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LIPOPROTEIN(A): AN EMERGING RISK FACTOR FOR CARDIOVASCULAR DISEASE

Cardiology

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KEYWORDS

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a genetically determined lipoprotein variant composed of an LDL-like particle (containing apolipoprotein B-100) covalently bound to apolipoprotein(a). The apo(a) component contains multiple plasminogen.like kringle domains (especially variable copies of kringle IV type 2), and carries oxidized phospholipids (OxPL) that confer proinflammatory and pro-atherogenic properties[1]. Plasma Lp(a) levels are highly heritable (>70–90% determined by the LPA gene) and remain essentially constant after early childhood[2]. Approximately 20–25% of people worldwide have an "elevated" Lp(a) (typically defined as ≥50 mg/dL or ≥125 nmol/L)[2][3]. Levels vary by ethnicity: persons of African ancestry have substantially higher median Lp(a) than Caucasians or Asians[2]. Because Lp(a) levels are stable over life (aside from acute illness or kidney/liver disease[2]), a single measurement in early adulthood has been recommended for lifetime risk assessment[1].

Elevated Lp(a) has emerged as an independent causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve disease[1][2]. Large genetic and epidemiologic studies consistently show a continuous relationship between Lp(a) and coronary artery disease, stroke, peripheral arterial disease, and aortic stenosis[1][2]. In practice, high Lp(a) explains part of the residual ASCVD risk seen in many patients whose LDL cholesterol is well controlled, and is especially implicated in premature or familial ASCVD. For example, a 2022 EAS consensus emphasizes that elevated Lp(a) confers increased ASCVD and valve calcification risk even at very low LDL levels, and does not appear to influence venous thrombosis[1]. The clinical implications of Lp(a) (including screening and management) are now recognized by experts and guidelines worldwide[1].

Pathophysiology

Structure and Genetics

Lp(a) is essentially an LDL-sized particle whose apoB-100 is covalently linked via a disulfide bond to a unique glycoprotein, apolipoprotein(a). Apo(a) is homologous to plasminogen, containing multiple kringle domains (KIV1–KIV10 and KV), including a highly polymorphic KIV_2 domain that varies enormously in copy number (1–>40 repeats). Small apo(a) isoforms (few KIV_2 repeats) are secreted more readily and result in very high Lp(a) levels; by contrast, large apo(a) isoforms yield low Lp(a) concentrations[1] . This size polymorphism has complicated assay standardization[2]. Clinically, Lp(a) mass is reported in mg/dL and particle concentration in nmol/L; a rough conversion is ~2.5 nmol/L per 1 mg/dL[4].

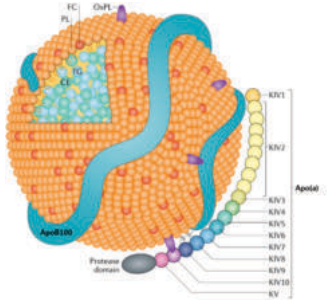

Figure: Structure of lipoprotein(a). An LDL-like core (orange spheres, containing cholesterol esters [CE], triglycerides [TG], phospholipids [PL]) carries apolipoprotein B-100 (blue ribbon) and is covalently linked (disulfide bond) to apolipoprotein(a). Apo(a) bears multiple kringle IV (KIV) and one KV domain (colored rings), including a variable KIV_2 copy number. Apo(a) also carries oxidized phospholipids (OxPL, purple) that mediate proinflammatory activity[1].

Atherogenic and Pro-inflammatory Effects

Lp(a) promotes atherosclerosis by multiple mechanisms. Its LDL-like component readily enters the vascular wall, contributing cholesterol to plaque growth. Apo(a) and its OxPL cargo induce vascular inflammation: in vitro and genetic studies show that Lp(a) activates inflammatory signaling (e.g. via interleukin-6) and impairs endothelial function[1]. A recent systems-biology study found that Lp(a) directly primes circulating monocytes: high-Lp(a) individuals had monocytes with increased tissue factor (TF) expression. Mechanistically, Lp(a) itself engages Toll-like receptor 2 and the NF-κB pathway in monocytes, driving TF production and immunothrombosis[5]. Thus Lp(a) links cholesterol-driven plaque with thrombotic potential, in part by mounting monocyte-dependent TF activation.

Lp(a) also resembles plasminogen, and many authors have hypothesized that it competes with plasminogen at fibrin or cell surfaces, potentially inhibiting fibrinolysis. Indeed, in vitro apo(a) has been shown to reduce plasmin generation[6]. However, large-scale clinical data have not confirmed Lp(a) as a major cause of venous thrombosis or impaired fibrinolysis[1]. Overall, Lp(a)'s prothrombotic effect in vivo remains somewhat controversial, but its net impact on atherosclerotic plaque formation and progression is well supported.

Calcific Aortic Stenosis

Unlike most lipid factors, Lp(a) strongly promotes calcific aortic valve disease (CAVD). OxPL in Lp(a) are thought to trigger valvular endothelial inflammation, leading to osteogenic changes in the valve leaflets. Epidemiologic and genetic studies consistently link high Lp(a) to faster progression and higher risk of aortic stenosis[1][2]. In vivo, Lp(a) co-localizes with valve calcification, and apo(a) has been shown to enhance valvular interstitial cell calcification in models. Thus Lp(a) is considered a causal factor in CAVD, and this has prompted ongoing trials of Lp(a) lowering specifically for valve outcomes.

Association with Cardiovascular Disease

Extensive evidence ties elevated Lp(a) to atherosclerotic events across vascular beds. Mendelian randomization and large cohorts show a continuous, dose-dependent association between Lp(a) concentration and risk of coronary artery disease (CAD), stroke, and CAVD[1][2]. For example, in one global ASCVD registry (>48,000 patients), over 25% had Lp(a)>50 mg/dL[3] and these individuals carried significantly higher CAD burden. Meta-analyses also support stroke risk: a pooled analysis found mean Lp(a) was substantially higher in patients with large-artery ischemic stroke than in controls[7]. In secondary prevention (patients with known CAD), a high Lp(a) correlates with recurrent events: a meta-analysis showed an odds ratio ≈1.4 for recurrent ASCVD in statin-treated patients with Lp(a) >80th percentile[4].

Race/ethnicity influences Lp(a) distribution but not its pathogenic role.

African-ancestry individuals have higher Lp(a) medians yet similar concentration-to-risk slopes as Caucasians[2]. Thus any population can have a subset at high Lp(a). Overall, Lp(a) is now recognized as an independent risk factor: it confers residual risk beyond traditional factors and LDL-C[1][2]. Importantly, Lp(a) contributes to the "residual risk" seen after intensive LDL-lowering: many patients with optimal LDL still suffer events if Lp(a) remains elevated. This justifies targeting Lp(a) in risk stratification, especially for premature or familial ASCVD.

Screening and Diagnostic Approaches

Given its stability and genetic nature, most experts recommend one-time Lp(a) screening in adults for cardiovascular risk stratification[1]. High-risk groups include those with premature CAD, familial hypercholesterolemia (FH), a family history of elevated Lp(a), or unexplained ASCVD at a young age[1]. Because Lp(a) can be falsely elevated by acute inflammation or renal/liver disease, measurements should be done in a clinically stable state[2][2]. Thereafter, a single baseline is sufficient since levels remain unchanged through adulthood[2].

Lp(a) is quantified by immunoassay or mass-based methods, but heterogeneity of apo(a) isoform size complicates accuracy[2]. Modern assays report in nmol/L (particle concentration) and/or mg/dL (mass); reporting both is encouraged. The World Health Organization recommends nmol/L for standardization, noting that a fixed conversion factor (≈2.5) is approximate[4][2]. Clinically, <30 mg/dL (≈75 nmol/L) is generally considered normal, 30–50 mg/dL intermediate, and >50 mg/dL high; some guidelines use >100–125 nmol/L (≈40–50 mg/dL) as a high-risk cutoff[2]. (Notably, different societies define risk thresholds variably[2].) Interpretation of results should consider ethnicity (since a given mg/dL may correspond to different percentiles in different populations) and concomitant risk factors.

Current Guidelines

International lipid guidelines now acknowledge Lp(a) as a risk enhancer. The 2022 European Atherosclerosis Society consensus explicitly recommends that all adults have Lp(a) measured at least once[1]. U.S. guidelines (ACC/AHA) include Lp(a)>50 mg/dL as a "risk-enhancing" factor that may sway decisions on statin therapy in borderline cases. In practice, most experts agree on targeted screening: measure Lp(a) in those with high baseline risk or unexplained ASCVD, and perform cascade testing of first-degree relatives when Lp(a) is very high.

Management guidelines emphasize aggressive control of modifiable risk factors in high-Lp(a) patients[1]. Because specific Lp(a)-lowering drugs were long unavailable, the consensus is to achieve very low LDL-C and treat hypertension, diabetes, etc., to offset the Lp(a)-driven risk[1]. For extremely high Lp(a) (often >180 mg/dL) with progressive CVD, lipoprotein apheresis is recommended in some regions (e.g. Europe)[1]. Emerging guidelines also encourage clinicians to inform high-Lp(a) patients about their inheritability and consider earlier lifestyle intervention for family members. In summary, current guidance is to recognize Lp(a) as a potent risk factor, to test for it at least once, and to treat traditional risk factors intensively if Lp(a) is elevated[1].

Therapeutic Strategies

Conventional Therapies

No widely used lipid-lowering therapy is targeted to Lp(a) per se. Statins, while effective at lowering LDL-C, do not lower Lp(a); indeed, statin therapy tends to raise Lp(a) modestly (on the order of 10–20%)[8]. Niacin can reduce Lp(a) by ~20–30%, but randomized trials failed to show outcome benefit of niacin therapy and its adverse effects limit use[8]. Other common agents have minimal impact: ezetimibe may lower Lp(a) only slightly (~7–8%)[2], bile-acid sequestrants and fibrates have inconsistent effects, and bempedoic acid has no meaningful benefit (in one trial it slightly increased Lp(a) by ~2–3%)[2].

PCSK9 inhibitors are the most potent approved drugs for reducing Lp(a) alongside LDL: evolocumab and alirocumab have been shown to lower Lp(a) by ≈20–30% on top of statins[2][2]. For example, the FOURIER and ODYSSEY trials reported ~23–27% Lp(a) reduction with PCSK9 blockade[2]. This Lp(a)-lowering may have contributed to the extra outcome benefit seen in those trials, but no trial was designed to isolate that effect. At present, these drugs are used primarily for LDL-lowering; their modest Lp(a) effect is a secondary consideration. No outcome trial has yet definitively proven that lowering Lp(a) with PCSK9 inhibitors or other standard therapies improves clinical events.

Lipoprotein apheresis is the only current therapy specifically aimed at high Lp(a). In centers where available, regular apheresis (every 1–2 weeks) can acutely reduce Lp(a) by ~60–70%. Long-term apheresis in high-risk patients (e.g. with homozygous FH or recurrent CVD) has been associated with slowed progression of disease, although these data are from observational series. Apheresis is labor-intensive and costly, so guidelines reserve it for very high Lp(a) with refractory CVD despite maximal therapy[1].

Emerging Lp(a)-Targeted Therapies

In the past few years, novel agents designed to lower Lp(a) dramatically have entered clinical trials, based on antisense and RNA technologies. Antisense oligonucleotides (ASO): Pelacarsen (AKCEA-APO(a)-LRx, developed by Tsimikas and colleagues) binds LPA mRNA in the liver, reducing apo(a) production. In phase II trials, pelacarsen produced dose-dependent Lp(a) reductions of ~30–80%, with the highest doses achieving ~80% lowering of Lp(a)[9]. This agent is currently being tested in a large phase III outcome trial (Lp(a)HORIZON) in patients with established ASCVD and high Lp(a).

siRNA therapies: Small-interfering RNAs offer another approach. Olpasiran (formerly AMG 890) targets LPA mRNA and is given subcutaneously. In the OCEAN(a)-DOSE trial (phase II), olpasiran doses produced >90% reductions in Lp(a) levels versus placebo[10] (e.g. ~97% reduction with the highest dose). Similarly, zerlasiran (AMG4/AZD8233) is another GalNAc-conjugated siRNA; in a 36-week study it lowered Lp(a) by ~85–90%[11]. These therapies have generally been well tolerated, with injection-site reactions being the most common side-effect to date. Larger phase III trials are planned or underway to test their cardiovascular impact.

Small-molecule inhibitors: Recently, novel small molecules that block Lp(a) assembly have been described. For example, muvalaplin (LY3473329) interferes with the binding of apo(a) to apoB, thereby halting Lp(a) production. In preclinical studies, such compounds potently inhibited Lp(a) formation[12]. Muvalaplin has advanced to early-phase human trials, representing the first oral Lp(a)-lowering drug candidate.

Other Considerations

Given the lack of approved Lp(a)-specific drugs until now, management still emphasizes overall risk reduction. For example, even in patients with high Lp(a), goal LDL-C is set very low (often <55–70 mg/dL) so that the residual risk is minimized. Antiplatelet therapy and hypertension control become particularly important when Lp(a) is elevated, due to its prothrombotic/inflammatory profile. In some centers, niacin or estrogens have been used off-label to lower Lp(a), but these are not standard of care and are discouraged by guidelines due to lack of outcome benefit and side effects. Omega-3 fatty acids and other nutraceuticals have no proven effect on Lp(a).

Gaps in Research and Future Perspectives

Despite strong observational and genetic evidence, key knowledge gaps remain. Most importantly, it is not yet proven that lowering Lp(a) will improve clinical outcomes. Mendelian randomization studies imply that very large absolute reductions in Lp(a) (on the order of >50–100 mg/dL) would be needed to meaningfully cut short-term cardiovascular risk[4]. Ongoing outcome trials (e.g. Lp(a)HORIZON with pelacarsen, OCEAN(a)-Outcomes with olpasiran) are crucial to test whether Lp(a)-lowering translates to fewer heart attacks, strokes, or valve surgeries. The results of these trials will determine if Lp(a) should be a routine therapeutic target.

Other research needs include: optimal thresholds and target levels for intervention (current guidelines use cut-offs like 50 mg/dL, but risk is continuous); screening strategies (should all adults be screened or only high-risk groups?); and cost-effectiveness analyses of screening and new therapies. Long-term safety of novel Lp(a) inhibitors must also be established. There is limited data on Lp(a) lowering in diverse populations – given ethnic variability, more studies are needed in underrepresented groups. Gene therapy or genome editing (e.g. CRISPR targeting the LPA gene) is a speculative future direction but is not yet in clinical testing.

Technological advances may improve risk stratification. For instance, genetic risk scores now routinely include LPA variants, and Lp(a) measurement could be integrated into personalized risk models for CVD. Imaging studies (such as coronary calcium scoring) may also help refine risk in high-Lp(a) individuals. In summary, Lp(a) is poised to enter mainstream care as both a risk marker and (if trials are positive) a modifiable risk factor. The next few years of research will clarify how best to incorporate Lp(a) screening and Lp(a)-lowering therapies into cardiovascular prevention and treatment.

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