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From genetic causality to cardiovascular benefit: Translational lessons from Lp(a)HORIZON

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Lipoprotein(a) [Lp(a)] has long been regarded as one of the most attractive residual-risk targets in the field of atherosclerotic cardiovascular disease. Unlike low-density lipoprotein cholesterol (LDL-C), circulating Lp(a) levels are largely genetically determined and are minimally influenced by diet and lifestyle. Meanwhile, Lp(a) possesses multiple biological properties, including ApoB particle-related proatherogenic effects, oxidized phospholipid-mediated proinflammatory effects, and potential effects related to thrombosis and impaired fibrinolysis. Over the past two decades, extensive epidemiological, genetic, and Mendelian randomization studies have supported the association between elevated Lp(a) and increased risks of coronary heart disease, myocardial infarction, ischemic stroke, peripheral artery disease, and calcific aortic valve stenosis.[1-2] Therefore, apart from LDL-C, Lp(a) has been considered one of the most promising modifiable targets in cardiovascular prevention.

Based on this accumulating evidence, the results of pelacarsen and its phase III outcome trial, Lp(a)HORIZON, were highly anticipated. Pelacarsen is an antisense oligonucleotide targeting apolipoprotein(a) mRNA, designed to reduce Lp(a) production at its source by suppressing hepatic apo(a) synthesis. A previous phase II study published in the *New England Journal of Medicine* showed that, among patients with elevated Lp(a) and established cardiovascular disease, pelacarsen produced dose-dependent and substantial reduction in Lp(a) levels, with an extent of nearly 80% in the high-dose group.[3] Subsequently, Lp(a)HORIZON, one of the first large-scale cardiovascular outcomes trials specifically targeting Lp(a), randomized 8,323 high-risk patients with elevated Lp(a) and established cardiovascular disease across 797 sites in 42 countries, aiming to answer a central question: on the basis of contemporary guideline-directed therapy, can selective Lp(a) lowering further reduce major cardiovascular events?[4]

Much to our disappointment, the topline results announced by Novartis in September 2026 showed that Lp(a)HORIZON did not meet its primary endpoint. Although pelacarsen administration did substantially lower serum Lp(a) levels, this biomarker reduction did not translate into a significant reduction in the risk of major composite cardiovascular events in the overall study population. As the complete data of Lp(a)HORIZON have not been fully released, interpretation of the trial should be cautious. In general, Lp(a)HORIZON should not be simply interpreted as the end of the Lp(a) hypothesis, rather, it should be viewed as an important reminder that genetic causality, biomarker reduction, and clinical outcome benefit represent three distinct levels of evidence.

First, the neutral result of Lp(a)HORIZON reminds us that genetic causality does not automatically translate into short-term pharmacological benefit. Human genetic studies have provided strong support for a causal link between genetically elevated Lp(a) levels and coronary heart disease risk.[1] However, genetic studies reflect differences in lifelong exposure to a given risk factor beginning at birth and persisting for several decades, whereas clinical outcome trials usually test the effects of pharmacological intervention within a limited follow-up period after disease has already developed, or even after clinical events have already occurred. In patients with established ASCVD, atherosclerotic plaques, vascular inflammation, calcification and thrombosis, microvascular dysfunction and myocardial injury may have accumulated over many years. Lowering Lp(a) at this stage may therefore be unable to fully reproduce the lifelong protective effect associated with genetically lower Lp(a) exposure. Thus, what Lp(a)HORIZON truly challenges are not whether Lp(a) is causally related to ASCVD, but whether relatively late initiation and several years of sustained Lp(a) lowering are sufficient to produce a detectable and clinically meaningful reduction in cardiovascular events among patients with established CVD receiving contemporary therapy.

Second, baseline Lp(a) level and absolute reduction may be key to interpreting the trial results. The inclusion threshold for Lp(a)HORIZON was Lp(a) ≥ 70mg/dL, and prespecified subgroup analyses were planned for participants with higher Lp(a) levels.[4] This design is reasonable from an epidemiological perspective, but from the standpoint of an outcome trial, the risk of effect dilution may still exist. Lp(a)-associated risk is likely to depend not only on whether Lp(a) is elevated, but also on how high it is and how large an absolute reduction is achieved after treatment. After the full data are released, the most important issue will not merely be the average percentage reduction in Lp(a) produced by pelacarsen, but the absolute reduction across different baseline Lp(a) strata, the proportion of patients who achieved lower Lp(a) levels, and whether a dose–response relationship exists between these changes and clinical events.

Third, the efficacy of contemporary secondary prevention may have substantially compressed the short-term residual risk that can be modified by Lp(a). Lp(a)HORIZON enrolled patients with established cardiovascular disease who were receiving guideline-directed therapy, including lipid-lowering, antihypertensive, antiplatelet, and other secondary-prevention measures. With the widespread use of high-intensity statins, ezetimibe, PCSK9 inhibitors, antiplatelet therapy, novel antidiabetic drugs, and stricter blood-pressure control, the overall event rate and modifiable residual risk in contemporary secondary-prevention populations may be lower than those inferred from earlier observational or genetic studies. In this context, even if Lp(a) is a true causal risk factor, the absolute risk contribution that can be modified by a single pharmacological intervention over several years may be limited. In other words, Lp(a)HORIZON may have tested an Lp(a)-lowering strategy in a residual-risk environment already "squeezed" by multiple effective therapies.

Fourth, circulating Lp(a) concentration alone may not fully capture the biological heterogeneity and atherothrombotic potential of Lp(a) particles. Lp(a) particles not only carry cholesterol but are also enriched in oxidized phospholipids and may contribute to the progression of ASCVD and aortic valve stenosis through multiple pathways, including inflammation, endothelial dysfunction, plaque vulnerability, platelet activation, augmented coagulation, and interference with fibrinolysis.[2] Therefore, two patients with the same Lp(a) concentration may not necessarily have the same Lp(a)-mediated risk. If pelacarsen primarily lowers Lp(a) concentration but does not sufficiently modify certain key downstream inflammatory or thrombotic biological effects, or if there is substantial heterogeneity in Lp(a) particle biology across patients, then using Lp(a) concentration alone as both a therapeutic target and a surrogate marker of risk may be an oversimplification. Future studies need to answer whether Lp(a) lowering, oxidized phospholipid reduction, and clinical benefit are concordant. In addition, studies are warranted to determine which biological features of Lp(a) best identify residual risk truly driven by Lp(a).

The results of Lp(a)HORIZON will also influence how we understand Lp(a) testing strategies. In recent years, consensus statements from organizations such as the European Atherosclerosis Society recommended that adults measure serum levels of Lp(a) at least once in their lifetime, in order to identify genetically mediated lifelong risk and assist overall ASCVD risk assessment.[2] The neutral result of Lp(a)HORIZON does not necessarily invalidate this recommendation, because Lp(a) can still serve as a risk-enhancing biomarker. It can help identify familial clustering of premature ASCVD, explain

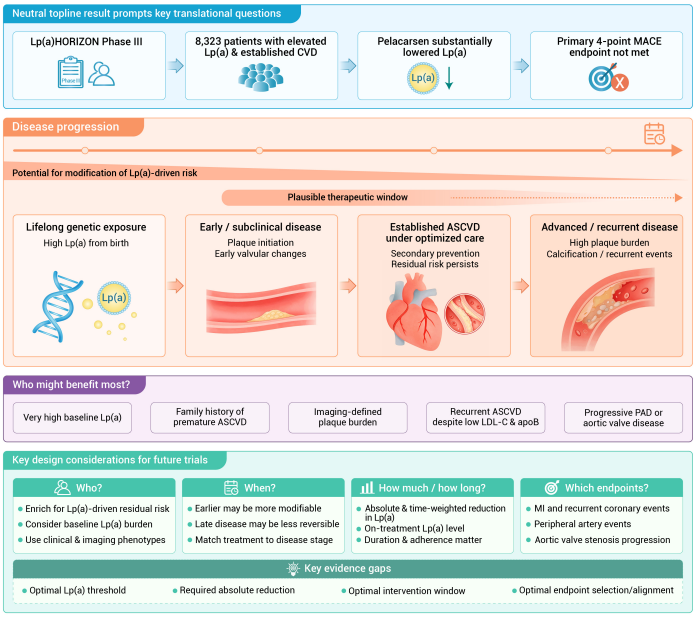

Figure 1. Translational framework for future Lp(a)-lowering trials after Lp(a)HORIZON.

residual risk that cannot be fully accounted for by traditional risk factors, and prompt more aggressive control of LDL-C, blood pressure, glucose metabolism, smoking, and lifestyle-related risk. However, the neutral result requires us to more clearly distinguish two concepts: the value of Lp(a) as a risk marker, and the value of Lp(a) as a therapeutic target proven by outcome trials. The former remains valid, whereas the latter requires further support from randomized clinical trials.

For other Lp(a)-targeted therapies currently in development, the implications of Lp(a)HORIZON are equally profound. Small interfering RNA agents such as olpasiran have shown deeper and more durable Lp(a) reductions in phase II studies[5]. However, the neutral topline result of pelacarsen indicates that future drug development cannot regard the magnitude of Lp(a) lowering alone as a marker of success; instead, it must demonstrate that such lowering improves hard clinical outcomes. Subsequent trials need to address several questions with greater precision: Is a higher baseline Lp(a) threshold required? Should phenotypes more likely to be influenced by Lp(a), such as coronary artery events, peripheral artery disease, or aortic valve stenosis, be selected? Is earlier intervention needed rather than limiting treatment to secondary prevention after ASCVD has already occurred? Should oxidized phospholipids, apo(a) isoforms, imaging-defined plaque burden, or genetic risk be incorporated for more precise stratification? These questions will determine whether Lp(a)-targeted therapy can truly move from biomarker lowering to clinical benefit. A proposed translational framework for future Lp(a)-lowering trials after Lp(a)HORIZON is summarized in Figure 1. These considerations can be translated into several concrete design principles for future Lp(a)-lowering outcome trials. First, patient enrichment should move beyond a single concentration threshold and aim to identify individuals whose residual cardiovascular risk is plausibly driven by Lp(a) and remains modifiable. Such patients may include those with very high baseline Lp(a), large absolute Lp(a) burden, premature or recurrent ASCVD despite optimized ApoB lowering, progressive peripheral artery disease, aortic valve disease, or biomarker and imaging evidence suggesting Lp(a)-related inflammatory or atherothrombotic activity. Second, the treatment window should be aligned with disease stage. In advanced secondary prevention, accumulated plaque burden, calcification, and thrombotic susceptibility may be less reversible, whereas earlier intervention may require longer exposure before event curves separate. Third, endpoint selection should match the biology of Lp(a). Broad composite MACE endpoints are efficient, but future trials should prespecify analyses of event types more strongly linked to Lp(a), including myocardial infarction, recurrent coronary events, peripheral artery events, and aortic valve stenosis progression. Finally, treatment effect should be interpreted according to achieved absolute and time-weighted Lp(a) reduction, on-treatment Lp(a) levels, treatment duration, and adherence, rather than percentage reduction alone. These design elements may help determine whether future trials are testing Lp(a) lowering in the right patients, at the right time, and against the right clinical endpoints.

From the perspective of current clinical practice, Lp(a)HORIZON should not lead to therapeutic nihilism. For patients with elevated Lp(a) and established ASCVD, the most evidence-based strategy remains maximal control of all known modifiable risk factors, including lowering LDL-C and ApoB to sufficiently low levels, strictly controlling blood pressure and glucose metabolism, smoking cessation, weight reduction, lifestyle improvement, and appropriate use of antiplatelet and other secondary-prevention therapies according to updated guidelines. For individuals with markedly elevated Lp(a) who have not yet experienced cardiovascular events, Lp(a) testing can still help identify lifelong risk and encourage physicians and patients to manage traditional risk factors earlier and more aggressively. In other words, before Lp(a)-targeted therapies with proven outcome benefits become widely available, elevated Lp(a) should serve as a signal to strengthen global cardiovascular risk management, rather than as a reason to wait for a single targeted drug.

Overall, the Lp(a)HORIZON topline results represent an important moment for careful reassessment in the Lp(a) field and should not be interpreted as the end of the Lp(a) hypothesis. They do not overturn the genetic and epidemiological foundation of Lp(a), but they do force us to reconsider the distance between a causal biomarker and a therapeutically actionable target. This result reminds us that even when a risk factor is supported by strong causal evidence, more specific clinical questions must still be answered: in what type of population should it be lowered, when should lowering begin, how much lowering is required, how long should it be sustained, and whether lowering can generate a sufficiently large absolute clinical benefit. The release of the complete data of Lp(a)HORIZON, together with the results of other Lp(a)-lowering outcome trials, will determine the next direction of this field. Regardless of the final answer, Lp(a)HORIZON has already provided an important lesson for cardiovascular prevention research: precision medicine is not only about identifying a causal target, but also about finding the right patients, the right therapeutic window, the right intensity of intervention, and the right clinical endpoints.

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DECLARATION OF INTERESTS

The authors declare no competing interests.