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State-of-the-Art Review

Rethinking cardiovascular risk: The emerging role of lipoprotein (a) screening

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a genetically inherited, independent risk factor for cardiovascular disease (CVD), affecting approximately 20–25% of the global population. Elevated Lp(a) levels are associated with a 2–3-fold increased risk of myocardial infarction and aortic valve stenosis, comparable to the risk seen in individuals with familial hypercholesterolemia. Despite its clinical relevance, the integration of Lp(a) screening into routine practice has been limited by inconsistent measurement techniques and a lack of targeted treatments. Recent advancements, including improved assays and the development of potential Lp(a)-lowering therapies, have renewed focus on the importance of Lp(a) screening.

This review aims to clarify the role of Lp(a) in cardiovascular health by examining current evidence on who should be screened, when screening should occur, and the most accurate methods for measuring Lp(a). Key recommendations include universal, one-time screening for adults, selective screening for high-risk pediatric patients, and special considerations for individuals with conditions such as familial hypercholesterolemia and chronic kidney disease. Advances in assay technology now allow for more precise Lp(a) measurement, supporting better risk stratification. Additionally, emerging therapies that specifically target elevated Lp(a) levels could lead to more personalized management of CVD risk.

Our findings support the integration of Lp(a) screening into routine cardiovascular risk assessment, highlighting its potential to improve early detection and prevention strategies across diverse patient populations.

1. Introduction

Lipoprotein (a) [Lp(a)] is a genetically determined causal and independent risk factor for the development of cardiovascular disease (CVD). It is believed to be the most common genetic disorder of cholesterol, affecting between 20–25% of the world population [1]. Individuals with high Lp(a) (>50 mg/dL) have a 2–3-fold increased risk of myocardial infarction (MI) [2] and aortic valve stenosis (AVS) [3], while those with extremely elevated levels (>180 mg/dL) exhibit a CVD risk comparable to those with untreated Familial Hypercholesterolemia (FH), an autosomal co-dominant disorder characterized by an extremely high CVD risk [4].

Despite its well-established role as a CVD risk factor, the integration of Lp(a) testing into routine clinical practice remains limited. Recent studies have highlighted alarmingly low testing rates, with only 0.3% of adults undergoing Lp(a) testing in a major academic health system over a decade, even among high-risk populations such as those with CVD or a family history of premature cardiovascular events [5]. This low uptake reflects several barriers, including limited awareness among clinicians about Lp(a) as a risk factor, inconsistent guidelines, and uncertainties about clinical management for patients with elevated levels [5–9]. Additionally, variations in assay techniques and concerns over insurance coverage have further hindered broader adoption [5].

Fortunately, this landscape is advancing for the better. Advances in our understanding of Lp(a) pathophysiology have highlighted the significance of genetics and isoform size. Elevated Lp(a) is now recognized as a universal risk factor across ethnicities [10], in those without a family history of ASCVD [11], and even in the young [12]. The clinical implications of elevated Lp(a) have expanded beyond MI and AVS to include peripheral arterial disease, abdominal aortic aneurysms, and major adverse limb events [13]. Improvements in measurement techniques now provide more accurate Lp(a) assessments, enhancing risk

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evaluation [14,15]. Moreover, the development of Lp(a)-targeted therapies, such as siRNA treatments, alongside evidence suggesting that lipoprotein apheresis can improve cardiovascular outcomes in patients with elevated Lp(a) levels [15,16]' underscores the growing clinical relevance and potential for targeted intervention [1,2].

Given these advancements, it is important to enhance the clinical understanding and utility of Lp(a) measurements. This paper aims to synthesize current evidence, focusing on refining screening practices and ensuring accurate Lp(a) level reporting. By addressing these aspects, we seek to clarify Lp(a)'s role in cardiovascular health and propose more targeted strategies for understanding its associated risks.

1.1. Who to screen

Previously, the 2018 AHA Multi-Society Cholesterol Guidelines suggested Lp(a) screening for individuals with a family history of premature ASCVD or a personal history of unexplained ASCVD, but no formal recommendations were provided [6]. By 2019, the National Lipid Association (NLA) emphasized Lp(a) testing for individuals with a first-degree relative with premature ASCVD, personal history of premature ASCVD, LDL-C >190 mg/dL, or heterozygous familial hypercholesterolemia (HeFH) to better identify those who may benefit from PCSK9 inhibitors [7]. Most recently, the updated NLA guidelines and European guidelines now recommend universal Lp(a) testing at least once in a lifetime for all adults, given the growing evidence of its significance in cardiovascular risk assessment [9,17].

Recent advancements in research have confirmed that the benefits of screening for Lp(a) outweigh the risks [18]. Early detection of elevated Lp(a) offers additional prognostic insights for ASCVD, MI, and AVS [19], facilitating personalized management strategies that can lead to significant cost savings and improved patient outcomes, even in the absence of Lp(a)-targeting therapies [18]. As targeted therapies for Lp(a) continue to advance, recent reviews have emphasized the importance of leveraging existing methodologies to lower Lp(a) levels and achieve significant improvements in cardiovascular health [20,21]. Preventive measures, including healthy lifestyle modifications and cholesterol-lowering medications such as statins, have been shown to effectively reduce cardiovascular risk in patients with elevated Lp(a) levels [11]. Additionally, evidence supports the use of PCSK9 inhibitors, which lower Lp(a) by approximately 25%, alongside their LDL-cholesterol-reducing effects, offering tangible benefits for high-risk individuals [22,23]. Aspirin and prolonged dual antiplatelet therapy (DAPT) have also shown promise in reducing cardiovascular events, particularly in specific high-risk scenarios [24,25]. For the most severe cases, lipoprotein apheresis provides an effective, though invasive, method to lower Lp(a) levels [26]. These strategies underscore that Lp(a) screening is not just diagnostic but actionable, allowing for targeted interventions that can meaningfully reduce cardiovascular risks and improve long-term outcomes.

Thus, and in line with the latest institutional recommendations [17], **we advocate for universal Lp(a) screening for every adult at least once in their lifetime.** Given the substantial cardiovascular risk associated with elevated Lp(a), independent of traditional risk factors, a one-time measurement is essential for identifying individuals at higher risk for cardiovascular disease, even if other risk factors are well-managed. We will discuss specific screening recommendations for different populations in more detail below.

1.2. Pediatrics

The clinical significance of elevated Lp(a) in children remains complex and controversial. While some studies have linked elevated Lp(a) to arterial ischemic stroke in the pediatric population [27], there is insufficient evidence to definitively establish a relationship between elevated Lp(a) levels and first-time arterial ischemic stroke, cerebral sinus vein thrombosis, or venous thromboembolism in children [28]. However, research by DeVeber et al. demonstrated that isolated elevated Lp(a) levels (>30 mg/dL) were independently associated with an increased risk of recurrent stroke, with a median time to recurrence of three months [29]. Although more well-designed and larger studies are necessary to confirm the role of Lp(a) in childhood-onset stroke and thromboembolism, **it is currently recommended that Lp(a) be measured in all children with a history of arterial ischemic stroke to mitigate the risk of recurrence** [17]. Observational studies in these patients have shown a significant reduction in recurrent cerebrovascular events with the use of lipoprotein apheresis [27].

There is also a strong correlation between childhood and adult Lp(a) levels, with significant clinical implications for early-onset ASCVD [30,31]. Elevated Lp(a) (>30 mg/dL) measured in individuals aged 9 to 24 years has been linearly associated with an increased incidence of cardiovascular events in middle adulthood. Specifically, children with Lp(a) above 30mg/dL have approximately twice the risk of ASCVD events as adults compared to those without elevated Lp(a) [32]. These findings were corroborated by the Bogalusa Heart Study, which revealed that individuals aged 8 to 17 with high Lp(a) levels had a 2.5-fold greater risk of developing CVD in adulthood compared to those with normal levels [33]. Furthermore, Lp(a) was found to independently and additively confer risk alongside low-density lipoprotein cholesterol (LDL-C). Children with both elevated Lp(a) and elevated LDL-C levels (>130 mg/dL) exhibited more than a fourfold increased risk for premature ASCVD in adulthood.

These results bolster the argument for pediatric Lp(a) screening, particularly in children with cardiovascular risk factors or those with established or suspected FH [32]. This approach is consistent with the American Academy of Pediatrics' recommendations for universal lipid screening in pediatric patients, aimed at addressing the growing rates of dyslipidemia and CVD among youth in the United States [34]. Although the clinical manifestations of atherosclerosis typically present in adulthood, it is well established that the disease's pathological origins begin in childhood. **Therefore, it is reasonable to also include Lp(a) screening as part of a comprehensive lipid panel for children with cardiovascular risk factors such as obesity, hypertension, diabetes, familial dyslipidemia, family history of premature ASCVD (before age 55 in men and 65 in women), or first-degree relatives with elevated Lp(a)** [17,35]**.** This recommendation is especially pertinent for patients with established or suspected FH, as will be discussed in more detail below.

1.3. Familial hypercholesterolemia

Individuals with FH face a particularly high risk of ASCVD due to their elevated LDL-C levels (typically >150mg/dL) [36]. This risk is further compounded by elevated Lp(a) levels [37]. Elevated Lp(a) significantly contributes to arterial wall thickening, a surrogate marker for atherosclerosis, in those with FH [38]. Compared to individuals without FH, those with the condition generally have higher Lp(a) concentrations, irrespective of their CVD history [39,40]. This relationship is partly driven by genetic variants that cause FH, such as mutations in the LDL receptor (LDLR) gene, which can lead to increased Lp(a) levels [36]. High Lp(a) levels in FH patients are associated with an increased risk of CVD [40,41]. Specifically, FH patients with Lp(a) levels >30 mg/dL have a 1.5-fold increased risk of cardiovascular events [42], while those with Lp(a) levels >56 mg/dL have a 2.5-fold greater risk [43]. **These findings underscore the importance of routine screening and vigilant management of both LDL-C and Lp(a) in this high-risk population** [44].

In patients where FH is suspected but not confirmed, screening for elevated Lp(a) levels is crucial. Elevated Lp(a) can contribute to the FH phenotype, even in the absence of a detectable genetic mutation for FH [45]. This is because the proportion of LDL-C attributable to Lp(a) cannot be distinguished unless Lp(a) is specifically measured (*See more in the section: LDL-C Screening)*. Consequently, elevated Lp(a) levels may

lead to an overestimation of LDL-C, potentially resulting in a false diagnosis of FH. This issue is particularly significant in cases with very high Lp(a) levels, where the median error in estimated LDL-C can increase substantially—by up to 30 mg/dL when Lp(a) exceeds 50 mg/dL—further complicating clinical management [46]. The LIPIGEN Network study confirmed that very high Lp(a) levels accounted for some misdiagnoses of FH in individuals with elevated LDL-C but negative genetic testing for FH [45]. Moreover, patients phenotypically suggestive of FH but with negative genetic testing were found to have higher median Lp(a) levels compared to those with genetically confirmed FH, who already have higher-than-average Lp(a) levels [39]. These findings suggest that elevated Lp(a) may pose a greater cardiovascular risk than a genetic diagnosis of heterozygous FH [35].

Therefore, when FH is suspected based on extremely high LDL-C levels, it is essential to screen for elevated Lp(a) before proceeding with genetic testing. This recommendation applies even in pediatric cases where FH is suspected. Differentiating between FH, elevated Lp(a), or a combination of both is crucial for accurate risk stratification and treatment. (*See more in the section: Cascade Testing).*

1.4. Ethnicity

The implications of elevated Lp(a) across different ethnicities are intricate, and the debate around appropriate screening recommendations is ongoing. Large, multi-ethnic epidemiologic studies have demonstrated a trend of increasing median Lp(a) values across East Asian, Latino, White, South Asian, and Black ethnic groups, respectively [10,47–49]. However, despite consistent reporting of population-specific median Lp(a) levels, the clinical implications remain variable. (*See more in the sections: Black Ethnicity, South Asian Ethnicity, and Hispanic Ethnicity under SCREENING INTERPRETATION).* This variability has led some researchers to suggest ethnicity-specific Lp(a) cutoff levels [47], but there has been a reluctance to adopt these due to historically limited sample sizes of non-White ethnic groups and inconsistencies in measurement techniques. As a result, there is a growing call for more comprehensive studies to better understand Lp(a) levels across different ethnicities [50,51].

The UK Biobank study, the largest study of its kind, made significant strides in this area by employing a uniform calibrated assay and offering detailed characterization of Lp(a) risk across multiple populations [10]. This study was pivotal in defining the linear relationship between Lp(a) levels and cardiovascular risk across different racial and clinical subgroups. However, while the study included individuals from various ethnicities, the cohort was predominantly White (>90%), limiting its ability to fully capture the implications of elevated Lp(a) in underrepresented populations.

Despite differences in population median Lp(a) levels, the study affirmed a universal principle: increased median Lp(a) levels correspond to a linear increase in ASCVD risk across included ethnic groups [10]. Notably, a 50 nmol/L increase in median Lp(a) concentration was associated with a consistent hazard ratio among ethnic groups [10]. In other words, while ethnic groups with higher median Lp(a) levels may face greater absolute risks compared to those with lower levels, the relative increase in risk across different ethnic groups remains similar. This suggests that despite varying average Lp(a) levels among populations, elevated Lp(a) levels pose a comparable risk to individuals across various ethnicities.

As our understanding of the ethnicity-specific implications of elevated Lp(a) improves, ethnicity-specific Lp(a) cutoffs may become more appropriate, particularly as we observe the impact of Lp(a)-lowering agents on clinical risk across different populations. **However, with current data, it remains premature to establish ethnicity-specific screening recommendations. Further studies with more diverse and representative cohorts are necessary to determine whether ethnicity-dependent cutoffs should be developed and implemented in clinical practice.** The data on specific ethnicities will be discussed in greater detail below.

Summary of WHO TO SCREEN Recommendations:

- **General Population:** Universal Lp(a) screening is recommended for every adult at least once in their lifetime, regardless of traditional cardiovascular risk factors.
- **Pediatric Patients:** We recommend including Lp(a) screening as part of the initial comprehensive lipid panel for children, particularly those who are considered high-risk. This group includes children with:
  1. History of ischemic stroke
  2. Clinically suspected or genetically confirmed FH.
  3. First-degree relatives with a history of premature ASCVD (age <55 years in men, <65 years in women).
  4. First-degree relatives with elevated Lp(a).
  5. Other cardiovascular risk factors including obesity, hypertension, diabetes or other glucose metabolism disorders, or familial dyslipidemia.
- **Familial Hypercholesterolemia:**
  1. Individuals with FH should undergo regular screening and management of both LDL-C and Lp(a) levels.
  2. Lp(a) levels should be measured in all individuals, including children, with presumed FH before genetic testing
- **Patients of Different Ethnicities:** While ethnicity-specific screening recommendations are not yet established, screening should be considered for all ethnicities, as Lp(a) poses a comparable cardiovascular risk across different populations.

1.5. When to screen

Lp(a) is a well-established independent and causal risk factor for cardiovascular disease, particularly in young patients with premature CVD [12]. **Therefore, if Lp(a) levels have not already been assessed during pediatric lipid screening, it is recommended that Lp(a) be included in an individual's first adult lipid panel to ensure early identification and risk stratification for cardiovascular disease.** The necessity for additional screenings will be discussed in the following sections.

1.6. Pediatric screening

The COMPARE study demonstrated that Lp(a) levels are low at birth and gradually rise during early childhood, with most infants reaching adult-like levels by 15 months [52]. This aligns with the full expression of the LPA gene, supporting earlier findings that adult levels were reached by age two [53]. However, a more recent study by de Boer et al., which tracked Lp(a) levels in nearly 3000 children, found that Lp(a) levels continue to rise throughout childhood [38]. The study revealed that the majority of children showed at least a 20% variation between two measurements, with intra-child differences reaching up to 70%. While some children had stable Lp(a) levels by 15 years of age, others continued to show increasing levels up to age 20. As a result, the latest guidelines now recommend considering five years of age as the point of stabilization [8,17]. **Therefore, if Lp(a) screening is indicated based on previously outlined criteria, an initial screen around 2 years of age is reasonable. If the levels are already high (>50mg/dL), the patient can be categorized as high-risk. If levels are in the intermediate range (30–50mg/dL), repeat testing through early adulthood is advisable until stabilization occurs.**

1.7. Repeat screening

Lp(a) levels generally remain stable throughout adulthood and are minimally influenced by lifestyle factors such as diet or physical activity [54]. However, notable exceptions include individuals undergoing menopause, those with liver or kidney disease, individuals on exogenous hormonal treatments, or those with thyroid hormone imbalances, as these conditions can lead to significant fluctuations in Lp(a) levels [55]. These variations will be explored further in the following sections. **Therefore, serial Lp(a) testing is not typically recommended for adult patients, as repeated measurements do not improve risk prediction** [56]. **Even with advancements in measurement**

methods, repeating screening in individuals previously identified with pathologically high Lp(a) levels remains unnecessary, as a single Lp(a) measurement is sufficient to determine elevated levels, regardless of variations in cut-off points or assay types [57]. However, with the development of Lp(a)-specific lowering therapies, serial monitoring for 'target Lp(a)' levels may become more relevant, warranting further research and exploration.

1.8. Repeat screening special cases– sex

Lp(a) levels tend to increase with age in both sexes, although the pattern differs [58]. In men, the rise is gradual, while women experience a significant surge around the age of 50, which may be linked to post-menopausal hormonal changes (Fig. 1) [59]. In the Copenhagen General Population Study, women aged 50 to 59 showed an 18% increase in Lp(a) levels compared to those aged 20 to 49, even after adjusting for factors such as eGFR, estradiol, and hormone replacement therapy (HRT) [58]. This trend has been observed in prior studies and referenced in society guidelines [60]. Notably, in the Copenhagen General Population Study, age-related differences in Lp(a) levels between women and men were not linked to differences in CVD morbidity or mortality [58]. However, a systematic review suggested that elevated Lp(a) levels are associated with an increased risk of coronary heart disease (CHD) in postmenopausal women, though a similar relationship with other CVD events has not been established [61].

It remains unclear whether the rise in Lp(a) is driven by menopause or age, but it may be reasonable to recheck peri- and post-menopausal women's Lp(a) levels, especially if they were previously in the intermediate risk range (30–50mg/dL). Further research is needed to clarify the impact of elevated Lp(a) levels on CVD risk in aging women.

1.9. Repeat screening special cases– liver disorders

Since the liver is the primary site for the synthesis of Lp(a) molecules, liver disease can significantly alter Lp(a) levels [55]. Generally, Lp(a) levels have been observed to significantly decrease in association with liver disease, likely due to impaired Lp(a) synthesis [55,62–64]. For instance, a study of patients with non-alcoholic fatty liver disease (NAFLD) found that Lp(a) levels were significantly lower in patients with advanced fibrosis (stage 3–4) compared to those with non-advanced fibrosis (stage 0–2) [63]. While these findings are consistent with previous research, this was the first study to evaluate the implications of decreased Lp(a) levels for CVD risk. The study concluded that the reductions in Lp(a) due to liver dysfunction complicate its use as a reliable predictor of CVD risk and likely reflect impaired liver function rather than changes in cardiovascular risk. **Therefore, despite fluctuations in Lp(a) levels—sometimes as high as 41%** [64]**—rechecking Lp(a) is not recommended for assessing changes in cardiovascular risk in patients with liver disease.**

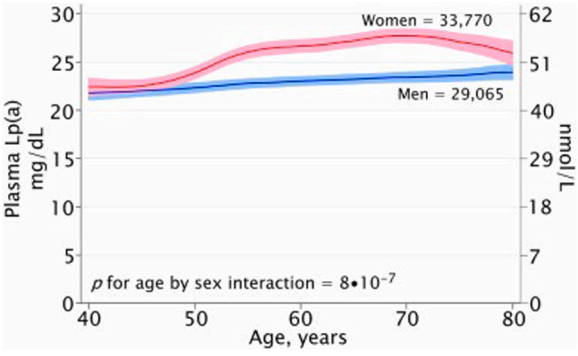

Fig. 1. Average Plasma Lipoprotein(a) Levels Across Different Ages in Women and Men
The data shows a trend of increasing Lp(a) levels with age, with women generally having higher average levels compared to men. Statistical significance for the interaction between age and sex is indicated by the p-value.

1.10. Repeat screening special cases– kidney disorders

Contrary to liver disease, which usually results in reduced Lp(a) levels, kidney disease tends to significantly elevate Lp(a) concentrations [55]. Even at the early stages of renal impairment, Lp(a) levels rise as kidney function (measured by eGFR) decreases, and in severe chronic kidney disease (CKD), particularly in patients on dialysis, Lp(a) levels can be five to ten times higher than in those with mild CKD [65,66]. Interestingly, this increase in Lp(a) in CKD patients appears to be influenced by isoform size, with larger isoforms being more prevalent [67].

Multiple studies have explored whether elevated Lp(a) levels contribute to increased cardiovascular risk in CKD patients. However, their conclusions have been inconsistent. Lp(a) elevations in non-nephrotic CKD are generally seen in individuals with larger apo(a) isoform sizes, which correlates with lower genetically determined plasma Lp(a) levels. Consequently, even a large relative increase in plasma Lp(a) in these individuals might only yield a small absolute difference in Lp(a) levels and a correspondingly small increase in cardiovascular risk [68]. For example, doubling Lp(a) from 5 to 10 mg/dL is expected to increase risk by just 5% [68]. This may explain the inconsistency in study outcomes. In the Cardiovascular Health Study, no significant association between Lp(a) and cardiovascular mortality was found among 1249 CKD patients, despite a significant association in non-CKD individuals [69]. Conversely, other studies have shown that higher Lp(a) levels and smaller apo(a) isoform sizes are independent risk factors for cardiovascular disease in hemodialysis patients, potentially due to the prolonged residence time of Lp(a) in circulation in these patients.

For instance, Kronenberg et al. demonstrated that small apo(a) isoform size was an independent predictor of coronary events in 440 hemodialysis patients, showing a two-fold increased risk of atherosclerosis [70]. The CHOICE study, a prospective analysis of outcomes among Black and White dialysis patients, found that both apo(a) size and high Lp(a) levels predict ASCVD risk in dialysis patients [71]. However, the association of ASCVD with small apo(a) isoforms was stronger than the association with high Lp(a) concentrations. Specifically, Lp(a) levels in the top 10% ($\geq$206 nmol/L) were associated with a 60–90% increased risk of ASCVD (relative hazard [RH] = 1.71; 95% CI: 1.11–2.65; p = 0.015), while small apo(a) isoforms ($\leq$16 K-IV repeats) were linked to a 40–100% increase in ASCVD risk (RH = 2.0; 95% CI: 1.27–3.14; p = 0.003). Similarly, small apo(a) isoforms have been linked to carotid atherosclerosis in ESRD patients [72]. The 4D study of 1255 hemodialysis patients with type 2 diabetes, however, found no significant association between higher Lp(a) levels or small isoforms with combined cardiovascular events (HR 1.04; 95% CI, 0.97–1.11; $P = 0.30$) [73].

More recently, the CRIC study, which followed nearly 4000 non-dialysis dependent CKD patients for 7.5 years, found a weak positive association between elevated Lp(a) and myocardial infarction risk [74]. However, event rates were unexpectedly lower in the second quartile of Lp(a) levels compared to the first, raising additional questions and highlighting the need for more research in this area.

Given the already elevated cardiovascular risk in patients with renal impairment, alongside data suggesting a potential increased Lp(a)-associated cardiovascular risk, especially in advanced CKD stages, it may be prudent to consider rechecking Lp(a) levels in CKD patients who previously had intermediate-range Lp(a) levels. This reassessment may be particularly relevant for patients starting dialysis, as their Lp(a) levels could rise significantly, warranting closer monitoring and potentially more aggressive management to mitigate further cardiovascular risk.

1.11. Repeat screening special cases – hormone replacement therapy

HRT significantly reduces Lp(a) concentrations, with oral administration being more effective than transdermal methods [55]. Meta-analyses have shown that HRT can result in up to a 20% reduction in Lp(a) levels, which was once considered a potential strategy to offset the increased CVD risk observed in post-menopausal women due to elevated post-menopausal Lp(a) levels [75]. However, recent studies examining the change in CVD risk in individuals taking HRT have shown that, despite the observed decrease in Lp(a) levels, there was no corresponding reduction in CVD risk [61,76]. **As a result, rechecking Lp(a) levels in individuals on HRT is not recommended as a means of evaluating CVD risk.**

1.12. Repeat screening special cases—thyroid hormone imbalances

Thyroid hormones play a crucial role in lipid metabolism, synthesis, and mobilization, and both overt and subclinical hypothyroidism have been shown to significantly alter lipid profiles and increase cardiovascular risk. In hyperthyroidism, lipid levels tend to decrease, while in hypothyroidism, lipid levels, including Lp(a), tend to increase [55]. Thyroid disease impacts Lp(a) levels due to its effect on the expression of the LDL-C receptor gene, through which Lp(a) is processed [77]. Recent studies have demonstrated that Lp(a) levels are significantly elevated in both hypothyroid and subclinical hypothyroid groups, which contributes to an increased risk of CVD [78]. **Therefore, rechecking Lp(a) levels in patients with hypothyroidism who were previously in an intermediate range is reasonable.**

1.13. Cascade screening

Cascade testing for elevated Lp(a) is a highly effective and reasonable strategy for identifying new cases of elevated Lp(a) [79]. This approach is widely recognized as an efficacious and cost-effective method for screening FH. Given that Lp(a) also exhibits autosomal co-dominant heritability, with a high correlation between parents and offspring levels, cascade screening is particularly pertinent. A recent study of the UK Biobank demonstrated that nearly 47% of first-degree relatives and 32% of second-degree relatives of individuals with elevated Lp(a) levels (≥125 nmol/L) were similarly affected, compared to only 16% of unrelated individuals. The study also found that the number needed to screen was only 2.1 for first-degree relatives and 3.1 for second-degree relatives, underscoring the efficiency of cascade screening for identifying at-risk family members [80]. Furthermore, extremely high Lp(a) levels (>180mg/dL) are associated with a CVD risk comparable to that of FH, and such levels are found in approximately twice as many individuals, strengthening the case for cascade testing as a screening tool for elevated Lp(a) [81].

The SAFEHEART trial in 2019 demonstrated that incorporating Lp(a) testing into cascade screening for FH was both valuable and effective [41]. Since then, multiple guidelines have recommended Lp(a) screening during cascade screening for FH [7,2,82]. Following these recommendations, a smaller study from Australia found that cascade testing for elevated Lp(a) in families with isolated elevated Lp(a) (>100 mg/dL) and no family history of FH is also an effective screening method [79]. In this study, one new case of elevated Lp(a) (>50mg/dL) was detected for every 1.5 relatives tested, with a higher yield of detection in families with higher Lp(a) levels.

Therefore, individuals with a family history of elevated Lp(a) should undergo cascade screening, including pediatric patients, to effectively identify and manage elevated Lp(a) levels. This strategy is particularly crucial for first-degree relatives, as studies have shown they are significantly more likely to inherit elevated Lp(a) levels.

Summary of WHEN TO SCREEN Recommendations:

(continued on next column)

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- •**First Time Adult Screening:** Lp(a) should be included as part of an individual's first adult lipid panel.
- **Pediatric Screening:**
  1. If indicated, pediatric patients can be screened as early as 2 years old or during their first comprehensive pediatric lipid screen.
  2. For patients determined to be in the intermediate risk range (30–50 mg/dL), it is reasonable to obtain repeat measurements until levels stabilize.
- **Repeat Screening:** Once Lp(a) levels have stabilized, serial Lp(a) testing is generally not recommended as it does not improve risk prediction. However, repeat screening should be considered in patients who were previously in the intermediate risk range (30–50mg/dL) and have:
  1. Undergone menopause
  2. Kidney disease, particularly CKD or nephrotic syndrome, or have initiated dialysis
  3. Hypothyroidism
- **Cascade Screening:** Cascade screening should be performed on individuals with a family history of elevated Lp(a), including pediatric patients, with a focus on first-degree relatives who are significantly more likely to inherit elevated Lp(a) levels.

2. How to screen

2.1. Assay type

Historically, measuring Lp(a) has been challenging due to assay sensitivity to the variable number of repeat Kringle IV (KIV) units on the apo(a) component of Lp(a) [83]. Older polyclonal antibody assays often targeted these variable KIV subunits, potentially binding multiple times to larger isoforms on a single Lp(a) molecule, leading to false inflation of measured levels. Consequently, these "isoform-sensitive" assays tended to overestimate levels in patients with large isoforms and underestimate them in patients with small isoforms—sometimes by as much as 25–35% [84]. This affects most clinical assays, regardless of whether they report Lp(a) levels in mass units (mg/dL) or molar concentrations (nmol/L). While molar assays are preferred due to fewer assumptions and the ability to calibrate using a reference standard, many still exhibit isoform sensitivity because they rely on polyclonal antibodies. Moreover, evidence suggests that Lp(a) molar concentration correlates with ASCVD risk independent of Lp(a) mass, but not vice versa [85].

Newer monoclonal antibody assays have been developed to bind only the non-repeat segments of Lp(a), addressing this limitation [83]. By binding to Lp(a) just once, regardless of KIV unit variation, these assays are considered "isoform-insensitive" and are now the gold standard for Lp(a) measurement [54].

While monoclonal assays have shown promise in research settings, they are not yet clinically available. For example, a monoclonal antibody assay recently developed at the University of California San Diego [14] offers comparable accuracy to the University of Washington's assay [54], raising hopes for future clinical implementation. Additionally, the University of Washington has pioneered a reference method using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to standardize assays to the International System of Units (SI) [86,87]. This method has been found comparable to the monoclonal antibody assay and is currently used for biomarker standardization, though it is not yet available for commercial clinical use. The Denka-Seiken assay (Japan), which minimizes sensitivity to apo(a) isoform size and provides results in nmol/L, is another widely available option [15]. This assay has been calibrated with reference materials from the World Health Organization (WHO) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), significantly improving assay accuracy. Although WHO/IFCC reference materials are no longer available, this validation method supports the use of these assays until new reference materials become available [15]. While global standardization remains a critical challenge, collaborative initiatives to standardize assay methods globally are underway, with particular emphasis on molar concentration reporting (nmol/L) to ensure consistent cardiovascular risk assessments across different clinical settings [88].

In conclusion, we recommend monoclonal antibodies that measure Lp(a) in nmol/L as the gold standard for Lp(a) quantification. It is crucial to note that values in nmol/L do not always indicate the use of these assays, as some laboratories use a proxy conversion factor to derive nmol/L from mg/dL [83]. **If these assays are unavailable, using assays validated by the University of Washington or the Denka-Seiken assay provides accurate results suitable for clinical settings. Overall, most currently available assays, including those reporting values in mg/dL, are suitable for general risk assessment, such as determining whether Lp(a) levels indicate low or high cardiovascular risk** [54].

2.2. Mg/dL to nmol/L conversion

There is no standard factor to accurately convert between mg/dL and nmol/L for Lp(a) concentrations [89]. Although a conversion factor of 2–2.5 has been suggested, it is only an approximation and should not be relied upon [86,87]. A study by Tsimikas et al. demonstrated that conversion factors between nmol/L and mg/dL can vary significantly depending on the assay method and the apo(a) isoform size [89]. For example, conversion factors ranged from as low as 0.50 to as high as 11.46 across different assays.

Interestingly, the conversion factor tended to be larger with fewer KIV repeats, likely due to the higher mass concentration for the same molar concentration observed in smaller isoforms. This is attributed to the greater protein density in Lp(a) molecules with fewer KIV repeats. This variability underscores the challenge of using a single conversion factor and highlights the importance of applying validated reference methods when comparing Lp(a) levels across studies. It is also important to note that this study was conducted predominantly in a European patient population, which may limit the generalizability of the findings to other ethnic groups. (*See more in the section: Genetic Determinants and Clinical Implications of Lp(a) Concentration and Isoform Size)*

To illustrate this point, Table 1 includes data from a study by Tsimikas et al. and demonstrates how Lp(a) levels measured in mg/dL can vary when converted to nmol/L, depending on the number of Kringle IV repeats. The table compares examples with very few Kringle repeats (e.g., 15) versus those with many (e.g., 30) Kringle repeats.

Given the variability in conversion factors and the influence of isoform size on Lp(a) mass, the clinical implications are significant. Misinterpreting Lp(a) levels could lead to either overestimating or underestimating a patient's cardiovascular risk, which could impact clinical decision-making. **Therefore, using a conversion factor is not appropriate; the only valid way to compare assay data in mg/dL to nmol/L is by utilizing validated data with reference methods previously described** [86,87].

2.3. Calculating Lp(a) levels from the lipid panel

This paper has previously discussed the complexities of Lp(a) measurement, which can complicate its interpretation in cardiovascular risk assessment. Given these difficulties, researchers have explored supplementary methods to estimate Lp(a) by leveraging other lipid panel components, such as LDL-C and apoB. Since Lp(a) consists of apoB, an LDL-like particle, there has been interest in calculating Lp(a)'s contribution to LDL-C and apoB levels [46]. Such calculations could help distinguish how much of the LDL-C and apoB burden is attributable to Lp(a) and could be compared to the calculated Lp(a) particle number for better clinical interpretation [46].

Table 1
Mg/dL to nmol/L conversion based on kringle IV repeats.

	Number of Kringle IV Repeats	Lp(a) Concentration (nmol/L)	Lp(a) Mass (mg/dL)	Conversion Factor
Low	12	240.1	51.4	4.67
	15	160.5	62.7	2.57
	18	122.8	46.1	2.66
Medium	22	82.7	36.9	2.24
	24	29.6	19.5	1.52
	25	28.2	17.6	1.60
High	30	14.6	14.6	1.00
	34	7.5	6.9	1.09
	36	4.3	7.8	0.55

The proposed method to estimate Lp(a)'s contribution to LDL-C involves dividing Lp(a)-P (in nmol/L) by a conversion factor of 2.4 to convert it to mass (mg/dL), followed by multiplying the result by 30% [90]. However, this approach relies on a fixed conversion factor, which—as discussed earlier—can introduce significant inaccuracies [86]. Studies have shown that this method often leads to an overestimation of Lp(a) and an underestimation of Lp(a)-free LDL-C, potentially resulting in the undertreatment of high-risk patients [46]. **Therefore, calculating Lp(a) from LDL-C is not recommended, as no reliable method currently exists to accurately distinguish the contribution of Lp(a) to LDL-C ASCVD burden** [46].

Alternatively, calculating Lp(a) from apoB may be more appropriate, as apoB levels have been shown to be superior predictors of both incident and residual cardiovascular risk compared to LDL-C [5]. Unlike Lp(a), apoB levels can be easily converted from milligrams per deciliter (mg/dL) to nanomoles per liter (nmol/L). A method for calculating the Lp(a)-derived proportion of apoB has been outlined in Table 2 [91]. This approach was highlighted in the 2021 AHA scientific statement as it allows for a clearer understanding of how much of the total apoB pool is attributable to Lp(a) [91].

However, as with LDL-C-based calculations, this method is not without limitations. Currently, there is no evidence to suggest that evaluating the proportion of apoB attributable to Lp(a) significantly improves risk stratification beyond existing methods, such as particle number calculations. Instead, it serves as a useful supplementary tool that may aid in providing additional insights into Lp(a)'s contribution to the overall atherogenic particle load. **We recommend comparing these results with the Lp(a) particle number to achieve a more precise particle-for-particle representation, thereby enhancing the precision of risk stratification** [46].

Summary of HOW TO SCREEN Recommendations:

- **Assay Type:**
  1. Monoclonal antibodies that measure the molar concentration of Lp(a) in nmol/L are recommended as the gold standard for Lp(a) quantification.
  2. If monoclonal antibody assays are not available, using an assay validated by the University of Washington or a Denka-Seiken assay is recommended as they offer precise data suitable for clinical use.
  3. Most currently available assays, including those reporting values in mg/dL, are generally reasonable to use for suitable for general risk assessment, such as determining whether Lp(a) levels indicate low or high cardiovascular risk
- **Mg/dL to nmol/L conversion:** There is no standard factor to accurately convert between mg/dL and nmol/L. The commonly used conversion factor of 2–2.5 is approximate and should not be relied upon. Accurate comparison of assay data should use validated reference methods.
- **Calculating Lp(a) from Lipid Panel Components:**
  1. *LDL-C*: The currently proposed method for calculating Lp(a)'s contribution to LDL-C is inaccurate and may lead to the undertreatment of high-risk patients. Therefore, this approach is not recommended.
  2. *ApoB:* It is appropriate to calculate Lp(a)'s contribution from the apoB pool, which can then be compared to the Lp(a) particle number for a more accurate representation of its contribution to the overall atherogenic particle load.

3. Screening interpretation

When interpreting Lp(a) screening results, cardiovascular risk is generally categorized based on Lp(a) concentrations, reported in either mg/dL or nmol/L. Low cardiovascular risk is typically associated with Lp(a) levels below 30 mg/dL (75 nmol/L) [17]. Medium or intermediate risk is observed with levels between 30–50 mg/dL (75–125 nmol/L)

Table 2
Steps to calculate proportion of ApoB attributable to Lp(a).

1. Convert total apoB from mg/dL to nmol/L:
○ Multiply the total apoB level (in mg/dL) by 20 to convert to nmol/L
If apoB = 120 mg/dL, then 120 mg/dL×20=2400 nmol/L
2. Identify Lp(a) concentration in nmo/L:
○ Obtain the Lp(a) concentration in nmol/L directly from lab results
If Lp(a) = 48 nmol/L
3. Calculate the proportion of apoB due to Lp(a):
○ Divide the Lp(a) concentration (in nmol/L) by the total apo(b) concentration (in nmol/L) and multiply by 100 to get the percentage

$$\frac{2400\ \boldsymbol{nmol/L}}{48\ \boldsymbol{nmol/L}} \times 100 = 2\%$$

[17]. High risk is identified when concentrations exceed 50 mg/dL (125 nmol/L) [17], with extremely elevated risk seen above 180 mg/dL (430 nmol/L) [9]. Given Lp(a)'s unique characteristics—such as its high heritability [1], variations in isoform size [92], and its association with other cardiovascular risk factors [93]—understanding how elevated Lp (a) levels impact different patient populations and pathologies, especially from a genetic perspective, is crucial. This nuanced understanding allows for more comprehensive risk assessments and can guide treatment strategies more effectively. The sections below will explore these genetic and clinical considerations in the interpretation of Lp(a) screening.

3.1. Genetic determinants and clinical implications of Lp(a) concentration and isoform size

The genetic determinants of Lp(a) are governed by variations in the LPA gene, which encodes the apo(a) component of Lp(a) [94]. The size of Lp(a) isoforms, determined by the number of Kringle KIV-2 repeats in

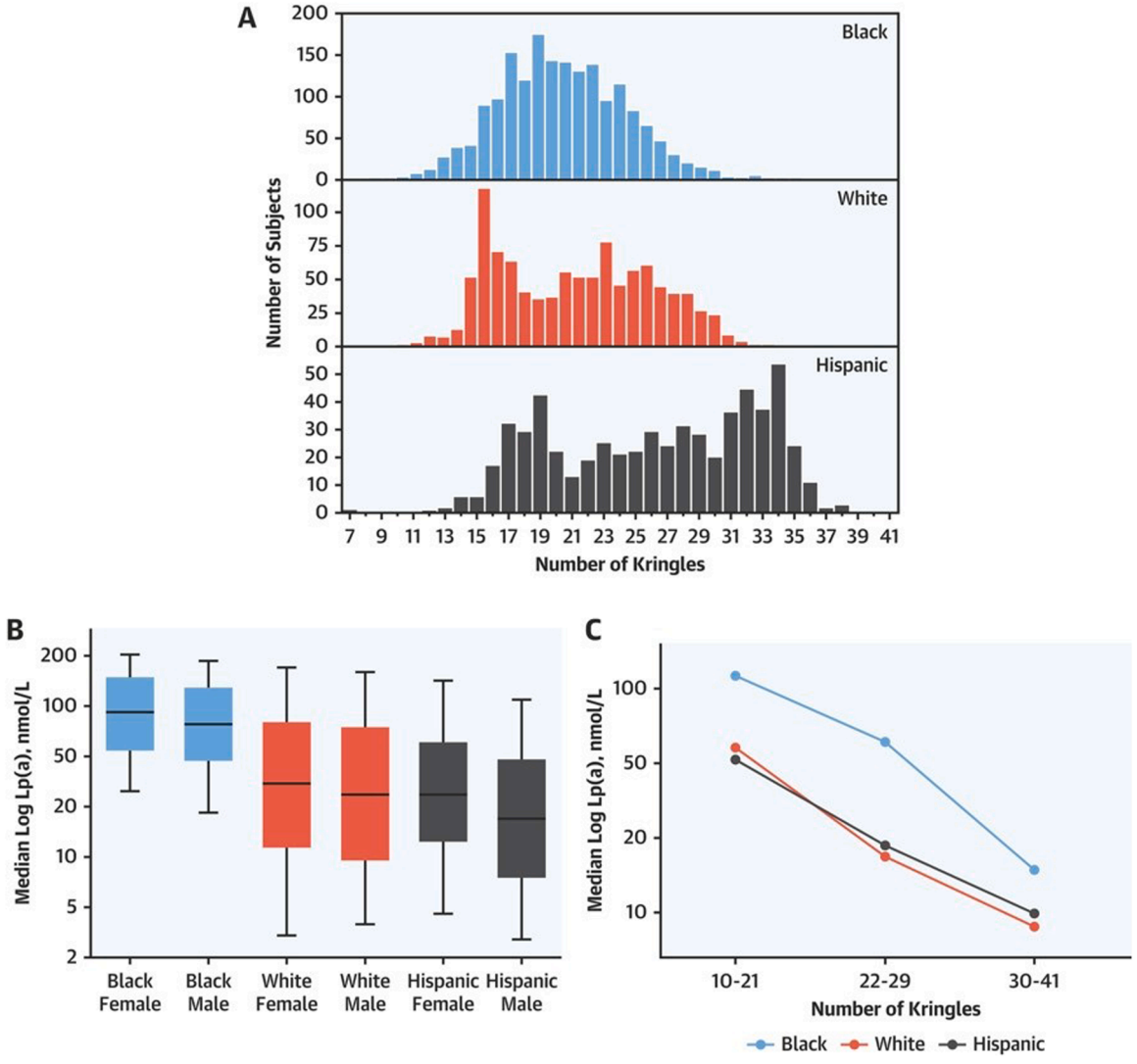


Fig. 2. Relationship Between Predominant Isoform Size and Lp(a) Levels
(A) Distribution of major apolipoprotein(a) isoform sizes among U.S. Black, White, and Hispanic populations, based on data from the Dallas Heart Study. (B) Median log-transformed lipoprotein(a) (Lp [a]) levels across U.S. Black, White, and Hispanic participants, differentiated by sex. (C) Median log Lp(a) levels presented according to tertiles of the predominant isoform size.

the apo(a) protein, is a major factor influencing plasma Lp(a) levels [94]. These isoforms can range from 1 to over 40 repeats, with smaller isoforms (10–22 KIV) generally associated with higher Lp(a) concentrations compared to larger isoforms (>22 KIV). This inverse relationship arises because smaller isoforms are synthesized at a faster rate by hepatocytes, contributing to higher plasma concentrations. Though, this inverse correlation is not strictly linear, as previously thought [95]. Genetic variations, including single nucleotide polymorphisms (SNPs) and structural variations within the LPA gene, further modulate Lp(a) levels and contribute to substantial inter-individual and population-level variability [95]. As a result, Lp(a) levels can vary significantly among different apo(a) phenotypes, with the most variation observed among individuals with small apo(a) isoforms [96].

The strong genetic control of Lp(a) plasma concentration, along with these genetic variabilities, results in significant differences in the distribution of Lp(a) isoforms and concentrations across different ancestries and geographic regions [92]. For example, individuals of European descent typically have a higher proportion of small isoforms, which are associated with elevated Lp(a) levels. Conversely, East Asian populations tend to have a greater prevalence of larger isoforms, resulting in generally lower Lp(a) concentrations. South Asian populations exhibit a more balanced distribution of large and small isoforms, while African populations commonly show a higher prevalence of medium-sized isoforms. These differences contribute to distinct population-specific Lp(a) levels and associated cardiovascular risk profiles, as seen in Fig. 2 [1].

Isoforms with fewer KIV-2 repeats (<22 KIV) are associated with an increased risk of CVD [97]. There has been debate regarding whether this increased risk is due to the higher concentration of Lp(a) particles in the blood or whether smaller isoforms possess intrinsic harmful properties [98]. While the generally increased number of circulating Lp(a) particles certainly contributes to the associated increased CVD risk, studies also indicate that Lp(a) particles with smaller apo(a) isoforms tend to circulate in the plasma for extended periods, potentially increasing their contribution to arterial plaque formation [99]. Additionally, smaller isoforms are associated with elevated levels of oxidized phospholipids, which are known to exacerbate atherosclerosis and inflammation [100,101].

However, clinical evidence regarding the role of apo(a) isoform size as an independent risk factor for atherosclerosis is mixed. Several smaller or single-center studies have identified high Lp(a) concentrations and small-sized apo(a) isoform as independent risk factors for CHD [102–104]. Afanasieva et al. were the first to show that the low molecular weight apo(a) phenotype, even with Lp(a) levels below 50 mg/dL, is significantly associated with increased risk of CHD, MI, and multivessel coronary lesions compared to the high molecular weight apo (a) phenotype [104]. In contrast, large-scale studies have generally found that when adjusted for Lp(a) concentration, apo(a) isoform size alone does not independently contribute to the risk of MI [97,105]. These studies suggest that the effect of KIV-2 repeats on CHD risk is mediated through their impact on Lp(a) levels, implying that the absolute level of Lp(a), rather than apo(a) isoform size, is the main determinant of CHD risk. However, some studies have shown the impact of isoform size on CVD risk to be more significant in Black [106,107] and South Asian populations [108].

Overall, high Lp(a) concentrations (>50 mg/dL) are a well-established independent risk factor for CVD and should continue to be treated as such. Small apo(a) isoforms are also consistently associated with increased CVD risk, though the exact mechanism remains unclear. Regardless, there is sufficient evidence to consider individuals with small apo(a) isoforms at higher risk compared to those with larger isoforms, whether due to higher Lp(a) concentrations or other factors. Unfortunately, determining apo(a) size in a clinical setting is not practical with current techniques. **Therefore, Lp(a) concentration should remain the primary assessment for CVD risk.** Given the significant genetic influence and the strong population-specific trends in apo(a) isoform size, it is reasonable to consider a patient's likely apo(a) isoform size in the context of their ethnicity, as discussed in further detail below.

Furthermore, while the high heritability and population-specific trends in Lp(a) have prompted debate regarding the use of population-specific thresholds, we do not recommend their adoption. Although ethnicity-specific cutoffs might reflect population variability, they may also introduce further uncertainty for clinicians regarding screening and interpretation. A uniform threshold, as advocated by the 2024 NLA statement, could provide clarity, streamline public health responses, and ensure prioritization of individuals at the highest CVD risk [17]. More detailed discussions regarding Lp(a) trends and their implications for specific ethnicities will be addressed in the sections below.

3.2. *Black ethnicity*

Studies have consistently demonstrated that Black individuals have the highest median Lp(a) levels among various ethnic groups [10,48,109–112]. For example, in the Dallas Heart Study, median Lp(a) concentrations were found to be three times higher in Black individuals (N=1792) compared to White (N=1030) and Hispanic individuals (N=597), with median levels of 79.0 nmol/L, 26.9 nmol/L, and 21.3 nmol/L, respectively [49]. Similarly, the UK Biobank study reported median Lp(a) levels of 19 nmol/L in White individuals (N=434,058), 31 nmol/L in South Asian individuals (N=8940), 75 nmol/L in Black individuals (N=7144), and 16 nmol/L in Chinese individuals (N=1435) [10]. Another study by Colantonio et al. found that Black individuals with a history of ASCVD (N=2616) had median Lp(a) concentrations more than four times those seen in White individuals (N=4008).

Interestingly, despite these elevated Lp(a) levels, studies have not consistently demonstrated a proportionately higher risk of adverse cardiovascular outcomes in the Black population. Some studies report a relatively equal risk between Black and White individuals, while others have observed no increased risk at all. This discrepancy is often attributed to the smaller sample sizes of Black participants in some studies. For example, in a study by Pare et al., which evaluated the association between Lp(a) levels and the risk of MI across seven ethnic groups using an isoform-insensitive assay, Africans had the highest median Lp(a) concentrations but did not show a significant association with increased MI risk [48]. In contrast, White, South Asian, and Hispanic individuals demonstrated a significant association between elevated Lp(a) and MI risk [48]. Africans made up less than 6% of the study population, which may explain this lack of association. Similarly, a Mendelian randomization analysis by Satterfield et al. found that elevated Lp(a) levels in individuals of African ancestry were not associated with several cardiovascular traits, including valve disease, CHD, CVD, and heart failure [113]. However, individuals of European ancestry comprised 89% of the study population, possibly influencing these findings.

Another possible explanation for the discrepancy in cardiovascular risk associated with high Lp(a) levels in Black individuals may lie in the size of the apo(a) isoforms. While apo(a) isoform size alone has not been consistently identified as an independent risk factor, research by Paultre et al. suggests that a combination of high Lp(a) concentrations and small apo(a) isoforms may elevate CVD risk in Black individuals [106]. The study found that while Black individuals generally have higher median Lp(a) concentrations, they also tend to have larger apo(a) isoforms compared to White individuals. In their analysis, 80% of White individuals with elevated Lp(a) had at least one small apo(a) isoform (<22 KIV-2 repeats), compared to only 26% of Black individuals. This finding aligns with prior research demonstrating a lower frequency of small apo (a) isoforms in Black individuals and a higher prevalence of intermediate-sized isoforms [1]. The higher prevalence of larger isoforms among Black individuals, despite their elevated Lp(a) levels, may explain why cardiovascular risk does not increase proportionately in this population, even in studies where Black individuals are equally represented compared to other ethnic groups [109].

Where elevated Lp(a) may pose a significant risk to Black individuals is in those with a history of ASCVD and in CVD outside of the coronaries.

Colantonio found that increasing Lp(a) was associated with a greater CHD risk in both Black and White individuals with a history of ASCVD, with no race-associated difference [114]. Several studies have found elevated Lp(a) to be correlated with a greater risk of ischemic stroke in Black individuals, potentially at a higher risk than in White individuals [107,115]. Elevated Lp(a) levels in Africans were associated with an increased risk of PAD and AAA, although the risk was lower than in individuals of European ancestry [113]. Additionally, the MESA trial found that elevated Lp(a) was associated with aortic valve calcification in White and Black individuals [116].

The data on Lp(a)-driven cardiovascular risk in Black individuals has led some to suggest that modifications to current Lp(a) risk thresholds for this population [10,113]. **While we do not believe that it is appropriate to adjust these risk thresholds based on the existing data, it may be reasonable that when elevated Lp(a) levels are detected in Black patients, particular attention should be given to mitigating cardiovascular risk, especially in those with a history of CVD, and to prioritizing stroke prevention strategies.** Given the significant risk that elevated Lp(a) poses to the general population, further studies using isoform-insensitive assays, reporting in molar concentrations, and including larger Black population sample sizes are necessary before any changes to guidelines can be considered.

3.3. South Asian ethnicity

The South Asian population presents another interesting situation in evaluating Lp(a) mediated cardiovascular risk. Though median Lp(a) levels are not as high in South Asian individuals as in Black individuals, as a population, South Asian individuals have a severely elevated rate and premature onset of CAD compared to other ethnic groups. CAD is reported to be 89%-300% more prevalent among Indian men than among White individuals in the US [117]. When compared to White individuals in the UK, the incidence of acute coronary syndrome is five times higher in young (<45 years in men and <50 years in women) Indians [118]. Despite the young age, multivessel diffuse disease is found in nearly 80% of patients, a finding typically associated with older patients [119]. This clinical pattern of premature, diffuse, and severe CVD seen in South Asian individuals is also the hallmark of CVD in those with elevated Lp(a) [120]. Therefore, understanding the role of Lp(a)-mediated CVD has become increasingly important in the South Asian population.

South Asian individuals have high median Lp(a) levels compared to other ethnic groups, including other Asian populations, such as Chinese and Japanese individuals [10,48,121,122]. Across three Asian ethnicities (Indian, Malaysian, and Chinese), Loh et al. found that elevated Lp(a) levels were associated with the presence of CAD, and, among those with CAD, Lp(a) was also associated with increased risk of acute MI [121]. There was no association based on ethnicity. When compared to other non-Asian ethnic groups, Pare et al. found that high Lp(a) concentrations were particularly burdensome to South Asian individuals, with an odds ratio for acute MI more than double that of White individuals (OR 2.14 vs 1.36, $p<0.001$) [48]. This has led to arguments to lower the risk threshold for high Lp(a) determination in patients of South Asian descent to 30 mg/dL, rather than the current universal 50 mg/dL [120].

A large Mendelian randomization trial by Saleheen et al. further contributes to our understanding of Lp(a) in South Asian individuals, revealing that both smaller apo(a) isoform size and elevated Lp(a) concentrations are independent risk factors for CAD [108]. The study demonstrated that for every 1-SD decrease in apo(a) isoform size, the odds ratio for myocardial infarction was 0.93 (95% CI 0.90–0.97; $p<0.0001$), while for every 1-SD increase in Lp(a) concentration, the odds ratio was 1.10 (95% CI 1.05–1.14; $p<0.0001$). These findings suggest that even at comparable Lp(a) levels, smaller isoform sizes significantly contribute to the elevated CAD risk observed in this population, potentially explaining why South Asian individuals experience a heightened burden of early-onset and multivessel disease.

Given the heightened risk of CAD in South Asian patients and the observed association between elevated Lp(a) levels and cardiovascular events in this population, it may be prudent to consider adopting a more aggressive CVD prevention strategy when Lp(a) levels reach 30 mg/dL, as has been suggested. This lower threshold for intervention could help mitigate the increased CAD risk that South Asian individuals face, allowing for earlier and more targeted preventive efforts. However, conflicting studies have emerged [122,123], so, as with Black individuals, more research is needed within the South Asian population to confirm these findings before making definitive adjustments to current guidelines.

3.4. Hispanic ethnicity

Patients of Hispanic ethnicity are among the least studied groups in terms of the clinical risk associated with elevated Lp(a) levels. Several multi-ethnic studies have shown that Hispanic individuals generally have intermediate Lp(a) levels, which are lower than those seen in Black and South Asian populations but similar to or slightly higher than those in White and Chinese populations [48,110,111]. However, these inconsistent findings are likely due to the considerable heterogeneity within the Hispanic population [110]. Individuals who identify as Hispanic often have ancestral overlap with European, African, and Native American populations, with studies showing as much as 65% of shared ancestry with European Americans [124]. This diversity makes it challenging to establish a median Lp(a) value for the Hispanic population, and to date, no studies have specifically focused on determining the clinical risk associated with elevated Lp(a) in this group. Notably, Hispanic individuals were not included as a represented group in the UK Biobank study. **Overall, just as with Black and South Asian individuals, more studies are needed to fully understand the cardiovascular risk posed by elevated Lp(a) in Hispanic individuals, but a cutoff of 50 mg/dL is currently considered reasonable.**

3.5. Extremely elevated lipoprotein(a)

Extremely elevated Lp(a) levels are defined as Lp(a) >180 mg/dL or >430 nmol/L [9]. It has been suggested that individuals with such high Lp(a) levels may have a lifetime risk of ASCVD equivalent to those with HeFH [125]. This elevated risk is likely due to recent genetic analyses demonstrating that Lp(a) particles are significantly more atherogenic than LDL particles, with a per-particle atherogenicity approximately six times greater [126]. In individuals with extremely elevated Lp(a), the particle number may approach or surpass that of LDL particles, amplifying their cardiovascular risk [126]. Additionally, given that Lp(a) levels have a heritability rate of nearly 90%, individuals with extremely elevated Lp(a) might represent a new genetic lipid disorder with a very high lifetime risk of ASCVD, much like HeFH, but twice as common [125].

Those with extremely high Lp(a) levels have a 2.5 to 3-fold increased risk of ASCVD compared to individuals with normal Lp(a) levels [81,93]. A cohort from the Copenhagen City Heart Study found that individuals with Lp(a) levels above 120mg/dL had a hazard ratio of 3.6 for women and 3.7 for men compared to those with Lp(a) levels below 5mg/dL [127]. In individuals with high-risk comorbidities, such as smoking or hypertension, the 10-year absolute risk of MI was twice as high for those with elevated Lp(a) [127]. Importantly, there was no threshold effect; the risk of MI increases progressively with higher Lp(a) levels [127]. The prevalence of PAD and stroke has also been found to be higher, though not statistically significant, in those with extremely elevated Lp(a) [81].

This significantly increased risk is one of the reasons for the growing consensus on a once-in-a-lifetime screening of serum Lp(a) levels for every individual. Unfortunately, genetic studies suggest that a robust reduction in Lp(a) would be necessary to significantly reduce ASCVD-

related events in these patients [125], making the development of novel Lp(a)-lowering therapies, which promise a dramatic reduction in Lp(a) levels, all the more critical [128].

In conclusion, given the extremely high cardiovascular risk associated with Lp(a) levels greater than 180 mg/dL, these individuals should be regarded as having a risk profile comparable to those with HeFH, warranting aggressive cardiovascular risk management strategies.

3.6. Isolated elevated lipoprotein(a) levels

Elevated Lp(a) levels often [93], though not always [129], coincide with elevated LDL-C levels. Individuals with normal levels of LDL-C but elevated Lp(a) exhibit an increased risk for several cardiovascular conditions, including acute MI, stroke, cardiovascular death, aortic stenosis progression, and unstable angina [130]. Currently, plasma apheresis (PA) is the only FDA-approved method for reducing high serum Lp(a) levels. While research has confirmed the effectiveness of lipoprotein apheresis in patients with elevated levels of both LDL-C and Lp(a) [26], only a few small studies have explored the effects of PA in patients with elevated Lp(a) alone. A retrospective single-center study by Rosada et al. analyzed the cardiovascular outcomes in 37 patients with elevated Lp(a) (average 112 mg/dL) and low LDL-C (<100 mg/dL) at baseline [131]. Regular apheresis reduced serum Lp(a) levels by 68% and LDL-C by 60%. Post-apheresis, event-free survival rates significantly improved to 75%, compared to 38% pre-apheresis, within one year. Similarly, Schumann et al. examined the long-term effects of PA on cardiovascular events among high-risk patients with isolated Lp(a) elevations (Lp(a) > 60 mg/dL and LDL < 100mg/dL) [129]. The study revealed a significant decrease in cardiovascular events from 0.87 events per patient per year pre-PA to 0.24 post-PA, along with a marked reduction in major adverse cardiac events from 0.34 to 0.006 post-treatment.

It is also important to note that patients currently on statin or other lipid-lowering therapies may present with the isolated Lp(a) phenotype due to reduced LDL-C levels. In such cases, clinicians should consider the patient's highest recorded LDL-C prior to therapy to determine whether they fall into this group. Patients with previously elevated LDL-C who now exhibit normal or low LDL-C levels due to lipid-lowering therapy should not be classified as having isolated elevated Lp(a).

Given these findings and the development of novel Lp(a)-specific lowering therapies, isolated elevated Lp(a) levels can now be considered a targetable high-risk group for cardiovascular intervention.

3.7. Aortic valve stenosis

The primary focus of this paper has been on the relationship between Lp(a) and ASCVD. However, it is important to also consider the significant role Lp(a) plays in the development of AVS. The LPA locus is well-established as a significant contributor to AVS risk, as demonstrated by multiple genetic and Mendelian randomization studies [3,132–134]. The association between Lp(a) and AVS is particularly strong, surpassing its link to other cardiovascular outcomes [135]. This is primarily due to Lp(a)'s content of oxidized phospholipids, which play a crucial role in valve calcification [136].

In a large study from Copenhagen, involving over 77,000 individuals, those with Lp(a) levels between the 90th and 95th percentiles (65–90 mg/dL) were found to have a two-fold increased risk of developing aortic stenosis [3]. For those with Lp(a) levels above the 95th percentile (>90 mg/dL), the risk was even more pronounced, with a 2.9-fold increase compared to those with levels below the 22nd percentile [3]. The risk is especially high in relatively young, healthy individuals aged 45 to 54 years [2]. In this age group, those with Lp(a) levels above the 80th percentile had a three-fold higher risk of aortic valve calcification compared to indivuals with lower levels (15.8% vs. 4.3%, respectively) [2].

High Lp(a) levels may also contribute to faster progression of aortic stenosis, leading to earlier interventions such as aortic valve replacement or increased mortality [137]. However, while Lp(a) is closely associated with the initiation of aortic valve calcification, it does not seem to significantly affect the progression of existing calcification [138]. This suggests that Lp(a)-lowering therapies may be most effective if administered in the early stages, before significant calcification has occurred.

These findings highlight Lp(a) as both a crucial biomarker for assessing AVS risk and a potential therapeutic target for prevention. **As such, patients with elevated Lp(a) levels should be carefully monitored for signs of developing AVS to enable timely intervention.**

Summary of SCREENING INTERPRETATION Recommendations:

- **Clinical Implications of Lp(a) Concentration vs Isoform Size:** Both high Lp(a) concentrations and small apo(a) isoforms are associated with increased CVD risk, though the mechanism behind the elevated risk linked to smaller apo(a) isoform sizes remains unclear. Given current technologies, assessing apo(a) isoform size is not yet feasible in clinical settings. Therefore, measuring high Lp(a) concentrations, preferably with isoform-insensitive assays, should remain the gold standard for assessing Lp(a)-related CVD risk.
- **Ethnicity:**
  1. *Black Population:* While we do not believe that it is appropriate to adjust these risk thresholds based on the existing data, it may be reasonable that when elevated Lp(a) levels are detected in Black patients, particular attention should be given to mitigating cardiovascular risk, especially in those with a history of CVD, and to prioritizing stroke prevention strategies.
  2. *South Asian Population:* It may be reasonable to consider a more aggressive CVD prevention strategy in South Asian patients when Lp(a) levels reach 30 mg/dL due to their heightened CAD risk.
  3. *Hispanic Population:* More studies are needed to fully understand the cardiovascular risk posed by elevated Lp(a) in Hispanics, but a cutoff of 50 mg/dL is currently considered reasonable.
- **Extremely Elevated Lp(a):** Given the extremely high cardiovascular risk associated with Lp(a) levels greater than 180 mg/dL, these individuals should be regarded as having a risk profile comparable to those with HeFH, warranting aggressive cardiovascular risk management strategies.
- **Isolated Elevated Lp(a):** Isolated elevated Lp(a) levels can now be considered a targetable high-risk group for cardiovascular intervention.
- **Aortic Valve Stenosis:** Patients with elevated Lp(a) levels should be carefully monitored for signs of developing AVS to enable timely intervention.

4. Conclusion

Since Lp(a) was first described in 1963 [139], there has been growing interest in understanding the genetic, independent, and causal CVD risk posed by this lipoprotein. We now know that risk of elevated Lp(a) is linear [10] and those with extremely high Lp(a) levels (>180mg/dL) have the same clinical risk of someone with untreated FH [81]. While there have historically been challenges in measuring Lp(a) levels, improvements in our current commercial assays are adequate to determine low vs high risk, and new isoform-independent assays are being developed, which raises hope for a future in which Lp(a) measurement is harmonized [83]. Furthermore, new therapeutic methods that have demonstrated a significant reduction in Lp(a) levels are now in phase 3 clinical trials and have inspired hope that Lp(a) will become a targetable clinical biomarker [140][130]. In the interim, aggressively addressing other cardiovascular risk factors, such as LDL, has shown to improve clinical outcomes for those with elevated Lp(a) [35]. The ongoing Lp(a) HORIZON trial and SLN360 APOLLO trial, with results expected to be released later this year, will hopefully shed light on the CVD risk-reduction possible with lowering Lp(a).

In addition to these advancements, healthcare system challenges must also be addressed to ensure that expanded Lp(a) testing can be implemented efficiently. Systems-based solutions, such as integrating best practice advisories into electronic medical records (e.g., EPIC), can aid physicians in identifying and managing patients at particularly high risk. These tools would ensure that Lp(a) testing is utilized effectively, prioritizing those at the highest CVD risk while maintaining a resource-efficient approach. Such strategies are actively being explored by our

lab, whose ongoing work aims to provide a deeper analysis of these considerations.

Summary of Recommendations:WHO TO SCREEN

- **General Population:** Universal Lp(a) screening is recommended for every adult at least once in their lifetime, regardless of traditional cardiovascular risk factors.
- **Pediatric Patients:** We recommend including Lp(a) screening as part of the initial comprehensive lipid panel for children, particularly those who are considered high-risk. This group includes children with:
  1. History of ischemic stroke
  2. Clinically suspected or genetically confirmed FH.
  3. First-degree relatives with a history of premature ASCVD (age <55 years in men, <65 years in women).
  4. First-degree relatives with elevated Lp(a).
  5. Other cardiovascular risk factors including: obesity, hypertension, diabetes or other glucose metabolism disorders, or familial dyslipidemia.
- **Familial Hypercholesterolemia:**
  - Individuals with FH should undergo regular screening and management of both LDL-C and Lp(a) levels.
  - Lp(a) levels should be measured in all individuals, including children, with presumed FH before genetic testing
- **Patients of Different Ethnicities:** While ethnicity-specific screening recommendations are not yet established, screening should be considered for all ethnicities, as Lp(a) poses a comparable cardiovascular risk across different populations.

WHEN TO SCREEN

- **First Time Adult Screening:** Lp(a) should be included as part of an individual's first adult lipid panel.
- **Pediatric Screening:**
  - If indicated, pediatric patients can be screened as early as 2 years old or during their first comprehensive pediatric lipid screen..
  - For patients determined to be in the intermediate risk range (30–50 mg/dL), it is reasonable to obtain repeat measurements until levels stabilize.
- **Repeat Screening:** Once Lp(a) levels have stabilized, serial Lp(a) testing is generally not recommended as it does not improve risk prediction. However, repeat screening should be performed in patients who were previously in the intermediate risk range (30–50mg/dL) and have:
  1. Undergone menopause
  2. Kidney disease, particularly CKD or nephrotic syndrome, or have initiated dialysis
  3. Hypothyroidism
- **Cascade Screening:** Cascade screening should be performed on individuals with a family history of elevated Lp(a), including pediatric patients, with a focus on first-degree relatives who are significantly more likely to inherit elevated Lp(a) levels.

HOW TO SCREEN

- **Assay Type:**
  - Monoclonal antibodies that measure the molar concentration of Lp(a) in nmol/L are recommended as the gold standard for Lp(a) quantification.
  - If monoclonal antibody assays are not available, using an assay validated by the University of Washington or a Denka-Seiken assay is recommended as they offer precise data suitable for clinical use.
  - Most currently available assays, including those reporting values in mg/dL, are generally reasonable to use for suitable for general risk assessment, such as determining whether Lp(a) levels indicate low or high cardiovascular risk
- **Mg/dL to nmol/L conversion:** There is no standard factor to accurately convert between mg/dL and nmol/L. The commonly used conversion factor of 2–2.5 is approximate and should not be relied upon. Accurate comparison of assay data should use validated reference methods.
- **Calculating Lp(a) from Lipid Panel Components:**
  - *LDL-C*: The currently proposed method for calculating Lp(a)'s contribution to LDL-C is inaccurate and may lead to the undertreatment of high-risk patients. Therefore, this approach is not recommended.
  - *ApoB:* It is appropriate to calculate Lp(a)'s contribution from the apoB pool, which can then be compared to the Lp(a) particle number for a more accurate representation of its contribution to the overall atherogenic particle load.

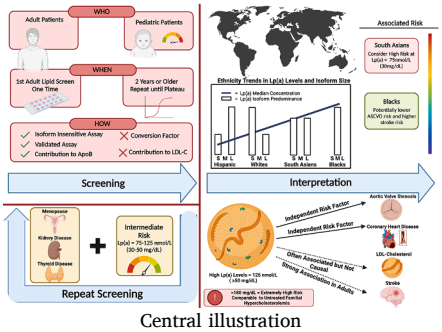
SCREENING INTERPRETATION

- **Clinical Implications of Lp(a) Concentration vs Isoform Size:** Both high Lp(a) concentrations and small apo(a) isoforms are associated with increased CVD risk, though the mechanism behind the elevated risk linked to smaller apo(a) isoform sizes remains unclear. Given current technologies, assessing apo(a) isoform size is not yet feasible in clinical settings. Therefore, measuring high Lp(a) concentrations, preferably with isoform-insensitive assays, should remain the gold standard for assessing Lp(a)-related CVD risk.
- **Ethnicity:**
  - *Black Population:* While we do not believe that it is appropriate to adjust these risk thresholds based on the existing data, it may be reasonable that when elevated

(*continued on next column*)

(*continued*)

Lp(a) levels are detected in Black patients, particular attention should be given to mitigating cardiovascular risk, especially in those with a history of CVD, and to prioritizing stroke prevention strategies.
  - *South Asian Population:* It may be reasonable to consider a more aggressive CVD prevention strategy in South Asian patients when Lp(a) levels reach 30 mg/dL due to their heightened CAD risk.
  - *Hispanic Population:* More studies are needed to fully understand the cardiovascular risk posed by elevated Lp(a) in Hispanic individuals, but a cutoff of 50 mg/dL is currently considered reasonable.
- **Extremely Elevated Lp(a):** Given the extremely high cardiovascular risk associated with Lp(a) levels greater than 180 mg/dL, these individuals should be regarded as having a risk profile comparable to those with HeFH, warranting aggressive cardiovascular risk management strategies.
- **Isolated Elevated Lp(a):** Isolated elevated Lp(a) levels can now be considered a targetable high-risk group for cardiovascular intervention.
- **Aortic Valve Stenosis:** Patients with elevated Lp(a) levels should be carefully monitored for signs of developing AVS to enable timely intervention.



Central illustration

Author declaration template

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work. Edward Gill has received funding from Kaneka Medical America LLC for other research related to Lp(a). No funding from Kaneka was used for this paper. All other authors report no conflicts of interest.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

CRediT authorship contribution statement

Victoria Clair: Writing – review & editing, Writing – original draft, Conceptualization. **Francis M. Zirille:** Writing – review & editing. **Edward Gill:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Edward Gill reports a relationship with Kaneka Medical America LLC that includes: funding grants. Dr. Edward Gill is a co-author of the most recent statement published by the National Lipid Association If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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