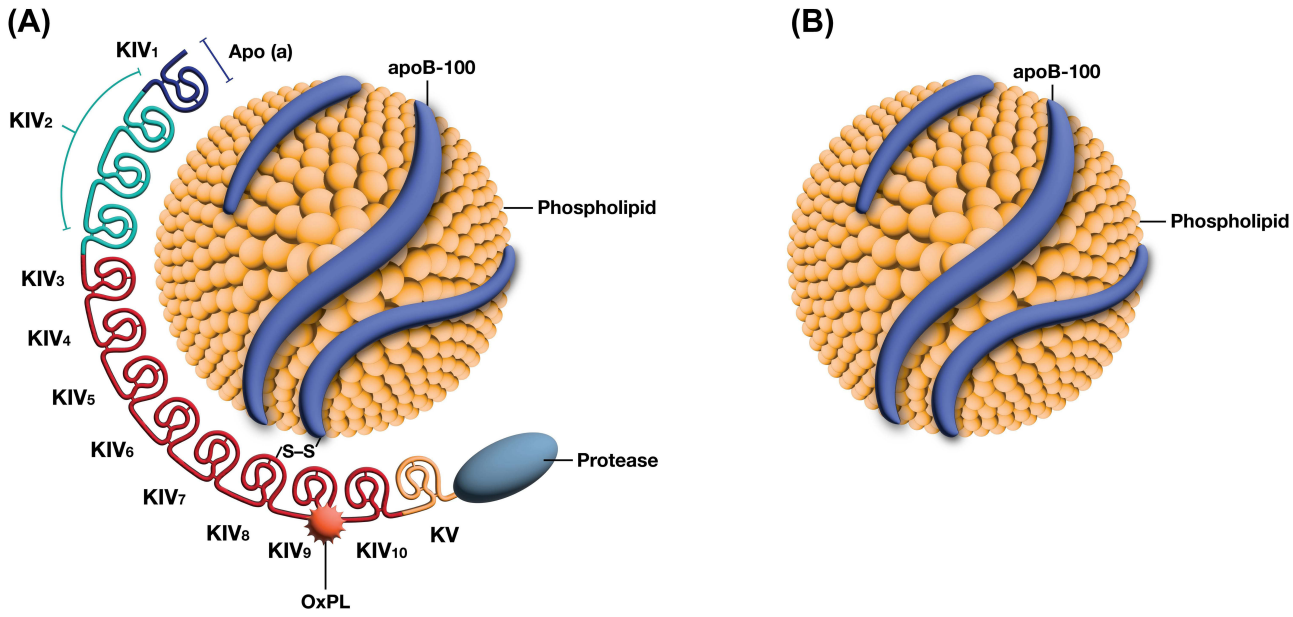

Figure 1 Schematic representation of the Lp(a) molecule (**A**), compared to an LDL molecule (**B**). The Apo(a) subunit, attached to Lp(a), is composed of kringle domains and a serine protease domain.

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molecular weight of apo(a) ranges from 400 to 700 kDa.[6,7] Apo(a) shares structural homology with plasminogen and contains protein domains known as kringles (named for their resemblance to Scandinavian pastries).[8–10] Apo(a) composes two kringle domains—kringle IV (KIV) and V (KV)—and a catalytically inactive serine protease domain. Each individual carries a single copy of KIV subtypes 1 and 3–10, as well as KV and the protease domain, whereas KIV type 2 (KIV-2) is present in 3–> 40 identical repeats.[6,8–12] This KIV-2 copies number variation (CNV) accounts for the substantial size heterogeneity of apo(a). Notably, KIV type 9 (KIV-9) contains an unpaired cysteine residue that forms a disulfide linkage with apo-B100.

Lp(a) particles consist of an LDL-like core comprising neutral lipids, phospholipids, and apoB-100, surrounded by a phospholipid monolayer and covalently attached to apo(a) via disulfide bonds. Apo(a) contains multiple KIV domains, particularly the variable number of KIV-2 repeats, KV, and protease domains. Oxidized phospholipids (OxPLs) preferentially bind to KIV-9, contributing to the atherogenic and pro-inflammatory potential of Lp(a).

The physiological functions of Lp(a) have not been fully established;[13] however, it exhibits antifibrinolytic properties by competing with plasminogen for fibrin binding through apo(a)[14] (Figure 2). In addition, Lp(a) binds to tetranectin, a protein that typically accelerates plasminogen activation via tissue plasminogen activator,[15] further inhibiting fibrinolysis. Activated plasmin may paradoxically enhance Lp(a) binding to fibrin, thus impeding plasmin-mediated fibrin degradation.[16]

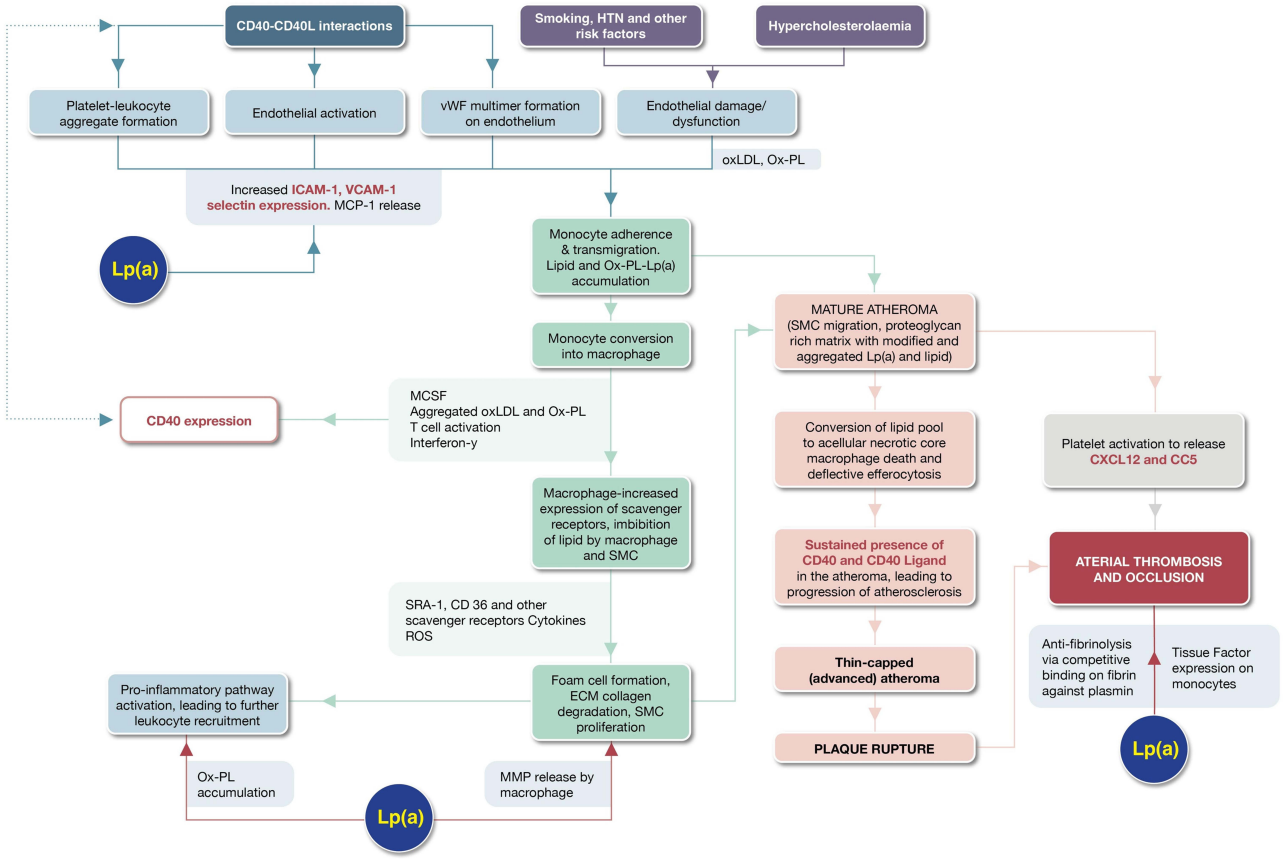

Figure 2 Lp(a) contributes to atherogenesis by promoting endothelial activation, monocyte recruitment, and macrophage-derived foam cell formation—processes mediated in part by OxPLs and CD40–CD40 ligand (CD40L) signaling. These pathways promote smooth muscle cell (SMC) proliferation, extracellular matrix (ECM) degradation, and the formation of lipid-rich, rupture-prone plaques. Lp(a) further increases thrombotic risk by competing with plasminogen, impairing fibrinolysis, and inducing tissue factor (TF) expression on monocytes, thereby facilitating arterial thrombosis after plaque rupture. This figure illustrates the integration of Lp(a) into the inflammatory, lipid-mediated, and thrombotic pathways central to cardiovascular disease (CVD) progression.

Abbreviations: CCL5, chemokine ligand 5; CD, cluster of differentiation; CD40L, CD40 ligand; CXCL12, C-X-C motif chemokine 12; CVD, cardiovascular disease; ECM, extracellular matrix; HTN, hypertension; ICAM-1, intercellular adhesion molecule 1; Lp(a), lipoprotein(a); MCP-1, monocyte chemoattractant protein 1; MCSF, macrophage colony-stimulating factor; MMP, matrix metalloproteinase; OxLDL, oxidized low-density lipoprotein; OxPL, oxidized phospholipid; SMC, smooth muscle cell; SRA-1, scavenger receptor A1; TF, tissue factor; VCAM-1, vascular cell adhesion molecule 1; vWF, von Willebrand factor.

Lp(a) may also exert prothrombotic effects by upregulating tissue factor expression in monocytes and interacting with the tissue factor pathway inhibitor (TFPI)[17] (Figure 2). Although some studies suggest that Lp(a) enhances platelet aggregation via thrombin receptor-activating peptide (SFLLRN), others report decreased aggregation in response to collagen, adenosine diphosphate, or platelet-activating factor, indicating that the effect of Lp(a) on platelets may depend on the surrounding biochemical milieu.[18]

These prothrombotic and antifibrinolytic properties of Lp(a) may support physiological wound healing.[17] However, current evidence does not consistently support a direct thrombogenic role for elevated Lp(a) levels, except in individuals with markedly elevated concentrations and in children with venous thromboembolism.[19]

Lp(a) also binds and degrades OxPLs—molecules with proinflammatory and carcinogenic properties—via lipoprotein-associated phospholipase A2 (Lp-PLA2), which is bound to Lp(a).[16,20,21] The degradation products of OxPLs are proinflammatory but typically cleared by albumin at low-to-moderate Lp(a) levels, suggesting a potential anti-inflammatory function under physiologic conditions.[21]

Kringles on apo(a) perform crucial functions. For example, KIV-10 mediates the lysine-binding properties of Lp(a),[8,9,22,23] enhancing its adherence to vascular wall cells and fibrin.[24] Other kringles, such as KIV-6 and KIV-7, contribute to pathobiological processes by interacting with scavenger receptors on foam cells.[24,25] These interactions promote the secretion of proinflammatory cytokines, including interleukin (IL)-1 and IL-6, as well as matrix metalloproteinases, which amplify local inflammation and stimulate vascular smooth muscle cell (VSMC) proliferation and early migration toward atherosclerotic lesions.[24–30]

Pathogenicity of Lp(a)

The role of Lp(a) in PAD is summarized in Table 1, which outlines the principal pathobiological mechanisms involved. These include contributions to early atherogenesis, impaired vascular repair, increased thrombotic risk, and genetic

Table 1 Integrated Mechanistic and Translational Domains of Lipoprotein(a) in Peripheral Arterial Disease

Domain	Pathobiological Mechanism	Molecular and Cellular Mediators
Atherosclerosis Initiation and Progression[26–28]	Lp(a) facilitates early atherogenesis by delivering oxidized phospholipids (OxPL) to the subendothelial space, promoting endothelial activation, monocyte adhesion, transendothelial migration, and foam cell formation. It acts synergistically with proinflammatory cytokines and matrix-degrading enzymes to destabilize plaque architecture.	OxPL, ICAM-1/VCAM-1, CD40/CD40L axis, MMP-2/9, NF-κB, and SMC phenotypic switching
Adverse Outcomes Post-Vascular Intervention[10,29]	Elevated Lp(a) levels have been implicated in unfavorable procedural outcomes due to delayed endothelial restitution, exaggerated neointimal proliferation, and sustained thrombotic potential. Its antifibrinolytic activity, stemming from apolipoprotein(a) homology to plasminogen, reduces clot resolution and promotes vascular occlusion.	Apo(a)-plasminogen competition, thrombin generation, impaired endothelial regeneration, tissue factor, and neointima formation
Genetic Architecture and Causal Risk Attribution[30,31]	Lp(a) levels are largely genetically determined by the *LPA* locus, particularly the kringle IV type 2 (KIV-2) copy number variation. Mendelian randomization studies confirm a causal link between genetically elevated Lp(a) and atherosclerotic cardiovascular disease, including PAD.	LPA gene variants, KIV-2 CNV, genome-wide association signals, and causal effect estimation models
Sex- and Ethnicity-Dependent Risk Stratification[32–35]	Sex hormones and ancestry influence Lp(a) concentrations, isoform size, and inflammatory potential. Individuals of African descent tend to exhibit higher Lp(a) levels and distinct isoform distributions. Postmenopausal women may experience greater Lp(a)-associated vascular inflammation.	Hormonal milieu, isoform heterogeneity, inflammatory biomarkers (IL-6, hsCRP), and Lp(a) molar mass

Abbreviations: AUC, area under the curve; LS, least squares; NE, not estimable.

susceptibility, considering sex and ethnic differences. By integrating clinically relevant molecular mediators, this framework highlights Lp(a) as a key prognostic biomarker and a promising therapeutic target for vascular disease.

The expanded mechanistic and clinical domains summarized in the table highlight the multifaceted role of lipoprotein(a) [Lp(a)] in peripheral arterial disease (PAD), encompassing its contributions to atherogenesis, post-intervention outcomes, genetic predisposition, and demographic variability. By integrating molecular pathways and translational insights, this framework reinforces the potential of Lp(a) as both a therapeutic target and a prognostic biomarker for vascular disease.

Role of Lp(a) in Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arterial wall that initiates with endothelial dysfunction and fatty streak formation and culminates in complex plaques with a lipid-rich core and fibrous cap that may ulcerate or rupture (Figure 3). Lp(a) contributes to plaque development via multiple mechanisms.

The atherogenic process begins with endothelial dysfunction, often triggered by reactive oxygen species, which increase endothelial permeability to lipoproteins, promoting subendothelial accumulation and leukocyte recruitment[13,16] (Figure 4a). Lp(a) can enter and accumulate within the arterial intimal[31–39] (Figure 4a) via mechanisms influenced by

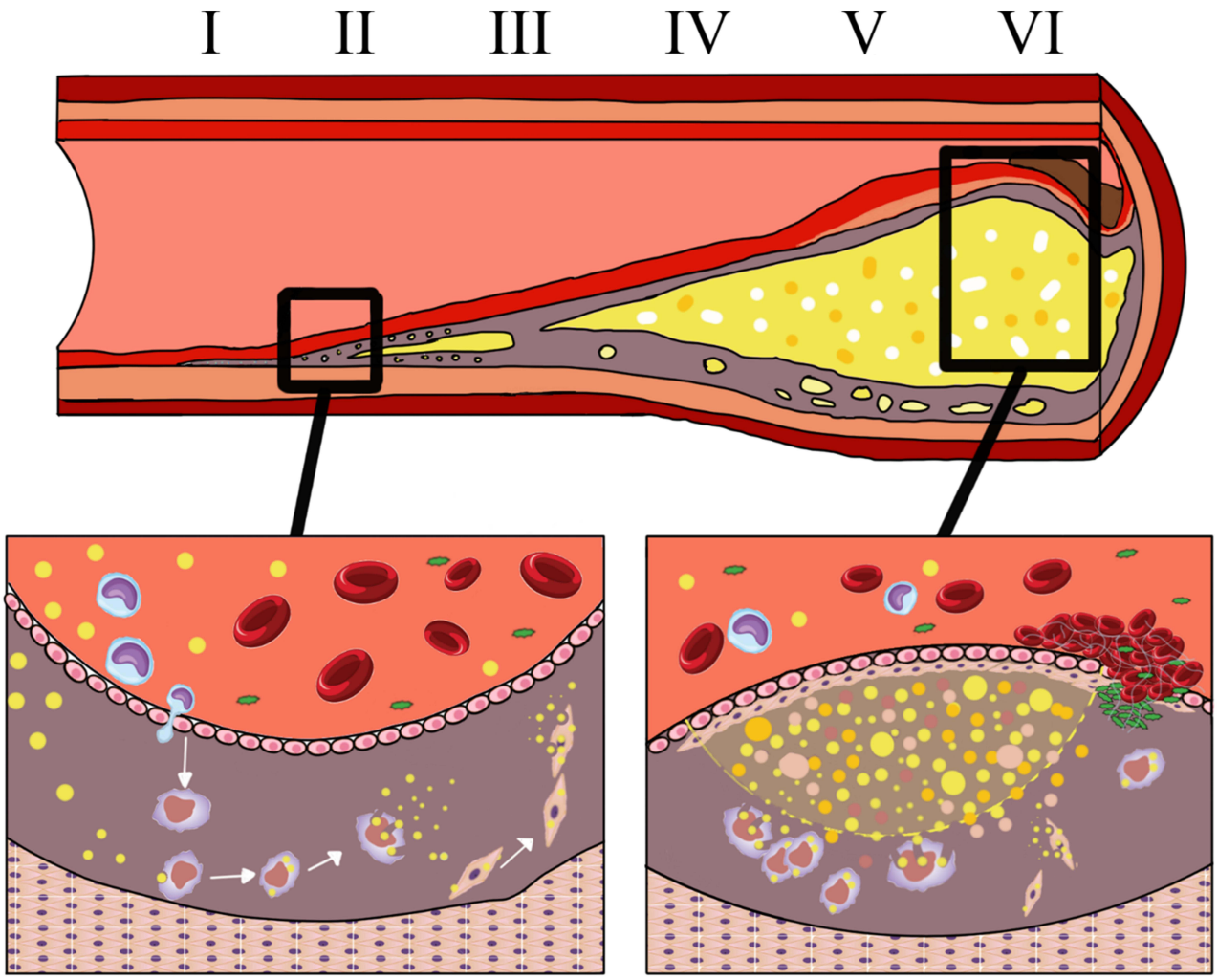

Figure 3 American Heart Association classification of atherosclerosis, illustrating representative histomorphological features across six lesion types.[36–38] Type I (initial lesion) is characterized by isolated macrophages and foam cells. Type II (fatty streak) features intracellular lipid accumulation. Type III (intermediate lesion) includes extracellular lipid pools. Type IV (atheroma) features a well-formed extracellular lipid core. Type V (fibroatheroma) contains a lipid core and fibrous cap, often with calcification. Type VI (complicated plaque) is defined by surface disruption, intraplaque hemorrhage, and luminal thrombus formation.

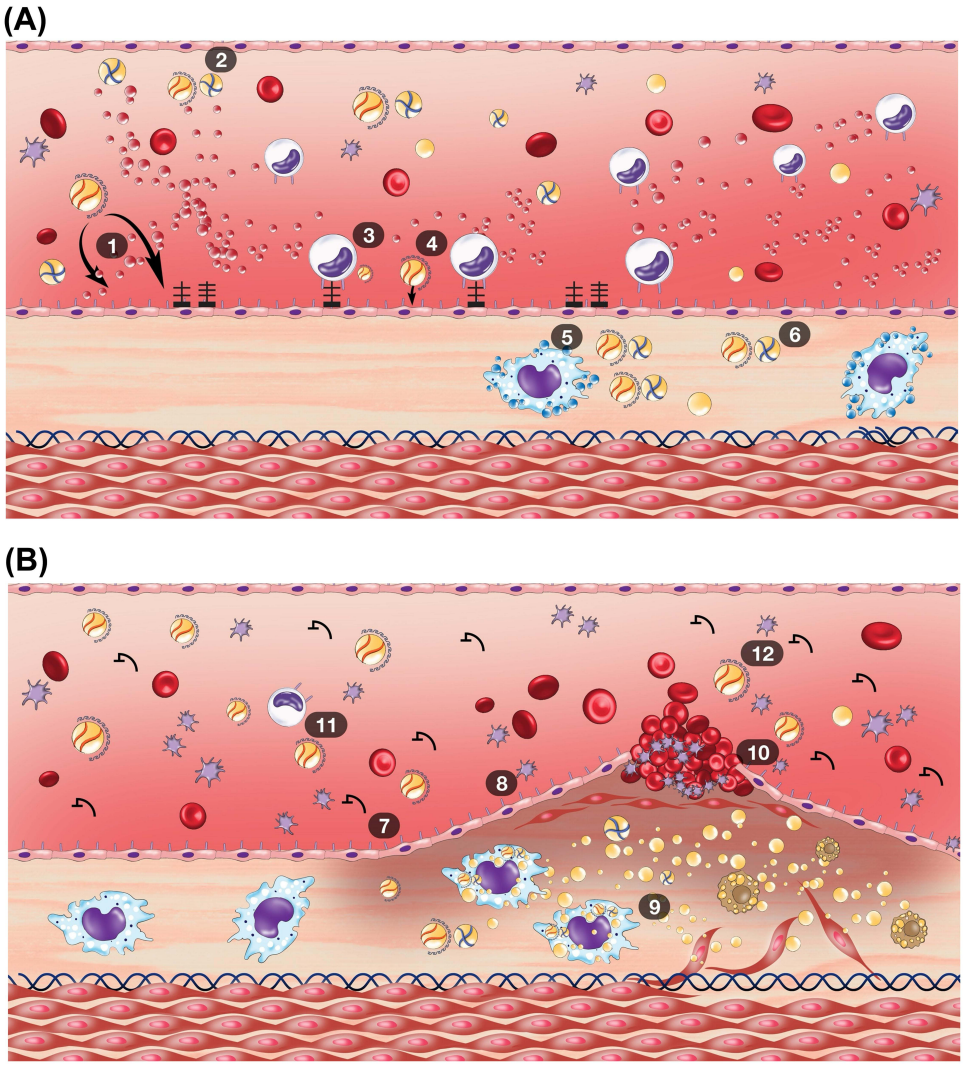

Figure 4 Pathophysiology of Lp(a) in atherogenesis. (**A**) illustrates early atherogenic events: (1) Lp(a) upregulates monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1); (2) binds oxidized phospholipids (OxPL) and MCP-1; (3) facilitates monocyte adhesion via MAC-1 and ICAM-1; (4) promotes reactive oxygen species (ROS) generation, increasing endothelial permeability; (5) induces macrophage infiltration and matrix metalloproteinase-9 (MMP-9) release, leading to collagen degradation; (6) drives the accumulation of Lp(a), OxPL, and lipids within the intima. (**B**) illustrates plaque progression and thrombotic complications: (7) vascular smooth muscle cells (VSMCs) proliferate to form a fibrous cap; (8) foam cells are formed by macrophage uptake of modified lipoproteins; (9) macrophage death contributes to necrotic core formation; (10) plaque rupture leads to thrombus formation with red blood cells, platelets, and fibrin; (11) Lp(a) upregulates tissue factor expression on monocytes; and (12) Lp(a) binds fibrinogen and impairs plasmin binding, exerting antifibrinolytic effects.

plasma concentration, particle size, blood pressure, and arterial wall permeability—distinct from receptor-mediated entry of LDL cholesterol.[40,41] Unlike other apoB-containing lipoproteins, which localize to plaques, Lp(a) distributes broadly throughout the intimal layer owing to its strong affinity for the vascular wall and interactions with proteoglycans and fibronectin on endothelial cells.[40]

Lp(a) promotes endothelial activation by upregulating adhesion molecules, including vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and P-selectin, thereby enhancing leukocyte recruitment[42,43] (Figure 4a). It also induces monocyte chemotaxis via monocyte chemoattractant protein-1 and activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, which regulates proinflammatory cytokine expression, leukocyte recruitment, and cell survival.[44] Together with β2 integrin Mac-1, Lp(a) facilitates monocyte infiltration.[45] These infiltrating monocytes and VSMC secrete cytokines such as IL-1β, IL-12, and IL-6, amplifying the inflammatory milieu.[16] Oxidized LDL and OxPLs are catabolized by macrophages, leading to foam cell formation and contributing to the necrotic lipid core.[15,16]

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Lp(a) serves as a source of free fatty acids and monoacylglycerols via lipoprotein lipase-mediated cleavage, further promoting local immune-mediated inflammation.[46] As the primary carrier of OxPLs, Lp(a) modulates this inflammation. At low levels, Lp(a) may facilitate OxPL clearance from the plasma, potentially exerting a protective effect. However, when bound to apo(a), OxPLs competitively inhibit Lp-PLA2, reducing its enzymatic activity and promoting OxPL accumulation in an autocrine manner.[16] This effect is attenuated in the absence of apo(a), highlighting its contributory role.[47]

Chronic macrophage-mediated inflammation degrades the fibrous cap, producing thin-cap fibroatheromas that are prone to rupture, thereby increasing plaque vulnerability and the risk of cardiovascular events[16] (Figure 4b). Elevated Lp(a) levels are associated with atherosclerotic plaques of complex morphology that are more susceptible to recurrent rupture and healing,[16,19] thereby accelerating disease progression. Incorporating Lp(a) into traditional cardiovascular risk algorithms has improved the prediction of future events[48–50] in both primary and secondary prevention cohorts.[15,16]

Lp(a) exerts prothrombotic and antifibrinolytic effects. Elevated levels may promote thrombosis[51] (Figure 4b) by impairing plasminogen activation, increasing TFPI levels, and potentially enhancing platelet aggregation.[52]

Given that atherosclerosis is a primary contributor to PAD,[53] elevated Lp(a) levels likely play a key role in its pathogenesis.

Role of Lp(a) in Outcomes Following Vascular Intervention

Evidence indicates that Lp(a) contributes to vascular restenosis, a major concern during postoperative surveillance following lower limb endovascular procedures. Elevated Lp(a) levels have been associated with an increased risk of vein graft stenosis after coronary artery bypass grafting,[54] and apo(a) has been detected in stenotic vein grafts, implicating Lp(a) in this complication.[55] Several studies support a relationship between circulating Lp(a) concentrations and restenosis after percutaneous transluminal coronary angioplasty (PTCA), identifying Lp(a) as an independent predictor of both restenosis risk[56–59] and the extent of restenosis.[60] However, some studies have reported no significant association between Lp(a) and restenosis post-PTCA.[61,62]

Restenosis arises from elastic recoil, thrombosis, vessel wall remodeling, inflammation, and neointimal hyperplasia.[63] A key link between Lp(a) and post-angioplasty inflammation is macrophage accumulation at the injury site.[64] Lipid-laden neointimal tissue has been observed,[65,66] and restenotic lesions 5 years after stent implantation contain cholesterol clefts, necrotic foam cells, and inflammatory cells.[67]

In primate models, thrombus and Lp(a) promoted restenosis driven by neointimal hyperplasia.[68,69] This response to vascular injury, involving all layers of the arterial wall, is characterized by VSMC proliferation.[70] Platelet-rich thrombus contributes to this process by releasing chemotactic and growth factors, such as platelet-derived growth factor, which stimulate extracellular matrix (ECM) synthesis and form a scaffold for intimal thickening.[57,68,71] Coagulation factors, including thrombin and Factor Xa, also induce VSMC mitosis in vitro.[72,73] Lp(a) indirectly exacerbates neointimal hyperplasia by promoting thrombosis and inactivating TFPI,[74] which limits post-angioplasty neointimal growth primarily by inhibiting thrombus formation.[75–77]

Importantly, Lp(a) exerts direct effects on VSMC biology. It inhibits plasminogen activation and plasmin generation, resulting in decreased active TGF-β, a regulator of VSMC migration and proliferation.[75,78] Neutralization of TGF-β permits Lp(a)-induced VSMC proliferation, suggesting a mitogenic role for the LDL moiety within Lp(a).[79] Notably, Lp(a)-positive lesions often lack overt thrombi, highlighting their thrombus-independent role in promoting neointimal growth.

Emerging strategies targeting Lp(a) may offer therapeutic benefits. In a carotid artery ligation model, a DNA vaccine targeting apo(a) reduced neointimal formation, indicating a potential role for Lp(a)-directed interventions in restenosis prevention.[80] Collectively, these data support a multifaceted contribution of Lp(a) to neointimal hyperplasia through its effects on VSMC dynamics, lipid-mediated signaling, and ECM remodeling, positioning it as a key mediator in post-intervention vascular pathology.

In addition to the established role of dyslipidemia, recent histopathological and clinical evidence has demonstrated that age and sex significantly modify the risk of carotid plaque instability. In a large observational histology-based study of 354 carotid plaques, Servadei, Scimeca, Palumbo, Oddi, Bonfiglio, Giacobbi, Menghini, Casagrande, Cardellini, Martelli, Candi, Melino, Federici, Ippoliti & Mauriello[81] reported unstable plaques in 45.2% of cases. Elevated LDL

cholesterol was the strongest predictor of plaque instability (odds ratio [OR] 2.38, 95% CI 1.49–3.81), and its destabilizing effect was magnified when combined with elevated triglycerides or remnant cholesterol, with ORs approaching 4.0. Subgroup analyses demonstrated that patients < 70 years of age with elevated LDL-C and triglyceride levels had a nearly tenfold higher risk of plaque instability (OR 9.91, 95% CI 2.6–38.4). Similarly, women with concomitant high LDL-C and triglyceride levels exhibited an almost ninefold higher risk (OR 8.92, 95% CI 1.6–48.9) than men (OR 3.54, 95% CI 1.4–9.0). These data highlight the importance of age- and sex-specific risk stratification in carotid disease, as dyslipidemia-related vulnerability is not uniform across demographic subgroups. Although Lp(a) has been implicated in graft failure after coronary bypass,[54] and apo(a) has been detected in diseased vein grafts, suggesting a possible role for Lp(a) in this complication[55]—no study has investigated its effect on lower limb bypass patency.

Lp(a) Concentration and Genetic Associations with PAD

Lp(a) Genetics and PAD

Plasma Lp(a) levels arise from the codominant expression of two *LPA* alleles located on the long arm of chromosome 6 (6q2.6–2.7), with high expression in the liver.[82–87] Most individuals express two circulating Lp(a) isoforms, which differ in apo(a) size; the smaller isoform is typically more abundant in plasma.[88–92]

Lp(a) concentration is influenced by multiple factors. Apo(a) isoform size accounts for 30–70% of the inter-individual variability.[84,93] The KIV-2 CNV, which reflects the number of KIV-2–encoding exons in *LPA*,[94] determines apo(a) isoform size: larger CNVs result in larger apo(a) isoforms.[16,87,95,96] Larger isoforms are generally associated with lower plasma Lp(a) levels, indicating an inverse relationship.[93,97] This may reflect faster maturation of smaller isoforms and isoform-dependent differences in protein folding, transport, and secretion.[16,93]

Several single-nucleotide polymorphisms (SNPs) also contribute to the Lp(a) concentration. For example, the KIV-2 4925G>A splice variant is associated with lower Lp(a) levels, even among carriers of smaller isoforms.[98] In contrast, rs10455872 is associated with higher Lp(a) levels;[99] this high-risk variant, which has an allele frequency of approximately 7%, is also linked to symptomatic and asymptomatic PAD.[100] Another Lp(a)-related SNP associated with PAD is rs7452960.[101]

Transcriptional regulation of *LPA* may further influence Lp(a) levels, although the mechanisms remain incompletely characterized.[84,93] Candidate regulatory mechanisms include upstream transcription factor-binding sites for HNF1α and HNF4α, erythrocyte transformation-specific elements within the promoter region,[84] and repression mediated by liver bile acids.[84]

Lp(a), Sex, and Ethnicity

Earlier studies examining the relationship between sex and Lp(a) levels in patients with PAD found no significant association.[6] However, data from the Multi-Ethnic Study of Atherosclerosis (MESA), which included 4,618 participants, demonstrated that women consistently exhibited higher Lp(a) levels than men did across all ethnic groups (including European, Chinese, African, and Hispanic Americans).[102] Furthermore, Lp(a) levels were higher in postmenopausal than in premenopausal women, suggesting a hormonal influence.[86]

Racial and ethnic differences affect the heritability and distribution of Lp(a). African American individuals show lower heritability of apo(a) than Caucasian individuals do, yet they tend to have the highest absolute Lp(a) levels.[103] Multiethnic cohort studies also reveal that Black Americans of African descent have higher Lp(a) levels than Hispanic, Chinese American, and White individuals.[104,105]

Certain SNPs exhibit a population-specific prevalence. For instance, the rs10455872 variant is more common in Caucasians (14.3%) than in Hispanic (5.5%) and Black (1.8%) populations.[106]

Several studies have explored the relationship between Lp(a) and PAD in different ethnic populations. A 2008 case-control study conducted in Kuala Lumpur analyzed 100 patients with PAD from Malay, Chinese, and Indian subgroups. Although elevated Lp(a) levels were associated with PAD, no differences in Lp(a) concentration or PAD risk were observed across ethnicities.[107]

In a cohort of 2,229 African American and non-Hispanic White individuals, Khawaja et al[108] reported an inverse association between Lp(a) levels and the ABPI (a common bedside measure of PAD severity), with a stronger relationship in African American participants. Moreover, African American individuals exhibited slightly lower mean ABPI than non-Hispanic White individuals (0.99 vs 1.13; P<0.01).[109]

According to the MESA study, a one-log unit increase in Lp(a) concentration was associated with an OR of 1.12 for PAD (95% CI, 1.01–1.25). The strongest associations were observed in Hispanic American men (OR, 1.73; 95% CI, 1.07–2.80) and women (OR, 1.49; 95% CI, 1.07–2.08), whereas no significant associations were noted in other ethnic groups.[102]

Research examining the intersection of Lp(a), PAD, and ethnicity is limited. Studies in African populations have reported conflicting findings regarding the association between genetic variants and elevated Lp(a) levels.[110,111] In addition, the interpretation of genetic data among African American populations is complicated by mixed ancestry, including European, Asian populations, and diverse African genetic backgrounds. Further research is warranted to elucidate the role of LPA in CAD and, by extension, PAD in African populations.[108,112–116]

Therapeutic Strategies Targeting Lp(A): Evidence from Population Studies, PCSK9 Inhibition, and Emerging Agents

Recent studies in large, contemporary cohorts from Copenhagen have illuminated a significant and consistent relationship between elevated Lp(a) levels and atherosclerotic cardiovascular disease (ASCVD). The Copenhagen City Heart Study demonstrated that individuals with extraordinarily high Lp(a) concentrations have a three- to fourfold increased risk of myocardial infarction with no apparent threshold effect. Notably, the absolute 10-year risk of myocardial infarction among high-risk men in the upper percentiles of Lp(a) approaches 35%.[117]

Similarly, findings from the Copenhagen General Population Study indicate that both elevated Lp(a) levels and pathogenic LPA genotypes are associated with a two- to three-fold increased risk of PAD, AAA, and significant limb events. The absolute 10-year risk of PAD is particularly pronounced among older smokers with Lp(a) levels at or above the 99th percentile, highlighting the urgent need for targeted preventive measures.[118]

Post-hoc analyses from the ODYSSEY OUTCOMES trial provide robust evidence that the clinical benefits of alirocumab are partially attributable to reductions in Lp(a) concentrations, independent of its effects on LDL cholesterol. In a cohort of 18,924 patients with a history of acute coronary syndrome receiving high-intensity statin therapy, alirocumab treatment was associated with a reduction in total cardiovascular events, evidenced by a hazard ratio (HR) of 0.85.[119] In addition, each 5 mg/dL decrease in Lp(a) corresponded to an estimated 2.5% additional relative reduction in cardiovascular events, highlighting the considerable therapeutic potential of lowering Lp(a), particularly among patients in the highest baseline quartile.[119]

Moreover, a prespecified analysis indicated a decrease in PAD events among patients receiving alirocumab, with an HR of 0.69.[120] In contrast, the risk of PAD in the placebo group progressively increased with higher baseline Lp(a) levels.[120] Collectively, these findings strongly support Lp(a) lowering as a clinically relevant mechanism that contributes to the advantages of PCSK9 inhibition in high-risk populations.

Pelacarsen, an antisense oligonucleotide, was evaluated in a randomized, dose-ranging Phase 2 trial involving 286 patients with established ASCVD and elevated Lp(a).[121] The results showed dose-dependent reductions in Lp(a) concentrations, ranging from approximately 35% to 80%.[121] An ongoing pivotal Phase 3 trial, Lp(a)HORIZON, aims to determine whether these reductions lead to fewer major adverse cardiovascular events.

Similarly, olpasiran, a small interfering RNA, was investigated in the OCEAN(a)-DOSE phase 2 trial.[122] Participants receiving doses of ≥ 75 mg every 12 weeks exhibited reductions in Lp(a) concentrations exceeding 95% at 36 weeks, with sustained suppression maintained for nearly 1 year during the off-treatment extension phase.[122] A subsequent phase 3 trial, OCEAN(a)-Outcomes, is currently underway to evaluate the clinical outcomes associated with olpasiran.

Muvalaplin (previously known as movalaplin) represents the first oral agent designed to inhibit the assembly of Lp(a) particles by blocking the interaction between apo(a) and B.[123] Findings from a first-in-human Phase 1 trial indicated that 14 days of oral administration resulted in placebo-adjusted reductions in Lp(a) of approximately 63–65%, with a rapid

onset of action observed within 24 h of the initial dose and an excellent tolerability profile.[123] This proof-of-concept study suggests that oral therapy may provide better accessibility than injectable alternatives.

Collectively, these findings unequivocally reinforce the imperative for ongoing research on Lp(a) as an essential therapeutic target. Effective reduction strategies must be implemented to substantially improve cardiovascular outcomes in high-risk individuals.

Discussion

Lp(a) is increasingly recognized as a key contributor to the pathogenesis of atherosclerosis, particularly in PAD.[124] Further investigation is needed to clarify its contribution to PAD, including its effects on inflammation and thrombosis.[125] This narrative review provides an updated overview of the role of Lp(a) in PAD development, progression, and outcomes following revascularization.

In clinical practice, the measurement of Lp(a) concentration is important but remains technically challenging owing to the variability in apo(a) isoform size and Lp(a) mass. Most immunoassays, such as the Denka–Seiken assay, use 5-point calibrators to correct for apo(a) isoform variability and are considered more reliable. This assay targets the KIV-2 domain and yields results independent of apo(a) size,[126] although it may overestimate the concentration at low levels and underestimate it at high levels.[127] The widely used Abbott assay yields results similar to those of the Denka–Seiken assay at lower concentrations but diverges substantially at higher levels.[128] As calibration protocols are proprietary and not disclosed by manufacturers, assay comparability remains problematic. In addition, conversion from mass to particle concentration lacks standardization and may be inappropriate in clinical risk stratification.[129,130]

Chronic limb-threatening ischemia (CLTI), the most advanced stage of PAD, is associated with a poor prognosis, including approximately 25% mortality within 1 year, 40% limb loss by 3 years, and < 30% survival at 5 years.[131,132] Patients with diabetes face worse outcomes and higher amputation risk than those without diabetes.[133,134] In the BASIL trial,[135] 26% of patients with CLTI treated with percutaneous transluminal angioplasty required reintervention within 1 year. Given the growing burden and poor prognosis of CLTI, there is a pressing need for innovative therapies to stimulate angiogenesis, including gene- and cell-based approaches.

Beyond dyslipidemia, sex-specific differences significantly influence the presentations and outcomes of CLTI. The CLIMATE Italian Registry,[136] which included 2399 patients (69.8% men), showed that women were significantly older at presentation (median 79 vs 73 years, $p<0.0001$) and more frequently aged over 75 years (63.2% vs 40.1%, $p<0.0001$). Despite having fewer comorbidities, such as diabetes (52.8% vs 61.9%, $p<0.0001$) and coronary disease (29.4% vs 43.9%, $p<0.0001$), women underwent more endovascular revascularizations (61.6% vs 55.2%, $p=0.004$) and experienced higher rates of major amputation (9.6% vs 6.9%, $p=0.024$). In contrast, men underwent more open or hybrid revascularization procedures and minor amputations. Multivariable Cox regression identified age >75 years as the strongest independent predictor of both 30-day (HR 3.63, $p=0.003$) and 1-year (HR 2.14, $p<0.0001$) mortalities, along with nephropathy (HR 1.54, $p<0.0001$), coronary disease (HR 1.26, $p=0.036$), and foot infection/necrosis (HR up to 2.04, $p<0.0001$). Despite these differences, 1-year mortality was similar between the sexes (14.9% in women vs 12.8% in men, $p=0.167$), suggesting that older age at onset in women offsets their more favorable comorbidity profile. These findings underscore the importance of integrating sex-specific considerations into the management strategies for CLTI.

The management of elevated Lp(a) levels in patients with PAD has evolved substantially. Exercise enhances perfusion and vascular function, and smoking cessation reduces vascular injury. Diets rich in fruits, vegetables, and whole grains may slow down plaque development. Novel therapies targeting Lp(a), including RNA-based agents, show promise in lowering Lp(a) concentrations and reducing cardiovascular risk in this high-risk population.[137]

Conclusion

PAD is a complex manifestation of systemic atherosclerosis that predominantly affects the lower extremity vasculature. Among the emerging biomarkers, Lp(a) has garnered increasing attention for its role in PAD initiation and progression. Owing to its proatherogenic, proinflammatory, and prothrombotic properties, Lp(a) promotes lipid accumulation and arterial wall remodeling, thereby accelerating vascular occlusion and calcific plaque formation. Elevated Lp(a) levels highlight its potential as a therapeutic target for cardiovascular diseases.

When combined with the standard management of cardiovascular risk factors, including hypertension, dyslipidemia, and diabetes mellitus, Lp(a)-lowering strategies may provide an additional approach to slow disease progression and improve clinical outcomes. Early identification of at-risk patients can guide timely interventions, helping to prevent disease progression and identify patients who require close surveillance pre- and post-revascularization. This approach requires integrated pharmacological and lifestyle strategies to support long-term vascular protection and limb preservation.

This review outlines the multifaceted role of Lp(a) in PAD and emphasizes its influence on disease progression and post-intervention outcomes. Further research is needed to clarify the mechanisms through which Lp(a) promotes vascular injury and to refine therapeutic strategies. Lp(a) serves as both a risk biomarker and a potential therapeutic target, offering new opportunities for the precision management of patients with PAD.

Abbreviations

PAD, peripheral arterial disease; Lp(a), lipoprotein(a); CVD, cardiovascular disease; LDL, low-density lipoprotein; ABPI, ankle–brachial pressure index; T2DM, type 2 diabetes mellitus; VSMC, vascular smooth muscle cell; OxPL, oxidized phospholipids; TFPI, tissue factor pathway inhibitor; ECM, extracellular matrix; SMC, smooth muscle cell; IL, interleukin; CNV, copy number variation; SNP, single nucleotide polymorphism; MESA, Multi-Ethnic Study of Atherosclerosis; ASCVD, atherosclerotic cardiovascular disease; CLTI, chronic limb-threatening ischemia.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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