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A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice

Marlys L. Koschinsky, PhD, Archna Bajaj, MD, MSCE, Michael B. Boffa, PhD, Dave L. Dixon, PharmD, Keith C. Ferdinand, MD, Samuel S. Gidding, MD, Edward A. Gill, MD, Terry A. Jacobson, MD, Erin D. Michos, MD, MHS, Maya S. Safarova, MD, PhD, Daniel E. Soffer, MD, Pam R. Taub, MD, Michael J. Wilkinson, MD, Don P. Wilson, MD, Christie M. Ballantyne, MD*

Department of Physiology & Pharmacology and Robarts Research Institute, Schulich School of Medicine & Dentistry, Western University, London, Ontario, Canada (Drs Koschinsky, Boffa); Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA (Drs Bajaj, Soffer); Department of Pharmacotherapy & Outcomes Science, Virginia Commonwealth University School of Pharmacy, Richmond, VA, USA (Dr Dixon); Department of Medicine, Tulane University School of Medicine, New Orleans, LA, USA (Dr. Ferdinand); Department of Genomic Health, Geisinger. Danville, PA, USA (Dr Gidding); Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA (Dr Gill); Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA (Dr Jacobson); Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Dr Michos); Division of Cardiovascular Medicine, Department of Internal Medicine, Froedtert & the Medical College of Wisconsin, Milwaukee, WI, USA (Dr Safarova); Department of Medicine, University of California San Diego, La Jolla, CA, USA (Drs Taub, Wilkinson); Department of Pediatric Endocrinology and Diabetes, Cook Children's Medical Center, Fort Worth, TX, USA (Dr Wilson); Department of Medicine, Baylor College of Medicine, Houston, TX, USA (Dr Ballantyne)

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Since the 2019 National Lipid Association (NLA) Scientific Statement on Use of Lipoprotein(a) in Clinical Practice was issued, accumulating epidemiological data have clarified the relationship between lipoprotein(a) [Lp(a)] level and cardiovascular disease risk and risk reduction. Therefore, the NLA developed this focused update to guide clinicians in applying this emerging evidence in clinical practice. We now have sufficient evidence to support the recommendation to measure Lp(a) levels at least once in every adult for risk stratification. Individuals with Lp(a) levels <75 nmol/L (30 mg/dL) are considered low risk, individuals with Lp(a) levels ≥125 nmol/L (50 mg/dL) are considered high risk, and individuals with Lp(a) levels between 75 and 125 nmol/L (30–50 mg/dL) are at intermediate risk. Cascade screening of first-degree relatives of patients with elevated Lp(a) can identify additional individuals at risk who require intervention. Patients with elevated Lp(a) should receive early, more-intensive risk factor manage-

* Corresponding author at: Christie M. Ballantyne, Baylor College of Medicine, One Baylor Plaza, MS BCM285, Houston, TX 77030.
E-mail address: cmb@bcm.edu (C.M. Ballantyne).
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ment, including lifestyle modification and lipid-lowering drug therapy in high-risk individuals, primarily to reduce low-density lipoprotein cholesterol (LDL-C) levels. The U.S. Food and Drug Administration approved an indication for lipoprotein apheresis (which reduces both Lp(a) and LDL-C) in high-risk patients with familial hypercholesterolemia and documented coronary or peripheral artery disease whose Lp(a) level remains ≥60 mg/dL [∼150 nmol/L)] and LDL-C ≥ 100 mg/dL on maximally tolerated lipid-lowering therapy. Although Lp(a) is an established independent causal risk factor for cardiovascular disease, and despite the high prevalence of Lp(a) elevation (∼1 of 5 individuals), measurement rates are low, warranting improved screening strategies for cardiovascular disease prevention.

Introduction (Preface)

The lipoprotein(a) [Lp(a)] field is rapidly evolving on many fronts, warranting this focused update to the 2019 National Lipid Association (NLA) Scientific Statement on Use of Lipoprotein(a) in Clinical Practice.[1] Recent evidence has influenced our understanding of whom should have Lp(a) levels measured, how to interpret Lp(a) levels for use in risk assessment, and clinical management of patients with elevated Lp(a). The NLA now recommends: (1) measurement of Lp(a) levels at least once in every adult; (2) classification of individuals with Lp(a) levels <75 nmol/L (30 mg/dL) as low risk, individuals with Lp(a) levels ≥125 nmol/L (50 mg/dL) as high risk, and individuals with Lp(a) levels between 75 and 125 nmol/L (30–50 mg/dL) as intermediate risk; and (3) use of lipoprotein apheresis as now indicated by the U.S. Food and Drug Administration (FDA) in high-risk patients with familial hypercholesterolemia (FH) and documented coronary or peripheral artery disease whose Lp(a) level remains ≥60 mg/dL [∼150 nmol/L)] and low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dL on maximally tolerated lipid-lowering therapy. This statement expands on new and emerging evidence supporting these recommendations (Table 1).

A. What new evidence has emerged regarding Lp(a) as a cardiovascular risk factor since the last NLA scientific statement?

Accumulating data from large, population-based studies indicate that elevated plasma Lp(a) is an important independent, causal risk factor for atherosclerotic cardiovascular disease and calcific aortic valve stenosis

The most notable of these studies are two analyses of the UK Biobank.[2,3] Their enormous sample sizes ($n = 460{,}506$ and 413,734, respectively) allowed several key questions to be addressed with unprecedented statistical power.

First, a continuous, log-linear relationship between baseline Lp(a) and risk for atherosclerotic cardiovascular disease (ASCVD) events was observed, with a significant (albeit small) increase in risk at what would usually be considered "low-risk" levels of Lp(a) (25–50 nmol/L).[2,3] This finding should prompt the retirement of the old concept of a dichotomous threshold, i.e., 125 nmol/L or 50 mg/dL. Indeed, the continuous gradient of risk with increased Lp(a) implies that clinical decision-making should be influenced by the degree of Lp(a) elevation and the patient's other risk factors, not the mere presence of elevated Lp(a).

Second, while substantial differences in median Lp(a) levels and the distribution of Lp(a) levels between different racial/ethnic groups were observed in UK Biobank (in accordance with prior research[4]), no impact of race on Lp(a)-attributable risk was found.[2,3] ASCVD risk attributable to elevated Lp(a) was similar for White, South Asian, and Black individuals (hazard ratios [HRs] 1.11, 1.20, and 1.07 per 50-nmol/L increase in Lp(a), respectively).[2] Further, a recent analysis of a large multiethnic US pooled cohort of five prospective studies showed consistent increases in ASCVD risk associated with higher Lp(a) levels by sex and race/ethnicity, with particularly stronger relationships noted in individuals with versus without diabetes.[5] Some (but not all) studies—generally with smaller sample sizes and fewer ASCVD events—have shown similar results.[4,6-8] Accordingly, there is no evidence for the establishment of race-based definitions of elevated Lp(a).

Additional evidence has emerged supporting the unique impact of elevated Lp(a) on multiple cardiovascular diseases

The most consistent and quantitatively substantial associations between elevated Lp(a) and cardiovascular disease (CVD) events are for myocardial infarction (MI) and calcific aortic valve stenosis (CAVS).[2,3,9-11] Higher Lp(a) levels are also associated with a stepwise increase in the risk of peripheral artery disease, abdominal aortic aneurysms, and major adverse limb events.[12] However, in comparison, associations of Lp(a) with ischemic stroke,[2,3,9,10] heart failure,[3,9] and cardiovascular mortality[3,10,13,14] are less strong, and a higher Lp(a) level is required to see a similar increment in risk for these outcomes. For example, in participants of European ancestry in the Copenhagen General Population Study, the Lp(a) level associated with HR of 1.5 for MI was 193 nmol/L (89.5 mg/dL) and for CAVS was 154 nmol/L (71.3 mg/dL), whereas the levels were higher for ischemic stroke (323 nmol/L [150 mg/dL]) and heart failure

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Table 1 What is new.

Epidemiological Data
- The relationship between baseline Lp(a) level and ASCVD events is continuous and log-linear, with increased risk even at "lower-risk" levels.
- Despite differences in Lp(a) levels among racial/ethnic groups, Lp(a)-attributable risk is similar, eliminating previous race-based definitions of elevated Lp(a).
- Because accepted conversion factors to adjust for Lp(a)-C in LDL-C calculation have proven inaccurate, leading to undertreatment of high-risk patients, such adjustments should not be used.

Treatment
- Lipoprotein apheresis is the first therapy to receive a U.S. Food and Drug Administration indication for Lp(a) reduction, for use in high-risk patsients with FH, ASCVD, elevated Lp(a), and elevated LDL-C (see Table 2).
- Emerging pharmacological agents that specifically target Lp(a) are in development and undergoing testing in clinical trials as potential future therapies.

Recommendations
- Adults (aged ≥18 y): Measurement of Lp(a) in all adults is reasonable to refine risk assessment for ASCVD events (COR I, LOE B-NR).
- When Lp(a) levels are used for ASCVD risk assessment, it is reasonable to use measurements ≥125 nmol/L (≥50 mg/dL) as levels suggesting high risk, levels <75 nmol/L (<30 mg/dL) as low risk, and levels between as intermediate risk (COR IIa, LOE B-NR).
- The use of an adjustment factor to estimate Lp(a)-C for correction of calculated LDL-C is not recommended (COR III [no benefit], LOE C-EO).
- Lipoprotein apheresis is an FDA-approved therapy for high-risk patients with FH and ASCVD (coronary or peripheral arteries) whose Lp(a) level remains ≥60 mg/dL (~150 nmol/L) and LDL-C ≥ 100 mg/dL on maximally tolerated lipid-lowering therapy (COR IIa, LOE B-NR).

(261 nmol/L [121 mg/dL]).[9] Recent studies have also reinforced the strong evidence base that elevated Lp(a) is not a risk factor for venous thromboembolism.[9,15]

Accumulating clinical evidence allows refined incorporation of Lp(a) levels into clinical decision-making

Lp(a) levels provide incremental and independent prognostic information to C-reactive protein levels for risk estimates of ASCVD, MI, and CAVS.[16] Elevated Lp(a) remains a risk factor for ASCVD even with aggressive LDL-C lowering by statins and nonstatins (proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors, bempedoic acid, and ezetimibe).[17-19] Nonetheless, early and more-intensive management of modifiable risk factors, including LDL-C and non–high-density lipoprotein cholesterol (non-HDL-C) levels, is warranted in at-risk patients who have elevated Lp(a), as their risk is potentiated to a greater extent at a given Lp(a) concentration.[9] Estimates of the incremental reduction in LDL-C needed to mitigate the additional risk posed by elevated Lp(a), based on the patient's age at the time treatment is initiated, have been published[9]; however, these estimates have not been tested in randomized controlled outcomes trials.

B. Recommendations for Lp(a) screening

The adult population

The risk for ASCVD events that is associated with Lp(a) is independent of LDL-C and is attributed to the atherogenic, proinflammatory, and prothrombotic properties of Lp(a).[20] Lp(a) is associated with an increased risk of incident ASCVD even in the absence of a family history of heart disease.[21] Systematic universal Lp(a) screening can improve health outcomes by increasing awareness of, and enabling precision in, ASCVD prevention strategies[22] and individualization of therapy selection.[23] Preventive strategies with healthy lifestyle and LDL-C/apolipoprotein B (apoB)–lowering pharmacotherapies (especially statins) reduce risk across almost all patient groups, and incorporation of Lp(a) into risk assessment can inform decision-making for these patients since treatment is tied closely to overall risk. However, whether Lp(a)-specific therapies reduce ASCVD risk in adulthood is an ongoing subject of intensive investigation.[24,25] Nonetheless, observational studies of lipoprotein apheresis in patients with and without FH[26] and in children with ischemic stroke[27] demonstrated improvement in cardiovascular outcomes in cohorts with high Lp(a) and progressive disease despite optimal medical therapy.

We recommend measuring Lp(a) in every adult at least once for cardiovascular risk assessment (see Table 1; COR I, LOE B-NR).

The pediatric population

In the pediatric population (i.e., children <18 years of age), elevation of Lp(a) has been linked to the occurrence of arterial ischemic stroke.[28,29] Given the time necessary for atherosclerosis to cause arterial ischemia and occlusion, impaired fibrinolysis and the formation of emboli are the most likely causal links to childhood-onset ischemic stroke in the presence of elevated Lp(a). A meta-analysis showed an odds ratio of 6.3 (95 % CI 4.5–8.7) for ischemic stroke in chil-

dren with Lp(a) levels >30 mg/dL (75 nmol/L) versus those without elevated Lp(a).[29] Increased levels of Lp(a) in arterial ischemic stroke may also occur in the setting of other prothrombotic risk factors, including elevations in homocysteine, deficiencies of the anticoagulants protein C, protein S, and antithrombin III, and the presence of factor V Leiden G1691A mutation, as well as the prothrombin gene G20210A mutation.[30] Aspirin is commonly used as an antiplatelet therapy in children with ischemic stroke.[31] Although aspirin has been shown to lower Lp(a), it is not recommended primarily for this purpose. Observational studies in children with ischemic stroke demonstrate significant improvement in cardiovascular outcomes and reduced repeat cerebral vascular events in response to lipoprotein apheresis.[27]

We recommend selective screening of Lp(a) in high-risk children <18 years of age. This includes children with:

1) clinically suspected or genetically confirmed FH;
2) first-degree relatives with a history of premature ASCVD (age <55 years in men, <65 years in women);
3) ischemic stroke of unknown cause; or
4) first-degree relatives with elevated Lp(a)[1]

Moreover, a finding of elevated Lp(a) in a child should trigger cascade screening of immediate family members. It has been reported that the concentration of Lp(a) reaches adult levels by age 5 years and that an Lp(a) level ≥90th percentile at birth is a good predictor for levels >42 mg/dL (88 nmol/L) at age 15 m.[32] More recent data have shown that levels of Lp(a) may increase until early adulthood.[32,33]

Knowledge that a child has elevated Lp(a) has the potential of changing the parents' health beliefs and parenting practices, including helping their child: (1) improve adherence to a lifelong heart-healthy lifestyle, starting at a very young age; (2) understand the benefits of maintaining a healthy weight; (3) avoid smoking, vaping, and secondhand smoke exposure; (4) avoid illicit drugs such as cocaine, which are associated with premature MI in the young as a result of vasospasm and other mechanisms[34]; and (5) understand the importance of routine monitoring and optimal management of other risk factors, such as blood lipids, blood glucose, and blood pressure. On a case-by-case basis, lipid-modifying therapies should be considered. With Lp(a) measurement and other genetic testing, efforts should be made not to label or stigmatize children with elevated Lp(a).

In children with elevated Lp(a), treatment of conventional risk factors to guideline-based goals becomes particularly important, as these children are likely to be at higher risk compared with children with the same risk factors without elevated Lp(a). Individuals with elevated Lp(a) (≥30 mg/dL) as children had ∼2 times higher risk for ASCVD events as adults compared with individuals without elevated Lp(a) as children, and individuals with both elevated Lp(a) and elevated LDL-C (≥130 mg/dL) as children had ∼4 times higher risk for ASCVD events as adults,[35] suggesting an opportunity for early intervention to enhance ASCVD prevention in high-risk children.[36]

C. New thinking on Lp(a) measurement

How should Lp(a) be measured?

Lp(a) measurement is complicated by the unique structure of apolipoprotein(a) [apo(a)]. Apo(a) is characterized by a variable number of identically repeated kringle IV type 2 (KIV2) sequences (ranging from 3 to >40 copies) that correspond to differently sized isoforms of Lp(a).[37] Therefore, antibodies that recognize epitopes in the KIV2 sequence tend to underestimate the concentrations of smaller Lp(a) isoform sizes (which tend to be associated with higher Lp(a) levels and higher ASCVD risk), while overestimating those of larger isoforms. This has made the standardization and harmonization of Lp(a) measurements challenging. A second, related point of controversy has been the units that should be used for Lp(a) measurement—i.e., reporting of Lp(a) in units of particle concentration (nmol/L) versus mass concentration (mg/dL). From a technical perspective, the isoform size heterogeneity of Lp(a) supports the use of particle concentration units (nmol/L) rather than mass units, because the latter are dependent on the isoform size. Although both are acceptable measures when performed by skilled laboratories using state-of-the-art techniques, and both were found to be similarly predictive of cardiovascular event risk and risk reduction,[38] the NLA continues to favor Lp(a) measurement in nmol/L. However, Lp(a) measurement in mg/dL is far better than no Lp(a) measurement and should be used if a healthcare provider has access only to Lp(a) measurement with a mass assay. In addition, the NLA strongly recommends against converting Lp(a) values in mg/dL to values in nmol/L or vice versa using a fixed conversion factor (see Table 1; COR III [no benefit], LOE C-EO).

Efforts by the International Federation of Clinical Chemistry to develop global standardization of Lp(a) measurement are ongoing. In the interim, all current analytical methods to measure Lp(a) (many of which use a 5-point calibrator) are sufficient to assess risk associated with Lp(a) in the general population.[39] However, the administration of new Lp(a)-lowering therapies will require accurate measurement of Lp(a) to determine the eligibility of individuals for therapy as well as to monitor the effectiveness of Lp(a) lowering.

Quantification of the contribution of Lp(a) to LDL-C levels

The cholesterol carried by Lp(a) (Lp(a)-C) is included in both calculated and direct measurements of LDL-C, as well as in calculated non-HDL-C.[40] Based on early biochemical studies indicating that 30 % of the mass of Lp(a) particles is cholesterol,[40] a correction factor for Lp(a)-C was developed to adjust LDL-C calculation in patients, particularly those with elevated Lp(a). However, more recently the cholesterol content of Lp(a) has been shown to be highly variable and on average much lower than 30 %.[40] Lp(a)-C estimations using fixed conversion factors significantly overestimate Lp(a)-C and, as a consequence, underestimate Lp(a)-free LDL-C,

particularly at clinically relevant Lp(a) concentrations.[41] The application of inaccurate Lp(a)-C estimates to correct LDL-C assessment may lead to the undertreatment of high-risk patients, and therefore such corrections should not be used (see Table 1; COR III [no benefit], LOE C-EO). A recently proposed formula that uses molar concentrations of Lp(a) for correction of LDL-C for Lp(a)-C requires further clinical validation and is therefore not recommended for use at this time.[42]

Use of genetic risk scores as a surrogate for Lp(a) measurement

While genetic risk scores incorporating genetic variants at or near the *LPA* locus are increasingly accurate for identifying individuals likely to have elevated Lp(a) and to develop CVD,[10,43,44] Lp(a) genetic risk score appears to add no incremental value for CVD risk classification compared with Lp(a) concentrations alone.[10] Additionally, the generalizability of genetic risk scores to groups with non-White ancestry remains uncertain. Therefore, at this time, Lp(a) measurement is preferable for risk ascertainment; all the necessary information for appraisal of Lp(a)-attributable cardiovascular risk is embodied in the measurement of plasma Lp(a) concentration itself, mandating increased screening to identify individuals with elevated Lp(a) and high risk for CVD.

D. How should Lp(a) be incorporated into clinical decision-making to assess and mitigate risk?

Risk assessment

The assessment of CVD risk offers the opportunity to implement tailored risk-reducing strategies, matching the intensity of pharmacological treatments to the absolute global risk of the patient. Several professional cardiology societies have identified high Lp(a) as a "risk-enhancing" or "risk-modifying" factor. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Primary Prevention of CVD identified an elevated Lp(a) ≥125 nmol/L as a "risk-enhancing" factor that would favor the initiation or intensification of statin therapy for primary prevention in individuals otherwise deemed to be at borderline or intermediate risk by the pooled cohort equations.[45] The 2022 European Atherosclerosis Society consensus statement on Lp(a) recommends measuring Lp(a) at least once in all adults, also uses levels ≥125 nmol/L to "rule-in" ASCVD risk, and endorses interpretation of elevated Lp(a) in the context of a patient's absolute global CVD risk[9]; individuals who would otherwise be considered at low or moderate 10-year CVD risk by the Systematic Coronary Risk Evaluation (SCORE) estimator tool would be recommended for more intensive treatment of LDL-C, systolic blood pressure, and lifestyle risk factors in the setting of elevated Lp(a). The Canadian Cardiovascular Society recommends measuring Lp(a) level once in a patient's lifetime with the initial lipid screening and considers Lp(a) ≥50 mg/dL (or ≥100 nmol/L) as a risk modifier, warranting statin therapy in intermediate-risk patients and earlier, more-intensive lifestyle modification and management of other ASCVD risk factors in low-risk patients including primary prevention.[46] In patients with severely elevated Lp(a), especially those with a family history of early-onset CVD or with high risk as estimated by AHA Predicting Risk of CVD Events (PREVENT)[47] or SCORE risk calculators, healthcare providers should be particularly attentive to CVD risk and screen for ASCVD and, if warranted by physical examination, possibly aortic stenosis.

The previous NLA recommendation for using Lp(a) levels in ASCVD risk assessment was dichotomous and derived from the 80th percentile of White primary prevention participants in the Framingham Offspring Study (≥100 nmol/L); therefore, application was limited to White patients. Based on subsequent data, including the much larger dataset from UK Biobank, we now recognize the continuous increase in CVD risk across increasing Lp(a) levels and have also redefined high-risk levels to represent better the multiethnic US population.

In the risk continuum across Lp(a) levels, individuals with Lp(a) levels <75 nmol/L (30 mg/dL) can be considered low risk and individuals with Lp(a) levels ≥125 nmol/L (50 mg/dL) should be considered high risk (see Table 1; COR IIa, LOE B-R). This approach allows for the consideration of repeat measurement of Lp(a) in patients with levels within a "gray zone" of intermediate risk between 75 and 125 nmol/L (30–50 mg/dL). Because Lp(a) levels are relatively stable in primary prevention patients, measurement of Lp(a) once for individuals in the low-risk or high-risk category in this population is reasonable[39,48]; however, this needs to be verified in secondary prevention populations.[39] A substantial percentage of individuals with intermediate-risk Lp(a) levels may move into the high-risk category, especially women after menopause, individuals who develop proteinuria and chronic kidney disease, and individuals with hypothyroidism.[49,50] Therefore, repeat measurement may be warranted for these patients.

Coronary artery calcium (CAC) is a well-established prognostic marker of ASCVD risk as it is a useful surrogate of total coronary atherosclerosis burden.[51] However, elevated Lp(a) is independently associated with incident ASCVD even after adjusting for the CAC score. In the Multi-Ethnic Study of Atherosclerosis (MESA), the highest quintile of Lp(a) compared with the lower quintiles was associated with a 29 % increased risk of incident ASCVD after adjusting for other risk factors and CAC (HR 1.29 [95 % CI 1.04–1.61]), with a similar trend noted in the Dallas Heart Study.[52] While MESA participants with both high CAC score and elevated Lp(a) were at the greatest ASCVD risk, a trend of increased risk was observed in participants with high Lp(a) but CAC score of 0 (HR 1.31 [95 % CI 0.73–2.35]). In addi-

tion to promoting atherosclerosis, elevated Lp(a) is purported to increase CVD risk through other mechanisms such as being prothrombotic and proinflammatory. In addition, elevated Lp(a) is not consistently associated with baseline CAC and CAC progression,[53] implying a distinct underlying pathobiology. Thus, a CAC score of 0 does not eliminate the risk associated with elevated Lp(a), particularly in younger adults, in whom a CAC score of 0 may underestimate the lifetime risk of ASCVD and provide false reassurance.

What recommendations should be offered to patients?

Lifestyle modification

Adoption of a healthy lifestyle is the foundation of all prevention guidelines. Although diet and physical activity have minor and variable impacts on Lp(a) concentrations, a healthy lifestyle is clearly associated with reduced vascular risk and should be recommended for all adults and children, particularly high-risk patients such as those with elevated Lp(a). In a large prospective observational study, individuals with elevated Lp(a) (≥∼125 nmol/L) but otherwise optimal cardiovascular health scores had lower risk of incident CVD compared with individuals with lower Lp(a) levels but poor cardiovascular health.[54]

Statins

Across all professional society guidelines, statins remain first line-therapy for mitigating LDL-C–driven ASCVD risk in both secondary and high-risk primary prevention patients.[55] Although statins do not lower Lp(a) and may slightly increase Lp(a), statins clearly lower ASCVD risk, reducing major adverse cardiovascular events (MACE) by approximately 22 % for each 1-mmol/L (38.7 mg/dL) reduction in LDL-C.[56] In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), median Lp(a) was not affected by rosuvastatin treatment, but Lp(a) distribution was shifted toward higher percentiles; patients with Lp(a) level above or below the median had similar benefit with rosuvastatin, and risk for MACE was increased in patients with higher baseline or on-treatment Lp(a) levels.[18] The Lp(a)-raising effects of statins are minimal on average, with an approximate 1.1-mg/dL increase or 0.1 % relative increase in Lp(a) on statin treatment as seen in a large meta-analysis.[57] Although some individuals may have greater increases, especially after high-intensity statin therapy, concerns about Lp(a) elevation should not be a reason to discourage or discontinue statins. Of note, ongoing clinical trials of targeted Lp(a) therapeutics in high-risk ASCVD patients are all being conducted on a background of statin therapy, as statin therapy remains the standard of care for secondary prevention patients.

Ezetimibe and bempedoic acid

Ezetimibe does not affect Lp(a) levels appreciably. A statistically significant 7.1 % Lp(a) reduction in one meta-analysis (including 7 trials and 2337 patients with primary hypercholesterolemia) was not considered clinically significant by the investigators,[58] and another meta-analysis (including 10 trials and 5188 patients with primary hypercholesterolemia) showed no effect on Lp(a) level with ezetimibe as monotherapy or in combination with statin.[59] Bempedoic acid also does not affect Lp(a) level.[60]

PCSK9-directed therapies

PCSK9 inhibitors, including monoclonal antibodies (evolocumab and alirocumab) and small interfering RNAs (siRNAs; inclisiran), can lower Lp(a) by approximately 20–30 %,[19,61,62] although they are not approved for this indication. Moreover, in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial in stable ASCVD patients, evolocumab conferred a greater relative risk reduction among individuals with elevated Lp(a) compared with those without elevated Lp(a), another indication that higher risk patients derive more benefit from intensive LDL-C/apoB–lowering therapy, which may include benefit from Lp(a) lowering.[19] The reduction in MACE with evolocumab was 25 % in patients with baseline Lp(a) above the median (120 nmol/L; HR 0.75 [95 % CI 0.64–0.88]) vs 11 % in those with baseline Lp(a) at or below the median (HR 0.89 [95 % CI 0.79–1.01]; p-interaction = 0.096), and the reduction in MACE appeared proportional to Lp(a) level achieved. Similarly, in ODYSSEY Outcomes, each 1-mg/dL reduction in Lp(a) with alirocumab was associated with HR of MACE of 0.994 (95 % CI 0.990–0.999; $p = 0.0081$).[63] Thus, if a high-risk patient needs additional LDL-C lowering after maximally tolerated statin therapy and also has elevated Lp(a), a PCSK9 inhibitor may be a good choice to address residual risk from both LDL-C and Lp(a).

Niacin

Niacin may lower Lp(a) concentration by decreasing apo(a) production rate. In a meta-analysis of 14 randomized placebo-controlled trials of extended-release niacin (including a total of 9013 patients), niacin was associated with a significant 23 % reduction in Lp(a) levels.[64] Although niacin monotherapy provided ASCVD benefit in men in the secondary-prevention Coronary Drug Project,[65,66] more recent studies of statin combined with niacin as an HDL-C–raising agent did not show clinical benefit despite ∼20 % reductions in Lp(a) level.[67,68] Therefore, niacin is not recommended for Lp(a) lowering.

Aspirin

Although aspirin remains a class I recommendation for the secondary prevention of ASCVD, its use is less well established for primary prevention, with recent clinical trials suggesting more harm than benefit. As such, the 2019 ACC/AHA Guideline on the Primary Prevention of CVD gave aspirin only a class IIb recommendation for primary prevention in adults with elevated ASCVD risk but at low risk of bleeding.[45] However, secondary analyses of primary prevention trials such as the Women's Health Study[69] and

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Table 2 Summary table of recommendations.

Recommendation	COR	LOE
I. Laboratory measurement of Lp(a)		
1. For the measurement of Lp(a), it is recommended that an immunochemical assay that is calibrated against the WHO/IFCCLM secondary reference material should be used and reported in nmol/L	I	B-NR
2. When using values of Lp(a) for clinical risk assessment and treatment decisions, the use of a factor to convert Lp(a) values from mg/dL to nmol/L is not recommended	III (no benefit)	C-EO
3. The use of an adjustment factor to estimate Lp(a)-C for correction of calculated LDL-C is not recommended	**III (no benefit)**	**C-EO**
II. Lipoprotein(a) testing in clinical practice		
1. Adults (aged ≥18 y): Measurement of Lp(a) in all adults is reasonable to refine risk assessment for ASCVD events	**I**	**B-NR**
2. Youth (aged <18 y): Selective screening of Lp(a) is recommended in high-risk patients (e.g., clinically suspected or genetically confirmed FH, ischemic stroke of unknown cause, first-degree relatives with a history of premature ASCVD [age <55 years in men, <65 years in women], or first-degree relatives with elevated Lp(a))	IIb	C-LD
3. When Lp(a) levels are used for ASCVD risk assessment, it is reasonable to use measurements ≥125 nmol/L (≥50 mg/dL) as levels suggesting high risk, levels <75 nmol/L (<30 mg/dL) as low risk, and levels between as intermediate risk	**IIa**	**B-R**
III. Treatment		
1) In adults aged 40–75 y with a 10-y ASCVD risk of 7.5 %–19.9 %, the finding of an Lp(a) ≥125 nmol/L or ≥50 mg/dL is reasonable to be used as a risk-enhancing factor to favor initiation of a moderate- or high-intensity statin in those with on-treatment LDL-C ≥ 70 mg/dL (or non-HDL-C ≥ 100 mg/dL)	IIa	B-NR
2) In high-risk* or very-high-risk** patients with Lp(a) ≥125 nmol/L or ≥50 mg/dL, it is reasonable to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction	IIa	A
3) In high-risk* or very-high-risk** patients taking a maximally tolerated statin, with Lp(a) ≥125 nmol/L or ≥50 mg/dL, the addition of ezetimibe is reasonable in those with on-treatment LDL-C ≥ 70 mg/dL (or non-HDL-C ≥ 100 mg/dL)	IIa	B-R
4) In high-risk* or very-high-risk** patients taking a maximally tolerated statin, with Lp(a) ≥125 nmol/L or ≥50 mg/dL, the addition of a PCSK9 inhibitor is reasonable in those with on-treatment LDL-C ≥ 70 mg/dL (or non-HDL-C ≥ 100 mg/dL)	IIa	B-R
5) **Lipoprotein apheresis is reasonable for high-risk patients with FH and ASCVD (coronary or peripheral arteries) whose Lp(a) level remains ≥60 mg/dL (∼150 nmol/L) and LDL-C ≥ 100 mg/dL on maximally tolerated lipid-lowering therapy**	**IIa**	**B-NR**
6) Niacin or HRT with estrogen and progesterone, which lower Lp(a) concentration, is not recommended to reduce ASCVD risk	III (Harm)	A, B-R

Adapted from Wilson DP, Jacobson TA, Jones PH, et al. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol.* 2022;16:e77-e95. 10.1016/j.jacl.2022.08.007.

Bold indicates new/updated recommendations.

*High-risk patients: clinical ASCVD including myocardial infarction, acute coronary syndrome, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral artery disease, including aortic aneurysm, all of atherosclerotic origin.

**Very-high-risk patients: history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

ASCVD risk categories adapted from Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:3168–3209. doi:10.1016/j.jacc.2018.11.002.

COR and LOE categories adapted from Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149:e1-e156. doi:10.1161/CIR.0000000000001193.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; COR, class (strength) of recommendation; FH, familial hypercholesterolemia; HRT, hormone-replacement therapy; IFCCLM, International Federation of Clinical Chemistry and Laboratory Medicine; LDL-C, low-density lipoprotein cholesterol; LOE, level (quality) of evidence; Lp(a), lipoprotein(a); Lp(a)-C, lipoprotein(a) cholesterol; non-HDL-C, non–high-density lipoprotein cholesterol; WHO, World Health Organization.

the Aspirin in Reducing Events in the Elderly (ASPREE) trial[70] suggested that individuals with genetically predicted elevated Lp(a) might derive a net benefit from aspirin therapy. Given Lp(a)'s purported prothrombotic characteristics, aspirin might be of particular benefit in patients with elevated Lp(a), with greater reduction in vascular events and no increased risk of bleeding compared with the use of aspirin in primary prevention patients without elevated Lp(a) reported in ASPREE.[70] We recommend having a risk–benefit discussion about aspirin in primary prevention patients with elevated Lp(a), for use as a risk-lowering—not a lipid-lowering—agent, although some studies have reported Lp(a)

reduction with high doses of aspirin.[71] As noted, aspirin may also be used in children with high Lp(a) and prior stroke.[31]

Lipoprotein apheresis

Currently, the only FDA-approved therapy for treating high Lp(a) is lipoprotein apheresis, based on observational data (see Table 1; COR IIa, LOE B-NR). In addition to indications defined by LDL-C levels, apheresis is now also approved for use in high-risk patients with FH and ASCVD (coronary or peripheral arteries) whose Lp(a) level remains ≥60 mg/dL [~150 nmol/L)] and LDL-C ≥ 100 mg/dL on maximally tolerated lipid-lowering therapy.[72] Because lipoprotein apheresis removes all apoB-containing lipoproteins, both LDL-C and Lp(a) are substantially reduced acutely but return toward pretreatment levels between procedures. However, apheresis is not available at all centers and can be expensive and time-consuming. A need remains for additional treatment options to address Lp(a)-related residual risk.

New therapies under investigation

Pelacarsen is an antisense oligonucleotide targeting the mRNA transcribed from the *LPA* gene and can reduce Lp(a) levels by >80 %.[73] Olpasiran is an siRNA that also prevents the translation of the apo(a) protein with up to ~100 % reduction in circulating Lp(a) levels.[74] However, whether these therapies can reduce MACE has not yet been established and is currently being tested in large ongoing cardiovascular outcome trials in secondary prevention patients with elevated Lp(a) levels: pelacarsen in Assessing the Impact of Lipoprotein (a) Lowering with Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients with CVD (Lp(a)HORIZON)[75] and olpasiran in Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction (OCEAN(a))–Outcomes Trial.[76] Other siRNA therapies targeting Lp(a) (zerlasiran [SLN360][77] and lepodisiran [LY3819469])[78] are being tested in phase 2 trials.[79] Additionally, an oral agent (muvalaplin [LY3473329]) that works by a different mechanism of disrupting the formation of Lp(a), by interfering with the apo(a) and apoB interaction, is being tested in early-phase trials.[80]

Challenges in increasing rates of Lp(a) testing

Despite the knowledge that Lp(a) elevation is common and affects at least ~1/5 of individuals worldwide, current rates of testing for Lp(a) in clinical practice remain extremely low.[81,82] Several studies have examined the prevalence of Lp(a) testing across single centers and large health systems.

In the US, the prevalence of Lp(a) testing across 6 centers in the University of California health system in 2012–2021 (5,553,654 patients) was only 0.3 %, with low Lp(a) testing rates observed in patients with ischemic heart disease (2.9 %), peripheral vascular disease (2 %), and stroke (1.8 %).[81] A similar study examined the prevalence of Lp(a) testing across 11 US health systems (PCORnet) in 2015–2019 and found that Lp(a) was measured in only 0.06 % of patients per year.[83]

Thus, while rates of Lp(a) testing are low when examining large health systems, heterogeneity exists in the prevalence of Lp(a) testing among single centers, specific patient populations, and differing healthcare reimbursement policies. For example, the prevalence of Lp(a) testing may be higher at individual centers, among patients with conditions known to be impacted by Lp(a) (e.g., ASCVD, CAVS), and when steps are taken to increase Lp(a) testing (e.g., educational efforts, incorporation of testing into aspects of the electronic health record system).[84-87] Expansion of lower-cost direct-to-consumer testing may be an important approach to increase access to testing. While a cost-effectiveness analysis is beyond the scope of this manuscript, the average cost of an Lp(a) test is currently $30–100.[86]

Table 3 Take home points.

- The relationship between Lp(a) level and cardiovascular disease risk is continuous and log-linear
- Rather than a single dichotomous cutpoint defining a risk threshold, Lp(a) levels represent a continuum of cardiovascular disease risk spanning low, intermediate, and high risk
- Individuals with Lp(a) levels <75 nmol/L (30 mg/dL) may be considered low risk, individuals with Lp(a) levels ≥125 nmol/L (50 mg/dL) may be considered high risk, and individuals with Lp(a) levels in the "gray zone" between 75 and 125 nmol/L (30–50 mg/dL) are at intermediate risk and may warrant repeat measurement
- Lp(a) risk categories apply across races and ethnicities
- Lp(a) should be measured at least once in every adult for cardiovascular risk assessment
- Lp(a) should be measured and reported in nmol/L; Lp(a) values should not be converted between mg/dL and nmol/L using a fixed conversion factor
- The previously proposed correction factor for Lp(a)-C used to adjust LDL-C calculation may lead to the undertreatment of high-risk patients and therefore should not be used
- Although statins may increase Lp(a) levels, concerns about Lp(a) elevation should not be a reason to discourage or discontinue statins
- In high-risk patients with elevated Lp(a) who need additional LDL-C lowering after maximally tolerated statin therapy, a PCSK9 inhibitor may address residual risk from both LDL-C and Lp(a)
- Lipoprotein apheresis was approved by the FDA for use in patients with clinically diagnosed heterozygous familial hypercholesterolemia and either documented coronary artery disease or documented peripheral artery disease who have Lp(a) level ≥60 mg/dL (~150 nmol/L) and LDL-C ≥ 100 mg/dL despite maximally tolerated lipid-lowering therapy

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E. Summary

While specific Lp(a)-lowering therapies are not currently available, elevated Lp(a) is actionable now[88] (Table 2; Table 3). Lp(a) level should be measured at least once in all adults to identify individuals with high Lp(a) levels for implementation of early and intensive risk factor management. For CVD risk assessment, Lp(a) levels should be used to stratify patients as low risk (<75 nmol/L) or high risk (≥125 nmol/L), and individuals with Lp(a) levels in between should be considered as intermediate risk and also may be considered for repeat measurement. As a risk-enhancing factor, Lp(a) level can also help reclassify individuals with overall borderline, intermediate, or high risk, and this information may impact the choice of lifestyle modification and intensification of lipid-lowering therapy with statin and other drugs, including PCSK9 inhibitors. In addition, identification of individuals with high levels of Lp(a) also identifies a family at risk, and cascade screening for elevated Lp(a) should be performed in first-degree family members. Lipoprotein apheresis is indicated for patients with clinically diagnosed FH and either documented coronary artery disease or documented peripheral artery disease whose Lp(a) level remains ≥60 mg/dL (∼150 nmol/L) and LDL-C ≥ 100 mg/dL despite maximally tolerated lipid-lowering therapy.

Disclosure

Use of AI and AI-assisted Technologies Statement

AI has not been used in the writing process.

Ethical Statement

This work does not involve the use of human subjects or animals.

Declaration of interest statement

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CRediT authorship contribution statement

Marlys L. Koschinsky: Conceptualization, Writing – original draft, Writing – review & editing. **Archna Bajaj:** Writing – review & editing. **Michael B. Boffa:** Writing – original draft, Writing – review & editing. **Dave L. Dixon:** Writing – review & editing. **Keith C. Ferdinand:** Writing – review & editing. **Samuel S. Gidding:** Writing – original draft, Writing – review & editing. **Edward A. Gill:** Writing – review & editing. **Erin D. Michos:** Writing – original draft, Writing – review & editing. **Maya S. Safarova:** Writing – original draft, Writing – review & editing. **Daniel E. Soffer:** Writing – review & editing. **Pam R. Taub:** Writing – original draft, Writing – review & editing. **Michael J. Wilkinson:** Writing – original draft, Writing – review & editing. **Don P. Wilson:** Writing – original draft, Writing – review & editing. **Christie M. Ballantyne:** Conceptualization, Writing – original draft, Writing – review & editing.

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