Review Article

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Lipoprotein(a) and Cardiovascular Disease: A Review of Current Evidence and Future Directions

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Abstract:

Lipoprotein(a), Lp(a), is a type of low-density lipoprotein (LDL) that is now widely understood to be an independent and direct risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis (CAVS). Plasma Lp(a) levels are predominantly (over 90%) genetically determined, making them relatively stable throughout life and unresponsive to lifestyle modifications or most currently available lipid-lowering therapies. The pathophysiology of Lp(a) is complex, involving pro-atherogenic, pro-inflammatory, and pro-thrombotic mechanisms, primarily driven by its unique protein component, apolipoprotein (a) (apo(a)), and its role as the primary carrier of oxidized phospholipids (OxPL). Despite challenges in measurement standardization, a global clinical consensus is emerging, recommending at least a one-time screening for Lp(a) in all adults. The field is on the cusp of a major therapeutic breakthrough with the development of specific Lp(a)-lowering RNA-based therapies, such as pelacarsen and olpasiran, as well as a novel oral agent, muvalaplin, which are in late-stage trials and promise to address this long-recognized risk factor for the first time.

Keywords: Lipoprotein(a), low-density lipoprotein (LDL), Oxidized phospholipids (OxPL), Atherosclerotic cardiovascular disease (ASCVD), Calcific aortic valve stenosis (CAV)

Introduction: The Reemergence of a Causal Risk Factor

Search Strategy

The authors conducted a comprehensive search of PubMed, Scopus, and Google Scholar using keywords: "Lipoprotein(a)", "Low-density lipoprotein (LDL)", "Oxidized phospholipids (OxPL)", "ASCVD", and "CAVS". The search focused on articles published up to July 2025, including meta-analyses, Genome-Wide Association Studies (GWAS), Mendelian randomization, and results from Phase 2 and 3 clinical trials.

Historical Context and Clinical Inertia

Lipoprotein(a) was first discovered in 1963 by Kåre Berg as an LDL antigen.[1] For decades, its role in cardiovascular disease was widely debated, partly due to inconsistent results from early studies that

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used isoform-sensitive assays for apo(a), which failed to measure Lp(a) concentration accurately.[2] This long history led to clinical inertia and a widespread lack of Lp(a) testing, a situation that is only now beginning to change.

Understanding the history of Lp(a) is a critical case study in identifying cardio vascular risk factors. It demonstrates how technical and methodological limitations (i.e., measurement technology) can delay the clinical acceptance of a genuine causal risk factor for decades. Early studies yielded conflicting results regarding the link between Lp(a) and CVD. It was later discovered that early immunoassays were biased by the variable size of apo(a) isoforms, leading to inaccurate quantification.[3] Specifically, smaller, more pathogenic Lp(a) isoforms were often underestimated. The development of isoform-insensitive assays, combined with the power of large-scale genetic studies such as Mendelian randomization, has overcome these limitations.[4] This combination of improved measurement and enhanced causal methodology provided definitive, robust evidence that finally cemented Lp(a)'s role. This is a key lesson for cardiologists: we must critically evaluate not only the clinical data but also the measurement technology and study design behind it when assessing new biomarkers. The "noise" from poor assays obscured the clear "signal" of this risk factor for nearly 50 years.[2]

The Paradigm Shift: Establishing Causality

The turning point in the Lp(a) story occurred around 2009, driven by high-quality epidemiological data, large-scale meta-analyses, Genome-Wide Association Studies (GWAS), and, crucially, Mendelian randomization studies.[5,6] These genetic studies provided strong evidence that elevated Lp(a) is a causal risk factor for ASCVD and CAVS, not merely a biomarker, as they are less susceptible to confounding and reverse causation than observational studies.[2]

The Problem of Residual Risk

Residual cardiovascular risk refers to the risk of cardiovascular events that persists even after patients have achieved guideline-recommended targets for LDL-C, blood pressure, and other modifiable risk factors. Elevated Lp(a) is a significant factor that contributes to this ongoing risk, as it still poses a substantial threat even for patients taking strong statin medications and who have their LDL-C levels well controlled. Approximately 20-25% of the global population, or over 1.4 billion people, have elevated Lp(a) levels (e.g., >50 mg/dL or >125 nmol/L).[2]

The Lp(a) Particle: Structure, Genetics, and Metabolism

A Unique Molecular Architecture

The Lp(a) particle has a core like LDL, which includes lipids and one molecule of apolipoprotein B-100 (apoB), and it has a large protein called apolipoprotein A (apo(a)) attached to it by a single disulfide bond. The Lp(a) particle has a core like LDL, which includes lipids and one molecule of apolipoprotein B-100 (apoB), and it has a large protein called apolipoprotein A (apoA) attached to it by a single disulfide bond.

The structure of apo(a) is remarkable for its high homology to plasminogen, comprising multiple copies of a kringle IV (KIV) domain (specifically KIV-2 repeats), one kringle V (KV) domain, and a proteolytically inactive protease domain.[7] This structural mimicry is the basis for Lp(a)'s antifibrinolytic properties.[7,8]

The Genetic Basis of Lp(a) Levels

Plasma Lp(a) levels are overwhelmingly (70% to ≥ 90%) genetically determined, making it one of the most heritable cardiovas-

cular risk factors. The primary genetic locus is the LPA gene on chromosome 6q2.6-2.7, which evolved from the plasminogen (PLG) gene approximately 40 million years ago in Old World primates.[9]

The most important genetic determinant is the KIV-2 copy number variation (CNV), which is strongly and inversely correlated with plasma Lp(a) concentration.[10] A lower number of KIV-2 repeats results in a smaller apo(a) isoform, which is more efficiently synthesized and secreted from hepatocytes, leading to higher plasma Lp(a) levels. Conversely, larger isoforms are more prone to intracellular degradation.[10] This inverse relationship between KIV-2 CNV and Lp(a) concentration is a central tenet linking genetics, molecular biology, and clinical risk. An LPA gene with many KIV-2 repeats produces a large, complex apo(a) protein that is more difficult to fold and secrete, leading to increased intracellular retention and degradation.

In contrast, a gene with fewer repeats produces a smaller, simpler apo(a) protein that is synthesized and secreted much more efficiently. Thus, a "smaller gene" (fewer repeats) leads to a "bigger clinical problem" (higher plasma Lp(a)). This theory explains why Lp(a) is a lifelong trait, not regulated by feedback mechanisms like LDL-C, but rather a consequence of the inherent efficiency of a genetically determined production line, accounting for the 1,000-fold variation in levels across the population.[2]

Other genetic factors, such as single-nucleotide polymorphisms (SNPs) in and around the LPA locus (e.g., rs10455872, rs3798220), also independently influence Lp(a) levels and are associated with ASCVD risk. Lp(a) levels and LPA gene architecture also vary significantly between ethnicities. For example, individuals of African ancestry have, on average, 2- to 3-fold higher Lp(a) concentrations than those of European or Asian descent.[2]

Synthesis and Catabolism

ApoA is synthesized primarily in the liver. The assembly of the mature Lp(a) particle (covalent linkage of apo(a) to apoB on an LDL particle) is thought to occur extracellularly, possibly on the hepatocyte surface.[11] The catabolic pathway for Lp(a) is not fully understood. Still, it appears to be largely independent of the LDL receptor, which is why statins are not effective at lowering Lp(a) levels. The kidney is known to play a role in the excretion of apo(a) fragments.[12]

Pathophysiology: The Triple Threat of Atherogenesis, Inflammation, and Thrombosis

The pathophysiology of Lp(a) can be understood through three synergistic mechanisms, rendering it a "triple threat." It delivers cholesterol to the plaque (atherogenesis), incites potent inflammation via OxPL (inflammation), and impairs the body's ability to dissolve clots (thrombosis), creating a perfect storm for atherothrombotic events.

Pro-Atherogenic Effects

Like LDL, the Lp(a) particle can penetrate the endothelium and accumulate in the arterial intima. The LDL-cholesterol component of the Lp(a) particle directly contributes to the lipid content of the plaque and promotes foam cell formation. On an equimolar basis, Lp(a) is considered more atherogenic than LDL.[13]

Pro-Inflammatory Cascade

This is a key mechanism that distinguishes Lp(a) from LDL. Lp(a) is the primary carrier of pro-inflammatory oxidized phospholipids (OxPL) in human plasma.[14,15] Lp(a)'s role as the primary carrier of OxPL is perhaps its most critical pathological feature, making it a "Trojan horse" that delivers a potent inflammatory payload

directly to the vessel wall. This characteristic explains why its cardiovascular risk is greater than what would be predicted by its cholesterol content alone.[14] Measuring Lp(a) is not just measuring another cholesterol particle; it is assessing the body's burden of a highly inflammatory and prothrombotic molecule. This is why simply lowering LDL-C is insufficient in patients with high Lp(a), as the inflammatory and thrombotic risk persists.

These OxPL promote endothelial dysfunction, induce the expression of adhesion molecules like VCAM-1, and stimulate monocyte recruitment into the vessel wall. Furthermore, OxPL stimulates macrophages to adopt a pro-inflammatory phenotype, secreting cytokines such as IL-1β, IL-6, and TNF-α, perpetuating a local inflammatory cycle within the plaque.[15,16]

Pro-Thrombotic and Antifibrinolytic Actions

This mechanism is a direct consequence of the structural homology between apo(a) and plasminogen.[7] Apo(a) competes with plasminogen for binding to fibrin and cell surfaces, thereby inhibiting the conversion of plasminogen to plasmin, the primary enzyme for clot dissolution. This antifibrinolytic effect promotes clot persistence and stabilization, which is particularly dangerous in the context of plaque rupture, directly linking atherosclerosis to thrombosis.[8]

The Clinical Spectrum of Lp(a)-Associated Disease

Atherosclerotic Cardiovascular Disease (ASCVD)

* Coronary Artery Disease (CAD): There is robust evidence from meta-analyses and Mendelian randomization studies showing a continuous, independent, and causal relationship between Lp(a) levels and the risk of Myocardial Infarction (MI) and CAD. The association is influential in the development of premature ASCVD. For instance, one meta-analysis found that elevated Lp(a) increased the odds ratio for premature CAD by 2.44.[17]

* Ischemic Stroke and Peripheral Artery Disease (PAD): The association extends to ischemic stroke and PAD, although the relationship may not be as strong as for CAD. A meta-analysis found an odds ratio of 2.56 for premature PAD.[18]

Calcific Aortic Valve Stenosis (CAVS)

CAVS is a significant health issue that is strongly linked to high levels of Lp(a), as demonstrated by various studies and genetic research.[19-21] The proposed mechanism is that Lp(a) particles and their OxPL cargo infiltrate the aortic valve leaflets, promoting inflammation, osteogenic differentiation of valvular interstitial cells, and microcalcification, which drives the progression from aortic sclerosis to clinically significant stenosis.[20]

The causal link between Lp(a) and CAVS has challenged the traditional view of aortic stenosis as a purely "degenerative" or "wear-and-tear" disease of aging, reframing it as a lipid-driven, inflammatory disease process akin to atherosclerosis. This is a significant paradigm shift. Suppose CAVS is a modifiable, lipid-driven disease. In that scenario, it presents a novel opportunity for the development of pharmacological therapies aimed at slowing or preventing the progression of CAVS, which are currently unavailable. The cardiovascular outcome trials of Lp(a)-lowering drugs (e.g., Lp(a) HORIZON, OCEAN(a)-Outcomes) are therefore not just testing the hypothesis for ASCVD, but also for CAVS. A positive result would revolutionize the management of valvular heart disease.

Evidence also suggests that high Lp(a) is associated not only with the incidence of CAVS but also with faster hemodynamic progression and a higher risk of adverse outcomes, including the need for aortic valve replacement (AVR).[4,22,23] One study found that patients with Lp(a) ≥125 nmol/L had a 58% higher risk of AVR.

Measurement and Clinical Application

The Standardization Challenge

A major challenge in measuring Lp(a) is the vast size heterogeneity of the apo(a) protein among individuals, due to the KIV-2 CNV. Many early immunoassays used antibodies that bound to the repetitive KIV-2 domains, making them "isoform-sensitive." This phenomenon led to an underestimation of Lp(a) in individuals with minor, high-risk isoforms and an overestimation in those with large, lower-risk isoforms. Modern, standardized assays are therefore designed to be "isoform-insensitive", a critical requirement for accurate risk assessment.[24,25]

Units of Measurement: Mass (mg/dL) vs Molar (nmol/L)

Lp(a) is reported in two central units: mass (mg/dL), which measures the total weight of the Lp(a) particle (protein, lipid, carbohydrate), and molar concentration (nmol/L), which measures the number of Lp(a) particles. There is a clear consensus from expert bodies (e.g., IFCC, EAS) that nmol/L is the preferred unit because it reflects the particle number, which is the actual driver of risk, and is not confounded by the variable molecular weight of different apo(a) isoforms.[3,26]

Crucially, there is no reliable universal conversion factor between mg/dL and nmol/L, as the conversion depends on the patient's specific apo(a) isoform size. While a rough approximation of nmol/L ~2.0-2.5 x mg/dL is sometimes used, it is imprecise and should be avoided for clinical decision-making purposes.[3]

Screening and Risk Assessment Guidelines

Recommendations from major professional societies are becoming increasingly aligned, with a growing consensus in favor of universal screening (see Table 1).

* 2022 EAS Consensus & 2019 ESC/EAS Guidelines: Recommend measuring Lp(a) at least once in every adult's lifetime. They state that having a very high level of Lp(a) over 180 mg/dL (or over 430 nmol/L) indicates a lifetime risk like that of someone with heterozygous familial hypercholesterolemia (HeFH).

* 2018 AHA/ACC Guideline: Classifies Lp(a) ≥50 mg/dL (or ≥125 nmol/L) as a "risk-enhancing factor" that can be used to guide the decision to initiate statin therapy in patients with borderline or intermediate 10-year ASCVD risk.

* National Lipid Association (NLA) & Canadian Cardiovascular Society (CCS): Also recommend screening in adults, particularly those with a personal or family history of premature ASCVD, using risk thresholds around 50 mg/dL or 100-125 nmol/L.

Table 1 Summary of International Professional Society Guideline Recommendations for Lp(a)

Society/Guideline	Screening Recommendation	Key Risk Thresholds
2022 EAS Consensus[2]	Recommends measuring Lp(a) at least once in all adults to assess lifetime ASCVD risk.	≥50 mg/dL (≥125 nmol/L) considered a risk factor.
2019 ESC/EAS Guidelines[27]	Lp(a) measurement should be considered at least once in each adult's lifetime to identify those with very high inherited levels.	>180 mg/dL (>430 nmol/L) confers a lifetime risk equivalent to HeFH.
2018 AHA/ACC Guideline[28]	Measurement may be considered to aid in clinical decision-making for statins in adults with borderline (5% to <7.5%) and intermediate (≥7.5% to <20%) 10-year risk.	≥50 mg/dL (≥125 nmol/L) considered a "risk-enhancing factor."
2021 Canadian Cardiovascular Society (CCS)[29]	Recommends a one-time measurement of Lp(a) in all adults to refine risk assessment.	>50 mg/dL (>100 nmol/L) considered high risk.
2019 HEART UK[30]	Lp(a) should be measured in those with a personal/family history of premature ASCVD, first-degree relatives with high Lp(a), FH, or borderline 10-year risk.	Graded risk: Moderate (90-200 nmol/L), High (200-400 nmol/L), Very High (>400 nmol/L).
2019 National Lipid Association (NLA)[31]	Measurement is reasonable for risk assessment in adults with a family history of premature ASCVD, a personal history of premature ASCVD, or severe hypercholesterolemia.	≥50 mg/dL (≥100 nmol/L).

Pharmacological Management: From Current Limitations to Emerging Hope

Effects of Current Lipid-Lowering Therapies

* Lifestyle Modification: Diet and exercise have little to no effect on Lp(a) levels.[2]

* Statins: The effect is controversial and variable. Some meta-analyses suggest statins may modestly increase Lp(a) levels (8-24%), while others show no significant change. However, statins remain critical for reducing overall ASCVD risk via LDL-C lowering.[32]

* Ezetimibe: Reported to have a modest ~7% lowering effect on Lp(a), which is likely not clinically significant, and some studies show no effect.[33]

* Niacin: While niacin can lower Lp(a) by ~20-25%, significant side effects and a lack of evidence for cardiovascular event reduction in the statin era limit its use.[34,35]

* PCSK9 Inhibitors (Evolocumab, Alirocumab): These agents moderately lower Lp(a) by ~20-30%. Post-hoc analyses of the cardiovascular outcome trials (e.g., FOURIER, ODYSSEY OUTCOMES) suggest that patients with higher baseline Lp(a) derive greater absolute benefit from treatment, likely due to the combination of profound LDL-C reduction and moderate Lp(a) lowering.[36,37]

* Lipoprotein Apheresis: This is the only currently approved and highly effective treatment, achieving a mean interval reduction of 25-40%.[38] However, it is invasive, expensive, and accessible to only a minimal number of high-risk patients.

The New Frontier: Specific Lp(a)-Lowering Drugs

This is the most exciting area of current research, with drugs specifically designed to inhibit the synthesis of apo(a) in the liver.

Antisense Oligonucleotides (ASOs): Pelacarsen (TQJ230)

* Mechanism of Action: A GalNAc-conjugated ASO that specifically targets hepatocytes. It binds to the LPA mRNA, leading to its degradation by RNase H and preventing the translation of the apo(a) protein.[39]

* Clinical Data: Phase 2 results showed a potent, dose-dependent reduction in Lp(a) of up to 80%.[40,41]

* Pivotal Trial: Lp(a) HORIZON (NCT04023552): An ongoing Phase 3 Cardiovascular Outcome Trial (CVOT) of 8,325 participants with established CVD and Lp(a) ≥70 mg/dL, testing pelacarsen 80 mg subcutaneously monthly vs. placebo, with MACE as the primary endpoint. Topline results are expected in 2025.

Small Interfering RNA (siRNA): Olpasiran (AMG 890), Zerlasiran, and others

* Mechanism of Action: Also, GalNAc-conjugated, these siRNAs use the RNA interference (RNAi) mechanism to cleave and degrade LPA mRNA, thereby inhibiting apo(a) synthesis.[42]

* Clinical Data (Olpasiran): The Phase 2 OCEAN (a)-DOSE study demonstrated profound Lp(a) reductions of >95% with doses of 75 mg or 225 mg every 12 weeks. The effect is durable, with a ~40-50% reduction maintained nearly a year after the last dose.[42,43]

* Pivotal Trial: OCEAN (a)-Outcomes (NCT05581303): An ongoing and fully enrolled Phase 3 CVOT of ~7,000 patients with ASCVD and Lp(a) ≥ 200 nmol/L, testing olpasiran vs. placebo every 12 weeks. The primary endpoint is CHD death, MI, or urgent coronary revascularization. Results are anticipated around 2026.

Novel Oral Agent: Muvalaplin

* Mechanism of Action: A first-in-class oral small molecule that acts via a different mechanism, disrupting the non-covalent interaction between apo(a) and apoB, thereby inhibiting the final step of Lp(a) particle assembly.[44]

* Clinical Data: Phase 1 results showed a 63-65% reduction in Lp(a) versus placebo. The Phase 2 study (ALPACA) is now fully enrolled. This represents a desirable option for patients who prefer an oral therapy.[44]

Table 2 Efficacy of Current and Emerging Therapies in Lowering Lp(a)

Therapy/Class	Mechanism of Action	Average Percent Lp(a) Reduction	Key Evidence/Trials
Statins	HMG-CoA reductase inhibitor	8% to 24% or no effect	Meta-analyses[32,45]
Ezetimibe	NPC1L1 inhibitor	~7% reduction or no effect	Meta-analyses33
Niacin	Unclear	~20-25% reduction	AIM-HIGH, HPS2-THRIVE[34,35]
PCSK9 Inhibitors	Inhibit PCSK9, upregulate LDLR	~20-30% reduction	FOURIER, ODYSSEY OUTCOMES[36,37]
Lipoprotein Apheresis	Removes apoB-containing lipoproteins	~25-40% reduction (mean interval)	Observational studies[38]
Pelacarsen (ASO)	Degrades LPA mRNA (RNase H)	~80% reduction	Phase 2 trial[39,40,41]
Olpasiran (siRNA)	Degrades LPA mRNA (RNAi)	>95% reduction	OCEAN(a)-DOSE (Phase 2)[42,46,47]
Muvalaplin (Oral)	Inhibits Lp(a) assembly	~63-65% reduction	Phase 1 trial[14,48]

Table 3 Design and Key Features of Pivotal Phase 3 Lp(a)-Lowering Trials

Trial Name	Investigational Drug	Mechanism of Action	Patient Population	Lp(a) Inclusion Criteria	Primary End-point	Expected Completion
Lp(a) HORIZON[49]	Pelacarsen	Antisense Oligonucleotide (ASO)	Patients with established ASCVD	≥70 mg/dL	MACE-4 (CV death, non-fatal MI, non-fatal stroke, urgent coronary revascularization)	2025
OCEAN(a)-Outcomes[50,51]	Olpasiran	Small Interfering RNA (siRNA)	Patients with established ASCVD	≥200 nmol/L	MACE-3 (CHD death, MI, urgent coronary revascularization)	~2026

Conclusion and Future Directions

Synthesizing the Evidence

Lp(a) is no longer an enigmatic biomarker but a validated, causal therapeutic target. The congruent evidence from genetics, epidemiology, and pathophysiology is undeniable. The immediate clinical imperative is to identify patients with high Lp(a) through screening and to aggressively manage all other modifiable risk factors (especially LDL-C and blood pressure) to mitigate their heightened global risk.

Testing the Lp(a) Hypothesis

The key unanswered question is the "Lp(a) hypothesis": will specific and substantial lowering of Lp(a) translate into a reduction in cardiovascular events? The ongoing Phase 3 CVOTs (Lp(a)HORIZON, OCEAN(a)-Outcomes) are designed to answer this question definitively.[52] Their results will be practice-changing, either by establishing Lp(a) as a new pillar of cardiovascular prevention or by questioning its role as a therapeutic target despite its causal association.

Unanswered Questions and the Path Forward

The field will still face important future questions: What is the optimal degree of Lp(a) lowering for clinical benefit? Are there any long-term, off-target effects of near-total Lp(a) elimination? What will be the role of these agents in primary prevention, especially in those with very high genetic risk but no overt disease? And finally, how will cost-effectiveness and access shape their role in clinical practice?

In conclusion, the field of preventive cardiology is poised for a new era. The clinical validation of Lp(a) lowering would represent one of the most significant advances since the introduction of statins.

References

1. Berg K. A new serum type system in man--the Lp system. Acta Pathol Microbiol Scand. 1963; 59: 369-82.
2. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022; 43 (39): 3925-47.
3. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. J Lipid Res. 2016; 57 (4): 526-37.
4. Capoulade R, Yeang C, Chan KL, et al. Association of Mild to Moderate Aortic Valve Stenosis Progression With Higher Lipoprotein(a) and Oxidized

Phospholipid Levels: A Substudy of the ASTRONOMER Trial. JAMA Cardiol. 2018; 3 (12): 1212-7.
5. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein (a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009; 302 (4): 412-23.
6. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009; 361 (26): 2518-28.
7. McLean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein (a) is homologous to plasminogen. Nature. 1987; 330 (6144): 132-7.
8. Boffa MB, Koschinsky ML. Lipoprotein (a) and cardiovascular disease. Biochem J. 2024; 481 (19):1277-96. doi: 10.1042/BCJ20240037.
9. Utermann G. The mysteries of lipoprotein (a). Science. 1989; 246 (4932): 904-10.
10. Kraft HG, Lingenhel A, Köchl S, et al. Apolipoprotein (a) Kringle IV-2 copy number is a major determinant of plasma lipoprotein(a). Hum Mol Genet. 1996; 5 (10):1599-606.
11. White AL, Lanford RE. Cell surface assembly of lipoprotein(a) in primary cultures of baboon hepatocytes. J Biol Chem. 1994; 269 (46): 28716-23.
12. Boffa MB, Koschinsky ML. Lipoprotein(a) metabolism: potential sites for therapeutic targets. Metabolism. 2013; 62 (4): 479-91.
13. Tsimikas S, Hall JL. Lipoprotein (a) as a Potential Causal Genetic Risk Factor of Cardiovascular Disease: A Rationale for Increased Efforts to Understand its Pathophysiology and Develop Targeted Therapies. JACC. 2012; 60 (8): 716-21.
14. Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. Nat Rev Cardiol. 2016; 13 (1): 35-46.
15. Tsimikas S, Witztum JL. The role of oxidized phospholipids in mediating the pro-inflammatory and pro-atherogenic effects of lipoprotein (a). J Lipid Res. 2008; 49 (8):1697-711.
16. Burkhardt R. Hyperlipidemia and cardiovascular disease: new insights on lipoprotein(a). Curr Opin Lipidol. 2019; 30 (3): 260-1. doi: 10.1097/MOL.0000000000000594.
17. Cai A, Li L, Li S, et al. Lipoprotein(a) and the risk of premature atherosclerotic cardiovascular disease: a systematic review and meta-analysis. EHJ Open. 2024; 4 (3): oeae031.
18. Paré G, Çaku A, McQueen M, et al. Lipoprotein(a) levels and the risk of myocardial infarction, ischemic stroke, and peripheral arterial disease: a Mendelian randomization analysis. Circ Cardiovasc Genet. 2013; 6 (3): 233-40.
19. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013; 368 (6): 503-12.
20. Capoulade R, Chan KL, Yeang C, et al. Causal association of lipoprotein(a) with aortic valve calcification and clinical aortic stenosis. Arterioscler Thromb Vasc Biol. 2015; 35 (8):1849-55.
21. Arsenault BJ, Boekholdt SM, Dubé MP, et al. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective Mendelian randomization study and replication in a case-control cohort. Circ Cardiovasc Genet. 2014; 7 (3): 304-10.
22. Bourgeois R, Gencer B, L'Allier PL, et al. Lipoprotein(a) and the risk of aortic stenosis progression. J Am Coll Cardiol. 2020; 75 (25): 3103-12.

23. Mathieu P, Boulanger MC, Bouchareb R, et al. Lipoprotein(a) and calcific aortic valve stenosis: a systematic review. Can J Cardiol. 2017; 33 (10): 1314-21.
24. Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for coronary artery disease. Am J Cardiol. 1998; 82 (12A): 57U-66U.
25. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. J Lipid Res. 2016; 57 (4): 526-37. doi: 10.1194/jlr.R061648.
26. Kotani K.The Importance of the Harmonization and Standardization of Lipoprotein(a) Measurements. J Atheros and Thromb. 2025; 32 (5). DOI: 10.5551/jat.ED279.
27. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41 (1): 111-88.
28. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2019; 73 (24): e285-e350.
29. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol. 2021; 37 (8): 1129-50.
30. Cegla J, Neely RDG, France M, et al. HEART UK consensus statement on Lipoprotein(a): A call to action. Atherosclerosis. 2019; 291: 62-70.
31. Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. 2019; 13 (3): 374-92.
32. Tsimikas S, et al. Statins increase lipoprotein (a) levels. Eur Heart J. 2020; 41(24): 2275-84.
33. Sahebkar A, Simental-Mendía LE, Pirro M, et al. Impact of ezetimibe on plasma lipoprotein(a) concentrations: Systematic review and meta-analysis of randomized controlled trials. Sci Rep. 2018; 8 (1): 17829.
34. Boden WE, Sidhu MS, Toth PP. The Therapeutic Role of Niacin in Dyslipidemia Management. J Cardiovas Pharmacol Therapeu. 2014; 19 (2): 141-58.
35. AIM-HIGH Investigators, Boden WE, Probstfield JL, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011; 365 (24): 2255-67.
36. Ruscica M, Greco MF, Ferri N, Corsini A. Lipoprotein (a) and PCSK9 inhibition: clinical evidences. Eur Heart J Suppl. 2020; 22 (Suppl L): L53–L56. doi: 10.1093/eurheartj/suaa135.
37. O'Donoghue ML, Fazio S, Giugliano RP, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. Circulation. 2019; 139 (12): 1483-92.
38. Thompson G. Lipoprotein apheresis. Curr Opin Lipidol. 2010; 21 (6): 487-91.
39. Tsimikas S, Viney NJ, Hughes SG, et al. Antisense inhibition of apolipoprotein (a) to lower lipoprotein(a) concentrations in humans. Lancet. 2015; 386 (10002): 1472-83.
40. Bhatia HS, Bajaj A, Goonewardena SN, Moriarty PM. Pelacarsen: Mechanism of action and Lp(a)-lowering effect. J Clin Lipidol. 2025; 19 (5): 1208-22.
41. Viney NJ, van Capelleveen JC, Geary RS, et al. Antisense oligonucleotides targeting apolipoprotein (a) in people with raised lipoprotein(a): two randomised, double-masked, placebo-

controlled, dose-ranging trials. Lancet. 2016; 388 (10057): 2239-53.
42. O'Donoghue ML, Rosenson RS, Gencer B, López JAG. Lepor NE, Baum SJ, et al. for the OCEAN (a)-DOSE Trial Investigators. Small Interfering RNA to Reduce Lipoprotein (a) in Cardiovascular Disease. N Engl J Med. 2022; 387 (20): 1855-64. DOI: 10.1056/NEJMoa2211023.
43. O'Donoghue ML, Rosenson RS, López JAG, Lepor NE, Baum SJ, Elmer Stout E, et al. The Off-Treatment Effects of Olpasiran on Lipoprotein(a) Lowering: OCEAN (a)-DOSE Extension Period Results. J Am Coll Cardiol. 2024; 84 (9): 790-7.
44. Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. JAMA. 2023; 330 (11):1042-53.
45. Tsimikas S, Gordts PLSM, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels. Eur Heart J. 2020; 41 (24): 2275-84. doi: 10.1093/eurheartj/ehz310.
46. O'Donoghue ML, López JAG, Knusel B, Gencer B, Wang H, Wuet Y, et al. Study design and rationale for the Olpasiran trials of Cardiovascular Events And lipoprotein(a) reduction-DOSE finding study (OCEAN(a)-DOSE). Am Heart J. 2022; 251: 61-69. doi: 10.1016/j.ahj.2022.05.004.
47. Rosenson RS, López JAG, Gaudet D, Baum SJ, Stout E, Lepor NE, et al. Olpasiran, Oxidized Phospholipids, and Systemic Inflammatory Biomarkers: Results From the OCEAN(a)-DOSE Trial. JAMA Cardiol. 2025; 10 (5): 482-6. doi: 10.1001/jamacardio.2024.5433.
48. Nicholls SJ, Nissen SE, Fleming C, et al. Muvalaplin, an Oral Small Molecule Inhibitor of Lipoprotein(a) Formation: A Randomized Clinical Trial. JAMA. 2023; 330 (11): 1042-53.
49. Novartis. A Randomized, Double-blind, Placebo-controlled, Multicenter Trial Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With Established Cardiovascular Disease (Lp(a)HORIZON). ClinicalTrials.gov Identifier: NCT04023552.
50. Amgen. A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Olpasiran on Major Cardiovascular Events in Participants with Atherosclerotic Cardiovascular Disease and Elevated Lipoprotein(a) (OCEAN(a) Outcomes). ClinicalTrials.gov Identifier: NCT05581303.
51. Amgen. Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction (OCEAN (a)) - Outcomes Trial. Available at: https://www.amgentrials.com/study/?id=20180244. Accessed July 13, 2025.
52. Tsimikas S. Lipoprotein (a) in the Year 2024: A Look Back and a Look Ahead. Arterio Thrombos, Vasc Biol. 2024; 44 (7): 1485-90. https://doi.org/10.1161/ATVBAHA.124.319483