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Editorial

Lipoprotein(a) Debate: Are We Losing, or Are We Asking the Wrong Question?

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Lipoprotein(a) [Lp(a)] is a genetically determined cardiovascular risk factor associated with atherosclerotic cardiovascular disease through proatherogenic, proinflammatory, and prothrombotic mechanisms. The neutral primary outcome of the Lp(a)HORIZON trial, despite pharmacologic Lp(a) lowering with pelacarsen, challenges assumptions about the clinical benefits of targeting Lp(a) in patients with established cardiovascular disease. However, these findings do not necessarily invalidate Lp(a) as a causal risk factor or the clinical value of measuring Lp(a). Lp(a)HORIZON primarily tested whether lowering Lp(a) after established disease reduces recurrent events, which is a different question from whether lifelong exposure to elevated Lp(a) contributes to disease development or whether earlier intervention can prevent first cardiovascular events. Ongoing primary- and mixed-prevention trials may help address this distinction. The Lp(a) experience highlights the importance of separating risk assessment from therapeutic efficacy and raises broader questions about the timing, magnitude, and duration of biomarker-targeted interventions. Adaptive guideline frameworks and AI-assisted evidence synthesis may help integrate emerging trial data more rapidly while preserving rigorous human clinical judgment.

KEYWORDS: Lipoprotein(a), Lp(a), cardiovascular risk, primary prevention, artificial intelligence, precision medicine, lipid

Lipoprotein(a) [Lp(a)] has been investigated for decades as a potential contributor to cardiovascular disease (CVD). Structurally, Lp(a) is a lipoprotein particle containing a single apolipoprotein B-100 molecule covalently linked to apolipoprotein(a). Unlike most traditional CVD risk factors, Lp(a) concentration is predominantly genetically determined and remains relatively stable throughout life.[1,2]

The biological rationale linking Lp(a) to atherosclerotic CVD (ASCVD) is compelling. Lp(a) has been hypothesized to promote atherosclerosis through proinflammatory, proatherogenic, and prothrombotic mechanisms.[1,2] Importantly, Lp(a) is a major carrier of oxidized phospholipids (OxPLs) in human plasma, providing a potential mechanistic link between genetically determined Lp(a) elevation, vascular inflammation, and atherothrombotic disease.[3] These mechanisms also provide a biologically plausible explanation for the association between elevated Lp(a) and atherothrombotic events, including acute coronary syndromes (ACS).

Recent observational studies have added nuance to this hypothesis. In a primary prevention cohort, the association between elevated Lp(a) and

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incident coronary artery disease (CAD) was modified by interleukin-6, with greater Lp(a)-associated risk observed at higher levels of inflammatory activity.[4] These findings raise the possibility that the clinical expression of Lp(a)-associated risk may depend not only on the magnitude of Lp(a) elevation but also on the activity of inflammatory pathways.

Additionally, elevated Lp(a) has been associated with a more severe CAD phenotype, including greater angiographic disease burden and more extensive coronary involvement.[5] Whether these associations reflect direct atherothrombotic effects of Lp(a), interactions with other CVD risk factors, or both remains uncertain. Surprisingly, Lp(a)-associated CAD risk may also occur in individuals without a reported family history of premature CAD.[6] Thus, relying solely on a family history of premature CAD may miss individuals carrying substantial inherited Lp(a)-mediated risk.

These observations provide a strong rationale for identifying elevated Lp(a). Consistent with this evidence, the 2026 American College of Cardiology/American Heart Association (ACC/AHA) dyslipidemia guideline recommends measuring Lp(a) at least once in adulthood for ASCVD risk assessment.[7] This recommendation is fundamentally a risk-assessment recommendation, rather than a recommendation to treat Lp(a) itself with dedicated pharmacologic therapy. The distinction is important.

However, the Lp(a)HORIZON results have sparked debate within cardiology, including on social media, about whether guidelines should wait for randomized controlled trial (RCT) evidence before recommending Lp(a) measurement. In our view, the recommendation to measure Lp(a) is defensible because it addresses risk assessment rather than targeted Lp(a)-lowering therapy. Nevertheless, future guideline updates may benefit from more explicit language distinguishing the role of Lp(a) measurement in primary prevention from its implications in secondary prevention, particularly as randomized outcomes trials become available.

The Lp(a)HORIZON Challenge

As the first cardiovascular outcomes trial specifically testing an Lp(a)-lowering therapy, Lp(a)HORIZON was expected to provide a critical test of the therapeutic hypothesis. Lp(a)HORIZON randomized 8,323 patients with elevated Lp(a) and established CVD to pelacarsen or placebo and evaluated a composite of CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, and urgent coronary revascularization requiring hospitalization.[8]

The topline result was unexpected: despite lowering Lp(a), pelacarsen did not significantly reduce the primary CVD endpoint compared with placebo.[8] The trial, therefore, raises an uncomfortable but important question: If elevated Lp(a) is causally related to ASCVD, why did lowering Lp(a) not reduce CVD events in this population?

The answer may be more nuanced than simply concluding that the Lp(a) hypothesis is wrong.

Biomarker Causality Is Not the Same as Therapeutic Efficacy

A genetically determined biomarker can be strongly associated with disease and still prove difficult to modify therapeutically. Lp(a)HORIZON tested a very specific clinical hypothesis: whether lowering Lp(a) in patients who already have established ASCVD, while they are receiving contemporary guideline-directed therapy, reduces MACEs.

That question is not necessarily equivalent to asking whether lifelong exposure to elevated Lp(a) contributes to the initiation and progression of atherosclerosis in individuals with no known CVD. Patients enrolled in Lp(a)HORIZON already had established CVD and were receiving intensive contemporary treatment, including lipid-lowering, antiplatelet and antihypertensive therapies.[8] By the time such patients enter a secondary-prevention trial, their vascular biology reflects decades of cumulative exposure to LDL cholesterol, hypertension, diabetes, chronic kidney disease, smoking, inflammation, and other common determinants of atherosclerosis.

It is therefore conceivable that, in established ASCVD, the incremental contribution of Lp(a) lowering is smaller than the effect predicted from lifelong genetic exposure. Atherosclerosis may already have reached a stage at which multiple pathways independently sustain plaque progression, instability, and recurrent events.

The Lp(a)HORIZON result therefore generates another hypothesis: Could identifying and modifying Lp(a)-associated risk earlier in life, before the development of clinical ASCVD, prevent CVD? That hypothesis remains unresolved.

Several ongoing outcomes trials will help address this question. OCEAN(a)-PreEvent is specifically evaluating olpasiran in individuals with elevated Lp(a) who are at risk for a first major CVD event. ACCLAIM-Lp(a) and MOVE-Lp(a) are evaluating Lp(a)-lowering therapies in broader populations that include both individuals with established ASCVD and those at risk for a first CVD event. These trials may provide important complementary evidence.

Lessons From PCSK9 Inhibition

The experience with PCSK9 inhibition provides important clinical lessons. In FOURIER, evolocumab reduced Lp(a) by a median of approximately 26.9%, and higher baseline Lp(a) was associated with greater CAD risk independent of LDL-C.[9] These observations generated the hypothesis that Lp(a) lowering might contribute to the clinical benefit of PCSK9 inhibition.

However, these studies do not establish that Lp(a) lowering itself is responsible for the observed reduction in CVD events. PCSK9 inhibitors produce profound reductions in LDL-C and apolipoprotein B, making it difficult to isolate the independent contribution of Lp(a).

Similarly, analyses from ODYSSEY OUTCOMES demonstrate the complexity of interpreting very low LDL-C concentrations after acute coronary syndrome but do not provide a randomized test of isolated Lp(a) lowering.[10] The distinction between an intervention that lowers both LDL-C and Lp(a) and an intervention that specifically targets Lp(a) is critical.

What Does Lp(a)HORIZON Actually Tell Us?

The topline Lp(a)HORIZON result should therefore be interpreted cautiously. It does not establish that: 1) Lp(a) is merely an epiphenomenon; 2) Measuring Lp(a) has no clinical value and 3) Lp(a) lowering will never prevent CVD.

Rather, the trial demonstrates that, in the population studied, pharmacologic lowering of Lp(a) with pelacarsen did not translate into a statistically significant reduction in the prespecified composite primary CVD endpoint.

The magnitude of Lp(a) reduction, achieved Lp(a) concentrations, duration of exposure, baseline cardiovascular risk, timing of intervention, and individual components of the composite endpoint will require careful evaluation.

The interpretation and critical appraisal of the full trial publication will be particularly important. The effect size, hazard ratio, 95% confidence interval, absolute event rates, and prespecified subgroup results will determine how confidently these findings should influence clinical interpretation. The topline announcement alone does not provide enough information to determine whether the observed result represents a true absence of benefit, insufficient treatment duration, an inadequate biological effect, treatment initiated too late in the disease course, or heterogeneity of treatment effect.[8]

The individual components of the composite endpoint will also deserve close scrutiny. A neutral composite could conceal heterogeneity among CVD death, stroke, and urgent revascularization. Conversely, apparent subgroup signals must be interpreted cautiously because subgroup analyses are generally hypothesis-generating rather than definitive.

Primary Prevention May Be the More Important Test

Lp(a) is largely genetically determined, and elevated levels can expose individuals to increased CVD risk over decades.[1,2] If cumulative exposure is a major driver of disease, waiting until an individual has established ASCVD may be analogous to treating hypertension only after a patient develops heart failure.

The biological hypothesis would instead support intervention earlier in the disease trajectory, potentially before clinical ASCVD develops and before multiple vascular risk factors have accumulated. This creates an important paradox: the population that may derive the greatest benefit from a preventive intervention may be the population least represented by the Lp(a)HORIZON results. The results of primary-prevention trials such as OCEAN(a)-PreEvent may therefore be necessary to answer a fundamentally different question: Can lowering Lp(a) before the development of clinical ASCVD prevent first CVD events?

The appropriate duration of therapy is another unresolved issue. If Lp(a) contributes to disease through cumulative lifetime exposure, a 3- to 5-year trial in patients with established ASCVD may not adequately capture the potential benefit of modifying a genetically determined risk factor decades earlier. Whether meaningful clinical benefit requires, or even longer exposure remains unknown.

What Should Guidelines Do?

In cardiology, developing guidelines is challenging because new clinical trial data emerge continuously. The Lp(a)HORIZON result creates a legitimate challenge for clinical guidelines.

The 2026 ACC/AHA dyslipidemia guideline recommends measuring Lp(a) at least once in adulthood for ASCVD risk assessment.[7] This recommendation remains defensible because it concerns risk identification, and the association between elevated Lp(a) and ASCVD is supported by extensive epidemiologic, genetic, and mechanistic evidence. The negative therapeutic result from Lp(a)HORIZON should not automatically invalidate the value of measuring a risk marker. The guideline also recommends optimal early control of modifiable CVD risk factors in individuals with elevated Lp(a).[7]

The more difficult question is how guidelines should respond when evidence evolves faster than guideline cycles. Traditional guideline development is deliberately rigorous, but it is also slow. Major CVD trials can change clinical practice within months, whereas comprehensive guideline documents may take years from evidence review to publication. The Lp(a) story illustrates the resulting tension between methodological rigor and clinical timeliness.

Rather than viewing guidelines as static documents, cardiovascular medicine may need a more adaptive model: living guidelines, focused updates, rapidly deployable evidence reviews, and explicit mechanisms for revisiting recommendations when pivotal randomized trials change the evidentiary landscape.

Importantly, this does not mean that every negative trial should trigger an immediate guideline reversal. It means that recommendations should clearly distinguish risk assessment, risk modification, and disease-modifying therapy and should communicate the strength and limitations of the evidence supporting each recommendation in sufficient detail to minimize misinterpretation.

The Role of AI in Clinical Trials and Guidelines

Lp(a)HORIZON may ultimately be remembered not as the trial that disproved the Lp(a) hypothesis, but as the trial that refined it. The key question may no longer be simply whether Lp(a) is causal. Instead, we need to determine when Lp(a) becomes clinically actionable, how much it must be lowered, for how long, and in whom.

Future studies should therefore examine the magnitude of Lp(a) reduction, achieved Lp(a) concentrations, duration of exposure, baseline Lp(a) burden, age at treatment initiation, primary versus secondary prevention, and interactions with LDL-C, inflammation, and other vascular risk factors.

This is also an area in which artificial intelli-

gence (AI) could become useful as a tool for identifying heterogeneity of treatment effect, modeling exposure-response relationships, and generating hypotheses about which patients may benefit most from earlier intervention. Such analyses must remain hypothesis-generating until validated prospectively.

More broadly, AI could potentially help create a more adaptive approach to clinical trial interpretation and guideline development. When pivotal results such as those from Lp(a)HORIZON become available, AI-assisted evidence systems could rapidly synthesize the new findings with ongoing trials such as OCEAN(a)-PreEvent, ACCLAIM-Lp(a), and MOVE-Lp(a). Such systems could identify where new evidence materially changes the certainty of existing recommendations and prompt focused guideline updates rather than waiting for the next full guideline cycle.

The goal should not be for AI to make guideline recommendations autonomously. Rather, AI could help guideline committees monitor emerging evidence, identify areas requiring reassessment, and accelerate the transition from new evidence to transparent expert review and, when appropriate, updated recommendations.

Are We Losing, or Are We Asking the Wrong Question?

For now, the most reasonable conclusion is neither that Lp(a) is "dead" nor that the Lp(a) therapeutic hypothesis has been proven. Lp(a) remains an important inherited CVD risk marker. The Lp(a) HORIZON results remind us, however, that establishing causality is not the same as demonstrating that pharmacologic modification of a biomarker will reduce clinical events in every population. The more important question may be whether we tested the right population, at the right time, for the right duration, and with the right magnitude of Lp(a) reduction.

The Lp(a) story also offers a broader lesson for guideline development. Risk assessment, risk modification, and disease-modifying therapy are distinct clinical questions and should not be conflated. A negative therapeutic trial should prompt critical reassessment of treatment recommendations without necessarily erasing the prognostic value of the biomarker itself.

The next generation of Lp(a) trials should therefore leverage AI and other emerging analytical approaches to extract the greatest possible value from ongoing studies, identify heterogeneity of treatment effect, and refine our understanding of when Lp(a) becomes clinically actionable.

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