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This publication is sponsored by Novartis AG.

The Role of Lipoprotein(a) As a Biomarker to Assess Cardiovascular Risk

KEY TAKEAWAYS:

- ▶ Lipoprotein a (Lp[a]) is a proatherogenic, proinflammatory and prothrombotic lipoprotein.¹
- ▶ Prospective, observational, and genetic evidence strongly supports a causal relationship between high plasma concentrations of Lp[a] and an increased risk of arteriosclerotic cardiovascular disease (ASCVD) and valvular aortic stenosis.¹⁻⁵
- ▶ Measurement of Lp[a] has been recommended to be useful to reclassify ASCVD risk and, selectively, to aid in pharmacotherapy decision-making.⁶

INTRODUCTION

Lipoproteins in the blood carry lipids to tissues for energy use, lipid deposition, and synthesis of steroid hormones and bile acids. Six major types of lipoproteins have been identified: chylomicrons, very low-density lipoproteins (VLDLs), intermediate-density lipoproteins, low-density lipoproteins (LDLs), lipoprotein a (Lp[a]), and high-density lipoproteins (HDLs). Lipoproteins are composed of cholesterol, triglycerides (TGs), phospholipids, and apolipoproteins.⁷

Lp(a) is a proatherogenic, proinflammatory, and prothrombotic lipoprotein that consists of an LDL-like particle covalently bound to an apo (a) protein via its apoB component.¹ An individual's Lp(a) level is 80% to 90% genetically determined in an autosomal codominant inheritance pattern with full expression by 1 to 2 years of age and adult-like levels achieved by approximately 5 years of age. Outside of acute inflammatory states, the Lp(a) level remains stable through an individual's lifetime regardless of lifestyle.⁶

Because of its small diameter (< 70 nm), Lp(a) can move freely across the endothelial barrier and, like LDL-C, can be retained within the arterial wall; this subendothelial retention is a key initial step in atherogenesis.^{7,8} Additionally, circulating Lp(a) particles are the main carrier of oxidized phospholipids, which also contribute to arteriosclerotic cardiovascular disease (ASCVD) pathogenesis by promoting endothelial cell dysfunction and inflammation among others.^{9,10}

Prospective, observational, and genetic evidence strongly supports a causal relationship between high plasma concentrations of Lp(a) and an increased risk of ASCVD and valvular aortic stenosis (VAS).¹⁻⁵ This article will provide an overview of the genetic cardiovascular (CV) risk biomarker Lp(a), its importance as an independent risk factor for CVD, the prevalence of elevated Lp(a) levels among the global population, and recommendations for lipid management. The objective is to increase awareness and understanding of the risk factors in patients with elevated levels of Lp(a).

EPIDEMIOLOGY

Levels of Lp(a) considered to be in the atherothrombotic range are those more than 30 mg/dL or more than 75 nmol/L.¹¹ It's estimated that more than 1 billion people globally have Lp(a) levels of at least 30 mg/dL with a prevalence ranging from 20% to 30%.^{1,11} The incidence in patients with

established ASCVD, calcific aortic valve disease, or chronic kidney disease may be even greater.¹¹

In the United States, a relatively large proportion of the population has elevated Lp(a) levels. In a study of 531,144 patients (median age, 57.0 years; female, 51.9%) seen at a referral diagnostic laboratory, 35.0% of patients had concentrations of Lp(a) greater than 30 mg/dL, and 24.0% had levels exceeding 50 mg/dL.¹²

Lp(a) levels appear to vary among different ethnicities. The lowest concentrations were observed in non-Hispanic Caucasian (median, 12 mg/dL), Chinese (median, 11 mg/dL), and Japanese (median, 13 mg/dL) populations. Higher Lp(a) levels were reported in Hispanics (median, 19 mg/dL) and those of African origin (median, 39 mg/dL).³

BURDEN OF ILLNESS AMONG PATIENTS WITH ELEVATED LP(A) LEVELS

Several studies have demonstrated an association between elevated Lp(a) levels and an increased risk of CV events. For example, results from a meta-analysis of 36 studies (126,634 individuals) conducted by the Emerging Risk Factors Collaboration indicated that the risk of coronary heart disease (CHD), when adjusted for age and sex, increased 16% for every 3.5-fold higher Lp(a) concentration in patients who were free from CHD or stroke at baseline.¹³ One study of 7863 patients from this meta-analysis included an upper decile of 789 patients with a median baseline Lp(a) level greater than 73.7 mg/dL.¹⁴ Compared with those with Lp(a) levels 13.9 mg/dL or less, patients in the upper decile were significantly more likely to experience CHD events (nonfatal myocardial infarction [MI] and CHD death) (HR, 1.24; 95% CI, 1.02-1.52; $P = .03$) and revascularization events (HR, 1.45; 95% CI, 1.20-1.75; $P < .001$). However, these results need to be interpreted with caution because of the large difference between baseline Lp(a) values.

LP(A) LEVELS AND ASCVD RISK

Multiple lines of evidence suggest a strong link between Lp(a) levels and risk for ASCVD and VAS. Lp(a) contributes to total serum cholesterol: each molecule of Lp(a) is 30% cholesterol, when the Lp(a) concentration ranges from 9 mg/dL to 129 mg/dL.¹⁵ Apo(B), which is found in LDL-C and Lp(a), may be deposited in the arterial intima to and at aortic valve leaflets, contributing to atherosclerosis and VAS, respectively.^{7,8,16} This hypothesis is supported by findings from genetic Mendelian randomization (ie, the random assortment of parental genes in offspring) studies, which identified an association between lifelong high concentrations of LDL-C and Lp(a) with VAS and aortic valve calcification.^{1,16,17}

In addition, meta-analyses of prospective, population-based studies have shown an increased risk of CHD and MI in patients with high Lp(a) concentrations. For example, from the meta-analysis mentioned previously, adults had an increased risk of CHD (age- and sex-adjusted risk ratio [RR], 1.16 associated with 1 SD 3.5x higher Lp(a) concentration; 95% CI, 1.11-1.22) and an increased risk of ischemic stroke (age- and sex-adjusted RR, 1.11 associated with 1 SD

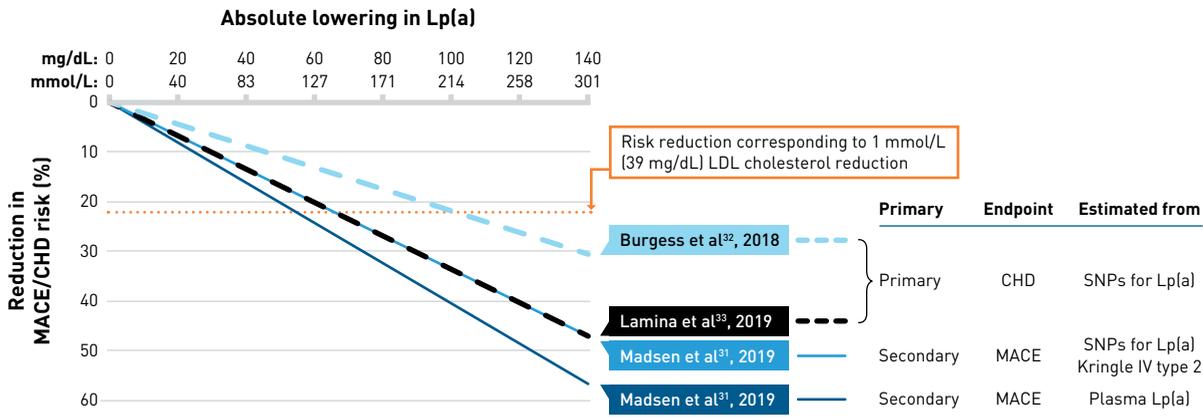
higher Lp(a) concentration; 95% CI, 1.02-1.20); the RRs were modestly lower when further adjustment was made for additional risk factors (1.13 [95% CI, 1.09-1.18] and 1.10 [95% CI, 1.02-1.18], respectively).¹⁸ An additional meta-analysis of prospective studies confirmed the risk of ischemic stroke is significantly increased with high Lp(a) concentrations (pool adjusted RR, 1.29; 95% CI, 1.06-1.58).¹⁹ Results from another meta-analysis demonstrated that individuals with smaller apo(a) isoforms, which tend to be associated with higher Lp(a) concentrations, had an approximately 2-fold higher risk of CHD and ischemic stroke than those with larger apo(a) isoforms (and low Lp(a) concentrations).²⁰ This link between Lp(a) level and risk of stroke has also been observed in children and adolescents. A meta-analysis of 4 studies of differing quality identified a substantial association between ischemic stroke risk and abnormal Lp(a) concentration in youth (odds ratio, 4.24).²¹

Large prospective, European population-based studies of high Lp(a) concentrations have demonstrated a high risk of MI, ischemic stroke, VAS, coronary artery stenosis, carotid stenosis, femoral artery stenosis, heart failure, CV mortality, and all-cause mortality. In studies of plasma Lp(a) measured in isoform-insensitive assays, individuals with Lp(a) concentrations in the top 5th percentile had a multivariable-adjusted 2.6- to 3.7-fold risk of MI and a 2.9-fold risk of VAS compared with those with in the less than 22nd percentile.²²⁻²⁴ In additional studies, individuals with highest versus lowest Lp(a) concentrations also had a 5-fold risk of coronary artery stenosis (adjusted for age and sex), a 1.7-fold risk of carotid stenosis (adjusted for age and sex), a 1.6-fold risk of femoral artery stenosis (adjusted for age and sex), a 1.6-fold risk of ischemic stroke (adjusted for age, sex, and CVD risk factors), a 2.5-fold increased risk of MI (adjusted for age, sex, and CVD risk factors), a 1.7-fold risk of CHD (adjusted for age, sex, and CVD risk factors), a 1.6- to 1.8-fold risk of heart failure (adjusted for CVD risk factors), a 1.5-fold risk of CV mortality (adjusted for multivariables, including CVD risk factors), and a 1.2-fold risk of all-cause mortality (adjusted for multivariables, including CVD risk factors).²⁵⁻²⁹ In a study of multi-ethnic patients, risk of heart failure associated with a high Lp(a) concentration (≥ 50 mg/dL) appeared to be limited to White patients (HR, 1.87; $P = .006$) and not Blacks, Hispanics, or Chinese Americans.³⁰

High Lp(a) levels also appear to increase the risk of recurrent CV events in patients with pre-existing CVD. In a recently published study of 2527 individuals with CVD at baseline, the absolute risk of major adverse CV events increased with stepwise increasing concentrations of Lp(a).³¹ The incidence of major adverse CV events was highest in patients with the highest Lp(a) levels: 54 per 1000 person-years for the group with an Lp(a) concentration of at least 100 mg/dL. Evidence from this study also suggests that an absolute reduction of 60 mg/dL in Lp(a) level for 5 years may lower the risk of secondary CV events by 20% (Figure 1³¹⁻³⁴).³¹

Studies of Mendelian randomization and genome-wide association studies, which are less prone to confounding and reverse causation than observational or randomized studies, have confirmed that a high Lp(a) level is a causal factor for ischemic stroke, CV mortality, and all-cause mortality.^{28,29,35,36}

Figure 1. Estimated Absolute Lp(a) Reduction Needed to Lower Risk of MACE and CHD³¹⁻³⁴



MACE risk reduction in secondary prevention		10%	20%	30%	40%	50%
Estimated Lp(a)-lowering required (95% CI)						
Plasma Lp(a)	mg/dL	25 [13-66]	50 [27-138]	74 [41-206]	99 [54-273]	124 [69-314]
	nmol/L	51 [25-140]	105 [55-297]	157 [86-445]	212 [114-592]	266 [147-681]
SNPs for Lp(a) and kringle IV type 2	mg/dL	30 [21-53]	60 [42-109]	90 [64-161]	120 [85-225]	150 [106-273]
	nmol/L	62 [42-112]	127 [88-234]	192 [136-347]	258 [181-487]	323 [227-591]

CHD, coronary heart disease; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular event; SNP, single-nucleotide polymorphism.

The solid dark blue line indicates the estimate based on plasma Lp(a) in 2527 individuals from the Copenhagen General Population Study with a median follow-up of 5 years from a multifactorially adjusted Cox proportional hazards regression. Multifactorial adjustment was for age, sex, lipid-lowering therapy, diabetes mellitus, hypertension, body mass index, smoking status, alcohol intake, physical activity, Lp(a)-corrected LDL cholesterol, and triglycerides. The solid medium blue line indicates the estimate based on single-nucleotide polymorphisms for Lp(a) and Kringle IV type 2 in 2131 individuals from the Copenhagen General Population Study from instrumental variable analysis scaled to a short-term clinical trial setting. The dashed lines indicate the predicted primary prevention trial estimates from Burgess et al³² (light blue) and Lamina et al³³ (black) for the end point coronary heart disease. The horizontal orange dotted line indicates the 22% major vascular event risk reduction per 1 mmol/L (39 mg/dL) reduction in LDL cholesterol observed in combined primary and secondary prevention statin outcome trials from the 2010 coronary heart disease Cholesterol Treatment Trialists' Collaboration meta-analysis.³⁴

Adapted with permission from Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-lowering by 50 mg/dL (105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study. *Arterioscler Thromb Vasc Biol.* 2020;40(1):255-266. doi:10.1161/ATVBAHA.119.312951

Plasma Lp(a) concentrations are largely determined by variation in the apo(a) gene: more than 90% of the variation in Lp(a) level is due to genetics.^{3,5,32,37} Therefore, Lp(a) is a lifelong, genetic causal factor independent of all other known causes and risk factors for ASCVD, VAS, and mortality, including LDL-C.⁶ Extremely high Lp(a) concentrations (eg, > 200 mg/dL) may represent a lipid disorder that is associated with a substantially increased lifetime risk of ASCVD (ie, 3- to 4-fold increased risk).³²

MEASURING LP(A) LEVELS

Evidence remains incomplete for the range of Lp(a) levels associated with high cardiac risk in individuals based on age, sex, and ethnicity.⁶ In current clinical practice, the concentration of plasma lipoproteins is typically measured indirectly by quantifying their cholesterol content.⁷ Total cholesterol (TC) is distributed mainly among VLDL cholesterol, LDL-C, and HDL cholesterol (HDL-C), and smaller quantities of cholesterol are contained in minor lipoprotein classes, including Lp(a). A standard serum lipid profile measures the concentrations of TC, HDL-C, and TGs.⁷

The use of cut points based on Lp(a) concentrations or percentiles for specific populations continues to be debated, in part, because different ethnic groups have different distributions of Lp(a) levels.^{6,38,39} For example, results from the prospective Multi-Ethnic Study of Atherosclerosis determined that an Lp(a) concentration of at least 50 mg/dL predicted CHD in Blacks, Caucasians, and Hispanics, whereas a cut point of at least 30 mg/dL was predictive of CHD only for Blacks.⁴⁰ Based on a large meta-analysis in various populations (N = 29,069), a tentative, universal Lp(a) cut point of at least 100 nmol/L (approximately ≥ 50 mg/dL) has been recommended by the National Lipid Association (NLA).^{6,10,41}

Clinical Practice Guidelines for Lp(a) Measurement

The NLA 2019 position statement on Lp(a) levels is based on the NLA recommendations part 1 (2014) and part 2 (2015) and updates an earlier NLA statement about the clinical utility of advanced lipoprotein testing. Recommendations had to garner a consensus of 60% of the expert panel drafting the statement, and they were graded according to the American College of Cardiology (ACC)/American Heart Association (AHA) Evidence-Based Grading System.⁶

The 2019 NLA Position Statement indicates that Lp(a) testing is reasonable as part of risk evaluation for primary prevention of ASCVD in individuals with the following characteristics⁶:

- First-degree relatives with premature ASCVD, defined as the occurrence of ASCVD in men younger than 55 years or women younger than 65 years
- A personal history of premature ASCVD
- Primary severe hypercholesterolemia (LDL-C \geq 190 mg/dL) or suspected familial hypercholesterolemia.

In addition, Lp(a) testing may be appropriate for some adults to assist in the clinician-patient discussion about the use of a statin in those between the age of 40 and 75 years with borderline 10-year ASCVD risk (5%-7.4%). Assessment of Lp(a) levels may also detect a potential cause for poor LDL-C reduction in patients given evidence-based therapy, assist in screening family members with severe hypercholesterolemia, and identify those at risk of progressive VAS.⁶

Although evidence surrounding the utility of Lp(a) testing in patients with known ASCVD continues to evolve, experts in lipidology consider Lp(a) testing reasonable for secondary prevention in particular populations of adults⁶:

- Adults with premature ASCVD (men < 55 years or women < 65 years) or ASCVD that is recurrent or progressive despite optimal lipid reduction treatment
- Adults with VAS, because the risk of calcific VAS is proportional to the Lp(a) concentration.

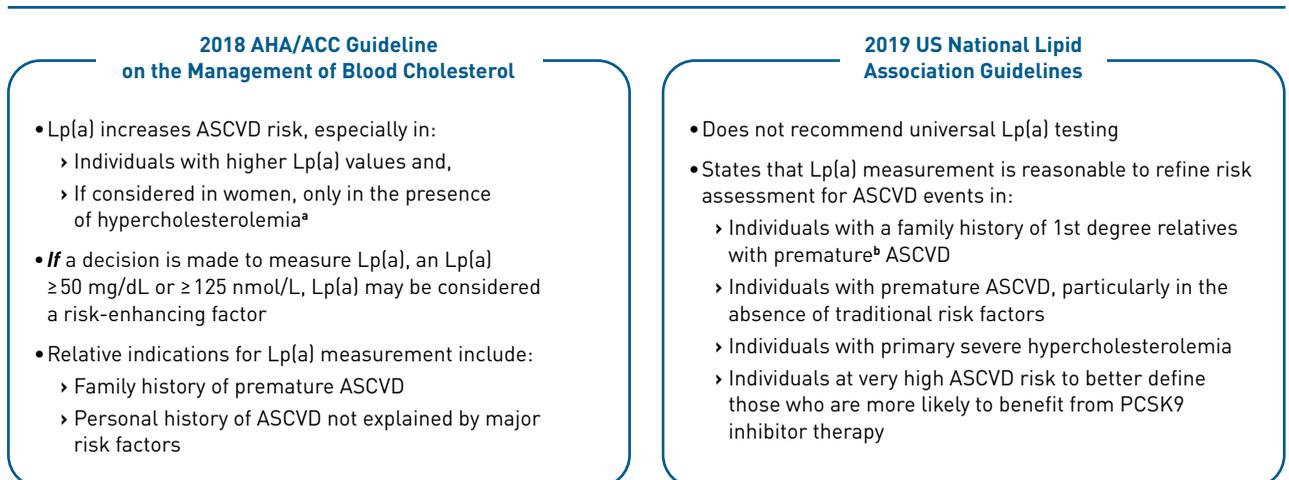
Large absolute decreases in Lp(a) concentration (eg, reductions \geq 60 mg/dL), particularly in patients with very high baseline concentrations, may be necessary to produce a significant clinical benefit.^{6,31,32,42}

The 2018 ACC/AHA multiorganization Guideline on the Management of Blood Cholesterol does not provide a recommendation on routine measurement of Lp(a), but lists a family history of premature ASCVD and a personal history of ASCVD not explained by major risk factors as relative indications for Lp(a) testing.⁴³ An Lp(a) concentration of at least 50 mg/dL (\geq 125 nmol/L) is considered to increase risk. A comparison of the Lp(a)-related information given in latest NLA and ACC/AHA guidelines is presented in **Figure 2**.^{6,43}

The 2019 European Society of Cardiology and European Atherosclerosis Society Guidelines for the management of dyslipidemias recommend that for all individuals, Lp(a) measurement should be considered at least once during their lifetime to identify if they have inherited a very high Lp(a) concentration (> 180 mg/dL or > 430 nmol/L) and thus have an increased risk of ASCVD that is similar to that associated with heterozygous familial hypercholesterolemia (Class IIa Level C recommendation). Testing all individuals would also detect less severe Lp(a) elevations that confer an increased risk but are not identified by the Systematic COronary Risk Evaluation (SCORE) or other lipid or lipoprotein assessments. Consideration should be given to Lp(a) measurement for possible CVD risk reclassification of those who are on the border between moderate risk (young patients [type 1 diabetes < 35 years; type 2 diabetes < 50 years] with no risk factors other than DM duration of < 10 years and a SCORE of \geq 1% and < 5% for a 10-year risk of fatal CVD) and high risk (patients with elevated risk factors such as TC > 310 mg/dL, LDL-C > 190 mg/dL, or BP \geq 180/110 mmHg; FH; DM without target organ damage and a DM duration of \geq 10 years or another risk factor; moderate CKD [chronic kidney disease]; a SCORE of \geq 5% and < 10% for 10-year risk of fatal CVD).⁷

The 2020 AACE/ACE guidelines for the management of dyslipidemia and prevention of cardiovascular disease recommends to consider

Figure 2. Current US Guidelines on Lp(a) Testing^{6,43}



AHA/ACC, American College of Cardiology and the American Heart Association; ASCVD, atherosclerotic cardiovascular disease; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin 9.

^aThe improvement in risk prediction in adult women in a large clinical trial was minimal.

^bPremature: < 55 years of age in men; < 65 years of age in women.

measurement of Lp(a) in the following patients: those with clinical ASCVD or a family history of it and/or increased Lp(a); patients who descend from South Asian or African ancestors; those with 10-year ASCVD risk of at least 10%; patients with a personal or family history of aortic valve stenosis; and patients with refractory LDL-C levels even with LDL-C lowering therapy. The guidelines state that, “currently, recommended treatment of patients with elevated Lp(a) is aggressive lowering of LDL-C, which mitigates the risk associated with the Lp(a) elevation.”⁴⁴

Two *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (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)).⁴⁵ 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.⁴⁶

Current Lp(a) Testing Utilization

An individual Lp(a) test is typically ordered in the outpatient setting with other CV laboratory tests. Although a study including over 500,000 patients in the United States observed that approximately one-third and one-quarter had LP(a) concentrations exceeding 30 mg/dL and 50 mg/dL, respectively, Lp(a) testing remains less common than traditional lipid testing.¹² In the United States, Lp(a)-inclusive panels are relatively common in both private and hospital laboratories and can be leveraged as a “value add” to differentiate services.

Lp(a) tests, which are often conducted in an automated chemistry analyzer, are relatively inexpensive. Private laboratories in the United States report the cost to process an Lp(a) test to be generally lower than \$5 per sample; reimbursement rates are often between \$14 and \$17. Out-of-pocket costs vary. Although measuring Lp(a) levels is relatively inexpensive and important in assessing CVD risk, treatment that specifically reduces Lp(a) concentrations remains an unmet need.

CURRENT TREATMENT OPTIONS FOR ELEVATED LP(A) LEVELS

Currently, there are no approved drugs that specifically lower elevated Lp(a) concentrations. Some interventions have shown modest effect in lowering Lp(a) concentrations, but lack cardiovascular outcomes data to support use in cardiovascular risk reduction.⁴⁷⁻⁴⁹

NEW APPROACHES TO REDUCING LP(A) LEVELS

Multiple approaches aimed at reducing LP(a) levels are currently being investigated. Among these include monoclonal antibodies, antisense oligonucleotides, and small interfering RNAs. These agents have been observed to reduce serum LP(a) levels and are in various stages of research and development.^{5,50}

CONCLUSIONS

Lp(a) measurement has been recommended to be useful to reclassify ASCVD risk and, selectively, to aid in pharmacotherapy

decision-making. The Lp(a) test is widely available and generally inexpensive, but infrequently utilized. Current guidelines consider measurement of Lp(a) concentration reasonable to help identify certain at-risk populations. However, current Lp(a) testing practices are heterogeneous in many ways, particularly with respect to assay types and measurement units. Better standardization of Lp(a) measurement and greater access to Lp(a) testing is needed to gain improved understanding of Lp(a) metabolism, physiology, and the pathologic mechanisms by which high Lp(a) levels contribute to ASCVD and VAS. Additional randomized trials of novel approaches to targeted Lp(a) reduction are needed to better define their role in reducing the risk of ASCVD and VAS progression. •

Acknowledgements

Medical writing support provided by Julia C. Jones, PharmD, PhD, MWC, ELS. Job Code: (12/20) HFS-1397798

REFERENCES

1. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69(6):692-711. doi:10.1016/j.jacc.2016.11.042
2. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data [published correction appears in *Arch Intern Med*. 2008;168(10):1089] [published correction appears in *Arch Intern Med*. 2008;168(10):1096]. *Arch Intern Med*. 2008;168(6):598-608. doi:10.1001/archinte.168.6.598
3. Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31(23):2844-2853. doi:10.1093/eurheartj/ehq386
4. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res*. 2016;57(11):1953-1975. doi:10.1194/jlr.R071233
5. Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med*. 2013;273(1):6-30. doi:10.1111/j.1365-2796.2012.02592.x
6. 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*. 2019;13(3):374-392. doi:10.1016/j.jacl.2019.04.010
7. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
8. Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116(16):1832-1844. doi:10.1161/CIRCULATIONAHA.106.676890
9. Tsimikas S, Brilakis ES, Miller ER, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*. 2005;353(1):46-57. doi:10.1056/NEJMoa043175
10. Boffa MB, Koschinsky ML. Oxidized phospholipids as a unifying theory for lipoprotein(a) and cardiovascular disease. *Nat Rev Cardiol*. 2019;16(5):305-318. doi:10.1038/s41569-018-0153-2
11. Tsimikas S, Fazio S, Ferdinand K, et al. NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. *J Am Coll Cardiol*. 2018;71(2):177-192. doi:10.1016/j.jacc.2017.11.014
12. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. *Arterioscler Thromb Vasc Biol*. 2016;36(11):2239-2245. doi:10.1161/ATVBAHA.116.308011
13. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302(4):412-423. doi:10.1001/jama.2009.1063
14. Nestel PJ, Barnes EH, Tonkin MA, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. *Arterioscler Thromb Vasc Biol*. 2013;33(12):2902-2908. doi:10.1161/ATVBAHA.113.302479
15. Kinpara K, Okada H, Yoneyama A, Okubo M, Murase T. Lipoprotein(a)-cholesterol: a significant component of serum cholesterol. *Clin Chim Acta*. 2011;412(19-20):1783-1787. doi:10.1016/j.cca.2011.05.036
16. Smith JG, Luk K, Schulz CA, et al; Cohorts for Heart and Aging Research in Genetic Epidemiology (CGARAGE) Extracoronary Calcium Working Group. Association of low-density lipoprotein cholesterol-related genetic variants with aortic valve calcium and incident aortic stenosis. *JAMA*. 2014;312(17):1764-1771. doi:10.1001/jama.2014.13959
17. Smith GD, Ebrahim S. ‘Mendelian randomization’: can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22. doi:10.1093/ije/dyg070
18. Erqou S, Thompson A, Di Angelantonio E, et al. Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. *J Am Coll Cardiol*. 2010;55(19):2160-2167. doi:10.1016/j.jacc.2009.10.080
19. Nave AH, Lange KS, Leonards CO, et al. Lipoprotein (a) as a risk factor for ischemic stroke: a meta-analysis. *Atherosclerosis*. 2015;242(2):496-503. doi:10.1016/j.atherosclerosis.2015.08.021
20. Erqou S, Thompson A, Di Angelantonio E, et al. Apolipoprotein(a) isoforms and the risk of vascular disease: systematic review of 40 studies involving 58,000 participants. *J Am Coll Cardiol*. 2010;55(19):2160-2167. doi:10.1016/j.jacc.2009.10.080

21. Sultan SM, Schupf N, Dowling MM, Devereux GA, Kirton A, Elkind MS. Review of lipid and lipoprotein(a) abnormalities in childhood arterial ischemic stroke. *Int J Stroke*. 2014;9(1):79-87. doi:10.1111/ijss.12136
22. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. 2008;117(2):176-184. doi:10.1161/CIRCULATIONAHA.107.715698
23. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA*. 2009;301(22):2331-2339. doi:10.1001/jama.2009.801
24. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol*. 2014;63(5):470-477. doi:10.1016/j.jacc.2013.09.038
25. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Genetic evidence that lipoprotein(a) associates with atherosclerotic stenosis rather than venous thrombosis. *Arterioscler Thromb Vasc Biol*. 2012;32(7):1732-1741. doi:10.1161/ATVBAHA.112.248765
26. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol*. 2013;61(11):1146-1156. doi:10.1016/j.jacc.2012.12.023
27. Kamstrup PR, Nordestgaard BG. Elevated lipoprotein(a) levels, LPA risk genotypes, and increased risk of heart failure in the general population. *JACC Heart Fail*. 2016;4(1):78-87. doi:10.1016/j.jchf.2015.08.006
28. Langsted A, Kamstrup PR, Nordestgaard BG. High lipoprotein(a) and high risk of mortality. *Eur Heart J*. 2019;40(33):2760-2770. doi:10.1093/eurheartj/ehy902
29. Langsted A, Nordestgaard BG, Kamstrup PR. Elevated lipoprotein(a) and risk of ischemic stroke. *J Am Coll Cardiol*. 2019;74(1):54-66. Published correction appears in *J Am Coll Cardiol*. 2020;75(18):2385. doi:10.1016/j.jacc.2019.03.524
30. Steffen B, Duprez D, Bertoni A, Guan W, Tsai M. Lp(a) [Lipoprotein(a)]-related risk of heart failure is evident in whites but not in other racial/ethnic groups. *Arterioscler Thromb Vasc Biol*. 2018;38(10):2492-2504. doi:10.1161/ATVBAHA.118.311220
31. Madsen CM, Kamstrup PR, Langsted A, Varbo A, Nordestgaard BG. Lipoprotein(a)-lowering by 50 mg/dL (105 nmol/L) may be needed to reduce cardiovascular disease 20% in secondary prevention: a population-based study. *Arterioscler Thromb Vasc Biol*. 2020;40(1):255-266. doi:10.1161/ATVBAHA.119.312951
32. Burgess S, Ference BA, Staley JR, et al; European Prospective Investigation Into Cancer and Nutrition-Cardiovascular Disease (EPIC-CVD) Consortium. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. *JAMA Cardiol*. 2018;3(7):619-627. doi:10.1001/jamacardio.2018.1470
33. Lamina C, Kronenberg F, Lp(a)-GWAS Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. *JAMA Cardiol*. 2019;4:575-579. doi:10.1001/jamacardio.2019.1041
34. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670-1681. doi:10.1016/S0140-6736(10)61350-5
35. Smith GD, Ebrahim S, Lewis S, Hansell AL, Palmer LJ, Burton PR. Genetic epidemiology and public health: hope, hype, and future prospects. *Lancet*. 2005;366(9495):1484-1498. doi:10.1016/S0140-6736(05)67601-5
36. Benn M, Nordestgaard BG. From genome-wide association studies to Mendelian randomization: novel opportunities for understanding cardiovascular disease causality, pathogenesis, prevention, and treatment. *Cardiovasc Res*. 2018;114(9):1192-1208. doi:10.1093/cvr/cvy045
37. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. *J Clin Invest*. 1992;90(1):52-60. doi:10.1172/JCI115855
38. Enkhmaa B, Anuurad E, Berglund L. Lipoprotein (a): impact by ethnicity and environmental and medical conditions. *J Lipid Res*. 2016;57(7):1111-1125. doi:10.1194/jlr.R051904
39. Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. *J Lipid Res*. 2016;57(4):526-537. doi:10.1194/jlr.R061648
40. Guan W, Cao J, Steffen BT, et al. Race is a key variable in assigning lipoprotein(a) cutoff values for coronary heart disease risk assessment: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2015;35(4):996-1001. doi:10.1161/ATVBAHA.114.304785
41. Willleit P, Ridker PM, Nestel PJ, et al. Baseline and on-treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. 2018;392(10155):1311-1320. doi:10.1016/S0140-6736(18)31652-0
42. Parish S, Hopewell JC, Hill MR, et al; HPS2-THRIVE Collaborative Group. Impact of apolipoprotein(a) isoform size on lipoprotein(a) lowering in the HPS2-THRIVE Study. *Circ Genom Precis Med*. 2018;11(2):e001696. doi:10.1161/CIRCGEN.117.001696
43. 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 [published correction appears in *J Am Coll Cardiol*. 2019;73(24):3234-3237]. *J Am Coll Cardiol*. 2019;73(24):3168-3209. doi:10.1016/j.jacc.2018.11.002
44. Handelsman Y, Jellinger PS, Guerin CK, et al. AACE/ACE consensus statement: consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm - 2020 executive summary. *Endocr Pract*. 2017;23(suppl 2):1-87. doi:10.4158/EP171764.APPGL
45. Engler RJM, Brede E, Villines T, Vernalis MN. Lipoprotein(a) elevation: a new diagnostic code with relevance to service members and veterans. *Fed Pract*. 2019;36(suppl 7):S19-S31.
46. Min WK, Lee JO, Huh JW. Relation between lipoprotein(a) concentrations in patients with acute-phase response and risk analysis for coronary heart disease. *Clin Chem*. 1997;43(10):1891-1895. doi:10.1093/clinchem/43.10.1891
47. Desai NR, Kohli P, Giugliano RP, et al. AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C Assessment with Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy (LAPLACE)-Thrombolysis in Myocardial Infarction (TIMI) 57 trial. *Circulation*. 2013;128(9):962-969. doi:10.1161/CIRCULATIONAHA.113.001969
48. Raal FJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol*. 2014;63(13):1278-1288. doi:10.1016/j.jacc.2014.01.006
49. Gaudet D, Watts GF, Robinson JG, et al. Effect of alirocumab on lipoprotein(a) over ≥ 1.5 years (from the Phase 3 ODYSSEY Program). *Am J Cardiol*. 2017;119(1):40-46. doi:10.1016/j.amjcard.2016.09.010
50. Katzmann JL, Packard CJ, Chapman MJ, Katzmann I, Laufs U. Targeting RNA with antisense oligonucleotides and small interfering RNA: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020;76(5):563-579. doi:10.1016/j.jacc.2020.05.070

Screening for Lipoprotein(a) to Uncover Additional Cardiovascular Risk: An Interview With Don P. Wilson, MD, Fellow of the National Lipid Association and Lipid Expert

An editor from *The American Journal of Managed Care*® (AJMC®) spoke with Don P. Wilson, MD, about lipoprotein(a) (Lp[a]), a genetically inherited molecule that, when elevated, is an independent risk factor for premature cardiovascular disease (CVD). Wilson was the lead author on the Lipoprotein(a) scientific statement published by the National Lipid Association¹ and is medical director of the Cardiovascular Health and Risk Prevention Program in the Department of Pediatric Endocrinology and Diabetes at Cook Children's Medical Center in Fort Worth, Texas.

AJMC®: What is Lp(a)?

Wilson: Lp(a) is a modified form of low-density lipoprotein cholesterol (LDL-C) [which], unlike acquired risk factors, is approximately 90% genetically determined.^{1,2} The cholesterol content of Lp(a) is included in standard laboratory estimates of LDL-C.³ Elevated levels lead to lifetime exposure to atherogenic lipoproteins, significantly increasing risk of premature CVD, as well as myocardial infarction (MI), ischemic stroke, and valvular aortic stenosis.⁴⁻⁸ Common lipid-lowering therapies, such as statins, lower LDL-C but do not lower Lp(a) levels.¹

Despite a significant reduction in CVD-related events following optimum management, both nonmodifiable and persistent modifiable risk factors (RFs), including elevated levels of Lp(a), predispose many to residual risk.⁹ To help at-risk patients avoid atherosclerotic cardiovascular disease (ASCVD)-related events following optimum LDL-C lowering with conventional therapy, health care providers focus on [lowering] residual risk. This means eliminating or optimizing other risk determinants to achieve the best outcomes. For example, although they effectively lower LDL-C, statins alone will not eliminate the entire risk of CVD in at-risk populations. People often have habits, which are inherently unhealthy, such as smoking, being sedentary, and consuming high-fat, high-carbohydrate diets, often leading to obesity and diabetes. Many develop medical conditions such as inflammatory diseases and systemic lupus, all of which increase the potential of vascular injury. The practical question becomes, "Is there anything [else] we can modify?" If we cannot prevent someone from having diabetes, for example, what else can be done to mitigate long-term harm? Obviously, we try to improve the patient's blood glucose control, and encourage weight loss if overweight or obese, by encouraging more physical activity and adherence to a heart-healthy diet. Our approach depends on the individual's risk. Individuals with high- and very-high CVD

risk benefit from more aggressive therapy. We may also look for biomarkers associated with CVD risk and determine if there are commercially available treatments. That is where Lp(a) comes up in the conversation.

Adult levels of Lp(a) are achieved by 5 years of age, and thereafter, may serve as a reliable biomarker in helping to assess CVD risk.¹ Early expression of the apolipoprotein (a) gene: relationships between infants' and their parents' serum apolipoprotein (a) levels.¹⁰ However, there are some exceptions. Inflammation, for example, may result in a short-term change in Lp(a) levels, but for the most part, Lp(a) levels are stable throughout a person's life.

Because there are no FDA-approved targeted treatments for elevated Lp(a) levels, many physicians incorrectly say, "Why measure it when we can't do anything about it?" That is not true; we can do a lot to improve health and reduce risk. It is important to know someone has an Lp(a) that is elevated for several reasons. The first is risk stratification. [Knowing a patient's Lp(a) levels] allows the clinician to appropriately assess risk. For example, patients with familial hypercholesterolemia (FH), who genetically have a high level of LDL-C, have an incredibly high risk of premature CVD. About 30% to 50% of individuals with FH also have elevated Lp(a).¹¹ If a patient has that combination, as opposed to only a genetic mutation for [high] LDL-C, their risk of CVD is substantially higher. In addition, even though standard LDL-C lowering reduces risk and improves outcomes in this vulnerable population, the presence of an increased level of Lp(a) represents residual risk. In the absence of a commercially available drug that targets Lp(a) lowering, a provider may choose to be more aggressive in lowering the patient's LDL-C level in hopes of improving outcomes.

The second reason it is important to know a person's Lp(a) levels is because it is genetically determined.¹² Elevated Lp(a) (defined as > 50 mg/dL or > 100 nmol/L), is the most common genetic dyslipidemia, affecting nearly 1 in 5 individuals in the United States. Lp(a) level is determined by an autosomal codominant inheritance. That means other family members are going to have it and should be encouraged to have their Lp(a) measured.¹ In children, when Lp(a) is elevated, that knowledge becomes part of the risk assessment and shared decision-making in terms of what can be done to lower the child's CVD risk. Families often use that information to ensure the child grows up with proper nutrition and avoids excessive weight gain, smoking, etc. This is particularly important in children because habits formed at an early age often persist into adulthood, affecting health behaviors

throughout life. Although not proven, lifestyle changes, implemented at an early age, such as dietary modification during the first year of life, may alter the expression of Lp(a), potentially reducing lifetime risk of CVD.¹³

A third reason for knowing a patient's Lp(a) level is to begin identifying a population that can take advantage of Lp(a)-directed therapy once it becomes commercially available. Currently, most of the medications we commonly use are those that are FDA approved for CVD treatment or risk prevention, such as statins; however, they do not lower Lp(a). PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors have been shown to have a modest impact of about 25% to 30%¹⁴⁻¹⁶; however, they are not specifically indicated for lowering Lp(a).

A final reason for knowing an individual's Lp(a) would be to guide treatment decisions in a very high-risk patient. In those who are optimally managed, until an effective and safe Lp(a) lowering drug becomes available, apheresis might prove beneficial. The FDA has recently revised its approval criteria for use of apheresis to include an elevated Lp(a) in its guidelines.¹⁷

It is hoped that in the near future, drugs will become commercially available to reduce Lp(a) levels. Several of those drugs are already in development. They [have] already been, to some degree, tested in adults [and] show promise.¹⁸ Similar studies are needed in children.

AJMC®: Are there any other additional risks that the managed care population should be aware of for patients with high Lp(a) levels?

Wilson: Two additional health risks for individuals with elevated Lp(a) include ischemic stroke and valvular aortic stenosis, for which there is ample supportive evidence. Lp(a) has 2 major properties: it is proatherogenic, hence the increase risk of CVD, and it is prothrombotic, that is, it has an ability to inhibit blood clots.⁸ Although Lp(a) may not directly cause an ischemic stroke, the presence of elevated Lp(a) may prolong or increase clot formation, enhancing risk of a stroke. For example, in my clinical practice, we have seen a fair number of young children, usually infants, who have had an unexplained ischemic stroke and the only [reason] you find after a blood workup is elevated Lp(a). It appears clear that although elevated Lp(a) may not be the primary cause of an ischemic stroke, elevated levels are associated with stroke and poor outcomes, even in children.¹⁹

One final observation. There is emerging evidence that individuals with coronavirus disease 2019 (COVID-19) often have a disturbance in lipid metabolism, which may contribute a broad spectrum of cardiovascular and thromboembolic complications, especially in vulnerable populations such as African Americans.²⁰ This is particularly relevant because in addition to a high prevalence of social disparities, African Americans have 2- to 3-fold higher levels of Lp(a) than Caucasians.²¹ Nonetheless, an Lp(a) of

at least 50 mg/dL has previously been reported to increase CVD risk in African Americans.²² This topic deserves more investigation, but provides another reason knowledge of an individual's Lp(a) can be useful.

AJMC®: Is there an ideal patient population that should be screened for Lp(a)?

Wilson: In my opinion, the question should really be at what age to screen, not whether screening should be performed. For example, the European Society of Cardiology and European Atherosclerosis Society Guidelines have called for considering universal testing of Lp(a) at least once in each adult's lifetime.³ It has been suggested that Lp(a) testing should begin in childhood.²³ Historically, many patients have only received lipid-lowering treatment once they already have evidence of atherosclerosis and are symptomatic, typically adults in their forties, fifties, or sixties. However, in those with conditions such as FH, for example, which is genetically determined, our thinking has changed. Current recommendations suggest that children who are at moderate to high risk should be started on lipid-lowering medications early, while they have a minimum disease burden, to avoid the risk of a fatal event or need for stents or coronary artery bypass grafting.²⁴ Preventing CVD by implementing early treatment can substantially reduce future health care costs to payers, the health system and society, by avoiding the need for more costly pharmacological treatment and medical procedures, but more importantly, improving the quality and longevity of people's lives.

Evidence supporting the benefits of earlier treatment was presented in a study recently published in *NEJM*. It is the longest study of statin treatment initiated among teenagers with genetically proven FH, who also had a parent who had experienced a fatal or nonfatal cardiovascular event [later in life]. These children were started on treatment when they were teens, and then followed over the next 20 years. The investigators looked at the occurrence of CVD and the anatomy of the arteries in children who had FH [and were treated with pravastatin] compared with their siblings without FH. When the children with FH were 39 years of age, they had a remarkable absence of major adverse cardiovascular events. After performing noninvasive studies such as carotid intima-media thickness measurements, [the investigators found that] the arterial function and anatomy was similar between the patients with FH and their siblings without FH. What is interesting about this study is that the children with FH had a mean Lp(a) that was over 30 mg/dL, which is often considered the threshold for risk. It is encouraging to learn that starting LDL-C lowering treatment during childhood resulted in a positive effect on their health outcomes 20 years later. It is still unknown what is going to happen to these children as they become older, but thus far, their outcomes have been much better than those of their parents, many of whom had experienced a fatal event.²⁵ The vast

majority of children who have elevated Lp(a), with or without FH, are asymptomatic. During childhood, those without FH who have elevated Lp(a) do not have cardiovascular events [and] lack direct evidence to suggest they have arteriosclerosis or the precursors of arteriosclerosis. A legitimate case could be made, therefore, to defer Lp(a) lowering treatment, when it becomes available, until adulthood. An exception, perhaps, would be in children who have an ischemic stroke. In that case, there is the concern for recurrent episodes. The argument could be made that this population needs to be treated earlier, after the first episode.

AJMC®: What is the prevalence of elevated Lp(a) levels in your practice?

Wilson: Our data may be slightly skewed because a large portion of our population is referred for FH, a population in which elevated Lp(a) levels are observed more frequently, and because we screen all of our referrals for Lp(a) [whereas most practices do not]. Unlike cholesterol, currently, there is no recommendation for universal screening of Lp(a) in children. Unfortunately, in the United States, the screening rate for cholesterol is about 4%. Our cholesterol screening is about 20% in our general pediatric neighborhood clinics.²

The population in our clinic may represent a bias, simply because we have a referral practice [where patients] are usually sent to us because of elevated LDL cholesterol. Remember that Lp(a) is essentially an LDL cholesterol molecule with an additional protein, so it contains cholesterol as well. Lp(a) contributes to the total cholesterol and calculated LDL cholesterol, so there is a bit of bias there in terms of the number of children in our practice with elevated Lp(a). But the answer is that the prevalence in our clinic is fairly high.

There are a number of families in our patient population in which the parent or members of the families have had some type of cardiovascular event, either fatal or nonfatal, and the only risk factor found was Lp(a). I mention this because there is every reason to expect that a similar finding will likely increase the risk of MI or stroke in the children when they become adults, and that may be a reason to implement drug therapy at a young age. Their LDL cholesterol level may be fairly close to the population mean, but the high Lp(a) still puts the child at risk.

AJMC®: How does knowing the Lp(a) level impact how you manage your patients?

Wilson: In the adult world, for example, recommendations from the National Lipid Association and the American Heart Association are tiered to indicate how aggressively patients should be treated to lower LDL cholesterol.^{1,24} This is based on total risk assessment, including Lp(a). If an adult has FH and elevated LDL cholesterol, genetically confirmed or clinically suspected, for example, the recommendation would be to use medication to achieve an LDL-C

of 100 mg/dL or less and a non-HDL cholesterol level of 130 [mg/dL] or less. If that same adult also had an elevated Lp(a), they may have a better outcome if we set a goal LDL-C between 50 [mg/dL] and 70 [mg/dL]. It is also possible that as a result of starting LDL-C lowering at an early age in children with or without FH, such aggressive goals may not be needed, at least during childhood. However, currently, there is limited proof of this. Long-term observation and epidemiologic studies are needed to help inform our clinical recommendations and management.

Even though there are no outcome studies and no specific recommendations to do so, we often tend to mirror adult recommendations when making treatment recommendations for children in our clinic. It's important to note that there is nothing inherently "normal" or even necessarily "healthy" about an LDL-C of 100 [mg/dL]. It is simply a reflection of the mean level or percentile in the population. The LDL cholesterol level in a newborn is approximately 40 [mg/dL] to 50 [mg/dL], increasing to about 100 mg/dL by 2 years of age and may further increase thereafter.

We do not have outcomes studies in children because we cannot measure—and we want to prevent—so called "hard outcomes," (ie, MI and stroke). As a pediatrician, I find that parents, for the most part, prefer to make decisions about the care of their children based on an informed discussion. By sitting down and objectively showing parents data in a way they can comprehend, without frightening them, allows them to feel empowered and comfortable with whatever decision they are implementing [to help their child.]

Furthermore, the details of ASCVD risk prevention and Lp(a) in individuals younger than 18 years of age are generally not included in a [pediatrician's] education, which focuses more on immunizations, health maintenance, growth, development, acute injuries, [and] episodic illnesses. If a pediatric health care provider takes a good family history, they will still miss about 30% to 60% of the children who have an elevated cholesterol level and who may benefit from some type of treatment.¹³ Recently, however, pediatricians are focusing more on the opportunity to improve lifelong health of children. To do that, we all have to understand the totality of the child's health risks.

It is worth repeating how important it is to make parents and children aware of the health risks without frightening them. Most parents are committed to doing everything they can to keep their children healthy. It is the responsibility of the health care provider, usually the pediatrician, to alert them if their child may be susceptible to health conditions that can increase risk of cardiovascular disease later in life, and carefully explain what can be done to help prevent it. The results of the 20-year pravastatin study in patients with FH are encouraging because they demonstrate that early reduction in LDL cholesterol can have a positive impact on cardiovascular disease in adulthood.²⁵ We should all be committed to true primary prevention, rather than waiting until someone has a heart attack to be able to initiate treatment. Many, unfortunately, die prematurely from the initial episode.

For those who have a fatal event, there is no second chance. Far too many children in my practice have lost a parent to premature CVD. It is a painful memory that never goes away.

AJMC®: Based on that information, what advice would you have for pediatric and adult health care providers who are encouraged by these results and are interested in adding this testing? How can they go about doing that in their practice?

Wilson: First, Lp(a) testing is reliable and readily available. Second, it is fairly inexpensive. At our clinic, we suggest pediatricians or family physicians focus on measuring LDL-C because guidelines suggest doing so, irrespective of a child's health status or family history, starting at around 10 years of age.² Although some also measure Lp(a) selectively in at-risk children, [in my experience] most are not aware of Lp(a) or prefer not to [evaluate it]. Pediatricians and family physicians do a great job taking care of children, but often they do not have enough time to sit down and properly counsel a large patient population about CVD risk prevention, and often they lack the training or experience to do so. The best service they can render the children entrusted to their care is to perform cholesterol screening on all children as outlined in the NHLBI 2011 Expert Panel recommendations.¹³ Children found to have elevated levels of cholesterol, who have a family history of hypercholesterolemia and/or premature CVD (men <55 years; women <65 years) or who have risk factors or risk conditions should be referred to a lipid specialist. Both the National Lipid Association and the American Heart Association can provide health care providers with a list of qualified lipid specialist in their area. Physicians who take care of adults should become familiar with the latest published guideline on Lp(a) screening and management.^{1,3,24}

Since 2016, several guidelines have been published to assist in the identification, treatment, and follow-up of adults with elevated levels of Lp(a).^{1,3,24} Considerable differences exist among published guidelines for adults on the use of Lp(a) in clinical practice, and recommendations for youth are limited. Although more work is needed to achieve harmonization and provide comprehensive guidelines for Lp(a) in clinical practice, these guidelines provide busy clinicians with practical advice for patient management.

Testing Lp(a) in children presents both an opportunity and a challenge. If tested, how do we ensure that information is conveyed to the child's future health care provider when they become adults? It is important to educate both the child and the family in order for them to be able to carry that message. Although it is unlikely that children understand [the] chemistry of Lp(a), in my experience, they are smart enough to understand health risks. Perhaps if these children, as they become young adults, are aware of their health risks and remember to mention "elevated Lp(a)" as they transition to an adult health care provider, it would be a great start! •

REFERENCES

- 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*. 2019;13(3):374-392. doi:10.1016/j.jacl.2019.04.010
- Wilson DP, Davis S, Matches S, et al. Universal cholesterol screening of children in community-based ambulatory pediatric clinics. *J Clin Lipidol*. 2015;9(suppl 5):S88-S92. doi:10.1016/j.jacl.2015.05.006
- Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188. doi:10.1093/eurheartj/ehz455
- Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data [published correction appears in *Arch Intern Med*. 2008;168(10):1089] [published correction appears in *Arch Intern Med*. 2008;168(10):1096]. *Arch Intern Med*. 2008;168(6):598-608. doi:10.1001/archinte.168.6.598
- Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31(23):2844-2853. doi:10.1093/eurheartj/ehq386
- Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. *J Lipid Res*. 2016;57(11):1953-1975. doi:10.1194/jlr.R071233
- Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med*. 2013;273(1):6-30. doi:10.1111/j.1365-2796.2012.02592.x
- Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69(6):692-711. doi:10.1016/j.jacc.2016.11.042
- Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation*. 2014;129(6):635-642. doi:10.1161/CIRCULATIONAHA.113.004406
- Wang XL, Wilcken DE, Dudman NP. Early expression of the apolipoprotein (a) gene: relationships between infants' and their parents' serum apolipoprotein (a) levels. *Pediatrics*. 1992;89(3):401-406.
- Vuori A, Watts GF, Schneider WJ, Tsimikas S, Kovanen PT. Familial hypercholesterolemia and elevated lipoprotein(a): double heritable risk and new therapeutic opportunities. *J Intern Med*. 2019;287(1):2-18. doi:10.1111/ijom.12981
- Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res*. 2016;57(8):1339-1359. doi:10.1194/jlr.R067314
- Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(suppl 5):S213-S256. doi:10.1542/peds.2009-2107C
- Desai NR, Kohli P, Giugliano RP, et al. AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C Assessment with Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy (LAPLACE)-Thrombolysis in Myocardial Infarction (TIMI) 57 trial. *Circulation*. 2013;128:962-969. doi:10.1161/CIRCULATIONAHA.113.001969
- Raal EJ, Giugliano RP, Sabatine MS, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolucumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol*. 2014;63(13):1278-1288. doi:10.1016/j.jacc.2014.01.006
- Gaudet D, Watts GF, Robinson JG, et al. Effect of alicumab on lipoprotein(a) over ≥1.5 years (from the Phase 3 ODYSSEY Program). *Am J Cardiol*. 2017;119(1):40-46. doi:10.1016/j.amjcard.2016.09.010
- Nugent AK, Gray JV, Gorby LK, Moriarty PM. Lipoprotein apheresis: first FDA indicated treatment for elevated lipoprotein(a). *J Clin Cardiol*. 2020;1(1):16-21.
- Tsimikas S, Karwowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med*. 2020;382(3):244-255. doi:10.1056/NEJMoa1905239
- Goldenberg NA, Bernard TJ, Hillhouse J, et al. Elevated lipoprotein (a), small apolipoprotein (a), and the risk of arterial ischemic stroke in North American children. *Haematologica*. 2013;98(5):802-807. doi:10.3324/haematol.2012.073833
- Moriarty PM, Gorby LK, Stroes ES, et al. Lipoprotein(a) and its potential association with thrombosis and inflammation in COVID-19: a testable hypothesis. *Curr Atheroscler Rep*. 2020;22(9):48e1-48e8. doi:10.1007/s11883-020-00867-3
- Marcovina SM, Albers JJ, Wijsman E, et al. Differences in Lp(a) concentrations and apo(a) polymorphs between black and white Americans. *J Lipid Res*. 1996;37(12):2569-2585.
- Virani SS, Brautbar A, Davis BC, et al. Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2012;125(2):241-249. doi:10.1161/CIRCULATIONAHA.111.045120
- Kohn B, Ashraf AP, Wilson DP. Should lipoprotein(a) be measured in youth? *J Pediatr*. 2020;S0022-3476(20)31028-3. doi:10.1016/j.jpeds.2020.08.042
- 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 [published correction appears in *J Am Coll Cardiol*. 2019;73(24):3234-3237]. *J Am Coll Cardiol*. 2019;73(24):3168-3209. doi:10.1016/j.jacc.2018.11.002
- Luirink IK, Wiegman A, Kusters M, et al. 20-Year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med*. 2019;381(16):1547-1556. doi:10.1056/NEJMoa1816454

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HFS-1397798