Lipoprotein(a) Risk: Define, Test Early, Optimise Management

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> The clinical dilemma of lipoprotein(a) (Lp(a)) lies in its under-recognition as an independent, causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis (CAVS).1 Despite its genetic determination and high prevalence, routine screening remains inconsistent, leading to missed opportunities for early risk stratification and optimised management. The immediate takeaway for clinicians is the imperative to define Lp(a) risk, test early, and optimise management strategies to mitigate long-term cardiovascular burden.

KEY TAKEAWAYS

- The Pivot: Lp(a) is now recognised as a distinct, causal, and genetically determined risk factor for ASCVD and CAVS, warranting specific clinical attention.
- The Data: Elevated Lp(a) levels are associated with a dose-dependent increase in cardiovascular risk, independent of traditional lipid parameters.
- The Action: Clinicians should consider routine Lp(a) testing in individuals with a family history of premature ASCVD, recurrent ASCVD despite optimal lipid management, or those with intermediate to high ASCVD risk.

Lipoprotein(a) is a low-density lipoprotein (LDL)-like particle with an apolipoprotein(a) (apo(a)) moiety covalently linked to apolipoprotein B-100. Its plasma concentration is largely genetically determined, with up to 90% of the variability attributed to the LPA gene locus. Elevated Lp(a) levels are an independent and causal risk factor for ASCVD, including myocardial infarction, stroke, and peripheral artery disease, as well as for CAVS. This risk is continuous and dose-dependent, meaning higher Lp(a) concentrations correlate with greater cardiovascular risk, even in individuals with otherwise optimal lipid profiles. Unlike LDL cholesterol, Lp(a) levels are relatively stable throughout an individual's life and are not significantly influenced by lifestyle interventions or most lipid-lowering therapies, with the notable exception of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Defining Risk and Early Testing

The clinical significance of Lp(a) stems from its atherogenic and thrombogenic properties. The apo(a) component shares structural homology with plasminogen, potentially interfering with fibrinolysis and promoting a prothrombotic state. Furthermore, Lp(a) can carry oxidised phospholipids, contributing to inflammation and plaque formation within the arterial wall. Current guidelines from various professional bodies, including the European Society of Cardiology (ESC) and the National Lipid Association (NLA), recommend considering Lp(a) measurement at least once in an individual's

lifetime to identify those at elevated risk. Specific indications for testing include a personal or family history of premature ASCVD (men 55 years, women 65 years), recurrent cardiovascular events despite optimal LDL-C lowering, familial hypercholesterolaemia, and individuals with an intermediate or high 10-year ASCVD risk score. A threshold of 50 mg/dL (approximately 125 nmol/L) is often cited as a general cut-off for elevated risk, though risk is continuous across the distribution.

Early identification of elevated Lp(a) allows for more precise risk stratification. For individuals with high Lp(a), this may prompt more aggressive management of other modifiable ASCVD risk factors, such as hypertension, diabetes, and dyslipidaemia. While specific Lp(a)-lowering therapies are currently under investigation, existing treatments like PCSK9 inhibitors have been shown to reduce Lp(a) levels by approximately 20-30%. Niacin can also lower Lp(a), but its use is limited by side effects and a lack of clear cardiovascular outcome benefit in contemporary trials. Lifestyle modifications, while crucial for overall cardiovascular health, do not significantly impact Lp(a) concentrations. Therefore, management primarily focuses on mitigating the overall ASCVD risk profile.

Optimising Management

Optimising management for individuals with elevated Lp(a) involves a multi-pronged approach. Firstly, achieving stringent control of traditional risk factors is paramount. This includes aggressive LDL-C lowering, often necessitating high-intensity statin therapy, and potentially ezetimibe or PCSK9 inhibitors, to compensate for the additional risk conferred by Lp(a). Secondly, clinicians should consider the use of antiplatelet therapy, such as low-dose aspirin, in select high-risk patients, although this decision must be individualised based on bleeding risk. Thirdly, patient education is vital. Individuals with elevated Lp(a) should understand their increased risk and the importance of adherence to prescribed therapies and lifestyle modifications. Genetic counselling may also be appropriate for families with a strong history of premature ASCVD and high Lp(a) levels.

Ongoing research into novel Lp(a)-lowering therapies, such as antisense oligonucleotides (ASOs) targeting apo(a) mRNA, shows promise. These investigational agents have demonstrated substantial reductions in Lp(a) levels, with some trials reporting reductions of over 80%. The long-term cardiovascular outcome benefits of these therapies are currently being evaluated in large-scale clinical trials. Should these trials demonstrate a significant reduction in ASCVD events, the landscape of Lp(a) management could undergo a substantial shift, moving from risk mitigation to direct Lp(a) lowering. Until then, the focus remains on comprehensive risk factor management and judicious use of currently available therapies that also impact Lp(a).

Furthermore, the interpretation of Lp(a) levels can be influenced by the assay used, as different methods may yield varying results. Standardisation of Lp(a) measurement is an ongoing effort to ensure consistent and comparable results across laboratories. Clinicians should be aware of the specific assay used in their practice and its potential implications for risk assessment. The integration of Lp(a) into routine clinical practice requires not only accurate measurement but also a clear understanding of its role in the overall cardiovascular risk assessment, particularly in diverse patient populations where its prevalence and impact may vary.

The economic implications of widespread Lp(a) testing and potential future Lp(a)-lowering therapies also warrant consideration. While early identification can lead to more targeted interventions and potentially prevent costly

cardiovascular events, the cost-effectiveness of these strategies needs to be rigorously evaluated. This includes assessing the cost of testing, the cost of novel therapies, and the long-term benefits in terms of reduced morbidity and mortality. Ultimately, a holistic approach that combines genetic insights, precise risk stratification, and emerging therapeutic options will be crucial in optimising the management of Lp(a)-related cardiovascular risk.

To explore current best practices in managing complex lipid disorders and other cardiovascular conditions further, readers may find the comprehensive Oxford Handbook of Cardiology a valuable resource.

CLINICAL IMPLICATIONS

The persistent under-recognition of lipoprotein(a) as a causal risk factor for ASCVD and CAVS represents a significant gap in preventative cardiology. GPs and specialists alike must integrate Lp(a) testing into their routine practice, particularly for patients presenting with a family history of premature cardiovascular events or those experiencing recurrent events despite optimal lipid management. Waiting for symptomatic disease is a missed opportunity for early intervention and risk modification. The cost-effectiveness of a single lifetime Lp(a) measurement is favourable, especially when considering the long-term burden of cardiovascular disease.

For the pharmaceutical industry, the development of novel Lp(a)-lowering therapies, such as antisense oligonucleotides, is a critical area of innovation. Should ongoing trials demonstrate a clear reduction in major adverse cardiovascular events, these agents could transform the treatment paradigm, moving beyond mere risk factor management to targeted Lp(a) reduction. This would necessitate a concerted effort from guideline bodies like the ESC and ACC/AHA to update recommendations, ensuring that clinicians are equipped with clear guidance on when to test, whom to treat, and with what agents.

Patients, particularly those with a genetic predisposition, stand to benefit immensely from earlier identification. Understanding their Lp(a) status empowers them to engage more proactively in their health management, adhere to lifestyle recommendations, and comply with prescribed therapies. It also provides a clearer rationale for aggressive management of other modifiable risk factors. The current landscape, where Lp(a) is often an afterthought, must evolve to one where it is a standard consideration in cardiovascular risk assessment, ensuring that individuals are not unknowingly carrying a significant, unaddressed risk.

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