Lipoprotein(a) Screening: A comprehensive update on its role in assessing cardiovascular risk

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ABSTRACT

Lipoprotein(a) has a significant role in cardiovascular risk assessment. According to multiple international guidelines, Lipoprotein(a) is a modified form of LDL with atherogenic potential. Elevated Lipoprotein(a) levels are independently associated with an increased risk of atherosclerotic cardiovascular disease, including myocardial infarction, stroke, and coronary heart disease death. Current guidelines recommend measuring Lipoprotein(a) in patients with a personal or family history of atherosclerotic cardiovascular disease, familial hypercholesterolemia, moderate to high cardiovascular risk, and family members with high lipoprotein(a). In general Lipoprotein(a) level of ≥50 mg/dL carries a clinically important risk-enhancing factor for atherosclerotic cardiovascular disease. This review covers pathophysiology, screening, risk assessment, potential treatment options, and current randomized clinical trials.

Keywords: Lipoprotein(a); Lp(a); cardiovascular diseases; acute-phase reaction

INTRODUCTION

Classical risk factors for cardiovascular diseases, such as smoking, obesity, and diabetes, have long been used in clinical practice. These factors primarily affect older patients. Recently, there has been growing awareness of cardiovascular disease occurring in younger individuals who do not have these classical risk factors, leading to the investigation of additional risk factors, such as familial hyperlipidemia.

Lipoprotein(a), or Lp(a), is a cholesterol-rich particle similar to low-density lipoprotein (LDL) that is independently associated with an increased risk of ischemic heart disease, atherosclerosis, and thrombosis. Elevated Lp(a) levels are quite common; approximately one in five individuals globally and one in four patients with atherosclerotic cardiovascular disease (ASCVD)—about 28%—have Lp(a) levels of 50 mg/dL (100-125 nmol/L) or higher.

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Clinical guidelines and recent publications recognize increased Lp(a) as an independent risk factor for cardiovascular disease, although specific thresholds have not yet been established. In addition, premature cardiovascular disease is defined as ASCVD occurring in women under 60 years of age and in men under 55 years old.[1]

PHYSIOPATHOLOGY

The relationship between hyperlipidemia, particularly low-density lipoprotein cholesterol (LDL-C), and cardiovascular disease is well-established and critical for treating and preventing ASCVD.

A key structural difference between Lp(a) and LDL-C is that Lp(a) contains an additional protein, apolipoprotein(a) [apo(a)], which is bound to apolipoprotein B (apoB) through a single disulfide bond.[2]

The levels of Lp(a) are largely determined by genetics, with approximately 90% of the variation attributed to genetic factors, particularly variations at the LPA locus.[3] In newborns, Lp(a) levels are typically low; however, these levels may indicate which individuals

are likely to develop higher concentrations later in life. Evidence suggests that Lp(a) levels significantly increase from childhood into adulthood. By the age of two, the LPA gene is fully expressed, and adult Lp(a) levels are usually reached by the age of five, continuing to rise until adulthood.[3–5]

Lp(a) inherits atherogenic properties from both apoB and apoA, along with prothrombogenic and proinflammatory characteristics from apoA, which together contribute to traits associated with an increased risk of cardiovascular disease.[6]

Lp(a) can easily penetrate the arterial lining and bind to components of the extracellular matrix, which promotes macrophage infiltration and smooth muscle cell proliferation. A key component of Lp(a) is the unique protein apo(a), which plays a crucial role in its atherogenic effects. Because apo(a) has a structure similar to plasminogen, Lp(a) may also be involved in the early stages of wound repair. When the extracellular matrix is exposed to blood due to tissue damage, Lp(a) can be recruited to the wound site, facilitating the influx of pro-inflammatory cells, such as monocytes, to the vascular endothelium. In this context, Lp(a) inhibits fibrinolysis and exerts a pro-thrombotic effect.[7]

Among all lipoproteins, Lp(a) is the primary carrier of oxidized phospholipids (OxPL), which are significant contributors to the pro-inflammatory and procalcific effects of Lp(a). The OxPL component of Lp(a) promotes the secretion of cytokines, enhances the transendothelial migration of monocytes, and increases the expression of adhesion molecules. In patients with elevated levels of Lp(a), immune cells show increased migration into atherosclerotic plaques. Currently, elevated plasma levels of Lp(a) are recognized as the strongest single inherited risk factor for early coronary artery disease and aortic valve stenosis.[7]

Risk assessment

The ability of Lp(a) to predict adverse cardiovascular outcomes has been found in patients with LDL cholesterol levels exceeding 70 mg/dL. Importantly, the cardiovascular risk associated with elevated Lp(a) levels significantly decreases in individuals whose LDL cholesterol has been reduced to below the more aggressive target of less than 70 mg/dL.[8]

Patients with high levels of Lp(a) (greater than 50 mg/dL) exhibited a higher prevalence of hyperlipidemia ($P = 0.024$). However, there were no significant differences found in smoking status, family history of cardiovascular disease, body mass index, hypertension, or diabetes ($P > 0.050$ for all).[9] Statin therapy led to a reduction in LDL cholesterol, with a mean change of −39% (95% CI −43 to −35), but did not result in a significant change in lipoprotein(a) levels.[10]

Currently, multiple international guidelines address the general indications to measure Lp(a) levels as well as its normal values (Table 1).

Lp(a) in premature cardiovascular disease

The relationship between Lp(a) and cardiovascular disease is well-established in the older population. However, its connection to premature cardiovascular

Table 1. Current Guidelines Recommendations of Lp(a) Levels

Guideline	Recommendation	Lp(a) Cutoff Value
American Heart Association (AHA)	Measure Lp(a) in adults with a family history of premature cardiovascular disease or elevated Lp(a)	>50 mg/dL
National Lipid Association (NLA)	Measure Lp(a) in individuals with a personal or family history of premature atherosclerotic cardiovascular disease	>30 mg/dL
Canadian Cardiovascular Society (CCS)	Measure Lp(a) in individuals with intermediate or high cardiovascular risk	>30 mg/dL
UK National Institute for Health and Care Excellence (NICE)	Measure Lp(a) in individuals with a family history of hyperlipidemia or cardiovascular disease	>50 mg/dL

disease is less clear, as there is conflicting evidence. The BIOSIGNAL study observed a significant association between elevated Lp(a) levels and large artery atherosclerosis stroke in individuals under 60 years of age. In addition, a prospective study conducted by Raitakari et al. with 3,596 patients found that higher Lp(a) levels were associated with premature ASCVD.[11] In contrast, studies by Cai et al. and Shi et al. reported no significant relationship between Lp(a) levels and acute myocardial infarction in younger individuals.[12,13]

A recent meta-analysis of 51 studies involving 100,540 patients found an association between Lp(a) and ASCVD, regardless of whether the cutoff for premature disease was set at 50 or 60 years or if the Lp(a) threshold was 50 mg/dL or 100 mg/dL. However, no association was observed in patients with a baseline LDL-C level of less than 100 mg/dL. The types of ASCVD that showed a positive association included coronary artery disease and peripheral artery disease, while no association was found with stroke.[10]

A Latin American study found a correlation between increased Lp(a) levels and a family history of premature ASCVD in patients with LDL levels greater than 160 mg/dL. These patients exhibited elevated Lp(a) levels.[14] In addition, the relationship between inflammation, macrophage migration, Lp(a), and premature ASCVD supports the previously explained pathophysiology.[15]

Lp(a) and Aortic Stenosis

Elevated levels of Lp(a) have been linked to calcific aortic valve stenosis. Research demonstrates that higher Lp(a) levels are associated with a more rapid progression of aortic stenosis. Hemodynamic measurements have revealed an increase in peak aortic jet velocity and a faster progression of the mean transvalvular gradient. However, the progression of the aortic valve area was similar across different groups. No significant differences were observed when Lp(a) levels were treated.[16]

Possible Management Options

Strong evidence supporting the causal relationship between Lp(a) and ASCVD has led to the development of new medications specifically designed to lower Lp(a) levels. Neither diet nor exercise has demonstrated significant effects on Lp(a) levels. However, some evidence suggests that a low-carbohydrate diet may reduce Lp(a) levels by approximately 14.7%.[17]

Several drugs have shown effectiveness in decreasing Lp(a) levels. Nevertheless, it remains unclear whether a reduction in Lp(a) levels leads to a decrease in cardiovascular disease.[6]

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)

PCSK9 inhibitors, such as evolocumab and alirocumab, effectively reduce Lp(a) levels, and this reduction is associated with a subsequent decrease in cardiovascular events, particularly in patients with elevated baseline Lp(a) levels.[18] A systematic review and meta-analysis further quantified the effects of PCSK9 inhibitors, including alirocumab and evolocumab, on Lp(a) levels. The analysis concluded that PCSK9 inhibitors resulted in a reduction of Lp(a) levels by approximately 26.7%, although significant heterogeneity was observed across the included studies.[19]

Niacin

Niacin has been demonstrated to exert a dose-dependent effect on Lp(a) levels. Clinical studies cited in the FDA drug label for Niaspan indicate that niacin doses of 1500 mg and 2000 mg lead to significant reductions in Lp(a) levels. Specifically, the administration of 1500 mg of niacin resulted in a mean percent change of −20% from baseline in Lp(a) levels, while the 2000 mg dose produced a mean reduction of −24%. These reductions were statistically significant when compared to the placebo, which showed no notable change in Lp(a) levels.[20]

In addition to the information provided in the FDA drug label, numerous clinical studies and meta-analyses have explained the effects of niacin on Lp(a) levels. A systematic review and meta-analysis of randomized, placebo-controlled trials demonstrated that extended-release niacin significantly reduces Lp(a)

levels, yielding a weighted mean difference of -22.90% (95% CI: −27.32, −18.48, $p < 0.001$). This reduction was observed consistently across various niacin doses, both below and exceeding 2000 mg/day.[21]

Further mechanistic insights into the effects of niacin on Lp(a) levels have been provided by studies investigating the kinetics of Lp(a) and its constituents. For example, in statin-treated men with type 2 diabetes mellitus, extended-release niacin resulted in a 26.5% reduction in plasma Lp(a) concentrations by lowering the production rates of apolipoprotein(a) and Lp(a)-apoB-100.[22] In addition, a separate study conducted in hypertriglyceridemia patients revealed that extended-release niacin reduced Apo(a) plasma concentrations by 20%, with a concomitant 50% reduction in production rates and a 37% decrease in catabolism.[23]

Randomized clinical trials in Lp(a)

There are multiple ongoing and finished randomized clinical trials that have involved the use of different medications and its impact in Lp(a) levels (Table 2).

- **PCSK9:** The FOURIER trial, a large-scale randomized study involving 25,096 patients, demonstrated that evolocumab significantly decreased Lp(a) levels by a median of 26.9%, which was correlated with a reduction in cardiovascular events, particularly in patients with elevated baseline Lp(a) levels.[18] Similarly, the LAPLACE-TIMI 57 trial assessed the effect of evolocumab) on Lp(a) levels in hypercholesterolemic patients on statin therapy. This trial revealed that evolocumab reduced Lp(a) levels by 32% compared to placebo, with the observed reduction correlating with a decrease in LDL-C levels.[24]
- **Muvalaplin:** A Phase 2, placebo-controlled, randomized, double-blind trial evaluated the efficacy of muvalaplin in reducing lipoprotein(a) Lp(a) levels. The study included 233 participants with elevated Lp(a) levels and underlying cardiovascular risk factors. Dosages of 10 mg/d, 60 mg/d, and 240 mg/d resulted in significant placebo-adjusted reductions in Lp(a) levels by 47.6%, 81.7%, and 85.8%, respectively, over 12 weeks.[25]
- **APO(a)-L:** APO(a)-L, a hepatocyte-targeted antisense oligonucleotide, was assessed in a randomized, double-blind, placebo-controlled trial involving 286 patients diagnosed with cardiovascular disease. The administration of APO(a)-L at varying dosages (20 mg to 60 mg) led to dose-dependent reductions in Lp(a) levels, with the highest dose achieving an 80% reduction.[26]
- **Lepodisiran:** A Phase 1 trial was conducted to investigate lepodisiran, a short interfering RNA designed to target the hepatic synthesis of apolipoprotein(a). The study included 48 participants and demonstrated dose-dependent reductions in

Table 2. Other Relevant Clinical Trials in Lp(a)

Trial Name	Objective	Status	Reference
HORIZON	Evaluate the effect of pelacarsen on cardiovascular outcomes in patients with elevated Lp(a)	Recruiting	https://clinicaltrials.gov/study/NCT04023552
OCEAN(a)-DOSE	Determine the optimal dose of Olpasiran for reducing Lp(a) levels	Completed	https://clinicaltrials.gov/study/NCT04270760
AKCEA-APO(a)-LRx	Investigate the safety and efficacy of AKCEA-APO(a)-LRx in lowering Lp(a)	Completed	https://pubmed.ncbi.nlm.nih.gov/31893580/
FOURIER	Evaluate the efficacy and safety of evolocumab, a PCSK9 inhibitor, among participants with elevated cardiovascular risk on statin therapy	Completed	https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2017/03/16/00/46/FOURIER

Lp(a) levels. The highest dose, 608 mg, resulted in a 97% reduction in Lp(a) levels.[27]

- **Olpasiran:** Olpasiran, a small interfering RNA, was evaluated in a dose-finding trial involving 281 patients with atherosclerotic cardiovascular disease. The results indicated that olpasiran significantly reduced Lp(a) levels in a dose-dependent manner, with the highest dose (225 mg administered every 12 weeks) achieving a 101.1% reduction in Lp(a) levels.[28]

Conclusion

The panel recommends a more intensive approach to managing risk factors as Lp(a) concentrations increase, particularly for individuals with a higher baseline risk. This personalized strategy aims to improve cardiovascular risk management. Elevated levels of Lp(a) are strong indicators of the likelihood of recurrent cardiovascular events, highlighting the need for intensified LDL-lowering therapy, which may include the use of PCSK9 inhibitors.

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