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EDITORIAL

Lipoprotein(a): what clinicians need to know

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Abstract

Lipoprotein(a) [Lp(a)] is a plasma particle structurally similar to LDL, distinguished by the presence of apolipoprotein(a), and has evolved from plasminogen. Lp(a) concentration is 90% genetically determined and largely stable throughout life. Black individuals exhibit the highest Lp(a) levels, followed by South Asians, Whites, Hispanics, and East Asians, with a 2- to 4-fold median difference across ancestral groups. Approximately 1.5 billion people worldwide (~20% of the population) have elevated Lp(a) levels (>125 nmol/L or >50 mg/dL). Notably, women experience 17% higher levels than men post-menopause. Mendelian randomization studies have established Lp(a) as a strong cardiovascular disease (CVD) risk factor, implicated in coronary artery disease, peripheral artery disease (PAD), ischemic stroke, heart failure, and aortic stenosis. Risk increases linearly with Lp(a) levels, with concentrations >90 mg/dL (>190 nmol/L) associated with a 1.6-fold higher risk of ischemic stroke, 1.7-fold for heart failure, 2-fold for PAD, and 3-fold for aortic stenosis and myocardial infarction. Lp(a) levels between 130–391 mg/dL (280–849 nmol/L) confer atherosclerotic CVD risk equivalent to familial hypercholesterolemia. Universal screening of once Lp(a) test is now recommended for all adults in guidelines across the US, Europe and Canada. However, Lp(a) testing is severely underutilized with studies showing 0.3% testing frequency amongst 5.5 million US patients. Even in high-risk patients with established ASCVD, only 13.9% are tested for Lp(a). Existing treatment options for elevated Lp(a) include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and lipoprotein apheresis. Emerging therapies include antisense oligonucleotides such as pelacarsen, small-interfering RNA such as zerlasiran, olpasiran, and lepodisiran, and oral agents such as muvalaplin. These medications have shown a significant reduction in plasma levels up to 80% (pelacarsen), 96.9% (olpasiran), 97% (lepodisiran) and 99% (zerlasiran) in phase 1 and 2 trials, with larger studies ongoing to assess cardiovascular outcomes. With advancing therapies, clinician awareness, early detection, and risk management of Lp(a) are critical to improving outcomes.

Key words: Lipoprotein(a); cardiovascular disease; heart failure.

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Structure and epidemiology

Lipoprotein(a) [Lp(a)] is a plasma particle that was first introduced in 1963 by the Norwegian physician Kåre Berg.[1] Structurally, Lp(a) is a macromolecule with a chemical composition similar to low-density lipoprotein (LDL), comprising triglycerides, cholesterol, and phospholipids. It differs from LDL due to the presence of apolipoprotein(a), which is bound to apolipoprotein B100 via a single disulfide bridge.[2] During evolution, the *LPA* gene, which encodes apolipoprotein(a), emerged as a derivative of the *PLG* gene responsible for encoding plasminogen.[1]

While LDL cholesterol levels are influenced by a combination of genetic and lifestyle factors, Lp(a) concentrations are over 90% genetically determined across all ethnicities.[3] Among the racial and ethnic groups studied, Black individuals exhibit the highest Lp(a) levels, followed by South Asians, Whites, Hispanics, and East Asians.[4] While the median levels can differ by 2- to 4-fold among ancestral groups, current evidence suggests that the predictive value of Lp(a) does not vary sufficiently across these groups to warrant the use of different ancestry-specific risk thresholds.[5] As Lp(a) levels are predominantly governed by genetic factors, they remain largely stable throughout an individual's life. However, women are found to have 17% higher Lp(a) levels than men after the age of 50, a difference that coincides with and may be attributed to menopause.[6] It is estimated that as of 2022, 1.5 billion people worldwide (~20% of the population) is living with elevated Lp(a) levels, defined as Lp(a) greater than 125 nmol/L (50 mg/dL).[5]

Cardiovascular disease risk

Lipoprotein(a) is an established risk factor for cardiovascular disease (CVD), with evidence derived from multiple Mendelian randomization studies.[3] A comprehensive study analyzing 2,100 candidate genes identified the *LPA* gene as the most significant genetic determinant of CVD risk.[6] Unlike low-density lipoprotein cholesterol (LDL-C) which is primarily associated with atherosclerotic cardiovascular disease (ASCVD), elevated Lp(a) is also a significant risk factor for aortic stenosis.[3] Epidemiological studies using data from Biobanks in the UK and Copenhagen, Denmark have provided evidence of increased morbidity and mortality across a spectrum of CV diseases, including coronary artery disease (CAD), ischemic stroke, peripheral artery disease (PAD), and heart failure.[7]

The incidence of heart failure with preserved ejection fraction (HFpEF) was evaluated in relation to Lp(a) levels in a multi-ethnic cohort.[8] Individuals with Lp(a) levels ≥30 mg/dL exhibited an approximately two-fold increased risk of HFpEF *(p*=0.02) compared to those with lower levels. Moreover, the risk was significantly higher, approximately 2.5-fold *(p*=0.004), for individuals with Lp(a) levels ≥50 mg/dL.

Although no formal cutoff for risk thresholds exists, individuals with Lp(a) levels below 30 mg/dL (75 nmol/L) are considered to have low cardiovascular risk, while those with levels above 50 mg/dL (125 nmol/L) are classified as high risk.[9] Those with Lp(a) levels between 30 and 50 mg/dL (75-125 nmol/L) are considered intermediate risk.[9] Notably, however, there is a linear, incremental relationship between plasma Lp(a) and CV risk. Individuals with Lp(a) concentrations in the top 5% of the population (>90 mg/dL or >190 nmol/L) exhibit markedly increased risk, including a 1.6-fold higher risk of ischemic stroke, a 1.7-fold greater risk of heart failure, a 2-fold greater risk of PAD and a 3-fold greater risk of both aortic stenosis and myocardial infarction.[7] Lp(a) concentrations between 130–391 mg/dL (280–849 nmol/L) pose the same risk of ASCVD as familial hypercholesterolemia.[7] Plasma Lp(a) levels and associated CVD risk is summarized in Figure 1.

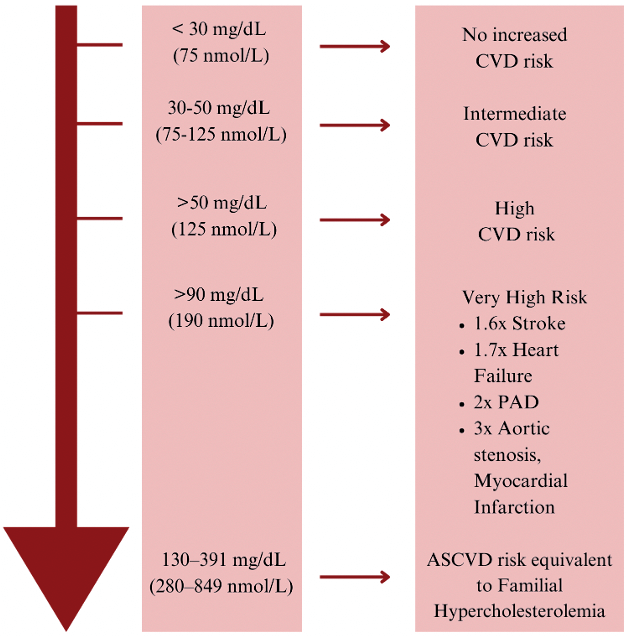

Figure 1. Lipoprotein(a) levels and cardiovascular disease risk.

Lipoprotein(a) testing guidelines and current trends

Earlier guidelines by the American Heart Association (AHA), American College of Cardiology (ACC), and American Association of Clinical Endocrinology (AACE) recommended Lp(a) testing in patients with premature CVD or a family history of CVD.[10] With accumulating evidence and widespread awareness of CV risk with elevated Lp(a), universal screening is now recommended once for all adults by guidelines from the European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS), the Canadian Cardiovascular Society, and more recently, the National Lipid Association (NLA).[9,10] Lp(a) test may be added as a part of the first lipid screening. With elevated Lp(a) levels in postmenopausal women, repeat measurement may be indicated in this population.

Despite the well-established cardiovascular risk associated with elevated Lp(a) and the current testing guidelines, clinical implementation of Lp(a) testing remains remarkably low. Multiple observational studies from large healthcare systems around the world demonstrate that <1% of individuals are tested for Lp(a). Amongst 5.5 million patients in a large US healthcare system, only 0.3% had undergone Lp(a) testing between 2012 and 2021.[11] A multicenter study involving over 48,000 patients with established ASCVD across 48 countries demonstrated that, despite being a high-risk population, only 13.9% had undergone prior Lp(a) testing.[12]

Existing and emerging therapies

A potential reason behind low testing rates may be that, historically, there has been a lack of effective treatment options for elevated Lp(a) levels. Modest reduction has been demonstrated by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[10] For high-risk patients with elevated Lp(a) levels, lipoprotein apheresis has been the treatment of choice, which leads to both a reduction in plasma concentration and also a parallel decrease in adverse CV outcomes.[10] However, due to it's invasive nature, it's utility has been limited.

Emerging therapies targeting Lp(a) show promise in reducing Lp(a) levels. These include antisense oligonucleotides such as pelacarsen, small-interfering RNA (siRNA) such as zerlasiran, olpasiran, and lepodisiran, and oral agents such as muvalaplin.[10,1]) Although we currently only have results from phase 1 and 2 trials, these agents have shown reduction in Lp(a) levels between

Table 1. Emerging Lp(a) lowering therapies.

Lp(a) drug	Mechanism	Current trials
Pelacarsen	Antisense oligonucleotide	Phase 3 Lp(a)HORIZON Trial - NCT04023552 (Enrollment Complete)
Olpasiran	Small interfering RNA	Phase 3 OCEAN(a) Trial - NCT05581303 (Enrollment Complete)
Lepodisiran	Small interfering RNA	Phase 2 Trial - NCT05565742 (Study Complete) Phase 1 Trial - NCT05841277 (In progress)
Zerlasiran	Small interfering RNA	Phase 2 ALPACAR Trial - NCT05537571 (Just published)
Muvalaplin	Oral agent	Phase 2 KRAKEN Trial - NCT05563246 (Just published)

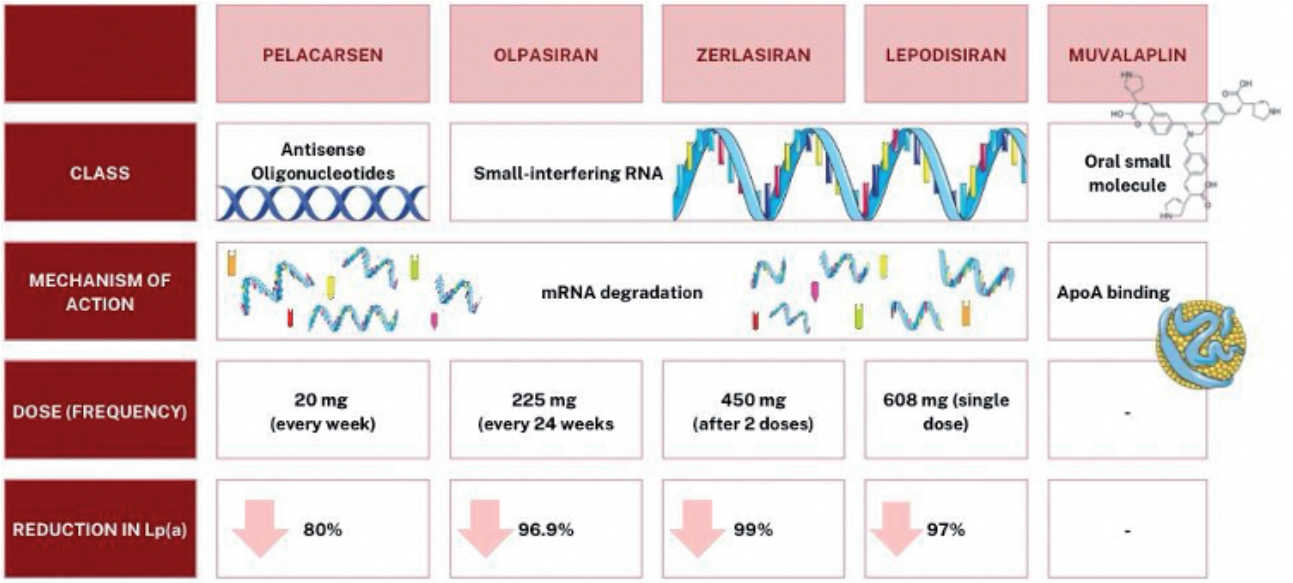

Figure 2. Lipoprotein(a) targeting therapies.

80% to 97%, summarized in Figure 2.[13] These encouraging results are currently being investigated further in larger phase 2 and phase 3 clinical trials to assess their impact on both Lp(a) reduction and cardiovascular outcomes. Table 1 summarizes these emerging Lp(a) lowering therapies, including their mechanism of action and current trials. With the possible utilization of these drugs for treating elevated Lp(a) in the future, Lp(a) testing may be needed more often to monitor treatment effects.

Future direction

Emerging research continues to highlight the complex and multifactorial nature of cardiovascular diseases (CVD). This has driven an expansion in risk assessment beyond traditional factors, including investigations into the role of inflammatory biomarkers, the impact of cachexia, and the influence of quality-of-life parameters on cardiovascular outcomes.[14,15] Among these, Lp(a) has emerged as a significant biomarker, with robust evidence supporting its causal role in cardiovascular risk. With emerging therapies and updated guidelines on testing indications, it is more imperative than ever for clinicians to be mindful of Lp(a) levels when assessing CV risk in their patients. Nearly a quarter of the world's population has elevated Lp(a) levels and clinician awareness can identify high-risk subgroups. Early detection of genetic predisposition provides opportunities for preventive counseling, aggressive risk factor mitigation, and timely interventions.

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