Lipoprotein(a) in Clinical Practice: From Risk Marker to Actionable Signal

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INTRODUCTION

Residual cardiovascular (CV) risk persists even when low-density lipoprotein cholesterol (LDL-C) is treated according to contemporary standards, and a meaningful portion of that burden reflects inherited biology that is not captured by routine lipid panels or by most commonly used risk calculators.[1,2] Lipoprotein(a), or Lp(a), represents a key component adding to CV risk, though it has only recently been comprehensively studied. It remains underrecognized and under tested in clinical practice. Lp(a) is a low-density lipoprotein (LDL)-like, apolipoprotein B (apoB)-containing particle with an attached apolipoprotein(a) (apo[a]) moiety that confers atherogenic, pro-inflammatory, and possibly antifibrinolytic/thrombogenic properties.[3,4]

Interest in Lp(a) has accelerated as the evidence base has moved beyond association toward causality, with genetic, epidemiologic, and mechanistic data linking elevated Lp(a) to both atherosclerotic CV disease (ASCVD) and calcific aortic valve stenosis.[5,6] Additionally, an expanding therapeutic pipeline has made identification of elevated Lp(a) more clinically relevant, though no approved Lp(a)-specific agents currently are available.[7,8]

Primary care clinicians (PCCs) are central to this shift because first-line preventive risk assessment often occurs in primary care. PCCs can determine whether a patient with borderline or intermediate risk needs treatment intensification, and Lp(a) can explain why a patient with a seemingly modest LDL-C level may carry substantial inherited risk.[9,10] However, testing for Lp(a) is rare in routine practice.

Key takeaways

- Elevated Lp(a) is common, largely inherited, and causally linked to ASCVD and calcific aortic valve stenosis, yet often missed in many routine preventive evaluations.
- One-time Lp(a) measurement in adulthood is recommended based on current evidence and guidelines, making primary care a critical setting for detection and risk classification.
- An elevated Lp(a) result is actionable because it supports earlier and more intensive management of LDL-C, blood pressure, diabetes risk, smoking, and other modifiable contributors to risk.
- Although lifestyle change does not meaningfully lower Lp(a) in most patients, therapeutic lifestyle changes reduce CV risk and are important as part of comprehensive CV risk reduction.
- Multiple investigational agents, including small interfering RNA, antisense, and small-molecule therapies, have lowered Lp(a) by roughly 80% to more than 95% in clinical trials. CV outcomes trials from Lp(a)-targeted therapies are ongoing with no results yet; comprehensive risk reduction remains the present standard of care.

In one recent US outpatient analysis, only 3.7% of 450,412 patients who had at least 1 lipid panel also had Lp(a) measured, despite rising order volumes over time.[11] Another US study assessed the electronic medical record data of 266,612 patients and found that only 0.8% of patients received Lp(a) testing, of whom 86% had clinical CV disease.[12] Broadening Lp(a) testing improves risk identification, supports family cascade testing, reframes conversations about lifelong risk,

and justifies more aggressive control of modifiable risk factors, especially LDL-C, in patients whose risk would otherwise be underestimated.[9,13] Accordingly, guidelines from the National Lipid Association (NLA) and the American College of Cardiology (ACC)/American Heart Association (AHA) multisociety collaboration now recommend at least 1 Lp(a) measurement in adulthood, moving Lp(a) testing from a niche specialty test toward a standard component of preventive lipid care.[9,14]

CASE STUDY

MR is a 45-year-old woman seen for an annual preventive visit. She has a history of hypertension, does not have diabetes, and has never smoked. Today, her laboratory and clinical findings are as follows:

- Total cholesterol: 214 mg/dL (5.5 mmol/L)
- High-density lipoprotein cholesterol (HDL-C): 54 mg/dL (1.4 mmol/L)
- LDL-C: 110 mg/dL (2.85 mmol/L)
- Triglycerides: 250 mg/dL
- Blood pressure: 128/78 mmHg
- Estimated glomerular filtration rate: 95 mL/min/1.73 m^2
- Glycated hemoglobin: 5.8%
- Body mass index: 28 kg/m^2

Her father had a myocardial infarction at age 52 years. She currently takes amlodipine 10 mg daily and losartan 100 mg daily.

Her 10-year ASCVD risk estimate is 1.4% and her 30-year ASCVD risk estimate is 8.9% (using the AHA PREVENT Calculator [available at https://professional.heart.org/en/guidelines-and-statements/prevent-calculator]), but the mismatch between that estimate and her family history raises concern for inherited residual risk not captured by traditional assessment tools.

WHAT IS Lp(a)?

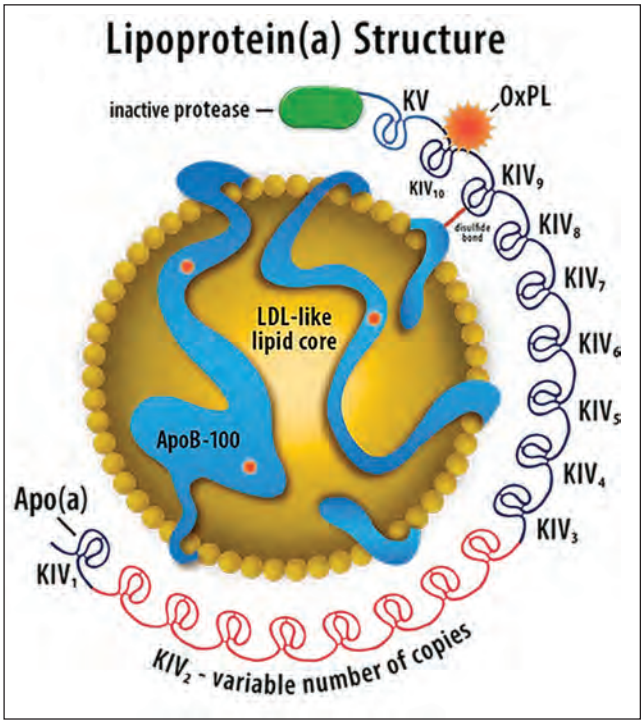
Lp(a) is an LDL-like particle that contains apoB and an additional apo(a) molecule linked by a disulfide bond to the apoB moiety; this apo(a) component is what makes Lp(a) biologically and clinically distinct from ordinary LDL (**FIGURE 1**).[3,5] Apo(a) contains a variable number of kringle IV type 2 repeats, creating marked size polymorphism between individuals and contributing to the wide variability in circulating Lp(a) concentrations across patients.[2,3]

The pathophysiology of Lp(a) is multifactorial. The LDL-like core contributes to arterial cholesterol delivery and plaque formation, whereas the apo(a) moiety has high affinity for oxidized phospholipids. Thus, Lp(a) is the major carrier of oxidized phospholipids into the arterial wall, which amplifies vascular inflammation, endothelial dysfunction, and plaque instability.[4,15] Because apo(a) is structurally homologous to plasminogen, Lp(a) also has biologic plausibility as an antifibrinolytic and prothrombotic factor, although the relative contribution of this pathway likely varies across clinical contexts.[5,16]

Elevated Lp(a) is common and affects roughly 1 in 5 people worldwide; however, the population distribution is highly skewed and varies by ancestry, with particularly high concentrations observed in individuals of African and South Asian ancestry.[1,9] Unlike LDL-C, Lp(a) is largely genetically determined, with approximately 70% to 90% of interindividual variation attributable to inherited factors, and it is not meaningfully lowered by diet or exercise.[1,3] Adult levels generally are reached by early childhood and remain relatively constant across adult life, so a single measurement is typically sufficient unless testing occurs during major inflammation, in settings such as menopause, or in the presence of significant liver or kidney disease that affects Lp(a) levels.[1,14,17]

The clinical importance of Lp(a) lies in causality as well as prevalence. Mendelian randomization, population studies, and consensus guidance support elevated Lp(a) as a likely risk factor for ASCVD, and additional data implicate it in calcific aortic valve disease and stenosis progression.[5,18] Risk rises in a continuous, approximately log-linear fashion rather than at

FIGURE 1. Structure of the Lp(a) molecule.



Abbreviations: Apo(a), apolipoprotein a; KIV, Kringle IV; KV, Kringle V; OxPL, oxidized phospholipid.

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Source: https://familyheart.org/family-sharing-tools/high-lpa-family-tools

TABLE 1. Practical interpretation of Lp(a) concentration and potential clinical actions.[9,13]

Lp(a) concentration[a]	Risk category	Practical interpretation	Potential clinical response
<75 nmol/L (<30 mg/dL)	Low	Lower Lp(a)-associated risk	Continue standard prevention according to the overall absolute risk
75 to <125 nmol/L (30 to <50 mg/dL)	Intermediate	Gray zone that can still meaningfully raise risk when other risk enhancers are present	Review family history, refine statin discussion, and optimize LDL-C and other modifiable factors
≥125 nmol/L (≥50 mg/dL)	High	Clear risk-enhancing factor for ASCVD and often for family screening discussions	Intensify LDL-C lowering and global risk-factor control; discuss cascade testing and referral when residual risk remains high

[a]Risk is continuous, and these thresholds are pragmatic clinical decision aids rather than biologic cliffs; the same Lp(a) value confers greater absolute risk when baseline CV risk is already high.

a single biologic cliff, which is why thresholds are best viewed as practical decision aids instead of absolute dividing lines.[1,2]

The continuous risk spectrum is reflected in recent US guidance, which links Lp(a) thresholds with different risk levels (**TABLE 1**). For example, an Lp(a) concentration of ≥125 nmol/L (≥50 mg/dL) is associated with about a 1.4-fold higher long-term risk of myocardial infarction or stroke, whereas an Lp(a) concentration around 250 nmol/L is associated with at least a doubling of long-term risk.[9,14] The same Lp(a) value, therefore, has a larger absolute-risk implication in a patient who already has hypertension, diabetes, smoking exposure, chronic kidney disease, or established ASCVD than in a patient with otherwise low baseline risk.[1,13] This is a primary reason Lp(a) is clinically useful in patients whose standard risk assessment seems discordant with their personal or family history. Most widely used risk calculators do not explicitly incorporate Lp(a), so risk may be underestimated when Lp(a) is high.[1,2] For patient-facing discussion, the Lp(a) Clinical Guidance tool (accessible at https://www.lpaclinicalguidance.com/) can help visualize how much incremental risk may be attributable to Lp(a) and how more aggressive LDL-C or blood pressure control can partially offset that burden. The tool also provides guidance on lowering risk with elevated Lp(a).

Lp(a) TESTING RECOMMENDATIONS

With the incorporation of Lp(a) testing recommendations into recent guidelines, the clinical takeaways for implementation into practice have become clearer (**TABLE 2**). The 2024 NLA focused update recommends risk stratification of

TABLE 2. Current guideline and consensus recommendations for Lp(a) testing.

Source	Lp(a) testing recommendation	Cascade testing	Implications for primary care
NLA 2024[9]	Measure Lp(a) at least once in every adult for risk stratification	Cascade screen first-degree relatives when Lp(a) is elevated	Use Lp(a) to refine risk when history and calculated risk do not match
ESC/EAS 2025[13]	Measure Lp(a) at least once in adults and interpret within absolute global risk	Consider cascade testing in families with premature ASCVD, FH, or very high Lp(a)	Integrate Lp(a) into broader prevention rather than treating it as an isolated number
ACC/AHA Multisociety 2026[14]	Measure Lp(a) at least once in adulthood	Cascade testing in first-degree family members of patients with elevated Lp(a)	Treat elevated Lp(a) as a risk-enhancing biomarker that can justify more intensive preventive therapy

Abbreviation: FH, familial hypercholesterolemia.

all adults by measuring Lp(a) at least once.[9] The 2025 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) update also recommends at least 1 lifetime measurement in adults; this also was recommended in the previous (2019) guideline and the 2022 EAS consensus document.[5,13,19] Similarly, the Brussels International Declaration on Lp(a) testing and management recommends testing all adults once during their lifetime, ideally at an early age.[20] Most recently, the 2026 ACC/AHA multisociety dyslipidemia guideline now explicitly recommends that Lp(a) be measured at least once in adulthood, noting that ASCVD risk is particularly high for patients with elevated Lp(a) who also have other risk factors. Lp(a) measurement helps with risk stratification,[14] and the best time to conduct Lp(a) testing is anytime in any clinical setting.

Lp(a) is inherited in an autosomal codominant fashion. Therefore, once a patient is found to have high Lp(a), cascade screening is recommended to identify family members with elevated Lp(a).[21] The NLA endorses cascade screening of first-degree relatives when a patient has elevated Lp(a), and ESC/EAS guidance likewise supports cascade testing in families with premature ASCVD, familial hypercholesterolemia, or very high Lp(a) concentrations.[9,13] The 2026 ACC/AHA multisociety guidelines suggest that cascade testing in first-degree family members of patients with elevated Lp(a) can identify other family members who may have increased ASCVD risk.[14]

Practical barriers, including cost and reimbursement, for Lp(a) are real but manageable. Insurance coverage of Lp(a) testing varies. Quest Diagnostics lists Lp(a) testing under CPT code 83695.[22] Coverage may be subject to Medicare policies requiring a signed advance beneficiary notice, while payer coverage policies vary and may limit reimbursement frequency. Some insurance carriers consider Lp(a) testing once per lifetime.[23] For patients facing access barriers, the Family Heart Foundation currently offers a free at-home Cholesterol Connect screening program that includes Lp(a), accessible at https://familyheart.org/cholesterol-connect. This can be useful for both index patients and relatives identified through cascade screening.

GUIDELINE-DIRECTED LIPID AND LP(a) MANAGEMENT

An elevated Lp(a) result is actionable now, even in the absence of an approved Lp(a)-specific drug, because it supports earlier and more intensive lowering of modifiable risk factors that reduce absolute CV risk.[9,10] The most important actionable target is LDL-C, since observational studies and post hoc analyses of randomized trials suggest that lowering LDL-C in a patient with elevated Lp(a) will mitigate some of the CV risk.[13,14]

In primary prevention, elevated Lp(a) can justify earlier initiation of statin therapy and support escalation to moderate- or high-intensity treatment when overall risk, family history, or subclinical atherosclerosis suggests that usual care may leave the patient undertreated.[1,9] Statins do not meaningfully lower Lp(a), and some studies suggest a modest increase, but this should not discourage their use because they remain the cornerstone of apoB and LDL-C lowering.[7,9] When LDL-C remains above goal, the addition of ezetimibe, bempedoic acid, or injectable LDL-lowering therapy should be considered according to overall risk and guideline thresholds, rather than waiting for recurrent events to justify intensification.[13,14]

In secondary prevention, elevated Lp(a) identifies a higher residual risk phenotype and should prompt aggressive management of LDL-C and other modifiable risk factors, including blood pressure, glycemia, smoking, body weight, physical activity, sleep, and diet quality.[9,24] It is also reasonable to consider therapies with modest Lp(a)-lowering effects when they otherwise align with guideline-based care. In the FOURIER trial, which was a randomized trial of evolocumab vs placebo in patients with established ASCVD, evolocumab reduced Lp(a) by a median of 26.9% at 48 weeks, while pooled phase 3 analyses showed that alirocumab lowered Lp(a) by approximately 25%.[25,26] Whether these reductions contribute independently to clinical benefit beyond LDL-C lowering remains uncertain.

Inclisiran appears to have a similar but smaller effect on Lp(a) than the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies. Across the phase 3 ORION-10 and ORION-11 programs, placebo-adjusted Lp(a) reductions were approximately 25.6% and 18.6%, respectively, which could be directionally helpful when combined with robust LDL-C lowering and improved adherence from infrequent dosing.[27,28]

Lipoprotein apheresis remains a niche option for select, very high-risk patients, particularly when elevated Lp(a) coexists with progressive ASCVD despite maximal medical therapy. US Food and Drug Administration approval of lipoprotein apheresis applies to high-risk patients with familial hypercholesterolemia and ASCVD whose Lp(a) is ≥60 mg/dL (approximately ≥150 nmol/L) and whose LDL-C remains ≥100 mg/dL despite maximally tolerated therapy.[9] A single apheresis session can acutely lower Lp(a) by approximately 60% to 75%, but the treatment burden and limited availability restrict use to a small subset of patients.[29,30]

CASE STUDY (CONTINUED)

In MR's case, a one-time Lp(a) measurement is ordered because her family history and standard risk estimate appear discordant. The result returns at 250 nmol/L, placing her in a high-risk cat-

egory by current guideline thresholds. Moreover, her Lp(a) doubles her estimated 10-year and 30-year ASCVD risk. The result does not mandate a unique Lp(a)-specific therapy, but it meaningfully shifts shared decision-making toward initiating statin therapy earlier, maintaining blood pressure control, adopting lifestyle strategies, and recommending cascade screening for first-degree relatives.

POTENTIAL LP(a)-TARGETING THERAPIES ON THE HORIZON

The therapeutic landscape for Lp(a)-targeting therapies is changing rapidly. Several targeted agents have produced reductions that are far greater than those achievable with currently available lipid therapies, making present-day testing increasingly relevant for future treatment eligibility and trial referral.[7,8]

In a phase 2b dose-finding study, pelacarsen, an antisense oligonucleotide, produced reductions in Lp(a) of up to 80% at the highest dose.[31]

Small interfering RNA therapies are injectable agents that degrade the mRNA responsible for apo(a) synthesis, showing evidence that hepatic apo(a) silencing can produce large and durable effects. Olpasiran has demonstrated reductions in Lp(a) concentrations. In the phase 2 OCEAN(a)-DOSE extension analysis, higher-dose olpasiran given every 12 weeks lowered circulating Lp(a) by more than 95%. Participants receiving doses of at least 75 mg every 12 weeks maintained an approximately 40% to 50% placebo-adjusted reduction nearly 1 year after the last dose.[32] Lepodisiran has shown significant and prolonged reductions in Lp(a). In the phase 2 ALPACA trial, placebo-adjusted, time-averaged daily reductions from day 60 to day 180 were 40.8% with 16 mg, 75.2% with 96 mg, and 93.9% in the pooled 400-mg groups.[33] Similarly, zerlasiran has produced robust Lp(a) reductions in clinical trials. In its phase 2 randomized trial, zerlasiran was well tolerated and reduced time-averaged Lp(a) concentrations by more than 80% during 36 weeks of treatment in patients with ASCVD.[34]

Muvalaplin is an oral small molecule therapy that inhibits Lp(a) particle assembly. In the phase 2 KRAKEN trial, it lowered Lp(a) by placebo-adjusted 47.6%, 81.7%, and 85.8% at week 12 with daily doses of 10 mg, 60 mg, and 240 mg, respectively, using an intact Lp(a) assay, without major safety or tolerability concerns.[35]

Phase 3 trials for investigational Lp(a)-targeting therapies are ongoing, with variable expected timelines for results. Results from the HORIZON study of pelacarsen (NCT04023552) are expected in late 2026. While the therapeutic pipeline for Lp(a)-targeting therapies may provide future options for additional CV risk reduction, current management remains centered on addressing modifiable risk factors and implementing available, evidence-based therapies.[9,13,14]

SUMMARY

Lp(a) has moved from a neglected biomarker to being recognized as an important CV risk modifier. Lp(a) is common, inherited, stable across adult life, and causally related to ASCVD and calcific aortic valve disease. Still, it is often absent from most routine risk calculations and is not frequently measured in practice. Current guidelines recommend measuring Lp(a) at least once in adulthood, interpreting the result in the context of absolute risk, intensifying LDL-C lowering and other modifiable risk-factor management when Lp(a) is elevated, and extending cascade testing to first-degree relatives when appropriate. As targeted therapies continue to mature, clinicians who identify elevated Lp(a) will now be better positioned to reduce excess CV risk and be prepared for potential future therapies directly targeting Lp(a). ●

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