Journal of Clinical Lipidology (2019) ■, ■–■

Journal of Clinical Lipidology

Original Research

Use of lipoprotein(a) in clinical practice: A biomarker whose time has come—A scientific statement from the National Lipid Association. Don P. Wilson, MD, on behalf of the Writing group

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KEYWORDS:
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Abstract: Lipoprotein(a) [Lp(a)] is a well-recognized, independent risk factor for atherosclerotic cardiovascular disease, with elevated levels estimated to be prevalent in 20% of the population. Observational and genetic evidence strongly support a causal relationship between high plasma concentrations of Lp(a) and increased risk of atherosclerotic cardiovascular disease–related events, such as myocardial infarction and stroke, and valvular aortic stenosis. In this scientific statement, we review an array of evidence-based considerations for testing of Lp(a) in clinical practice and the utilization of Lp(a) levels to inform treatment strategies in primary and secondary prevention.

Introduction

a. Question: What are the proposed pathophysiologic mechanisms supporting a causal link between increased circulating concentrations of Lp(a) and (1) atherosclerotic cardiovascular disease (ASCVD) and (2) valvular aortic stenosis (VAS)?

Observational and genetic evidence strongly support a causal relationship between high plasma concentrations of lipoprotein(a) [Lp(a)] and increased risk of ASCVD and VAS.[1–4] Although the precise pathophysiologic mechanism behind these relationships is not completely clear, the mechanism likely involves either or both components of Lp(a), that is, the low-density lipoprotein (LDL)-like

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Submitted April 24, 2019. Accepted for publication April 26, 2019.

1933-2874/
https://doi.org/10.1016/j.jacl.2019.04.010

particle and the apolipoprotein(a) [apo(a)] attached to apolipoprotein B (apoB) via a disulfide bridge (Fig. 1). The apo(a) protein has homology with plasminogen and in vitro, as well as in some animal models, and inhibits fibrinolysis.[2,5,6] Historically, it has been suggested that high concentrations of circulating Lp(a) could have provided a survival benefit by facilitating wound healing,[7,8] reduce bleeding, and aiding hemostasis during childbirth.[4,6]

Both ASCVD and VAS share elements of stenosis as well as cholesterol deposition in the arterial intima and aortic valve leaflets, respectively. In susceptible individuals, Lp(a) mediated promotion of thrombosis in vulnerable plaques of coronary arteries or at sites of stenosis may increase risk of myocardial infarction (MI), and thrombotic emboli may increase risk of ischemic stroke (Fig. 1).[4]

The cholesterol content of the LDL portion of Lp(a) may promote cholesterol deposition in the arterial intima and at aortic valve leaflets, leading, respectively, to symptomatic atherosclerosis resulting in MI and ischemic stroke, and VAS (Fig. 1). However, even at very high Lp(a) concentrations such as 100 mg/dL, the LDL cholesterol (LDL-C) portion of Lp(a) would only amount to 33 mg/dL,[9] which is unlikely to cause substantial deposition of cholesterol in tissues.

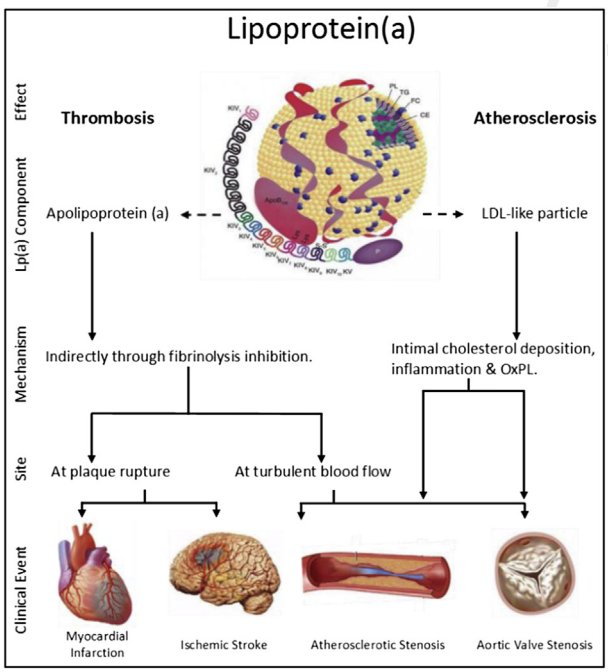

Figure 1 Proposed pathophysiologic mechanisms supporting a causal link between elevated circulating concentrations of Lp(a) and (1) atherosclerotic cardiovascular disease and (2) aortic stenosis. LDL, low-density lipoprotein; PL, phospholipids; TG, triglycerides; FC, free cholesterol; CE, cholesteryl ester; ApoB100, apolipoprotein B 100; KIV, kringle IV; KV, kringle V; P, protease; apo(a), apolipoprotein(a); OxPL, oxidized phospholipids.

Although ASCVD and VAS are distinct clinical entities, they have several risk factors in common and similar pathological processes. Evidence suggests that oxidized phospholipids, which modify Lp(a) primarily by covalent binding to its unique apo(a) component, might hold the key to Lp(a) pathogenicity and provide a mechanistic link between ASCVD and VAS. Oxidized phospholipids colocalize with apo(a)-Lp(a) in arterial and aortic valve lesions and directly participate in the pathogenesis of these disorders by promoting endothelial dysfunction, lipid deposition, inflammation, and osteogenic differentiation, leading to calcification. Genetic evidence for a contribution of oxidized phospholipids has been presented,[10] and associations between elevated oxidized phospholipids on Lp(a) and risk for coronary heart disease (CHD) and valvular aortic stenosis have been detected.[10,11]

Key points

- Apo(a), attached to the apoB segment of an LDL-like particle, is a unique protein contained within Lp(a).
- Apo(a) has homology with plasminogen and may inhibit fibrinolysis, thus increasing thrombosis.
- Through inhibition of fibrinolysis at sites of plaque rupture, apo(a) has the potential to cause MI and ischemic stroke.
- Thrombosis at sites of turbulent flow may promote atherosclerotic and valvular aortic stenosis.
- Apo(a) possesses unique properties that promote initiation and progression of atherosclerosis and calcific valvular aortic stenosis through endothelial dysfunction and proinflammatory responses, and calcification.
- Many of these effects are likely attributable to the oxidized phospholipids, of which Lp(a) is the preferential carrier, and which are covalently attached to apo(a).

b. Question: Do available, high-quality data from meta-analyses, large prospective, population-based studies, large Mendelian randomization studies, and genome-wide association (GWA) studies support a relationship between increased circulating Lp(a) concentrations and (1) ASCVD; (2) VAS; and (3) mortality?

Meta-analyses of prospective, population-based studies of adults show increased risk of CHD and MI at Lp(a) concentrations above 30 mg/dL (62 nmol/L) and increased risk of ischemic stroke at concentrations above 50 mg/dL (100 nmol/L) (Table 1). However, effect sizes were modest, likely due to inclusion of all available studies (1) irrespective of size, study quality, and quality of the Lp(a) assays used and (2) whether the plasma samples used were fresh or had been frozen for prolonged periods of time before measurement of Lp(a).[12–15]

Another meta-analysis found that individuals with smaller apo(a) isoforms [and high Lp(a) concentrations] had an approximately 2-fold higher risk of CHD and ischemic stroke than those with larger apo(a) isoforms

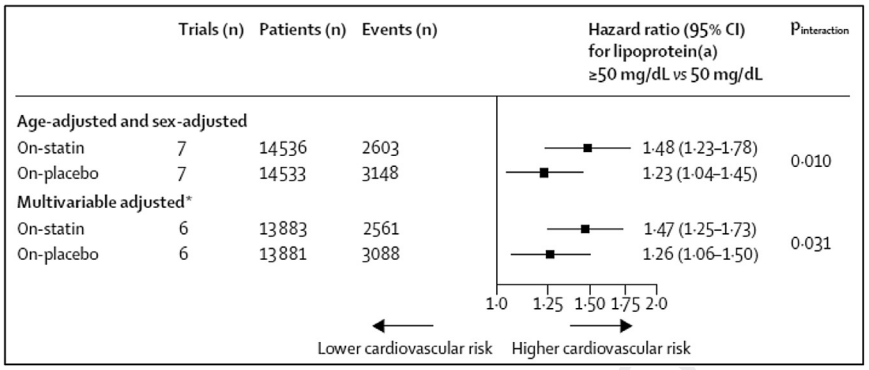

Figure 2 Predictive value of on-statin verses on-placebo lipoprotein(a) concentration for incident cardiovascular disease. Q15 Q16

(and low Lp(a) concentrations).[16] Finally, a meta-analysis of 4 small studies of varying study quality found a 4-fold risk of stroke in youth with high vs low Lp(a) concentrations.[17]

The INTERHEART study of 6086 cases of first MI and 6857 controls, stratified by ethnicity (Africans, Chinese, Arabs, Europeans, Latin Americans, South Asians, and Southeast Asians) and adjusted for age and sex, examined the contribution of Lp(a) concentration and isoform size (using an isoform insensitive assay) to MI risk in accordance with ethnicity. Concentrations of Lp(a) > 50 mg/dL were associated with an increased risk of MI (odds ratio 1.48; 95% CI 1.32–1.67; $P < .0001$), independent of established ASCVD risk factors. Although there was an inverse association between isoform size and Lp(a) concentration, this relationship did not persist after adjustment for Lp(a) concentration. The relationship between Lp(a) concentration and MI risk was significant for all ethnicities except for Africans and Arabs and was highest in South Asians and Latin Americans. Whether these findings are due to ethnic differences or smaller sample sizes of African and Arab subjects, as compared with other ethnic groups, is uncertain.[18]

Large prospective, population-based studies measuring plasma Lp(a) in fresh samples using isoform-insensitive measurements show that individuals with Lp(a) in the top 5th percentile (≥120 mg/dL; 258 nmol/L) vs those in the lower 20th percentile (<5 mg/dL; 7 nmol/L) have 3- to 4-fold risk of MI[19,20] and 3-fold risk of VAS (Table 1).[21] In corresponding studies, individuals with highest vs lowest Lp(a) concentrations had 5-fold risk of coronary artery stenosis, 1.7-fold risk of carotid stenosis, 1.6-fold risk of ischemic stroke, 1.6-fold risk of femoral artery stenosis, 1.5- to 2-fold risk of heart failure, 1.5-fold risk of cardiovascular mortality, and 1.2-fold risk of all-cause mortality.[4,22–25]

Large Mendelian randomization studies free of confounding and reverse causation[26–28] further support that increased Lp(a) in plasma represents an independent, genetic and causal factor for acute MI, ischemic stroke, VAS, coronary artery stenosis, carotid stenosis, femoral artery stenosis, heart failure, cardiovascular mortality, and all-cause mortality (Table 1).[20–24] Importantly, among all genetic instruments available for Mendelian randomization studies, those for Lp(a) have the greatest statistical power, where both a single-nucleotide polymorphism and Kringle IV type 2 number of repeats each explain more than 25% of all variations in plasma concentrations. In other words, of all evidence from Mendelian randomization studies for any biomarker and any disease, the evidence supporting high Lp(a) concentrations to causality of ASCVD and VAS is the strongest.

Finally, GWA studies focusing primarily on the direct association between genetic variation and risk of disease in large case-control consortia generally find that of all genetic variation in the human genome, those related to high Lp(a) concentrations confer the highest risk of ASCVD[29–31] and VAS.[32,33] Sometimes GWA studies are referred to as hypothesis-free testing, thereby implying that no bias can explain why genetic variation for high Lp(a) plasma concentrations associate with the highest risk of ASCVD and VAS.

Lp(a) concentrations in plasma are 80%–90% genetically determined[2,34] and represent a lifelong, genetic causal factor independent of all other known causes and risk factors for ASCVD, VAS, and mortality, including LDL-C.

Key points

- Meta-analyses of prospective, population-based studies of high Lp(a) demonstrate high risk of MI, CHD, and ischemic stroke.
- Large prospective, population-based studies of high Lp(a) demonstrate high risk of MI, ischemic stroke, VAS, coronary artery stenosis, carotid stenosis, femoral artery stenosis, heart failure, cardiovascular mortality, and all-cause mortality.
- Large Mendelian randomization and GWA studies confirm that high Lp(a) is a causal factor for MI, ischemic stroke, VAS, coronary artery stenosis, carotid stenosis, femoral artery stenosis, heart failure, cardiovascular mortality, and all-cause mortality.
- These causal relationships are independent of concentrations of other lipids and lipoproteins, including LDL-C.

Table 1 Do available, high-quality data from meta-analyses, large observational studies, Mendelian randomization studies, and genome-wide association studies support a relationship between increased circulating Lp(a) concentrations and (1) atherosclerotic cardiovascular disease, (2) valvular aortic stenosis, and (3) mortality?

	Atherosclerotic cardiovascular disease					
High-quality data source:	Myocardial Infarction	Ischemic stroke	Atherosclerotic stenosis*	Aortic valve stenosis	Cardiovascular mortality	All-cause mortality
Meta-analyses of observational studies	Yes	Yes	No	No	No	No
Large observational studies.†**	Yes	Yes	Yes	Yes	Yes	Yes
Large Mendelian randomization studies	Yes	Yes	Yes	Yes	Yes	Yes
Large genome-wide association studies	Yes	No	Yes	Yes	No	No

*Clinical symptoms in the form of stable angina pectoris or intermittent claudication or documented atherosclerotic stenosis in coronary, femoral, or carotid arteries.

†Using isoform insensitive Lp(a) measurements.

Laboratory measurement of lipoprotein(a)

a. Question: What are the key laboratory measurement issues which impact a clinician's interpretation of reported Lp(a) values?

Lp(a) has a highly heterogeneous structure owing to the presence of many different isoform sizes within the population. The distribution of plasma Lp(a) levels is highly skewed and differs considerably among different ethnic groups. From a clinical perspective, these factors have important implications for Lp(a) measurement.[35] Key issues include (1) the prevalence of assays reporting Lp(a) values as mass concentrations (units of mg/dL) vs particle concentrations (nmol/L); (2) the lack of standardization of Lp(a) assays; and (3) the absence of evidence-based Lp(a) cut points for different risk groups, ethnic populations, and comorbidities.

b. Question: What are the limitations of currently available assays and how does the performance characteristics of the test (ie, accuracy [bias] and precision) affect clinician interpretation of the results?

Currently available assays have not been subjected to a global standardization regime.[36] Although some commercially available assays use calibrators that are traceable, such as the WHO/IFCCLM secondary reference material PRM-2B,[37] this is not the case for all, notably those that report results in mg/dL. Moreover, harmonization of values obtained from different assays, even those reporting in nmol/L, has yet to be undertaken.[36] The potential exists, therefore, for bias in Lp(a) immunoassays because of the presence of variable numbers of repeated units in differently sized apo(a) isoforms.[35,38,39] Typically, this bias manifests as an underestimation of the levels of small Lp(a) isoforms and an overestimation of large Lp(a) isoforms.[35] This bias could result in misclassification of patients with Lp(a) levels close to a predefined cut point.[38] Some commercially available assays minimize isoform-dependent bias by using a 5-point calibrator, consisting of a range of Lp(a) isoforms.[35]

It has been recommended that use of mg/dL units be discontinued.[36] As the PRM-2B is in nmol/L, and Lp(a) isoforms have different molecular weights, unlike other lipids and lipoproteins, direct conversion between mg/dL and nmol/L is not possible. Universal use of nmol/L would (1) create an opportunity to standardize and harmonize Lp(a) assays, as the output is independent of the molecular weight of the Lp(a) species used as the calibrator and (2) facilitate future clinical studies of Lp(a) and the establishment of evidence-based guidelines. Therefore, in the absence of Lp(a) assay standardization, clinicians should use, where possible, assays that report results in nmol/L, using a 5-point or similar calibrator, and which are calibrated against the WHO/IFCCLM secondary reference material.

c. Question: What should be the population Lp(a) cut points for defining high risk, based on age, sex, and ethnicity?

The evidence base for specific cut points for high risk based on age, sex, and ethnicity is generally incomplete. This also applies to individuals with comorbid conditions such as familial hypercholesterolemia (FH), diabetes mellitus, or renal disease. There has been debate about whether cut points based on Lp(a) concentrations or population-specific percentiles are most appropriate. This is because the distribution of Lp(a) levels differs among ethnic groups (Table 2)[35] and is affected by certain disease conditions.[40] For example, the Multi-Ethnic Study of Atherosclerosis found that while a cut point of ≥50 mg/dL best predicted CHD in Caucasians, Chinese-Americans, and Hispanics, the corresponding value for blacks was ≥30 mg/dL.[41] On the other hand, the Atherosclerosis Risk in Communities study found no difference in risk between Caucasian and

Table 2 Distribution of Lp(a) levels by ethnic group*

		Lp(a) Level by percentile (nmol/L)					
	N	10th	50th	75th	80th	98th	95th
Caucasian Americans	2929	1	20	73	100	154	209
African Americans	1899	16	75	130	148	199	234
Japanese American	1379	3	19	40	49	75	103

*Data from Marcovina, 2016.

black subjects, irrespective of the cut point used.[42] Moreover, individual studies in different populations (eg, primary vs secondary prevention) have arrived at different cut points (≥30 mg/dL and ≥50 mg/dL, respectively).[36] It is unlikely that these observations reflect differences in the underlying pathobiology of Lp(a). Although different groups likely have varying risk factor profiles, which influence the contribution of Lp(a), it is also possible that the different observed cut points reflect selection bias, different statistical power in individual studies, and other confounding effects. Therefore, we recommend a tentative, universal cut point of ≥100 nmol/L (approximately ≥50 mg/dL), which is supported by the largest meta-analyses in a range of populations.[16,43]

d. Question: Because the cholesterol content of Lp(a) is included in the measurement of LDL-C, is there a level of LDL-C where the measurement of Lp(a) should be considered independent of clinical history?

Some studies have shown that lowering LDL-C attenuates or eliminates risk attributable to elevated Lp(a).[44,45] On the other hand, other studies have shown that Lp(a) clearly contributes to residual risk in statin-treated subjects.[43,46,47] In a 2018 meta-analysis, elevated Lp(a) was a stronger risk factor than LDL-C for incident CVD in statin-treated than in placebo-treated subjects.[43] Q7 Therefore, it may be reasonable to speculate that measuring Lp(a) in subjects with elevated LDL-C identifies subjects who could benefit from more intensive LDL-C–lowering therapy, including use of PCSK9 inhibitors, which have been shown to lower Lp(a) by ~20%–30%.[48,49] However, this proposition has yet to be directly tested in clinical studies. Notably, current risk prediction algorithms, such as the Framingham Risk Score or the Pooled Cohort Equations, do not include Lp(a), whereas recommendations from several organizations and societies suggest measuring Lp(a) in subjects with an intermediate risk score.[50,51] Therefore, at present, we recommend that measurement of Lp(a) should be considered when clinically indicated and not necessarily related to a high baseline level of LDL-C alone. Because statins and PCSK9 inhibitors lower LDL-C less effectively in the setting of a high Lp(a) concentration, the finding of less-than-anticipated LDL-C lowering in response to treatment with these agents should suggest the possibility of a markedly elevated Lp(a). Some patients with markedly elevated LDL-C values, with levels suggesting FH, have been found to have this clinical presentation primarily because of Lp(a) elevation.[52]

Key points

- Measurement of Lp(a) is currently not standardized or harmonized.
- Available assays report Lp(a) in either mg/dL or nmol/L and may exhibit Lp(a) isoform-dependent bias.
- Evidence is incomplete regarding the utility of using different risk cut points of Lp(a) based on age, gender, ethnicity, or the presence of comorbid conditions.
- Elevated Lp(a) appears to confer elevated risk for ASCVD over a wide range of LDL-C concentrations.
- An Lp(a) level >50 mg/dL (>100 nmol/L) may be considered as a risk-enhancing factor favoring the initiation of statin therapy. This level corresponds to the 80th population percentile in populations which are predominantly Caucasian.
- The corresponding 80th population percentile in African Americans is approximately 150 nmol/L, but it is unclear whether a different risk threshold or cut point should be applied. Clinicians should be aware that African Americans have an approximately 3-fold higher median Lp(a) than Caucasian populations (75 nmol/L vs 20 nmol/L)

Table of Recommendation	Class of Rec (strength)	Levels of Evidence	References/notes Q8
I. Laboratory measurement of lipoprotein(a)			
1. For the measurement of Lp(a), it is recommended that an immunochemical assay that is calibrated against the WHO/IFCCM secondary reference material should be used and reported in nmol/L.	I	B-NR	Marcovina, 2016; Tsimikas, 2018; Marcovina, 2000; Marcovina, 2003
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)	E-O	Marcovina, 2000, Marcovina, 2016; Tsimikas, 2018 JCL
3. When Lp(a) values are used for ASCVD risk assessment in Caucasian patients, it is reasonable to use measured values ≥ 50 mg/dL or ≥100 nmol/L as levels suggesting increased risk.	IIa	B-R	Nordestgaard, 2010; Willeit, 2018, Langsted, 2019

Lipoprotein(a) testing in clinical practice

a. The importance of shared decision-making

A decision to measure Lp(a) should be made after a thoughtful benefit-risk discussion between the patient and his/her health care provider. Shared decision-making should reflect an individual's preferences and values. Decisions should also be based on family history, the presence of comorbid conditions, race/ethnicity, and/or concern of future risk. In the absence of an acute illness, the level of Lp(a) is stable throughout an individual's lifetime and unaffected by lifestyle. Therefore, a case could be made to measure Lp(a) in all individuals, at least once in a lifetime, based on strong support for the association between elevated Lp(a) levels and increased risk, together with genetic findings that indicate elevated Lp(a) is causally related to premature ASCVD and VAS. However, there is no current evidence to substantiate the benefit of such an approach, and there is currently no targeted treatment(s) to lower Lp(a) levels that have been proven to affect ASCVD outcomes or progression of VAS. Therefore, although some panel members supported it, a recommendation for universal testing of Lp(a) was not made at this time. The Scientific Statement Committee acknowledges that there is likely little harm from a universal screening approach and that the cost of the test is relatively inexpensive compared with other cardiovascular disease screening tests. As more data become available in the future, the potential role of universal testing should be re-evaluated.

b Question: What clinical factors result in consideration of Lp(a) testing in primary prevention?

A large percentage of the world's population (20%) has an Lp(a) > 50 mg/dl.[53] A prospective population-based study showed that measurement of Lp(a) predicted not only 15-year CVD outcomes but improved CVD risk prediction.[54] Several national and international (ESC/EAS) guidelines[4,50,51,55] recommend Lp(a) testing if an individual has documented ASCVD (especially with recurrent events on optimal lipid-lowering therapy), severe hypercholesterolemia or genetic FH, premature ASCVD, or a first-degree family member with premature ASCVD, particularly in the absence of traditional risk factors. Based on the results of cascade screening of 797 patients from a Spanish registry of molecularly defined heterozygous FH patients, testing for Lp(a) during cascade screening was found to be an effective means to identify relatives of the proband with increased risk of clinical ASCVD, especially when FH and elevated Lp(a) coexist.[85]

The 2018 ACC-AHA Multi-Organization Guideline on the Management of Blood Cholesterol does not provide a recommendation on routine measurement of Lp(a).[56] However, the 2018 guideline further states that if the results of Lp(a) testing are available to the clinician, an elevated concentration of ≥50 mg/dL or ≥125 nmol/L may be considered to be a risk-enhancing factor favoring moderate-intensity statin therapy in patients at intermediate risk (7.5%–19.9% 10-year risk) (class IIa B-NR) who are aged 40–75 years and have an LDL-C of 70–189 mg/dL. In addition, an elevated Lp(a) may aid risk discussion in patients aged 40–75 years with borderline risk (5%–7.4%) and an LDL-C 70–189 mg/dL, when initiation of statin therapy is being considered (class IIb B-NR).

A potential caveat to consider in this recommendation emanates from a study examining Lp(a) levels in blood samples from female subjects as part of 2 large randomized clinical trials and one observational study, suggesting that Lp(a) concentrations of >50 mg/dL predicted increased cardiovascular risk only in those with total cholesterol >220 mg/dL.[57] However, other larger studies do not support this perspective.[14,19,58]

Two ICD-10 codes have been added to justify Lp(a) testing [E78.41 = elevated Lp(a) and Z83.430 = Family History of elevated Lp(a)]. The relative stability of Lp(a) levels over a lifetime supports the perspective that repeat measurement is generally unnecessary, provided that the initial blood sample was not obtained during an acute illness.[59]

Key points

Lp(a) testing is reasonable to refine risk assessment for ASCVD events in adults with:
- First-degree relatives with premature ASCVD (aged <55 y in men or <65 y in women).
- A personal history of premature ASCVD.
- Primary severe hypercholesterolemia (LDL-C ≥190 mg/dL) or suspected FH.

Lp(a) testing may be reasonable in adults:
- To aid in the clinician-patient discussion about whether to prescribe a statin in those aged 40-75 y with borderline (5%–7.4%) 10-y ASCVD risk.
- To identify a possible cause for a less-than-anticipated LDL-C lowering to evidence-based LDL-C–lowering therapy.
- To use in cascade screening of family members with severe hypercholesterolemia.
- To identify those at risk for progressive VAS.

c. Question: What is the effect of currently available therapies on lowering Lp(a) levels and is there evidence that reducing Lp(a) will reduce the incidence of ASCVD, VAS, or cerebrovascular disease?

Although in general beneficial, lifestyle changes, including low fat diets and moderate-to-vigorous daily physical exercise, have no significant effect on Lp(a) levels.[57,60,61]

Hormone replacement therapy (HRT) in women lowers Lp(a) levels, and in the Women's Health Study, HRT was observed to modify CVD risk across Lp(a) quintiles.[60] However, in the Heart and Estrogen/progestin Replacement Study (secondary prevention) and the Women's Health Initiative (primary prevention) randomized trials, HRT-related adverse events (breast cancer, stroke, thrombosis) outweighed any benefit on CVD. Therefore, HRT cannot be recommended as the sole purpose of lowering Lp(a).[62,63]

Niacin therapy is associated with a significant reduction in Lp(a) of approximately 23%.[64] However, its addition to statin therapy in high-risk ASCVD patients with LDL-C levels near or at goal (<75 mg/dl) has not been shown to improve ASCVD outcomes in AIM HIGH and HPS2 THRIVE and has been associated with increased harms (new onset diabetes, bleeding, myopathy, and infections).[47,65,66] One potential explanation for this finding is niacin's limited ability to reduce the concentration of Lp(a) in those with the highest baseline Lp(a) levels and small isoform size.[67]

Statin therapy has demonstrated a clinical benefit in patients with elevated Lp(a),[68] despite evidence that levels of Lp(a) may increase after initiation of therapy.[3] A 2018 meta-analysis of patients with elevated Lp(a) and history of CV events concluded that those with Lp(a) levels >50 mg/dL on statin therapy are at a significantly higher risk of CVD as compared with those with levels <30 mg/dL, independent of other conventional CVD risk factors.[43]

There is uncertainty about the clinical value of PCSK9 inhibitor–associated Lp(a) reduction. An analysis of the FOURIER trial demonstrated that evolocumab reduced Lp(a) by 27% and that the reduction in MACE was 23% (hazard ratio [HR] 0.77, 95% CI 0.67–0.88) in those patients with Lp(a) > median (37 nmol/L) and by 7% (HR 0.93, 0.80–1.08) in those ≤ median.[69] Patients with higher baseline Lp(a) levels had greater absolute reductions in Lp(a) and tended to derive greater benefit from PCSK9 inhibition. In ODYSSEY OUTCOMES, there was also a greater absolute benefit on MACE with alirocumab in patients with higher baseline levels of Lp(a).[70] In addition, baseline Lp(a) values predicted risk of MACE. Although the reduction of LDL-C was the dominant factor contributing to the event reduction with alirocumab, an independent contribution of lowering Lp(a) on MACE and total CV events was also demonstrated.[71] Additional analysis of the PCSK9 inhibitor outcomes trials will be needed to support their use in patients with elevated Lp(a) levels.

A modest reduction in Lp(a) of 20%–25% has been reported in homozygous FH patients treated with lomitapide, a microsomal triglyceride transfer protein inhibitor. However, there are no studies showing the incremental benefit in this unique population. In the absence of data, lomitapide is not indicated for Lp(a) lowering or for ASCVD risk reduction.

Lipoprotein apheresis (LA), which acutely lowers LDL-C by >60% and reduces plasma levels of oxidized phospholipid, known mediators of vascular inflammation and predictors of atherosclerosis progression found predominantly on Lp(a)-containing fractions,[72] may be offered to individuals with drug resistant, uncontrolled LDL-C levels (>160 mg/dL with and >300 mg/dL without CVD). In 2010, the German health care system approved LA therapy for ASCVD patients with an elevated Lp(a) (>60 mg/dL; >120 nmol/L) and recurrent ASCVD events, irrespective of LDL-C levels.[73] Currently, more than 1400 Germans receive weekly LA therapy for an elevated Lp(a) and CVD prophylaxis.[74] Since the initiation of LA therapy for Lp(a) reduction in Germany, three prospective/retrospective trials involving over 400 individuals have demonstrated a 70% reduction of MACE compared with preapheresis events.[75–77] In addition, Khan et al[78] conducted a single-blind, placebo-controlled, crossover trial, initiating weekly LA therapy for patients with refractory angina and elevated Lp(a) levels (>50 mg/dL). Myocardial perfusion reserve, the study's primary outcome, increased after LA compared with sham treatment, yielding a net treatment increase of 0.63 (95% CI 0.27–0.89; $P < .001$ between the groups). In the United States, LA is performed primarily to reduce LDL-C in patients with severe FH and ASCVD. Some specialized lipid centers have also used LA for both LDL-C and Lp(a) reduction in very selected very-high-risk patients, such as those with recurrent ASCVD events despite optimal lipid-lowering drugs.

Presently, no data exist on the lowering of Lp(a) for the treatment of VAS and the benefits of available lipid-lowering drug therapy, and LA on VAS outcomes is unknown. The use of statins in patients with calcific VAS may modestly raise Lp(a) and oxidized phospholipids, effects that theoretically could promote progression.[79]

Phase 2 clinical trials of apo(a) antisense oligonucleotide (AKCEA apo(a)-LRx) have been completed in patients with elevated Lp(a) and ASCVD. These studies demonstrated Lp(a) reductions of 35%–80%, depending on the dosage used; however, more trials are needed to show safety, and improved ASCVD outcomes, before the drug can be considered for clinical use.

Key points

- Lifestyle therapy, including diet and physical exercise, has no significant effect on Lp(a) levels.
- Statin therapy does not decrease Lp(a) levels.
- Patients with a history of ASCVD who are taking statins and have an Lp(a) ≥ 50 mg/dL are at increased risk for ASCVD events, independent of other risk factors.
- Niacin lowers Lp(a), has no demonstrated ASCVD risk reduction benefit in patients taking statins, and may cause harms.
- Lomitapide, which is indicated to lower LDL-C in patients with homozygous FH, also lowers Lp(a) but is not recommended for ASCVD risk reduction.
- PCSK9 inhibitors lower Lp(a), but the contribution of Lp(a) reduction to their ASCVD risk reduction benefit remains undetermined.
- LDL apheresis lowers Lp(a) and is sometimes used for those with elevated Lp(a) and recurrent ASCVD events.

d. Question: What clinical factors would result in consideration of Lp(a) testing in secondary prevention?

Recommendations for Lp(a) screening in patients with established ASCVD (stroke, CHD, peripheral arterial disease, and VAS) continue to evolve. The most consistent barrier to screening is based on a lack of evidence demonstrating that lowering Lp(a) independently of LDL-C reduces adverse CVD-related events. Although a case could be made by experienced lipidologists for screening Lp(a) in all secondary prevention patients, the following discussion provides the best available evidence to guide the clinical utility of measuring Lp(a).

Clinical situations in which Lp(a) screening may be reasonable in secondary prevention include adults (1) with premature ASCVD-related events,[80] (2) with recurrent ASCVD events, including individuals with target vessel restenosis after percutaneous intervention and bypass graft failure, despite adequate risk factor control,[69,81] and (3) with ischemic stroke who are aged <55 years.[15] Individuals aged <45 years with premature ASCVD-related events have been shown to be more likely to have a Lp(a) level >50 mg/dL, tripling the chance of an acute coronary syndrome compared with individuals aged >60 years.[82]

Lp(a) has been shown to be a strong predictor of risk when the risk attributable to LDL-C is reduced by statin therapy. A large meta-analysis of 29,069 patients enrolled in 7 primary and secondary prevention placebo-controlled statin trials[43] found that on-statin treatment patients with Lp(a) levels >50 mg/dL (15% of the population) had a MACE HR of 1.48 (1.23–1.78), compared with subjects with Lp(a) < 50 mg/dL in the placebo arm who had an HR of 1.23 (1.04–1.45).

Approximately 1 in 3 individuals with FH also have a Lp(a) level >50 mg/dL, which is a significant accelerant of ASCVD and is also an indication for cascade screening of Lp(a) in FH families.[83–85] These findings suggest that it is reasonable to measure Lp(a) in FH patients with ASCVD. The relationship of Lp(a) levels and stroke generally suggests that Lp(a) is a risk factor for cerebral vascular disease.[86–88] A meta-analysis of case-control prospective cohort studies, which included 5029 stroke events, found Lp(a) to be an independent risk factor for ischemic stroke, especially in adults aged <55 years.[15] Because the preponderance of evidence supports Lp(a) as an independent risk factor, it may be reasonable to measure Lp(a) in adults aged <55 years with ischemic stroke.

It may also be reasonable to measure Lp(a) in individuals with calcific VAS.[89] Two single-nucleotide polymorphisms (rs10455872 and rs3798220), which determine plasma levels of Lp(a) are associated with an increased risk of calcific VAS proportional to the Lp(a) level. One study reported HRs for calcific VAS ranging from 1.2 for a Lp(a) < 20 mg/dL to 2.9 for levels >90 mg/dL.[21] Another study reported an odds ratio of 1.61 for VAS per log-unit increase in plasma Lp(a) levels.[32]

The calculated LDL-C includes the cholesterol contained in Lp(a). Because the Lp(a) cholesterol is not reduced by statins, individuals with elevated Lp(a) may have a less-than-expected response in LDL-C reduction to statin therapy. Data from GWA studies have reported that several genetic variants, including rs10455872, within the *LPA* gene account for as much as a 4% attenuation in LDL-C lowering with statin treatment.[90,91]

A Mendelian randomization analysis concluded that large absolute reductions of Lp(a) may be needed to demonstrate a meaningful reduction in ASCVD risk.[92] The magnitude of this effect is significant, ranging from a proportional risk reduction of 1.3% when the change in Lp(a) is 5 mg/dL to a risk reduction of 27.7% if the change is 120 mg/dL.

Key points

- The measurement of Lp(a) is reasonable in adults with:
  - Premature ASCVD (men aged <55 y, women aged <65 y).
  - Recurrent or progressive ASCVD, despite optimal lipid lowering.
- Lp(a) is associated with an increased risk of calcific VAS proportional to the Lp(a) level, and measuring Lp(a) may be reasonable in patients with this disorder.
- Patients with high Lp(a) levels may have less-than-expected LDL-C lowering on statin therapy.
- There is a lack of current evidence demonstrating that lowering Lp(a), independently of LDL-C, reduces ASCVD events in individuals with established ASCVD. It appears that large absolute reductions in Lp(a) may be needed to demonstrate a significant clinical benefit.

Table of Recommendation	Class of Rec (strength)	Levels of Evidence	References/Notes
II. Lipoprotein(a) testing in clinical practice			
1. Adults (aged ≥20 y)			
a. Measurement of Lp(a) is reasonable to refine risk assessment for ASCVD events in:			
1) Individuals with a family history of first-degree relatives with premature ASCVD (males aged <55 y; females aged <65 y)	IIa	C-LD	Rallidis, 2018
2) Individuals with premature ASCVD (men aged <55 y and women aged <65 y), particularly in the absence of traditional risk factors.	IIa	B NR	Erqou, 2009; Kamstrup, 2013; Clarke 2009; CARDIoGRAMplus C4D Consortium, 2013; Genest, 1992
3) Individuals with primary severe hypercholesterolemia (LDL ≥190 mg/dL) or suspected FH.	IIa	B-NR	Pérez de Isla, 2017; Ellis, 2016; Langsted 2016; Ellis, 2019
4) Individuals at very-high-risk** of ASCVD to better define those who are more likely to benefit from PCSK9 inhibitor therapy	IIa	B-NR	O'Donoghue,2018; Bittner, 2018
b. Measurement of Lp(a) may be reasonable for individuals with:			
1) Intermediate (7.5%–19.9%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIa	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
2) Borderline (5%–7.4%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIb	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
3) Less-than-anticipated LDL-C lowering, despite good adherence to LDL-C lowering therapy.	IIb	C-LD	Yeang 2016; CARDIoGRAMplus C4D Consortium 2013; Langstead 2016
4) A family history of elevated Lp(a).	IIb	C-LD	Clarke 2009; CARDIoGRAMplus C4D Consortium 2013; Langsted 2016
5) Calcific valvular aortic stenosis.	IIb	C-LD	Thanassoulis 2013; Kamstrup 2014; Arsenault 2014; Vongpromek 2015; Capoulade 2015
6) Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy.	IIb	C-LD	Albers 2013; Khera 2014; Nestel 2013;

e. Question: What factors may be reasonable in considering measurement of Lp(a) levels in youth (aged <20 years)?

Limited data are available to assist in clinical decision-making regarding (1) criteria for measurement of Lp(a) in those 20 years of age or younger and (2) recommendations for intervention in those in whom elevated levels of Lp(a) have been identified. However, given its autosomal codominant mode of inheritance and causal role in ASCVD, selective screening of Lp(a) of youth who have informative clinical findings and/or family history is reasonable. The *LPA* gene is fully expressed by 1-2 years of age and the concentration of Lp(a) reaches adult levels by ~5 years of age. In the absence of inflammation, plasma levels of Lp(a) are stable and track into adulthood, as well as from one generation to the next.[2,93] Fasting is not required for Lp(a) measurement.

Evidence supports a link between elevated levels of Lp(a) and ASCVD-related events in adults, and ischemic stroke in both youth and adults.[16,24,94] Lifelong elevation of Lp(a), beginning at a very early age, predisposes to higher risk of premature ASCVD as an adult. Most youth with elevated levels of atherogenic lipoproteins, including Lp(a), are of normal weight and are asymptomatic. Longitudinal measurement of flow-mediated dilation of the brachial artery demonstrated attenuated endothelial function,[95] whereas a cross-sectional study found no difference in pulse wave velocity or carotid-intima-medial thickness when comparing youth with Lp(a) ≥30 mg/dL vs those with Lp(a) <30 mg/dL.[96] Long-term studies linking altered arterial function and/or structural changes in youth with elevated levels of Lp(a) to adult-onset ASCVD-related events are lacking.

Individuals with extremely elevated Lp(a) (>200 mg/dL) have a similar lifetime risk of CHD as heterozygous FH, although an estimated prevalence twice as high.[92] Such reports have led some to suggest a need for

universal as well as selective screening, beginning in childhood. While appealing, currently this approach is limited by lack of Lp(a)-lowering therapy that has been shown to be safe, effective, and approved for use in youth. Nonetheless, knowledge that a child has an elevated level of Lp(a) creates an opportunity to inform the family about the importance of (1) adherence to a heart-healthy lifestyle, starting at a very young age; (2) the benefits of maintaining a healthy weight; (3) smoking avoidance, including the health risks of secondhand exposure; and (4) the need for monitoring plasma lipids, blood glucose, and blood pressure. Identifying youth with an elevated level of Lp(a) level also facilitates reverse cascade screening to help identify relatives who may also be at risk.

Given the time necessary for atherosclerosis to cause arterial ischemia, impaired fibrinolysis and formation of emboli are the most likely causal link to childhood-onset ischemic stroke. Data supporting this putative mechanism are, however, limited. Case-control studies and meta-analysis have reported a significantly increased odds of incident idiopathic childhood-onset ischemic stroke in association with elevated levels of Lp(a).[94,97] Childhood ischemic stroke is linked to various prothrombotic risk factors, including elevations in homocysteine, deficiencies of anticoagulants protein C, protein S and antithrombin III, and the presence of factor V Leiden G1691A mutation as well as the prothrombin (PT) gene mutation G20210A. In contrast, although an independent study found Lp(a) to be a mild prognostic factor for recurrence ischemic stroke, no evidence was found of an association with incident childhood-onset ischemic stroke.[98] Such conflicting results raise an important but unanswered clinical question, as to whether measurement of Lp(a) is potentially more beneficial in secondary vs primary prevention of childhood-onset ischemic stroke.

Although additional evidence is needed, the presence of increased prothrombotic risk factors, including increased levels of Lp(a), has been suggested as potentially playing a role in venous thromboembolism. Compared with controls, the coexistence of Factor V G1691A (FV-Leiden) and elevated Lp(a) has been reported to be significantly more prevalent among individuals with venous thromboembolism, including some adolescents, although the role of increased Lp(a) in this setting is unknown.[99]

Depending on the underlying cause of stroke, current pediatric guidelines recommend the use of anticoagulants or antiplatelet agents in the acute setting. Such recommendations are generally based on adult studies, cohort studies, and/or expert opinion. Prolonged use of anticoagulants or antiplatelet agents requires careful consideration of potential benefits verses known risks of treatment.

Since 2011, published guidelines have recommended selective screening of cholesterol in youth 2 years of age and older, and universal screening beginning at age 10 years (range 9–11), regardless of general health or the presence or absence of CVD risk factors. Given the current evidence, to date, only selective measurement of Lp(a) has been recommended in (1) youth with a history of hemorrhagic or ischemic stroke and (2) offspring of a parent with premature CVD and no other identifiable risk factors.[100,101]

Youth with FH and family history of early-onset ASCVD were 3 times more likely to have high Lp(a) than those with a family history of late-onset ASCVD (OR: 3.77, 95% CI: 1.16–12.25, $P = .027$) but were not more likely to have highly elevated LDL-C ($> = 190$ mg/dL) (OR: 0.45, 95% CI: 0.11–1.80, $P = .26$). Lp(a) was reported to be more predictive than LDL-C for early onset of CVD in family members. Measurement of Lp(a) in youth with FH may better characterize their cardiovascular risk, particularly when knowledge of family history is limited and help identify those who could benefit from more aggressive management to reduce ASCVD risk.[102]

With its potential for risk enhancement, it seems reasonable to measure Lp(a) in youth with genetically confirmed or clinically suspected FH and offer screening to youth when a parent or sibling is found to have an elevated Lp(a).

Key points

- The *LPA* gene is fully expressed by 1-2 y of age and the concentration of Lp(a) reaches adult levels by ~5 y of age.
- Fasting is not required for Lp(a) measurement, and despite being genetically determined, levels may be influenced in the presence of inflammation.
- Because Lp(a) is genetically transmitted, youth whose parents have an elevated Lp(a) level are reasonable candidates for screening; conversely, reverse cascade screening is recommended when a child is found to have an elevated level of Lp(a).
- Even if the absence of approved Lp(a)-lowering medications in youth found to have an elevated level of Lp(a), it is important to emphasize early and lifelong adoption of a heart-healthy lifestyle by the child and family members, especially with respect to smoking avoidance or cessation, given the thrombotic risk attributable to Lp(a).
- Measurement of Lp(a) in youth with a history of ischemic stroke may be reasonable.

Table of Recommendation	Class of Rec (strength)	Levels of Evidence	References/notes
2. Youth (aged <20 y)			
a. Measurement of Lp(a) may be reasonable with:			
1) Clinically suspected or genetically confirmed FH.	IIb	C-LD	Burgess, 2018; Sultan, 2018
2) A family history of first-degree relatives with premature ASCVD (males aged <55 y, females aged <65 y).	IIb	C-LD	Sultan 2018; Expert Panel 2011
3) An unknown cause of ischemic stroke.	IIb	C-LD	Erqou,2009; Kenet, 2010; Goldenberg, 2013; Expert Panel 2011
4) A parent or sibling found to have an elevated Lp(a).	IIb	C-LD	Zawacki, 2018

Treatment

a Question: If Lp(a) is markedly increased, what are the implications with regard to further LDL-C–lowering therapy? Is there evidence that supports improved outcomes with greater LDL-C reductions in the presence of an increased Lp(a)?

In patients receiving LDL-C–lowering therapy, increased baseline and on-statin treatment Lp(a) concentrations remain a risk factor for ASCVD events.[43,46,47] In analyses of 29,000 patients from seven randomized statin trials, an Lp(a) ≥50 mg/dL (105 nmol/L) vs <15 mg/dL (29 nmol/L) conferred a 1.3-fold ASCVD risk for baseline and a 1.4-fold for on-statin Lp(a) concentrations.[43] Statin treatment did not affect Lp(a) concentrations, and high Lp(a) was a stronger ASCVD risk predictor in patients on statins vs placebo. Because patients on statins with markedly elevated Lp(a) concentrations have a higher absolute risk than those without Lp(a) elevation, such patients are likely to exhibit the greatest benefit from more aggressive LDL-C–lowering therapy. Therefore, as recommended in the 2018 ACC/AHA Cholesterol Guidelines, the following recommendations can be made. First, in primary prevention for adults aged 40–75 years with a 10-year ASCVD risk of 7.5%–19.9%, a Lp(a) ≥50 mg/dL or ≥100 nmol/L is reasonable to use as a risk-enhancing factor to favor initiation of a moderate- or high-intensity statin. Second, in high or very-high-risk patients with LDL-C ≥70 mg/dL (non–HDL-C ≥100 mg/dL) and a Lp(a) ≥50 mg/dl or ≥100 nmol/L on maximally tolerated statin intensity, it is reasonable to consider more intensive therapies (such as ezetimibe and PCSK9 inhibitors) to lower LDL-C (and non–HDL-C) to achieve greater ASCVD risk reduction.

In the FOURIER trial, the addition of evolocumab to the treatment regimen of high-risk patients already receiving intensive therapy with high- or moderate-intensity statin (69% vs 30%) +/− ezetimibe showed that the greatest treatment benefit was obtained in those with baseline Lp(a) at or above a clinical threshold of 120 nmol/L (50 mg/dL) as compared with those below the threshold.[69] Evolocumab reduced Lp(a) by 27%. However, it is not clear that this reduction contributed independently to the treatment benefit.[103] In the ODYSSEY OUTCOMES study, alirocumab use in high-risk/very-high-risk patients confers the greater absolute risk reduction in patients within the highest Lp(a) tertile (>60 mg/dL).[70] In addition, recent analysis from ODYSSEY OUTCOMES suggests that the Lp(a) reduction with alirocumab, independent of LDL-C, contributes to risk reduction.[71]

As noted in section Laboratory Measurement of lipoprotein(a) b, niacin and hormone replacement treatment can reduce Lp(a). However, because there is no evidence of ASCVD benefit, while there is a suggestion of harm, use of these therapies are not recommended.

Key points

- In statin-treated patients, a high Lp(a) is an independent ASCVD risk factor.
- In primary prevention for adults aged 40–75 y with a 10-y ASCVD risk of 7.5%–19.9%, an Lp(a) ≥50 mg/dL or ≥100 nmol/L is reasonable to be used as a risk-enhancing factor to favor initiation of a moderate or high-intensity statin.
- In high-risk* or very-high-risk** patients with LDL-C ≥70 mg/dL (non–HDL-C ≥100 mg/dL) and a Lp(a) ≥50 mg/dl or ≥100 nmol/L on maximally tolerated statin intensity, it is reasonable to consider more intensive therapies (such as ezetimibe and/or PCSK9 inhibitors) to lower LDL-C (and non–HDL-C) to achieve greater ASCVD risk reduction.
- The presence of an elevated Lp(a) in patients with very-high-risk** ASCVD and baseline LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL despite maximally tolerated statin ± ezetimibe may be used as a factor favoring addition of a PCSK9 inhibitor.
- Although niacin and hormone replacement therapy can reduce Lp(a) levels, these drugs are not recommended because of no demonstrated ASCVD benefit and the possibility of harm.

Table of recommendation	Class of Rec (strength)	Levels of evidence	References/notes
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) ≥50 mg/dL or ≥100 nmol/L[§] 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	Emerging Risk Factors Collaboration JAMA 2009; Clarke R et al. N Engl J Med 2009; Kamstrup PR et al. JAMA 2009
2. In high-risk* or very-high-risk** patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], it is reasonable to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.	IIa	A	Willeit, 2018); Khera, 2014; Baigent, 2000
3. In very-high-risk** patients, taking a maximally tolerated statin with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], 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	Cannon, 2015
4. In high-risk* patients taking a maximally tolerated statin, with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], the addition of ezetimibe may be reasonable in those with on-treatment LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL).	IIb	B-R	Cannon, 2015
5. In very-high-risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ≥70 mg/dL (or non–HDL-C ≥100 mg/dL) and an Lp(a) of ≥50 mg/dL or ≥100 nmol/L[§], the addition of a PCSK9 inhibitor is reasonable.	IIa	B-R	O'Donoghue,2018; Bittner, 2018; Sabatine, 2017; Schwartz, 2018
6. Niacin, which lowers Lp(a) concentration, is not recommended to reduce ASCVD risk in patients receiving moderate- to high-intensity statins +/− ezetimibe and an on-treatment LDL-C <80 mg/dL	III (harm)	A	Albers, 2013J; Parish, 2018
7. HRT with estrogen and progesterone, which lowers Lp(a) concentration, is not recommended in perimenopausal/ postmenopausal women to reduce ASCVD risk.	III (harm)	B-R	Hulley, 1998; Shlipak 2000; Writing Group for the WHI Investigators, 2002

ASCVD risk categories (adapted from Grundy, 2018)

*High risk = Individuals with clinical ASCVD including those with MI, ACS, 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 = Individuals with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Conclusion

With overwhelming support of elevated Lp(a) levels as an independent risk factor for ASCVD and VAS, based on a review of the current evidence, we have provided recommendations for clinicians on how best to deal with this lipoprotein in clinical practice. Although presently there is no global standardization of Lp(a) measurement, the preferred measurement unit is nmol/L, and although nmol/L cannot be converted directly to mg/dL, levels ≥50 mg/dL and ≥100 nmol/L each suggest increased risk of ASCVD and VAS. Currently available evidence indicates that Lp(a) measurement may be useful to reclassify ASCVD risk and, selectively, to aid in pharmacotherapy decision-making. Repeat measurement of Lp(a) is not recommended as the clinical value of serial measurements has not been established. Although adoption of a heart-healthy lifestyle and statins do not lower Lp(a) levels, it is still reasonable to intensify both in individuals with elevated Lp(a). In those with elevated Lp(a) and insufficient LDL-C lowering, it is reasonable to add ezetimibe and, in selected cases, PCSK9 inhibitors, whereas niacin and hormone replacement therapy should be avoided.

Future directions

While much is now known about Lp(a) and its role in ASCVD and valvular aortic disease, future recommendations for clinical practice still await additional evidence. For Lp(a) to be accepted as a risk factor for intervention, a randomized clinical trial of Lp(a) lowering in those at risk is required. Until we have the results of such a trial, several important unanswered questions remain. Is it reasonable to recommend universal testing of Lp(a) in everyone regardless of family history or health status, at least once to help

encourage healthy habits and inform clinical decision-making? Will earlier testing and effective interventions help to improve outcomes? What will be the benefit of medical interventions that target Lp(a) lowering and how will such therapies change the outcome of those at-risk and those currently affected by ASCVD? Will Lp(a)-lowering therapy be effective in those with low LDL-C, given the development of new promising LDL-C–lowering therapies beyond statins, ezetimibe, and PCSK9 inhibitors?

To answer these and a myriad of other questions, it is encouraging that a randomized, placebo-controlled, double-blind trial of Lp(a) reduction using antisense oligonucleotides to block the production of Lp(a) via *LPA* gene silencing is anticipated to start in 2020. Other pharmaceutical companies are developing other promising Lp(a)-lowering therapies such as small interfering RNA inhibitor technology. Thus, if these early studies continue to show both safety and efficacy, it is likely that more randomized trials will also be conducted with the aim of reducing ASCVD and possibly AVS progression through novel targeted Lp(a) reduction.

As discussed in this scientific statement, there is an urgent need for better standardization of Lp(a) measurement and an improved understanding of Lp(a) metabolism, physiology, and the pathologic mechanisms by which Lp(a) and oxidized phospholipids on Lp(a) leads to ASCVD and AVS. Finally, we need to address the knowledge gaps that currently exist for unique populations, including the relationship of high Lp(a) with stroke in children and to better define the unmet medical needs for Lp(a) reduction in individuals of all ethnicities. Additional data are urgently needed in blacks, South Asians, and those of Hispanic descent. We hope that this NLA scientific statement will help stimulate a thoughtful worldwide discussion that will result in improved health and outcomes of those entrusted to our care.

Table of recommendation	Class of Rec (strength)	Levels of evidence	References/notes
I. Laboratory measurement of lipoprotein(a)			
1. For the measurement of Lp(a), it is recommended that an immunochemical assay that is calibrated against the WHO/IFCCM secondary reference material should be used and reported in nmol/L.	I	B-NR	Marcovina, 2016; Tsimikas, 2018; Marcovina, 2000; Marcovina, 2003
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)	E-O	Marcovina, 2000, Marcovina, 2016; Tsimikas, 2018 JCL
3. When Lp(a) values are used for ASCVD risk assessment in Caucasian patients, it is reasonable to use measured values ≥ 50 mg/dL or ≥100 nmol/L as levels suggesting increased risk.	IIa	B-R	Nordestgaard, 2010; Willeit, 2018, Langsted, 2019
II. Lipoprotein(a) testing in clinical practice			
1. Adults (aged ≥ 20 y)			
a. Measurement of Lp(a) is reasonable to refine risk assessment for ASCVD events in:			
1) Individuals with a family history of first-degree relatives with premature ASCVD (males aged <55 y; females aged <65 y)	IIa	C-LD	Rallidis, 2018
2) Individuals with premature ASCVD (males aged <55 y and females aged <65 y), particularly in the absence of traditional risk factors.	IIa	B NR	Erqou, 2009; Kamstrup, 2013; Clarke 2009; CARDIoGRAMplus C4D Consortium, 2013; Genest, 1992
3) Individuals with primary severe hypercholesterolemia (LDL ≥190 mg/dL) or suspected FH.	IIa	B-NR	Pérez de Isla, 2017; Ellis, 2016; Langsted 2016; Ellis, 2019
4) Individuals at very high** risk of ASCVD to better define those who are more likely to benefit from PCSK9 inhibitor therapy	IIa	B-NR	O'Donoghue,2018; Bittner, 2018
b. Measurement of Lp(a) may be reasonable with:			
1) Intermediate (7.5%–19.9%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIa	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
2) Borderline (5%–7.4%) 10-y ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIb	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
3) Less-than-anticipated LDL-C lowering, despite good adherence to therapy.	IIb	C-LD	Yeang 2016; CARDIoGRAMplus C4D Consortium 2013; Langstead 2016

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(*continued*)

Table of recommendation	Class of Rec (strength)	Levels of evidence	References/notes
I. Laboratory measurement of lipoprotein(a)			
4) A family history of elevated Lp(a).	IIb	C-LD	Clarke 2009; CARDIoGRAMplus C4D Consortium 2013; Langsted 2016
5) Calcific valvular aortic stenosis.	IIb	C-LD	Thanassoulis 2013; Kamstrup 2014; Arsenault 2014; Vongpromek 2015; Capoulade 2015
6) Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy.	IIb	C-LD	Albers 2013; Khera 2014; Nestel 2013;
2. Youth (aged $<$ 20 y)			
a. Measurement of Lp(a) may be reasonable with:			
1) Clinically suspected or genetically confirmed FH.	IIb	C-LD	Burgess, 2018; Sultan, 2018
2) A family history of first-degree relatives with premature ASCVD (males with $<$55 y, females aged $<$65 y).	IIb	C-LD	Sultan 2018; Expert Panel 2011
3) An unknown cause of ischemic stroke.	IIb	C-LD	Erqou,2009; Kenet, 2010; Goldenberg, 2013; Expert Panel 2011
4) A parent or sibling found to have an elevated Lp(a).	IIb	C-LD	Zawacki,2018
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) $\geq$50 mg/dL or $\geq$100 nmol/L[§] 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 $\geq$70 mg/dL (or non–HDL-C $\geq$100 mg/dL).	IIa	B-NR	Emerging Risk Factors Collaboration JAMA 2009; Clarke R et al. N Engl J Med 2009; Kamstrup PR et al. JAMA 2009.
2. In high-risk* or very-high-risk** patients, with Lp(a) $\geq$50 mg/dL or $\geq$100 nmol/L[§], it is reasonable to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.	IIa	A	Willeit, 2018; Khera, 2014; Baigent, 2000
3. In very-high-risk** patients, taking a maximally tolerated statin with Lp(a) $\geq$50 mg/dL or $\geq$100 nmol/L[§], the addition of ezetimibe is reasonable in those with on-treatment LDL-C $\geq$70 mg/dL (or non–HDL-C $\geq$100 mg/dL).	IIa	B-R	Cannon, 2015
4. In high-risk* patients taking a maximally tolerated statin, with Lp(a) $\geq$50 mg/dL or $\geq$100 nmol/L[§], the addition of ezetimibe may be reasonable in those with on-treatment LDL-C $\geq$70 mg/dL (or non–HDL-C $\geq$100 mg/dL).	IIb	B-R	Cannon, 2015
5. In very-high-risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C $\geq$70 mg/dL (or non–HDL-C $\geq$100 mg/dL) and an Lp(a) of $\geq$50 mg/dL or $\geq$100 nmol/L[§], the addition of a PCSK9 inhibitor is reasonable.	IIa	B-R	O'Donoghue,2018; Bittner, 2018; Sabatine, 2017; Schwartz, 2018
6. Niacin, which lowers Lp(a) concentration, is not recommended to reduce ASCVD risk in patients receiving moderate- to high-intensity statins +/− ezetimibe and an on-treatment LDL-C $<$80 mg/dL	III (harm)	A	Albers, 2013J; Parish, 2018
7. HRT with estrogen and progesterone, which lowers Lp(a) concentration, is not recommended in perimenopausal/ postmenopausal women to reduce ASCVD risk.	III (harm)	B-R	Hulley, 1998; Shlipak 2000; Writing Group for the WHI Investigators, 2002

ASCVD risk categories (adapted from Grundy, 2018)

*High risk = Individuals with clinical ASCVD including those with MI, ACS, 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 = Individuals with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.

Acknowledgments

The authors would like to acknowledge Vivian Grifantini, Luke Hamilton and Dena Hanson for their assistance in preparing and editing this manuscript. A special thanks to Dr. Patrick Moriarty, who provided insightful comments and thoughtful suggestions during manuscript development. There was no funding for the study.

Authors' contribution: All authors contributed to this scientific statement, drafting and revising it critically for important intellectual content, and have approved the final version.

Financial disclosure

D.P.W. discloses that in the past 12 months, he has received speaking honorarium from Osler Institute, has received research grants from Merck Sharp & Dohme and Novo Nordisk, and has participated on the advisory board for Alexion Pharmaceuticals. T.A.J. discloses that in the past 12 months, he has received consulting fees from Amarin, Amgen, AstraZeneca, Esperion, Sanofi Regeneron, and Novartis. P.H.J. discloses that in the past 12 months, he has received advisory board honorarium from Amgen, Sanofi Regeneron, and AstraZeneca. M.L.K. discloses that in the past 12 months, she has received speaker and consulting honorarium from Eli Lilly, speaker honorarium from Pfizer, consulting honorarium from Amgen, and independent contractor fees from Pfizer, Eli Lilly, CardioVax, and Ionis. C.J.M. discloses that in the past 12 months, she has nothing to disclose. B.G.N. discloses that in the past 12 months, he has received consulting honorarium from Akcea, Amgen, Regeneron, Sanofi, and Kowa. C.E.O. discloses that in the past 12 months, he has nothing to disclose.

Conflict of interest

The authors have no conflicts of interest to disclose.

Uncited figure

Figure 2.

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