



Lipoprotein(a) as an Unmodifiable Risk Marker in a Modifiable Risk World: Testing, Interpretation and Communication

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Abstract

Lipoprotein(a) has long been taught as the archetypal unmodifiable cardiovascular risk marker: concentration is set overwhelmingly by the LPA locus, is largely fixed by early adulthood, and is essentially unmoved by diet, exercise or statin therapy. Genetic evidence, particularly Mendelian-randomization studies of the LPA variant rs10455872, supports a causal rather than merely associative relationship with calcific aortic-valve disease, and guideline bodies now recommend testing every adult at least once in a lifetime. But two things have changed the picture this decade. First, testing itself is not as simple as a single number: mass (mg/dL) and molar (nmol/L) results are not related by one fixed factor, because apolipoprotein(a) isoform size varies between patients, and population median levels vary several-fold by ancestry. Second, lipoprotein(a) is no longer pharmacologically unmodifiable: antisense and small-interfering-RNA therapies now lower it by 80% to over 100%, far beyond the roughly 25-27% achieved incidentally by PCSK9 inhibitors. What has not yet followed is proof that lowering it changes outcomes. Topline results from the Lp(a)HORIZON trial of pelacarsen, released in September 2026 in 8,323 patients with elevated lipoprotein(a) and established cardiovascular disease, showed substantial lipoprotein(a) reduction but did not meet its primary composite cardiovascular endpoint. This review sets out the genetic case for causality, the practical difficulty of testing and communicating a single risk number, and the widening gap between a marker that is now pharmacologically modifiable and one that has been shown to improve outcomes when modified.

Keywords: Lipoprotein(a); Cardiovascular risk; Aortic stenosis; Mendelian randomization; Antisense oligonucleotide; Small interfering RNA

Introduction

Lipoprotein(a), or Lp(a), is an LDL-like particle carrying an additional protein, apolipoprotein(a), attached to apolipoprotein B-100 by a single disulfide bond. Apolipoprotein(a) is highly polymorphic: the number of kringle IV type 2 (KIV-2) repeats it carries varies between people, and isoform size is inversely related to plasma concentration, so smaller isoforms generally produce higher Lp(a) levels [15]. Concentration is overwhelmingly under

genetic control, is largely established by early adulthood, and is essentially unmoved by diet, exercise, weight loss or standard statin therapy [4,11,12]. That combination — strongly genetically determined, biologically stable, and unresponsive to the interventions that work for most other lipid measures — is why Lp(a) has been taught for decades as the archetypal unmodifiable cardiovascular risk marker.

Between 20% and 25% of the global population has an Lp(a) concentration high enough to be considered clinically actionable, with substantial variation by ancestry [4]. The

European Atherosclerosis Society (EAS) and the 2019 European Society of Cardiology (ESC)/EAS dyslipidaemia guidelines both recommend measuring Lp(a) at least once in every adult's lifetime, reasoning that a single measurement is sufficient given how little it changes thereafter [1,3]. This review asks what that recommendation actually delivers in practice: how solid is the evidence that Lp(a) is a cause rather than a marker of disease; how much interpretive difficulty sits underneath a single reported number; and, now that pharmacological tools finally exist to lower it substantially, whether lowering it has been shown to change what happens to the patient.

Material and Methods

This is a narrative review, not a systematic review or a new meta-analysis. The literature was assembled by searching PubMed/MEDLINE for studies of lipoprotein(a) genetics, epidemiology, assay standardization and lipoprotein(a)-lowering trials, supplemented by the reference lists of the 2022 EAS consensus statement and the 2024 National Lipid Association (NLA) focused update, and by each named trial's own registry entry or design publication [1,13,14]. Where a trial has reported only topline results at the time of writing, that is stated explicitly rather than presented as a peer-reviewed final analysis.

Every percentage, odds ratio, hazard ratio and concentration reproduced here is taken directly from the cited primary source; none was recalculated by the present authors. Figures illustrating the relationship between mass and molar Lp(a) units, the shape of the population distribution, and the qualitative pattern of the Lp(a)HORIZON topline result are schematic representations built to illustrate a documented phenomenon, not reproductions of any single patient-level dataset, and are labelled as such.

Results

Establishing causality: genetics before pharmacology

The strongest evidence that Lp(a) is a cause of disease, rather than a bystander correlate of it, comes from Mendelian randomization: because the LPA variant rs10455872 is inherited essentially at random with respect to other risk factors, its association with disease is not confounded by lifestyle or socioeconomic factors in the way an observational Lp(a)-disease association could be. In a discovery cohort of more than 6,900 white participants across the Framingham Heart Study, the Age, Gene/Environment Susceptibility-Reykjavik Study, and the Multi-Ethnic Study of Atherosclerosis, each copy of rs10455872 was associated with roughly double the odds of aortic-valve calcification on computed tomography (odds ratio 2.05), an association replicated across Hispanic, African-American and German cohorts [5]. In a prospective analysis of more than 28,000 participants with independent replication in a Danish cohort, each copy was associated with a hazard ratio of 1.68 for incident aortic stenosis and 1.54 for aortic-valve replacement [5]. Figure 1 sets these three estimates side by side.

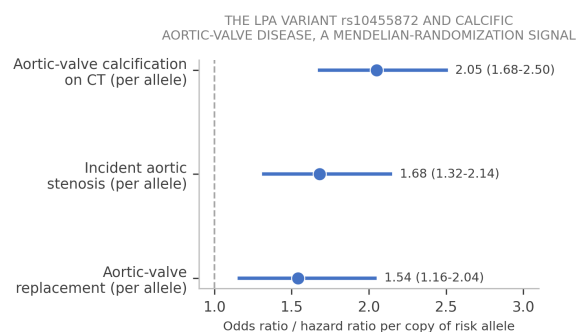


Figure 1: The LPA variant rs10455872 and calcific aortic-valve disease: odds ratio for aortic-valve calcification on CT, and hazard ratios for incident aortic stenosis and aortic-valve replacement, per copy of the risk allele [5].

Large prospective observational studies corroborate the genetic signal at the population level. A meta-analysis of prospective studies found that people in the top third of usual Lp(a) measurement had roughly 70% higher coronary heart disease risk than those in the bottom third, a gradient that persisted after adjustment for conventional risk factors [16]. A dedicated post-hoc analysis of the JUPITER trial of rosuvastatin similarly found that baseline Lp(a) predicted residual vascular risk even among patients who achieved very low LDL cholesterol on statin therapy, indicating that Lp(a)-associated risk is not simply a proxy for LDL cholesterol and is not resolved by treating LDL cholesterol alone [19]. Taken together, the EAS consensus statement concludes that the totality of genetic, epidemiological and biological evidence supports a causal, dose-dependent relationship between Lp(a) and both atherosclerotic cardiovascular disease and calcific aortic-valve disease [1].

Testing in practice: thresholds, grey zones, and a units problem that resists a single fix

Causality established at the population level does not automatically translate into a simple number for an individual patient. The relationship between Lp(a) concentration and cardiovascular risk is continuous, without a validated threshold below which risk is absent, which sits uneasily with the clinical need for an actionable cut-off [1,2]. The EAS consensus statement resolves this pragmatically with three bands rather than a single line: a concentration below roughly 30 mg/dL (75 nmol/L) where elevated Lp(a)-attributable risk can reasonably be "ruled out"; a concentration above roughly 50 mg/dL (125 nmol/L) where it should be "ruled in" as a contributor to the patient's overall risk; and a grey zone in between where Lp(a) is one contributing factor among several [2]. Figure 2 illustrates how a continuous, right-skewed population distribution is compressed into these three pragmatic bands, and Table 1 sets out the bands themselves.

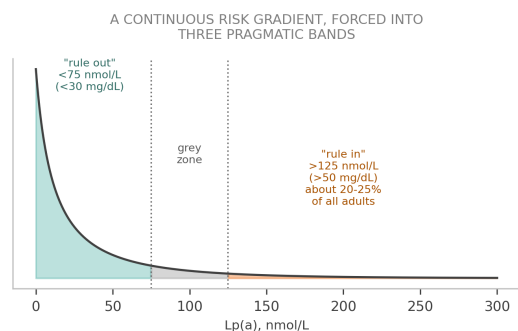


Figure 2: A continuous population risk gradient in lipoprotein(a) concentration, forced for clinical use into three pragmatic bands: "rule out", grey zone, and "rule in" [1,2].

Band	Threshold	Approximate population share	Interpretation
"Rule out"	<30 mg/dL (<75 nmol/L)	roughly 50-70%	Lp(a)-attributable risk low
Grey zone	30-50 mg/dL (75-125 nmol/L)	variable by ancestry	one contributing factor among several
"Rule in"	>50 mg/dL (>125 nmol/L)	roughly 20-25% globally	should factor into overall risk estimate

Table 1: The EAS consensus statement's three pragmatic interpretive bands for lipoprotein(a), applied to a risk relationship the statement itself describes as continuous and without a true threshold effect [1,2].

A second, more technical difficulty compounds the first: mass-based (mg/dL) and molar-based (nmol/L) Lp(a) assays are not related by one universal conversion factor, because the mass of an Lp(a) particle depends on the size of its apolipoprotein(a) component, which differs from patient to patient [2]. A commonly used approximation multiplies a mg/dL value by roughly 2 to 2.5 to estimate nmol/L, but because that ratio is isoform-dependent, the same mg/dL result

can correspond to a meaningfully different nmol/L value in different patients, and vice versa [2]. Figure 3 illustrates why no single line can convert one unit to the other exactly. In practice this means a result reported to a patient in one unit, by one laboratory, cannot always be compared directly with an earlier result in the other unit from a different laboratory — a genuine obstacle to the guideline-recommended "once in a lifetime" model of testing, which implicitly assumes results remain comparable over time and across care settings.

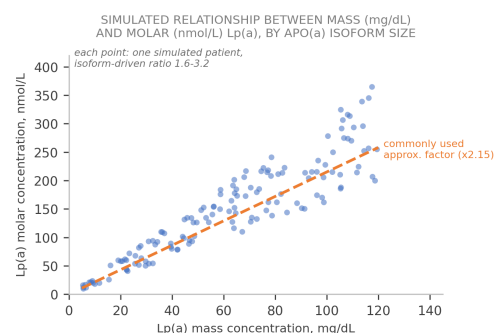


Figure 3: Simulated relationship between mass (mg/dL) and molar (nmol/L) lipoprotein(a) concentration: apolipoprotein(a) isoform size varies between patients, so a single multiplicative conversion factor is only an approximation [2].

Ancestry adds a further layer to interpretation and communication. In the UK Biobank, median Lp(a) ranged from 16 nmol/L in participants of Chinese ancestry to 75 nmol/L in participants of Black ancestry, a roughly five-fold difference in the population median alone [1,2]. Figure 4 sets out this gradient. Because a fixed mg/dL or nmol/L threshold was derived predominantly from European-ancestry cohorts, applying it uniformly risks under-flagging or over-flagging risk in populations whose typical distribution sits well above or below that of the original derivation cohort — a limitation the EAS statement itself acknowledges rather than resolves [1].

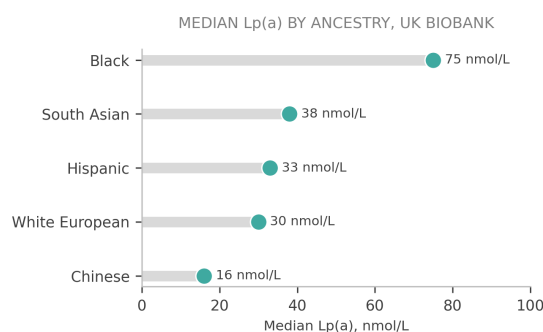


Figure 4: Median lipoprotein(a) concentration by ancestry group, UK Biobank. Population medians vary roughly five-fold across ancestry groups, complicating the use of a single fixed threshold derived predominantly from European-ancestry cohorts [1,2].

From unmodifiable to modifiable: a growing pharmacologic toolkit

Until recently, "largely unmodifiable" was not just a description of Lp(a)'s biology but an accurate summary of the available pharmacology. Statins do not lower Lp(a) and, in some analyses, modestly raise it: a systematic review and meta-analysis found a small but statistically significant increase in Lp(a) with statin therapy across the pooled trials examined [20], a pattern explored mechanistically in a separate analysis proposing that statins up-regulate hepatic LPA transcription [21]. Niacin lowers Lp(a) by a modest amount, but the two largest randomized trials of niacin, AIM-HIGH and HPS2-THRIVE, were designed around the HDL-cholesterol hypothesis rather than Lp(a) specifically, and both found no reduction in cardiovascular events, with HPS2-THRIVE also reporting an excess of serious adverse effects [17,18]; neither trial isolates whether niacin's modest Lp(a)-lowering effect specifically helped or was simply outweighed by those adverse effects. PCSK9 inhibitors lower Lp(a) as a secondary effect of their primary LDL-cholesterol-lowering mechanism: in the FOURIER trial, evolocumab produced a median 26.9% reduction in Lp(a) at 48 weeks, and patients with both a larger Lp(a) reduction and a lower achieved LDL cholesterol had the lowest subsequent cardiovascular event rates [6]. A parallel analysis of the ODYSSEY OUTCOMES trial of alirocumab found that each 5 mg/dL reduction in Lp(a) predicted an independent 2.5% relative reduction in cardiovascular events, separate from the benefit attributable to LDL-cholesterol lowering [7].

The newest drug classes lower Lp(a) far beyond anything achievable with statins, niacin or PCSK9 inhibitors. Pelacarsen, an antisense oligonucleotide, lowers hepatic apolipoprotein(a) production directly. Olpasiran, a small interfering RNA (siRNA) therapy targeting the same mRNA, produced dose-dependent reductions in the phase 2 OCEAN(a)-DOSE trial ranging from 70.5% at the lowest tested dose to a median reduction of just over 100% relative to placebo (which itself rose 3.6%) at the two highest-dose regimens, with nearly all treated patients falling below 125 nmol/L by week 36 [8]. Figure 5 and Table 2 set the full range of approaches side by side.

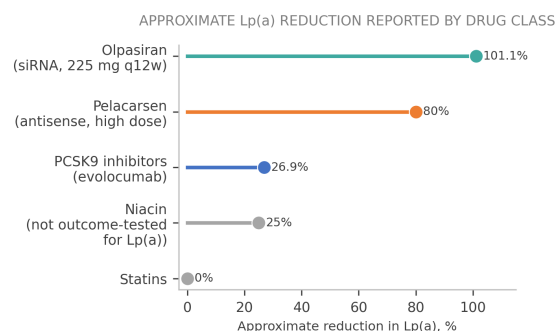


Figure 5: Approximate lipoprotein(a) reduction reported by drug class: statins are neutral to mildly Lp(a)-raising; niacin and PCSK9 inhibitors achieve modest reductions as a secondary effect; antisense and siRNA therapies achieve substantially larger reductions [6,8,20,21].

Agent (class)	Mechanism	Reported Lp(a) effect	Outcomes evidence
Statins	Not Lp(a)-specific	Neutral to mildly increased	Not an Lp(a)-lowering strategy
Niacin	Reduces hepatic apo(a) synthesis	Modest reduction	Negative (AIM-HIGH, HPS2-THRIVE); not Lp(a)-focused
PCSK9 inhibitors	Secondary to LDL-C lowering mechanism	~25-27% reduction	Per-mg/dL signal in FOURIER, ODYSSEY substudies
Pelacarsen (antisense)	Reduces hepatic apo(a) production	Substantial reduction	Primary CV endpoint not met (Lp(a)HO RIZON)
Olpasiran (siRNA)	Degrades apo(a) mRNA	Up to ~100%+ at highest doses	Dedicated outcomes trial ongoing (OCEAN(a)-Outcomes)

Table 2: Lipoprotein(a)-lowering approaches by drug class, their reported effect on Lp(a) concentration, and the current state of outcomes evidence for each [6,7,8,17,18,20,21,22].

The honest complication: a large reduction in Lp(a) has not yet been shown to reduce events

The per-unit signals from FOURIER and ODYSSEY OUTCOMES, together with the scale of Lp(a) reduction achievable with antisense and siRNA therapy, made pelacarsen's dedicated cardiovascular outcomes trial one of the most closely watched readouts in preventive cardiology. Lp(a)HORIZON was a phase 3, randomized, double-blind, placebo-controlled trial enrolling 8,323 patients with elevated Lp(a) (at least 70 mg/dL, with a pre-specified subpopulation at least 90 mg/dL) and established cardiovascular disease, testing whether pelacarsen would reduce a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent coronary revascularization requiring hospitalization [9,10]. Novartis announced topline results on 4 September 2026: pelacarsen achieved substantial reduction in Lp(a), but the trial did not meet its primary endpoint in the overall study population, and the company stated that the observed Lp(a) lowering "did not demonstrate that this translated into reduced cardiovascular risk" [10]. Figure 6 sketches the qualitative shape of that result schematically — a large, sustained reduction in Lp(a) alongside event curves that did not separate — since the full patient-level data have not yet been presented at a medical congress or published in a peer-reviewed journal at the time of writing [10].

Lp(a)HORIZON, SCHEMATIC OF THE REPORTED PATTERN (n=8,323)

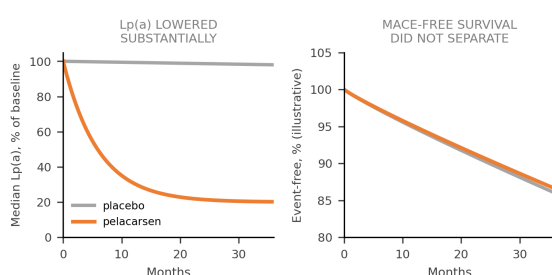


Figure 6: Schematic illustration of the qualitative pattern reported in the Lp(a)HORIZON topline announcement (n=8,323): lipoprotein(a) fell substantially on pelacarsen, but reported cardiovascular event rates did not separate from placebo. Illustrative only; detailed patient-level curves have not yet been published [9,10].

This is not evidence that Lp(a) is not causal — the genetic case in Figure 1 does not depend on any single drug trial. It is, however, a direct challenge to the assumption that any sufficiently large reduction in a causal risk marker will translate into a proportional reduction in events. Several explanations remain open pending the full published analysis: pelacarsen's enrollment threshold (Lp(a) at least 70 mg/dL) was more permissive than the very high concentrations typical of severe calcific aortic-valve disease cohorts, and the antisense mechanism differs from siRNA in duration and degree of knockdown between doses. A dedicated outcomes trial of olpasiran, OCEAN(a)-Outcomes, is ongoing and will

independently test whether a different mechanism, at the larger reductions olpasiran achieves, changes the answer [22].

Discussion

Two threads run through this review, and Lp(a)HORIZON's topline result sits at their intersection. The first thread is that the genetic case for Lp(a) as a cause of atherosclerotic and calcific aortic-valve disease is about as strong as genetic evidence gets in cardiovascular medicine, replicated across ancestries and corroborated by large observational cohorts [1,5,16,19]. The second is that testing and communicating that risk is harder in practice than "measure it once" suggests: a continuous risk relationship is compressed into pragmatic bands, a single reported number depends on which assay unit was used and on an isoform-dependent conversion that cannot be made exact, and population-derived thresholds do not transfer evenly across ancestries whose typical Lp(a) levels differ several-fold [1,2].

Those two threads used to converge on a consistent, if unsatisfying, clinical message: Lp(a) matters, but there is little a clinician can do about it beyond noting it as a risk-enhancing factor. That message no longer fits the pharmacology, since antisense and siRNA agents can now lower Lp(a) by a margin that dwarfs anything achievable a decade ago [8]. What Lp(a)HORIZON's topline result adds is a caution against assuming pharmacological modifiability implies outcome benefit by extrapolation from genetics and per-unit observational signals alone [6,7,9,10]. HDL cholesterol offers a precedent: once considered causally protective on similarly strong observational and genetic grounds, it nonetheless saw multiple HDL-raising drug classes fail to reduce events. Whether Lp(a) follows a similar path, or a different mechanism or population succeeds where pelacarsen's did not, is what OCEAN(a)-Outcomes and the peer-reviewed Lp(a)HORIZON analysis are positioned to clarify [10,22].

For clinical communication in the interim, the honest position is a specific one rather than a reassuring or alarming one: Lp(a) is very likely a cause of disease; it can now be measured with important but manageable interpretive caveats around units, thresholds and ancestry; it can now be substantially lowered pharmacologically; and lowering it has not yet been shown, in a completed adequately powered outcomes trial, to reduce cardiovascular events. Collapsing that last distinction — telling a patient that a drug lowering their Lp(a) will lower their risk — would currently overstate the evidence in exactly the way this review has tried to avoid throughout.

Study limitations

This is a narrative synthesis, not a systematic review, and although the search was broad it followed no pre-registered protocol. The Lp(a)HORIZON findings discussed here come from a topline company announcement rather than a peer-reviewed publication at the time of writing; detailed efficacy figures, subgroup analyses and safety data were not available, and Figure 6 illustrates the qualitative pattern reported rather than any actual patient-level curve [10]. The studies compared here differ substantially in population, assay method and era, and Lp(a) assays are not fully standardized across laboratories, itself part of the testing problem this review describes rather than a separate limitation. No attempt is made here to adjudicate why Lp(a)HORIZON's primary endpoint was not met; that awaits the full published analysis.

Conclusion

Lipoprotein(a) has moved from a marker clinicians could only note to one they can now substantially lower, but that pharmacological progress has outpaced the outcomes evidence: the first large randomized test of a purpose-built Lp(a)-lowering drug did not meet its primary cardiovascular endpoint despite achieving its Lp(a)-lowering goal [10]. Guideline-recommended once-in-a-lifetime testing remains reasonable given Lp(a)'s biological stability, but interpreting and communicating a single reported number requires acknowledging a continuous risk relationship, an imperfect unit conversion, and ancestry-dependent population norms [1,2]. Until a dedicated outcomes trial demonstrates that lowering Lp(a) reduces events, the accurate message for patients is that their risk marker is no longer unmodifiable, but that modifying it is not yet proven to help.

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