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LIPOPROTEIN(A) AS AN INDEPENDENT CARDIOVASCULAR RISK FACTOR

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ЛИПОПРОТЕИН (А) КАТО НЕЗАВИСИМ СЪРДЕЧНОСЪДОВ РИСКОВ ФАКТОР

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Abstract. Lipoprotein(a) (Lp(a)) is an independent, genetically determined cardiovascular risk factor that remains underrecognized in clinical practice. Elevated Lp(a) exerts pro-atherogenic, pro-thrombotic, and pro-inflammatory effects, contributing to coronary artery disease, ischemic stroke, and calcific aortic valve stenosis. About 20% of the global population has high Lp(a) (> 50 mg/dL or > 125 nmol/L), associated with a 2-4-fold increased risk of events, independent of low-density lipoprotein cholesterol (LDL-C). Unlike LDL-C, Lp(a) levels are ~90% genetically determined, minimally affected by lifestyle, and stable throughout life. Traditional lipid-lowering therapies (e.g., statins) have little effect on Lp(a). PCSK9 inhibitors provide modest reduction (~ 20-30%), while novel RNA-targeted agents (antisense oligonucleotides, siRNAs) and gene-editing approaches are under active investigation. Recent guidelines, including the 2025 ESC/EAS Focused Update, recognize Lp(a) > 50 mg/dL (~ 105 nmol/L) as a cardiovascular risk-enhancing factor (Class IIa, Level B). They recommend once-in-a-lifetime Lp(a) measurement, particularly in patients at high cardiovascular risk, and emphasize intensive LDL-C lowering in acute coronary syndrome. Bempedoic acid is endorsed for statin-intolerant patients (Class I, Level B), while evinacumab may be considered in homozygous familial hypercholesterolemia (Class IIa, Level B). Emerging evidence also links Lp(a) to atrial fibrillation, broadening its clinical relevance. Large outcome trials of Lp(a)-lowering agents are underway and will determine whether reduction translates into improved cardiovascular outcomes. As one in five adults worldwide has elevated Lp(a), integrating Lp(a) testing into risk assessment and preparing for targeted therapies are critical steps in modern cardiovascular prevention.

Key words: lipoprotein(a); atherosclerosis; thrombosis; risk factor; RNA therapeutics; gene editing; cardiovascular disease

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Резюме. Липопротеин (а) – Lp(a), е независим, генетично обусловен рисков фактор за сърдечносъдови заболявания, който все още не се признава в достатъчна степен в клиничната практика. Повишените нива на Lp(a) оказват проатерогенно, протромботично и провъзпалително действие, допринасяйки за развитието на коронарна болест, исхемичен инсулт и калцифицирана аортна клапна стеноза. Около 20% от световното население има високи нива на Lp(a) (> 50 mg/dL или > 125 nmol/L), което се свързва с 2-4-кратно повишен риск от сърдечносъдови събития, независимо от нивото на холестерола в липопротеините с ниска плътност (LDL-C). За разлика от LDL-C, нивата на Lp(a) са определени генетично в ~ 90%, минимално се влияят от начина на живот и остават стабилни през целия живот. Традиционните терапии за понижаване на липидите (напр. статини) оказват слабо въздействие върху Lp(a). Инхибиторите на PCSK9 осигуряват умерено намаление (~20–30%), докато нови средства, насочени към РНК (антисенсни олигонуклеотиди, siRNA), и подходи за генетично редактиране са в процес на активно проучване. Последните насоки, вкл. „Фокусираното актуализиране“ на ESC/EAS за 2025 г., признават Lp(a) > 50 mg/dL (~ 105 nmol/L) като фактор, повишаващ сърдечно-съдовия риск (Клас IIa, Ниво B). Те препоръчват еднократно измерване на Lp(a) през целия живот, особено при пациенти с висок сърдечно-съдов риск, и наблягат на интензивно понижаване на LDL-C при остър коронарен синдром. Бемпедоиновата киселина се препоръчва за пациенти с непоносимост към статини (Клас I, Ниво B), докато evinacumab може да се разгледа при хомозиготна фамилна хиперхолестеролемия (Клас IIa,

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Ниво B). Нови данни свързват Lp(a) и с предсърдно мъждене, което разширява клиничното му значение. В момента се провеждат мащабни проучвания за резултатите от прилагането на средства за понижаване на Lp(a), които ще установят дали това понижение води до подобрени сърдечносъдови резултати. Тъй като един на всеки 5 възрастни в света има повишени нива на Lp(a), включването на тестовете за Lp(a) в оценката на риска и подготовката за целеви терапии са от решаващо значение в съвременната сърдечно-съдова профилактика.

Ключови думи: липопротеин(а); атеросклероза; тромбоза; рисков фактор; РНК-терапии; генетично редактиране; сърдечно-съдови заболявания

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Introduction

Cardiovascular disease (CVD) remains the leading cause of death globally; according to the World Health Organization (WHO), CVD accounted for an estimated 19.8 million deaths in 2022 [7]. While traditional risk factors (e.g., LDL-C, hypertension, diabetes, smoking) are well established, lipoprotein(a) – abbreviated Lp(a) – has gained recognition as a genetic and independent contributor to atherosclerotic risk [1-2, 31] that historically has been underappreciated. Lp(a) is a plasma lipoprotein particle structurally similar to LDL, consisting of an LDL-like core (apolipoprotein B-100 plus cholesterol and triglyceride) covalently attached to apolipoprotein(a) (apo(a)). Apo(a) contains multiple kringle domains (resembling plasminogen) that endow Lp(a) with unique pathological properties [4]. Elevated Lp(a) levels are primarily genetically determined (heritability ≥70–90%) and largely unaffected by diet or lifestyle [3, 5, 30]. Concentrations are stable from early childhood onward and vary markedly between individuals and ethnic groups, with highest levels observed in those of African ancestry [5-6]. Notably, the risk conferred by a given Lp(a) concentration appears to be similarly elevated across different ethnicities [5], and women may experience slight Lp(a) increases after menopause (potentially due to hormonal changes).

The purpose of this work is to provide an updated overview of lipoprotein(a) [Lp(a)] as an independent, genetically determined risk factor for cardiovascular disease. Despite strong evidence linking elevated Lp(a) to atherosclerosis, thrombosis, and valvular disease, it remains underrecognized in clinical practice. This review aims to synthesize current knowledge on Lp(a) pathophysiology, epidemiology, and clinical impact, highlight recent guideline updates, and discuss emerging therapeutic strategies–including RNA-based and gene-editing approaches. By summarizing available evidence, the work seeks to emphasize the need for routine Lp(a) measurement, refine cardiovascular risk assessment, and prepare clinicians for the integration of novel Lp(a)-targeted therapies into practice.

Methods

This narrative review was informed by a focused literature search of PubMed from database inception to 15 December 2025, supplemented by manual review of reference lists and contemporary society guidelines and consensus statements. Search terms included “lipoprotein(a)”, “Lp(a)”, “LPA”, “atherosclerosis”, “calcific aortic valve stenosis”, “antisense oligonucleotide”, “small interfering RNA”, “pelacarsen”, “olpasiran”, and “outcomes trial”. We prioritized randomized trials, large prospective cohorts, meta-analyses, and guideline/consensus documents relevant to cardiovascular risk assessment and management.

Table 1. Practical interpretation of lipoprotein(a) for cardiovascular risk assessment

Domain	Practical guidance	Key notes
Who to test	Measure Lp(a) at least once in adulthood (earlier in high-risk settings).	Particularly useful in premature ASCVD, family history of premature (in men younger than 55 years or women younger than 65 years) ASCVD, severe hypercholesterolemia, or unexplained residual risk.
Units and assays	Report in nmol/L when available; interpret mg/dL with caution.	No universal conversion between mg/dL and nmol/L due to apo(a) isoform size and assay variability.
Risk-enhancing threshold	> 50 mg/dL or > 125 nmol/L is commonly used to define elevated Lp(a).	Interpret as a continuous risk factor; higher levels generally confer higher risk.
Repeat testing	Usually not required (levels largely genetically determined).	Repeat only if major physiological changes or suspected laboratory issues.
Management implication	Treat elevated Lp(a) as a residual risk marker: intensify LDL-C lowering and global risk factor control.	Dedicated Lp(a)-lowering outcome data are pending; current practice focuses on risk mitigation.
Calcific aortic valve stenosis	Consider Lp(a) assessment in patients with early/accelerated aortic valve calcification/stenosis.	Mechanistic link via oxidized phospholipids and pro-inflammatory signaling.

Table 2. Therapies influencing lipoprotein(a): expected effect and evidence status

Therapy	Typical effect on Lp(a)	Outcome evidence specific to Lp(a)	Practical notes / status
Statins	Neutral to modest increase (variable).	No evidence that Lp(a) reduction mediates benefit.	Remain foundational for LDL-C lowering and ASCVD risk reduction.
Ezetimibe	Minimal change (small reductions reported).	No Lp(a)-specific outcome evidence.	Adjunct for LDL-C targets.
PCSK9 inhibitors	Modest reduction (~20–30%).	Lp(a) reduction may contribute to observed outcome benefit, but causality not established.	Useful for high-risk patients; especially when LDL-C targets not achieved.
Niacin	Moderate reduction (~20–30%).	No net cardiovascular outcome benefit; adverse effects limit use.	Generally, not recommended for routine use.
Lipoprotein apheresis	Large acute reduction; requires repeated sessions.	Outcome data are observational/registry-based.	Consider in selected very-high-risk patients with progressive ASCVD.
Pelacarsen (ASO)	Large reductions in phase 2 studies.	Dedicated outcomes trial ongoing/awaited.	Targets hepatic apo(a) synthesis; not yet approved for outcomes indication.
Olpasiran / other siRNA agents	Large reductions in phase 2 studies.	Dedicated outcomes trials ongoing/awaited.	Long duration of effect; not yet approved for outcomes indication.
Gene-editing approaches	Preclinical/ early clinical exploration.	No evidence of outcomes.	Potential future approach; safety and long-term follow-up critical.

Pathophysiology of Lipoprotein(a)

Lp(a) shares structural elements with LDL but harbors the distinctive apo(a) tail, which fundamentally alters its biological behavior. Key pathophysiological properties of Lp(a) include:

Atherogenicity: Lp(a) avidly infiltrates the endothelium and binds to components of the arterial wall. Its content of cholesterol and oxidized phospholipids accelerates plaque formation. Lp(a) uptake by macrophages promotes foam cell formation and plaque growth. On a per-particle basis, Lp(a) may be substantially more atherogenic than LDL, likely due to its pro-oxidative and pro-inflammatory cargo [8-9].

Thrombogenicity: The kringle domains of apo(a) closely resemble plasminogen. However, apo(a) lacks plasminogen's enzymatic activity and instead acts as a competitive inhibitor of plasminogen binding to fibrin. High Lp(a) impairs fibrinolysis and promotes thrombus formation on ruptured plaques. Lp(a) also carries coagulation factor domains and pro-inflammatory oxidized phospholipids that stimulate tissue factor expression, compounding its thrombogenic potential [10].

Inflammation & Oxidized Lipids: Lp(a) is a carrier of oxidized phospholipids (OxPL), which are potent mediators of vascular inflammation. Elevated Lp(a) levels are associated with increased OxPL on apolipoprotein B-100 particles, which stimulate endothelial cells and immune cells to produce cytokines (e.g., interleukin-6, interleukin-1β, tumor necrosis factor-α) and adhesion molecules, contributing to endothelial dysfunction and plaque vulnerability [11, 48]. Lp(a)-associated OxPL have also been implicated in plaque calcification and aortic valve stenosis [11, 48], linking Lp(a) to valvular disease pathogenesis.

Lifelong Exposure: Because Lp(a) levels are genetically determined and stable from early life, individuals with elevated Lp(a) experience continuous, lifelong exposure to its atherothrombotic effects. Smaller apo(a) isoforms (fewer kringle IV repeats) are associated with higher Lp(a) levels due to faster hepatic production [5, 12], further amplifying cumulative risk over a lifetime.

Epidemiology and Clinical Significance

Lp(a) levels exhibit a skewed distribution in general population. While median levels are low (often < 10 mg/dL), a significant minority have markedly elevated Lp(a). Approximately 20% of individuals have Lp(a) > 50 mg/dL or > 125 nmol/L, and about 5-10% exceed 90 mg/dL [13]. Around 1% of the population may have extremely high Lp(a) levels (> 150 mg/dL) [13]. Lp(a) values are also presented in nmol/L, as this unit is more informative given the substantial interindividual variation in particle size, which renders expression in mg/dL insufficiently reliable for result comparability and accurate cardiovascular risk stratification. Genetic factors are the dominant determinant of Lp(a) concentration: the LPA gene – particularly the number of kringle IV repeats in apo(a) – governs over 90% of Lp(a) variability [12, 14]. Smaller apo(a) isoforms with fewer kringle repeats are associated with significantly higher Lp(a) concentrations, as noted above. Because the LPA genotype is stable throughout life, Lp(a) levels remain relatively constant from early childhood. Environmental and lifestyle factors have minimal impact on Lp(a) levels, though acute illness or systemic inflammation may cause temporary fluctuations [15].

Significant ethnic differences in Lp(a) distribution exist individuals of African descent tend to have higher median Lp(a) levels than those of European or Asian ancestry [6, 16]. Despite these differences, elevated Lp(a) appears to confer cardiovascular risk across all populations, and there is no established "ethnic-specific" threshold for risk [5]. Notably, some studies suggest post-menopausal women have slightly higher Lp(a) levels than pre-menopausal women, potentially due to hormonal influences [17].

Elevated Lp(a) increases the risk of coronary artery disease, ischemic stroke, and aortic valve stenosis, independent of traditional lipids and risk factors [1, 18-19]. Mendelian randomization analyses and large prospective studies have established Lp(a) as a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and for calcific aortic valve disease [20-21]. High Lp(a) contributes significantly to "residual risk" – the risk of events that remains in patients despite optimal control of LDL-C and other risk factors. Therefore, Lp(a) measurement can refine cardiovascular risk assessment by identifying individuals at higher risk that would not be evident from conventional risk factors alone. In clinical practice, Lp(a) should be considered in comprehensive risk assessment strategies, especially in patients with a family history of premature ASCVD or in those who, despite optimal therapy of standard risk factors, continue to experience vascular events.

Measurement of Lipoprotein(a)

Accurate measurement of Lp(a) is essential for proper risk assessment. However, measuring Lp(a) has historically been challenging due to the structural heterogeneity of apo(a) isoforms, particularly variations in the number of kringle IV repeats which affect the size of the molecule and immunoreactivity in assays. Key considerations in Lp(a) measurement include:

Assay Techniques: Immunoassays are the most widely used method for Lp(a) measurement, including enzyme-linked immunosorbent assays (ELISA), immunoturbidimetry, and latex-enhanced immunoassays. To minimize inaccuracies, assays should use isoform-insensitive antibodies that can detect different apo(a) isoforms regardless of size. Some newer methods employ monoclonal/polyclonal antibody blends or mass spectrometry for higher precision and consistency.

Units and Calibration: Lp(a) can be reported either in mass concentration (mg/dL) or molar concentration (nmol/L). The molar unit is increasingly preferred, as it reflects particle number and is less influenced by apo(a) isoform size. Importantly, conversion between mg/dL and nmol/L is non-linear and assay-dependent; there is no universal conversion factor. Standardization using international reference material (e.g., IFCC SRM 2B) is crucial to harmonize results across laboratories [22].

Pre-Analytical Considerations: Lp(a) levels are stable in both EDTA plasma and serum and do not require a fasting sample. Lp(a) shows no meaningful circadian variation or postural changes. However, during acute inflammatory illness or other acute-phase reactions, Lp(a) levels can transiently decrease (since Lp(a) behaves as a negative acute-phase reactant). Therefore, testing is ideally performed when the patient is in a steady, baseline state of health (i.e., not during acute illness) [23].

Repeat Testing: Because Lp(a) levels are genetically determined and generally stable over a lifetime, repeat testing is usually unnecessary. One measurement is often sufficient for risk stratification, unless a patient undergoes a specific Lp(a)-lowering therapy and the response needs to be evaluated. Even then, given the long half-life and production rate of Lp(a), frequent measurements are not typically required.

Interpretation: Risk thresholds for Lp(a) are not universally agreed upon, but consensus guidelines provide some guidance. Levels < 30 mg/dL (< 75 nmol/L) are generally considered low/normal, 30-50 mg/dL (75-125 nmol/L) intermediate, and > 50 mg/dL (> 125 nmol/L) high. Some experts propose that very high risk may be present at Lp(a) levels > 100 mg/dL (≈ 250 nmol/L), especially in the context of ASCVD. It is important to interpret Lp(a) values in the context of the patient's overall risk factor profile; for example, an Lp(a) of 60 mg/dL may have different implications in a young patient with premature family history versus an older patient with numerous other risk factors.

Current Challenges in Clinical Management

Despite growing recognition of Lp(a) as a causal cardiovascular risk factor, its routine assessment and management face several challenges:

Limited Awareness: Many clinicians and patients are unfamiliar with Lp(a) or unaware of its significance. Consequently, Lp(a) testing is often omitted in standard cardiovascular risk evaluations, particularly in primary prevention settings. Education is needed to increase awareness of Lp(a) and its risks.

Lack of Specific Therapies (Until Recently): Statins, while highly effective for lowering LDL-C, have minimal effect on Lp(a) levels and may even raise Lp(a) slightly in some individuals [27]. Other older therapies like niacin can reduce Lp(a) by ~20-30%, but niacin's use has declined due to its side effects and lack of clear cardiovascular outcome benefit in the modern era [25-26]. Likewise, estrogen therapy can lower Lp(a) modestly, but is not indicated for this purpose due to risk/benefit concerns. Until recently, no approved medications specifically targeted Lp(a) reduction, creating a gap in management for high-Lp(a) patients.

Residual Risk: Patients with elevated Lp(a) often remain at elevated risk for cardiovascular events even when LDL-C, blood pressure, and other factors are well-controlled. This "residual risk" has become increasingly recognized [20, 28]. For example, in post-ACS patients on intensive statin therapy, those with high Lp(a) continue to have higher event rates than those with low Lp(a) [28]. Thus, high Lp(a) is a major contributor to residual cardiovascular risk, emphasizing the need for therapies beyond standard LDL-lowering.

Lipoprotein Apheresis: In certain high-risk individuals with markedly elevated Lp(a) and progressive ASCVD (e.g., recurrent events despite optimal medical therapy), lipoprotein apheresis has been used as a treatment to acutely lower Lp(a). Apheresis can reduce Lp(a) levels by roughly 60–75% per session [29] and has been associated with slowed progression of ASCVD and event reduction in observational studies [29]. However, apheresis is costly, invasive, and not widely available; it typically needs to be performed every 1–2 weeks. Guidelines in some countries (e.g., Germany) recommend considering apheresis if Lp(a) >60 mg/dL and LDL-C is controlled but progressive disease continues [29]. The limited accessibility and burden of apheresis make it a niche therapy.

Guideline Implementation: As of 2022–2025, major society documents (including the 2022 European Atherosclerosis Society consensus statement and the 2025 ESC/EAS focused update) have incorporated Lp(a) testing recommendations – generally advocating at least once-in-a-lifetime measurement, especially in those at higher risk [4]. However, implementation in practice remains inconsistent globally. Many healthcare systems do not yet include routine Lp(a) screening, and insurance coverage for the test can be variable. Overcoming this inertia requires both physician education and possibly advocacy for guideline adoption.

Need for Education: Both healthcare providers and the public would benefit from greater education about Lp(a). Patients with a strong family history of premature heart disease, for example, should know how to ask about Lp(a) testing. Clinicians need up-to-date information on how to interpret Lp(a) levels and what to do if a patient has high Lp(a). Educational initiatives by cardiovascular societies and lipid organizations are underway to fill this gap.

Emerging Therapeutic Approaches

Given the limitations of traditional lipid-lowering therapies in addressing elevated Lp(a), a number of novel and targeted treatments have emerged. These therapies show substantial promise in meeting the unmet need for effective Lp(a) reduction:

PCSK9 Inhibitors: Originally developed to lower LDL-C, the monoclonal antibodies evolocumab and alirocumab have also been found to lower Lp(a) by roughly 20–30% on average [32-33]. This Lp(a)-lowering effect is thought to result from enhanced clearance of Lp(a) particles via upregulated LDL receptors when LDL-C levels are very low. While PCSK9 inhibitors are not specifically indicated for high Lp(a), patients with concomitant LDL-C and Lp(a) elevation may derive dual benefit. Notably, a post-hoc analysis of the ODYSSEY Outcomes trial (alirocumab in post-ACS patients) suggested that the reduction in Lp(a) contributed to a portion of the observed cardiovascular risk reduction [9]. PCSK9 inhibitors thus represent a partially effective therapy for Lp(a), pending the availability of dedicated Lp(a)-targeted drugs.

Antisense Oligonucleotides (ASOs): Antisense therapy targeting LPA mRNA has demonstrated substantial Lp(a) reductions in clinical trials. Pelacarsen (TQJ230), an antisense oligonucleotide against apo(a) mRNA, reduced Lp(a) in a dose-dependent manner (approximately 35% to 80% at 6 months, depending on dose) in patients with established ASCVD and elevated baseline Lp(a). [34] Pelacarsen is currently being evaluated in a phase 3 cardiovascular outcomes trial (Lp(a) HORIZON) to determine whether Lp(a) lowering translates into fewer cardiovascular events [35]. If positive, this could lead to the first approved therapy specifically targeting elevated Lp(a).

Small Interfering RNA (siRNA): Olpasiran (AMG 890) is an siRNA that reduces hepatic apo(a) production. In the OCEAN(a)-DOSE phase 2 program, olpasiran administered every 12 or 24 weeks produced dose-dependent reductions in Lp(a) (up to approximately 100% at higher doses) in patients with ASCVD and baseline Lp(a) >150 nmol/L. [37-38] Off-treatment follow-up showed persistent Lp(a) lowering for months after the last dose. [36] The phase 3 OCEAN(a)-Outcomes trial is ongoing to determine whether Lp(a) lowering reduces cardiovascular events [39].

Gene Editing: Genome editing technologies are being explored for several lipid targets, and may be adaptable to Lp(a) in the future; however, translation to LPA remains investigational. At present, clinical experience is limited, and rigorous evaluation of efficacy, durability, and off-target safety will be required before any genome-editing approach can be considered for routine Lp(a) management [40].

Vaccines and Other Approaches: Other innovative strategies under investigation include therapeutic vaccines to induce antibodies against apo(a), and small-molecule inhibitors that might disrupt the assembly of Lp(a) particles. These are mostly in preclinical stages. One such approach is an attempt to inhibit the binding of apo(a) to apoB, thereby preventing Lp(a) particle formation. While early, these explorations underscore the breadth of the Lp(a)-targeted therapeutic pipeline.

Overall, these emerging therapies represent a paradigm shift in the management of high Lp(a). Whereas patients and clinicians historically had to “accept” high Lp(a) as an untreatable risk factor (beyond managing other risks), the landscape is rapidly changing. Pending results of the ongoing outcome trials, it is anticipated that one or more of these novel agents will become available and can be integrated into practice – particularly for high-risk patients with established ASCVD and elevated Lp(a) levels.

Lp(a) and Atrial Fibrillation: An Emerging Link

Recent studies have begun to explore the association between elevated Lp(a) levels and atrial fibrillation (AF), the most common sustained cardiac arrhythmia. Traditionally, AF has been linked to factors such as aging, hypertension, obesity, and atrial remodeling. However, Lp(a) may also play a contributory role through inflammatory and pro-thrombotic mechanisms:

Epidemiological Data: Several observational studies have reported that individuals with Lp(a) concentrations ≥ 50 mg/dL are at increased risk of developing AF. In a retrospective cohort study involving more than 75,000 patients (pooled across three centers), those with Lp(a) ≥50 mg/dL had a significantly higher incidence of new-onset AF over a median ~9-year follow-up, compared to those with low Lp(a) [41-42]. The adjusted hazard ratio was around 1.11 (11% increased risk) per high Lp(a) status, even after controlling for other AF risk factors [41-42]. Additionally, genetic analyses (Mendelian randomization) support a potential causal link, as LPA gene variants associated with high Lp(a) have been linked to greater AF risk in some research.

Biological Plausibility: Lp(a) may promote atrial fibrillation via its contributions to vascular inflammation and thrombogenesis. High Lp(a) is accompanied by elevated circulating OxPL and inflammatory cytokines (e.g., IL-6, TNF-α), which could facilitate atrial fibrosis and structural remodeling – substrates for AF. Prothrombotic effects of Lp(a) (e.g., impaired fibrinolysis, microthrombosis in the atrium) might also create an environment that favors AF initiation or maintenance. These mechanisms are still being investigated, but they provide a plausible link between Lp(a) and the development of AF.

Conflicting Evidence: It should be noted that not all studies have found a positive association between Lp(a) and AF. For instance, an analysis from the ARIC cohort (a large community-based study) reported no significant association between Lp(a) levels and incident AF, and this null finding was consistent across sex and racial subgroups [43]. Similarly, some population studies (including one in a Chinese Han population) have even noted an inverse relationship (with very low Lp(a) in women linked to higher AF incidence), though the reasons for such findings remain unclear. These discrepancies may reflect differences in study design, populations, Lp(a) level cut-points, or simply the moderate effect size of Lp(a) on AF risk being hard to detect in some cohorts.

Clinical Implications: If the association between Lp(a) and AF is confirmed, it could refine AF risk prediction and suggest more personalized preventive strategies. For example, patients with high Lp(a) might merit closer surveillance for AF, or more aggressive management of other AF risk factors. There is also the intriguing question of whether Lp(a)-lowering therapy could reduce AF incidence or burden – something that might be examined in post-hoc analyses of the ongoing Lp(a)-lowering trials. At present, these implications are speculative, and AF is not a primary indication for Lp(a) measurement. Nonetheless, this emerging area of research further highlights the systemic impact of Lp(a) and will be important to watch.

In summary, the relationship between Lp(a) and AF remains an evolving story. While biologically plausible and supported by some data, further research is needed to conclusively establish causality and clinical relevance. Until then, traditional risk factors remain the cornerstone of AF risk assessment, with Lp(a) as a potential factor to consider in select cases.

Treatment Recommendations and Future Directions

Until dedicated Lp(a)-lowering agents become widely available, clinicians should focus on mitigating overall cardiovascular risk through comprehensive risk-factor optimization. Where available, referral to a dedicated lipid or Lp(a) clinic can facilitate family screening, integrated risk assessment, and access to advanced therapies (e.g., apheresis) or clinical trials [44]. Key recommendations and strategies include:

Maximize LDL-C Reduction: In patients with elevated Lp(a) – especially those with established ASCVD – intensive lowering of LDL-C is critical. Guideline-recommended LDL targets (e.g., < 55 mg/dL for very high-risk patients) should be achieved or surpassed. High-intensity statin therapy remains the first-line approach. While statins do not lower Lp(a), they dramatically reduce ASCVD risk from LDL and may offset some Lp(a)-mediated risk. For patients not reaching LDL goals on statin alone, add-on therapy with ezetimibe is indicated, and/or PCSK9 inhibitor therapy can be employed. PCSK9 inhibitors not only help attain very low LDL levels but also confer a modest reduction in Lp(a) (~20–30%) [32-33]. In acute coronary syndrome patients, current guidelines advocate starting high-intensity statin plus ezetimibe during the index hospitalization for early LDL lowering (Class IIa recommendation) [4] – an approach that would equally apply to those with high Lp(a) to mitigate near-term risk.

Address All Modifiable Risk Factors: A comprehensive approach to risk factor control is essential in individuals with high Lp(a). Blood pressure should be optimally controlled, glycemic status managed in diabetics, and healthy lifestyle habits (diet, exercise, weight management) should be encouraged. While lifestyle changes do not directly lower Lp(a), they improve overall cardiovascular health. Smoking cessation is particularly important, as smoking synergistically increases thrombotic risk on top of Lp(a)'s prothrom-

botic effect. In essence, patients with high Lp(a) should be treated as high-risk patients, warranting aggressive multifactorial prevention strategies.

Antithrombotic Therapy: There are no specific guidelines recommending antithrombotic therapy solely on the basis of elevated Lp(a). However, some experts have proposed considering low-dose aspirin for primary prevention in individuals with very high Lp(a) and multiple risk factors, provided their bleeding risk is low. This is controversial; the general primary prevention aspirin trials have not targeted Lp(a). A sub-analysis of the ASPREE genetic substudy suggested potential benefit of aspirin in carriers of specific LPA risk genotypes, but this finding requires careful individualized interpretation [45]. In secondary prevention (patients with ASCVD), standard antiplatelet therapy (e.g., aspirin, or dual therapy if indicated) should be continued as per guidelines – elevated Lp(a) would not detract from the indication, and indeed these patients' prothrombotic profile provides further rationale for antithrombotics. Lipoprotein(a)'s interference with fibrinolysis also raises the question of enhanced anticoagulation in select cases (e.g., AF patients with high Lp(a) might need full anticoagulation for stroke prevention, as per CHA_2DS_2-VASc scores). These decisions, however, are made based on overall risk and established criteria, not Lp(a) per se, until more evidence emerges.

Niacin (with Caution): Niacin (vitamin B3) in pharmacologic doses can lower Lp(a) by ~20-30% [25], likely by decreasing apo(a) production. In the past, niacin was used for mixed dyslipidemia (raising HDL, lowering LDL and Lp(a)). However, outcomes trials in the contemporary era (AIM-HIGH, HPS2-THRIVE) failed to show cardiovascular benefit of adding niacin to statins, and niacin's side effects led to a sharp decline in its use [46-47, 52]. Current guidelines do not recommend niacin specifically for Lp(a) lowering, as its risks outweigh proven benefits [26]. Nonetheless, in a patient who cannot access newer therapies, is statin-intolerant, and has very high Lp(a) with recurrent events, a carefully monitored niacin trial could be considered – but this is an individualized, off-guideline decision.

Lipoprotein Apheresis: In countries where available, Lp(a)-specific apheresis is an option for extreme cases. US and European authorities allow apheresis for patients with LDL-C > 100 mg/dL and Lp(a) > 60 mg/dL who have progressive ASCVD despite maximal therapy [29]. Apheresis typically produces an acute 60-80% drop in Lp(a) levels [29], but levels rebound within 1-2 weeks, necessitating repeated treatments. Case series have reported plaque stabilization and fewer events with regular apheresis in high-Lp(a) patients [29]. This invasive therapy is generally reserved for patients with refractory disease and no other options (e.g., in Germany, very high Lp(a) is an indication for apheresis if the patient has coronary disease). With new Lp(a) drugs on the horizon, apheresis will likely become even more niche.

Future Therapies: As discussed, dedicated Lp(a)-lowering drugs are in advanced clinical trials. Pelacarsen, an antisense oligonucleotide, and olpasiran, an siRNA, are both in Phase 3 outcome trials expected to read out by 2026 (and subsequent years). If these trials show a reduction in cardiovascular events by lowering Lp(a), these agents could become standard therapy for high-risk patients with elevated Lp(a) and ASCVD. It is conceivable that guidelines will adopt a threshold (e.g., Lp(a) > (50 or 100) mg/dL) above which patients with premature or progressive ASCVD should receive an Lp(a)-targeted therapy, analogous to how PCSK9 inhibitors are used today. Additionally, gene editing approaches (though farther in the future) could offer one-time solutions for those with the highest Lp(a) levels. The anticipation of these therapies means clinicians should begin identifying patients who might be candidates – for example, measuring Lp(a) in patients with premature coronary disease, recurrent events, or strong family history.

Importantly, routine Lp(a) testing is now recommended at least once in adulthood – often at the time of an initial lipid profile or cardiovascular risk assessment [4]. Knowing a patient's Lp(a) status early can inform the aggressiveness of risk factor management. For instance, an otherwise borderline-risk patient might be moved to a higher risk category and treated more intensively if Lp(a) is found to be high [4]. As Lp(a)-targeted therapies emerge, clinicians should be prepared to identify and treat high-Lp(a) individuals. This includes patient education: patients with elevated Lp(a) should understand that they have a unique risk factor and that more tailored therapies may soon be available.

Discussion and conclusion

Lipoprotein(a) has emerged as a central component of residual cardiovascular risk. Unlike LDL-C and most other modifiable risk factors, Lp(a) is largely genetically determined and remains relatively stable throughout life. Its unique structure – an LDL-like core attached to the plasminogen-mimicking apo(a) – gives rise to a multifaceted pathophysiological profile that includes atherogenesis, inflammation, and impaired fibrinolysis [49]. These properties help explain why Lp(a) contributes to atherosclerotic disease development and thrombotic complications.

Despite the accumulating evidence supporting Lp(a) as an independent causal factor in ASCVD, awareness among clinicians has been limited. Routine screening for Lp(a) is still underutilized, and until recently, few therapeutic options existed. Statins, the cor-

nerstone of lipid management, do not lower Lp(a); niacin is not widely used; and apheresis is impractical for most patients. Consequently, patients with high Lp(a) often have continued risk even when LDL-C and other factors are well-managed.

However, the landscape is rapidly changing. Promising results from antisense oligonucleotide and siRNA trials (pelacarsen and olpasiran) indicate that Lp(a) can be substantially reduced (often > 80%) with acceptable short-term safety in phase 2 studies. [34, 37] Longer-term follow-up suggests sustained pharmacodynamic effects for some agents. [36] The critical question addressed by ongoing phase 3 outcomes trials is whether lowering Lp(a) will translate into fewer cardiovascular events. Genome editing remains investigational; current clinical experience is largely in other lipid targets, and translation to LPA will require rigorous evaluation of efficacy, durability, and off-target safety. [40]

Meanwhile, clinical practice is beginning to catch up. The 2025 ESC/EAS focused update on dyslipidemias emphasizes several practical steps: early intensive LDL-C lowering in ACS (statin plus ezetimibe initiation), utilization of bempedoic acid for statin-intolerant patients, and consideration of evinacumab for homozygous familial hypercholesterolemia [4]. Notably, these guidelines also, for the first time, give Lp(a) a Class IIa recommendation as a risk modifier – advising at least once-in-a-lifetime measurement and risk re-stratification if Lp(a) is high [4]. This is a significant step towards integrating Lp(a) into routine practice. Other society statements and consensus documents have made similar recommendations [15]. Thus, we are on the cusp of a shift where checking Lp(a) becomes as common as checking LDL-C in preventive cardiology.

Clinical Take-Home Messages: (1) Measure Lp(a) at least once in adulthood – ideally at the initial lipid evaluation – and consider Lp(a) > 50 mg/dL or > 125 nmol/L as a risk-enhancing factor that may warrant more aggressive management [4]. (2) In patients with elevated Lp(a), focus on driving LDL-C to guideline-recommended targets (or lower) using high-intensity statins plus add-on therapy (ezetimibe, PCSK9 inhibitors) as needed [4, 50-51]. Add bempedoic acid for that intolerant to statins, and consider evinacumab in homozygous FH cases [4]. (3) Be prepared to identify candidates for forthcoming Lp(a)-targeted therapies – for example, patients with premature ASCVD or recurrent events and high Lp(a) – as they are likely to benefit once these treatments become available.

In conclusion, given its heritability and lifelong exposure, Lp(a) is best measured once per lifetime, ideally in early adulthood or at least by mid-life during cardiovascular risk workup. Identifying individuals with high Lp(a) allows for earlier and more tailored preventive strategies, including intensified control of other risk factors and possibly inclusion in trials or therapy with new Lp(a)-lowering agents. As the field awaits the outcome data from ongoing trials, clinicians should recognize the importance of Lp(a) as a driver of residual risk. With growing awareness, routine screening, and the advent of novel therapies, Lp(a) is poised to assume its rightful place as a key therapeutic target in cardiovascular prevention. The coming years may see a new chapter in lipidology – one in which Lp(a) joins LDL-C as a modifiable risk factor, enabling us to further reduce the burden of cardiovascular disease.

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