European Atherosclerosis Journal
www.eathj.org

EAJ 2025;3:61-74
https://doi.org/10.56095/eaj.v4i3.113

Lipoprotein(a) and cardiovascular risk: A roadmap for patient management

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Keywords
Lipoprotein(a);
low-density lipoprotein;
cholesterol;
cardiovascular risk;
atherosclerosis

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein that shares structural elements with low-density lipoprotein (LDL), such as apolipoprotein B-100 (apoB), but differs by the presence of apolipoprotein(a) [apo(a)], which is covalently linked to apoB via a disulphide bond. In recent years, interest in Lp(a) has increased considerably, as epidemiological, genetic and biological evidence supports its causal role in cardiovascular disease. Its heterogeneous structural features, metabolic peculiarities, and ability to transport biologically active and potentially pro- atherogenic, pro-inflammatory and pro-thrombotic molecules make Lp(a) a unique lipoprotein among the apoB-containing lipoproteins. Lp(a) is now recognised as an important risk factor in cardiovascular risk assessment, as it plays a causal and independent role in the development of both atherosclerotic disease and aortic valve stenosis. Measuring Lp(a), together with other determinants of cardiovascular risk, is now recognised as essential for appropriate clinical management and the identification of new therapeutic targets. Consequently, the need to include Lp(a) in global cardiovascular risk assessment has clearly emerged, especially in individuals with a personal history of early or recurrent events, familial hypercholesterolaemia, family history of early events, or family history of high Lp(a) levels.
This document, produced through the collaboration of the main Italian scientific societies in the field of cardiovascular disease management and laboratory medicine (SISA, SIC, ANMCO and SIBioC), analyses the pathogenetic role of lipoprotein(a) [Lp(a)] and the clinical significance of its measurement.

Received 20 November 2025; accepted 1 December 2025

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Introduction

Lipoprotein(a) [Lp(a)] is a plasma lipoprotein that shares structural elements with low-density lipoprotein (LDL), such as apolipoprotein B-100 (apoB), but differs by the presence of apolipoprotein(a) [apo(a)], which is covalently linked to apoB via a disulphide bond [1]. The unique characteristics of Lp(a) confer both pro-atherogenic and pro-thrombotic properties, making it of particular clinical and scientific interest. Although its physiological function is not yet fully understood, it is hypothesised that Lp(a) may be involved in tissue repair, the transport of cholesterol and oxidised phospholipids, and the maintenance of vascular wall structural integrity [2, 3]. Plasma Lp(a) concentrations are associated, independently of LDL-cholesterol (LDL-C) levels and other traditional risk factors, with a significant increase in cardiovascular risk, particularly for atherosclerotic diseases such as early coronary artery disease, ischaemic stroke, and calcific aortic valve stenosis [4].

In recent years, interest in Lp(a) has grown considerably due to epidemiological, genetic, and biological evidence supporting its causal role in cardiovascular disease. Consequently, the need to include Lp(a) in the assessment of overall cardiovascular risk has emerged, especially in individuals with a personal history of early or recurrent events, familial hypercholesterolaemia, a family history of early events, or a family history of elevated Lp(a) levels.

This document, developed through the collaboration of leading national scientific societies (SISA, Italian Society for the Study of Atherosclerosis; SIC, Italian Society of Cardiology, ANMCO, National Association of Hospital Cardiologists; SIBioC, Italian Society of Clinical Biochemistry and Clinical Molecular Biology) addresses the role of Lp(a) in cardiovascular risk and discusses the available methods for Lp(a) assessment. It aims to provide operational guidance, supported by the most recent evidence and international guidelines, on essential aspects of clinical practice: the pathogenetic importance of Lp(a) in cardiovascular risk, the relevance of its measurement, and, above all, the correct methods for using laboratory data in risk stratification.

Through a critical and integrated analysis of current knowledge, this document provides concrete answers to fundamental questions for clinicians: when, where, and why to measure Lp(a), and how to interpret the values obtained appropriately, with the ultimate goal of improving the management of residual cardiovascular risk, which remains largely unmet in daily practice.

The synergy between scientific societies with different areas of expertise adds value, ensuring a comprehensive and multidisciplinary perspective, aimed at translating the best available science into practical tools for clinicians and laboratory professionals.

Structure and metabolism of Lp(a)

Apo(a) consists of protein sequences called "kringles," which are triple-looped structures stabilised by three internal disulphide bonds, also found in other proteins such as plasminogen. Specifically, apo(a) contains several kringle IV domains and a kringle V, followed by an inactive catalytic domain similar to a serine protease. Kringle IV domains are categorised into 10 subtypes (designated K-IV type 1 to type 10), with subtype IV-2 present in multiple copies, in a pattern that varies between individuals (**Figure 1**) [1]. Compared to plasminogen, apo(a) lacks the activation sequence and has an inactive protease domain [1]. Kringles exhibit highly specific structural properties that determine the variability of the structure and circulating levels of Lp(a).

K-IV type 2 (K-IV2) is present in the apo(a) structure in a variable number of identical copies, repeated from 2 to 40 times (**Figure 1**). The variability in the number of repeats confirms the polymorphism of the *LPA* gene that encodes apo(a) and explains the different sizes of the various apo(a) isoforms [5-7]. K-IV7 and K-IV8 contain binding sites at the lysine level, which are essential for the non-covalent interaction between apo(a) and apoB. This interaction is in addition to the disulphide bond between a cysteine present on K-IV9 and an unpaired cysteine at position 4326 of apoB [5-7] (**Figure 1**).

The kringle K-IV type 10 is structurally very similar to plasminogen K-IV and is characterised by the presence of a high-affinity lysine-bind-

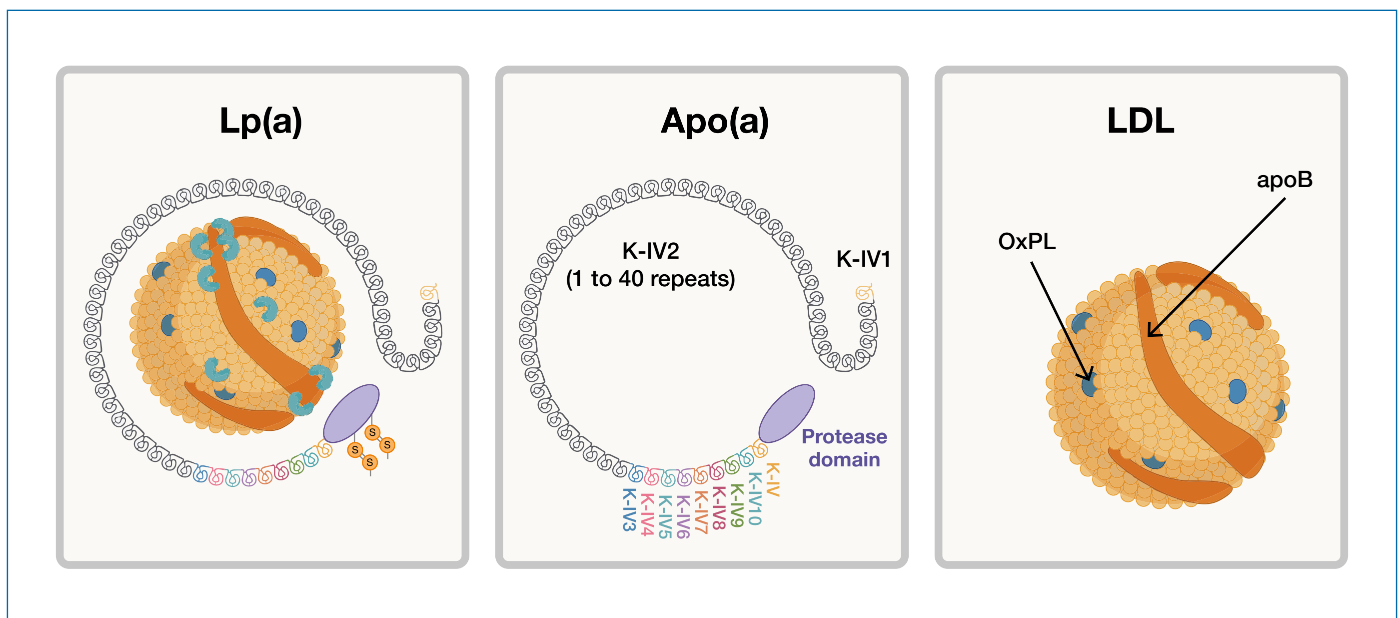

Figure 1 | **Structure and main components of lipoprotein(a).** apo(a), apolipoprotein(a); apoB: apolipoprotein B; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); OxPL, oxidised phospholipids.

ing site that plays a dominant role in the binding of apo(a) to fibrin and components of the vascular extracellular matrix [8, 9]. The lysine-binding site is also essential for binding to oxidised phospholipids [10] with pro-inflammatory activity [11]. Oxidised phospholipids are mainly present in the binding region between apo(a) and apoB.

At the transcriptional level, expression of the LPA gene is regulated by multiple factors. Among those that positively regulate gene transcription, the oestrogen receptor (ER-α) activated by estradiol should be mentioned, as it recognises and binds to a 26-kb oestrogen-dependent enhancer region (ERE) present in the *LPA* gene promoter [12]. Among the negative regulatory factors, HNF1A [13], HNF3A (FOXA1), and GATA4 [14] have been identified. The farnesoid X receptor (FXR), implicated in bile metabolism, can also negatively regulate expression of the *LPA* gene by binding the DR-1 control element located in the -826 region of the *LPA* gene [15]. Factors involved in inflammatory mechanisms are also known to promote LPA expression, including interleukin 6 (IL-6), or inhibit it, such as tumour necrosis factor-alpha (TNF-α) or transforming growth factor beta (TGF-β) [16].

Once the gene is transcribed and the protein is synthesised, apo(a) undergoes multiple post-translational modifications that regulate its secretion. N-glycosylation and protease inhibition occur during the passage of the lipoprotein containing apoB from the endoplasmic reticulum to the Golgi complex; calnexin acts as a chaperone for apo(a) in the endoplasmic reticulum and prevents its degradation. The lipidation processes of Lp(a) are common to those of all other apoB-containing lipoproteins.

During the passage from the endoplasmic reticulum to the Golgi apparatus, the structural variability of K-IV2 determines the likelihood of apo(a) proceeding through the assembly phases with the lipoprotein containing apoB and avoiding transfer to the proteasomal system [17]. A high number of K-IV2 repeats increases the molecular weight of apo(a) and its susceptibility to proteasome-mediated degradation, compared to a smaller number of repeats, which produces a protein with a lower molecular weight and less degradation [18, 19]. The regulatory mechanisms underlying apo(a) degradation have not yet been fully described, but they are crucial for understanding the impact of genetic determinism on plasma Lp(a) levels.

In circulation, like all other apoB-containing lipoproteins, Lp(a) can bind to the LDL receptor (LDLR) [20] as well as very-low-density lipoprotein receptor (VLDLR), LDL receptor-related protein 1 (LRP1), asialoglycoprotein receptor 1 (ASGR1), scavenger receptor class B type 1 (SR-B1), and the plasminogen receptor [21-24]. Furthermore, there is evidence that Lp(a) can bind to other receptors involved in inflammatory mechanisms, including Cluster of Differentiation 36 (CD36) and Toll-like receptors (TLRs) [23].

In kinetic studies using Lp(a) isolated from human donors and injected into various mouse models (which physiologically do not produce Lp(a)) knockout for LDLR or apoE, or treated with specific glycoproteins to saturate ASGR1, hepatic elimination of Lp(a) was comparable to that of wild-type models, suggesting a minimal contribution of these three pathways to the hepatic catabolism of Lp(a) [25]. In humans, studies on families with defective familial apoB or heterozygous familial hypercholesterolaemia (FH) have demonstrated that mutations in the *APOB* and *LDLR* genes can influence plasma Lp(a) concentrations [26].

Lp(a) has also been proposed as a non-competitive ligand with plasminogen for the plasminogen receptor (KT) (PlgRKT) [17, 19], which could partially explain additional catabolic pathways, independent of those of other apoB-containing lipoproteins. In any case, regardless of the receptor, the catabolic mechanism of Lp(a) and apo(a) once internalised in the liver is not yet completely clear.

Pathophysiological role of Lp(a)

The physiological function of Lp(a) has not yet been fully clarified, but several hypotheses have been proposed [27]. It is believed that Lp(a) may contribute to tissue repair and wound healing due to its structure, which is similar to that of plasminogen. This similarity allows Lp(a) to interact with fibrin and facilitate tissue remodelling after injury [27]. Supporting this, a recent study has shown that high levels of Lp(a), associated with the presence of oxidised phospholipids, are also involved in the formation of keloids [2]. Like other lipoproteins, Lp(a) may also play a role in the transport of cholesterol and phospholipids, contributing to the repair and maintenance of blood vessel structure. Furthermore, Lp(a) may have a function in the immune system, aiding in defence against pathogens and regulating inflammatory responses [28, 29].

Beyond these potential physiological activities, Lp(a) is recognised as a significant and independent risk factor for cardiovascular diseases, including atherosclerosis and aortic valve stenosis [28, 30]. This relationship has been confirmed in epidemiological, genetic, Mendelian randomisation studies, and meta-analyses [30-32].

Due to the high homology of apo(a) with plasminogen [33-35], Lp(a) was hypothesised to play a role in platelet activation and atherothrombosis [36]. Early in vitro studies showed that Lp(a) could accelerate thrombosis and slow clot lysis [37] by inhibiting plasminogen activation [38]. However, subsequent observational and genetic studies have questioned the clinical relevance of these pro-thrombotic and anti-fibrinolytic properties [4, 39, 40]. Instead, a role for Lp(a) has emerged in the development of ischaemic cardiovascular disease and atherosclerosis. Lp(a) appears to have a greater propensity for oxidation, to transport oxidised phospholipids, and is more significantly removed through the scavenging action of macrophages compared to other apoB-containing lipoproteins [41]. It also plays a role in the inflammatory activation of monocytes that infiltrate atherosclerotic plaque [42, 43]. Finally, Lp(a) plays a crucial role in the formation and progression of calcified aortic valvular and supravalvular stenosis.

Pro-atherogenic mechanisms

Lp(a) plays a crucial role in promoting atherosclerosis by transporting cholesterol esters and oxidised phospholipids. The latter are potent inflammatory molecules that stimulate endothelial cells to express adhesion molecules, such as VCAM-1 and selectins, facilitating leukocyte adhesion and migration into the vascular walls [43, 44]. The accumulation of these cells in the vascular system leads to the formation of vulnerable atherosclerotic plaques, increasing the risk of acute cardiovascular events [45]. The interaction of Lp(a) with macrophages also promotes the formation of foam cells: macrophages take up Lp(a) and release pro-inflammatory cytokines, amplifying local inflammation and lipid accumulation. This process contributes to the progression of atherosclerosis and destabilisation of plaques [4].

Pro-inflammatory properties

The structure of apo(a) gives Lp(a) specific inflammatory properties (11). Despite structural similarities to plasminogen, Lp(a) can inhibit the normal clot dissolution process, generating a pro-inflammatory environment and promoting persistent vascular inflammation [46, 47]. The oxidised phospholipids carried by Lp(a) stimulate the production of reactive oxygen species (ROS) and activate cytokine-mediated inflammatory pathways, further contributing to endothelial dysfunction [46, 48].

Pro-thrombotic role

Apo(a) appears to compete with plasminogen for binding to fibrin, interfering with the formation of plasmin and the process of fibrinolysis. This inhibition is thought to promote clot stability and increase the risk of thrombosis, especially in the presence of other cardiovascular risk factors [49]. Lp(a) also upregulates the expression of plasminogen activator inhibitor type 1 (PAI-1), which contributes to reduced clot degradation and promotes a pro-thrombotic environment [39].

The pathophysiological properties of Lp(a), including its pro-atherogenic, pro-inflammatory, and prothrombotic effects, make it a key risk factor for the development and progression of cardiovascular disease, a critical marker for cardiovascular risk stratification, and a potential target for future therapeutic strategies currently under development [4].

Role of Lp(a) as an independent, genetically determined causal risk factor for cardiovascular disease

Epidemiological evidence

Lp(a) is widely recognised as an independent, genetically determined cardiovascular risk factor. Epidemiological evidence shows that Lp(a) levels above 50 mg/dL (125 nmol/L) are associated with a significantly increased risk of cardiovascular events [31]. A meta-analysis of data from 24 cohort studies found that the rates of coronary heart disease in the upper and lower tertiles of Lp(a) were 5.6 (95% confidence interval [CI], 5.4–5.9) per 1,000 person-years and 4.4 (95% CI, 4.2–4.6) per 1,000 person-years, respectively. The adjusted hazard ratio for age and sex was 1.16 (95% CI, 1.11–1.22) for a 3.5-fold (i.e., 1 standard deviation) [50] increase in Lp(a) concentration. An increase in Lp(a) levels of 40 mg/dL (100 nmol/L) is associated with a 35% increased risk of cardiovascular events [4]. These data reinforce the importance of considering Lp(a) as a key risk factor in the assessment of cardiovascular risk.

Major international scientific societies, such as the European Atherosclerosis Society (EAS) and the American Heart Association (AHA), have recognised the threshold value of 50 mg/dL (125 nmol/L) for identifying high cardiovascular risk [4]. This value requires thorough re-evaluation in light of consolidated evidence indicating a continuous relationship between plasma concentrations of Lp(a) and the absolute risk of atherosclerotic cardiovascular disease (ASCVD). It is now clear that the cardiovascular risk associated with Lp(a) is not a threshold phenomenon, but rather a progressive gradient, in which each increase in plasma levels results in a proportional increase in risk, modulated by interaction with other traditional and non-traditional risk factors.

Although the adoption of cut-off values is useful in clinical practice to identify high-risk patients and facilitate operational decisions, it is important to emphasise that this approach does not fully capture the pathogenetic complexity of Lp(a). In particular, the use of discrete thresholds risks underestimating the overall impact of Lp(a) on cardiovascular risk when it acts in synergy with other determinants, such as hypercholesterolaemia, diabetes mellitus, arterial hypertension, chronic renal failure, and chronic inflammatory conditions.

Several studies, supported by genetic analyses and prospective meta-analyses, have shown that in individuals with Lp(a) levels above 180 mg/dL (450 nmol/L), the cumulative lifetime risk of cardiovascular events is comparable to that observed in subjects with heterozygous familial hypercholesterolaemia [51]. These data reinforce the need to consider Lp(a) not only as an isolated risk factor, but also as a modulator and amplifier of overall risk, capable of significantly altering the individual risk profile.

In this context, there is an urgent need to move beyond a dichotomous view of the risk associated with Lp(a) and to promote the adoption of dynamic and integrated stratification models that take into account overall risk and the interaction between multiple determinants. This approach is consistent with the recommendations of the most recent European guidelines (ESC/EAS) [52, 53], which emphasise the importance of a holistic and continuous assessment of cardiovascular risk.

Promoting a more sophisticated integration of Lp(a) into risk stratification systems represents not only a significant scientific advance, but also improves the precision and effectiveness of preventive and therapeutic interventions, supporting the ultimate goal of increasingly personalised medicine based on actual risk exposure.

It is therefore important to measure Lp(a) levels as part of cardiovascular risk assessment, as elevated concentrations are associated with increased risk of atherosclerotic cardiovascular disease and calcific aortic valve stenosis (CAVS), independently of other lipid and metabolic risk factors.

Regarding CAVS, recent studies have shown that elevated Lp(a) levels predict a higher risk of CAVS and disease progression [54]. The increased risk of developing CAVS is related to the ability of Lp(a) to transport oxidised phospholipids, which contribute to valvular calcification and aortic valve inflammation [4]. In patients with elevated Lp(a), the risk of progression of valvular stenosis is higher than in those with normal levels, indicating Lp(a) as an independent predictor of CAVS and a potential target for future therapies.

Genetic variability of Lp(a) associated with cardiovascular risk

Individual plasma Lp(a) concentrations are predominantly heritable. Approximately 90% of the variability in Lp(a) levels is determined by changes in the sequence of the gene encoding apo(a), and about 70% of the interindividual variability is explained by the number of KIV-2 repeats, with an inverse relationship between the size of the apo(a) isoform and plasma Lp(a) levels [4, 32, 55].

In addition to the genetic determinism dictated by KIV-2 copy number, several single-nucleotide polymorphisms (SNPs) have arisen over the course of evolution in the gene encoding apo(a), which significantly alter plasma Lp(a) levels depending on ethnicity [4, 56]. In the Dallas Heart Study, six SNPs in the gene locus encoding apo(a) (rs3798220, rs10455872, rs9457951, rs1801693, rs41272110, G+1/inKIV-8A) were sufficient to explain most of the variability in Lp(a) levels, regardless of the number of KIV-2 repeats [4, 57], with different distributions among white, black, and Hispanic individuals [57, 58].

Although some of these SNPs are in linkage disequilibrium with the copy number variant of KIV-2, SNPs have been identified that are independently associated with both high and low levels of Lp(a) [59]. Beyond the *LPA* gene locus, the APOE ε2 allele has been associated with lower levels of Lp(a), explaining approximately 0.5% of the variation in Lp(a) plasma levels. Recent GWAS studies have highlighted a relationship between Lp(a) levels and the *APOH36* gene, which encodes β2-glycoprotein 1, is associated with PCSK9, and interacts with apo(a) KIV-2 [60].

Significance of Lp(a) levels as a cardiovascular risk factor

All epidemiological and genetic studies agree that elevated Lp(a) levels increase the risk of atherosclerotic cardiovascular disease and aortic valve stenosis, similar to other apoB-containing lipoproteins [4, 39, 61-67]. However, increased plasma Lp(a) levels are more strongly associated with the risk of developing myocardial infarction than

with aortic valve stenosis or ischaemic stroke [31, 50, 68, 69]. Furthermore, gene variants that increase plasma Lp(a) levels result in a higher risk of major cardiovascular events, while gene variants that reduce plasma Lp(a) levels (such as certain forms of splicing, including 4733 G>A, KIV-2.2 -11G>A and 4925G>A, KIV-2.2 +0G>A), although less common in the population, provide significant protection and a reduced lifetime risk [70], further supporting the causality between Lp(a) levels and the pathophysiology of atherosclerotic disease.

Genetics also provides important information regarding the consideration and clinical use of Lp(a) as a risk factor. The relationship between genetically determined plasma Lp(a) levels and the risk of developing a first cardiovascular event is linear over a broad range between 50 and 300 mg/dL (125-700 nmol/L) in all primary prevention cohorts in which it has been evaluated [39, 62, 71, 72], while the association between the same levels and the risk of recurrence of a second event reaches a plateau between 150 and 300 mg/dL (125-700 nmol/L) [71].

These observations reinforce the need to consider Lp(a) levels at any level of cardiovascular risk, especially in patients already exposed to other risk factors [73], but they also highlight the importance of identifying a "threshold value". Scientific societies have proposed a threshold value of 50 mg/dL (125 nmol/L) as indicative of an increased risk of cardiovascular events over a ten-year period [59, 65]. However, it is important to emphasise that this value, although useful in clinical practice to guide risk management, does not fully reflect the continuous nature of the risk associated with Lp(a) or the complex interaction between Lp(a) and other cardiovascular risk factors. Several studies show that risk increases progressively with rising Lp(a) levels, without a precise threshold, and that this risk is further amplified by the presence of other clinical determinants.

Therefore, measuring Lp(a) alone may not be sufficient for an accurate assessment of cardiovascular risk. It is more appropriate to adopt an integrated approach, combining the Lp(a) value with personal medical history and exposure to the main risk factors, as suggested by the most recent international guidelines [4].

Measuring Lp(a): Methodological aspects

Pre-analytical phase

Sample collection: Fasting is not required for Lp(a) measurement [74]. No significant changes in Lp(a) levels have been reported from 1 to 6 hours after meals [39, 75]. Lp(a) can be measured in plasma or serum, but levels of several lipids, including Lp(a), are lower in plasma than in serum. It is therefore recommended to pay attention to the biological matrix specified for Lp(a) measurement and not to use plasma and serum interchangeably.

Centrifugation: The whole blood sample should be centrifuged at 1500 g for 15 minutes at 4°C.

Storage: After centrifugation, if samples are not processed immediately, they can be stored at 2-8°C if analysed within 8 hours of collection, or at -70°C if analysed within 48 hours. Long-term storage, for periods exceeding 24 months, at -80°C or -20°C, can cause significant changes in Lp(a) levels, with an average decrease of 7% and 13%, respectively [39], especially for the smaller isoforms [76]. It is strongly recommended to thaw samples only once, as repeated thawing and freezing results in a significant decrease in Lp(a) concentration, with a greater impact on samples stored at -20°C than at -80°C.

Analytical phase

The measurement of Lp(a) levels presents several critical issues, primarily due to the composition of Lp(a) itself. The highly dimensionally heterogeneous structure, the covalent association of apo(a) with apoB, and the high homology between apo(a) and plasminogen pose challenges for the development of tests that allow accurate measurement of Lp(a).

The ideal test for determining Lp(a) should use an antibody specific for the analyte being measured, and the analyte in the sample should have the same structural characteristics as the analyte in the assay calibrator to ensure the same degree of immunoreactivity per particle.

The main aspects of measuring Lp(a) concern the sensitivity of the measurement systems to KIV-2 isoforms and the calibrators used by the assay. The use of antibodies directed against a repetitive motif of the apo(a) protein (isoform-sensitive) introduces measurement bias: serum concentrations of small isoforms with a small number of KIV-2 repeats, usually associated with high levels, are underestimated, while serum concentrations of large isoforms with a high number of KIV-2 repeats, usually associated with low levels, are overestimated. The relative bias can be considerable, with an overestimation of 25-35% in carriers of large isoforms, while for most carriers of small isoforms it is about 10%, which translates to less than 5-10 nmol/L. However, in both cases, there are exceptions where the absolute bias can be quite high. For example, a relative underestimation of Lp(a) of 30–35% has been observed for individuals with 15 and 16 KIV-2 repeats, which translates to an absolute underestimation of 35–45 nmol/L, potentially altering the risk classification of these patients.

One approach to avoid this bias involves the use of a non-commercial immunoassay developed by the Northwest Lipid Metabolism and Diabetes Research Laboratories (NLMDRL) in Seattle, which uses a specific antibody directed against a unique epitope in KIV type 9: each Lp(a) particle is recognised only once, and the ratio in nmol/L can be calculated without ambiguity. Therefore, this test is considered an established reference method [77].

Another approach that avoids the sensitivity of the test to Lp(a) isoforms uses an antibody directed against Lp(a)-apoB, since each Lp(a) molecule contains only one apoB molecule. This approach is applicable with an enzyme-linked immunosorbent assay (ELISA) in which an antibody directed against apo(a) is bound to the ELISA plate to capture the Lp(a) particle; for detection, a second antibody directed against apoB is used. Since Lp(a) contains only one apoB molecule, each Lp(a) particle is recognised only once, allowing a molar measurement of Lp(a). However, it is not possible to distinguish "free" apo(a) from apo(a) not bound to Lp(a) [78].

Another important aspect for the accuracy of Lp(a) determination is the calibrator used by different assays. If the calibrator has an incorrect value, all measured samples will be systematically overestimated or underestimated. In 1999, a primary reference standard (IFCC PRM1) was created [79], which became the basis for the secondary reference standard (WHO/IFCC SRM-2B) (80), consisting of a pool of sera from 17 donors and used for the calibration of tests by diagnostic companies. The Lp(a) concentration in SRM-2B was assigned with an ELISA method using a monoclonal antibody directed against a unique epitope located in KIV type 9, with no reactivity with the K-IV2 apo(a) region, making this method insensitive to variability in the size of apo(a). However, the impending depletion of supplies of this reference material prompted researchers to prepare an optimal and more widely available reference material using mass spectrometry [74, 81]. Currently, to calibrate different instruments, five independent standards with values ranging from low to high for the apo(a) isoforms are used, rather than serial dilutions of a single standard with elevated Lp(a) levels.

Lipoprotein(a) determination methods

Lp(a) is measured primarily using immunochemical methods that detect the apo(a) component. As previously reported, a major

challenge in quantifying Lp(a) is the size polymorphism of apo(a).

The main methods for determining circulating Lp(a) levels and their characteristics are shown in **Table 1**.

Various ELISA tests for determining Lp(a) have been developed since 1985. However, the test with the best characteristics and performance appears to be the one developed by Marcovina et al. This isoform-independent ELISA test provides values in moles/L and is considered the gold standard, on which the SRM-2B reference standard was based [77].

The gold standard ELISA showed an excellent linear relationship with mass spectrometry (LC-MS/MS) in a series of 64 samples with well-characterised apo(a) isoforms, and excellent agreement with the value of the WHO/IFCC SRM-2B secondary reference material: 104.7±8.4 nmol/L compared to the assigned value of 107 nmol/L. The gold standard ELISA method is not commercially available.

Alternative methods to the gold standard ELISA are based on immunoturbidimetry and nephelometry.

Immunoturbidimetric methods use five-point calibration curves constructed with five different lyophilised standards, covering a range of apo(a) isoform values from low to high, and have demonstrated concordance with the gold standard ELISA [82].

Immunonephelometric tests use a five-point calibration curve generated from serial dilutions of a single Lp(a) standard, providing calibration values in mg/dL and nmol/L; this reduces concordance with the reference ELISA [83].

A recent study compared the performance of six commercially available tests (immunoturbidimetric and nephelometric) in 144 serum samples [84] against the previously validated reference immunoturbidimetric test. The tests used different calibrators and produced significantly different results across the clinically relevant concentration range.

Another study compared immunoturbidimetric methods based on mass or molarity, demonstrating that these tests were interchangeable for measuring Lp(a) [85]. Latex immunoturbidimetric methods have also recently been described, providing rapid and automated results, potentially suitable for routine clinical assessment [86].

Another reference method is targeted liquid chromatography with tandem mass spectrometry (LC-MS/MS), which measures a peptide specific to the analyte of interest. This is the method of choice for biomarker standardisation, but it is not currently available in routine clinical laboratories.

In conclusion, all assay methods should express levels in nmol/L. The gold standard assay is an ELISA, which is not commercially available. Among available tests, immunoturbidimetric assays using calibration curves constructed with five different standards (covering low and high isoform values) give the best results. The extreme variability of results obtained with other commercially available methods requires further comparative studies with the gold standard and particular attention from clinicians regarding the method used in the population under study.

Post-analytical phase

In laboratory medicine, the post-analytical phase is extremely important as it represents the interface between the laboratory, the clinic, and the patient. It is essential to provide clinicians and patients with the tools to interpret laboratory data appropriately.

Therefore, defining reference ranges, threshold values, and biological variables that can influence the levels of a risk factor are fundamental steps for introducing it into clinical practice.

First, it is important to define the unit of measurement for Lp(a). Plasma Lp(a) concentration can be expressed in milligrams per decilitre (mg/dL), which indicates the mass of Lp(a) particles per volume, but ignores the high variability of Lp(a) mass, or in nanomoles per litre (nmol/L), which indicates the actual number of Lp(a)

Table 1 | Main immunological methods for the determination of commercially available Lp(a) levels.

Kit Name (Manufacturer)	Single calibrator vs independent calibrators	Unit of measurement	Reference Material	Detection antibody
Immunonephelometry test				
Siemens N Latex	Serial dilutions of a single calibrator	10-100 (mg/dL)	Internal Standard	Rabbit polyclonal Ab
LPAX (Beckman)	5 Independent calibrators	2-128 (mg/dL)	Not specified	Rabbit polyclonal Ab
Immunoturbidimetry test				
Lp(a)-Latex SEIKEN (Denka Seiken)	5 Independent calibrators containing specific isoforms of apo(a)	nmol/L or 3-90 mg/dL	WHO/IFCC SRM-2B	Rabbit polyclonal Ab
TinaQuant Lipoprotein(a) Gen.2 (Roche) (Beckman)	5 Independent calibrators	7-240 nmol/L	WHO/IFCC SRM-2B	Rabbit polyclonal Ab
Lipoprotein(a) Assay (Randox)	5 Independent Calibrators Licence from Denka	nmol/L or 3-90 mg/dL	WHO/IFCC SRM-2B	Rabbit polyclonal Ab
Abbott Alinity c Lp(a) (Abbot)	5 Independent calibrators	3.1-90 mg/dL	In-house Reference Material	Rabbit polyclonal Ab
ADVIA Chemistry Lipoprotein(a) (Siemens)	5 Independent calibrators	10-85 mg/dL	In-house standards	Rabbit polyclonal Ab
Lipoprotein(a) (Mannheim Herb)	Serial dilutions of a single calibrator	6-260 nmol/L	Not specified	Rabbit polyclonal Ab
DiaSys 21 FS (DiaSys)	5 Independent calibrators	6-260 nmol/L	WHO/IFCC SRM-2B	Rabbit polyclonal Ab
Lipoprotein(a) assay (Diazyme)	5 Independent calibrators	5.4-100 mg/dL	Declaration of equivalence with Denka assay	Rabbit polyclonal Ab

particles per volume and is therefore the most appropriate unit of measurement. The conversion between these two units is nonlinear and varies depending on the composition of the particle. This discrepancy makes standardisation of levels complex and can lead to errors in interpretation if the units used are not taken into account. Therefore, it is recommended not to perform conversions between these units of measurement.

However, in clinical practice, to approximately convert mg/dL to nmol/L, a conversion factor of ×2–2.5 can be used, and to convert nmol/L to mg/dL, the value can be multiplied by 0.4 [87]. This is currently also accepted by the Consensus Statement of the European Atherosclerosis Society (EAS) [4].

Lp(a) values should be interpreted as follows:

- <75 nmol/L (<≈30 mg/dL): low risk;
- 75–125 nmol/L (≈30–50 mg/dL): intermediate risk;
- >125 nmol/L (>≈50 mg/dL): high risk.

Plasma Lp(a) concentration exhibits wide inter-individual variability in the general population, with values ranging from <1 mg/dL (2 nmol/L) to >1000 mg/dL (2000 nmol/L) [88], but low intra-individual variability. In particular, the levels observed in adulthood are reached by 2 years of age and remain stable throughout the lifespan in males, while in females they tend to increase after menopause.

Factors influencing circulating Lp(a) levels include genetics, ethnicity, kidney function, liver function, inflammatory status, and hormonal changes (**Figure 2**).

As genetics is not the only determinant of Lp(a) levels, genotyping is not entirely accurate for predicting plasma Lp(a) levels. Among non-genetic factors, different ethnic groups show significantly different Lp(a) levels, with lower concentrations in individuals from East Asia, Europe, and Southeast Asia, intermediate levels in those from South Asia, the Middle East, and Latin America, and higher levels in individuals from Africa [28, 89].

Conflicting evidence exists regarding the possible influence of age and sex on Lp(a) levels, with some studies showing higher levels in women than in men and in elderly individuals compared to younger people. However, this evidence has not been sufficiently confirmed. Some authors have suggested that diet, particularly a high intake of unsaturated fatty acids, may cause a negligible increase in Lp(a) levels, in contrast to the effect on LDL-C (90). The postprandial state does not significantly affect Lp(a) levels.

An inverse association between circulating Lp(a) levels and renal function has been described. The kidney is involved in the catabolism of Lp(a); therefore, renal disorders, such as chronic kidney disease and nephrotic syndrome lead to increased Lp(a) levels [90]. Conversely, as Lp(a) is produced in the liver, liver damage, such as that caused by viral hepatitis, results in reduced levels.

Thyroid hormones, growth hormone, and sex hormones (oestrogen and testosterone), which are known to influence lipid metabolism, also affect Lp(a) levels. In particular, pregnancy, menopause, hypothyroidism, and low testosterone levels increase Lp(a) levels, while growth hormone strongly stimulate lipoprotein synthesis in both patients with acromegaly and those receiving replacement therapy [90].

An acute inflammatory state, such as sepsis, inflammatory bowel disease, or acute myocardial infarction, also increases Lp(a) levels due to the interaction of acute-phase reactants, such as IL-6, with binding sites in the *LPA* gene promoter [91].

It is important to note that the cholesterol present in Lp(a) can affect LDL-C measurement, especially in individuals with high Lp(a) levels. A portion of the cholesterol attributed to LDL may actually be contained in Lp(a), resulting in an overestimation of LDL-C. As an Lp(a) particle is composed of cholesterol for approximately 30% of its weight, individuals with high Lp(a) concentrations experience a significant overestimation of the LDL-C concentration. Therefore,

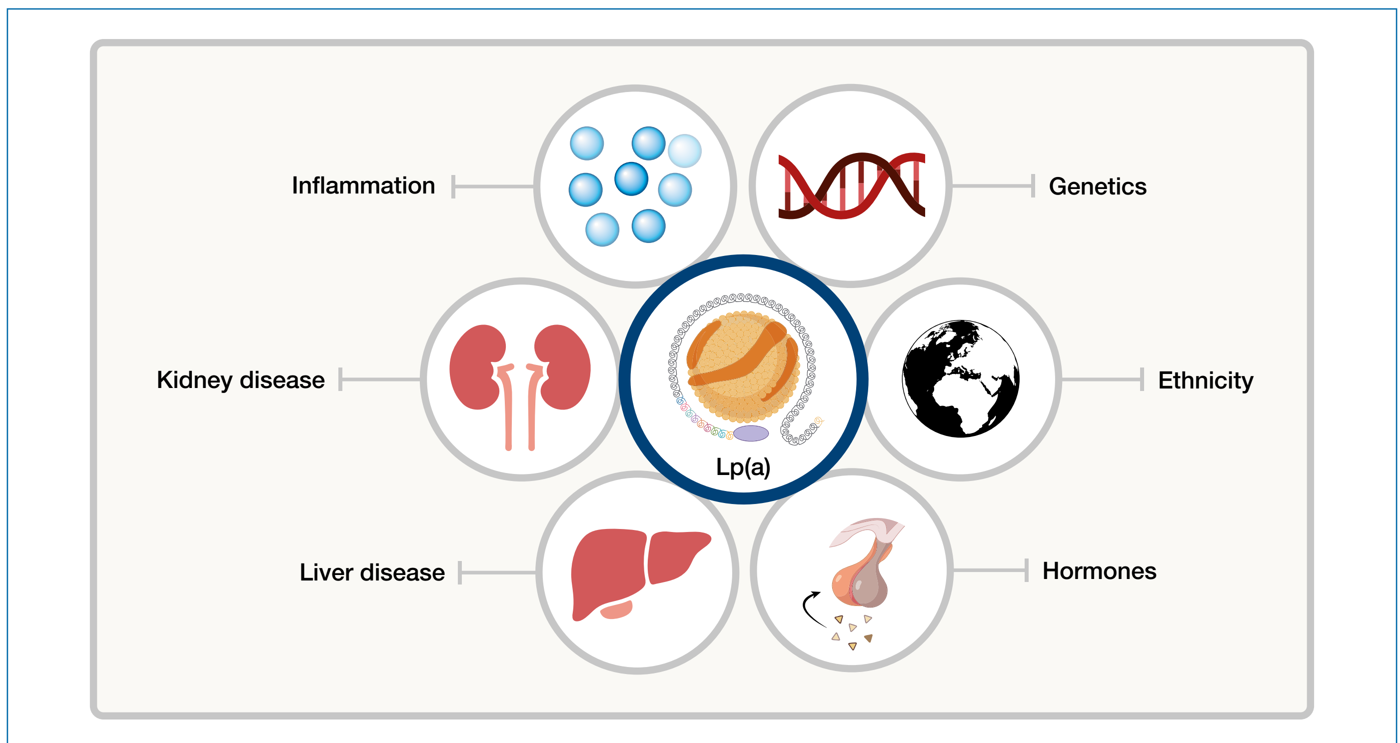

Figure 2 | **Factors influencing plasma Lp(a) levels.**

it is appropriate to correct LDL-C levels for Lp(a), particularly in groups such as those with high Lp(a) concentrations or those who do not respond adequately to therapy to reduce LDL-C levels [92].

Due to the lack of commercially available methods to directly measure the cholesterol content of Lp(a), the most common approach is to use the Dahlen formula, in which each individual is assigned an Lp(a) cholesterol value equivalent to 30% of the Lp(a) mass. The known LDL-C values (calculated using the Friedewald formula) are then adjusted by multiplying by the Lp(a) levels in mg/dL by a correction factor.

– *Dahlen formula:* ([LDLFriedewald] - 0.3× Lp(a) in mg/dL) [93]

Another formula for calculating Lp(a) levels is the Yeang formula, which uses the correction factor -0.173:

– *Yeang formula:* ([LDLFriedewald] - 0.173× Lp(a) in mg/dL) [94]

However, these formulas provide only a rough estimate of the contribution of Lp(a) to LDL-C and, therefore, their use is not recommended.

ApoB measurement has also been proposed as an indicator of all atherogenic lipoproteins, replacing LDL-C measurement [67]. Because there is a 1:1 molar relationship between apoB and each individual atherogenic lipoprotein, the relative contribution of Lp(a) to an individual's total atherogenic lipoprotein burden can be estimated by dividing apoB into Lp(a) and non-Lp(a) components. For example, apoB can be converted to molar concentration (nmol/L) using a conversion factor of 19.49; therefore, an apoB level of 100 mg/dL is equivalent to 1.949 nmol/L. By measuring Lp(a) in molar concentration, the ratio of apoB between the two lipoproteins can be determined.

However, some limitations remain: adjusting for apoB can explain almost all of the LDL-C-mediated risk but does not account for the Lp(a)-mediated risk, and measuring apoB can improve risk prediction in epidemiological studies, but it may be difficult to choose targeted therapies without measuring all atherogenic lipoproteins.

Accurate measurement of the cholesterol content of Lp(a) and its contribution to LDL-C has important implications for the risk assessment, diagnosis, and treatment of both atherosclerotic cardiovascular disease and familial hypercholesterolaemia, whether genetically confirmed or genetically negative [95]. **Figure 3** describes the steps in the analytical process.

Clinical critical issues and practical indications for interpreting Lp(a) measurements in cardiovascular risk stratification

Cardiovascular risk stratification in relation to Lp(a) concentration

The relationship between Lp(a) concentration and cardiovascular risk is continuous; as Lp(a) levels increase, cardiovascular risk rises linearly. Interpreting Lp(a) values as a dichotomous variable is limiting; instead, it is appropriate to use an integrated approach that considers Lp(a) levels as a continuum, in the context of other cardiovascular risk factors such as LDL-C, hypertension, and diabetes [91]. According to this approach, the clinical decision-making process does not depend exclusively on the presence of an elevated Lp(a) value, but on the degree of increase in Lp(a) in association with other individual risk factors, thus allowing estimation of the contribution of Lp(a) to an individual's overall risk.

For example, an Lp(a) concentration of 150 mg/dL results in an almost threefold increase in cardiovascular risk, regardless of the individual's baseline risk defined by canonical risk factors [96]. In a subject with a baseline risk of 20%, an Lp(a) concentration of 150 mg/dL (300 nmol/L) leads to an estimated overall risk increase of almost 50%, while in a subject with a baseline risk of 5%, the same Lp(a) concentration results in a relatively small overall risk increase

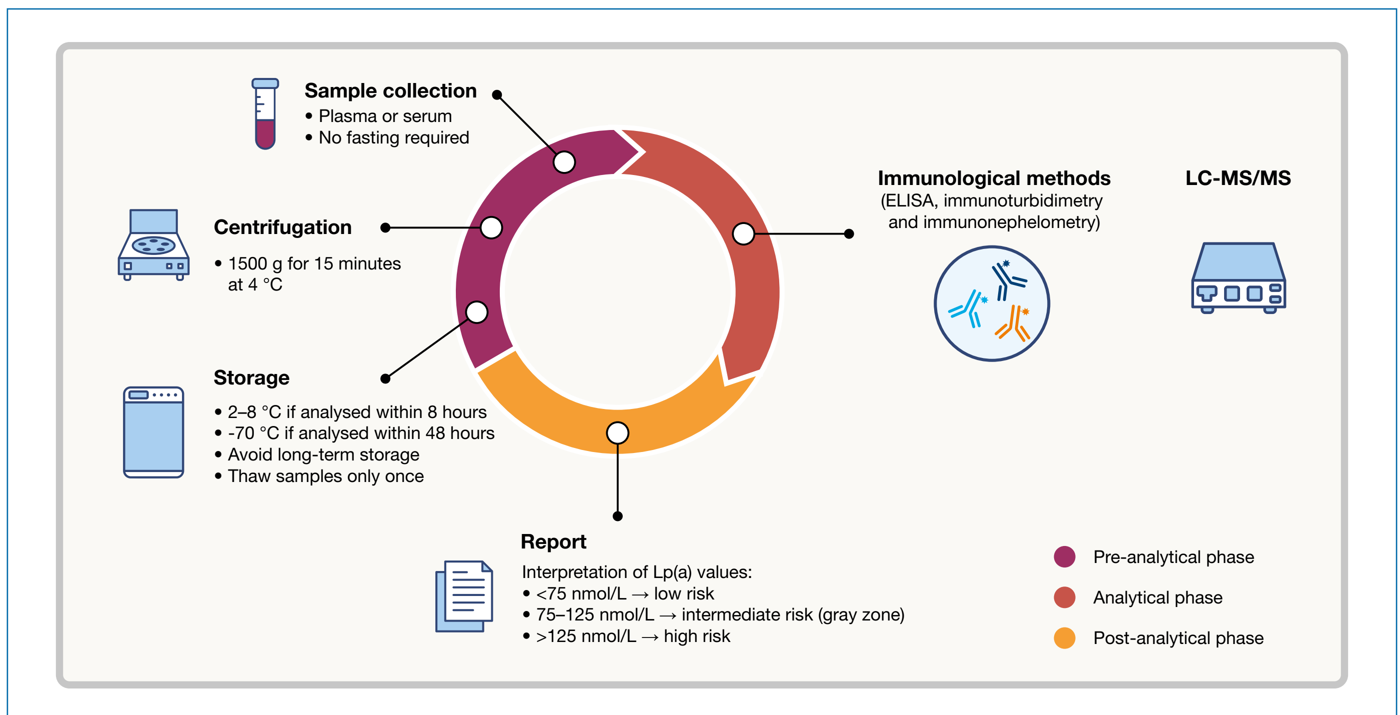

Figure 3 | **Phases of the analytical process in the determination of Lp(a) levels and reporting.** Note that the pragmatic approach to Lp(a) level and risk must be integrated with the overall risk assessment.

(approximately 15%). Therefore, Lp(a) can be considered a risk "enhancer".

Data on the association between Lp(a) levels and the risk of developing type 2 diabetes remain controversial. Lp(a) concentration does not appear to be associated with the risk of developing type 2 diabetes in individuals with prediabetes [97]. Post-hoc analyses of the ODYSSEY OUTCOMES trial have shown that baseline Lp(a) levels are inversely associated with the risk of developing diabetes, which, however, is not influenced by treatment with alirocumab [98].

Monitoring Lp(a) levels

Given the pathophysiological role of Lp(a), there is no category of subjects for whom its measurement is not recommended. Considering the cardiovascular risk associated with high levels of Lp(a) and their substantial stability in adulthood, guidelines recommend measuring Lp(a) at least once in each individual's lifetime (52, 99), to identify subjects at high risk of events and optimise primary prevention strategies [100].

From this perspective, Lp(a) can also serve as a parameter for reclassifying patients at moderate cardiovascular risk [52]. Several studies have shown that adding Lp(a) improve the prediction of traditional risk scores such as the Framingham risk score, Reynolds risk score, or Pooled Cohort Equations [101-104].

However, there are certain categories of subjects in whom there is a significant probability of elevated Lp(a) levels, which should necessarily be included in risk assessment. Among these are patients with a premature cardiovascular event (before age 55 for men or 65 for women). Patients with extreme Lp(a) values (≥180 mg/dL, 360 nmol/L) have a cardiovascular risk comparable to that of subjects with heterozygous familial hypercholesterolaemia [51], and cumulative exposure from a young age can result in a cardiovascular event in young subjects, even in the absence of other risk factors. Another group to consider is patients who experience recurrent events despite optimisation of classic cardiovascular risk factors [105].

Lp(a) is one of the risk factors that constitute the so-called "residual risk" in patients with atherosclerosis [106] and has been identified as an independent predictor of events, regardless of LDL-C levels [107-109]. Several studies have demonstrated a neutral effect or even an increase in Lp(a) levels with statin therapy [110, 111]. For this reason, in patients whose LDL-C values respond poorly to traditional lipid-lowering therapy, it is advisable to measure Lp(a), as it is possible that most of the LDL-C is incorporated into Lp(a) itself [112].

Finally, since Lp(a) is genetically determined, it is essential to perform cascade screening of first-degree relatives of patients with elevated Lp(a) levels [113].

Management of patients with elevated Lp(a) levels: Current pharmacological perspectives for reducing elevated Lp(a) levels

Current pharmacological perspectives for controlling Lp(a)

Lp(a) is considered an important pharmacological target for substantially reducing cardiovascular risk. However, the most commonly used lipid-lowering therapies, statins and ezetimibe, do not significantly lower Lp(a) levels [114-116].

A reduction in Lp(a) levels has been reported with PCSK9 inhibitors, including the monoclonal antibodies evolocumab and alirocumab (20-30%) [117, 118], as well as inclisiran (PCSK9 gene silencing therapy, -18.6% and -25.6% in ORION-10 and ORION-11 trial, respectively) [119, 120]. In the FOURIER study, patients treated with evolocumab who had Lp(a) levels >50 mg/dL benefited from a greater reduction in the risk of major atherosclerotic cardiovascular events (MACE) compared to those with lower Lp(a) (-2.4% in the first group vs -1.4% in the second group) [117]. Similarly, in a sub-analysis of the ODYSSEY OUTCOMES study, the absolute reduction in the risk of MACE was 3.7% in patients with Lp(a) >60 mg/dL compared to 0.5% in patients with Lp(a) <7 mg/dL at baseline [121]. In this study, 25% of the observed reduction in cardiovascular events was attributed to the 20 mg/dL reduction in Lp(a) by alirocumab in patients with Lp(a) >60 mg/dL at baseline [121]. This evidence confirms the need to evaluate Lp(a) as a pharmacological target.

The extent of Lp(a) reduction achieved with drugs that promote LDL-C catabolism is very similar to that observed with drugs that block the production of apoB-containing lipoproteins in the liver, including mipomersen (which inhibits apoB synthesis, reducing Lp(a) by 26%) [122] and lomitapide (which inhibits microsomal triglyceride transfer protein activity, stopping the assembly/lipidation of lipoproteins, and reduces Lp(a) by 17%) [123].

Evinacumab, which inhibits angiopoietin-like protein 3 (ANGPTL3) and thereby increases the lipolytic activity of endothelial lipases, promoting the catabolism of apoB-containing lipoproteins, is effective in reducing LDL-C levels in patients with HoFH, who do not express hepatic LDLR, but does not affect Lp(a) levels [124]. This suggests that forcing the catabolism of apoB-containing particles by an LDLR-independent mechanism does not increase Lp(a) catabolism. It is plausible that robust elimination of Lp(a) from the circulation could be achieved by exploiting catabolic pathways alternative to those of all apoB-containing lipoproteins, even when LDLR is deficient.

One clue in this regard may come from data showing that some emerging therapies for cardiovascular prevention can ensure a more robust reduction of Lp(a). For example, resmetirom, a selective agonist for the hepatic thyroid hormone receptor β and recently approved for the treatment of patients with chronic steatohepatitis and liver fibrosis, has demonstrated a reduction in Lp(a) of approximately 33%, compared with a more modest reduction in LDL-C (20%) [125].

The most potent inhibitors of cholesteryl ester transfer protein (CETP), involved in the exchange of cholesterol esters (CE) from apoB-containing particles to high-density lipoprotein (HDL) cholesterol, are also able to reduce Lp(a) levels. In addition to increasing HDL cholesterol (by an average of 104%) and reducing LDL-C (by an average of -41%), anacetrapib can reduce Lp(a) by -10 to -30% [126], while obicetrapib can reduce it by up to -56% [127]. The mechanism underlying this difference is unknown.

In summary, a reduction in Lp(a) levels of up to 25% can be achieved with approved LDL-C-lowering drugs. Mendelian randomisation studies suggest that a 22% reduction in cardiovascular risk (as observed, for example, following a ~40 mg/dL or 1 nmol/L reduction in LDL-C) is achieved when Lp(a) levels are reduced by at least 100 mg/dL [73, 128]. This implies that only a large and robust reduction in Lp(a) would translate into an effective reduction in cardiovascular risk. To date, therefore, all pharmacological approaches developed specifically against Lp(a) must reduce this lipoprotein to a greater extent in order to achieve a benefit in reducing risk.

The approaches currently under development are based on antisense oligonucleotides (ASOs) (pelacarsen) and small interfering RNA (siRNAs) (olpasiran, lepodisiran, and zerlasiran), designed with GalNAc technology to selectively target the liver [114]. The mechanism of action aims to degrade apo(a) mRNA, thus reducing its hepatic synthesi. In clinical studies, these therapies are showing a reduction in Lp(a) of over 80%, sustained over time.

In 2026, the results of the Lp(a)HORIZON study for pelacars-

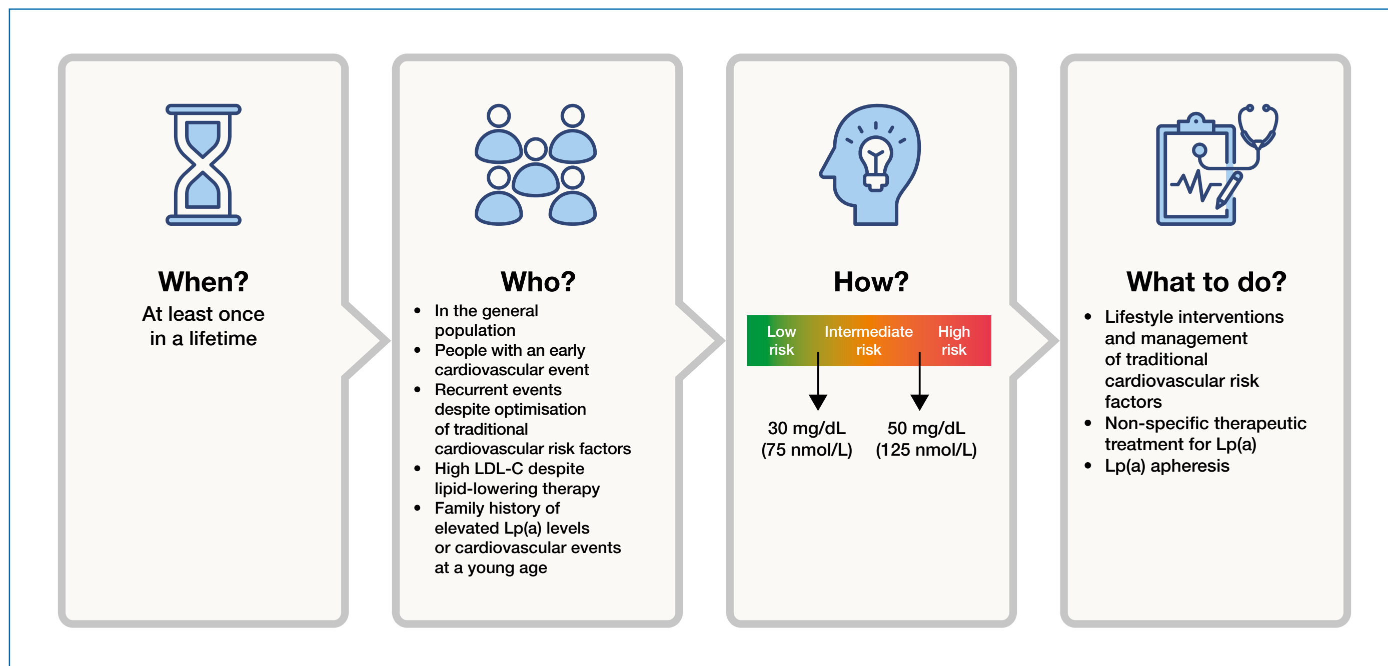

Figure 4 | **Roadmap for the assessment of Lp(a) levels in clinical practice.**

en (NCT04023552) [129] and the OCEAN(a) study for olpasiran (NCT05581303) on cardiovascular outcomes are expected. Both studies enrolled subjects at very high cardiovascular risk, but baseline Lp(a) levels differed (Lp(a) >70 mg/dL in the Lp(a)HORIZON study and Lp(a) ≥200 nmol/L in the OCEAN(a) study). A high intra-individual variability in serial Lp(a) measurements has been observed, suggesting the need for routine clinical assessment of Lp(a) to determine the reliability of single Lp(a) measurements.

Two additional approaches to target Lp(a) have been proposed:
1) an oral inhibitor of apo(a) assembly with apoB-containing lipoprotein (muvalaplin) [130], and
2) gene editing, either via CRISPR-Cas9 [131] or TALEN technology (132), both of which are currently under development.

Current management perspectives for patients with elevated Lp(a) levels

For patients at higher cardiovascular risk, with a history of recurrent cardiovascular events, even if all risk factors are already controlled, and with very high Lp(a) levels, Lp(a) plasmapheresis is currently the most effective available strategy, although it is a highly invasive procedure [4, 133, 134]. It should be emphasised that Lp(a) plasmapheresis has demonstrated significant efficacy in reducing cardiovascular events in treated patients [135, 136].

The first essential step in treating patients with elevated Lp(a) levels is to optimise lifestyle and all other cardiovascular risk factors, based on the goals recommended for the risk class determined by multiparametric assessment (**Figure 4**).

Conclusions

Lp(a) is now recognised as a key risk factor in cardiovascular risk assessment, due to its causal and independent role in the development of both atherosclerotic disease and aortic valve stenosis. Its heterogeneous structural characteristics, metabolic specificities, and ability to transport pro-atherogenic, pro-inflammatory, and pro-thrombotic components make it unique among apoB-containing particles.

Accurate measurement of Lp(a) remains challenging, mainly due to the variability of apo(a) isoforms, which can significantly influence test results. Standardisation of analytical methods and the use of molar units (nmol/L) are essential to effectively integrate this risk factor into clinical practice. It is also important to consider the contribution of Lp(a) when estimating LDL-C, particularly in patients with elevated Lp(a) levels, to avoid underestimating risk and to optimise therapeutic strategies.

Current guidelines recommend measuring Lp(a) at least once in a lifetime, highlighting its usefulness in stratifying and reclassifying cardiovascular risk, especially in cases of premature or recurrent events, or in patients with a suboptimal response to lipid-lowering therapy. Early identification of high-risk individuals is a crucial step towards personalised medicine, which also considers the residual risk that cannot be modified with conventional treatments.

Although currently available therapeutic options have a limited impact on Lp(a) levels, specific therapies are in advanced stages of development and promise significant reductions in plasma Lp(a). The expected results from large ongoing clinical trials will be crucial in clarifying the actual cardiovascular benefit of targeted Lp(a) reduction and could pave the way for new paradigms in secondary prevention.

In conclusion, Lp(a) is now not only an emerging risk factor, but a consolidated and recognised determinant of cardiovascular risk, whose integration into clinical assessment has become essential. Lp(a) measurement, if appropriately interpreted within a comprehensive approach to risk stratification, allows for more precise and personalised management of cardiovascular patients, improving the ability to identify individuals at high residual risk who cannot be fully identified with traditional factors alone.

In this process of clinical innovation, a fundamental role has been played by the relevant scientific societies, such as SISA, SIC, AN-

MCO, and SIBIOC. These societies, through careful analysis of the most up-to-date scientific evidence and a shared vision of real clinical needs, have helped promote a cultural and operational change that has led to the recognition of Lp(a) as a key element in modern cardiovascular prevention.

The resulting document therefore represents a milestone in this process, laying the foundation for the increasingly widespread dissemination of knowledge and clinical use of Lp(a), and for the development of future targeted therapeutic strategies, with a view to increasingly predictive, preventive, and personalised medicine.

Acknowledgements

The authors wish to thank Novartis Pharma for their unconditional support for the project.

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