





Clinical approach and emerging therapies for elevated lipoprotein(a): current evidence and guideline-based recommendations

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ABSTRACT

Elevated lipoprotein(a) [Lp(a)] is a genetically mediated, independent, and causally implicated risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis. Approximately one quarter of adults worldwide have Lp(a) concentrations ≥ 50 mg/dl (≥ 125 nmol/L), representing a substantial component of residual cardiovascular risk even when low-density lipoprotein cholesterol (LDL-C) is well controlled. Conventional lipid-lowering therapies have little influence on Lp(a), underscoring the need for targeted approaches. Recent development of antisense oligonucleotide (ASO) and small-interfering RNA (siRNA) therapies has generated considerable interest, with early-phase trials reporting reductions nearing 80–90%. Several phase 3 outcome studies are ongoing and are expected to clarify whether these marked biochemical reductions translate into clinical benefit. This review discusses the clinical relevance of elevated Lp(a), summarises current and emerging therapeutic strategies, and contextualises existing evidence within contemporary international guideline recommendations. Despite major advances, important gaps remain regarding screening strategies, assay standardization, and understanding the long-term clinical impact of emerging therapies. As these uncertainties are addressed, Lp(a) testing and targeted treatment are likely to become integral components of personalised cardiovascular prevention.

Keywords: Lipoprotein(a), cardiovascular risk, aortic valve stenosis, antisense therapy, siRNA therapy

INTRODUCTION

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein-like particle composed of apolipoprotein B-100 covalently linked to apolipoprotein(a) [apo(a)], a highly polymorphic glycoprotein structurally related to plasminogen. This distinctive configuration confers atherogenic, pro-inflammatory, and antifibrinolytic properties. Large epidemiological cohorts and Mendelian-randomisation studies have firmly established Lp(a) as a causal contributor to atherosclerotic cardiovascular disease (ASCVD), independent of traditional lipid parameters such as LDL-C, triglycerides, and HDL-C.¹⁻⁴

Circulating Lp(a) levels are determined predominantly by inherited variation in the LPA gene on chromosome 6q26–27, particularly by the number of kringle IV type-2 repeats; individuals with fewer repeats tend to exhibit markedly higher plasma concentrations.^{4,5} Unlike other atherogenic lipoproteins, Lp(a) levels remain remarkably stable throughout life and are minimally influenced by diet, physical activity, or other lifestyle factors.⁶ As a result, elevated Lp(a) has emerged as a key component of residual cardiovascular

risk, persisting even when LDL-C is successfully lowered to guideline-recommended targets.

For decades, clinical interest in Lp(a) was limited partly due to the absence of effective therapeutic options and partly due to substantial inter-assay variability.⁷ Considerable heterogeneity persists among available measurement methods, and the lack of universal standardisation continues to complicate interpretation across laboratories and clinical settings. A further practical challenge is the absence of a fixed conversion between mg/dl and nmol/L, as apo(a) molecular weight varies widely with kringle IV-2 repeat number; therefore, direct numerical conversion between units is not recommended. However, the development of RNA-targeted therapies capable of producing profound reductions in Lp(a) has renewed enthusiasm for this long-neglected risk factor. In parallel, major international societies have begun to integrate Lp(a) measurement into contemporary risk-assessment algorithms, underscoring its growing relevance in preventive cardiology.⁸⁻¹⁰

CLINICAL IMPLICATIONS OF ELEVATED Lp(a)

Coronary Artery Disease

Extensive observational cohorts and Mendelian-randomisation analyses consistently demonstrate a graded, approximately linear association between circulating Lp(a) levels and coronary artery disease (CAD). Each 50 mg/dl increase in Lp(a) confers an estimated 15–20% rise in CAD risk, and elevated concentrations predict recurrent events even in patients receiving intensive lipid-lowering therapy with statins or PCSK9 inhibitors. These observations highlight Lp(a) as a key determinant of residual cardiovascular risk. Mechanistically, oxidised phospholipids carried on apo(a) promote endothelial dysfunction, macrophage activation, smooth-muscle proliferation, and foam-cell formation, providing a biologically plausible link to atherogenesis.¹¹⁻¹⁵

Aortic-Valve Stenosis

Beyond its atherogenic effects, Lp(a) plays an active role in the development of calcific aortic-valve stenosis. Genome-wide association studies have identified robust links between LPA gene variants, elevated Lp(a) levels, and calcific valve disease, suggesting a causal pathway mediated by deposition of oxidised phospholipids within valvular interstitial cells. These lipids stimulate osteogenic differentiation, thereby accelerating valve calcification and the progression from aortic sclerosis to hemodynamically significant stenosis. Importantly, high Lp(a) levels predict faster disease progression independent of LDL-C or blood pressure, reinforcing its distinct pathogenic contribution.¹⁶

Stroke and Peripheral Artery Disease

Prospective cohort meta-analyses indicate that elevated Lp(a) is associated with approximately 30% higher risk of ischaemic stroke, particularly among younger individuals or those lacking conventional vascular risk factors.¹⁹ Elevated Lp(a) is also linked to peripheral arterial disease (PAD), greater symptom burden, and increased frequency of limb revascularisation procedures.²⁰ Lp(a)'s thrombogenicity driven by competitive inhibition of plasminogen binding and impaired fibrinolysis provides mechanistic insight into its contribution to cerebrovascular and peripheral arterial events.¹⁷⁻¹⁹

Microvascular and Inflammatory Pathways

Emerging data suggest that Lp(a) may exert important effects on the coronary microcirculation. Associations have been reported between high Lp(a) levels and coronary microvascular dysfunction (CMD) or the coronary slow-flow (CSF) phenomenon, supported by evidence of endothelial inflammation, nitric oxide depletion, and heightened oxidative stress. Patients with elevated Lp(a) frequently demonstrate impaired microvascular reactivity despite angiographically normal epicardial arteries.^{20,21} However, current evidence remains preliminary, and mechanistic pathways linking elevated Lp(a) to microvascular dysfunction require confirmation in larger, dedicated studies.

Collectively, elevated Lp(a) identifies a subgroup of patients at persistently increased cardiovascular risk despite optimisation of traditional risk factors. This underscores the importance of aggressive risk-factor modification and supports the rationale for dedicated Lp(a)-lowering therapies

now under development. Thresholds commonly used for risk stratification in clinical practice are summarised in **Table 1**.²²⁻²⁴

Table 1. Lipoprotein(a) risk thresholds (EAS Consensus 2022)

Category	Lp(a), mg/dl	Lp(a), nmol/L	Clinical interpretation
Normal	<30	<75	No additional risk
Intermediate risk	30–50	75–125	Possible risk-enhancing ≥125 nmol/L level
High risk	≥50	≥125	Strong risk-enhancing factor; consider aggressive LDL-C lowering and family screening

Thresholds are intended for clinical guidance but are not universally standardised across assays or societies.

THERAPEUTIC STRATEGIES

Conventional and Indirect Approaches

Most traditional lipid-lowering therapies have little meaningful effect on circulating Lp(a) concentrations. Statins may even lead to a modest increase of approximately 10–15%, potentially through up-regulation of hepatic LPA gene expression, although this effect is generally considered clinically modest.¹³ Niacin can reduce Lp(a) by roughly 20%; however, major outcome trials such as AIM-HIGH and HPS2-THRIVE failed to demonstrate cardiovascular benefit, resulting in its near disappearance from contemporary clinical practice.^{14,25,26}

Lipoprotein apheresis remains the only licensed treatment in Europe for patients with markedly elevated Lp(a) levels (≥180 mg/dl or >430 nmol/L). It produces acute reductions of 60–70%, although the effect is transient and supported primarily by small registries suggesting improvements in event rates.

PCSK9 inhibitors (evolocumab, alirocumab) lower Lp(a) by approximately 25–30%, primarily through enhanced LDL-receptor recycling. In secondary analyses of the FOURIER and ODYSSEY OUTCOMES trials, the degree of Lp(a) reduction correlated with fewer cardiovascular events independent of LDL-C lowering, implying potential clinical relevance.²⁷⁻²⁹

A comparative overview of available and emerging Lp(a)-lowering agents, their mechanisms, and key clinical trials is summarised in **Table 2**.

Antisense Oligonucleotide (ASO) Therapies

ASOs reduce Lp(a) synthesis by inhibiting apo(a) mRNA translation in hepatocytes. Pelacarsen (AKCEA-APO(a)-LRx) demonstrated dose-dependent reductions of 80–90% in phase 2 studies.

The ongoing Lp(a)HORIZON phase 3 trial (NCT04023552), enrolling more than 8,000 patients with established ASCVD and elevated Lp(a), is expected to determine whether these marked biochemical reductions translate into clinical outcome benefit. Results are anticipated in 2025.³⁰

Small-Interfering RNA (siRNA) Therapies

siRNA therapies silence LPA gene expression post-transcriptionally via RNA-induced silencing complexes.

Table 2. Major Lp(a)-lowering agents and ongoing clinical trials

Agent	Mechanism	Phase/trial	Mean Lp(a) reduction %	Key reference
Pelacarsen (AKCEA-APO(a)-LRx)	Antisense oligonucleotide inhibiting apo(a) mRNA	Phase 3–Lp(a)HORIZON (NCT04023552)	80–90%	Viney NJ et al., Lancet 2016
Olpasiran (AMG 890)	siRNA targeting LPA expression	Phase 3–OCEAN(a) (NCT05581303)	90–95%	Nissen SE et al., NEJM 2022
SLN360	siRNA blocking LPA mRNA translation	Phase 2–NCT04606602	>90%	Tsimikas S, Mayo Clin Proc 2023
Zerlasiran (ALN-Lp(a)01)	Long-acting siRNA formulation	Phase 2–NCT06070725	>90%	Reyes-Soffer G et al., Circulation 2023
PCSK9 inhibitors	Monoclonal antibodies–indirect and modest Lp(a) reduction	Approved – FOURIER, ODYSSEY OUTCOMES	25–30%	O'Donoghue ML et al., Circulation 2019
Lipoprotein apheresis	Physical removal of Lp(a) particles	Clinical practice	60–70% (transient)	Paragh G et al., Life 2024

Lp(a) reductions shown are mean values from phase-specific clinical trials; therapeutic availability varies by regulatory region.

Olpasiran (AMG 890) achieved median reductions of approximately 95% in the phase 2 OCEAN(a)-DOSE trial, with effects persisting for ≥ 48 weeks after the final dose.

SLN360 and zerlasiran (ALN-Lp(a)01) demonstrated similar >90% reductions in early-phase studies.³¹

The OCEAN(a) phase 3 outcomes trial (NCT05581303) is currently underway to evaluate whether these therapies reduce ASCVD events. A practical distinction between these platforms is dosing frequency: ASO therapies generally require monthly or quarterly administration, whereas siRNA agents achieve sustained LPA suppression with twice-yearly dosing.

Future Perspectives

Several emerging strategies have the potential to broaden the therapeutic landscape for elevated Lp(a). Combining PCSK9 inhibitors with RNA-targeted therapies may offer additive or synergistic effects, particularly in individuals with markedly elevated baseline concentrations or accelerated atherosclerotic progression. Gene-editing approaches most notably CRISPR/Cas9-based Technologies are being explored in preclinical models with the aim of achieving durable or potentially permanent LPA silencing, although safety, immunogenicity, and off-target effects will require rigorous evaluation before clinical translation.^{11,12}

Beyond pharmacologic innovation, future risk assessment may shift toward more personalised frameworks. Integration of Lp(a) levels with inflammatory biomarkers, coronary or valvular imaging indices, and polygenic-risk scores could refine global cardiovascular risk prediction and guide tailored prevention strategies.¹¹ Such multidimensional models may be particularly relevant in populations with intermediate risk, where treatment thresholds remain uncertain.

Another key research direction involves determining whether profound Lp(a) lowering approaching >90% reductions achieved with siRNA or antisense therapies translates into proportional clinical benefit. The results of large phase 3 outcome trials, including Lp(a)HORIZON and OCEAN(a), will be critical in shaping future treatment algorithms and informing regulatory decisions. Long-term safety data will also be essential, as the clinical implications of achieving extremely low Lp(a) concentrations remain unknown.

Finally, successful implementation of Lp(a)-targeted therapies will require addressing practical challenges such as assay standardisation, testing accessibility, cost considerations, and integration into routine lipid management pathways. As these scientific and operational advances converge, they collectively signal a movement toward precision lipidology, in which Lp(a) becomes an integral component of individualised cardiovascular prevention and therapy.

GUIDELINE RECOMMENDATIONS

Major international societies now recognise elevated Lp(a) as a clinically meaningful contributor to cardiovascular risk, as reflected in the 2019 ESC/EAS Dyslipidaemia Guidelines, the 2022 European Atherosclerosis Society (EAS) Lp(a) Consensus Statement, and the 2025 ESC/EAS Focused Update, all of which recommend at least one lifetime Lp(a) measurement as part of comprehensive cardiovascular risk assessment.^{2,10,32} These documents further emphasise that individuals with premature ASCVD, familial hypercholesterolaemia, or a family history of markedly elevated Lp(a) may warrant repeat testing.² The updated ESC/EAS guidance also notes that Lp(a) levels ≥ 50 mg/dl (≈ 125 nmol/L) may justify more intensive LDL-C lowering approaches, effectively reclassifying certain patients into a higher-risk category.³² Clinical decision thresholds endorsed by major societies are summarised in **Table 1**.

The 2018 AHA/ACC Cholesterol Guideline similarly identifies Lp(a) ≥ 50 mg/dl as a risk-enhancing factor that may support more intensive LDL-C lowering in borderline, intermediate, or high-risk individuals. Subsequent AHA/ACC scientific statements reinforce the value of incorporating Lp(a) into shared decision-making, particularly when treatment thresholds are uncertain.²⁷ Complementing these recommendations, the 2024 National Lipid Association (NLA) Scientific Statement advocates cascade screening of first-degree relatives and early initiation of high-intensity statin therapy, with consideration of PCSK9 inhibitor therapy when LDL-C remains above goal in the presence of markedly elevated Lp(a).⁹

Although no pharmacologic agent is yet formally approved specifically for lowering Lp(a), the 2025 ESC/EAS Focused Update identifies antisense and siRNA-based agents as promising investigational therapies.³² Ongoing phase 3 outcome trials including Lp(a)HORIZON and OCEAN(a)

are expected to clarify whether profound reductions in circulating Lp(a) translate into clinically meaningful reductions in ASCVD events.^{30,31} Until such treatments become available, clinicians should incorporate Lp(a) into global risk estimation and ensure optimal management of all modifiable cardiovascular risk factors as part of routine care.^{2,10,32}

CONCLUSION

Elevated Lp(a) represents a major and persistent contributor to global cardiovascular risk. It influences both atherosclerotic disease progression and calcific aortic valve stenosis. Even in patients who have achieved optimal LDL-cholesterol control, markedly elevated Lp(a) levels may sustain a substantial residual risk, reinforcing the need for systematic and routine assessment. The convergence of international guidelines recommending at least one lifetime Lp(a) measurement reflects its growing relevance in contemporary cardiovascular prevention.

Traditional lipid-lowering therapies have little impact on Lp(a), but the emergence of antisense and siRNA-based agents has introduced a fundamentally new therapeutic paradigm. These agents achieve profound reductions in circulating Lp(a), and the results of large phase 3 outcome trials most notably Lp(a)HORIZON and OCEAN(a) are expected to determine whether these biochemical improvements translate into meaningful reductions in cardiovascular events. Until these data become available, clinicians should incorporate Lp(a) into global risk estimation, ensure optimisation of all modifiable risk factors, and identify individuals who may ultimately benefit from targeted therapies.

Despite substantial scientific progress, several important challenges remain. Access to Lp(a) testing is inconsistent, assay standardisation is incomplete, and the long-term implications of achieving very low Lp(a) levels are not yet known. Addressing these gaps will be essential as the field advances toward more precise, mechanism-driven lipid management. Ultimately, increased awareness, systematic screening, and integration of next-generation Lp(a)-lowering therapies hold significant promise for reducing the overall burden of Lp(a)-mediated cardiovascular disease worldwide.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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