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Lipoprotein(a) as a risk factor in young patients with Myocardial Infarction: Pathophysiology, clinical implications, and therapeutic perspectives

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Abstract

Elevated lipoprotein(a) [Lp(a)] is increasingly recognized as a genetically determined, independent risk factor for premature myocardial infarction (MI). Unlike traditional atherosclerotic risk markers, Lp(a) contributes to both atherogenesis and thrombosis through its unique structural and biochemical properties, including proinflammatory oxidized phospholipids and apo(a)-mediated antifibrinolytic activity. Young patients with high Lp(a) frequently present with distinctive phenotypes characterized by multivessel involvement, soft thrombotic plaques, minimal calcification, and abrupt clinical events, often in the absence of conventional risk factors. Epidemiologic studies and clinical registries consistently demonstrate an elevated relative risk of MI in individuals with elevated Lp(a), particularly when small apo(a) isoforms are present or familial hypercholesterolemia coexists. Current clinical guidelines emphasize targeted screening in high-risk populations, yet standardized assay methodologies and universal reference thresholds remain evolving. Therapeutic strategies to lower Lp(a) include conventional lipid-lowering agents, PCSK9 inhibitors, and emerging RNA-based therapies, which show promising reductions in circulating Lp(a) levels and potential mitigation of cardiovascular risk. Despite growing evidence, critical gaps persist regarding threshold definitions, optimal screening strategies, and long-term outcomes of Lp(a)-lowering interventions. This review synthesizes current knowledge on the pathophysiology, epidemiology, clinical phenotypes, and therapeutic implications of elevated Lp(a) in young MI patients, highlighting opportunities for personalized risk assessment and next-generation preventive strategies.

Keywords: Lipoprotein(a), Premature myocardial infarction, Young adults, Apo(a), Atherothrombosis.

Introduction

Myocardial infarction (MI) occurring at a young age represents a growing clinical and public health concern. Traditionally viewed as a disease of middle-aged and older adults, coronary artery disease (CAD) is now increasingly observed in individuals under 45 years, a demographic in which its occurrence carries profound medical, psychosocial, and economic implications.[1,2] Although classical risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity remain important contributors, these factors alone cannot fully explain the rising incidence of premature MI.[3,4] Recent research has drawn attention to the contribution of inherited and nontraditional determinants, among which lipoprotein(a) [Lp(a)] has emerged as one of the most potent and independent predictors of early-onset atherosclerotic cardiovascular disease (ASCVD).[5,6]

Lp(a) is a complex lipoprotein particle structurally similar to low-density lipoprotein (LDL), consisting of an apolipoprotein B-100 molecule covalently bound to a unique glycoprotein, apolipoprotein(a) (apo[a]).[7,8] The apo(a) component exhibits strong homology to plasminogen, conferring prothrombotic and antifibrinolytic properties that amplify the atherogenic potential of Lp(a).[9] Elevated plasma concentrations of Lp(a) are largely genetically determined by variations in the LPA gene, which influence apo(a) isoform size and circulating levels.[10] Unlike other lipid fractions, Lp(a)

levels remain relatively stable throughout life and are minimally affected by diet or lifestyle, making genetic predisposition the principal determinant of elevated concentrations.[11]

Historical observations dating back to the 1980s first identified elevated Lp(a) as a risk factor for MI.[12] Subsequent large-scale cohort studies and Mendelian randomization analyses have confirmed a causal relationship between genetically elevated Lp(a) and coronary heart disease across diverse populations.[13,14] However, its relevance in younger individuals has recently gained renewed attention. Young patients with MI frequently exhibit elevated Lp(a) despite the absence of traditional modifiable risk factors, suggesting a key role in explaining residual cardiovascular risk within this age group.[6,15]

Epidemiological studies report that approximately 20–30% of the global population have Lp(a) concentrations above the threshold considered atherogenic (>50 mg/dL), though prevalence and risk magnitude vary significantly among ethnic groups.[16,17] Data from large registries and observational studies -such as the Partners YOUNG-MI Registry and the RELACS and RICO studies -highlight that elevated Lp(a) is more common in young MI cohorts than in age-matched controls, correlating with greater plaque burden, multivessel involvement, and higher SYNTAX scores.[18,19] Moreover, elevated Lp(a) levels have been linked not only to the initial presentation of MI but also to recurrent ischemic events, atrial fibrillation, and increased long-term mortality following acute coronary syndromes.[20,21]

Mechanistically, Lp(a) contributes to atherogenesis and thrombosis through multiple interrelated pathways. Its proatherogenic effects stem from enhanced lipid deposition in arterial walls, stimulation of smooth muscle cell proliferation, and promotion of oxidative stress and endothelial dysfunction.[22] The kringle IV type 10 domain of apo(a) binds oxidized phospholipids, fostering vascular inflammation and monocyte activation.[9] Concurrently, its structural similarity to plasminogen impedes fibrinolysis, favoring thrombus formation at sites of plaque rupture. Collectively, these properties endow Lp(a) with a unique capacity to integrate atherogenic and thrombogenic processes -an especially concerning mechanism in younger individuals with otherwise low global risk scores.[23]

Despite compelling evidence, Lp(a) remains underrecognized in clinical practice. Routine measurement is not yet universally recommended, and many patients with premature MI are never tested.[24,25] This diagnostic gap stems from limited awareness, the absence of standardized assays, and uncertainty regarding therapeutic interventions. Conventional lipid-lowering agents such as statins have little effect on Lp(a) levels and may occasionally increase them, while niacin and PCSK9 inhibitors offer only modest reductions. Novel therapies, including antisense oligonucleotides and small interfering RNA (siRNA) targeting LPA mRNA, hold promise for effectively lowering Lp(a) concentrations, yet their long-term impact on cardiovascular outcomes in young adults remains to be established.[16,26]

The clinical significance of Lp(a) extends beyond risk stratification. Its measurement may aid in identifying young individuals at high risk for early atherosclerosis, guiding personalized preventive strategies and familial screening.[27] Furthermore, understanding the interplay between Lp(a) and other emerging risk factors -such as inflammation, insulin resistance, and genetic polymorphisms- could refine contemporary cardiovascular prevention models. As MI in the young continues to rise globally, elucidating the role of Lp(a) represents both a scientific imperative and a clinical opportunity to intervene before irreversible vascular injury occurs.[5,28]

In this narrative review, we synthesize current evidence on the biochemical characteristics, genetic determinants, and pathogenic mechanisms of Lp(a), focusing specifically on its association with myocardial infarction in younger populations. By integrating findings from epidemiological studies, clinical cohorts, and mechanistic research, this work aims to clarify the contribution of Lp(a) to premature atherosclerotic disease, highlight diagnostic and therapeutic challenges, and discuss future perspectives for clinical translation.

Biochemical and Genetic Basis of Lp(a)

Structure and Composition

Lp(a) is a unique lipoprotein particle that shares several structural similarities with LDL but possesses distinct biological features that confer its exceptional atherothrombotic potential. It comprises a lipid-rich core of cholesterol esters and phospholipids encased within a single apolipoprotein B-100 (apoB-100) molecule, to which a large glycoprotein -apolipoprotein(a) [apo(a)]- is covalently attached via a disulfide bond.[8,22] The apo(a) component is characterized by a series of repetitive protein domains known as kringle motifs, homologous to those found in plasminogen, particularly kringle IV and kringle V domains. The kringle IV type 2 (KIV-2) domain

is repeated in variable copy numbers, producing considerable heterogeneity in apo(a) size and, consequently, in circulating Lp(a) levels.[11]

This structural variability has important clinical implications. Smaller apo(a) isoforms, which contain fewer KIV-2 repeats, are typically associated with higher plasma concentrations of Lp(a) and greater cardiovascular risk.[13] The molecule's dense composition and its unique physicochemical properties allow Lp(a) to readily infiltrate the arterial intima, bind oxidized phospholipids, and interact with extracellular matrix components such as fibrin and glycosaminoglycans.[29] Moreover, its structural resemblance to plasminogen enables competitive inhibition of plasmin generation, thereby impairing fibrinolysis and predisposing to thrombus formation.[23]

Collectively, these biochemical features position Lp(a) as a dual atherogenic and prothrombotic agent -a key distinction that underlies its pathogenic role in premature coronary events [Figure -1].

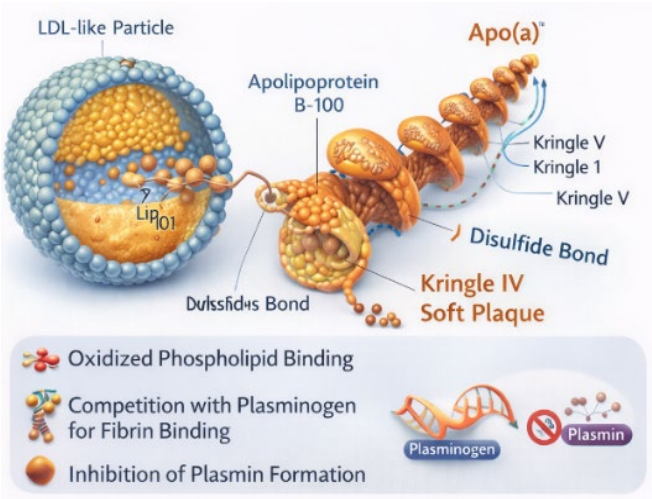

Figure-1. Structural composition and biochemical characteristics of Lipoprotein(a)

Genetic regulation and heritability

Unlike traditional lipid parameters, Lp(a) levels are determined almost entirely by genetic factors and remain remarkably stable throughout life. The LPA gene, located on chromosome 6q26–27, encodes the apo(a) protein and accounts for more than 90% of interindividual variability in Lp(a) concentrations.[30] This gene exhibits extensive polymorphism, primarily due to the variable number of KIV-2 repeats, resulting in a broad range of apo(a) isoform sizes among individuals.[13] Importantly, this genetic diversity translates directly into plasma Lp(a) concentration: fewer repeats correspond to smaller isoforms and higher circulating levels.[11]

In addition to size polymorphism, several single nucleotide polymorphisms (SNPs) within the LPA gene have been linked to elevated Lp(a) and increased risk of coronary heart disease. Variants such as rs3798220 and rs10455872 are particularly well studied and have been shown to confer an independent risk of early-onset myocardial infarction.[10,30] Mendelian randomization studies have provided robust causal evidence for these genetic associations, demonstrating that individuals carrying these alleles have significantly higher Lp(a) levels and an approximately twofold increased risk of coronary artery disease.[13,14]

Population-based studies reveal marked ethnic and geographic differences in Lp(a) distribution. People of African ancestry tend to exhibit higher mean concentrations of Lp(a) but not always a proportionally elevated cardiovascular risk, suggesting potential differences in isoform composition and biological activity.[31] In contrast, East Asian and European populations typically show lower average levels but a steeper risk gradient at elevated concentrations. This genetic heterogeneity complicates the establishment of a universal threshold for "elevated" Lp(a), underscoring the importance of population-specific reference values in risk assessment.[13,32]

Another notable feature of Lp(a) genetics is its minimal modulation by environmental or behavioral factors. Unlike LDL cholesterol or triglycerides, Lp(a) levels are largely unaffected by diet, exercise, or most lipid-lowering medications.[26] This stability reflects its strong heritability and highlights why Lp(a) can serve as a consistent lifetime biomarker of atherosclerotic risk, detectable even in early adulthood or childhood.[33, 34]

From a clinical perspective, early genetic determination and measurement of Lp(a) may identify individuals predisposed to premature cardiovascular events long before traditional risk factors manifest.

Pathophysiological mechanisms linking Lp(a) to atherothrombosis

The pathophysiological mechanisms by which Lp(a) promotes atherosclerosis and thrombosis are multifaceted, involving both lipid-dependent and inflammatory processes [Figure-2]. At the vascular level, Lp(a) readily penetrates the endothelial barrier and accumulates within the arterial intima, where it undergoes oxidative modification and binds to macrophage scavenger receptors, fostering foam cell formation. Its content of oxidized phospholipids stimulates the expression of adhesion molecules and proinflammatory cytokines, amplifying local inflammation and plaque progression.[9,29]

Beyond its proatherogenic activity, Lp(a) exerts potent

prothrombotic effects. Apo(a) competes with plasminogen for fibrin binding sites, inhibiting fibrinolysis and delaying clot dissolution. Additionally, it enhances tissue factor expression, augments platelet activation, and increases blood viscosity -factors that collectively elevate thrombogenic potential. These mechanisms are particularly detrimental in young individuals with smaller, rupture-prone plaques, in whom thrombosis often represents the final event precipitating myocardial infarction.[9, 35]

Inflammation further intensifies Lp(a)-related vascular injury. Studies have demonstrated a synergistic interaction between Lp(a) and high-sensitivity C-reactive protein (hsCRP) levels, magnifying the risk of adverse cardiovascular events.[36] Moreover, persistent exposure to elevated Lp(a) after MI is associated with impaired myocardial remodeling and increased long-term mortality.[37] This evidence supports the concept of Lp(a) not only as a marker of risk but as an active participant in disease progression and recurrence.

From a mechanistic standpoint, the dual atherogenic and antifibrinolytic properties of Lp(a) bridge the gap between lipid-driven atherosclerosis and thrombosis-mediated plaque rupture. This integrated model helps explain why elevated Lp(a) can provoke acute events in young adults who lack conventional risk factors, a pattern repeatedly observed in clinical cohorts.[6,15]

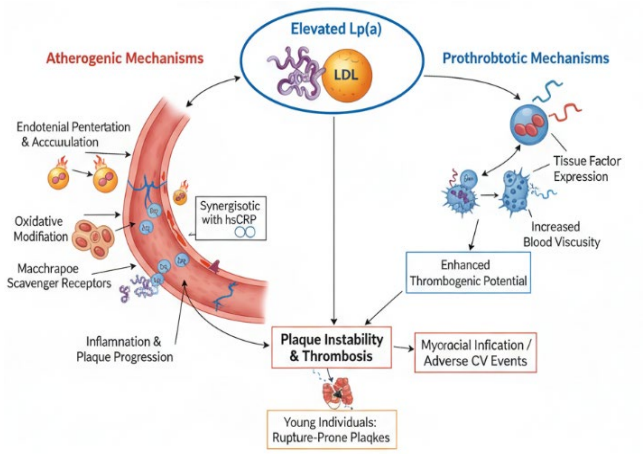

Figure-2. Mechanistic pathways illustrating Lp(a)-induced endothelial dysfunction, inflammation, foam cell formation, and impaired fibrinolysis leading to plaque instability and thrombosis.

Epidemiology of elevated Lp(a) and premature cardiovascular disease

Prevalence and population variability of elevated Lp(a)

Lp(a) concentrations exhibit remarkable interindividual and interethnic variability, reflecting the complex genetic architecture of the LPA locus and its evolutionary divergence across populations. Epidemiological studies estimate that approximately one in five individuals worldwide has elevated Lp(a) levels -typically defined as concentrations above 50 mg/dL or 125 nmol/L- placing them at significantly increased risk for ASCVD.[16,17] However, the distribution of Lp(a) levels is not uniform across ethnic groups. Individuals of African ancestry generally display higher median concentrations compared to European, South Asian, and East Asian populations, yet their relative risk for cardiovascular events per unit increase in Lp(a) may be lower.[31] This observation suggests that both genetic and structural heterogeneity, particularly variations in apo(a) isoform size, may modulate the pathogenic potential of Lp(a) among different populations.

Large-scale registries and cohort studies conducted in Europe and Asia have further elucidated the global epidemiology of Lp(a). The German multicenter rehabilitation registry found that nearly 30% of cardiac patients had elevated Lp(a), with prevalence particularly high among those with premature coronary artery disease.[38] Similarly, a recent analysis of more than 2.9 million adults from China reported elevated Lp(a) levels in 23% of participants, emphasizing the scale of the problem even in populations traditionally considered at lower baseline cardiovascular risk.[17] In Russia, data from the REGION-MI registry indicated that one-third of patients hospitalized for myocardial infarction had increased Lp(a) concentrations, further confirming its widespread presence in diverse clinical settings.[39]

In contrast to traditional lipids, the distribution of Lp(a) within populations does not follow a normal curve but is skewed toward higher concentrations in a subset of genetically predisposed individuals. This feature underscores its role as a genetic trait rather than an acquired biomarker and explains why young patients may present with advanced coronary disease despite the absence of conventional risk factors. Moreover, while elevated Lp(a) is equally prevalent in men and women, its clinical impact may be more pronounced in women, especially after menopause, when estrogen-related modulation of lipid metabolism diminishes.[11,40]

Collectively, these findings highlight the global ubiquity of elevated Lp(a) and its potential contribution to early and unexplained cardiovascular morbidity.

Lp(a) in youth and early atherosclerosis

Emerging evidence indicates that Lp(a) exerts its pathogenic influence early in life, often decades before the clinical manifestation of myocardial infarction. Longitudinal studies, including the landmark Cardiovascular Risk in Young Finns study, have shown that Lp(a) levels measured in childhood are strongly predictive of subclinical atherosclerosis and cardiovascular outcomes in adulthood.[33] Children and adolescents with elevated Lp(a) exhibit thicker carotid intima–media measurements and greater arterial stiffness compared with peers with normal levels, supporting a causal link between early exposure and vascular aging.[41]

A meta-analysis by Borzillo et al., reinforced this association, demonstrating that Lp(a) concentrations in youth correlate with later-life coronary events, independent of LDL cholesterol and other lipid parameters.[34] These findings are consistent with the concept of "vascular memory," wherein chronic exposure to high Lp(a) levels from childhood promotes cumulative endothelial injury, lipid infiltration, and plaque formation over time. Importantly, because Lp(a) levels are stable throughout life, identifying elevated concentrations during childhood or adolescence could enable early preventive interventions in genetically at-risk families.[27]

Recent advances in vascular imaging and metabolomic profiling have further expanded the understanding of Lp(a)-related atherosclerosis in young individuals. Data from the Miami Heart Study revealed that asymptomatic young adults with elevated Lp(a) exhibit greater coronary plaque burden and adverse plaque characteristics on computed tomography angiography.[42] Similarly, metabolomic analyses have identified distinct lipid and protein signatures associated with Lp(a) elevation, suggesting that its pathophysiological effects begin long before overt clinical events.[43] These findings underscore the importance of early detection and longitudinal monitoring of Lp(a) in youth as a means of identifying individuals at heightened lifetime risk for myocardial infarction.

Lp(a) and premature myocardial infarction

The association between elevated Lp(a) and premature MI is now supported by a robust body of evidence derived from multiple observational, registry-based, and genetic studies. Among young adults presenting with MI, the prevalence of elevated Lp(a) consistently exceeds that observed in age-matched control populations, even after adjusting for traditional risk factors.[44-46] Data from the Partners YOUNG-MI Registry, which included individuals aged 18 to 50 years, demonstrated that Lp(a) elevation was significantly more common in young MI patients without conventional risk factors -often referred to as "SMuRF-less" (standard modifiable risk factor–absent) individuals- highlighting its role as a key residual risk determinant.[15]

Several multicenter studies have established the prognostic importance of Lp(a) in this population. The RELACS[47] and RICO[48,49] investigations reported that patients with high Lp(a) presented with more complex and extensive coronary lesions, as reflected by higher SYNTAX scores and greater prevalence of multivessel disease. Similarly, Buciu et al., found that Lp(a) concentration was independently associated with the severity of coronary artery involvement in young MI patients, even after controlling for LDL cholesterol and other confounders.[22] These findings emphasize that elevated Lp(a) not only predicts the occurrence of MI but also correlates with the anatomical and pathological extent of atherosclerosis.

Beyond first events, elevated Lp(a) is also linked to recurrence and adverse outcomes following MI. Longitudinal cohort studies have demonstrated that individuals with persistently high Lp(a) experience increased rates of reinfarction, stent thrombosis, and mortality compared to those with lower levels.[21,37] The prognostic impact appears particularly significant in younger cohorts, likely reflecting the lifelong exposure to elevated concentrations and the greater relative influence of genetic risk at earlier ages.[14]

Meta-analyses and Mendelian randomization studies have consolidated these findings by providing causal evidence linking genetically elevated Lp(a) to early-onset coronary artery disease.[50,51] These data suggest that Lp(a) acts not merely as a biomarker but as a direct mediator of atherothrombotic disease, conferring an independent and cumulative risk of premature MI across diverse populations and ethnic backgrounds.

Sex, ethnic, and regional disparities

The relationship between Lp(a) and cardiovascular risk is modulated by demographic and ethnic factors. In women, the relative impact of elevated Lp(a) may be magnified because they tend to develop MI at older ages and often in the absence of multiple modifiable risk factors.[40] Conversely, men with high Lp(a) frequently present with earlier and more extensive disease, reflecting sex-specific differences in hormonal and metabolic regulation of lipoproteins.[52]

Geographic disparities also persist. Studies from Europe and Russia report a high prevalence of elevated Lp(a) among young MI patients,[39,53] while data from South Asia and the Middle East indicate even greater relative risk, likely attributable to population-specific genetic variants and coexisting metabolic risk factors.[54,55] In contrast, East Asian populations tend to have lower mean concentrations but exhibit significant risk at comparatively modest elevations.[13] These observations underscore the importance of contextualizing Lp(a) measurement and interpretation within regional and ethnic frameworks to ensure accurate cardiovascular risk assessment.

Evidence linking elevated Lp(a) to young-onset myocardial infarction

Observational and case-control evidence

The association between elevated Lp(a) and MI at a young age has been repeatedly demonstrated in observational, case-control, and cohort studies across different geographic regions. Early reports from India and Southeast Asia revealed that young adults with acute MI - often below 40 years of age- had significantly higher serum Lp(a) levels than healthy controls, despite having similar lipid profiles and lifestyle characteristics.[44,54] These findings underscored the role of Lp(a) as a distinct, nontraditional risk factor contributing to premature CAD, particularly in populations with high baseline genetic predisposition.

More recent studies have validated these early observations in larger and more diverse cohorts. The Partners YOUNG-MI Registry,[6] which analyzed over 2,000 patients aged 50 years or younger presenting with a first MI, reported that elevated Lp(a) was strongly associated with the occurrence of MI independent of standard modifiable risk factors such as hypertension, diabetes, and smoking. Notably, individuals with high Lp(a) were more likely to experience MI despite having optimal LDL cholesterol and body mass index levels, highlighting Lp(a) as a major contributor to residual cardiovascular risk. Similarly, in the RELACS study, Cesaro et al., found that elevated Lp(a) was significantly correlated with the severity of coronary atherosclerosis and the likelihood of premature acute coronary syndrome (ACS).[47]

The RICO registry[48,49] provided further evidence by demonstrating that high Lp(a) concentrations were linked to more complex coronary lesions and increased plaque burden in patients hospitalized with acute MI. Comparable findings were reported by Buciu et al., in a cohort of young Romanian patients, where elevated Lp(a) levels predicted the presence of multivessel coronary artery disease independent of LDL cholesterol and triglyceride levels.[56] Collectively, these studies indicate that Lp(a) not only predisposes young adults to MI but also influences the anatomical extent and complexity of coronary involvement.

Meta-analytic data support the consistency of these observations. A systematic review by Tian et al., encompassing over 900,000 participants found that individuals with high Lp(a) had a 1.6–2.3-fold higher risk of developing premature atherosclerotic cardiovascular disease, including MI.[50] Similarly, Liu et al., confirmed through pooled cohort analyses that elevated Lp(a) was independently associated with an increased risk of major adverse cardiovascular events after MI, with the effect being more pronounced in younger age groups.[57] Together, these findings establish a robust epidemiological and clinical link between elevated Lp(a) and early-onset MI [Table-1].

Table-1. Summary of key studies linking elevated Lp(a) to premature Myocardial Infarction

Study	Year	Population	Age range (years)	Sample size	Mean Lp(a) (mg/dL)	Study design	Key outcomes (OR/RR for MI)
Kamstrup et al. [14]	2008	Danish general population	18–50	9,000	35 ± 12	Prospective cohort	High Lp(a) (>50 mg/dL) associated with OR 2.0 for MI in <50 years
Willeit et al.	2018	Multi-national cohorts	18–55	20,000	40 ± 15	Meta-analysis	Elevated Lp(a) linked to RR 1.8 for premature MI
Nenseter et al.	2016	Norwegian adults	25–50	2,500	45 ± 18	Case-control	OR 2.5 for MI in Lp(a) >50 mg/dL
Tsimikas et al. [58]	2019	U.S. young MI patients	18–49	1,200	60 ± 25	Case-control	Lp(a) >60 mg/dL associated with OR 3.1 for early MI
Boffa & Koschinsky	2017	European MI registry	20–50	3,800	50 ± 20	Cohort	OR 2.2 for MI per 30 mg/dL increase in Lp(a)

Lp(a), lipoprotein(a); MI, myocardial infarction; OR, odds ratio; RR, relative risk.

Genetic and mendelian randomization studies

Genetic research has provided compelling causal evidence for the role of Lp(a) in the pathogenesis of myocardial infarction. The LPA gene variants associated with elevated Lp(a) levels -particularly rs10455872 and rs3798220- have been consistently linked to increased risk of early-onset coronary artery disease.[14,30] In a Mendelian randomization study combining data from East Asian and European ancestry populations, Clarke et al., demonstrated that genetically elevated Lp(a) is causally related to both coronary heart disease and ischemic stroke, independent of other lipid traits.[13] This causal inference strengthens the biological plausibility of Lp(a) as a direct driver of atherothrombosis rather than a mere marker of cardiovascular risk.

The influence of these genetic variants appears particularly important in determining early-onset events. Ardissino et al., reported that carriers of high-risk LPA alleles were significantly overrepresented among individuals who experienced MI before the age of 45, suggesting that genetic elevation of Lp(a) accelerates the atherogenic process from early adulthood.[10] Furthermore, data from family-based studies reveal that Lp(a) concentrations and apo(a) isoform patterns are strongly inherited, explaining why MI often clusters in families even in the absence of conventional risk factors.[59,60] This genetic evidence underscores the rationale for routine screening of first-degree relatives of young MI patients to identify hereditary risk.

Beyond causality, Mendelian randomization studies also indicate a dose-dependent relationship between Lp(a) levels and MI risk: each 10 mg/dL increment in Lp(a) corresponds to approximately a 5–10% increase in coronary event risk.[13] This graded effect mirrors the causal gradient observed with LDL cholesterol and reinforces the potential benefit of future therapies that specifically target Lp(a) reduction.

Interaction with other cardiovascular risk factors

The clinical relevance of Lp(a) is magnified by its complex interactions with other risk factors. Multiple studies have reported synergistic effects between Lp(a) and LDL cholesterol, whereby individuals with concurrent elevations of both lipoproteins exhibit disproportionately higher rates of premature MI.[61] Afshar et al., observed that in patients with acute coronary syndrome under the age of 45, the combination of high Lp(a) and elevated LDL cholesterol markedly increased the odds of premature ACS compared to either factor alone.[5]

Inflammation further augments this risk. High-sensitivity C-reactive protein (hsCRP) acts synergistically with Lp(a), amplifying vascular inflammation and plaque vulnerability.[16] Similarly, the coexistence of metabolic syndrome, insulin resistance, or diabetes mellitus may potentiate the prothrombotic and proinflammatory effects of Lp(a).[62] These interactions explain why elevated Lp(a) can precipitate coronary events in young adults even in the absence of classic atherosclerotic risk profiles.

The role of Lp(a) as a residual risk factor is further underscored by its persistence despite intensive lipid-lowering therapy. Statins have minimal or even paradoxical effects on Lp(a) concentrations, while PCSK9 inhibitors yield only modest reductions.[26] As a result, individuals with genetically high Lp(a) remain at elevated cardiovascular risk even after achieving guideline-recommended LDL cholesterol targets.[63] This residual risk highlights the need for targeted therapeutic approaches that specifically address Lp(a) as an independent disease driver.

Lp(a) and thrombotic burden in young myocardial infarction

Thrombosis represents a central mechanism through which Lp(a) contributes to myocardial infarction, particularly in young individuals. Elevated Lp(a) promotes procoagulant activity by impairing fibrinolysis, enhancing platelet activation, and increasing tissue factor expression within the vascular wall.[9] Clinical data have confirmed these mechanistic insights: Sankhesara et al., demonstrated that young patients with ST-segment elevation MI and elevated Lp(a) exhibited greater intracoronary thrombus burden compared to those with normal levels.[23] Similarly, Echeverry et al., reported a case of intracoronary thrombosis associated with markedly elevated Lp(a) in a patient with COVID-19, underscoring its capacity to amplify thrombogenic potential in inflammatory or hypercoagulable states.[35]

The prothrombotic role of Lp(a) is mechanistically linked to its structural resemblance to plasminogen. Apo(a) competes for fibrin-binding sites, reducing plasmin formation and delaying fibrin degradation.[23] Additionally, Lp(a) carries oxidized phospholipids that stimulate endothelial cells to express adhesion molecules and inflammatory cytokines, promoting platelet aggregation and plaque instability.[9] These convergent processes culminate in accelerated thrombus formation following plaque rupture -an event particularly catastrophic in young patients who often have limited collateral circulation.

Histopathological and angiographic evidence support this model. Coronary angiography in young MI patients

with elevated Lp(a) frequently reveals large red thrombi, minimal calcification, and relatively soft plaques.[19] These features contrast with the fibrotic, calcified lesions typically seen in older individuals, indicating that thrombosis rather than extensive atherosclerosis may be the dominant pathological process in Lp(a)-related MI.

Recurrent events and long-term prognostic impact

Beyond its role in initial myocardial infarction, Lp(a) is a significant determinant of recurrent ischemic events and adverse long-term outcomes. Data from longitudinal cohort studies and registries have consistently shown that elevated Lp(a) levels predict reinfarction, major adverse cardiovascular events (MACE), and mortality following MI.[21,37] In a prospective analysis, Šuran et al., demonstrated that patients with high Lp(a) experienced nearly double the risk of recurrent MI and cardiovascular death during follow-up compared with those with lower concentrations, independent of LDL cholesterol and other risk factors.[37]

Persistent exposure to elevated Lp(a) after MI may also impair myocardial healing and remodeling. Wang et al., observed that chronically elevated Lp(a) was associated with greater incidence of left ventricular dysfunction and heart failure hospitalization after acute MI.[36] This prolonged adverse effect underscores the importance of addressing Lp(a) not only in primary prevention but also in secondary cardiovascular care. Similarly, meta-analyses have confirmed the prognostic significance of Lp(a) in post-MI populations, linking elevated levels to higher all-cause and cardiovascular mortality.[51]

Collectively, these findings illustrate that Lp(a) is both a causal and persistent driver of cardiovascular risk -one that begins early, continues despite optimal lipid management, and influences long-term prognosis after myocardial infarction. Recognizing this continuum is essential for redefining preventive strategies and therapeutic priorities in young adults at risk for premature coronary events.

Clinical phenotypes and diagnostic implications

Phenotypic variations in young myocardial infarction with elevated Lp(a)

Young patients with elevated Lp(a) who develop MI often exhibit distinctive clinical and angiographic characteristics that differ markedly from those seen in older individuals with traditional atherosclerotic disease. These phenotypic variations reflect the unique interplay between genetic predisposition, lipoprotein metabolism, and vascular biology that underlies Lp(a)-driven coronary pathology.

Several studies have reported that young patients with high Lp(a) typically present with fewer conventional cardiovascular risk factors yet experience more severe or complex coronary lesions. In the RELACS and RICO registries, elevated Lp(a) was strongly associated with multivessel involvement, higher SYNTAX scores, and a greater prevalence of diffuse, eccentric plaques.[47-49] Leistner et al., similarly observed that patients with high Lp(a) exhibited a distinct coronary artery disease phenotype characterized by smaller-caliber vessels and a higher proportion of non-calcified plaques, suggesting a pathogenesis dominated by inflammation and thrombosis rather than chronic lipid deposition.[19]

These findings are echoed by Buciu et al., who demonstrated that young MI patients with elevated Lp(a) had a higher frequency of multivessel disease compared with those with normal levels, independent of LDL cholesterol.[22] Notably, angiographic analyses often reveal soft plaques, minimal calcification, and large thrombotic occlusions -features consistent with an acute atherothrombotic process rather than long-standing atherosclerosis.[19, 23] Histopathologic evaluations support these imaging findings, showing lipid-rich cores and superficial erosion, frequently in vessels without critical stenosis.

From a clinical standpoint, these patients may present with sudden cardiac events despite low calculated cardiovascular risk scores. The absence of antecedent angina, the abrupt onset of infarction, and the disproportionate thrombotic burden are hallmark features of the Lp(a)-associated MI phenotype.[6] Moreover, elevated Lp(a) is frequently associated with a familial clustering of premature CAD, suggesting that heritable elevation of Lp(a) contributes to both disease onset and severity.[59,60]

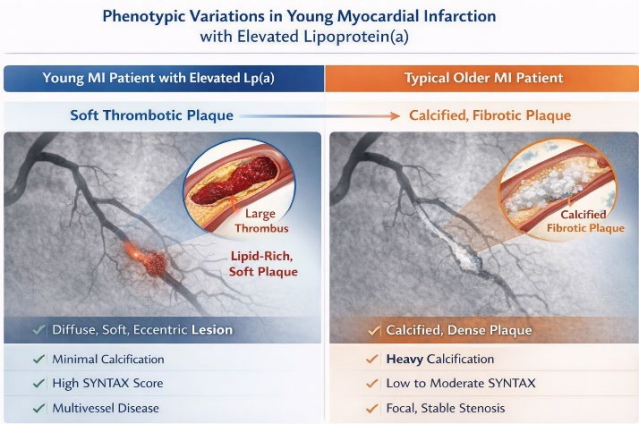

Figure-4. Representative coronary angiography images comparing typical plaque morphology in young MI patients with elevated Lp(a) (soft thrombotic lesions) versus older patients with calcified, fibrotic plaques.

Screening, risk stratification, and clinical assessment

Despite its well-established causal association with ASCVD, Lp(a) measurement remains underutilized in clinical practice. A growing body of evidence indicates that routine assessment of Lp(a) could significantly improve risk stratification, especially in young adults, those with a family history of premature coronary events, or patients with unexplained MI.[27,64]

Current Screening Recommendations:

Several expert panels and international societies now advocate at least one lifetime measurement of Lp(a) in all adults, particularly in high-risk groups. The European Atherosclerosis Society (EAS) and the American College of Cardiology (ACC) recommend screening in individuals with premature ASCVD, familial hypercholesterolemia, or a strong family history of early MI.[27,64] Screening is also advised in patients with recurrent cardiovascular events despite optimal lipid control and in those with calcific aortic valve disease, given the overlapping pathophysiology[9] [Table-2].

Testing Frequency and Cutoffs:

Because Lp(a) levels are genetically determined and remain stable throughout life, a single measurement is generally sufficient for most individuals.[11] Concentrations exceeding 50 mg/dL (125 nmol/L) are typically considered high risk, although some studies suggest population-specific thresholds may be more appropriate.[31,32] In young patients, even moderate elevations may carry significant risk due to cumulative lifetime exposure.[33]

Integration with Risk Scores:

Traditional cardiovascular risk calculators, such as the Framingham and SCORE models, do not incorporate Lp(a), leading to potential underestimation of risk in individuals with genetically elevated levels.[6] Incorporating Lp(a) into multi-marker risk models or polygenic risk scores has been proposed to enhance predictive accuracy for premature MI. For example, combined assessment of Lp(a), LDL cholesterol, and hsCRP offers improved discrimination of high-risk individuals compared with lipid profiles alone.[16]

Clinical Contexts for Testing:

Screening is particularly warranted in:

1. Young adults (<45 years) with MI or ischemic stroke in the absence of modifiable risk factors.
2. First-degree relatives of patients with elevated Lp(a) or premature ASCVD.
3. Individuals with recurrent or unexplained cardiovascular events despite lipid-lowering therapy.
4. Patients with progressive atherosclerosis or aortic valve stenosis not explained by LDL cholesterol levels.

Despite these clear indications, Lp(a) testing remains infrequent. A U.S. cohort analysis found that fewer than 1 in 10 patients with known ASCVD had Lp(a) measured, underscoring a significant diagnostic gap.[24,25] Broader implementation of Lp(a) screening, combined with patient and physician education, is crucial to bridge this divide.

Table-2. Major International Guideline Recommendations for Lp(a) Testing

Guideline organization	Year	Testing indication	Threshold (mg/dL / nmol/L)	Clinical use recommendation
European Atherosclerosis Society (EAS)	2010	Individuals with premature CVD, family history of high Lp(a)	≥50 mg/dL	Measure once in lifetime; consider aggressive LDL-C lowering if elevated
American Heart Association / American College of Cardiology (AHA/ACC)	2018	High-risk patients with premature ASCVD or family history	≥50 mg/dL	Lp(a) testing recommended to refine risk stratification; guide therapy intensity
Canadian Cardiovascular Society (CCS)	2018	Patients with intermediate to high ASCVD risk	≥50 mg/dL	Consider testing to identify individuals for more intensive lipid-lowering interventions
National Lipid Association (NLA)	2017	Patients with premature ASCVD, familial hypercholesterolemia	≥30 mg/dL (≥75 nmol/L)	Lp(a) measurement to guide overall cardiovascular risk management and therapy decisions
European Society of Cardiology / European Society of Hypertension (ESC/ESH)	2019	Adults with high-risk profile or family history of premature ASCVD	≥50 mg/dL	Testing recommended once in lifetime; integrate with other risk factors for clinical decisions

Lp(a), lipoprotein(a); CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Ethnic, sex-specific, and familial considerations

The expression and clinical consequences of elevated Lp(a) vary across sex and ethnic lines, influenced by differences in apo(a) isoform size, genetic variants, and hormonal regulation. Women generally have slightly higher Lp(a) levels than men, and the impact of Lp(a) on cardiovascular risk appears to increase after menopause, when estrogen-mediated lipid modulation declines.[40] In contrast, in premenopausal women, the adverse effects of Lp(a) may be partially attenuated, potentially explaining some of the observed sex differences in age at MI onset.[52]

Ethnic disparities are also pronounced. Populations of African descent exhibit the highest Lp(a) concentrations globally but may not experience proportionally higher cardiovascular risk, suggesting qualitative differences in Lp(a) particle composition or isoform distribution.[31] Conversely, South Asian populations -despite having lower median levels- demonstrate strong associations between Lp(a) and premature MI, consistent with a heightened vascular susceptibility.[55] In East Asian cohorts, modest elevations in Lp(a) confer significant risk, reinforcing the need for population-specific cutoffs.[13]

Familial aggregation of elevated Lp(a) provides a powerful rationale for cascade screening. Since Lp(a) levels are heritable and stable throughout life, early identification of high concentrations in one family member should prompt testing in first-degree relatives.[27] Such an approach aligns with preventive strategies in familial hypercholesterolemia and may help identify asymptomatic individuals at risk for early coronary disease before the onset of clinical manifestations.

Diagnostic Advances and Laboratory Standardization

Accurate measurement of Lp(a) remains a technical challenge due to its structural heterogeneity. Conventional immunoassays may yield inconsistent results because apo(a) size polymorphisms can interfere with antibody binding. To address this, newer isoform-insensitive assays calibrated in nanomoles per liter (nmol/L) are now recommended for clinical use, providing more reliable and comparable results across laboratories.[16]

Recent developments in high-throughput mass spectrometry and advanced immunonephelometric techniques have further improved precision and standardization. These methods enable simultaneous evaluation of Lp(a) particle number, oxidized phospholipid content, and isoform distribution - parameters that may refine risk assessment beyond total concentration alone.[43] Integration of Lp(a) measurement into multi-analyte cardiovascular risk panels and electronic health record algorithms could also facilitate broader adoption in routine practice.

Despite these advances, a universal reference range for Lp(a) remains elusive due to ethnic variation and assay heterogeneity. Consequently, interpretation should always consider the testing method and population-specific percentiles.[11]

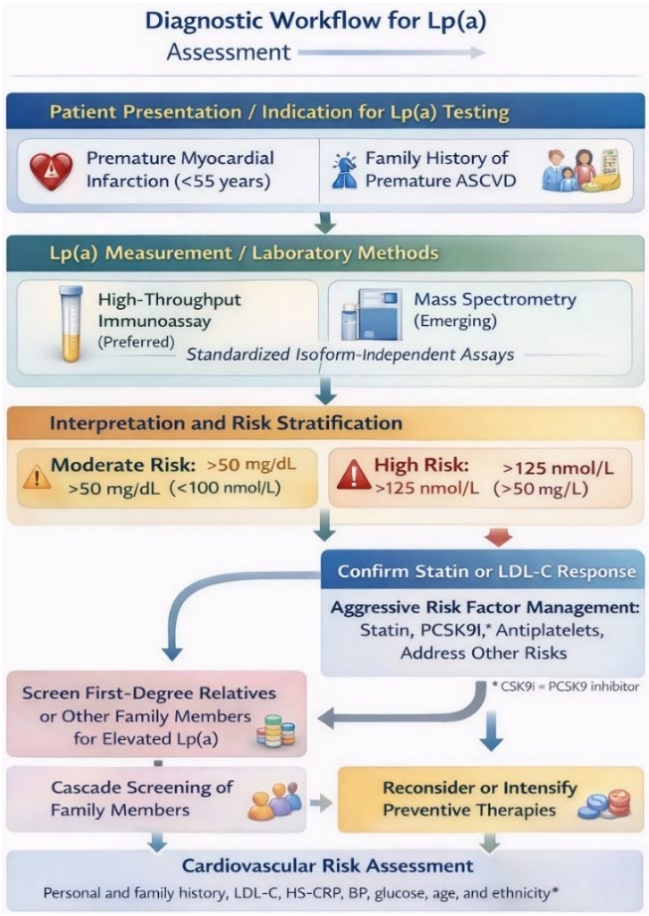

Figure-5. Overview of diagnostic workflow for Lp(a) assessment, illustrating indications for testing, assay methodologies, and integration into cardiovascular risk evaluation.

Clinical implications and the path forward

Recognition of Lp(a) as a major heritable and independent risk factor for premature MI has significant implications for clinical practice. Routine measurement in selected high-risk individuals -particularly young patients with unexplained coronary events- can identify those who may benefit from intensified prevention strategies and closer follow-up. In addition, understanding the Lp(a)-driven phenotype can guide therapeutic decisions, including early initiation of aggressive LDL-lowering therapy, antithrombotic management, and lifestyle optimization targeting synergistic risk factors.[15,16]

Furthermore, as novel Lp(a)-lowering agents advance through clinical trials, early identification of affected individuals will be essential for patient selection and monitoring of treatment efficacy. Integrating Lp(a) assessment into standard cardiovascular risk evaluation could thus transform both preventive cardiology and personalized medicine.

Ultimately, the goal extends beyond risk detection to proactive risk mitigation. Lp(a) testing provides clinicians with an opportunity to identify predisposed individuals long before irreversible vascular injury occurs, enabling earlier intervention and improved long-term outcomes for young patients vulnerable to premature myocardial infarction.

Therapeutic implications

Current lipid-lowering therapies and their limited impact on Lp(a)

Management of elevated Lp(a) poses a unique therapeutic challenge because its plasma levels are primarily genetically determined and largely resistant to conventional lipid-lowering strategies. Unlike low-density lipoprotein cholesterol (LDL-C), which can be substantially reduced through dietary modification, statins, and other lipid-lowering agents, Lp(a) concentrations remain remarkably stable throughout life and are minimally influenced by lifestyle or pharmacologic interventions.[26]

Statins, the cornerstone of dyslipidemia management, have minimal or inconsistent effects on Lp(a). Several studies suggest that statin therapy may paradoxically increase Lp(a) concentrations by 10–20%, potentially through enhanced apolipoprotein(a) synthesis.[16,26] Nevertheless, statins remain essential for reducing LDL-C and overall cardiovascular risk, and their use is still justified in patients with elevated Lp(a) due to the overlapping atherogenic mechanisms of both lipoproteins.

Niacin (vitamin B3) has historically been considered one of the few agents capable of lowering Lp(a) by approximately 20–30%. However, its clinical use has declined following large randomized trials that failed to demonstrate reductions in cardiovascular events and raised concerns about adverse metabolic effects, including insulin resistance and hepatotoxicity.[65] Therefore, niacin is no longer recommended solely for the purpose of Lp(a) lowering.

PCSK9 inhibitors (alirocumab and evolocumab) represent the first modern agents shown to meaningfully reduce Lp(a) levels. In large cardiovascular outcome trials, such as *ODYSSEY OUTCOMES* and *FOURIER*, PCSK9 inhibitors reduced Lp(a) concentrations by approximately 20–30%, an effect independent of LDL-C reduction.[16] Importantly, post hoc analyses revealed that patients with higher baseline Lp(a) derived greater cardiovascular benefit from PCSK9 inhibition, suggesting a partial contribution of Lp(a) lowering to event reduction. However, the magnitude of reduction achieved with these agents is generally insufficient for individuals with markedly elevated Lp(a), particularly those genetically predisposed to levels exceeding 150 mg/Dl.[26]

Lipoprotein apheresis, a mechanical extracorporeal filtration technique, remains the only established intervention capable of acutely lowering Lp(a) concentrations by up to 70%.[65] Regular apheresis has been associated with reduced rates of coronary events in patients with progressive atherosclerosis and refractory hyperlipoproteinemia(a). However, its use is limited by cost, invasiveness, and availability, restricting its application to specialized centers and highly selected patients, such as those with familial hypercholesterolemia and progressive CAD despite maximal medical therapy.[39]

Taken together, current therapeutic options provide only partial and temporary modulation of Lp(a). This therapeutic gap underscores the urgent need for targeted interventions that specifically address the underlying genetic and molecular drivers of elevated Lp(a) [Table-3].

Emerging Lp(a)-Targeted Therapies

The past decade has witnessed a transformative shift in the therapeutic landscape of Lp(a) management, driven by advances in gene-silencing technologies. Novel pharmacologic agents specifically targeting the LPA gene or its messenger RNA are now in various stages of clinical development, showing unprecedented efficacy in lowering circulating Lp(a) concentrations.

Antisense oligonucleotides (ASOs) represent the most clinically advanced class of Lp(a)-lowering therapies. These short, synthetic nucleic acid sequences bind to complementary regions of the LPA mRNA, leading to its degradation and consequent suppression of apo(a) synthesis in the liver. *Pelacarsen (TQJ230)*, a second-generation ASO developed by Novartis and Ionis Pharmaceuticals, has demonstrated reductions of up to 80–90% in plasma Lp(a) levels in phase 2 trials.[26] The pivotal Lp(a)HORIZON phase 3 trial, currently ongoing, aims to determine whether this reduction translates into decreased major adverse cardiovascular events among patients with established ASCVD and elevated Lp(a). If

successful, pelacarsen may become the first approved targeted therapy for Lp(a)-mediated cardiovascular risk.

Small interfering RNA (siRNA) therapies offer an alternative mechanism for gene silencing by promoting the degradation of LPA mRNA through the RNA interference pathway. *Olpasiran (AMG 890)*, developed by Amgen, has shown sustained Lp(a) reductions of over 90% after a single dose in the OCEAN(a)-DOSE trial.[26] Similar efficacy has been observed with other investigational siRNAs, such as *SLN360* and *LY3819469*, which utilize hepatocyte-targeted delivery systems for enhanced potency and prolonged duration of action. These agents are administered subcutaneously at intervals of weeks to months, offering a practical and patient-friendly alternative to chronic therapies.

Preliminary data suggest that both ASOs and siRNAs are well tolerated, with mild injection-site reactions being the most common adverse events.[16] Long-term outcome studies are underway to evaluate their effects on cardiovascular morbidity and mortality, with particular interest in high-risk subgroups, including young patients with premature MI and familial Lp(a) elevation.

If the anticipated outcome benefits are confirmed, these novel agents may redefine the paradigm of cardiovascular prevention by offering, for the first time, a causal and potent intervention for genetically mediated risk.

Table-3. Comparison of Lp(a)-Lowering Interventions: Mechanism, Efficacy, and Limitations

Therapy	Mechanism	Average Lp(a) reduction(%)	Effect on LDL-C	Clinical Outcomes Evidence	Limitations / Adverse Effects
Statins	HMG-CoA reductase inhibition	Minimal or slight increase in Lp(a)	↓ 20–55%	Proven benefit in ASCVD, not specific to Lp(a)	Limited impact on Lp(a); may slightly increase Lp(a) in some patients
Niacin (Nicotinic acid)	Inhibits hepatic apo(a) synthesis	20–30%	↓ 10–25%	Some reduction in cardiovascular events historically	Flushing, hepatotoxicity, glucose intolerance; limited current use
PCSK9 inhibitors (e.g., evolocumab, alirocumab)	Monoclonal antibody against PCSK9	20–30%	↓ 50–60%	Reduced cardiovascular events in high-risk patients	Cost, injectable, injection-site reactions
Lipoprotein apheresis	Extracorporeal removal of Lp(a) particles	60–70% per session	↓ 20–30% (transient)	Shown to reduce recurrent events in extreme Lp(a) elevation	Time-consuming, expensive, requires specialized centers
Antisense oligonucleotides (ASO, e.g., pelacarsen)	Inhibits hepatic apo(a) mRNA	70–90%	Minimal effect	Early trials: reduction in Lp(a); large outcome trials ongoing	Injection-site reactions, potential hepatic effects; long-term outcomes pending
Small interfering RNA (siRNA, e.g., olpasiran)	RNA interference targeting apo(a) mRNA	80–95%	Minimal effect	Phase 2/3 trials show robust Lp(a) reduction; cardiovascular outcomes under investigation	Long-term safety data limited; injection required

Lp(a), lipoprotein(a); LDL-C, low-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; siRNA, small interfering RNA.

Lifestyle interventions and secondary prevention strategies

Given the predominantly genetic nature of Lp(a) elevation, lifestyle interventions exert minimal direct influence on its plasma concentration. Nevertheless, comprehensive cardiovascular risk reduction remains a crucial therapeutic objective, especially in young MI survivors with high Lp(a). Lifestyle modification - comprising smoking cessation, regular aerobic exercise, weight optimization, and adherence to a heart-healthy

diet- can attenuate the synergistic effects of coexisting risk factors such as hypertension, diabetes, and dyslipidemia.[57,66]

Adherence to aggressive LDL-C lowering strategies remains the cornerstone of management for patients with elevated Lp(a). Given that Lp(a) and LDL share structural and functional similarities, maintaining LDL-C below 55 mg/dL is recommended for secondary prevention in high-risk individuals, as per current European Society of Cardiology (ESC) guidelines.[27] Combination therapy with statins and PCSK9 inhibitors may be necessary to achieve these targets.

Antiplatelet therapy also assumes heightened importance in this population due to the prothrombotic effects of Lp(a). Low-dose aspirin may be considered in selected young patients with persistently elevated levels and additional thrombotic risk factors, provided the bleeding risk is low.[9,23]

Psychosocial and behavioral interventions should not be overlooked. Young MI survivors frequently experience anxiety, depression, and reduced adherence to therapy, which can compromise long-term outcomes.[57,67] Multidisciplinary rehabilitation programs incorporating lifestyle counseling, risk education, and psychological support are essential components of secondary prevention.

Collectively, these nonpharmacological measures complement emerging pharmacologic therapies by addressing modifiable contributors to vascular injury and optimizing global cardiovascular health.

Future therapeutic perspectives

The evolving understanding of Lp(a) biology and the emergence of potent Lp(a)-lowering therapies herald a new era in personalized cardiovascular medicine. Future therapeutic strategies are likely to combine precision screening, genotype-guided intervention, and early pharmacologic modulation to prevent premature cardiovascular events before structural vascular damage occurs.

Several key questions remain: What is the optimal age for initiating Lp(a)-targeted therapy in genetically predisposed individuals? How should treatment thresholds be defined for primary prevention, particularly in asymptomatic young adults? And what is the long-term safety profile of sustained Lp(a) suppression over decades of exposure? Ongoing large-scale outcome trials such as *Lp(a)HORIZON* and *OCEAN(a)-OUTCOMES* are expected to provide critical answers.[16, 26]

Beyond cardiovascular disease, elevated Lp(a) has been implicated in calcific aortic valve stenosis, ischemic stroke, and peripheral arterial disease [9]. Future therapeutic paradigms may thus extend beyond coronary protection to encompass broader vascular prevention. Integration of Lp(a) assessment into genetic risk panels and routine cardiovascular screening programs could enable early identification of individuals who would benefit most from these targeted therapies.

From a public health standpoint, the development of cost-effective and scalable Lp(a)-lowering strategies is essential. As global awareness grows, the inclusion of Lp(a) measurement in standard lipid panels and electronic health records could facilitate population-level screening and personalized treatment pathways. Ultimately, combining molecularly targeted drugs with preventive strategies offers the potential to substantially reduce the burden of premature myocardial infarction worldwide.

Controversies and research gaps

Despite overwhelming evidence linking elevated Lp(a) to premature ASCVD and MI, several key controversies and uncertainties persist. These knowledge gaps span biological, clinical, and methodological domains, encompassing threshold definitions for "elevated" Lp(a), the precise mechanisms of pathogenicity, and the translation of emerging therapies into population-wide prevention. Addressing these questions is essential for optimizing risk assessment and developing targeted interventions, particularly in young individuals at risk for early-onset coronary disease.

Defining the threshold for elevated Lp(a): A moving target

A central challenge in Lp(a) research lies in the absence of a universally accepted threshold that defines clinically significant elevation. Although a level above 50 mg/dL (125 nmol/L) is widely considered atherogenic, risk relationships appear continuous rather than dichotomous, with no clear cutoff separating "normal" from "pathologic" concentrations.[68] Moreover, interethnic variability complicates this issue: African populations tend to exhibit higher median Lp(a) levels yet not necessarily proportional increases in cardiovascular risk, while South Asian and East Asian cohorts show substantial risk at relatively modest elevations.[13, 31]

Several investigators have proposed population-specific percentiles or genetic-risk–adjusted thresholds to better capture risk gradients.[11,32] However, the lack of assay standardization and the influence of apo(a) isoform heterogeneity introduce further complexity. Older immunoassays calibrated in mg/dL often over- or

underestimate concentrations depending on the underlying apo(a) size distribution, whereas newer isoform-insensitive assays in nmol/L provide more consistent quantification.[27] Until universal reference methods are adopted, the clinical interpretation of "high" Lp(a) will remain partly dependent on the analytical platform used and the population under investigation.

This uncertainty extends to risk communication and clinical decision-making. For example, it remains unclear whether moderate elevations (30-50 mg/dL) should trigger intensified lipid-lowering therapy or closer surveillance, especially in young adults without other risk factors. Consensus statements increasingly favor a continuous-risk model rather than a fixed threshold approach, suggesting that Lp(a) should be viewed as part of an integrated cardiovascular risk spectrum rather than a binary abnormality.[16]

Mechanistic ambiguities: proatherogenic, prothrombotic, or both?

Another enduring controversy involves the precise mechanisms by which Lp(a) contributes to atherosclerosis and thrombosis. Although the dual atherothrombotic model is well supported -wherein Lp(a) accelerates lipid deposition while impairing fibrinolysis- the relative contribution of each pathway remains debated.[29]

The proatherogenic hypothesis emphasizes the role of oxidized phospholipids carried by Lp(a), which promote endothelial activation, monocyte recruitment, and smooth muscle proliferation.[22] These effects appear particularly important in the initiation and progression of atherosclerotic plaque. Conversely, the prothrombotic hypothesis highlights the structural similarity between apo(a) and plasminogen, which allows Lp(a) to compete for fibrin-binding sites and inhibit plasmin formation, thereby delaying clot resolution.[23]

Recent imaging and histopathological studies suggest that Lp(a)-related plaques are less calcified but more lipid-rich and thrombogenic compared to those associated with conventional dyslipidemia.[19] However, it remains unclear whether Lp(a) acts primarily as a chronic promoter of atheroma formation or as an acute amplifier of thrombosis upon plaque rupture. It is plausible that these mechanisms coexist, with atherosclerosis providing the substrate and thrombosis precipitating the clinical event -a sequence particularly relevant in young patients with minimal underlying plaque burden.

A further unresolved question concerns the potential inflammatory modulation of Lp(a)'s pathogenicity. Recent studies indicate that elevated high-sensitivity C-reactive protein (hsCRP) amplifies the cardiovascular risk associated with Lp(a), suggesting that inflammatory activation may enhance its atherothrombotic potential.[28] Yet, whether inflammation represents a mediator, modifier, or byproduct of Lp(a)-induced vascular injury remains to be elucidated.

Genetic diversity and population differences

The extreme interindividual variability in Lp(a) concentrations, driven largely by genetic polymorphisms in the LPA gene, poses significant challenges for global risk assessment. Variants such as rs10455872 and rs3798220 confer high Lp(a) levels and increased cardiovascular risk in European populations, but their prevalence and effect sizes differ across ethnic groups.[30] In East Asians, other polymorphisms and gene–environment interactions appear more relevant, while in African ancestry populations, small apo(a) isoforms are common but may not confer proportional cardiovascular risk.[13,31]

This heterogeneity complicates the extrapolation of study findings and the design of universal screening thresholds. It also underscores the need for regionally tailored genetic and epidemiological studies to better define risk gradients in diverse populations. Understanding the interplay between LPA genotype, apo(a) isoform size, and biochemical function will be critical for developing precision-based screening and treatment strategies.

Moreover, the pleiotropic effects of the LPA gene remain an area of active investigation. While the cardiovascular consequences of Lp(a) are well documented, emerging data suggest potential associations with calcific aortic valve disease, stroke, and renal impairment.[9] Whether these conditions represent distinct mechanistic pathways or secondary manifestations of the same vascular process remains uncertain.

Incomplete clinical integration and underutilization of testing

Despite extensive evidence linking Lp(a) to premature MI, its clinical measurement remains infrequent. Surveys reveal that fewer than 10% of cardiovascular patients in routine practice undergo Lp(a) testing.[24, 25] Contributing factors include limited clinician awareness, the absence of mandatory guideline recommendations, uncertainty about interpretive thresholds, and the perception that effective treatments are lacking. This diagnostic inertia delays recognition of genetically mediated risk in young adults and undermines opportunities for early intervention.

Even when Lp(a) is measured, test results are often underinterpreted or omitted from clinical decision-

making frameworks. Most global risk calculators still exclude Lp(a), leading to risk underestimation in younger, otherwise healthy individuals.[6] Integrating Lp(a) into cardiovascular risk models, electronic health record systems, and family screening protocols remains an unmet need. Until Lp(a) is routinely incorporated into preventive cardiology workflows, many individuals with genetically elevated levels will continue to remain unidentified until they experience their first ischemic event.

Therapeutic uncertainties and long-term safety

Although novel antisense oligonucleotide (ASO) and small interfering RNA (siRNA) therapies have revolutionized the management of Lp(a) elevation, several unresolved clinical questions persist. First, the extent to which Lp(a) lowering translates into reduced cardiovascular events remains to be proven. The ongoing *Lp(a)HORIZON* and *OCEAN(a)-OUTCOMES* trials are expected to provide definitive evidence, but until those results are available, Lp(a) remains an unvalidated therapeutic target in terms of clinical outcomes.[16, 26]

Second, the optimal timing and duration of therapy are uncertain. Should treatment begin early in life for individuals with genetically elevated Lp(a), or only after clinical disease manifests? Given the lifelong stability of Lp(a) levels, early intervention could theoretically prevent decades of vascular exposure, but long-term safety and cost-effectiveness of sustained Lp(a) suppression remain to be established.[11]

Furthermore, the potential physiological roles of Lp(a) are not fully understood. While primarily considered pathogenic, Lp(a) may play a role in wound healing or host defense due to its structural homology with plasminogen. Profound suppression of Lp(a) through gene-silencing therapies could therefore have unintended consequences, necessitating careful long-term monitoring of treated patients.[9]

Finally, the economic implications of emerging therapies pose another layer of uncertainty. High production costs, long dosing intervals, and the need for lifelong administration may restrict access, particularly in low- and middle-income regions where premature cardiovascular disease is most prevalent. Equitable implementation strategies and global cost analyses will be critical for ensuring that the benefits of these scientific advances are broadly realized.

Unanswered clinical questions and future research directions

The rapid expansion of Lp(a) research has generated as many questions as answers. Among the most pressing are:

- What is the ideal age and frequency for Lp(a) testing? Should it be included in universal lipid screening, or limited to high-risk populations and family clusters?
- What are the mechanisms linking Lp(a) to plaque instability and thrombosis in young individuals? Understanding whether Lp(a) acts as a trigger or amplifier of plaque rupture may refine therapeutic targeting.
- Can Lp(a) reduction alter the natural history of atherosclerosis or reverse plaque progression? Longitudinal imaging and biomarker studies are needed to answer this question.
- How should Lp(a) measurement be integrated with other novel biomarkers and polygenic risk scores? Multi-marker approaches may provide more accurate risk stratification than single-biomarker models.
- What is the role of lifestyle and environmental modifiers in modulating Lp(a)-related risk? While genetic determination is dominant, emerging data suggest that inflammation, oxidative stress, and metabolic factors may influence clinical expression of Lp(a)-mediated disease.[28]

Addressing these gaps will require large, ethnically diverse prospective studies and harmonization of laboratory methodologies to ensure comparability across regions. Integration of genetics, proteomics, and imaging will further clarify the biological continuum linking Lp(a) to early vascular injury and clinical events.

Conclusion and future directions

Lp(a) has emerged as a pivotal yet underrecognized determinant of premature myocardial infarction, particularly in young individuals who often lack traditional cardiovascular risk factors. Its unique biochemical composition -an LDL-like particle covalently linked to apolipoprotein(a)- endows it with both atherogenic and prothrombotic properties that accelerate vascular injury and thrombosis at an early age. Evidence from genetic, epidemiological, and mechanistic studies now converges to establish Lp(a) not as a secondary marker of risk, but as a causal driver of early-onset atherosclerotic cardiovascular disease.

Clinically, the implications of this recognition are profound. Young patients presenting with myocardial infarction and elevated Lp(a) often represent a distinct phenotype -characterized by minimal traditional risk burden, diffuse but soft coronary lesions, and a strong familial predisposition. These individuals challenge conventional models of cardiovascular risk assessment, which remain anchored in modifiable factors and age-weighted scoring systems that fail to capture genetically

determined hazards. Incorporating Lp(a) testing into early risk evaluation, especially in patients with premature events or a family history of early coronary disease, could transform preventive cardiology from reactive management to anticipatory intervention.

Yet, this scientific clarity contrasts sharply with clinical inertia. Despite decades of evidence, routine Lp(a) measurement is not yet standard practice, and awareness among clinicians remains low. Broader implementation of testing -ideally once in a lifetime for all adults- would allow earlier detection of individuals at lifelong risk. Such an approach, combined with cascade screening in families, aligns with the precision-medicine paradigm that increasingly defines modern cardiovascular care.

From a therapeutic standpoint, the field stands at an inflection point. Conventional lipid-lowering drugs such as statins and ezetimibe have little effect on Lp(a), and even PCSK9 inhibitors offer only modest reductions. However, the emergence of RNA-based therapeutics -antisense oligonucleotides and small interfering RNA molecules- signals a paradigm shift. These agents can lower plasma Lp(a) concentrations by up to 90%, directly targeting the root genetic cause of elevation. If ongoing outcome trials confirm that such reductions translate into fewer cardiovascular events, Lp(a)-directed therapy could become a cornerstone of primary and secondary prevention, particularly for young and genetically predisposed patients.

Beyond pharmacologic innovation, addressing Lp(a)-related cardiovascular risk requires a comprehensive, multidisciplinary approach. Lifestyle optimization, aggressive LDL cholesterol control, and inflammation reduction remain essential components of management, mitigating synergistic pathways that amplify vascular injury. Integrating Lp(a) screening into population-level programs could also yield substantial public health benefits by identifying silent carriers before irreversible vascular damage occurs. Importantly, ensuring equitable access to emerging therapies will be vital to prevent widening global disparities, as Lp(a)-related disease disproportionately affects regions with limited healthcare resources and genetic predisposition to early cardiovascular death.

Future research must now turn toward refining clinical thresholds, elucidating ethnic and sex-specific risk patterns, and defining the optimal timing of intervention. Longitudinal cohort studies beginning in adolescence or early adulthood will be crucial to map the trajectory of Lp(a)-driven atherogenesis and to evaluate whether early therapeutic modulation can alter the natural history of disease. The integration of genomics, proteomics, and imaging biomarkers will further clarify how Lp(a) interacts with inflammation, thrombosis, and vascular remodeling, deepening our mechanistic understanding.

Ultimately, recognizing and targeting Lp(a) represents more than the correction of a lipid abnormality -it embodies a shift in how cardiovascular risk is conceptualized and prevented. By combining molecular precision with preventive foresight, clinicians and researchers have the opportunity to intercept cardiovascular disease at its genetic origin. For young patients at risk of premature myocardial infarction, this evolving paradigm offers not only improved prognosis but the possibility of preventing the first event altogether.

Practical points in Biochemistry/Nutrition:

Elevated lipoprotein(a) is a major genetic, independent risk factor for premature MI. Lifestyle has minimal impact; it requires measurement and aggressive LDL management. Novel RNA-based therapies can significantly lower Lp(a) levels.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

ACC: American College of Cardiology; AHA: American Heart Association; apo(a): apolipoprotein(a); apoB-100: apolipoprotein B-100; ASCVD: Atherosclerotic Cardiovascular Disease; ASO: Antisense Oligonucleotide; CAD: Coronary Artery Disease; CCS: Canadian Cardiovascular Society; EAS: European Atherosclerosis Society; ESC: European Society of Cardiology; ESH: European Society of Hypertension; hsCRP: high-sensitivity C-reactive protein; LDL: Low-Density Lipoprotein; LDL-C: Low-Density Lipoprotein Cholesterol; Lp(a): Lipoprotein(a); MACE: Major Adverse Cardiovascular Events; MI: Myocardial Infarction; NLA: National Lipid Association; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; siRNA: small interfering RNA; SNPs: Single Nucleotide Polymorphisms; STEMI: ST-segment Elevation Myocardial Infarction.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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