Elevated Lipoprotein(a) in Patients Without Comorbidities: Which Imaging Tests Should be Ordered?

Eduardo Gomes Lima,[1,2] *Leticia Neves Solon Carvalho,*[1,3] *Tatiane Mascarenhas Santiago Emerich,*[1,4] *Eduardo Ferreira Amorim,*[1] *Fabiana Hanna Rached*[1,5]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da USP (InCor-HCFMUSP),[1] *São Paulo, SP – Brazil*
Hospital 9 de Julho - Rede Américas,[2] *São Paulo, SP – Brazil*
Hospital de Messejana Dr. Carlos Alberto Studart Gomes,[3] *Fortaleza, CE – Brazil*
Centrocor,[4] *Vitória – ES, Brazil*
Hospital Israelita Albert Einstein,[5] *São Paulo, SP – Brazil*

The incorporation of lipoprotein(a) [Lp(a)] into contemporary cardiovascular risk assessment has introduced a practical question that is increasingly common in clinical practice: when faced with an elevated result, how should risk be reclassified and what management should be adopted, given that current guidelines recommend measuring Lp(a) at least once in adulthood and recognize it as a risk-modifying factor.[1,2] However, the cardiovascular risk estimation proposed by these same guidelines — based on prognostic scores such as Predicting Risk of Cardiovascular Disease EVENTs - atherosclerotic cardiovascular disease (PREVENT-ASCVD), developed in 2023 by the American Heart Association — does not, *a priori*, account for the impact of elevated Lp(a) levels in its calculation.[2] This creates a clinical scenario that is both concrete and challenging: the possibility that an asymptomatic patient, without traditional risk factors, may carry a biologically relevant risk factor that the score simply does not "see." Thus arises the central question: what should be done when Lp(a) is elevated? In particular, should cardiovascular imaging be used to refine risk stratification?

A reasonable answer to these important questions requires an analysis of the biology and evidence that have propelled Lp(a) to its newly acquired prominence in the field of primary prevention in cardiology. Lp(a) is a particle similar to low-density lipoprotein (LDL), composed by an apolipoprotein B-100 molecule covalently bound to apolipoprotein(a), with levels predominantly determined by the *LPA* gene and relative stability throughout life.[2,3] Its association with atherosclerotic cardiovascular disease is supported by epidemiological, genetic, and Mendelian randomization evidence, giving the particle a status stronger than that of a simple associative marker.[2,3] Data from 450,000 patients demonstrate a strong linear correlation between elevated Lp(a) levels and atherosclerotic disease, with an approximate 11% increase in relative risk for every 50 nmol/L.[4]

Keywords

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Mailing Address: Eduardo Gomes Lima •
Universidade de São Paulo, Instituto do Coração. Av Dr Enéas de C Aguiar, 44. Postal code: 05403-000. São Paulo, SP – Brazil
E-mail: eduglima@yahoo.com.br

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In addition to its atherogenic properties related to its LDL-like core, lipoprotein(a) [Lp(a)] carries oxidized phospholipids and acts through multiple inflammatory, thrombotic, and pro-calcifying pathways. For this reason, Lp(a) not only contributes to overall cardiovascular risk but also serves as an independent factor for the development and progression of calcific aortic stenosis.[5] This process occurs through the osteogenic differentiation of valvular interstitial cells, resulting in the mineral deposition of hydroxyapatite.[6] Lp(a) levels above 35 mg/dL have been identified as independent predictors of increased calcification activity, assessed by Positron emission tomgraphy — computer tomography (PET-CT) — and are also associated with accelerated hemodynamic progression on echocardiography, greater need for aortic valve replacement, and increased mortality.[7]

As previously discussed, the incorporation of Lp(a) into contemporary cardiovascular risk assessment has introduced a practical dilemma: what should be done when elevated values are detected that traditional scores, such as PREVENT-ASCVD, fail to capture? This growing body of evidence has ultimately repositioned Lp(a) measurement within clinical guidelines. The 2026 American College of Cardiology / American Heart Association (ACC/AHA) guideline recommends measuring Lp(a) in all adults at least once in their lifetime for cardiovascular risk assessment.[2] The 2025 Brazilian Guideline on Dyslipidemias and Atherosclerosis Prevention further recognizes that Lp(a) levels ≥50 mg/dL or ≥125 nmol/L act as risk enhancers, potentially reclassifying a patient from low to intermediate risk or from intermediate to high risk.[1] At very high levels (Lp(a) >180 mg/dL or >390 nmol/L), the patient should be considered high risk.

Once it is acknowledged that Lp(a) modifies risk interpretation, the next step is to clarify how to proceed when elevated values are identified in individuals reclassified based on this parameter. In the context of primary prevention, the Brazilian guideline also supports the use of imaging methods for early detection of subclinical atherosclerosis in selected individuals with elevated Lp(a).[1]

A reflection is warranted on the evolution of imaging methods which, in addition to becoming more accessible, are now capable of detecting atherosclerosis at its earliest stages. This early detection through tomographic or ultrasound-based techniques, combined with the ability to adjust therapy intensity based on imaging findings, creates a scenario in which documenting plaque fundamentally

changes the direction of treatment. In this context, the coronary artery calcium (CAC) score plays a central role in most asymptomatic patients, including those without extreme Lp(a) values. The reason is not only its extensive validation in primary prevention, but also the nature of the question it answers: if Lp(a) raises the suspicion of underestimated biological risk, CAC reveals whether this vulnerability has already manifested as subclinical coronary atherosclerosis. In other words, Lp(a) indicates predisposition, while CAC reveals its current anatomical expression.[8,9] It is probability versus the reality of risk.

This link between Lp(a) and CAC is not merely conceptual, but also clinical and prognostic. In a recent meta-analysis involving more than 40,000 individuals, elevated Lp(a) levels were associated with a higher prevalence of CAC greater than zero and with greater CAC progression over time, with a particularly relevant signal in asymptomatic populations.[10] This reinforces that when Lp(a) modifies risk interpretation, CAC serves as a coherent marker of the subclinical manifestation of a biologically more atherogenic phenotype.[10]

In an analysis of asymptomatic individuals from MESA and the Dallas Heart Study, Mehta and colleagues demonstrated that elevated Lp(a) and CAC are independent markers of risk for cardiovascular events.[8] More importantly, the combination of both elevated markers identified a particularly high-risk phenotype: participants with Lp(a) ≥50 mg/dL and CAC ≥100 had a 10-year cumulative incidence of atherosclerotic events exceeding 20%, approaching levels typically observed in secondary prevention populations.[8] Among individuals with CAC = 0, on the other hand, elevated Lp(a) remained associated with relative risk, but absolute event rates were much lower in the short and medium term.[8,9] Bhatia and colleagues[9] expanded this understanding in a multicenter cohort of more than 11,000 participants without known atherosclerotic disease. Lp(a) >50 mg/dL and CAC >0 remained independently associated with events, reinforcing the notion of complementarity between biomarker information and imaging findings. However, the highest risk was concentrated in the strata with higher CAC scores, especially when elevated Lp(a) coexisted with CAC ≥300.[9]

The value of CAC, therefore, is not only prognostic but also decisional. A score of zero can reduce the urgency of pharmacologic escalation in patients who are truly low risk, whereas scores ≥100 shift the patient into a category in which intensifying preventive therapy becomes much more compelling.[4,5] At higher strata, such as CAC ≥300, the risk burden approaches that observed in secondary-prevention populations, reinforcing the need for more aggressive LDL-cholesterol reduction targets.[2,9] In addition, in carefully selected patients with low bleeding risk, higher CAC values may help identify individuals who are likely to derive net benefit from the initiation of antiplatelet therapy in a primary-prevention setting.[11]

It is precisely here that tomographic imaging distinguishes itself from other modalities. Coronary CT angiography can identify non-calcified plaque and provide more detailed anatomical characterization, which is physiopathologically appealing – especially because the biology of Lp(a) is not limited to calcified disease. Even so, its routine use as a first-line test in asymptomatic individuals with elevated Lp(a) appears excessive in most cases: it involves greater complexity, iodinated contrast, higher cost, and often yields findings whose incremental therapeutic impact is less clear than the pragmatic value of CAC. In high-risk cardiovascular patients, however, some expert statements consider the use of coronary CT angiography for risk re-stratification in asymptomatic individuals.[12]

The use of carotid ultrasound to identify atherosclerotic plaques has also been shown to be associated with elevated Lp(a) levels and may imply up to a four-fold higher risk of cardiovascular events when plaque is present in individuals with Lp(a) ≥30 mg/dL, compared with those with Lp(a) <30 mg/dL and no plaques.[13] Thus, because this method is more affordable and accessible, it may serve as an alternative to CAC for risk prediction. However, unlike CAC – which not only identifies the presence or absence of disease but also quantifies plaque burden in a numerical and continuous manner – ultrasound documents plaque and estimates the severity of obstruction. This difference in the nature of the methods explains the preference for CAC as a predictor of cardiovascular events, especially myocardial infarction.

This does not mean turning CAC into a universal test for all individuals with elevated Lp(a). The marker should never be interpreted in isolation from the clinical context. Age, family history of premature atherosclerotic disease, the magnitude of Lp(a) elevation, concomitant LDL-cholesterol levels, the presence of other risk-enhancing factors, and – above all – the likelihood that the result will meaningfully change management must all be considered. It is also reasonable to acknowledge that very high Lp(a) levels, especially when accompanied by a strong family history or other signs of atherosclerotic susceptibility, may lower the threshold for investigation and therapeutic intensification, even when clinical scores appear reassuring. Still, in asymptomatic patients without significant comorbidities and without extreme Lp(a) values, CAC seems to offer the best balance between diagnostic parsimony and clinical utility.

Despite the strong correlation between elevated Lp(a) and calcific aortic stenosis, there are currently no recommendations for routine echocardiographic screening in asymptomatic patients. Patients with a diagnosis of aortic stenosis, however, should have Lp(a) measured, as this may benefit family members through cascade screening.[2,13,14]

In summary, as is natural with the introduction of new paradigms, the universal recommendation to measure Lp(a) has expanded our ability to recognize cardiovascular risk, but it has also generated uncertainties along the way: how should we act when the factor that modifies clinical interpretation is not incorporated into the score that guides the initial decision? In this context, it is important to remember that identifying established atherosclerosis is not a prerequisite for action: even in the absence of imaging, the adoption of healthy lifestyle habits has been shown to substantially reduce cardiovascular risk, reinforcing the central role of lifestyle as an immediate tool for primary prevention. Imaging, in turn, should not be viewed as technological excess, but rather as an instrument of clinical precision and therapeutic individualization. Among the available methods, the CAC

score emerges as a rational strategy to refine risk in most asymptomatic individuals without comorbidities and with elevated Lp(a), especially when the question is whether subclinical atherosclerotic burden is already sufficient to warrant intensification of treatment targets and to support patient engagement in prevention and consequent reduction of cardiovascular event risk.

If Lp(a) measurement introduced a new element in risk prediction within the realm of serum biomarkers, imaging – through its ability to detect nascent, established, or unstable disease – refines this prediction by guiding the intensity of the therapeutic approach. Until new prediction methods using genomics or proteomics are validated, the best way to position ourselves in relation to cardiovascular risk is by observing the presence of disease and its progression as a continuum. In this regard, plaque detection, its location, and its quantification remain the most useful markers for guiding therapeutic decision-making.

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