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A Position Paper on Lipoprotein(a) From the Lipoprotein(a) Task Force of the Korean Society of Lipid and Atherosclerosis: Current Evidence, Clinical Applications, and Future Directions

Youngwoo Jang, MD, PhD[1], Jang Hoon Lee, MD, PhD[2], Sang-Guk Lee, MD, PhD[3], Hun Jee Choe, MD, PhD[4], Sang Min Park, MD, PhD[5], In-Kyung Jeong, MD, PhD[6], Byung Jin Kim, MD, PhD[7], and on behalf of the Lipoprotein(a) Task Force of the Korea Society of Lipid and Atherosclerosis

[1]Division of Cardiology, Department of Internal Medicine, Gachon University Gil Medical Center, Gachon University College of Medicine, Incheon, Korea
[2]Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[3]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea
[5]Department of Cardiology, Nowon Eulji Medical Center, Eulji University, Seoul, Korea
[6]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea
[7]Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

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Correspondence to
Byung Jin Kim, MD, PhD
Division of Cardiology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29, Saemunan-ro, Jongno-gu, Seoul 03181, Korea.
Email: bjjake.kim@samsung.com

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ORCID iDs
Youngwoo Jang
https://orcid.org/0000-0002-8802-268X
Jang Hoon Lee
https://orcid.org/0000-0002-7101-0236
Sang-Guk Lee
https://orcid.org/0000-0003-3862-3660
Hun Jee Choe
https://orcid.org/0000-0001-5318-0859
Sang Min Park
https://orcid.org/0000-0001-6521-303X

AUTHOR'S SUMMARY

Elevated lipoprotein(a) (Lp[a]) is increasingly recognized as an independent cardiovascular risk factor, yet awareness, standardized measurement, and treatment strategies remain limited in Korea. This position paper from the Lipoprotein(a) Task Force of the Korean Society of Lipid and Atherosclerosis highlights unmet needs in screening, summarizes Korean epidemiologic and clinical evidence, and reviews current and emerging therapies. By contextualizing global advances within the Korean healthcare system, this work provides guidance for clinicians and underscores the need for future research and therapeutic development to reduce the burden of Lp(a)-related cardiovascular disease.

ABSTRACT

Lipoprotein(a) [Lp(a)] is a genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis (CAVS), with plasma levels largely unaffected by lifestyle modification or conventional lipid-lowering therapy. Although international guidelines increasingly recognize Lp(a) as a risk-enhancing factor, in many Asian populations thresholds for high Lp(a) and treatment strategies remain undefined. This Korean position paper, developed by the Lp(a) Task Force of the Korean Society of

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In-Kyung Jeong
https://orcid.org/0000-0001-7857-546X
Byung Jin Kim
https://orcid.org/0000-0002-9008-8506

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Lipid and Atherosclerosis, presents an evidence-based summary of the pathophysiology, clinical relevance, and therapeutic landscape surrounding Lp(a), with a focus on Korean-specific data. It reviews the genetic architecture of Lp(a), ethnic variability in concentrations, and its mechanistic roles in inflammation, thrombosis, and calcification. Based on large Korean cohorts, a 3-tiered classification is proposed of normal (<30 mg/dL), borderline high (30–49 mg/dL), and high (≥50 mg/dL), harmonizing global thresholds with local data. The document also highlights the limitations of current Lp(a) assays in Korea, and calls for standardized, isoform-insensitive testing. Novel therapeutics, including antisense oligonucleotides, small interfering RNAs, and small molecular inhibitors, have shown promising Lp(a)-lowering effects, with multiple phase 3 trials currently ongoing, or in planning. Given the unmet clinical need, the paper recommends incorporating Lp(a) into cardiovascular risk assessment, and calls for Korean-specific longitudinal studies, national screening strategies, and participation in clinical trials. These efforts will help clarify Lp(a)-associated risk in Korean patients and guide the adoption of future targeted therapies.

Keywords: Cardiovascular disease; Korea; Lipoprotein(a); Practice guidelines as topic; Risk assessment

INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, and in Korea.[1)2)] Despite substantial advances in the identification of CVD risk factors and the widespread use of pharmacological therapies, considerable residual CVD risk persists, even among well-treated individuals. Among the various contributors to this residual risk, lipoprotein(a) [Lp(a)] has been firmly established as a causal factor for atherosclerotic cardiovascular diseases (ASCVDs).[3)]

In 1963, Berg[4)] first identified Lp(a), demonstrating its heritable nature through studies that involved 34 families. In 1974, he further reported that individuals with familial hypercholesterolemia and coronary heart disease were more likely to have elevated Lp(a) levels.[5)] In 1977, a method to quantify plasma Lp(a) concentrations was developed.[6)] By 1981, elevated Lp(a) levels (≥30 mg/dL) were linked to the risk of first myocardial infarction (MI).[7)] In the late 1980s, cloning of the apolipoprotein(a) [apo(a)] gene revealed that the *LPA* gene, the gene that encodes apo(a), originated from a duplication of the plasminogen gene, providing important insights into the pathophysiology of Lp(a).[8)] Subsequent large-scale epidemiologic and Mendelian randomization (MR) studies have confirmed Lp(a) as a causal factor in MI, ischemic stroke, heart failure (HF), and calcific aortic valve stenosis (CAVS).[9-12)]

Given the established causal role of Lp(a) in CVD, recent guidelines increasingly recommend its measurement as part of individual CVD risk assessment. Additionally, the role of Lp(a) as a risk-enhancing factor has been increasingly emphasized across recent international guidelines.[3)13-15)] However, despite this growing international consensus, there is currently no clearly defined high Lp(a) threshold or treatment recommendation tailored to the Korean population. Other key challenges also remain; these include assay standardization, the development of generalized guidelines, and the establishment of therapeutic targets. This position paper provides a comprehensive overview of the biology, pathophysiology, clinical evidence, and therapeutic landscape of Lp(a), with particular focus on Korean data. It also outlines current knowledge gaps, and proposes future directions to address Lp(a)-associated ASCVD risk in Korea.

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BASIC CONCEPT OF LIPOPROTEIN(a)

Structure of lipoprotein(a)

Lp(a) consists of a low-density lipoprotein (LDL)-like particle that contains apolipoprotein B (ApoB)-100 with a similar lipid composition to LDL.[16] The key distinguishing feature of Lp(a) is the presence of Apo(a), a unique glycoprotein that is covalently linked to ApoB-100 of the LDL-like particle via a disulfide bond between cysteine residues (**Figure 1**).[17]

Apo(a) is a large glycoprotein characterized by substantial size heterogeneity across individuals. It is encoded by the LPA gene, which is located on chromosome 6 at 6q26-27, adjacent to the human plasminogen gene.[18] The LPA gene shares high sequence homology with the plasminogen gene, having arisen through gene duplication during primate evolution.[8] As a result, Apo(a) shares significant sequence homology with plasminogen, which contains 5 domains, named kringles I to V (KI to KV), and a C-terminal serine protease domain. In contrast, Apo(a) contains 2 different types of kringle domains, multiple kringle IV (KIV) repeats and a single kringle V (KV), as well as one inactive protease domain. The KIV domain is subdivided into 10 types (KIV-1 to KIV-10), among which KIV-1 and KIV-3 through KIV-10 are present in a single copy, while KIV-2 exists in variable numbers ranging (2 to over 40) copies. This copy number variation in KIV-2 results in marked size polymorphism of the Apo(a) molecule, which in turn leads to significant heterogeneity among Lp(a) particles. Notably, particle size is inversely correlated to plasma Lp(a) concentrations. The cysteine-cysteine disulfide bond that links Apo(a) to ApoB–100 is located within the KIV-9 domain.[19]

Another key structural feature of Lp(a) is its enrichment in oxidized phospholipids (OxPLs). Unlike LDL, Lp(a) carries a substantially higher OxPL burden, with these pro-inflammatory lipids being transported both by the ApoB-100 component of the LDL-like particle, and by being covalently bound to the Apo(a) moiety (**Figure 1**).[20] Experimental studies have demonstrated that OxPLs can be transferred from LDL to Lp(a) in vitro, supporting the

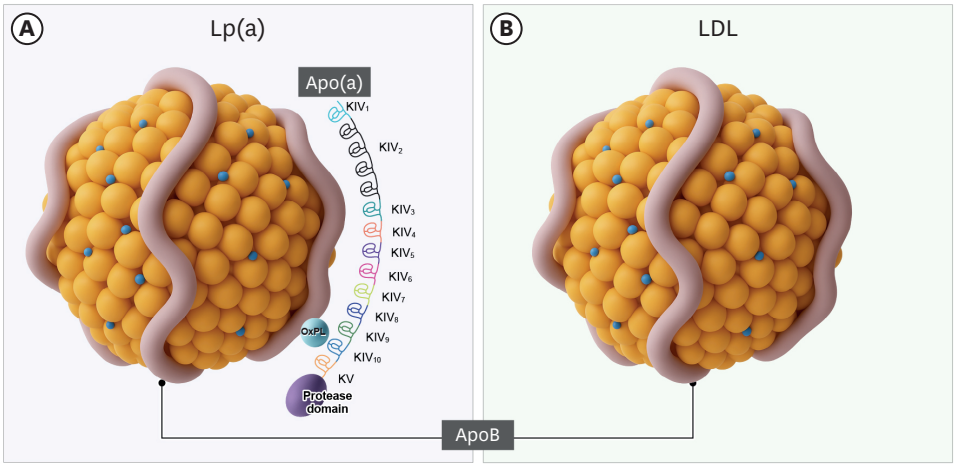

Figure 1. Structural comparison between Lp(a) and LDL. Schematic illustration showing the major structural components of Lp(a) (A) and LDL (B). Lp(a) consists of an LDL-like particle containing ApoB-100 covalently linked via a disulfide bond to Apo(a), which contains multiple KIV repeats, a single KV domain, and an inactive protease domain. OxPL are carried primarily on Apo(a). The LDL particle lacks Apo(a) and OxPL, highlighting the structural and functional distinction between the 2 lipoproteins.
Apo(a) = apolipoprotein(a); ApoB = apolipoprotein B; KIV = kringle IV; KV = kringle V; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); OxPL = oxidized phospholipid.

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notion that Lp(a) serves as the preferential carrier of OxPLs in plasma.[21] Within the human KIV-10 domain of Apo(a), a high-affinity lysine-binding site facilitates the binding of OxPLs, thereby mediating the pro-inflammatory properties of Lp(a). The abundant presence of OxPLs on Lp(a) has been shown to significantly contribute to its atherogenic potential.

Metabolism of lipoprotein(a): synthesis, metabolism, and clearance

Lp(a) is produced independently of very low density lipoprotein (VLDL) and LDL, and is secreted as a distinct lipoprotein particle.[22] Apo(a) is synthesized exclusively in the liver.[23] While the exact site of Lp(a) assembly remains uncertain, kinetic studies have suggested that a substantial fraction of Lp(a) assembly occurs extracellularly, although the exact proportion remains uncertain, as briefly illustrated in **Figure 2**.[3][24-28]

Plasma Lp(a) concentrations are primarily regulated at the level of biosynthesis, rather than catabolism.[29] Among the determinants of Lp(a) production, Apo(a) isoform size plays a central role. It is well established that Lp(a) levels are inversely correlated to Apo(a) isoform size, as smaller isoforms are synthesized at significantly higher rates than larger ones. Interestingly, marked inter-individual variability in Lp(a) concentrations persists even among those with identical Apo(a) isoform sizes, primarily reflecting differences in production rates.[26][28][30][31]

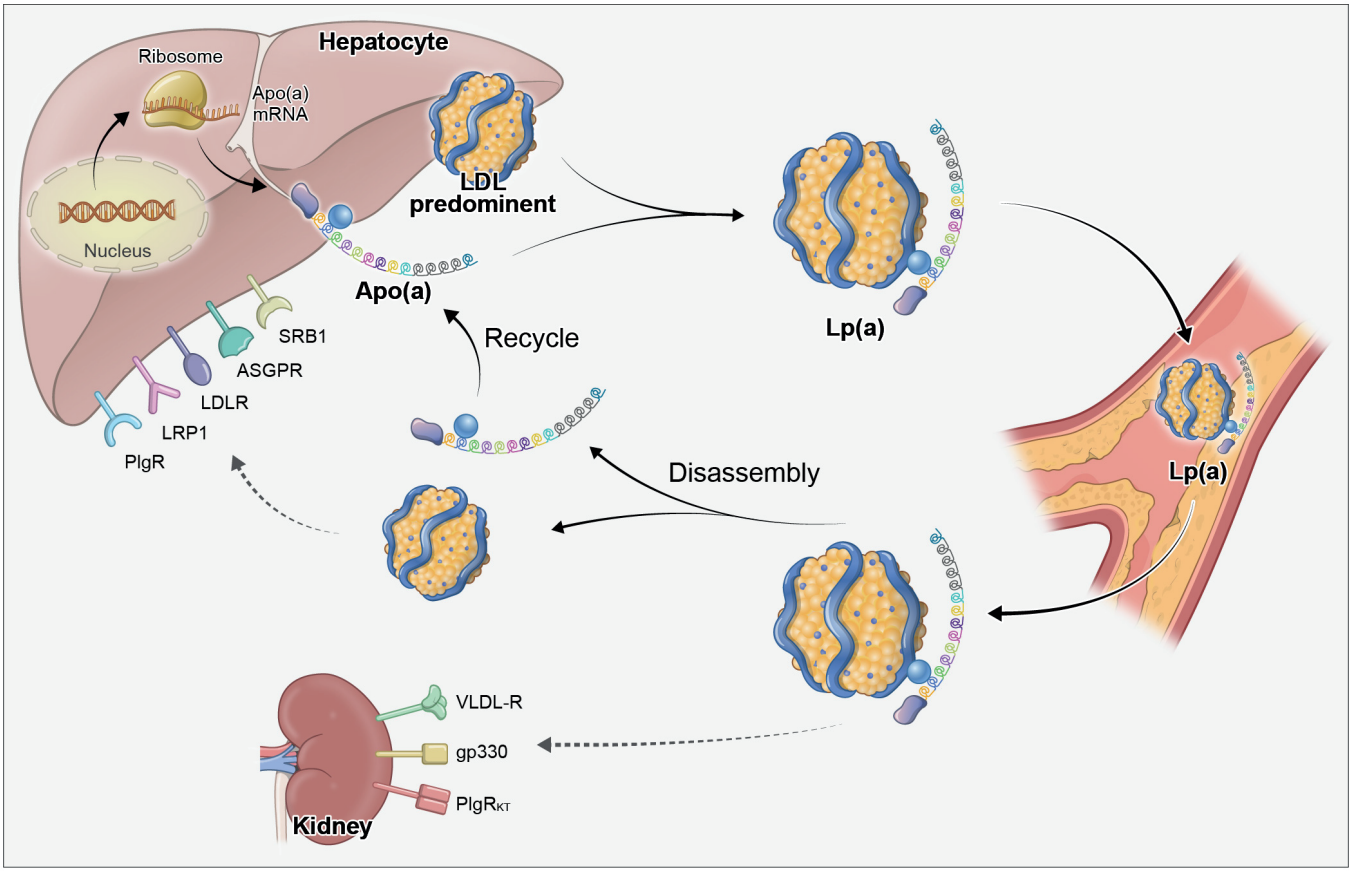

Figure 2. Production and metabolism of Lp(a). Apo(a) is synthesized in hepatocytes and covalently attached to ApoB-100 on a triglyceride-rich lipoprotein to form Lp(a), which is secreted into the circulation. Lp(a) interacts with multiple hepatic receptors, including LDLR, LRP1, SRB1, ASGPR, and PlgR, and with renal receptors such as VLDL-R, gp330/megalin, and PlgRKT.
Apo(a) = apolipoprotein(a); ApoB = apolipoprotein B; ASGPR = asialoglycoprotein receptor; LDL = low-density lipoprotein; LDLR = low-density lipoprotein receptor; Lp(a) = lipoprotein(a); LRP1 = low-density lipoprotein receptor-related protein-1; PlgR = plasminogen receptor; PlgRKT = plasminogen receptor with a C-terminal lysine; SRB1 = scavenger receptor B1; VLDL-R = very low density lipoprotein receptor.

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Although the mechanism of Lp(a) clearance remains incompletely understood, current evidence suggests that it is primarily eliminated by the liver, with secondary contributions from the kidneys and macrophage-expressed receptors involved in cell signaling (**Figure 2**).[24)32)33)] Multiple receptors have been implicated in the clearance of Lp(a), with 5 major receptor classes identified: (1) lipoprotein receptors (LDL receptor, VLDL receptor, and LDL receptor-related protein), (2) Toll-like receptors, (3) scavenger receptors class B type 1, (4) lectins, such as Galectin-1 and asialoglycoprotein receptor 1, and (5) plasminogen receptors, including annexin A2, S100 calcium binding protein A10, and plasminogen receptor with a C-terminal lysine.[34)] Apo(a), ApoB, and OxPLs carried by the Lp(a) particle have been identified as ligands for these receptors. The role of LDL receptor in Lp(a) catabolism remains controversial; the current genetic data does not strongly support a direct role for the LDL receptor in mediating Lp(a) clearance.[35)]

DETERMINANTS OF LIPOPROTEIN(a)

Genetic: Kringle IV repeat polymorphism

There is substantial variation in measured plasma Lp(a) levels across individuals from different racial and ethnic backgrounds,[36)] which can largely be attributed to genetic variants within the LPA gene locus.[3)] Most individuals (>80%) express 2 different Apo(a) isoforms,[20)] each inherited from one parent, contributing to Lp(a) levels in a codominant manner.[20)22)] Median Lp(a) levels are 4 to 5 times higher in individuals with small Apo(a) isoforms (<22 KIV-2 repeats), compared to those with only large isoforms (≥22 KIV-2 repeats).[3)] However, the contribution of Apo(a) isoform size to observed Lp(a) levels varies among different racial and ethnic groups by as much as 80%.[37)] The inverse correlation between isoform size and Lp(a) concentration appears stronger in individuals of European and Asian ancestry, than in those of African descent.[23)]

Regarding LPA gene polymorphisms and alternative splicing, complex relationships have been identified among genetic factors affecting Lp(a) levels. The effect of allele size on Lp(a) concentrations is modulated by numerous functional single nucleotide polymorphisms (SNPs) spanning the full spectrum of LPA allele frequencies, as well as interactions between SNPs and short tandem repeats.[38)] **Table 1** summarizes SNPs known to significantly influence phenotypic Lp(a) concentrations.[3)38-44)]

Non-genetic

A range of non-genetic factors have been implicated in the regulation of Lp(a) concentration (**Table 2**).[45-52)] Physical activity appears to have no or minimal effect on Lp(a) levels,[41)] whereas the influence by dietary modifications were inconsistent.[51)53)] Thyroid function can be another modulator: Lp(a) concentrations increase following thyroidectomy or the administration of antithyroid agents in overt hyperthyroidism, and conversely decrease with levothyroxine replacement in overt hypothyroidism.[50)] Hormonal status also plays a role: low testosterone levels in men have been associated with elevated Lp(a),[49)] while menopausal transition is linked to rising Lp(a) levels, but hormone replacement therapy may have a lowering effect.[47)52)] In addition, chronic kidney disease is consistently associated with elevated Lp(a) concentrations,[45)] whereas hepatic dysfunction, especially hepatocellular damage, tends to reduce Lp(a) levels.[48)] These observations reflect the potential impact of various non-genetic factors on Lp(a) regulation beyond genetics, although their clinical significance remains incompletely understood.

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Table 1. The impact of single-nucleotide polymorphisms on Lp(a) levels

	Effect on Lp(a) levels	Association with race and ethnicity
Variants associated with increased Lp(a)		
rs10455872 (intronic polymorphism)[41]	· ~30 mg/dL increase in Lp(a) · Explains ~25% of Lp(a) variance	· Most common in White individuals (14.3%), less common in Hispanic (5.5%) and Black populations (1.8%)
rs3798220 (I4339M mutation in the protease like domain)[41]	· A rare variant associated with small apo(a) isoforms · Explains ~8% of Lp(a) variance · ~45 mg/dL increase in Lp(a) levels	· Most common in Hispanic individuals (42.4%), less common in White individuals (4.3%), and rare in Black individuals (1.5%) · Moderately frequent in South Asian populations (~12%)
Variants associated with decreased Lp(a)		
rs143431368[38]	· Splice site mutation · ~9 mg/dL decrease in Lp(a) levels	· 10× more frequent in people of Finnish descent (~5%), compared with non-Finnish Europeans
rs41272114 (G+1/in kringle IV-8A)[39][40]	· Loss of function mutation · (5–17) mg/dL decrease in Lp(a) levels	· Most frequent loss of function mutation in White individuals, accounting for ~25% of all null alleles · Frequencies range 0 to 18% between populations: 0.7% in African American individuals and 4.7% in European American individuals; 3% in European populations (PROCARDIS cohort); 18 % in Peruvians
rs41272110 (T3888P)[44]	· Early studies suggest Lp(a)-lowering effect	· Identified in European American (14.3%), African American (2.4%), White (26.7%), Black (4.5%), and Hispanic (17.4%) individuals
4925G>A[38][44]	· Splice variant · The second strongest influence on Lp(a) levels after apo(a) isoform size: ~31 mg/dL decrease in Lp(a) levels	· Common in White European individuals (22%)
4733G>A[43]	· The third strongest influence on Lp(a) levels after isoform size: ~14 mg/dL decrease in Lp(a) levels	· Common in White European individuals (35.1%) and Latin American populations (26.3%) · Rarer in South Asian (5.2%) and Black (1.5%) individuals, and undetectable in East Asian populations

Lp(a) = lipoprotein(a); PROCARDIS = precocious coronary artery disease.

Table 2. Non-genetic determinants of plasma Lp(a) levels

	Drugs and comorbidities	Effect on Lp(a) levels
Conditions associated with increased Lp(a)		
Overt hyperthyroidism	· Thyroidectomy · Antithyroid drug · Radioactive iodine	↑ (mean 4.18 mg/dL)[50]
Hypogonadal men	· Low serum testosterone (<15 nmol/L) · Human growth hormone	↑ (×3 the upper limit of normal)[49] ↑[48]
Postmenopausal women	· ↓Estrogen	↑ (up to 13% higher than premenopausal women)[47]
Saturated fatty acid	· ↓Intake	↑ (R=−0.43, p=0.02)[51]
Chronic kidney disease	· Hemodialysis	↑ (×5–10 higher than stage 1 to 2 chronic kidney disease)[45]
Conditions associated with decreased Lp(a)		
Overt hypothyroidism	· Levothyroxine	↓ (mean −5.6 mg/dL)[50]
Postmenopausal women	· Hormone replacement therapy	↓ (−5.8 mg/dL)[52]
Liver disease	· Hepatitis, liver cirrhosis	↓[48]
Low-carbohydrate diet	· Intake	↓ (mean −14.7%, p<0.001)[53]

Lp(a) = lipoprotein(a).

PATHOPHYSIOLOGY OF LIPOPROTEIN(a) ON CARDIOVASCULAR DISEASE

Inflammation

Lp(a) promotes inflammation by inducing OxPL-driven transcriptomic changes in endothelial cells and monocytes, thereby enhancing monocyte chemotaxis, transendothelial migration, and endothelial permeability.[54] Individuals with elevated Lp(a) levels have greater potential for OxPL-mediated atherogenic activation.[54][55] Lp(a) has also been implicated in various inflammatory conditions, including coronavirus disease 19, chronic kidney disease, and rheumatoid arthritis. Since the LPA promoter contains interleukin-6 (IL-6) response elements, a positive association between Lp(a) and IL-6 levels has been observed.[56][57] Lp(a)

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may further act as a monocyte chemoattractant and regulate IL-6 expression and endothelial adhesion molecules, promoting early plaque development.[54)55)]

Thrombosis and venous thromboembolism

Lp(a) may contribute to thrombosis via mechanisms that extend beyond the inhibition of fibrinolysis. It promotes coagulation by binding to and inactivating tissue factor pathway inhibitor, and by enhancing tissue factor expression on monocytes.[58)59)] Due to its structural homology with plasminogen, Lp(a) competitively inhibits plasminogen binding to fibrin and endothelial surfaces, thereby reducing plasmin-mediated fibrinolysis.[55)] However, clinical studies suggest that antifibrinolytic activity alone does not fully account for the prothrombotic potential of Lp(a).[55)60-63)] The association between elevated Lp(a) levels and venous thromboembolism remains inconclusive, as most MR and cohort studies have not demonstrated a strong relationship.[60-63)]

Calcification

Elevated Lp(a) levels are strongly associated with CAVS, primarily due to the OxPLs carried by Lp(a). These OxPLs promote the osteogenic differentiation of valvular interstitial cells by upregulating transcription factors such as RUNX2 and BMP2, ultimately leading to aortic valve calcification.[64)65)] Autotaxin, an enzyme transported by Lp(a) and secreted by valvular interstitial cells, converts lysophosphatidylcholine into lysophosphatidic acid (LysoPA).[64)] LysoPA activates inflammatory pathways, including nuclear factor-kappa B, further contributing to the calcification process. In addition, Lp(a) promotes cholesterol deposition and fibrin accumulation on the aortic valve, exacerbating lesion progression.[66)]

EPIDEMIOLOGY OF LIPOPROTEIN(a)

Highlights

- Lp(a) distribution varies markedly by ethnicity, with East Asians generally showing lower median concentrations, as seen in large Korean cohorts where median levels are approximately 18 to 19 mg/dL, compared to higher levels in Black or South Asian populations.
- No unified threshold for high Lp(a) exists in Asia; as both >30 and >50 mg/dL are used in China and Japan, while Korean data support a 3-tiered risk classification with normal (<30 mg/dL), borderline high (30 to 49 mg/dL), and high (≥50 mg/dL).
- Elevated Lp(a) is a strong and independent risk factor for ASCVD, aortic valve disease, and HF, as confirmed by multiple MR and large-scale epidemiologic studies across diverse ethnic groups.
- Korean studies on both primary and secondary prevention have demonstrated that elevated Lp(a) is associated with increased cardiovascular (CV) mortality, MI, and subclinical atherosclerosis.

Distribution of lipoprotein(a) levels in various populations: ethnic differences

The distribution of Lp(a) levels varies significantly across populations due to genetic, environmental, and methodological factors, as illustrated in **Tables 1** and **2**. Multiple studies have investigated the variability in Lp(a) concentrations and their implications for CVD risk. In the UK Biobank study, which included 6,857 participants from diverse ethnic backgrounds, median Lp(a) concentrations in Chinese, Europeans, South Asians, Arabs, and Africans were 9.8, 11.5, 12.9, 18.1, and 27.1 mg/dL, respectively.[36)67)] In the Multi-Ethnic Study of Atherosclerosis, which evaluated 6,814 participants primarily for primary prevention, Black participants exhibited the highest median Lp(a) levels at 35 mg/dL, followed by Whites, Hispanics, and Chinese Americans at 12, 8, and 6 mg/dL, respectively.[68)] The effect of potentially modifiable risk factors associated with MI in 52 countries (INTERHEART) study reported Lp(a) concentrations in nmol/L. Among the Chinese subset, the median level was

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16 nmol/L (6.4 mg/dL), compared to 31, 19, and 75 nmol/L or 12.4, 7.6, and 30 mg/dL in South Asians, Whites, and Black individuals, respectively.[65] These findings consistently highlight marked ethnic differences in Lp(a) concentrations, with Black individuals exhibiting the highest levels across cohorts.[69][70] Korean data also demonstrate variability in Lp(a) levels across different cohorts, with most studies conducted in primary prevention setting.[71-78] The Kangbuk Samsung Health Study assessed Lp(a) levels in a large cohort of individuals undergoing routine health check-ups,[71] with a subset also evaluated for coronary artery calcium scoring.[72] Median Lp(a) concentration was 18.5 mg/dL, measured using the Roche Diagnostics Modular P Analyzer and Cobas 8000 c702 system.[71] Choi et al.[73] also analyzed data from 14,158 adults who underwent Lp(a) testing across 82 hospitals and clinics nationwide. The study reported a median Lp(a) level of 19.6 nmol/L, with 15.3 and 7.9% of individuals exceeding 75 and 120 nmol/L, respectively, thereby providing a reference distribution for the Korean population. In secondary prevention settings, 2 Korean studies have reported median Lp(a) levels. In a cohort of patients with acute MI, the median Lp(a) level was 17 mg/dL, with a median age of 62 years.[79] In a post-percutaneous coronary intervention (PCI) cohort, the median Lp(a) level was 18.6 mg/dL (interquartile range: 9.2 to 35.5 mg/dL), among patients aged 65 years.[80]

Despite ethnic differences in median Lp(a) concentrations, the association between Lp(a) levels and ASCVD risk appears to be consistent across populations. This consistency is further supported by findings from a large Korean study.[71] However, current evidence remains insufficient to determine whether absolute or ethnicity-specific Lp(a) cut-off values are more appropriate for risk assessment in the Korean population.

Lipoprotein(a) as a cardiovascular risk

Interpretation of lipoprotein(a) levels in the context of overall cardiovascular disease risk

Unlike other lipoproteins, Lp(a) levels are primarily influenced by genetic factors, rather than lifestyle. MR studies conducted across multiple ethnic groups have demonstrated a strong association between Lp(a) concentration and CVD risk.[11][81-84] Individuals from various ethnicities who carry polymorphisms associated with smaller Apo(a) isoforms but higher Lp(a) levels exhibit an increased risk of CVD.[81] As discussed in section 'Genetic: Kringle IV repeat polymorphism' and shown in **Table 1**, specific SNPs, such as rs3798220 and rs10455872, are linked to a lower number of KIV-2 repeats. This leads to smaller Apo(a) isoforms, and consequently, higher Lp(a) concentrations.[9] These variants are also strongly associated with increased odds ratios for coronary artery disease (CAD). Notably, individuals carrying both SNPs have more than a 4-fold increase in CAD risk, exceeding that of most traditional CAD risk factors.[9]

Several large-scale epidemiologic studies have consistently confirmed that elevated Lp(a) is an independent risk factor for ASCVD. The Emerging Risk Factors Collaboration[10] and the Copenhagen reported a dose-dependent increase in MI risk with rising Lp(a) levels.[85] Furthermore, a recent Chinese study involving 2.9 million adults reinforced the association between Lp(a) levels and subclinical atherosclerosis across multiple vascular territories.[70]

Genetic associations with calcific aortic valve stenosis and heart failure

Lp(a) has been identified as a major contributor to CAVS and HF, with MR studies supporting its causal role.[84][86-90] A case-control study revealed that patients with CAVS exhibited elevated levels of Lp(a), OxPL-ApoB, and autotaxin, suggesting that Lp(a) functions as a carrier of OxPL and autotaxin to valvular tissues, exacerbating inflammation and calcification.[91]

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Moreover, in individuals with mild-to-moderate aortic stenosis, higher levels of OxPL-ApoB, OxPL-Apo(a), and Lp(a) were associated with more rapid disease progression, and a greater likelihood of requiring aortic valve replacement.[59]

Lp(a) has also been linked to an increased risk of HF by MR studies. However, it remains open to debate whether this phenomenon is confounded by CAD. In addition, mechanisms such as direct structural damage to the heart valves and myocardium may also contribute,[92] although further research is needed.

Lipoprotein(a) as a risk-enhancing factor in primary prevention

In the context of primary prevention, elevated Lp(a) has been associated with a range of ASCVD outcomes, along with increased risks of CAVS, CV mortality, and all-cause mortality. Across major international guidelines, Lp(a) ≥50 mg/dL (≥100–125 nmol/L) is recognized as a risk-enhancing factor in primary prevention.[93] Elevated Lp(a) warrants intensified management of traditional risk factors and consideration of more aggressive low-density lipoprotein cholesterol (LDL-C)-lowering strategies, even among individuals with otherwise optimal lipid profiles. Furthermore, Lp(a) ≥180 mg/dL (≥430 nmol/L) confers a lifetime ASCVD risk comparable to that of untreated heterozygous familial hypercholesterolemia.

Multiple Korean observational studies have reinforced the role of Lp(a) as a risk-enhancing factor for ASCVD, consistent with international evidence (**Figure 3A**, **Table 3**). In a large-scale general health check-up cohort (n=275,430), elevated Lp(a) was significantly associated with increased CVD, MI, and all-cause mortality, underscoring its prognostic value in the general population.[71] Among 662 individuals with type 2 diabetes mellitus and no history of CVD, higher Lp(a) levels were linked to carotid atherosclerosis, defined as carotid intima-media thickness ≥1.0 mm or the presence of carotid plaque, indicating a potential role in early vascular disease progression.[77] In a coronary computed tomography angiography study of 7,201 asymptomatic individuals, high Lp(a) levels were associated with subclinical coronary atherosclerosis, including both calcified and non-calcified plaques, suggesting its involvement in early plaque development prior to the onset of clinical events.[74] A recent study further extended these findings by evaluating 2,750 adults without known ASCVD, specifically assessing CAC progression. The study demonstrated that higher Lp(a) tertiles were significantly associated with greater CAC progression.[75] In addition, a large echocardiography-based cohort of 44,742 Korean adults revealed that individuals

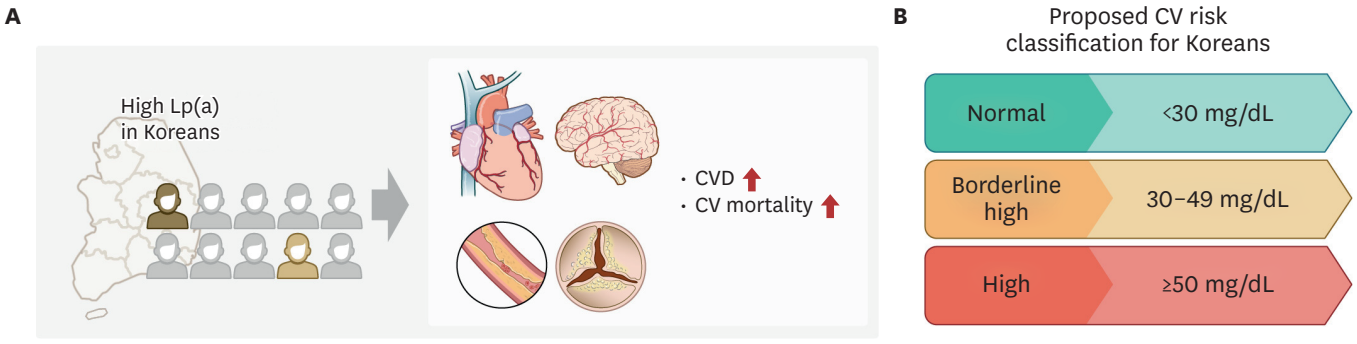

Figure 3. Summary of Korean data and proposed cardiovascular risk classification according to Lp(a) levels. (A) Conceptual summary of findings from Korean cohorts demonstrating that individuals with elevated Lp(a) levels exhibit a higher risk of CVD and CV mortality. (B) Proposed Lp(a)-based cardiovascular risk classification for the Korean population: normal (<30 mg/dL), borderline high (30–49 mg/dL), and high (≥50 mg/dL). These thresholds align with major international guidelines while reflecting population-specific distributions observed in Korean studies.
CV = cardiovascular; CVD = cardiovascular disease; Lp(a) = lipoprotein(a).

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Table 3. Lp(a) levels related to CV outcomes in primary and secondary prevention of Korean patients

	Cohort type/author	Sample size	Study population	Results
Primary prevention	Observational/Kim et al.[71]	275,430	General health check-up cohort	High Lp(a) was related to CV mortality and all-cause death
	Observational/Kim et al.[72]	44,354	General health check-up cohort undergoing CAC measurements	High Lp(a) levels and CAC are independently associated with ASCVD
	Observational/Jun et al.[77]	662	T2DM patients without prior CV disease	Lp(a) associated with carotid atherosclerosis (CIMT ≥1.0 mm or carotid plaque)
	Observational/Lee et al.[74]	7,201	Asymptomatic individuals undergoing CCTA	High Lp(a) associated with subclinical coronary atherosclerosis (calcified and non-calcified plaques)
	Observational/Lee et al.[75]	2,750	General health check-up population	Higher Lp(a) levels were associated with coronary artery calcification progression
	Observational/Kim et al.[94]	44,742	Korean adults undergoing echocardiography and Lp(a) testing	High Lp(a) (>100 mg/dL) independently associated with increased risk of severe degenerative aortic stenosis and need for AVR
Secondary prevention	Observational/Park et al.[79]	1,908	AMI cohort with stratified Lp(a) levels	No independent association between baseline Lp(a) and major adverse CV events
	Observational/Yoon et al.[80]	12,064	Post-PCI cohort	High Lp(a) associated with increased recurrent ischemic CV events

AMI = acute myocardial infarction; ASCVD = atherosclerotic cardiovascular disease; AVR = aortic valve replacement; CAC = coronary artery calcium; CCTA = coronary computed tomographic angiography; CIMT = carotid intima-media thickness; CV = cardiovascular; Lp(a) = lipoprotein (a); PCI = percutaneous coronary intervention; T2DM = type 2 diabetes mellitus.

with very high Lp(a) concentrations (>100 mg/dL) had an approximately 2-fold higher risk of developing severe degenerative aortic stenosis and requiring aortic valve replacement, independent of traditional risk factors.[94]

Taken together, these findings from Korean cohorts highlight the relevance of Lp(a) as a risk-enhancing factor in primary prevention, with consistent associations observed across mortality outcomes and subclinical atherosclerosis, even in asymptomatic populations.

Prognostic significance of lipoprotein(a) in secondary prevention

In secondary prevention, elevated Lp(a) has been associated with an increased risk of major adverse cardiovascular events (MACE), including recurrent MI, stroke, and CV death.[3][14] Meta-analyses have shown that patients with Lp(a) levels above the 80th percentile have a 40% higher risk of recurrent events, particularly among statin-treated individuals with CAD.[95] The impact of Lp(a) may be influenced by LDL-C levels. Some studies report a stronger association between Lp(a) and CV outcomes in patients with LDL-C ≥130 mg/dL, while others have observed residual risk even at LDL-C <70 mg/dL.[96] In post-PCI cohorts, elevated Lp(a) has also been linked to increased ischemic events, including restenosis and stent thrombosis, emphasizing its contribution to residual CV risk.[80] Despite these associations, current lipid-lowering strategies, including statins and PCSK9 inhibitors, do not adequately address Lp(a)-associated risk, reinforcing the need for targeted Lp(a)-lowering therapies.[97] Recent analyses from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) and SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) trials have further confirmed that Lp(a) is an independent predictor for MACE, MI, and peripheral artery disease in secondary prevention, irrespective of baseline inflammation status.[98] Section 'Novel drugs targeting lipoprotein(a): antisense oligonucleotide, small interfering RNA, and oral small molecule inhibitor' discusses ongoing phase 3 trials of Lp(a)-lowering therapies in the secondary prevention settings.

In Korean secondary prevention cohorts, the prognostic significance of Lp(a) has been variable (**Table 3**). In an acute MI cohort of 1,908 patients, baseline Lp(a) levels were

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not independently associated with MACE at 3 years, suggesting a more complex role in post-MI risk stratification.[79] Meanwhile, in a larger cohort of 12,064 post-PCI patients, elevated Lp(a) was significantly linked to increased recurrent ischemic CV events, including MI, stroke, and CV death, reinforcing its clinical relevance in long-term risk assessment following revascularization.[80]

Defining high lipoprotein(a) thresholds in Koreans

There is no universally accepted consensus on the threshold for elevated Lp(a), although many lipid societies and national guidelines commonly adopt >50 mg/dL (>100 to 125 nmol/L depending on converting method) as a clinically meaningful cut-off.[14][99-105] The European Atherosclerosis Society expert consensus recommends >50 mg/dL, based on large-scale epidemiological and MR studies.[3] Similarly, the 2022 National Lipid Association (NLA) statement defines >50 mg/dL as a risk-enhancing level for CVD, particularly in the context of global CV risk stratification.[14] Consensus documents and position statements from several non-Asian countries adopt similar thresholds.[100-105]

In Asia, a unified threshold for high Lp(a) has not been established. Although Chinese academic societies have defined high Lp(a) as >30 mg/dL (>62 or 75 nmol/L depending on converting method),[99][106] the most recent large population-based cohort study in China demonstrated more pronounced CV risk at levels exceeding 50 mg/dL.[70] In Japan, the Japan Atherosclerosis Society guidelines do not specify a clinical cut-off for elevated Lp(a)[107]; however, a recent Japanese cohort study of 2,170 patients found that both (>30 and >50) mg/dL were predictive of CV events. As mentioned previously, a large Korean cohort demonstrated elevated risk of mortality due to CV disease and MI in individuals with Lp(a) levels ≥50 mg/dL.[71] In addition, a post-MI cohort study showed a trend toward increased event rates was observed in individuals with Lp(a) levels of 30–49 and ≥50 mg/dL, compared to those with <30 mg/dL.[75] Another post-PCI cohort demonstrated that high Lp(a) levels (≥30 mg/dL) were significantly associated with increased CV event risks, compared to low Lp(a) levels (<30 mg/dL).[76] Considering the results of both primary and secondary prevention studies, the Korean task force has proposed the following practical 3-tiered classification (**Figure 3B**):

- Normal: <30 mg/dL
- Borderline high: 30–49 mg/dL
- High: ≥50 mg/dL

LIPOPROTEIN(a) TESTS

Highlights

- Lp(a) measurement is technically challenging due to isoform size variability from KIV-2 repeats; most assays are isoform-sensitive, and tend to underestimate risk in individuals with small Apo(a) isoforms.
- Isoform-insensitive assays calibrated to World Health Organization (WHO)/International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Secondary Reference Material-2B (SRM-2B) are recommended, with results ideally reported in nmol/L rather than mg/dL, to minimize misclassification.
- In Korea, most laboratories still report Lp(a) in mg/dL, while many do not employ WHO/IFCC-traceable calibration methods, highlighting the need for standardization and harmonization.
- The Korean Society of Lipid and Atherosclerosis discourages fixed conversion between mg/dL and nmol/L, citing unreliability due to isoform-dependent variability.
- High-risk cut-off values vary globally, with most guidelines recommending >50 mg/dL, though some Asian sources propose 30 mg/dL for greater sensitivity.
- Despite lower median Lp(a) levels in Koreans, ASCVD risk increases consistently with Lp(a) elevation, supporting its utility as a biomarker across ethnicities, and emphasizing the need for population-specific validation.

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Introduction of lipoprotein(a) measurement: isoform sensitive versus insensitive

Measuring Lp(a) is inherently challenging due to the distinctive structure of Apo(a). A key feature of Apo(a) is the presence of a variable number of repeated KIV-2 repeats.[108][109] These repeats produce Apo(a) isoforms of differing sizes, complicating accurate quantification. Ideally, clinical assays should target a unique, non-repetitive epitope on Apo(a) to eliminate the variability introduced by KIV-2 copy number. Assays designed in this way, termed isoform-insensitive assays, quantify each Lp(a) particle once, and report concentrations in nmol/L. However in practice, developing antibodies specific to non-repetitive epitopes is difficult, due to the high sequence homology (approximately 75–94%) among Apo(a) kringle domains.[5] Consequently, most commercially available assays use polyclonal antibodies that bind to multiple epitopes, including the repeated KIV-2 domains, making them isoform-sensitive.[3] Isoform-sensitive assays tend to underestimate Lp(a) concentrations in individuals with small Apo(a) isoforms, who typically have higher Lp(a) levels and greater ASCVD risk, while overestimating levels in those with large isoforms.[109] To reduce isoform-related measurement bias, some assays incorporate 5 or more independent calibrators that include a representative distribution of Apo(a) isoform sizes.[14][110]

Despite these advances, the use of isoform-insensitive assays or isoform-sensitive assays with 5-point calibrators does not ensure full standardization or harmonization. True standardization requires calibration against certified reference materials traceable to the WHO/WHO/IFCC SRM-2B. This material assigns values in nmol/L based on a one-to-one antibody-apo(a) interaction and provides a common reference point for assay comparability. Although some assays are traceable to WHO/IFCC SRM-2B, many—particularly those reporting results in mg/dL—are not. Adding to the challenge, the current SRM-2B material is nearly depleted. The IFCC is developing new reference materials and reference measurement procedures to facilitate global standardization of Lp(a) testing.

Recommended lipoprotein(a) measurement

The variability in Lp(a) isoform sizes highlights the importance of reporting results in particle concentration units (nmol/L), rather than mass units (mg/dL), as the latter are influenced by isoform size. Both the IFCC and the NLA advocate standardized Lp(a) measurements in nmol/L.[109] These assays should ideally employ multi-point calibration, such as a 5-point calibrator, and be traceable to the WHO/IFCC SRM-2B reference material.[14] The growing availability of Lp(a)-lowering therapies further underscores the need for accurate and standardized measurement. Reliable quantification is essential, not just to identify patients who may benefit from treatment, but also to monitor therapeutic efficacy.[109] Therefore, there is an urgent need to develop and implement isoform-insensitive assays that report results in nmol/L. While conversion factors ranging from 2 to 2.5 (mg/dL to nmol/L) are sometimes being used in clinical practice, these represent only rough estimates, and are unreliable, due to isoform-dependent variability.[3]

In Korea, substantial progress is still needed to achieve assay harmonization for Lp(a) measurement. Currently, most laboratories report Lp(a) concentrations in mass units (mg/dL), rather than particle concentrations (nmol/L) (**Table 4**). These mass-based results are often not traceable to the WHO/IFCC SRM-2B reference standard. For laboratories using calibrators expressed in nmol/L, it is essential that results are reported in molar units, without conversion to mass units. As emphasized earlier, arbitrary conversion between mass and molar units are unacceptable and may lead to clinically misleading interpretations.

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Table 4. Methods for lipoprotein(a) measurement in clinical laboratories participating in the external quality assurance program provided by the Korean Association of External Quality Assessment Service

Method	Number of laboratories
Roche	24 nmol/L
Roche	23 mg/dL*
Roche	2 (both nmol/L and mg/dL)
Sekisui	21 mg/dL
Siemens Atellica	6 mg/dL
Siemens BN™ II System	1 mg/dL
Nittobo	6 mg/dL
Denka Seiken	3 mg/dL
Randox	2 mg/dL
Genematrix	1 mg/dL
Total	89

Data kindly provided by the Korean Association of External Quality Assessment Service (2024).
*Results reported by labs in mg/dL using conversion factor [mg/dL=(nmol/L+3.83)×0.4587].

Although Lp(a) concentrations are largely genetically determined and remain relatively stable over time, emerging evidence indicates measurable intra-individual variability, particularly among individuals with borderline Lp(a) levels, elevated LDL-C, or those receiving statin therapy.[111)112)] Accordingly, we recommend that Lp(a) should be measured at least once in adulthood, while repeat testing may be considered in selected patients when initial values are borderline or when clinical circumstances that could influence Lp(a) levels change.

CURRENT AND EMERGING TREATMENT STRATEGIES

Highlights
· Lifestyle interventions (diet, exercise) have minimal to no effect on lowering Lp(a) concentrations, underscoring the strong genetic regulation of Lp(a) levels.
· Most currently available lipid-lowering agents (e.g., CETP inhibitors, niacin, PCSK9 inhibitors) reduce Lp(a) by 20 to 40%, but their CV outcome benefits in patients with high Lp(a) remain limited or inconsistent.
· Lipoprotein apheresis is one of the few existing therapies shown to reduce CV events in very high-risk patients with markedly elevated Lp(a), though its use is limited by cost and accessibility.
· MR studies suggest that a reduction of Lp(a) by approximately 80 to 100 mg/dL may be required to achieve a 20 to 40% decrease in CV events, supporting the need for potent, targeted therapies.
· Antisense oligonucleotides (ASOs, pelacarsen), small interfering RNAs (olpasiran, zerlasiran, lepodisiran), and oral Lp(a) assembly inhibitor (muvalaplin) have demonstrated >80% reductions in Lp(a) levels; most of them are currently being evaluated in phase 3 CV outcome trials.

Therapeutic lifestyle change for lipoprotein(a) concentration

Therapeutic lifestyle change is a well-established approach to reduce CV risk in both primary and secondary prevention. However, dietary interventions have shown minimal effect on lowering Lp(a) concentrations. Several randomized trials have demonstrated unexpected findings, such as higher Lp(a) levels with a low-fat, high-vegetable diet, compared to a low-fat, low-vegetable diet.[113)114)] Similarly, the Dietary Approaches to Stop Hypertension diet with higher unsaturated fat intake resulted in greater Lp(a) levels than high-protein or carbohydrate-based diets.[115)] While unsaturated fats generally improve other lipid profiles like LDL-C, their effect on Lp(a) remains unclear. A comprehensive diet score incorporating fish and whole grain intake showed only modest impacts on Lp(a) levels, despite improving overall CVD outcomes.[116)]

The association between physical activity and Lp(a) levels also remains inconclusive.[41)] Some studies suggest an inverse correlation,[117)] while others report no significant association with

exercise capacity, age, sex, or body composition.[118] Collectively, these findings suggest that diet and exercise have little to no meaningful impact on Lp(a) levels, reinforcing the predominant role of genetic regulation. Therefore, the development of novel Lp(a)-targeted therapies is essential.

Evaluation of pre-existing lipid-lowering therapeutics for cardiovascular benefit in high lipoprotein(a) concentration

A meta-analysis on statin therapy showed that while statins effectively reduce conventional CV risk factors, they do not lower Lp(a) levels.[95][119] Notably, patients with Lp(a) ≥50 mg/dL at baseline and follow-up experienced worse CV outcomes, suggesting that elevated Lp(a) contributes to residual CV risk despite statin use.

Several Lp(a)-lowering therapies have been explored for their potential CV benefits. Lipoprotein apheresis, primarily used in patients with Lp(a) >95th percentile, was associated with substantial reductions in MI (97%) and composite CV events (86%).[120] A subsequent multicenter observational study in 170 high-risk patients (mean LDL-C: 99.0 mg/dL, mean Lp(a): 104.9 mg/dL) reported similar reduction in CV events (–78%), MI (–85.7%), and revascularization (–68.2%).[121] While these findings suggest benefit, the evidence is limited by small sample sizes, retrospective nature, and lack of replication. Extended-release niacin, when combined with statins in the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial, achieved a 19% reduction in Lp(a), but failed to reduce CV events, likely due to inadequate statistical power.[122] Cholesteryl ester transfer protein inhibitors also demonstrated a 20 to 40% reduction in Lp(a). However, 3 agents (torcetrapib, evacetrapib, dalcetrapib) were discontinued, due to toxicity or lack of efficacy.[123-125] Anacetrapib and TA-8995 showed Lp(a) lowering effects, but no clear CV benefit was demonstrated.[126][127] PCSK9 monoclonal antibodies have consistently lowered Lp(a), as shown in the FOURIER trial, where evolocumab reduced Lp(a) by 26.9%, regardless of baseline LDL levels. Importantly, patients with Lp(a) >37 nmol/L experienced greater absolute risk reduction (1.41%), and a lower number needed to treat (=71).[33] Inclisiran, a small interfering RNA (siRNA) therapy targeting PCSK9, demonstrated durable LDL-C lowering, but only modest Lp(a) reduction of 18.6 to 25.6% in ORION (Organized Research on Inclisiran for Ongoing Lowering of LDL-C)-10 and ORION-11.[128] However, in ORION-18,which specifically enrolled Asian patients, inclisiran reduced Lp(a) by 41%, suggesting a potentially enhanced response in this population.[129] Mipomersen, an ASO targeting ApoB, reduced Lp(a) by 26.4% in patients with familial hypercholesterolemia, though its impact on CV outcomes remains unproven.[130] These findings underscore the limited efficacy of existing therapies in addressing elevated Lp(a)-associated risk. They highlight the need for novel, potent Lp(a)-targeted agents to effectively reduce CV events in high-risk populations.

A need for novel agents with extensive lipoprotein(a)-lowering effect

For clinically significant CV benefits, greater Lp(a) reductions may be required. MR studies suggest that an 80–90% reduction in Lp(a) among individuals with baseline levels (>90–100) mg/dL (225–250 nmol/L) could lead to a 15–20% decrease in CV events.[83] The equivalence between LDL-C and Lp(a) lowering remains open to debate. Earlier estimates proposed that reducing Lp(a) by 101.5 mg/dL (253.8 nmol/L) yields a similar benefit to lowering LDL-C by 38.7 mg/dL; however, more recent data suggest that a reduction of 65.7 mg/dL may be sufficient to achieve comparable risk reduction.[82] Furthermore, secondary prevention studies indicate that Lp(a) reductions of 50 to 99 mg/dL are associated with 20 to 40% reduction in

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CVD risk, respectively.[131] These findings collectively highlight the need for novel therapeutics that are able to reduce Lp(a) by 60–100 mg/dL, with efficacy validated through large-scale randomized trials to establish their CV benefit.

Novel drugs targeting lipoprotein(a): antisense oligonucleotide, small interfering RNA, and oral small molecule inhibitor

Pelacarsen, an N-acetylgalactosamine-conjugated ASO, has been shown to reduce Lp(a) levels by up to 92%.[132] Comparable reductions have been observed with RNA-based siRNA agents, such as olpasiran,[133] zerlasiran,[134][135] and lepodisiran.[136] In addition, muvalaplin, an oral-molecule Lp(a) assembly inhibitor, blocks the interaction between apo(a) and ApoB-100, thereby preventing Lp(a) formation.[137]

Phase II studies of all 5 agents demonstrate consistent and robust Lp(a) reductions, with each showing a reduction of over 80%, highlighting their potential as highly effective Lp(a)-lowering therapies.[132][133][135][138][139]

Three phase 3 clinical trials investigating ASO or siRNAs are currently underway (**Table 5**). The Lp(a) HORIZON (Phase 3 Trial of Pelacarsen) trial is investigating pelacarsen in 8,323 patients with ASCVD and Lp(a) ≥70 mg/dL (≥175 nmol/L) (NCT04023552).[132][140] The OCEAN(a) (Olpasiran Cardiovascular Outcomes Study) outcomes trial is evaluating olpasiran in approximately 7,000 patients with ASCVD and Lp(a) ≥200 nmol/L (NCT05581303), while the ACCLAIM-Lp(a) (Lipoprotein(a) Lowering Outcomes Trial of Lepodisiran) (NCT06292013) trial is assessing lepodisiran in 12,500 individuals with Lp(a) ≥175 nmol/L, and either established ASCVD or high-risk individuals (NCT06292013).

Table 5. Summary of ongoing major trials to lower Lp(a)

Drug	Trial name (NCT ID)	Phase	Inclusion criteria	Number	Dose	Dose interval	Primary endpoint	Time frame/ estimated completion
Pelacarsen	Lp(a) HORIZON (NCT04023552)	Phase 3	Secondary prevention, Lp(a) ≥70 mg/dL	8,325	80 mg	Every 4 weeks	MACE (CV death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization)	4 years/ February, 2026
Olpasiran	OCEAN(a) outcomes trial (NCT05581303)	Phase 3	Secondary prevention, Lp(a) ≥200 nmol/L	7,297	142 mg	Every 12 weeks	CHD death, MI, urgent coronary revascularization	4 years/ December, 2026
Lepodisiran	ACCLAIM-Lp(a) (NCT06292013)	Phase 3	Secondary prevention, Lp(a) ≥175 nmol/L Primary prevention, Lp(a) ≥175 nmol/L	12,500	400 mg	· Initial 3 injections: every 6 months · Following injections: every 12 months	MACE (CV death, nonfatal MI, nonfatal stroke, and urgent coronary revascularization)	4.5 years/ March, 2029
Zerlasiran[130]	ALPACAR-360 (NCT05537571)	Phase 2	Stable ASCVD, Lp(a) ≥125 nmol/L	178	300 or 450 mg	Every 16 or 24 weeks	Time-averaged % change in Lp(a) over 36 weeks	1.2 years (60 weeks)/ published
Muvalaplin[133] (oral)	KRAKEN (NCT05563246)	Phase 2	High-risk (ASCVD, DM, or FH), Lp(a) ≥175 nmol/L	233	10, 60, or 240 mg	Daily (for 12 weeks)	Placebo-adjusted % change in Lp(a) at week 12	12 weeks/ published

ACCLAIM-Lp(a) = A Study to Investigate the Effect of Lepodisiran on the Reduction of Major Adverse Cardiovascular Events in Adults With Elevated Lipoprotein(a); ALPACAR-360 = Assessment of Lipoprotein(a) lowering in Cardiovascular Disease with SLN360; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CV = cardiovascular; DM = diabetes mellitus; FH = familial hypercholesterolemia; HORIZON = Phase 3 Trial of Pelacarsen; KRAKEN = Trial of Muvalaplin in High-Risk Patients; Lp(a) = lipoprotein(a); MACE = major adverse cardiovascular events; MI = myocardial infarction; OCEAN(a) = Olpasiran Trials of Cardiovascular Events And LipoproteiN(a) Reduction.

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RESEARCH GAPS AND FUTURE DIRECTIONS

Highlights

- Korean-specific cohort studies are essential to assess Lp(a)-related CV risks considering genetic and environmental factors.
- Further research is needed to clarify how genetic variation, metabolic diseases, and environmental influences affect Lp(a) levels in the Korean population.
- Standardized, isoform-insensitive Lp(a) assays should be developed to improve measurement accuracy and clinical applicability in Korea.
- Clinical trials in the Korean population are necessary to evaluate the safety and efficacy of emerging Lp(a)-lowering therapies, such as ASO and siRNA.
- Implementing family-based screening and establishing national Lp(a) registries could facilitate early detection and strengthen CV risk management strategies.
- CV risk prediction models should incorporate Lp(a) to enhance accuracy and support personalized patient care.
- Further studies are warranted to elucidate the pathogenic mechanisms of Lp(a), particularly its roles in OxPL-mediated inflammation and thrombosis.

The need for Korean-specific longitudinal studies on lipoprotein(a)

The clinical importance of Lp(a) as a genetically determined and independent risk factor for ASCVD and CAVS has gained substantial global recognition. However, significant research gaps remain, particularly concerning Korean populations. These gaps underscore the need for region-specific studies to better understand how genetic, environmental, and metabolic factors interact to influence Lp(a)-related CV risk. Globally, no universally accepted threshold for defining high Lp(a) levels has been established, and this uncertainty extends to Korea. Determining the Lp(a) threshold associated with increased CV risk is therefore a crucial area of investigation. Conducting well-designed, representative longitudinal studies in Korean cohorts will be essential to define appropriate thresholds and guide future risk assessment and management strategies that are tailored to the Korean population.

Exploration of genetic and environmental factors unique to Korea

While Lp(a) concentrations are primarily influenced by genetic factors, the role of other modifying factors, such as comorbidities and environmental exposures, remains incompletely understood in Korean populations. Genome-wide association studies specific to Koreans are needed to identify population-specific genetic determinants, such as unique SNPs, or variations in KIV-2 repeats. Emerging therapies targeting Lp(a), such as ASOs and siRNAs, show great promise to reduce residual CV risk. However, their efficacy and safety remain largely untested in East Asians, including Koreans. To address this gap, Korean participation in global trials and dedicated local studies is essential. Pharmacogenomic research is also needed to identify population-specific differences in treatment response.

The interplay between Lp(a) and common metabolic disorders in Korea, such as diabetes or fatty liver disease, warrants further study. Environmental factors, like diet, pollution, and traditional Korean medical practices, should also be examined for their potential influence on Lp(a) levels.

Development of cost-effective and standardized testing methods

Accurate measurement of Lp(a) is globally challenged by isoform size heterogeneity and assay variability, with Korea being no exception. Most laboratories still rely on isoform-sensitive assays, leading to inconsistent and potentially misleading values. There is a critical need to develop cost-effective, isoform-insensitive assays that are calibrated to global reference standards, such as the WHO/IFCC SRM-2B. Standardizing the reporting of Lp(a) in nmol/L, rather than mg/dL, is essential to harmonize data and enable meaningful clinical

interpretation. In the near future, integrating Lp(a) testing into routine CV risk assessments within Korean healthcare systems is key to more accurately identifying high-risk individuals, and facilitating timely intervention.

Cascade screening program in Korea

Major CV prevention guidelines recommend measuring Lp(a) either once in a lifetime for individuals with potential CV risk, or selectively in those at the highest CV risk.[3)105)109)141)] These conditions include family hypercholesterolemia, CAVS, moderate to high CV risk, and insufficient LDL-C reduction despite aggressive lipid-lowering therapy. Given the hereditary nature of Lp(a) concentrations, family-based screening can be a proactive measure for the early detection of individuals at risk. Implementing cascade screening programs that target families with a history of high Lp(a) or premature ASCVD is an important step.[3)109)] Establishing national databases for Lp(a) levels would facilitate better tracking and identification of familial clusters. These efforts would also help assess the cost-effectiveness and feasibility of family-based interventions within the Korean healthcare system.

Integrating lipoprotein(a) into risk prediction and mechanistic research

Conventional CV risk calculators do not adequately incorporate Lp(a), potentially underestimating risk in individuals with elevated levels. Developing and validating risk prediction models that include Lp(a) as a weighted variable, especially in the Korean population, is essential to improve risk stratification.

Further mechanistic studies are needed to elucidate how Lp(a) contributes to atherosclerosis and thrombosis. This includes investigating OxPL, inflammation, and the interactions of Lp(a) with other lipoproteins, such as LDL and ApoB. Advanced imaging techniques and biomarker research may aid in identifying early signs of Lp(a)-mediated vascular injury and guide the development of targeted intervention.

Recommendations on lipoprotein(a) in the Korean population

Since the publication of the 2022 Korean dyslipidemia guidelines,[142)] scientific evidence regarding Lp(a) has been increasingly accumulating in Korea. In line with international guidelines and consensus statements, and considering the Korean context, key recommendations were developed and are summarized in the Recommendation box.

Recommendation box. Proposed recommendations for lipoprotein(a) screening and risk thresholds in Korea

Proposed recommendations
· Lp(a) screening should be considered at least once in all adults to refine ASCVD risk assessment, particularly in those with a family history of premature ASCVD or familial hypercholesterolemia.
· Cascade screening should be considered in individuals with elevated Lp(a) levels.
· An Lp(a) level ≥50 mg/dL (approximately 120 nmol/L) is generally considered a cut-off value for increased ASCVD risk; however, in the Korean population, elevated risk may be observed at levels ≥30 mg/dL, particular in individuals with additional CV risk factors.
· Lp(a) may be considered as a potential risk enhancer in determining the intensity of treatment for CV risk factors.
· Although Lp(a) assays are not fully standardized, reporting in nmol/L is preferable, whenever possible.

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SUMMARY

Lp(a) is a genetically determined, independent risk factor for ASCVD and CAVS, with consistent associations across diverse populations. Despite growing global consensus on its clinical importance, Lp(a) measurement and management remain underutilized in Korean practice. This position paper consolidates current evidence on Lp(a) biology, distribution, assay methodology, thresholds, and therapeutic strategies, with a focus on Korean data. It proposes a practical 3-tiered classification, underscores the need for isoform-insensitive assays calibrated to WHO/IFCC standards, and reviews novel therapies, such as ASOs, siRNAs, and small-molecule inhibitors. Emphasis is placed on the importance of integrating Lp(a) assessment in routine practice. A call to action is extended to healthcare providers, policymakers, and researchers to prioritize national strategies for screening, research, and equitable access to future Lp(a)-targeted therapies.

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REFERENCES

1. Kwon O, Lee SY, Kim B, et al. Dyslipidemia fact sheet in South Korea, 2024. *J Lipid Atheroscler* 2025;14:298-311. PUBMED | CROSSREF
2. Kang HJ, Wang J, Cho EJ, et al. Addressing cardiovascular diseases challenges in South Korea: strategies to improve outcomes. *Korean Circ J* 2025;55:557-83. PUBMED | CROSSREF
3. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J* 2022;43:3925-46. PUBMED | CROSSREF
4. Berg K. A new serum type system in man--the Lp system. *Acta Pathol Microbiol Scand* 1963;59:369-82. PUBMED | CROSSREF
5. Berg K, Dahlén G, Frick MH. Lp(a) lipoprotein and pre-beta1-lipoprotein in patients with coronary heart disease. *Clin Genet* 1974;6:230-5. PUBMED | CROSSREF
6. Albers JJ, Adolphson JL, Hazzard WR. Radioimmunoassay of human plasma Lp(a) lipoprotein. *J Lipid Res* 1977;18:331-8. PUBMED | CROSSREF
7. Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. *Atherosclerosis* 1981;38:51-61. PUBMED | CROSSREF
8. McLean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature* 1987;330:132-7. PUBMED | CROSSREF
9. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009;361:2518-28. PUBMED | CROSSREF
10. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009;302:412-23. PUBMED | CROSSREF
11. Saleheen D, Haycock PC, Zhao W, et al. Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis. *Lancet Diabetes Endocrinol* 2017;5:524-33. PUBMED | CROSSREF

12. Jang AY, Han SH, Sohn IS, Oh PC, Koh KK. Lipoprotein(a) and cardiovascular diseases - revisited. *Circ J* 2020;84:867-74. PUBMED | CROSSREF
13. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2019;140:e596-646. PUBMED | CROSSREF
14. Wilson DP, Jacobson TA, Jones PH, et al. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol* 2022;16:e77-95. PUBMED | CROSSREF
15. Mach F, Koskinas KC, Roeters van Lennep JE, et al. Focused update of the 2019 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2025;46:4359-78. PUBMED | CROSSREF
16. Toth PP. Familial hypercholesterolemia and lipoprotein(a): unraveling the knot that binds them. *J Am Coll Cardiol* 2020;75:2694-7. PUBMED | CROSSREF
17. Utermann G, Weber W. Protein composition of Lp(a) lipoprotein from human plasma. *FEBS Lett* 1983;154:357-61. PUBMED | CROSSREF
18. Lawn RM, Schwartz K, Patthy L. Convergent evolution of apolipoprotein(a) in primates and hedgehog. *Proc Natl Acad Sci U S A* 1997;94:11992-7. PUBMED | CROSSREF
19. Koschinsky ML, Côté GP, Gabel B, van der Hoek YY. Identification of the cysteine residue in apolipoprotein(a) that mediates extracellular coupling with apolipoprotein B-100. *J Biol Chem* 1993;268:19819-25. PUBMED | CROSSREF
20. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol* 2017;69:692-711. PUBMED | CROSSREF
21. Bergmark C, Dewan A, Orsoni A, et al. A novel function of lipoprotein [a] as a preferential carrier of oxidized phospholipids in human plasma. *J Lipid Res* 2008;49:2230-9. PUBMED | CROSSREF
22. Krempler F, Kostner G, Bolzano K, Sandhofer F. Lipoprotein (a) is not a metabolic product of other lipoproteins containing apolipoprotein B. *Biochim Biophys Acta* 1979;575:63-70. PUBMED | CROSSREF
23. Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res* 2016;57:1339-59. PUBMED | CROSSREF
24. Cain WJ, Millar JS, Himebauch AS, et al. Lipoprotein [a] is cleared from the plasma primarily by the liver in a process mediated by apolipoprotein [a]. *J Lipid Res* 2005;46:2681-91. PUBMED | CROSSREF
25. Rader DJ, Cain W, Ikewaki K, et al. The inverse association of plasma lipoprotein(a) concentrations with apolipoprotein(a) isoform size is not due to differences in Lp(a) catabolism but to differences in production rate. *J Clin Invest* 1994;93:2758-63. PUBMED | CROSSREF
26. Utermann G, Menzel HJ, Kraft HG, Duba HC, Kemmler HG, Seitz C. Lp(a) glycoprotein phenotypes. Inheritance and relation to Lp(a)-lipoprotein concentrations in plasma. *J Clin Invest* 1987;80:458-65. PUBMED | CROSSREF
27. Watts GF, Chan DC, Somaratne R, et al. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. *Eur Heart J* 2018;39:2577-85. PUBMED | CROSSREF
28. White AL, Hixson JE, Rainwater DL, Lanford RE. Molecular basis for "null" lipoprotein(a) phenotypes and the influence of apolipoprotein(a) size on plasma lipoprotein(a) level in the baboon. *J Biol Chem* 1994;269:9060-6. PUBMED | CROSSREF
29. Krempler F, Kostner GM, Bolzano K, Sandhofer F. Turnover of lipoprotein (a) in man. *J Clin Invest* 1980;65:1483-90. PUBMED | CROSSREF
30. White AL. Biogenesis of Lp(a) in transgenic mouse hepatocytes. *Clin Genet* 1997;52:326-37. PUBMED | CROSSREF
31. White AL, Lanford RE. Cell surface assembly of lipoprotein(a) in primary cultures of baboon hepatocytes. *J Biol Chem* 1994;269:28716-23. PUBMED | CROSSREF
32. Hrzenjak A, Frank S, Wo X, Zhou Y, Van Berkel T, Kostner GM. Galactose-specific asialoglycoprotein receptor is involved in lipoprotein (a) catabolism. *Biochem J* 2003;376:765-71. PUBMED | CROSSREF
33. Seimon TA, Nadolski MJ, Liao X, et al. Atherogenic lipids and lipoproteins trigger CD36-TLR2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. *Cell Metab* 2010;12:467-82. PUBMED | CROSSREF
34. McCormick SPA, Schneider WJ. Lipoprotein(a) catabolism: a case of multiple receptors. *Pathology* 2019;51:155-64. PUBMED | CROSSREF
35. Trinder M, DeCastro ML, Azizi H, et al. Ascertainment bias in the association between elevated lipoprotein(a) and familial hypercholesterolemia. *J Am Coll Cardiol* 2020;75:2682-93. PUBMED | CROSSREF

36. Patel AP, Wang M, Pirruccello JP, et al. Lp(a) (lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol* 2021;41:465-74. PUBMED | CROSSREF

37. Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. *J Lipid Res* 2016;57:1111-25. PUBMED | CROSSREF

38. Coassin S, Kronenberg F. Lipoprotein(a) beyond the kringle IV repeat polymorphism: the complexity of genetic variation in the LPA gene. *Atherosclerosis* 2022;349:17-35. PUBMED | CROSSREF

39. Chretien JP, Coresh J, Berthier-Schaad Y, et al. Three single-nucleotide polymorphisms in LPA account for most of the increase in lipoprotein(a) level elevation in African Americans compared with European Americans. *J Med Genet* 2006;43:917-23. PUBMED | CROSSREF

40. Kyriakou T, Seedorf U, Goel A, et al. A common LPA null allele associates with lower lipoprotein(a) levels and coronary artery disease risk. *Arterioscler Thromb Vasc Biol* 2014;34:2095-9. PUBMED | CROSSREF

41. Lee SR, Prasad A, Choi YS, et al. LPA gene, ethnicity, and cardiovascular events. *Circulation* 2017;135:251-63. PUBMED | CROSSREF

42. Lim ET, Würtz P, Havulinna AS, et al. Distribution and medical impact of loss-of-function variants in the Finnish founder population. *PLoS Genet* 2014;10:e1004494. PUBMED | CROSSREF

43. Schachtl-Riess JF, Kheirkhah A, Grüneis R, et al. Frequent LPA KIV-2 variants lower lipoprotein(a) concentrations and protect against coronary artery disease. *J Am Coll Cardiol* 2021;78:437-49. PUBMED | CROSSREF

44. Grüneis R, Lamina C, Di Maio S, et al. The effect of LPA Thr3888Pro on lipoprotein(a) and coronary artery disease is modified by the LPA KIV-2 variant 4925G>A. *Atherosclerosis* 2022;349:151-9. PUBMED | CROSSREF

45. Aggarwal HK, Jain D, Lathar M, Yadav RK, Sawhney A. Lipoprotein-A and carotid intima media thickness as cardiovascular risk factors in patients of chronic kidney disease. *Ren Fail* 2010;32:647-52. PUBMED | CROSSREF

46. Angelin B, Kristensen JD, Eriksson M, et al. Reductions in serum levels of LDL cholesterol, apolipoprotein B, triglycerides and lipoprotein(a) in hypercholesterolaemic patients treated with the liver-selective thyroid hormone receptor agonist eprotirome. *J Intern Med* 2015;277:331-42. PUBMED | CROSSREF

47. Boffelli D, Zajchowski DA, Yang Z, Lawn RM. Estrogen modulation of apolipoprotein(a) expression. Identification of a regulatory element. *J Biol Chem* 1999;274:15569-74. PUBMED | CROSSREF

48. Enkhmaa B, Berglund L. Non-genetic influences on lipoprotein(a) concentrations. *Atherosclerosis* 2022;349:53-62. PUBMED | CROSSREF

49. Kaplan SA, Lin J, Johnson-Levonas AO, Shah AK, Meehan AG. Increased occurrence of marked elevations of lipoprotein(a) in ageing, hypercholesterolaemic men with low testosterone. *Aging Male* 2010;13:40-3. PUBMED | CROSSREF

50. Kotwal A, Cortes T, Genere N, et al. Treatment of thyroid dysfunction and serum lipids: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2020;105:dgaa672. PUBMED | CROSSREF

51. Matveyenko A, Seid H, Kim K, et al. Association of free-living diet composition with plasma lipoprotein(a) levels in healthy adults. *Lipids Health Dis* 2023;22:144. PUBMED | CROSSREF

52. Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. *JAMA* 2000;283:1845-52. PUBMED | CROSSREF

53. Ebbeling CB, Knapp A, Johnson A, et al. Effects of a low-carbohydrate diet on insulin-resistant dyslipoproteinemia-a randomized controlled feeding trial. *Am J Clin Nutr* 2022;115:154-62. PUBMED | CROSSREF

54. Schnitzler JG, Hoogeveen RM, Ali L, et al. Atherogenic lipoprotein(a) increases vascular glycolysis, thereby facilitating inflammation and leukocyte extravasation. *Circ Res* 2020;126:1346-59. PUBMED | CROSSREF

55. van der Valk FM, Bekkering S, Kroon J, et al. Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans. *Circulation* 2016;134:611-24. PUBMED | CROSSREF

56. Dzobo KE, Kraaijenhof JM, Stroes ESG, Nurmohamed NS, Kroon J. Lipoprotein(a): an underestimated inflammatory mastermind. *Atherosclerosis* 2022;349:101-9. PUBMED | CROSSREF

57. Nurmohamed NS, Collard D, Reeskamp LF, et al. Lipoprotein(a), venous thromboembolism and COVID-19: a pilot study. *Atherosclerosis* 2022;341:43-9. PUBMED | CROSSREF

58. Boffa MB. Beyond fibrinolysis: the confounding role of Lp(a) in thrombosis. *Atherosclerosis* 2022;349:72-81. PUBMED | CROSSREF

59. Capoulade R, Chan KL, Yeang C, et al. Oxidized phospholipids, lipoprotein(a), and progression of calcific aortic valve stenosis. *J Am Coll Cardiol* 2015;66:1236-46. PUBMED | CROSSREF

60. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. *J Am Coll Cardiol* 2012;60:722-9. PUBMED | CROSSREF

61. Kamstrup PR, Tybjærg-Hansen A, Nordestgaard BG. Genetic evidence that lipoprotein(a) associates with atherosclerotic stenosis rather than venous thrombosis. *Arterioscler Thromb Vasc Biol* 2012;32:1732-41. PUBMED | CROSSREF

62. Lamina C. Mendelian randomization: principles and its usage in Lp(a) research. *Atherosclerosis* 2022;349:36-41. PUBMED | CROSSREF

63. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res* 2016;57:1953-75. PUBMED | CROSSREF

64. Bouchareb R, Mahmut A, Nsaibia MJ, et al. Autotaxin derived from lipoprotein(a) and valve interstitial cells promotes inflammation and mineralization of the aortic valve. *Circulation* 2015;132:677-90. PUBMED | CROSSREF

65. Yu B, Hafiane A, Thanassoulis G, et al. Lipoprotein(a) induces human aortic valve interstitial cell calcification. *JACC Basic Transl Sci* 2017;2:358-71. PUBMED | CROSSREF

66. Hu J, Lei H, Liu L, Xu D. Lipoprotein(a), a lethal player in calcific aortic valve disease. *Front Cell Dev Biol* 2022;10:812368. PUBMED | CROSSREF

67. Mehta A, Jain V, Saeed A, et al. Lipoprotein(a) and ethnicities. *Atherosclerosis* 2022;349:42-52. PUBMED | CROSSREF

68. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2015;35:996-1001. PUBMED | CROSSREF

69. Paré G, Çaku A, McQueen M, et al. Lipoprotein(a) levels and the risk of myocardial infarction among 7 ethnic groups. *Circulation* 2019;139:1472-82. PUBMED | CROSSREF

70. Man S, Zu Y, Yang X, et al. Prevalence of elevated lipoprotein(a) and its association with subclinical atherosclerosis in 2.9 million Chinese adults. *J Am Coll Cardiol* 2025;85:1979-92. PUBMED | CROSSREF

71. Kim BJ, Lee MY, Choi HI, Kwon MJ, Kang JG. Lipoprotein(a)-related cardiovascular and all-cause mortalities in Korean adults. *Eur J Prev Cardiol* 2023;30:308-17. PUBMED | CROSSREF

72. Kim BJ, Kang J. Association of lipoprotein(a) and coronary artery calcium with atherosclerotic cardiovascular disease. *J Clin Lipidol* 2025;19:521-30. PUBMED | CROSSREF

73. Choi R, Park M, Oh Y, et al. Prevalence of elevated lipoprotein(a) levels in Korean: a large population-based study. *Clin Investig (Lond)* 2019;9:47-53.

74. Lee H, Park KS, Jeon YJ, et al. Lipoprotein(a) and subclinical coronary atherosclerosis in asymptomatic individuals. *Atherosclerosis* 2022;349:190-5. PUBMED | CROSSREF

75. Lee A, Koh HM, Jang JY, et al. Association of lipoprotein(a) with progression of coronary artery calcification: retrospective longitudinal study. *Korean J Fam Med* 2025;46:176-84. PUBMED | CROSSREF

76. Choi R, Lee SG, Lee EH. Lipoprotein(a) in the Korean pediatric population visiting local clinics and hospitals. *Nutrients* 2022;14:2820. PUBMED | CROSSREF

77. Jun JE, Kang H, Hwang YC, Ahn KJ, Chung HY, Jeong IK. The association between lipoprotein (a) and carotid atherosclerosis in patients with type 2 diabetes without pre-existing cardiovascular disease: a cross-sectional study. *Diabetes Res Clin Pract* 2021;171:108622. PUBMED | CROSSREF

78. Lim TS, Yun JS, Cha SA, et al. Elevated lipoprotein(a) levels predict cardiovascular disease in type 2 diabetes mellitus: a 10-year prospective cohort study. *Korean J Intern Med* 2016;31:1110-9. PUBMED | CROSSREF

79. Park JS, Cho KH, Hong YJ, et al. Baseline lipoprotein(a) levels and long-term cardiovascular outcomes after acute myocardial infarction. *J Korean Med Sci* 2023;38:e102. PUBMED | CROSSREF

80. Yoon YH, Ahn JM, Kang DY, et al. Association of lipoprotein(a) with recurrent ischemic events following percutaneous coronary intervention. *JACC Cardiovasc Interv* 2021;14:2059-68. PUBMED | CROSSREF

81. Sandholzer C, Saha N, Kark JD, et al. Apo(a) isoforms predict risk for coronary heart disease. A study in six populations. *Arterioscler Thromb* 1992;12:1214-26. PUBMED | CROSSREF

82. Lamina C, Kronenberg F; Lp(a)-GWAS-Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. *JAMA Cardiol* 2019;4:575-9. PUBMED | CROSSREF

83. Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. *JAMA Cardiol* 2018;3:619-27. PUBMED | CROSSREF

84. Arsenault BJ, Boekholdt SM, Dubé MP, et al. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. *Circ Cardiovasc Genet* 2014;7:304-10. PUBMED | CROSSREF

85. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331-9. PUBMED | CROSSREF

86. Satterfield BA, Dikilitas O, Safarova MS, et al. Associations of genetically predicted Lp(a) (lipoprotein [a]) levels with cardiovascular traits in individuals of European and African ancestry. *Circ Genom Precis Med* 2021;14:e003354. PUBMED | CROSSREF

87. Emdin CA, Khera AV, Natarajan P, et al. Phenotypic characterization of genetically lowered human lipoprotein(a) levels. *J Am Coll Cardiol* 2016;68:2761-72. PUBMED | CROSSREF

88. Kamstrup PR, Nordestgaard BG. Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure in the general population. *JACC Heart Fail* 2016;4:78-87. PUBMED | CROSSREF

89. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013;368:503-12. PUBMED | CROSSREF

90. Arsenault BJ, Loganath K, Girard A, et al. Lipoprotein(a) and calcific aortic valve stenosis progression: a systematic review and meta-analysis. *JAMA Cardiol* 2024;9:835-42. PUBMED | CROSSREF

91. Nsaibia MJ, Mahmut A, Boulanger MC, et al. Autotaxin interacts with lipoprotein(a) and oxidized phospholipids in predicting the risk of calcific aortic valve stenosis in patients with coronary artery disease. *J Intern Med* 2016;280:509-17. PUBMED | CROSSREF

92. Januzzi JL Jr, van Kimmenade RRJ, Liu Y, et al. Lipoprotein(a), oxidized phospholipids, and progression to symptomatic heart failure: the CASABLANCA study. *J Am Heart Assoc* 2024;13:e034774. PUBMED | CROSSREF

93. Wadström BN, Wulff AB, Pedersen KM, Nordestgaard BG. Remnant cholesterol in the era of intensive lipid-lowering therapies. *Eur Heart J* 2023;44:3483. PUBMED | CROSSREF

94. Kim AR, Ahn JM, Kang DY, et al. Association of lipoprotein(a) with severe degenerative aortic valve stenosis. *JACC Asia* 2024;4:751-60. PUBMED | CROSSREF

95. Willeit P, Ridker PM, Nestel PJ, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet* 2018;392:1311-20. PUBMED | CROSSREF

96. Verbeek R, Hoogeveen RM, Langsted A, et al. Cardiovascular disease risk associated with elevated lipoprotein(a) attenuates at low low-density lipoprotein cholesterol levels in a primary prevention setting. *Eur Heart J* 2018;39:2589-96. PUBMED | CROSSREF

97. Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol* 2020;75:133-44. PUBMED | CROSSREF

98. Small AM, Pournamdari A, Melloni GEM, et al. Lipoprotein(a), C-reactive protein, and cardiovascular risk in primary and secondary prevention populations. *JAMA Cardiol* 2024;9:385-91. PUBMED | CROSSREF

99. Li JJ, Zhao SP, Zhao D, et al. 2023 Chinese guideline for lipid management. *Front Pharmacol* 2023;14:1190934. PUBMED | CROSSREF

100. Ward NC, Watts GF, Bishop W, et al. Australian Atherosclerosis Society position statement on lipoprotein(a): clinical and implementation recommendations. *Heart Lung Circ* 2023;32:287-96. PUBMED | CROSSREF

101. Chiesa G, Zenti MG, Baragetti A, et al. Consensus document on lipoprotein(a) from the Italian Society for the Study of Atherosclerosis (SISA). *Nutr Metab Cardiovasc Dis* 2023;33:1866-77. PUBMED | CROSSREF

102. Delgado-Lista J, Mostaza JM, Arrobas-Velilla T, et al. Consensus on lipoprotein(a) of the Spanish Society of Arteriosclerosis. Literature review and recommendations for clinical practice. *Clin Investig Arterioscler* 2024;36:243-66. PUBMED | CROSSREF

103. Cegla J, Neely RDG, France M, et al. HEART UK consensus statement on lipoprotein(a): a call to action. *Atherosclerosis* 2019;291:62-70. PUBMED | CROSSREF

104. Sosnowska B, Stepinska J, Mitkowski P, et al. Recommendations of the Experts of the Polish Cardiac Society (PCS) and the Polish Lipid Association (PoLA) on the diagnosis and management of elevated lipoprotein(a) levels. *Arch Med Sci* 2024;20:8-27. PUBMED | CROSSREF

105. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in adults. *Can J Cardiol* 2021;37:1129-50. PUBMED | CROSSREF

106. Li JJ, Ma CS, Zhao D, Yan XW; Beijing Heart Society and Expert Committee. Lipoprotein(a) and cardiovascular disease in Chinese population: a Beijing Heart Society expert scientific statement. *JACC Asia* 2022;2:653-65. PUBMED | CROSSREF

107. Okamura T, Tsukamoto K, Arai H, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2022. *J Atheroscler Thromb* 2024;31:641-853. PUBMED | CROSSREF

108. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. *J Lipid Res* 2016;57:526-37. PUBMED | CROSSREF

109. Koschinsky ML, Bajaj A, Boffa MB, et al. A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice. *J Clin Lipidol* 2024;18:e308-19. PUBMED | CROSSREF

110. Cegla J, France M, Marcovina SM, Neely RDG. Lp(a): when and how to measure it. *Ann Clin Biochem* 2021;58:16-21. PUBMED | CROSSREF

111. Awad K, Mahmoud AK, Abbas MT, et al. Intra-individual variability in lipoprotein(a) levels: findings from a large academic health system population. *Eur J Prev Cardiol* 2025;32:716-21. PUBMED | CROSSREF

112. Gaba P, Rosenson RS, López JAG, et al. Intraindividual variability in serial lipoprotein(a) concentrations among placebo-treated patients in the OCEAN(a)-DOSE trial. *J Am Coll Cardiol* 2025;85:550-3. PUBMED | CROSSREF

113. Silaste ML, Rantala M, Alfthan G, et al. Changes in dietary fat intake alter plasma levels of oxidized low-density lipoprotein and lipoprotein(a). *Arterioscler Thromb Vasc Biol* 2004;24:498-503. PUBMED | CROSSREF

114. Faghihnia N, Tsimikas S, Miller ER, Witztum JL, Krauss RM. Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J Lipid Res* 2010;51:3324-30. PUBMED | CROSSREF

115. Haring B, von Ballmoos MC, Appel LJ, Sacks FM. Healthy dietary interventions and lipoprotein (a) plasma levels: results from the Omni Heart trial. *PLoS One* 2014;9:e114859. PUBMED | CROSSREF

116. Perrot N, Verbeek R, Sandhu M, et al. Ideal cardiovascular health influences cardiovascular disease risk associated with high lipoprotein(a) levels and genotype: the EPIC-Norfolk prospective population study. *Atherosclerosis* 2017;256:47-52. PUBMED | CROSSREF

117. Taimela S, Viikari JS, Porkka KV, Dahlen GH. Lipoprotein (a) levels in children and young adults: the influence of physical activity. The Cardiovascular Risk in Young Finns Study. *Acta Paediatr* 1994;83:1258-63. PUBMED | CROSSREF

118. Israel RG, Sullivan MJ, Marks RH, Cayton RS, Chenier TC. Relationship between cardiorespiratory fitness and lipoprotein(a) in men and women. *Med Sci Sports Exerc* 1994;26:425-31. PUBMED | CROSSREF

119. de Boer LM, Oorthuys AOJ, Wiegman A, et al. Statin therapy and lipoprotein(a) levels: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2022;29:779-92. PUBMED | CROSSREF

120. Jaeger BR, Richter Y, Nagel D, et al. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. *Nat Clin Pract Cardiovasc Med* 2009;6:229-39. PUBMED | CROSSREF

121. Leebmann J, Roeseler E, Julius U, et al. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease: prospective observational multicenter study. *Circulation* 2013;128:2567-76. PUBMED | CROSSREF

122. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). *J Am Coll Cardiol* 2013;62:1575-9. PUBMED | CROSSREF

123. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;357:2109-22. PUBMED | CROSSREF

124. Nicholls SJ, Brewer HB, Kastelein JJ, et al. Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. *JAMA* 2011;306:2099-109. PUBMED | CROSSREF

125. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;367:2089-99. PUBMED | CROSSREF

126. Cannon CP, Shah S, Dansky HM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med* 2010;363:2406-15. PUBMED | CROSSREF

127. Hovingh GK, Kastelein JJ, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* 2015;386:452-60. PUBMED | CROSSREF

128. Ray KK, Wright RS, Kallend D, et al. Two Phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;382:1507-19. PUBMED | CROSSREF

129. Huo Y, Lesogor A, Lee CW, et al. Efficacy and safety of inclisiran in Asian patients: results from ORION-18. *JACC Asia* 2024;4:123-34. PUBMED | CROSSREF

130. Santos RD, Raal FJ, Catapano AL, Witztum JL, Steinhagen-Thiessen E, Tsimikas S. Mipomersen, an antisense oligonucleotide to apolipoprotein B-100, reduces lipoprotein(a) in various populations with hypercholesterolemia: results of 4 phase III trials. *Arterioscler Thromb Vasc Biol* 2015;35:689-99. PUBMED | CROSSREF

131. Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lp(a) (lipoprotein[a])-lowering by 50 mg/dL (105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study. *Arterioscler Thromb Vasc Biol* 2020;40:255-66. PUBMED | CROSSREF

132. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med* 2020;382:244-55. PUBMED | CROSSREF

133. O'Donoghue ML, Rosenson RS, Gencer B, et al. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. *N Engl J Med* 2022;387:1855-64. PUBMED | CROSSREF

134. Nissen SE, Wolski K, Balog C, et al. Single ascending dose study of a short interfering RNA targeting lipoprotein(a) production in individuals with elevated plasma lipoprotein(a) levels. *JAMA* 2022;327:1679-87. PUBMED | CROSSREF

135. Nissen SE, Wang Q, Nicholls SJ, et al. Zerlasiran-a small-interfering RNA targeting lipoprotein(a): a phase 2 randomized clinical trial. *JAMA* 2024;332:1992-2002. PUBMED | CROSSREF

136. Nissen SE, Linnebjerg H, Shen X, et al. Lepodisiran, an extended-duration short interfering RNA targeting lipoprotein(a): a randomized dose-ascending clinical trial. *JAMA* 2023;330:2075-83. PUBMED | CROSSREF

137. Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an oral small molecule inhibitor of lipoprotein(a) formation: a randomized clinical trial. *JAMA* 2023;330:1042-53. PUBMED | CROSSREF

138. Nicholls SJ, Ni W, Rhodes GM, et al. Oral muvalaplin for lowering of lipoprotein(a): a randomized clinical trial. *JAMA* 2025;333:222-31. PUBMED | CROSSREF

139. Nissen SE, Ni W, Shen X, et al. Lepodisiran - a long-duration small interfering RNA targeting lipoprotein(a). *N Engl J Med* 2025;392:1673-83. PUBMED | CROSSREF

140. Cho L, Nicholls SJ, Nordestgaard BG, et al. Design and rationale of Lp(a)HORIZON trial: assessing the effect of lipoprotein(a) lowering with pelacarsen on major cardiovascular events in patients with CVD and elevated Lp(a). *Am Heart J* 2025;287:1-9. PUBMED | CROSSREF

141. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88. PUBMED | CROSSREF

142. Korean Society of Lipid and Atherosclerosis. Korean Guidelines for the Management of Dyslipidemia (the 5th edition) [Internet]. Seoul: Korean Society of Lipid and Atherosclerosis; 2022 [cited 2022 November 30]. Available from: https://www.lipid.or.kr/reference/guideline.php?boardid=guideline&-mode=view&idx=1281&sk=&sw=&offset=&category.