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Why routine lipoprotein (a) screening matters in clinical practice

Abstract

Lipoprotein (a) [Lp(a)] is a genetically determined and causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis. Unlike other risk factors, circulating Lp(a) levels are determined early in life and have lifelong stability. This opinion piece advocates the implementation of routine Lp(a) screening in current risk scoring. Identifying individuals with elevated Lp(a) leads to more precise risk strategies, earlier application of long-term preventive interventions targeting modifiable risk factors, and the initial selection of desirable candidates for future Lp(a)-specific therapies. Given that RNA-targeting agents (antisense oligonucleotides and small-interfering RNA [siRNA]) have produced 80 to 95% reductions in Lp(a) levels in phase II and III trials, with cardiovascular outcomes studies set to report results during the timeframe of 2025–2026, it is highly relevant from a clinical standpoint now. In addition, cascade screening of first-degree relatives will allow the preventive impact to reach other families. With an increasingly personalized preventive approach that places the patient at the center of care, routine measurement of Lp(a) is a simple and cost-effective action step toward identifying inherited CV risk, as well as preparing for when targeted therapies are integrated.

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Anish A Iyyavoo,[1] Loida Nguyen,[2] Adarsh A Iyyavoo,[1] Quang T Nguyen[2]
[1]University of California, USA
[2]Las Vegas Endocrinology, USA

Correspondence: Quang T Nguyen, DO, Las Vegas Endocrinology, Touro University Nevada, Nevada, USA

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Despite substantial advances in cardiovascular prevention, clinicians continue to encounter patients whose disease burden appears disproportionate to their traditional risk profile. Individuals with acceptable low-density lipoprotein cholesterol (LDL-C) levels may nonetheless present with premature myocardial infarction, rapidly progressive atherosclerosis, or recurrent cardiovascular events despite guideline-directed therapy. In such cases, lipoprotein (a) [Lp (a)] represents an important and often under recognized contributor to lifelong cardiovascular risk.

Lp (a) is a genetically determined lipoprotein particle whose circulating concentration is largely established early in life and remains remarkably stable over time. Unlike LDL-C, blood pressure, or glycemic status, Lp (a) levels are minimally influenced by lifestyle modification or environmental factors. As a result, individuals with elevated Lp (a) experience decades of cumulative exposure to cardiovascular risk that is not captured by routine lipid panels. This biological stability is precisely what makes Lp (a) well-suited for one-time measurement in routine cardiovascular risk assessment.[1,2]

The argument for general (vs. selective) screening is largely an issue of prevalence, as a substantial amount of the global population has elevated LP (a) levels. This burden is too widely spread to be unmasked with just clinical suspicion. In contrast to rare genetic conditions, for which focused disease-specific screening may be adequate, the high prevalence of elevated Lp (a) dictates that relying on family history or premature disease to identify affected individuals can miss many who would benefit from intensified prevention.

A growing body of epidemiologic and genetic evidence has established elevated Lp (a) as an independent and causal risk factor for atherosclerotic cardiovascular disease. Large observational studies demonstrate a consistent, dose-dependent association between Lp (a) concentration and cardiovascular events, even after adjustment for LDL-C and other conventional risk factors. Mendelian randomization analyses further support causality, showing that inherited variants associated with elevated Lp (a) confer increased cardiovascular risk, while lifelong deficiency appears protective.[3–5] Elevated Lp (a) has also emerged as a strong risk factor for calcific aortic valve stenosis, a condition for which effective medical therapies remain limited.[6]

Despite these data, Lp (a) measurement has not been uniformly integrated into clinical practice. Historically, this was driven by uncertainty surrounding assay interpretation and the absence of targeted therapies. More recently, however, professional society guidelines have begun to recommend at least one lifetime measurement of Lp (a), particularly in individuals with premature cardiovascular disease, a family history of early events, or unexplained residual risk.[7–9] Concurrently, the rapid evolution of the scientific landscape surrounding Lp (a) underscores the importance of early identification of affected individuals.

Importantly, the clinical utility of Lp (a) screening extends beyond long-term risk prediction. Identification of elevated Lp (a) can refine overall cardiovascular risk assessment and support more intensive preventive strategies in selected patients. In everyday clinical practice, elevated Lp (a) often supports earlier initiation or intensification of LDL-C–lowering therapy, closer longitudinal monitoring, and heightened attention to other modifiable risk factors. Lp (a) should be viewed as a modifier of baseline risk that complements, rather than replaces, existing risk assessment tools.

Practical considerations related to test availability and insurance coverage also merit brief attention. While lipoprotein (a) testing is increasingly available through standard clinical laboratories, inconsistent coverage may still pose a barrier in some settings. Importantly, Lp (a) testing is typically performed once in a lifetime, which limits cumulative cost and distinguishes it from biomarkers that require repeated monitoring. As professional society guidelines increasingly endorse Lp (a) measurement, greater alignment between clinical recommendations and coverage policies may help facilitate equitable implementation in routine practice.

Lp (a) screening also has important implications for family-based prevention. Because circulating levels are highly heritable, detection

of elevated Lp(a) in one individual provides a rationale for cascade testing among first-degree relatives. Early identification of genetically mediated risk creates opportunities for preventive counselling and risk factor optimisation long before clinical disease develops.[1,6]

Some clinicians reasonably worry that identifying elevated Lp (a) in the absence of specific therapies may increase patient anxiety. In clinical experience, however, many patients find value in understanding contributors to their cardiovascular risk, particularly when disease severity appears discordant with traditional risk factors. When communicated effectively, Lp (a) measurement can enhance patient understanding and engagement rather than foster therapeutic nihilism.

Historically measuring Lp (a) wasn't a consistent standard in clinical practice, due to the uncertainty about assay interpretation and lack of targeted therapies.[2] However, the landscape has now changed dramatically. Recent professional society guidelines from the 2022 European Atherosclerosis Society (EAS) consensus statement;[10] 2019 ESC/EAS dyslipidaemia guidelines,[9] National Lipid Association (NLA),[11] and American Heart Association scientific statement on measurement of Lp (a)) now advocate that at least one lifetime measurement of Lp (a). This is especially true for people with premature CVD, a family history of early events or unexplained residual risk. This is critical, as the Lp (a) therapeutics has moved from hypothetical to near clinical. Several RNA-targeted therapies such as antisense oligonucleotide pelacarsen[12] and siRNA compounds olpasiran,[13] lepodisiran[14] and zerlasiran[15] have reported 80–95% decreases in Lp (a) levels in phase II studies. These agents are currently being evaluated in phase III cardiovascular outcomes trials, with results anticipated for Lp (a) HORIZON (pelacarsen) and OCEAN (a)-Outcomes (olpasiran) by 2025–2026. We are now in an age of how to find patients with manageable risk not an era of identifying risk unless we can do something about it.

Most importantly, the results of a screen are actionable today, not only predictive. The 2022 EAS consensus statement stated that low-dose aspirin may be reasonable in adults with Lp (a) >50 mg/dL at very high risk for CVD, partly based on genetic subanalyses demonstrating preferential benefit among carriers of LPA risk variants.[11] Lp (a)-targeted therapies are now increasingly prevalent with antisense oligonucleotide and siRNA agents have demonstrated lowering of Lp(a) by 80–95% in phase II trials,[12–15] and two large cardiovascular outcomes trials L p(a)HORIZON and OCEAN(a)-Outcomes reporting results in 2025. Currently, pre-screening is able to detect such patients who would potentially benefit from approved therapies within a near timeframe. In addition to estimation of potential pharmacologic intervention, detection of high Lp (a) can further stratify atherothrombotic risk and guide the intensity of preventative measures.[8,11,16] In routine clinical practice, elevated Lp (a) typically leads to earlier or intensification of LDL-C–lowering therapy, alongside more frequent long-term surveillance and enhanced focus on other modifiable risk factors.

As cardiovascular care continues to move toward more personalised prevention, routine consideration of Lp (a) measurement represents a practical and educational step forward. Incorporating one-time Lp (a) screening into contemporary practice can help clinicians identify inherited risk earlier, refine preventive strategies, and prepare for the thoughtful integration of emerging evidence.[17,18]

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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