Korean Circ J. 2026 Apr;56(4):289-300
https://doi.org/10.4070/kcj.2025.0380
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

State of the Art Review

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The Emerging Lipid Risk: Lipoprotein(a)

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OPEN ACCESS

Received: Sep 4, 2025
Revised: Sep 9, 2025
Accepted: Sep 10, 2025
Published online: Oct 20, 2025

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Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

AUTHOR'S SUMMARY

Lipoprotein(a) (Lp(a)) has recently attracted attention as a cardiovascular risk factor. Causal relationships between Lp(a) and atherosclerotic cardiovascular disease and aortic stenosis have been consistently reported. Although pathogenetic mechanisms are not sufficiently understood, effects of Lp(a) on vascular cells, thrombosis, and valve calcification have been suggested. Several new therapeutics specifically targeting Lp(a) are being tested in clinical trials. The results of those trials will determine whether these agents can be used for cardiovascular prevention.

ABSTRACT

Based on epidemiological and genetic studies in recent decades, lipoprotein(a) (Lp(a)) has been accepted as a causal risk factor for atherosclerotic cardiovascular disease and aortic stenosis. Although inter-ethnic differences exist, Lp(a) level ≥50 mg/dL is commonly reported to indicate elevated cardiovascular risk. Blood Lp(a) levels are largely determined based on genetic background, and the kringle IV type 2 repeat variant is a major factor. Lp(a) is structurally similar to low-density lipoprotein (LDL) but also contains apolipoprotein(a) (apo(a)), which includes kringle domains associated with diverse effects depending on particles and individuals. The LDL-like property of Lp(a) and effect of apo(a) on vascular cells can promote atherosclerosis. Apo(a) competes with plasminogen and can inhibit the role of plasmin during fibrinolysis. Furthermore, oxidized phospholipids on apo(a) may induce oxidative stress to enhance atherosclerosis and can affect valve calcification. Trials on new therapeutics targeting Lp(a) RNA, including antisense oligonucleotide (e.g., pelacarsen), siRNAs (e.g., olpasiran, lepodisiran, and zerlasiran), and small molecules (e.g., muvalaplin), are under way. Depending on the study or dose, these agents lowered Lp(a) levels by 80–100% compared with the control; however, results of clinical outcomes have yet to be reported.

Keywords: Preventive medicine; Coronary artery disease; Lipids; Pharmacology

Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions
Conceptualization: Lee SH, Han KH; Methodology: Lee SH, Han KH; Writing - original draft: Lee SH, Han KH; Writing - review & editing: Lee SH, Han KH.

INTRODUCTION

Lipoprotein(a) (Lp(a)) is structurally similar to low-density lipoprotein (LDL), a core risk factor for cardiovascular disease, but includes an additional apoprotein, apolipoprotein(a) (apo(a)). Furthermore, Lp(a) has numerous oxidized phospholipids (OxPLs) that supposedly contribute to promotion of atherosclerosis.[1)2)] Blood Lp(a) levels typically show non-normal distribution in the general population.[2)] In several studies, including a large European study,[3)] the effects of Lp(a) levels on cardiovascular outcomes were reported. Lp(a) was first reported in Norway in 1963,[4)] and the gene that encodes Lp(a) was identified in 1987.[5)] In the late 2000s, the number of kringle IV type 2 (KIV-2) repeats and single nucleotide polymorphisms (SNPs) on the *LPA* locus were investigated in genetic studies. The results of these studies demonstrated Lp(a) as a risk factor with a causal relationship with coronary artery disease.[3)6)]

After the effects of Lp(a) on cardiovascular risk were established, major academic societies officially acknowledged the value of Lp(a) measurement. They considered that combining Lp(a) levels with cardiovascular risk assessment would prevent underestimation of atherosclerotic cardiovascular disease (ASCVD) risk and enhance personalized treatment.[7)] The American College of Cardiology and American Heart Association recommend Lp(a) measurement in individuals with family history of premature ASCVD.[8)] The European Society of Cardiology and European Atherosclerosis Society recommend Lp(a) measurement at least once in a lifetime.[2)] Because specific Lp(a)-targeting drugs are not yet available, lifestyle modification and aggressive pharmacological therapy for other risk factors are advised to individuals at high cardiovascular risk due to high Lp(a) levels.[2)]

EPIDEMIOLOGY

An association between blood Lp(a) levels and cardiovascular risk has been reported. Levels >30 mg/dL are commonly regarded as risk enhancer, and 100–125 nmol/L (or 50 mg/dL) are considered clearly elevated. Among general population, 20–30% supposedly have elevated Lp(a) levels, with females having Lp(a) levels 5–10% higher than males.[9)10)]

Blood Lp(a) levels are largely (approximately 90%) determined by genetic factors and levels differ by ethnicity: higher in Africans and South Asians and lower in East Asians and Europeans. Compared to 7 other ethnicities, the lowest median Lp(a) level of 7.8 mg/dL was observed in a Chinese population.[11)] Thus, different cut-off levels may be needed for different ethnic groups. A blood Lp(a) level between 30% and 70% is affected by KIV repeat polymorphism.[9)] As much as 70% of the *LPA* gene is encoded by the hypervariable KIV-2 repeat. In addition, more than 500 variants have been found in the hypervariable KIV-2 repeat and can affect cardiovascular risk. Asians have a higher prevalence of alleles with more frequent KIV-2 repeats and generally show larger apo(a) isoforms.[12)] Furthermore, several single nucleotide variants associated with higher Lp(a) levels are less frequent in East Asians. Consequently, the median Lp(a) level is lower in the East Asian population. However, higher Lp(a) levels are still associated with a greater risk of ASCVD in Asians.[12)]

https://doi.org/10.4070/kcj.2025.0380

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RELATIONSHIP BETWEEN LIPOPROTEIN(A) AND CARDIOVASCULAR RISK: CLINICAL AND GENETIC STUDIES

Associations between Lp(a) levels and coronary and peripheral artery diseases, heart failure, aortic valve disease, and ischemic stroke have been reported.[10] Lp(a) levels ≥75% were associated with increased myocardial infarction and aortic stenosis and levels >90% with heart failure (**Figure 1**).[9] The relationship between Lp(a) levels and clinical outcomes is less consistent in terms of secondary cardiovascular prevention. In a meta-analysis, although recurrence of cardiovascular events was higher when Lp(a) levels were ≥80%, the recurrence was not the same in the group with relatively low LDL-cholesterol (LDL-C) levels.[13] However, the association between Lp(a) levels and cardiovascular risk was independent of LDL-C levels.[14] Furthermore, the effect of Lp(a) on coronary artery disease in patients with familial hypercholesterolemia was reported in a Mendelian randomization study.[10]

The *LPA* locus has been associated with aortic stenosis.[15] The risk of aortic valve calcification was increased, and progression of stenosis faster when Lp(a) was high.[16] Both Lp(a) and the *LPA* genotype were associated with non-cardioembolic stroke. However, the association between Lp(a) and stroke was not observed in some subgroups.[17]

Genetic investigations, including Mendelian randomization studies, have found extensive evidence on the causal relationship between high Lp(a) levels and ASCVD or aortic stenosis.[3] Variants associated with high Lp(a) levels are more common in individuals with cardiovascular events. Rare loss-of-function or common variants in KIV-2 regions were related with significantly low Lp(a) levels and showed cardioprotective effects.[18] Conversely, a minimal association was found between high Lp(a) levels and thrombosis risk, and a causal relationship was not found in Mendelian randomization studies.[19]

Epidemiological and genetic data on Lp(a) and ASCVD risk in Asians, including Koreans, are consistent. A Korean cohort including >270,000 individuals mainly screened for primary prevention was analyzed. In the study, subjects with Lp(a) levels ≥50 mg/dL had 83% higher cardiovascular mortality and 20% higher total mortality than individuals with Lp(a) levels <50 mg/dL.[20] These results are concordant with other ethnicities. Conversely, in a single center study from Korea, significant association was not found between Lp(a) levels and incident 3-point major adverse cardiovascular events (MACEs) in patients with acute myocardial infarction.[21] However, in another Korean single-center study with >12,000 patients undergoing percutaneous coronary intervention, an association between Lp(a) levels >30 mg/dL and cardiovascular events was identified.[22] Taken together, these findings indicate that Lp(a) level ≥50 mg/dL generally indicates elevated cardiovascular risk. In a Chinese cohort including >8,000 individuals, the group with the highest Lp(a) tertile showed 34% higher stroke risk than the group with the lowest tertile.[23] However, the association between Lp(a) and stroke is weaker than that between Lp(a) and coronary artery disease. Therefore, further studies are needed in Asian populations.

STRUCTURE

Lp(a) has a diameter 25 nm and density 1.05–1.12 g/mL and is similar to the cholesterol-rich LDL particle (free cholesterol 8% and cholesterol ester 35%), though it also contains 2–3% triglycerides. While LDL has a single protein component (apolipoprotein B100 [apoB100]),

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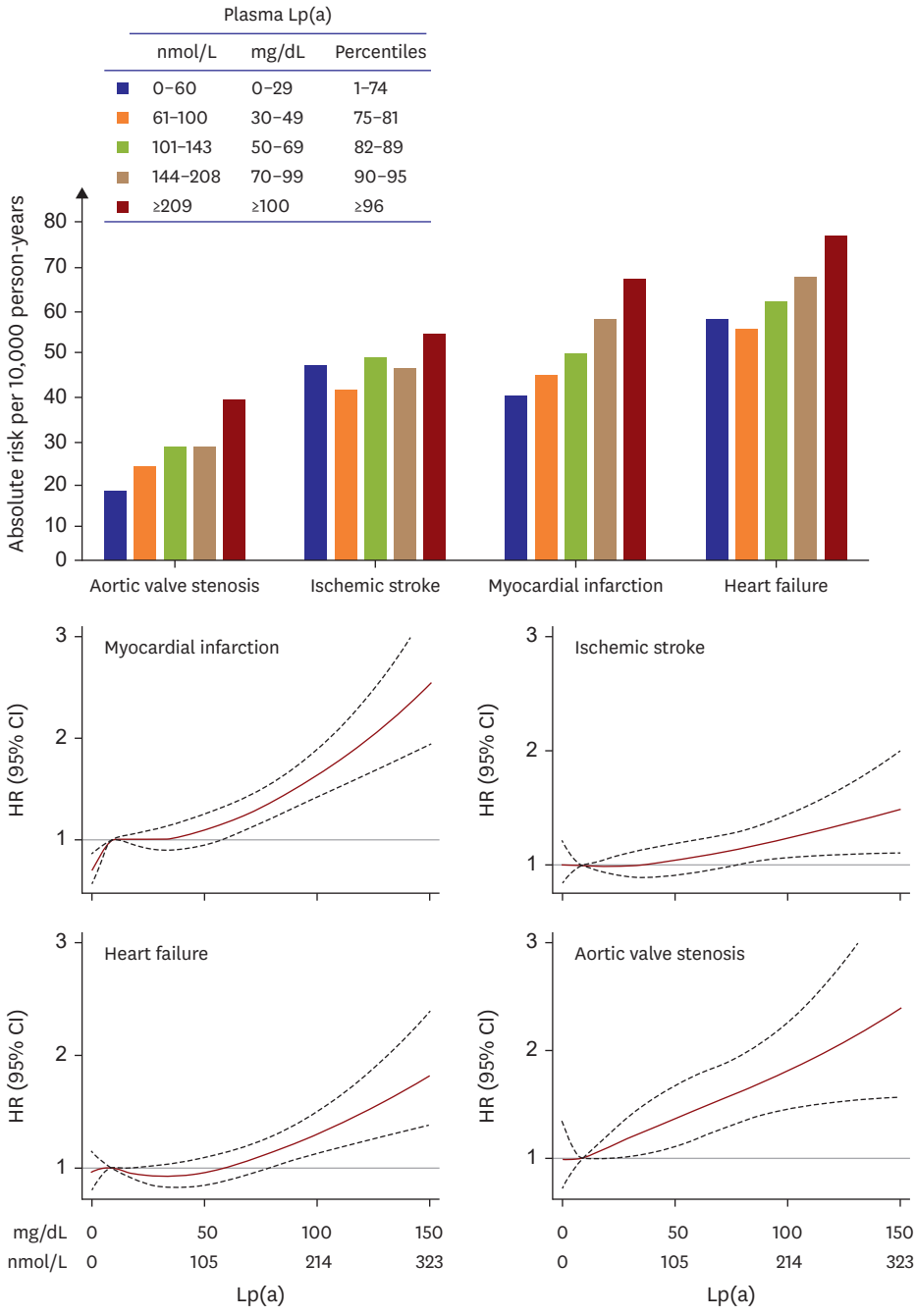

Figure 1. Lp(a) levels and cardiovascular risk. Absolute and relative risk of aortic stenosis, ischemic stroke, myocardial infarction, and heart failure based on blood Lp(a) levels. The top panel shows the absolute risk/10,000 person-years, and the lower panel shows HRs with 95% CIs. When the lower 95% CI no longer overlapped the reference value of 1.0 for the median Lp(a) level, risk was significantly elevated based on data from 70,286 individuals in the Copenhagen General Population Study. From Kronenberg et al.[9] with permission.
CI = confidence interval; HR = hazard ratio; Lp(a) = lipoprotein(a).

Lp(a) has an additional single copy of glycoprotein apo(a) tethered to apoB100 (**Figure 2**). In each Lp(a) particle, an average 88% of the protein mass is the apoB100-apo(a) complex and >30 other proteins are known to associate on the surface.[24][25] Binding between apo(a) and apoB100 is completed in 2 steps: noncovalent docking of KIV-5–8 domains to

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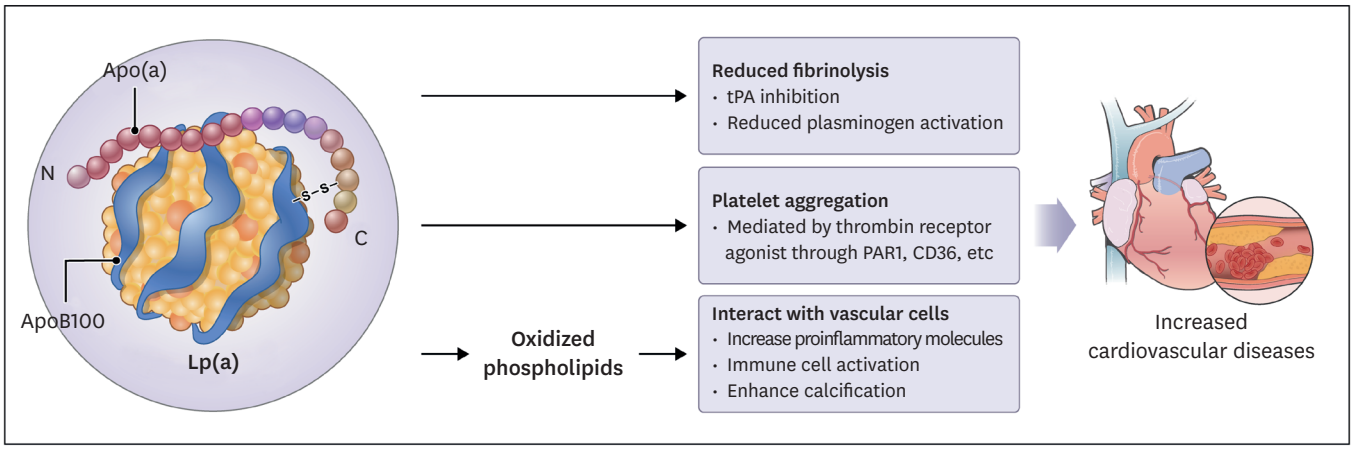

Figure 2. Lp(a) structure and pathogenic mechanisms in cardiovascular diseases. Lp(a) is a carrier of OxPLs and has a cholesterol-risk core and surrounding apoB100 bound to apo(a). Apo(a) contains a chain of kringle domains. Lp(a) increases the production of plasminogen activator inhibitor 1, inhibiting the conversion of plasminogen to plasmin. OxPLs interact with several vascular cells and enhance inflammation. Interaction with smooth muscle cells can lead to calcification. Lipids may activate platelet aggregation.
Apo(a) = apolipoprotein(a); apoB100 = apolipoprotein B100; Lp(a) = lipoprotein(a); OxPL = oxidized phospholipid; tPA = tissue-type plasminogen activator.

the N-terminus of apoB100 and a disulfide bond between Cys1568 in the KIV-9 domain and Cys3734 or Cys4326 in apoB100.[26)27)] The binding sites are similar to those of apoB100 to the LDL receptor (LDLR), which could explain why Lp(a) may not be cleared efficiently through LDLR.[28)] The apo(a) gene (*LPA* [MIM 152200; ENSG00000198670]) is located on the long arm of chromosome 6 (6q26-27) and shows high proximity with the plasminogen gene (*PLG*). Overall, the human *LPA* gene has 94% homology to the *PLG* gene, and the *LPA* gene is thought to be duplicated and evolved from the *PLG* gene approximately 40 million years ago.[5)29)] *PLG* has 5 kringle structures (KI–KV) and a trypsin-like protease domain. Apo(a) does not have KI–KIII and has a maximum of 10 KIV domain types and a KV domain followed by a protease domain. The KIV-2 domain shows multiallelic (1 to >40 copies) intragenic copy number variation (CNV; i.e., KIV-2 CNV), which results in high size heterogeneity (between 300 and 800 kDa; the size varies due to glycosylation) in apo(a) polymorphism. Currently, 34 isoforms of apo(a) have been reported. A protease domain of apo(a) shows >90% homology to *PLG* but cannot be cleaved by plasminogen activators and does not retain protease activity.[30)31)] Individual Lp(a) level is largely determined by genetic background (70–90%). The APOE e3 allele is associated with lower Lp(a) levels and contributes 0.5% of Lp(a) concentration. APOH encoding beta2-glycoprotein1 may also affect Lp(a) levels through binding to apo(a) KIV-2.[32)33)] Conversely, acute conditions (e.g., acute coronary syndrome) elevate Lp(a) level, indicating Lp(a) is an acute phase reactant. The existence of several interleukin (IL)-6-responsive elements in the promoter region of the *LPA* gene may partly explain such phenomenon. However, increased Lp(a) level is not induced by other potential pro-inflammatory mediators. IL-2, IL-8, and hepatocyte growth factor do not change and transforming growth factor (TGF)-beta1 or tumor necrosis factor-alpha even reduce Lp(a) levels.[34-36)]

PATHOGENICITY FOR CARDIOVASCULAR DISEASES: INFLAMMATION AND THROMBOSIS

Because Lp(a) retains apoB-associated LDL-like lipoprotein, Lp(a) has atherogenic properties of LDL particles, which have been extensively studied. Patients with familial

hypercholesterolemia may show relatively higher serum Lp(a) levels (approximately 10–15%). Conversely, extremely elevated Lp(a) levels also account for the majority of the measured high LDL-C levels in familial hypercholesterolemia. However, the effects of Lp(a) levels on premature ASCVD appear weaker than those of LDL levels in general, likely due to a relatively lower concentration of Lp(a).[37-39]

In addition, the associated apo(a) may cause several pathological processes. Several lysine binding sites exist in KIV. Lysine binding sites in the KIV-10 domain are relatively strong, while binding sites in KIV-5–8 domains are weak and may interact and bind various components of the vascular wall and extracellular matrix (fibrin, fibronectin, glycosaminoglycans, proteoglycans, and neural crest epidermal growth factor-like proteins such as DANCE, also known as FIBULIN 5 (FBLN5); DANCE/FNLN5 may also interact with KIV-2 central nervous system.[40-42] Lysine binding sites in apo(a) interact with macrophages, endothelial cells, smooth muscle cells, fibroblasts, and platelets, which may be enhanced by neutrophil-derived defensins.[43] These properties may facilitate wound healing and tissue repair but also could accumulate those substances and Lp(a) particles within the arterial wall and aggravate atherosclerosis. Although apo(a) has high homology with plasminogen in KIV, KV, and the protease domain, the serine protease-like domain of apo(a) cannot be activated by tissue-type plasminogen activator (tPA) due to evolutionary mutation on the cleavage site and apo(a) lacks fibrinolytic activity. However, similar to plasminogen, a strong lysine binding site in the KIV-10 domain non-covalently binds fibrin, indicating that apo(a) in Lp(a) and plasminogen can compete for tPA and may hamper the role of plasmin in the process of fibrinolysis.[44][45] Notably, Lp(a) shows both pro- and anti-aggregatory platelet effects. Approximately 70–700 Lp(a) molecules can bind per platelet through a lysin-binding pocket on the KIV-10 domain. Lp(a)-stimulated pro-aggregatory platelet effects can be mediated by thrombin receptor agonist (e.g., peptide SFLLRN) through platelet PAR1, CD36, neutrophil extracellular trap, and arachidonic acid. Conversely, anti-aggregatory effects are exerted through functional inhibition of collagen, fibroblast activation protein (PAF), and alpha-IIb-beta integrin. Numerous pro-aggregatory effects possibly result from associated OxPLs and TXA2-mediated platelet aggregation experimentally induced by a recombinant apo(a), 17K-apo(a). However, a detailed mechanism remains largely unknown, especially whether apo(a) might be directly involved in the phenomenon. Conversely, the inhibitory effect of Lp(a) on PAF-induced platelet aggregation was consistently observed even after apo(a) was washed off, indicating a role of PAFAH on an apo(a)-free Lp(a) particle.[46] Among kringles on apo(a), domains such as KIV-10, KIV-7, and KIV-8 may interact with scavenger receptors expressed on macrophages, which may provoke pro-inflammatory responses required for atherogenesis.[47] In general, disulfide bonds and lysine binding conform to the shape of apo(a) on the surface of LDL-like particles. The bulk of apo(a) is extended from the surface and the floating N-terminal tail side, especially in the KIV-10 domain, which may potentially interact with unveiled ligands.[48]

Furthermore, apo(a) carries OxPLs, and the atherogenic property of the Lp(a) particle stems from the associated OxPLs as well as from LDL-like particles. Notably, oxidative stress elicited by both is the primary contributor to the atherogenic process. Therefore, the detailed mechanism by which Lp(a) initiates and facilitates the process of atherosclerosis will not be discussed any further in this review. Recently, interest has focused on the role of Lp(a) on the development of calcific aortic valve disease (CAVD). In a genetic study, Lp(a)-raising variants including SNPs (such as rs10455872) elevated CAVD risk by 20–40%.[49][50] OxPLs, covalently linked to the KIV-10 domain in apo(a), and ectonucleotide pyrophosphatase/

https://doi.org/10.4070/kcj.2025.0380

phosphodiesterase family member 2 (ENPP2; also known as autotaxin) are delivered to the aortic valve, most notably to CD44-high valvular interstitial cells (VICs). Then, OxPLs are transformed into lysophosphatidic acid (LysoPA) by ENPP2, to induce mineralization through activation of the LysoPA receptor 1/NF-kappa/bone morphogenic 2 (BMP2) protein signaling pathway. The other processes related to valvular calcification, such as TGF-1beta (induces fibrosis, collagen synthesis, and smooth muscle cell regulation), downstream of BMP2 (ENPP1 and alkaline phosphatase-mediated phosphate synthesis), WNT, and NOTCH/RUNX2 (transformation of VIC to osteoblast-like cells), may be minimally affected by Lp(a). Collectively, Lp(a) may facilitate calcification of the aortic valve at an earlier stage.[51] The late stage of valvular calcification mimics the process of atherosclerosis, and numerous immune and inflammatory cells and mediators play a role, all of which can also be exacerbated by OxPLs and their derivatives. OxPLs can bind either apo(a) or the phospholipid shell on any type of apoB-containing lipoproteins; however, Lp(a) carries 85% of OxPLs in plasma.

The origin of OxPLs bound to Lp(a) remains questionable. The results of in vitro assays indicated OxPLs are incorporated during the synthesis of Lp(a). Conversely, Lp(a) may accumulate OxPLs in inflammatory foci (e.g., atheroma). Recently, the functional relevance of phospholipase A2 (PLA2) has attracted increased attention. PLA2 is present in soluble and lipoprotein-associated (Lp-PLA2) forms. The Lp-PLA2 amount in Lp(a) was 2-fold higher than in LDL or high-density lipoprotein particles. In the presence of Lp-PLA2, OxPLs in Lp(a) were hydrolyzed to lysophosphatidylcholine, released from Lp(a), and bound and inactivated by albumin in circulation. Small-sized apo(a) is associated with higher risk of ASCVD and shows lower catalytic activity of the associated Lp-PLA2. Therefore, Lp(a) with smaller apo(a) isoforms possibly contains more OxPLs without hydrolysis and can deliver OxPLs to atheromas and accelerate the process of atherosclerosis.[52]

NEW PHARMACOLOGICAL AGENTS TARGETING LIPOPROTEIN(A)

Currently, RNA-targeted therapy includes antisense oligonucleotides (ASOs) and siRNAs. An ASO is a single-stranded nucleic acid that binds target mRNA to inhibit translation and protein synthesis. siRNA is double-stranded RNA that assembles a silencing complex that blocks translation and protein production after removing one strand. ASOs are usually administered once monthly, whereas siRNAs are used 2–4 times yearly by subcutaneous injection (**Figure 3**).[53]

Pelacarsen, a subcutaneously administered ASO targeting Lp(a), has been developed by Novartis and Ionis Pharmaceuticals. Pelacarsen inhibited apo(a) synthesis and dose-dependently lowered Lp(a) levels up to 80% in phase 2 clinical trials with acceptable safety.[54] A large phase 3 outcome trial, Lp(a) HORIZON, is currently ongoing and scheduled to be completed by early 2026. In the trial, the effects of pelacarsen on MACE risk in patients with cardiovascular disease and Lp(a) levels ≥70 mg/dL are investigated.[55] In addition, Lp(a) FRONTIERS CAVS is a phase 2 trial planned to be finalized in 2029, in which the effects of pelacarsen on the progression of calcific aortic stenosis are assessed.[56]

Olpasiran, a subcutaneously administered siRNA, was developed by Amgen and Arrowhead Pharmaceuticals. In a phase 2 trial, olpasiran lowered Lp(a) levels by up to 101% and LDL-C by 23–25% compared with the control.[57] OCEAN(a)-Outcomes, a phase 3 trial, enrolled

https://doi.org/10.4070/kcj.2025.0380

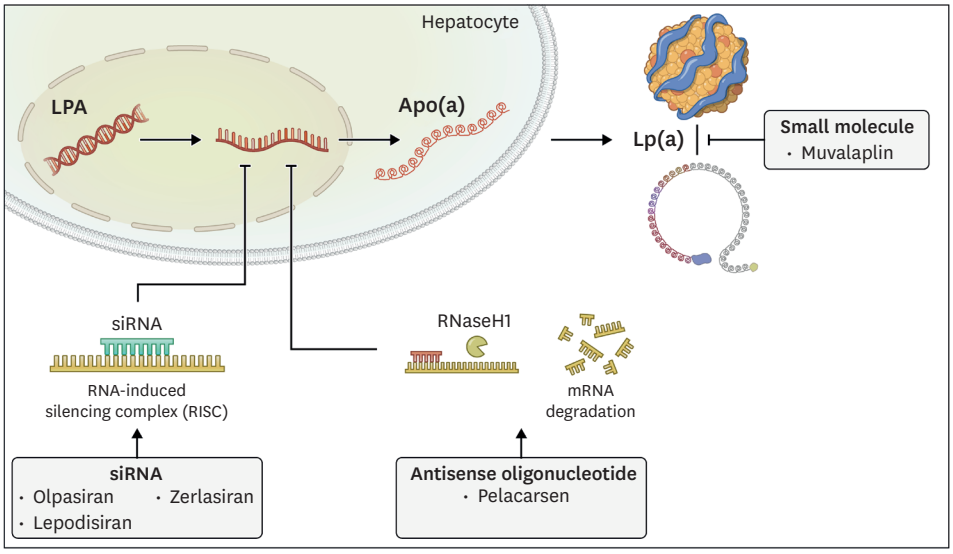

Figure 3. Novel therapeutics specifically targeting Lp(a). Several agents have been developed to degrade Lp(a) mRNA and decrease apo(a) synthesis or inhibit binding of apo(a) to apoB. Pelacarsen, an antisense oligonucleotide, degrades Lp(a) mRNA by activation of ribonuclease III. Olpasiran, lepodisiran, and zerlasiran are siRNAs that degrade mRNA transcripts by RNA-induced silencing complex. Muvalaplin is a small molecule that inhibits Lp(a) synthesis by blocking the formation of a disulfide bond between Lp(a) and apoB.
Apo(a) = apolipoprotein(a); apoB = apolipoprotein B; Lp(a) = lipoprotein(a).

approximately 7,000 patients undergoing coronary revascularization or vascular events and with Lp(a) levels ≥200 nmol/L (80 mg/dL) and is scheduled to be finished in late 2026.[56] Lepodisiran was developed by Eli Lilly and Dicerna Pharmaceuticals, and the phase 1 trial showed a median Lp(a) reduction of 97% at its maximum dose.[58] A phase 3 trial included >12,000 patients with cardiovascular disease, familial hypercholesterolemia, or high cardiovascular risk and with Lp(a) levels ≥175 nnol/L. This trial is ongoing and scheduled to be completed in March 2029.[56] In addition, zerlasiran was developed by Silence Therapeutics and showed to reduce Lp(a) by up to 96% compared with the control in a phase 2 trial.[59]

Muvalaplin, a small molecule developed by Eli Lilly, inhibits non-covalent binding of apo(a) and apoB and interferes with formation of a functioning Lp(a) particle. This agent lowered Lp(a) by up to 86% compared with placebo.[60] Clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein-9 (Cas9) is an in vivo genome-editing technique and cleaves target genes. Based on this technique, adeno-associated virus vector delivery of CRISPR-Cas9 disrupted the *LPA* transgene in the liver in a mouse model.[61]

CONTROVERSIES AND UNSOLVED QUESTIONS

Diverse hepatic receptors, including LDLR, could hypothetically remove Lp(a) in specific metabolic conditions. However, mechanisms promoting Lp(a) clearing remain uncertain.[62] Lack of a standardized assay for measuring Lp(a) is problematic in clinical practice as well as in research on this lipoprotein. There are several isoforms based on KIV-2 repeats of apo(a), and this structural variability can cause bias during Lp(a) measurement. A small isoform may be underestimated due to fewer antibody binding sites; however, a larger isoform can be overestimated. Furthermore, calibration bias can affect assay results because most assays use calibrators rich in small isoforms. Lp(a) levels can be presented in 2 ways: mass

https://doi.org/10.4070/kcj.2025.0380

concentration (mg/dL) and particle concentration (nmol/L). However, due to the inaccuracy in the conversion factor, directly converting between mg/dL and nmol/L is not desirable because small and large isoforms have different molecular weights and a high possibility of errors during calibration.[63]

In Mendelian randomization studies, decreasing Lp(a) levels by 66 mg/dL or more was shown to reduce coronary artery disease risk.[64] In a study including a secondary prevention cohort, cardiovascular risk was predicted to be decreased by approximately 20% when Lp(a) level was lowered by 50 mg/dL.[14] Thus, the effect of pharmacological Lp(a) lowering on cardiovascular outcomes could be limited if an individual is at high risk of vascular disease when Lp(a) is mildly elevated. Furthermore, an association between low Lp(a) levels and bleeding risk was observed in a Chinese study,[65] and long-term data on side effects after a significant decrease in Lp(a) levels are needed to establish therapeutic safety. Based on epidemiological and genetics studies, a causal relationship between Lp(a) levels and aortic valve stenosis is reasonable. However, it is unclear whether Lp(a) lowering therapy can attenuate aortic valve stenosis progression. Because there are no definite pharmacological measures in aortic stenosis, the significance of lowering Lp(a) levels in this field should be further investigated.

CONCLUSION

Lp(a) has been established as a causal factor for cardiovascular pathologies including ASCVD and aortic stenosis. Blood Lp(a) level is substantially affected by genetic background and ethnicity. Lp(a) influences vascular cells and platelets, and mechanisms underlying promotion of atherosclerosis and valve calcification have begun to be elucidated. Limitations remain in measurement standardization, and clinical outcome benefits of Lp(a)-lowering therapeutics are unavailable. However, the results of several clinical trials on new drugs targeting Lp(a) may be published in a few years to answer questions regarding Lp(a) in the field of cardiovascular prevention.

ACKNOWLEDGMENTS

Medical illustration & Design (MID), a member of the Medical Research Support Services of Yonsei University College of Medicine, provided excellent support with medical illustration.

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