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Review

Lipoprotein(a) and Cardiovascular Risk in Asian Populations: A Comprehensive Review

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein particle that plays a causal role in atherosclerotic cardiovascular disease (ASCVD), ischemic stroke, and calcific aortic valve stenosis. Structurally similar to low-density lipoprotein, Lp(a) contains apolipoprotein(a) [apo(a)], which imparts unique atherogenic properties. Although Lp(a) levels vary significantly by ethnicity, East Asians generally have lower median concentrations, attributed to a higher frequency of large apo(a) isoforms and fewer high-risk *LPA* gene variants. However, even modest elevations in Lp(a) are associated with increased ASCVD risk in Asians, especially among high-risk populations. Observational studies from Asian populations have shown that elevated Lp(a) levels are linked to coronary artery calcification, myocardial infarction, stroke, and recurrent cardiovascular events. Novel therapeutic agents, including proprotein convertase subtilisin/kexin type 9 inhibitors, inclisiran, and antisense oligonucleotides such as pelacarsen, have demonstrated promising effects in lowering Lp(a). These therapies are currently under investigation in outcome trials, including Asian subgroups. Given the high burden of cardiovascular disease and ethnic variability in Lp(a) distribution and genetic determinants, routine measurement of Lp(a) could improve risk stratification and therapeutic decision-making. This review summarizes current evidence regarding the epidemiology, genetic background, clinical relevance, and emerging therapeutic strategies targeting Lp(a) in Asian populations, highlighting the need for population-specific thresholds and further research to guide clinical practice.

Keywords: Lipoprotein(a); Cardiovascular diseases; Atherosclerosis; Asian

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a cholesterol-rich lipoprotein particle associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD). Structurally, it resembles low-density lipoprotein (LDL) but is distinguished by apolipoprotein(a) [apo(a)], which confers unique proatherogenic, proinflammatory, and prothrombotic properties.[1,2] Numerous studies, including large-scale meta-analyses and Mendelian randomization trials, have established elevated Lp(a) as an independent and causal risk factor for ASCVD.[3,4]

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Plasma Lp(a) levels are primarily genetically determined and exhibit wide interindividual and interethnic variation.[5] Asian populations typically have lower circulating Lp(a) concentrations compared to other ethnic groups, likely due to differences in apo(a) isoform size and LPA gene polymorphisms. Nonetheless, even modest elevations in Lp(a) are linked to increased ASCVD risk among Asians, underscoring the importance of understanding population-specific thresholds and therapeutic implications.[6,7]

This review summarizes the current understanding of Lp(a) biology and its clinical implications in Asian populations.

ETHNIC VARIATION IN Lp(a) LEVELS AND GENETIC DETERMINANTS IN ASIANS

Lp(a) consists of an LDL-like core containing apoB-100 covalently linked to apo(a), a highly polymorphic glycoprotein structurally homologous to plasminogen.[1] Apo(a) contains multiple Kringle domains, notably the Kringle IV type 2 (KIV-2) domain, which varies considerably in copy number, ranging from fewer than 5 to over 40 repeats.[8] Variation in KIV-2 repeat number generates apo(a) isoforms of different sizes, which undergo distinct intracellular processing. This isoform size variation inversely correlates with plasma Lp(a) concentration: individuals with larger apo(a) isoforms (higher KIV-2 repeat number) tend to have lower Lp(a) levels, whereas fewer repeats result in smaller isoforms and higher Lp(a) concentrations.[9] Mendelian randomization studies, including the Pakistan Risk of Myocardial Infarction Study (PROMIS)[10] and the CARDIoGRAMplusC4D consortium,[11] have consistently demonstrated that smaller apo(a) isoforms and elevated plasma Lp(a) independently and causally increase coronary heart disease risk. Asian populations generally have larger apo(a) isoforms due to a higher prevalence of alleles with more KIV-2 repeats, contributing to relatively lower plasma Lp(a) levels compared to other ethnicities. For example, the INTERHEART study showed that Chinese individuals have the lowest Lp(a) levels and largest isoform sizes among studied ethnic groups.[6] Additionally, data from the UK biobank[7] revealed substantial ethnic differences in median Lp(a) concentration (19 nmol/L in Whites, 31 nmol/L in South Asians, 75 nmol/L in Blacks, and 16 nmol/L in Chinese).

In addition to KIV-2 copy number variation, specific single nucleotide polymorphisms (SNPs) in the *LPA* gene influence Lp(a) levels. Several SNPs associated with high Lp(a) levels in European populations, such as rs10455872 and rs3798220, are either absent or extremely rare in East Asian populations, partly explaining ethnic differences in Lp(a) concentrations.[5] Conversely, SNPs more commonly identified in Asians may be associated with lower Lp(a) levels,[12] although these variants are less characterized due to limited genome-wide association studies in Asian populations. Some studies have identified Asian-specific or enriched SNPs, such as rs6415084 and rs9457951, that may influence Lp(a) regulation within these populations.[13]

Overall, the combination of larger apo(a) isoforms due to increased KIV-2 repeats and the lower prevalence of high-risk *LPA* alleles explains the lower median Lp(a) levels observed in East Asians. Additionally, emerging evidence suggests that epigenetic modifications and regulatory elements outside the *LPA* coding region may partially explain the lower Lp(a) concentrations commonly observed in Asian populations.[14] However, despite lower average levels, individuals with genetically elevated Lp(a) in these populations still exhibit significantly increased ASCVD risk, highlighting the need for ethnicity-specific genetic and clinical assessment frameworks.

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PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING THE ATHEROGENICITY OF Lp(a)

Lp(a) exerts proatherogenic effects through multiple distinct mechanisms.[2] First, due to the structural homology between apo(a) and plasminogen, Lp(a) interferes with the fibrinolytic system by competing with plasminogen binding and inhibiting plasmin generation *in vitro*,[15] although supporting clinical evidence remains limited.[16,17] Second, similar to LDL, Lp(a) delivers cholesterol to the arterial wall; however, it is more atherogenic because of its high content of oxidized phospholipids (OxPLs). These OxPLs serve as key mediators of vascular inflammation, endothelial dysfunction, smooth muscle cell proliferation, and foam cell formation.[18] Specifically, Lp(a)-bound OxPLs activate monocyte and macrophage pathways, accelerating atherosclerotic plaque formation and instability.[19] Furthermore, Lp(a) exhibits both pro-inflammatory and pro-thrombotic properties, contributing to oxidative stress and immune responses within the vascular wall. These characteristics position Lp(a) not merely as an LDL subclass but as a potent and independent risk factor for ASCVD.

EPIDEMIOLOGICAL EVIDENCE LINKING Lp(a) TO ASCVD IN ASIAN POPULATIONS

Plasma Lp(a) levels display a highly skewed distribution, with a small subset of individuals exhibiting markedly elevated concentrations.[20] Given the lifelong genetic determination of Lp(a) levels and its causal relationship with cardiovascular disease, routine measurement of Lp(a) at least once in a lifetime is now widely recommended. Epidemiological studies have consistently demonstrated that elevated Lp(a) levels are associated with increased ASCVD risk. However, universally accepted thresholds for risk stratification have yet to be established. The National Lipid Association (NLA) recommends an Lp(a) threshold of >50 mg/dL to identify a high-risk group for cardiovascular events,[21] whereas Chinese guidelines propose a lower cut-off of 30 mg/dL.[22] In South Korea, although no consensus currently exists, a large-scale cohort study suggested that Lp(a) levels >50 mg/dL are associated with increased all-cause and cardiovascular mortality.[23] The 2022 European Atherosclerosis Society (EAS) consensus statement introduced stratified cut-offs: <30 mg/dL (or <75 nmol/L) to "rule out" risk, >50 mg/dL (or >125 nmol/L) to "rule in" risk, and 30–50 mg/dL (75–125 nmol/L) as an intermediate gray zone.[24]

Numerous epidemiological studies, including prospective cohorts and Mendelian randomization analyses, have demonstrated a strong and graded association between Lp(a) concentrations and ASCVD risk, independent of LDL cholesterol (LDL-C) and other traditional risk factors. In the UK Biobank study, Lp(a) ≥150 nmol/L was observed in 12.2% of individuals without ASCVD and 20.3% with established ASCVD. Elevated Lp(a) levels were associated with a 50% increased risk of incident ASCVD in primary prevention (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.44, 1.56) and a 16% increased risk in secondary prevention (HR, 1.16; 95% CI, 1.05, 1.27).[7] The Copenhagen City Heart Study similarly demonstrated that elevated Lp(a) predicted myocardial infarction (MI), ischemic heart disease (IHD), and aortic stenosis (AS), independently of other risk factors.[17] A meta-analysis involving over 100,000 young individuals showed an especially strong association in South Asians (odds ratio [OR], 3.71; 95% CI, 2.31, 5.96), followed by Caucasians (OR, 3.17; 95% CI, 2.22, 4.52).[25] Additionally, the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial highlighted residual ASCVD risk among

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individuals with optimally controlled LDL-C, indicating a potential role for Lp(a) in residual risk stratification.[26]

These findings support the predictive value of Lp(a) in both primary and secondary prevention contexts, emphasizing the importance of better understanding and addressing Lp(a)-related risk across diverse populations. Herein, we summarize epidemiological evidence on the association between Lp(a) levels and cardiovascular risk specifically in Asian populations (**Table 1**).

Table 1. Epidemiological studies of the association between Lp(a) levels and cardiovascular risk in Asian populations

Study/Year	Population	Study design	Participants	Sample size	Lp(a) cut-off value	Key findings	Ref.
Primary prevention							
Hu et al. (2020)	Chinese	Retrospective case-control study	First incident AMI	1,522 cases, 1,691 controls	24.7 mg/dL < Lp(a) ≤213.8 mg/dL	The OR for the first incident AMI was 2.66 (95% CI, 1.88, 3.76) in the 5th quintile group. When both LDL-C and Lp(a) were elevated, the risk compared to the first quintile was an OR of 7.48 (95% CI, 4.90, 11.44).	31
Chung et al. (2021)	Korean	Cross-sectional	General health checkup	2,019	50 mg/dL	CAC score was significantly higher in the Lp(a) >50mg/dL group.	28
Lee et al. (2022)	Korean	Cross-sectional	General health checkup	7,201	Fourth quartile of Lp(a): ≥20.2 mg/dL	The highest quartile of Lp(a) was associated with any coronary plaque (OR, 1.21; 95% CI, 1.04, 1.42) and significant stenosis (OR, 1.54; 95% CI, 1.15, 2.05) compared to the first quartile.	29
Kim et al. (2022)	Korean	Cohort study	Health screening	275,430	Lp(a) ≥50 mg/dL	Individuals with Lp(a) ≥50 mg/dL had significantly increased CV mortality (HR, 1.83) and all-cause mortality (HR, 1.20); those with Lp(a) ≥100 mg/dL had >2-fold increased CV risk.	23
Qiu et al. (2024)	Asian	Meta-analysis	Mostly free of CVD	40,073	Lp(a) 30 mg/dL, 50 mg/dL, or the highest quartile (33–38.64 mg/dL)	Elevated Lp(a) was not associated with prevalence of CAC (OR, 1.28, 95% CI, 0.94, 1.75) or progression of CAC (OR, 1.73; 95% CI, 1.02, 2.94).	27
Kim et al. (2025)	Korean	Cross-sectional	Health screening	44,354	Lp(a) ≥120 nmol/L	High Lp(a) (11.9% prevalence) and a CAC score >0 were independently associated with prevalent ASCVD; joint elevation yielded an OR of 2.40 for ASCVD.	30
Secondary prevention							
Cao et al. (2020)	Chinese	Prospective cohort study	Post MI patients	3,864	Fourth quartile of Lp(a): ≥41.43 mg/dL	The highest Lp(a) quartile (≥41.43 mg/dL) had a 65% increased risk of recurrent CV events and an 84% higher risk of cardiac mortality compared to the lowest quartile (<8.19 mg/dL).	36
Liu et al. (2020)	Asian	Prospective cohort study	CAD undergoing PCI	4,078	Lp(a) ≥30 mg/dL	High Lp(a) group had significantly lower cumulative event-free survival and an independently increased risk of cardiovascular events after PCI.	37
Zhang et al. (2020)	Chinese	Prospective observational cohort study	T2DM	2,284	Lp(a) >30 mg/dL	Lp(a) ≥30 mg/dL was associated with a more than 2-fold increased risk of recurrent ASCVD events (HR, 2.05; 95% CI, 1.31, 3.21), independent of baseline HbA1c levels.	58
Yoon et al. (2021)	Korean	Prospective single-center study	Underwent PCI	12,064	Lp(a) >30 mg/dL	Lp(a) levels >30 mg/dL were associated with an increased risk of CV events (aHR, 1.17; 95% CI, 1.05, 1.30) and repeat revascularization (aHR, 1.18; 95% CI, 1.02, 1.25).	39
Loh et al. (2022)	Multi-ethnic Asian	Cross-sectional case-control study	Undergo coronary angiography	2,025	Lp(a) ≥120 nmol/L	Higher Lp(a) was linked to increased AMI risk (OR, 1.02 per 10 nmol/L) and greater CAD severity.	35
Park et al. (2023)	Korean	Prospective cohort study	Post AMI	1,908	Lp(a) ≥50 mg/dL	High baseline Lp(a) level was not an independent factor for an increased incidence of 3P-MACE.	38
Loh et al. (2024)	Multi ethnic Asian	Retrospective cohort study	Hospitalized patients with IHD	521	Lp(a) ≥120 nmol/L; Lp(a) ≥155 nmol/L in premature IHD	Lp(a) ≥155 nmol/L was independently associated with premature IHD (OR, 2.90; 95% CI, 1.26, 6.67).	41
Cheng et al. (2025)	Chinese	Prospective cohort study	Patients with ASCVD	26,752	Lp(a) ≥50 mg/dL	In very-high-risk ASCVD patients, elevated Lp(a) (≥50 mg/dL) was a significant predictor of 3-year cardiovascular events.	40

Lp(a), lipoprotein a; AMI, acute myocardial infarction; OR, odds ratio; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; CAC, coronary artery calcium; HR, hazard ratio; CV, cardiovascular; CVD, cardiovascular disease; ASCVD, Atherosclerotic cardiovascular disease; MI, myocardial infarction; CAD, carotid artery disease; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; aHR, adjusted hazard ratio; MACE, major adverse cardiovascular events; IHD, ischemic heart disease.

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Lp(a) AND ASCVD RISK IN PRIMARY PREVENTION AMONG ASIANS

Although the role of Lp(a) in predicting long-term ASCVD risk in primary prevention settings remains incompletely defined in Asians, several studies have demonstrated significant associations between Lp(a) and subclinical atherosclerosis. A meta-analysis involving 40,073 individuals found associations of elevated Lp(a) with both the presence (OR, 1.31; 95% CI, 1.06, 1.61) and progression (OR, 1.54; 95% CI, 1.23, 1.92) of coronary artery calcification (CAC).[27] Asian-specific subgroup analyses showed elevated Lp(a) levels (≥30 or ≥50 mg/dL, or highest quartile) were associated with a higher prevalence (OR, 1.28; 95% CI, 0.94, 1.75) and progression (OR, 1.73; 95% CI, 1.02, 2.94) of CAC.

Studies from Korean cohorts support these findings. Chung et al.[28] reported that elevated Lp(a) levels (≥50 mg/dL) were independently associated with coronary artery calcium scores, suggesting that Lp(a) is an independent marker of coronary atherosclerosis. Lee et al.[29] also showed individuals in the highest Lp(a) quartile (≥20.2 mg/dL) had significantly increased odds of coronary plaque (OR, 1.21; 95% CI, 1.04, 1.42) and ≥50% stenosis (OR, 1.54; 95% CI, 1.15, 2.05) compared to those in the lowest quartile. Moreover, Lp(a) ≥120 nmol/L combined with CAC was independently associated with elevated ASCVD risk.[30]

Several studies have also demonstrated an association between Lp(a) and cardiovascular disease in primary prevention. In a retrospective Chinese case-control study involving 1,522 patients experiencing a first acute myocardial infarction (AMI) and 1,691 control subjects without ASCVD, the risk of incident AMI progressively increased with higher Lp(a) levels. Compared with the lowest quintile of Lp(a), individuals in the second through fifth quintiles (Lp(a) >6.5 mg/dL) showed significantly higher ORs for AMI (1.51, 1.84, 1.86, and 2.66, respectively).[31] Additionally, incorporating Lp(a) into traditional risk models improved predictive accuracy by 21.3% among individuals at borderline or intermediate ASCVD risk.[32]

A cohort study including 275,430 Korean individuals (mean age: 38 years; 50.1% men) enrolled in a health screening program, where more than 98% had no history of cardiovascular disease, reported a median Lp(a) level of 18.5 mg/dL. The suggested Lp(a) threshold associated with increased mortality was 26.3 mg/dL.[23] This study demonstrated an 83% increased risk of cardiovascular death and a 20% increase in all-cause mortality among individuals with Lp(a) ≥50 mg/dL compared to those with levels <50 mg/dL, findings consistent with studies from other ethnic groups.[33,34] Specifically, individuals with Lp(a) ≥100 mg/dL exhibited a greater than 2-fold increase in cardiovascular risk.

Lp(a) AND RECURRENT CARDIOVASCULAR EVENTS IN SECONDARY PREVENTION

Several studies conducted in Asian populations have demonstrated that elevated Lp(a) significantly predicts adverse cardiovascular outcomes among individuals with established ASCVD. In a multi-ethnic study from Singapore, which included Chinese, Malay, and Indian participants, higher Lp(a) levels were associated with increased risk and severity of CAD among patients with pre-existing cardiovascular disease.[35] Specifically, Lp(a) levels ≥130 nmol/L, and more prominently ≥160 nmol/L, were significantly associated with a higher risk

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of acute AMI. Moreover, Lp(a) levels were independently associated with CAD presence (OR, 1.02 per 10 nmol/L increase; p=0.024) and disease severity (p=0.02).

A prospective cohort study of patients with previous MI revealed that individuals in the highest quartile of Lp(a) (≥41.43 mg/dL) had a 65% increased risk of recurrent cardiovascular events and an 84% increased risk of cardiac mortality compared to those in the lowest quartile (<8.19 mg/dL).[36] Similarly, a multicenter prospective study in China involving 4,078 CAD patients found that those with Lp(a) levels ≥30 mg/dL had a significantly higher risk of cardiovascular events compared to patients with levels <15 mg/dL.[37]

In South Korea, one single-center study reported no significant association between baseline Lp(a) levels and the incidence of 3-point major adverse cardiovascular events (MACE: cardiovascular death, MI, or stroke) in post-AMI patients.[38] However, another registry study from a single center involving 12,567 patients who underwent percutaneous coronary intervention indicated that Lp(a) levels >30 mg/dL were associated with an increased risk of cardiovascular ischemic events as well as a significantly higher risk of repeat revascularization.[39] This discrepancy may reflect differences in baseline Lp(a) concentrations, study designs, follow-up durations, or other potential risk modifiers.

Elevated Lp(a) has also been shown to confer additional risk in very high-risk patients—defined as individuals with established ASCVD experiencing either multiple major ASCVD events or a single major event accompanied by multiple high-risk conditions. A study conducted in an Asian cohort demonstrated that Lp(a) levels ≥50 mg/dL were independently associated with increased cardiovascular risk over 3 years.[40]

Collectively, these findings emphasize the clinical value of measuring Lp(a) in secondary prevention contexts. Among patients with established ASCVD, elevated Lp(a) not only identifies those at greater risk for recurrent events but may also guide therapeutic intensification, particularly as Lp(a)-targeted therapies become more widely available. Based on current data from Asian populations, an Lp(a) threshold >50 mg/dL appears reasonable for identifying individuals at elevated cardiovascular risk, consistent with recommendations from the EAS and the NLA.[21,24] However, individuals with Lp(a) levels >30 mg/dL should also be closely monitored, as emerging evidence indicates potential cardiovascular risk even at these intermediate levels.

Lp(a) AND PREMATURE ASCVD IN YOUNGER ASIAN POPULATIONS

Younger individuals, especially in Asian populations, appear more susceptible to Lp(a)-related premature ASCVD. A cohort study from Singapore found that patients with premature IHD had a higher prevalence of elevated Lp(a) (≥155 nmol/L), and this threshold corresponded to a 2.9-fold increased risk of early-onset IHD (adjusted OR, 2.9; 95% CI, 1.26, 6.67).[41] A meta-analysis revealed that individuals under 50 years with elevated Lp(a) demonstrated a stronger association with ASCVD risk (OR, 2.72) compared to those under 60 years (OR, 2.40).[25] Given that younger adults constitute a rising proportion of AMI cases, Lp(a) screening might offer considerable clinical value for early risk stratification and long-term preventive strategies, particularly in genetically predisposed Asian individuals.[42]

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Lp(a) AND ISCHEMIC STROKE RISK IN ASIANS

Due to structural similarity with plasminogen and its inherent pro-inflammatory and pro-thrombotic properties, Lp(a) also contributes to ischemic stroke risk.[43] The Copenhagen General Population Study demonstrated that individuals in the top 5% of the Lp(a) distribution exhibited a 60% higher risk of ischemic stroke.[44] Furthermore, a meta-analysis involving 16 studies including Asian populations found elevated Lp(a) significantly associated with ischemic stroke risk (standardized mean difference, 0.81; 95% CI, 0.56, 1.05).[45] A Chinese cohort study of 8,500 individuals revealed that those in the highest Lp(a) tertile (26–162 mg/dL) had a 34% increased risk of incident stroke compared to those in the lowest tertile (adjusted HR, 1.34; 95% CI, 1.06, 1.70).[46] Additionally, a multicenter registry from Asia indicated that high Lp(a) levels were associated with poorer functional outcomes following stroke.[47]

While most evidence supports a pathogenic role for Lp(a) in ischemic stroke, the strength of this association appears weaker than for coronary heart disease. Further mechanistic and prospective studies are necessary, particularly within Asian populations, where the stroke burden is high and stroke subtypes may differ. Nevertheless, given the contribution of Lp(a) to both large-artery atherosclerosis and thromboembolic risk, evaluating Lp(a) may offer additional prognostic insights in patients at risk for stroke or recovering from stroke.

Lp(a) AND THE PATHOGENESIS OF CALCIFIC AORTIC VALVE STENOSIS

Elevated Lp(a) has been established as a causal risk factor for calcific aortic valve stenosis, including the Asian populations. The underlying pathogenic mechanisms involve lipid deposition in valve leaflets, pro-thrombotic effects, and calcification promoted by OxPLs and inflammatory signaling.[48-50] A Korean study involving 44,742 patients over a median follow-up of 6.8 years demonstrated a progressively increased risk of severe degenerative AS with higher Lp(a) levels, yielding HRs of 1.02 (Lp(a): 30–50 mg/dL), 1.18 (50–100 mg/dL), and 1.96 (>100 mg/dL). Additionally, the risk of requiring aortic valve replacement was significantly increased in individuals with Lp(a) >100 mg/dL (adjusted HR, 2.05; 95% CI, 1.31, 3.19).[50] Findings from the Multi-Ethnic Study of Atherosclerosis also support an association between OxPL-bound Lp(a) and aortic valve calcification, reporting ORs per 1-SD increase of 1.19 for OxPL and 1.13 for Lp(a).[51] These findings collectively suggest that Lp(a) and OxPL could represent viable therapeutic targets for preventing and treating calcific AS.

Lp(a) AND ITS ASSOCIATION WITH METABOLIC DISEASES IN ASIAN POPULATIONS

1. Diabetes mellitus

Several large-scale cohort studies have identified an inverse association between circulating Lp(a) levels and the risk of type 2 diabetes mellitus (T2DM).[52-54] Although this inverse relationship was not confirmed by a Mendelian randomization study conducted within the Danish population,[55] Mendelian randomization analyses in a Chinese population indicated that genetically elevated Lp(a) levels were associated with a reduced risk of T2DM.[56]

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Despite this inverse relationship, elevated Lp(a) levels clearly predict increased cardiovascular risk among individuals with T2DM. In a large pooled multi-ethnic U.S. cohort with a median follow-up of 21.1 years, elevated Lp(a) (≥90th percentile) was more strongly associated with incident ASCVD among diabetic individuals (HR, 1.92; 95% CI, 1.50, 2.45) compared to those without diabetes (HR, 1.41; 95% CI, 1.28, 1.55), demonstrating a significant interaction (p=0.006).[57] Additionally, a prospective Chinese study reported that diabetic patients with established cardiovascular disease and Lp(a) ≥30 mg/dL exhibited more than a 2-fold increased risk of recurrent ASCVD events (HR, 2.05; 95% CI, 1.31, 3.21), independent of baseline HbA1c levels.[58]

Given these findings, Lp(a) measurement in individuals with diabetes—regardless of prior cardiovascular disease status—may enhance risk stratification and inform preventive strategies. While increased diabetes risk appears limited to individuals with very low Lp(a), therapies aimed at lowering Lp(a) may offer substantial cardiovascular benefits among those with concurrent T2DM.

2. Fatty liver disease

Lp(a) is synthesized in the liver, with plasma concentrations primarily determined by hepatic production of apo(a). Consequently, hepatic dysfunction related to conditions such as steatohepatitis or liver fibrosis can markedly influence circulating Lp(a) concentrations.[59,60] A systematic review of 10 observational studies indicated an association between Lp(a) and hepatic steatosis.[61] Thus, in patients with non-alcoholic fatty liver disease (NAFLD), steatohepatitis, or hepatic fibrosis, Lp(a) levels may not reliably reflect true cardiovascular risk. Caution is therefore advised when interpreting Lp(a) measurements in these clinical contexts, particularly in East and Southeast Asia, regions currently experiencing a rapidly increasing prevalence of NAFLD.

CURRENT AND EMERGING THERAPEUTIC OPTIONS AFFECTING Lp(a) LEVELS

While statins remain the cornerstone of LDL-C lowering therapy, their impact on Lp(a) levels remains controversial. Several studies, including randomized controlled trials, have reported that statins modestly increase Lp(a) concentrations by approximately 10%–20%, whereas other analyses suggest that statins have no significant effect on Lp(a) levels.[62,63] The variability in these findings may reflect differences in study populations, statin types, and measurement methodologies. Although the clinical significance of statin-induced Lp(a) changes remains uncertain, the overall cardiovascular benefit of statins is well-established and not adversely affected by these potential fluctuations in Lp(a).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab and alirocumab, have emerged as promising agents capable of dual action—lowering LDL-C and moderately reducing Lp(a). In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, evolocumab reduced median Lp(a) levels by 26.9% (interquartile range, 6.2%–46.7%) at 48 weeks.[64] Importantly, the reduction in MACE observed with evolocumab was consistent across ethnic groups, including Asians (HR, 0.79) and non-Asians (HR, 0.86), after adjusting for LDL-C changes.[65] Alirocumab, another fully human monoclonal antibody targeting PCSK9, demonstrated a reduction in Lp(a) of approximately 5 mg/dL in the ODYSSEY outcomes trial, significantly lowering MACE risk (HR, 0.85; 95% CI, 0.78, 0.93).[66] A regional sub-study, ODYSSEY KT, conducted in South Korea and Taiwan, also demonstrated that alirocumab significantly

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reduced Lp(a) levels in high-risk patients with inadequately controlled hypercholesterolemia, with a least square mean reduction of −33.6 nmol/L (95% CI, −41.9, −25.3) compared to controls.[67] Inclisiran, a small interfering RNA (siRNA) that inhibits hepatic PCSK9 synthesis, similarly showed moderate Lp(a)-lowering effects.[68] In Asian populations, inclisiran reduced Lp(a) levels by approximately 41% compared with placebo at day 330 (p<0.001).[69] Although PCSK9 inhibitors moderately reduce Lp(a) levels, recent evidence suggests that the magnitude of Lp(a) reduction achieved with existing PCSK9 therapies may be insufficient for clinically meaningful risk reduction. Mendelian randomization studies suggest that a reduction of approximately 65.7 mg/dL in Lp(a) is required to effectively lower coronary heart disease risk.[70] Data from secondary prevention cohorts also suggest that a 50 mg/dL reduction could decrease cardiovascular disease risk by approximately 20%.[71] These findings highlight the need for therapies explicitly designed to substantially reduce Lp(a).

Beyond PCSK9-targeted therapies, antisense oligonucleotides (ASOs) such as pelacarsen, which specifically target apo(a) mRNA, have emerged as promising agents directly targeting Lp(a). Pelacarsen has demonstrated robust and dose-dependent reductions in plasma Lp(a) of up to 80% in phase 2 clinical trials, with a favorable safety and tolerability profile.[72] Unlike conventional lipid-lowering therapies, ASOs act by inhibiting hepatic synthesis of apo(a), directly addressing the underlying cause of elevated Lp(a). Large-scale phase 3 outcome trials, including the ongoing Lp(a)HORIZON study, are evaluating whether these substantial reductions translate into meaningful reductions in MACE.[73] Crucially, these trials involve diverse populations, including Asian cohorts, to assess the efficacy and generalizability of Lp(a)-targeted therapies across ethnic groups.

In addition to pelacarsen, small molecule inhibitors and siRNA-based therapies are under investigation. Muvalaplin, a first-in-class oral small molecule inhibitor that disrupts the interaction between apo(a) and apoB, demonstrated significant Lp(a)-lowering efficacy (up to 85.8% placebo-adjusted reduction) in the KRAKEN trial, in which 27% of participants were Asian.[74] Similarly, zerlasiran (formerly SLN360), a GalNAc-conjugated siRNA targeting LPA mRNA, showed sustained Lp(a) reductions of up to 90% in early-phase studies. The ALPACAR-360 trial—a phase 2, multicenter, randomized, placebo-controlled study evaluating zerlasiran's efficacy and safety in patients with established ASCVD—showed a time-averaged, placebo-adjusted Lp(a) reduction of 85.6% from baseline to 36 weeks.[75] Together, these novel agents represent a new frontier in precision lipid management and hold particular promise for high-risk individuals with substantially elevated Lp(a), including those in Asian populations. Current Lp(a)-lowering therapies under investigation in Asian populations are summarized in **Table 2**.

Table 2. Lp(a)-lowering therapies currently being investigated in Asian populations

Drug	Class	Route of administration	Study	Population	Key findings	Ref.
Evolocumab	PCSK9 inhibitor	SC injection	FOURIER trial	Asian subgroup	Reduced MACE (HR, 0.79).	65
Alirocumab	PCSK9 inhibitor	SC injection	ODYSSEY KT	Korea, Taiwan	Reduced Lp(a) levels in high-risk patients, with a least square mean reduction of −33.6 nmol/L (95% CI, −41.9, −25.3) compared to control.	67
Inclisiran	siRNA (PCSK9 synthesis inhibitor)	SC injection	ORION-18	Asian subgroup	Reduced Lp(a) levels by approximately 41% from baseline.	69
Pelacarsen	ASO	SC injection	Randomized double-blind, placebo-controlled study	Japanese	Maximal, placebo-corrected reduction in Lp(a) of ~106% with 80 mg monthly dose.	72
Muvalaplin	Lp(a) assembly inhibitor	Oral	KRAKEN trial	~23% Asian	Eighty-five point eight percentage placebo-adjusted Lp(a) reduction.	74

Lp(a), lipoprotein-a; PCSK9, proprotein convertase subtilisin/kexin type 9; SC, subcutaneous; MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; ASO, antisense oligonucleotide.

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Additionally, emerging data indicate that beyond genetic and ethnic influences, Lp(a) levels may also be modifiable through physiological and environmental factors such as age, sex, systemic inflammation, physical activity, obesity, dietary patterns, fasting status, and comorbidities.[76] These findings highlight opportunities for integrated risk management strategies combining pharmacological and lifestyle interventions.

RESEARCH GAPS IN ASIAN POPULATIONS

Despite increasing recognition of the clinical significance of Lp(a) as an independent cardiovascular risk factor, data specific to Asian populations remain limited. Most available evidence in these populations comes from cross-sectional or observational studies, insufficient to establish causality or guide clinical decisions. There is a critical need for prospective longitudinal studies and randomized clinical trials to validate the prognostic value of Lp(a), clarify its role in cardiovascular risk stratification, and evaluate the efficacy and safety of emerging Lp(a)-lowering therapies in diverse Asian populations.

Mendelian randomization studies, instrumental in confirming the causal role of Lp(a) in ASCVD among European populations,[10,77] remain scarce among Asians. Given the pronounced interethnic variability in Lp(a) levels, apo(a) isoform size, and genetic architecture, population-specific Mendelian randomization analyses are essential. Such studies could identify genetic determinants of Lp(a) variability and define the magnitude of Lp(a) reduction necessary for meaningful cardiovascular benefit. Identifying these genetic variants and their phenotypic associations could enhance precision medicine approaches and support targeted interventions. Thus, expanded genomic, epidemiologic, and interventional research in Asian populations is urgently needed to facilitate the clinical translation of Lp(a)-targeted strategies within this understudied demographic.

CONCLUSIONS

Lp(a) has consistently been implicated as an independent and causal risk factor for ASCVD, ischemic stroke, and calcific aortic valve stenosis. This risk is particularly magnified in individuals with established ASCVD, diabetes, or a family history of premature cardiovascular disease. In Asian populations, where the burden of premature ASCVD is significant, incorporating Lp(a) measurement into routine cardiovascular risk assessment may enable earlier identification of high-risk individuals and facilitate more effective preventive strategies.

With advancements in novel therapies such as PCSK9 inhibitors, inclisiran, and ASO, the landscape of Lp(a)-targeted interventions is rapidly evolving. Incorporating Lp(a) measurement into cardiovascular risk assessment—particularly among high-risk Asian subgroups—represents a critical step towards precision prevention and personalized medicine in cardiovascular care.

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