

Exclusive Coverage of the

## AMERICAN HEART ASSOCIATION (AHA) SCIENTIFIC SESSIONS 2023

November 11-13, 2023 | Philadelphia, PA

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### Understanding Elevated Lipoprotein(a): A Focus on Cardiovascular Risk and Screening Recommendations

LIBBI GREEN, PHARM D

A panel discussion titled “Elevated Lipoprotein(a): Raise Your Game and Lower Your (Risk) Score?” presented at the American Heart Association (AHA) Scientific Sessions 2023, which convened in Philadelphia, Pennsylvania, from November 11 to 13, 2023, focused on elevated lipoprotein(a) as a risk for cardiovascular (CV) events, with speakers highlighting the need for awareness, testing, and personalized management strategies for patients with elevated lipoprotein(a).

#### Background, Prevalence, and Significance of Lp(a)

Lipoprotein(a), commonly referred to as “Lp little (a)” or “Lp(a),” is a type of lipoprotein particle found circulating in the blood. Lp(a) is an apolipoprotein(B) family member,

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### A Real-World Study of Patients With ASCVD Demonstrates Prevalence of High LDL-C, Demographic Disparities, and Underutilization of Lipid-Lowering Therapy

ERIN GARROW, PH D

The results of a recent retrospective analysis of patients with established atherosclerotic cardiovascular disease (ASCVD) demonstrated that prior testing for lipoprotein(a) (Lp[a]) was associated with an increased likelihood of attaining guideline-based targets for low-density lipoprotein cholesterol (LDL-C).<sup>1</sup> Study findings were presented as a poster, “Real-World Exploration of LDL-Cholesterol Management in Patients With Atherosclerotic Cardiovascular Disease,” at the American Heart Association (AHA) Scientific Sessions 2023, which took place from November 11 to 13, 2023, in Philadelphia, Pennsylvania.<sup>2</sup>

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**Understanding Elevated Lipoprotein(a)** (Continued from page 1)

but as presenter Leslie J. Donato, PhD, DABCC, associate professor and clinical chemist at Mayo Clinic, explained, the unique chemical feature of Lp(a) is the presence of the covalently bound apolipoprotein(a), or apo(a), to the core particle of this lipoprotein. Genetically, high expressers of the apo(a) protein will have high circulating concentrations of Lp(a) in their bloodstream.<sup>1</sup>

High Lp(a) concentrations have been causally associated with poor CV outcomes, such as myocardial infarction (MI), stroke, and aortic stenosis, and the discussion panelists underscored the importance of screening for this often-overlooked risk factor.<sup>1</sup> Presenter Leslee J. Shaw, PhD, FACC, professor at Icahn School of Medicine at Mount Sinai, explained that elevated Lp(a) is an independent and causal risk factor for atherosclerotic cardiovascular disease (ASCVD).<sup>2</sup> Through increased atherogenesis, inflammation, and thrombosis, elevated Lp(a) results in cholesterol accumulation in the arterial wall and downstream pro-inflammatory effects.<sup>2</sup> Despite the evidence demonstrating that elevated circulating concentrations of Lp(a) in the bloodstream are linked to increased risk for the development of ASCVD, Donato explained that many providers know little about this risk factor and subsequently don't usually test for it. An estimated 20% of all individuals in the general population have increased Lp(a) concentration,<sup>3</sup> but without adequate testing, those individuals are not being identified for intensive preventive measures.

**Lipoprotein(a) Identified as a Causal and Independent Risk Factor for ASCVD**

The presenters underlined the wealth of data implicating Lp(a) as a causal risk factor for CVD. Evidence such as epidemiologic meta-analyses, Mendelian randomization studies, and genome-wide association studies demonstrated that elevated Lp(a) levels play an additive and independent role in predicting CV risk.<sup>3,4</sup>

In comparing individuals with low Lp(a) to individuals with elevated Lp(a), Donato

explained that those with elevated Lp(a) have increased ASCVD risk, including increased risk of MI (3- to 4-fold), aortic valve stenosis (3-fold), ischemic stroke (1.6-fold), heart failure (1.5- to 2-fold), CV mortality (1.5-fold), and all-cause mortality (1.2-fold).<sup>5-11</sup>

Presenter Nathan D. Wong, PhD, MPH, FACC, a professor and director at the University of California, Irvine, School of Medicine, emphasized the additive role of both elevated LDL and elevated Lp(a) in further predicting risk.<sup>12</sup> "We know from the Bruneck population study that Lp(a) was associated with a 37% increased risk of cardiovascular disease over about 15 years of follow-up. And noteworthy was that they were able to show that when you add Lp(a) to 2 standard risk factors, you correctly reclassify risk in nearly 40% of individuals," said Wong. Additionally, he noted that higher levels of Lp(a) were directly related to the progression of coronary artery calcium, further compounding the increased CV risks of elevated Lp(a) concentrations.<sup>13</sup>

Evidence from imaging illustrated the effects of elevated Lp(a) on the progression of atherosclerosis. Shaw discussed the increase in the percent atheroma volume and necrotic core progression, markers associated with acute coronary rupture, as evidenced by studies utilizing intravascular ultrasound in patients with increased Lp(a) levels.<sup>14,15</sup> Studies with repeat coronary computed tomography angiography (CCTA) confirmed those findings, demonstrating that elevated Lp(a) was associated with increased progression of low-attenuation plaque volume in only 1 year of follow-up, a marked progression in such a short period.<sup>16</sup> "This is the lowest of the low in terms of the density of the plaque that we can see on CT, and it is lipid-rich plaque. This is one that is highly volatile and highly prone to rupture," said Shaw.

Study results also have shown that the increased risks of elevated Lp(a) levels persist despite lipid-lowering therapies and well-controlled LDL levels.<sup>17,18</sup> The presenters contended that elevated Lp(a) is

the strongest risk factor for predicting future CVD events, even in statin-treated patients, and identified risk stratification based on Lp(a) levels as an opportunity to target higher-risk patients who could benefit from more intensive control of LDL-C and other risk factors.

### Testing for Specific Populations

Lp(a) expression is genetic and can be detected within the first year of life, rising throughout childhood and reaching a stable plateau in adulthood.<sup>19</sup> Guidelines vary by country and organization but recommend testing for individuals with a family history of premature ASCVD.<sup>3,5,20-26</sup> According to the American Heart Association (AHA) and American Association of Clinical Endocrinologists (AACE), other clinical considerations for testing include a personal history of premature ASCVD, moderate to severe ASCVD risk, and patients who are refractory to current lipid-lowering therapy.<sup>3</sup> “If you live in Canada or the EU, their guidelines actually recommend at least once in a person’s lifetime. **Individuals can be walking around with completely normal lipid panels and be unaware that they are a high expressor of Lp(a),**” said Donato.<sup>23,24</sup>

Underscoring the silent nature of this biomarker, presenter Maurice Williams, PhD, MPH, a medical science liaison with Novartis, shared his personal experience as a patient with undiagnosed elevated Lp(a) levels. Williams suffered a massive intraoperative heart attack during a lumbar fusion surgery, resulting in the placement of 6 coronary artery stents and a lengthy recovery period following a 7-day coma. He described how he was an active 50-year-old man who exercised regularly with well-controlled LDL on a low-dose statin. After the CV event, Williams requested testing for elevated Lp(a) and discovered his levels were significantly elevated at 217 mg/dL, placing him at extremely high risk. As his insurance did not cover the Lp(a) testing, Williams elected to pay out of pocket and was stunned to find it only cost \$22 at his preferred laboratory. Cost can be a discouraging factor for many patients, and Williams was surprised that in his case, the price point was very accessible. Williams lamented not knowing about the availability of this relatively inexpensive test and being able to identify his risk sooner.

Presenter Emily E. Brown, MGC, CGC, a genetic counselor at The Johns Hopkins University School of Medicine, explained that despite the genetic component of elevated Lp(a) levels, testing is easily accessible as it can be measured with a simple blood test as opposed to a comprehensive genetic screening.<sup>27</sup> Clinicians have the opportunity to focus the conversation on shared clinical decision-making of whether patients want to know this information and how they can empower themselves with this guidance. In her experience, Brown explained that patients generally want to know about their Lp(a) levels and use the information to inform their health care decisions, including lifestyle modifications as well as considerations for financial planning.

In support of efforts to raise awareness of Lp(a), Novartis Pharmaceuticals sponsored experiential learning during the AHA Scientific Sessions on November 11 and 12, 2023, while the AHA offered onsite Lp(a) testing.

**A total of 1000 participants were tested and learned their Lp(a) levels!**

“Individuals can be walking around with completely normal lipid panels and be unaware that they are a high expressor of Lp(a).”

Given the heritable nature of Lp(a) expression, with studies demonstrating about 90% heritability, Brown explained that cascade screening is recommended to test Lp(a) concentrations in immediate family members of persons with elevated Lp(a) levels.<sup>28,29</sup> By taking this approach, Brown emphasized the impact that testing can have on an entire family or multiple generations, allowing for early intervention, enabling them to understand their genetic risks, and personalizing their treatment recommendations.

### Laboratory Perspectives: Measuring and Interpreting Lp(a) Results

A known limitation of the standard lipid panel is that the Lp(a) is included in the LDL-cholesterol value, unless it is accounted for by correcting the LDL-cholesterol and subtracting the Lp(a) mass.<sup>30-32</sup> For patients who are high expressors of Lp(a), Donato explained that the cholesterol in the Lp(a) is hidden within the LDL-cholesterol value, even in calculated LDL or the gold standard beta-quantification. There is no available assay in a standard lipid panel that can distinguish between the cholesterol within Lp(a) and the cholesterol within LDL, and clinical judgment must be applied.

Once the decision is made to test for Lp(a) in a patient, Donato explained there is a *Current Procedural Terminology (CPT)* code specific for the Lp(a) blood test (CPT 83695) as well as *International Classification of Diseases–Tenth Edition* codes associated with elevated Lp(a) in the patient (E78.41) and a family history of elevated Lp(a) (Z83.430).<sup>33,34</sup> The standard assay to measure Lp(a) in the clinical laboratory is an immunoassay; however, there are differences in the types of immunoassays that may be available to the clinician’s in-house laboratory or reference laboratory.

Historically, clinical trials utilized an assay measuring mass units in milligrams per deciliter (mg/dL), and these

measurements have been documented in the literature to guide clinical decision-making.<sup>27</sup> Donato described the unique challenge in accurately measuring these mass units due to variances in the size of the apo(a) isoform from patient to patient based on their genetic composition.<sup>1</sup> As a consequence of this size heterogeneity, there are inherent inaccuracies in utilizing this methodology. More recently, laboratory science has recognized that assays that are calibrated in molar units of nanomoles per liter (nmol/L) are slightly more accurate, but these molar assays are not as readily accessible for testing and lack sufficient population health data for clinical cut points. Still, Donato stressed the importance of testing regardless of the type of immunoassay available and addressing elevated Lp(a) levels in either test result.

Wong noted that several guidelines, including the American College of Cardiology/AHA Cholesterol Management Guideline and the National Lipid Association (NLA) identified Lp(a) greater than 50 mg/dL, or greater than 100-125 nmol/L, to be a risk enhancement factor.<sup>5,35</sup> Donato explained that many practices take a more conservative approach. “We know that statistically significant risk starts a little lower than what is published in the guidelines. In my laboratory, and in many reference laboratories, they start flagging results at 30 mg/dL,” said Donato.

### Impact on Treatment Decisions and Risk Modification

The speakers stressed the importance of individualized treatment based on the patient’s comprehensive CV risk profile, including factors such as family history, metabolic syndrome, and race/ethnicity, in addition to lipid levels and biomarkers such as elevated Lp(a).<sup>35,36</sup> “Beyond risk score in our risk assessment, guidelines recommend the consideration of several risk enhancement factors to further inform the treatment decision,” said Wong. He explained that elevated Lp(a) warrants more intensified risk-reduction efforts in those individuals whereby the decision may otherwise not be clear. For example, he noted that the risk-enhancing factor of high Lp(a) concentration favors initiating a statin in adults aged 40 to 75 years without diabetes and 10-year ASCVD risk between 5% and 20%.

Patients with elevated Lp(a) levels are at risk for progression of atherosclerosis.<sup>2</sup> Shaw noted that these patients are candidates for intensified preventive care and disease management. Further, as Wong explained earlier, studies demonstrated that residual risk remains even in patients on statin therapy, highlighting the importance of addressing elevated Lp(a) and targeting tight control of manageable CV risk factors.<sup>17,18</sup>

In considering approaches to disease management, Brown drew parallels to Alzheimer disease; similar to elevated Lp(a), she noted that there are not any targeted drug therapies to prevent Alzheimer disease, but it is possible to prevent disease progression.<sup>37</sup> Modification of lifestyle factors, such as diet, exercise, and smoking cessation, and managing comorbidities

such as diabetes and hypertension, can help mitigate overall CV risk for patients with high Lp(a) concentrations. Brown recognized the 2022 European Atherosclerosis Society (EAS) guidelines, citing the recommendation of managing LDL-C, glucose, blood pressure, and other lifestyle factors for patients with significantly elevated Lp(a).<sup>25</sup>

### Conclusion

Elevated Lp(a) is a highly prevalent and heritable risk factor for CV events, affecting an estimated 1 in 5 persons in the general population. Lp(a) is proatherogenic, prothrombotic, and proinflammatory, with studies demonstrating that elevated Lp(a) levels confer a higher risk for ASCVD events. This inherited biomarker is both an independent and causal risk factor, and the risk remains even in patients who have normal lipid panels or have statin-controlled LDL-cholesterol. Testing for elevated Lp(a) is simple, guideline-recommended, and provides valuable information for risk stratification. Lp(a) screening can inform treatment approaches and encourage shared clinical decision-making. Intensified preventive care for individuals with elevated Lp(a) involves a comprehensive approach that includes lifestyle modifications, management of other CV risk factors, and ongoing monitoring. This approach aims to mitigate the increased CV risk associated with elevated Lp(a) levels and improve overall CV health outcomes. ●

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## A Real-World Study (Continued from page 1)

Seeking to understand patient characteristics and regional patterns of care associated with LDL-C control, investigators analyzed electronic health record data from 5 health systems participating in the CardioHealth Alliance: Duke University Medical Center, University of Pittsburgh Medical Center, Vanderbilt University Medical Center, Allina Health, and Ochsner Health System.<sup>1,2</sup> Adults 18 years and older with established ASCVD were included in the study cohort if they received an LDL-C test in 2021, had experienced an ASCVD event in the 5 years prior to this test, and had at least 2 encounters with the health system between 2019 and 2020 (N = 216,074).<sup>1</sup> The index date was defined as the date of the last LDL-C test in 2021. At index, mean (SD) age was 70.3 (11.3) years and patients were predominantly White (85.3%) and male (55.4%). Overall, 77.2% had coronary artery disease and 88.0% had hypertension. Mean (SD) LDL-C level was 82.6 (34.1) mg/dL and 0.47% of patients had received a prior Lp(a) test. At index, 62.6% of patients had a prescription for

a statin medication and 65.1% had a prescription for 1 or more lipid-lowering therapies (LLT; a statin, monoclonal antibody-based proprotein convertase subtilisin/kexin type 9 inhibitor [PCSK9i], ezetimibe, or bempedoic acid). Overall, 3.8% had a prescription for a sodium glucose transporter 2 inhibitor and 4.5% had a prescription for a glucagon-like peptide-1 receptor agonist.<sup>1</sup>

Baseline characteristics and LLT patterns were compared among patients with serum LDL-C levels above and below 70 mg/dL, which the AHA and American College of Cardiology cite as a threshold for therapeutic intervention for ASCVD.<sup>1,3</sup> Investigators followed patients for 6 months and assessed LLT initiation, which was defined as receiving a prescription for LLT in the 6 months following an LDL-C test and having no evidence a prescription for LLT in the year prior to the index date.<sup>1</sup> To determine which clinical factors were associated with LDL-C levels below 70 mg/dL, investigators used multivariable regression modeling.

Results of the analysis demonstrated that 60% (n = 129,886) of patients did not have serum LDL-C levels below 70 mg/dL at

index. Among factors associated with not attaining this threshold were Black race (relative risk [RR] = 1.15; 95% CI, 1.14-1.16;  $P < .001$ ), Hispanic ethnicity (RR = 1.04; 95% CI, 1.01-1.06;  $P = .0001$ ), and female sex (RR = 1.13; 95% CI, 1.12-1.14;  $P < .001$ ).<sup>1</sup>

The National Lipid Association recognizes Lp(a) testing as reasonable to refine risk assessment for ASCVD events in certain patient populations and as potentially reasonable as a tool for treatment decision-making.<sup>4</sup> Receiving Lp(a) testing prior to the index was associated with attaining the LDL-C target (RR = 0.87; 95% CI, 0.82-0.92;  $P < .0001$ ).<sup>1</sup>

Among those with LDL-C serum levels of at least 70 mg/dL, only 20.8% had initiated LLT in the 6 months following the index LDL-C test.<sup>1</sup>

Diagnostic miscoding and missing data may have limited the data set, the study, and its findings. The small number of health systems from which the data were analyzed and laboratory testing challenges arising from the study's overlap with the COVID-19 pandemic may have served as additional limitations.<sup>1</sup>

The study demonstrated that over half of this population of patients with established ASCVD did not meet the guideline-based

target for LDL-C and that patients who were Black, Hispanic, and/or female were particularly unlikely to achieve this goal. Moreover, only 1 in 5 patients had initiated LLT in the 6 months following the index LDL-C test. However, Lp(a) testing was associated with attaining the LDL-C target. Investigators concluded that connecting health systems to the communities they serve through multidisciplinary and inclusive efforts is vital to improving LDL-C care nationally.<sup>1</sup> ●

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# Exploring Patterns in Lp(a) Testing and Lipid-Lowering Therapy Prescription Across 5 Major US Health Systems in Patients With Atherosclerotic Cardiovascular Disease

DOROTHY COOPERSON VIEWEG

The results of a recent retrospective analysis of electronic health record (EHR) data found that only 0.4% of patients with atherosclerotic cardiovascular disease (ASCVD) were tested for lipoprotein(a) (Lp[a]) across 5 large US health systems, with disparities seen in testing rates by race and gender.<sup>1</sup> Furthermore, data indicated that Lp(a) testing and scores were associated with differences in lipid-lowering therapy (LLT) use and initiation. The findings were presented as a poster, "Lipoprotein(a) Testing in Patients with Atherosclerotic Cardiovascular Disease in Five Large U.S. Health Systems" during a session at the American Heart Association Scientific Sessions 2023 in Philadelphia, Pennsylvania, which ran from November 11 to 13, 2023.<sup>1</sup>

Lp(a) is an apolipoprotein B-containing lipoprotein that is a genetic, independent, causal risk factor for ASCVD.<sup>2-4</sup> Approximately 20% of the general global population have increased Lp(a), making it the most common genetic dyslipidemia.<sup>2,3</sup> Measurement of Lp(a) can inform risk assessment for ASCVD events.<sup>3</sup>

Study investigators conducted a retrospective analysis of 2019-2021 EHR data from Allina Health, Duke University Medical Center, University of Pittsburgh Medical Center, Vanderbilt University Medical Center, and Ochsner Health System for

adults with ASCVD to identify patterns in Lp(a) testing based on patient demographics, as well as whether Lp(a) testing is associated with differences in LLT initiation. Data included in the analysis were from patients aged at least 18 years with established ASCVD during an Lp(a) test or a randomly selected outpatient encounter during the study period (if no Lp[a] test), and baseline characteristics and LLT initiations were compared between the 2 groups. To determine the clinical factors associated with Lp(a) testing, investigators used multivariable regression modeling. The index date was defined as the date of the Lp(a) test or random outpatient encounter in those without a test. LLT initiation was defined as no prescription in the year prior to the index date, but a new prescription in the 6 months following the index date.<sup>1</sup>

The cohort included 595,684 patients, of whom 2587 (0.4%) underwent Lp(a) testing. In the overall population, 45.0% of patients were female and 84.5% were White. The prevalence of Black race was lower among those who were in the Lp(a) tested cohort, while prevalence of Hispanic ethnicity was similar between the tested and untested cohorts. The average age was 70 years in the untested cohort, and 61 years in the tested cohort. Among those who underwent Lp(a) testing, there was a

higher prevalence of coronary artery disease, ischemic stroke or transient ischemic attack, and familial hypercholesterolemia, and a lower prevalence of hypertension and diabetes. The median total cholesterol was 156 mg/dL in the untested cohort and 162 mg/dL in the tested cohort.<sup>1</sup>

Patient demographics associated with lower likelihood of Lp(a) testing included Black race and older age. Among patients in the tested cohort, 75.5% were already prescribed any LLT (ie, statins, high-intensity statins, a PCSK9 inhibitor (PCSK9i), ezetimibe, bempedoic acid, or some combination) at the time of testing, while only 50.2% of those in the untested cohort were prescribed any LLT. **Patients who underwent Lp(a) testing were significantly more likely to initiate any LLT than were those who went untested** ( $P < .001$ ), and this difference was significant for each individual LLT therapy except for bempedoic acid, for which the  $P$  value was not calculated. Among patients in the tested cohort, those with Lp(a) levels above 50 mg/dL ( $n = 821$ ; 33.4%) were significantly more likely to initiate any LLT ( $P = .033$ ), and specifically a PCSK9i or ezetimibe (both  $P < .001$ ) than were patients with a tested Lp(a) threshold of 50 mg/dL or lower; however, differences in statin therapy initiation were not significant between groups.<sup>1</sup>

Limitations of this analysis include the potential lack of generalizability of results because the study data included only 5 health systems. Furthermore, the COVID-19 pandemic may have impacted lab frequencies, and data on medication intolerance and adherence was not available in the electronic health record.<sup>1</sup>

According to the American Association of Clinical Endocrinologists/American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease and a 2022 statement from the National Lipid Association, Lp(a) testing should be considered in patients with clinical ASCVD or a history of aortic valve stenosis, as well as in those with a family history of premature ASCVD, increased Lp(a), or aortic valve stenosis; Lp(a) measurement should also be considered in patients with South Asian or African ancestry, a 10-year ASCVD risk of at least 10% (including those at very high risk of ASCVD

to identify those who are more likely to benefit from PCSK9i therapy), primary severe hypercholesterolemia or suspected familial hypercholesterolemia, or refractory elevations of LDL cholesterol (LDL-C) regardless of aggressive LDL-C-lowering therapy (ie, statin resistance).<sup>2,3</sup> An Lp(a) of at least 50 mg/dL is a risk-enhancing factor.<sup>3,5</sup> For example, an increased risk of recurrent ASCVD events is seen in patients on statin therapy with Lp(a) levels of 50 mg/dL or greater.<sup>2</sup>

**“Patients who underwent Lp(a) testing were significantly more likely to initiate any LLT than were those who went untested.”**

Results of this study provide real-world patterns of Lp(a) testing and LLT initiation in over half a million adults with ASCVD, indicating differences in testing rates based on patient age and race, as well as notable associations between initiation of LLT and Lp(a) testing and values.<sup>1</sup> ●

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## Insights Into Lipoprotein(a) Screening Trends: Analysis of a Comprehensive US Health Care Dataset

AMANDA MEYER, MS

**A**ssessing lipoprotein(a) (Lp[a]) levels in US adults, both with and without atherosclerotic cardiovascular disease (ASCVD), was previously an uncommon practice but exhibited a notable surge post-2018, according to McGowan and colleagues.<sup>1</sup> The findings were presented as, “Lipoprotein(a) Screening

Practices in a Large US Health Care Dataset,” at the American Heart Association Scientific Sessions 2023, which ran from November 11 to 13, 2023, in Philadelphia, Pennsylvania.<sup>1</sup>

**Elevated Lp(a) is an independent and genetically determined risk factor for ASCVD, affecting approximately 20%**

**of the general population.**<sup>2</sup> Although European and Canadian guidelines advocate for Lp(a) screening across patients with an intermediate or high risk of cardiovascular disease or strong family history of premature atherothrombotic disease, the American College of Cardiology/American Heart Association Task Force guideline describes Lp(a) as a risk enhancer.<sup>3-5</sup>

Despite its high prevalence and role as a crucial ASCVD risk factor, testing for elevated Lp(a) is not commonly performed. Using a comprehensive real-world US database, McGowan and colleagues aimed to provide insight into the demographic and clinical profiles individuals undergoing Lp(a) assessment, as well as the patterns and attributes associated with health care professionals (HCPs) ordering these tests.<sup>1</sup>

“Elevated Lp(a) is an independent and genetically determined risk factor for ASCVD, affecting approximately 20% of the general population.”

The Family Heart Database is a comprehensive repository of data of medical claims, including diagnostic, procedural, and prescription data, along with laboratory information for more than 324 million individuals in the US. Data were collected from May 2012 to December 2021. Within this database, the investigators focused on a subset of 44 million adults with available laboratory data, predominantly lipid labs, and medical claims recorded 1 year before and after their initial lab date. Patients who underwent screening for Lp(a) were identified to calculate screening rates. Additionally, various patient characteristics, including demographics, ASCVD status, comorbidities, distributions of Lp(a) levels, and the clinicians responsible for ordering Lp(a) tests were examined.<sup>1</sup>

Analysis of real-world data extracted from the Family Heart Database revealed that Lp(a) screening among US adults, including those with a history of ASCVD, was infrequent. Specifically, only 1.1% of the overall adult population (500,899/44,857,734 individuals) underwent Lp(a) screening between 2012 and 2021. In the subgroup of adults with ASCVD, the screening rate marginally increased to 2.0% (218,331/10,658,820 individuals) over the same period.<sup>1</sup>

The cohort of adults who underwent Lp(a) testing exhibited specific demographic and health characteristics. The median age of these individuals was 60 years (IQR, 50-69 years). A slight majority, accounting for 55%, were female. A notable portion of this cohort, comprising 43.6% of individuals, had a history of ASCVD. Hypertension was prevalent among those tested for Lp(a) levels, affecting 33% of the group, and 34% had

hyperlipidemia. Additionally, 14% of the adults with Lp(a) tests had diabetes.<sup>1</sup>

Notable variations in Lp(a) testing were observed according to sex, race, and the clinicians placing orders. Women who underwent Lp(a) testing showed a higher median Lp(a) level of 36 nmol/L (IQR, 11-118) compared with that in men, who had a median level of 28 nmol/L (IQR, 10-95). Distinct racial disparities were observed, with the Black population demonstrating a median Lp(a) level that was 2-fold higher than those of the White and Hispanic populations, with values of 73 nmol/L (IQR, 24-170) for Black individuals, 29 nmol/L (IQR, 10-102) for White individuals, and 28 nmol/L (IQR, 10-85) for Hispanic individuals. Also, Lp(a) testing orders were concentrated, as only 1.6% of clinicians (687/41,976) were responsible for half of all Lp(a) tests.<sup>1</sup>

A notable surge in Lp(a) testing occurred in 2019, likely resulting from heightened awareness regarding Lp(a) and the introduction of an *International Classification of Diseases–Tenth Edition* code (E78.41) for elevated Lp(a) in 2018, according to the investigators.<sup>1,6</sup> Conversely, the reduction in Lp(a) testing after 2019 may be attributed to the influence of COVID-19 policies on health care practices, causing a shift in priorities and resource allocation away from routine screenings during the pandemic.<sup>1,7</sup>

Although Lp(a) testing is rare, patients who underwent Lp(a) assessment frequently presented with ASCVD and associated comorbidities. Furthermore, a limited number of HCPs were accountable for the majority of Lp(a) testing orders. Overcoming barriers and leveraging facilitators for Lp(a) screening necessitates dedicated research and strategic efforts.<sup>1</sup> ●

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## Lp(a): Evidence of a Link to Major Adverse Cardiovascular Events

JABIR BHUIYAN, MS

Despite its recognition as a highly prevalent and genetically determined causal risk factor for cardiovascular disease (CVD), relatively few investigations have been aimed at tying lipoprotein(a) (Lp[a]) directly to an elevated risk of major adverse cardiovascular events (MACE) among individuals in various atherosclerotic cardiovascular disease (ASCVD) 10-year risk categories.<sup>1,2</sup> Benbow and colleagues aimed to address this existing void in Lp(a) research by examining the impact of increased Lp(a) levels on MACE across different categories of ASCVD risk.<sup>2,3</sup> Study findings were presented during a session titled “Increased Risk of MACE Attributed to Lipoprotein(a) Across Current Atherosclerotic Cardiovascular Disease Risk Categories,” during the American Heart Association Scientific Sessions 2023, which ran from November 11 to 13, 2023, in Philadelphia, Pennsylvania.<sup>3</sup> Results of the study show a strong association between elevated Lp(a) increases and risk of MACE, independent of ASCVD risk score.

### Link Between Lp(a) and Risk of MACE

For the retrospective, observational study, investigators examined a primary prevention cohort of White (n = 355,784) and Black (n = 6277) patients from the UK Biobank during 2006 to 2020 who had an existing Lp(a) measurement and no diagnosis of ASCVD prior to enrollment.<sup>2,3</sup> The study included a large population (N = 362,061) in whom circulating Lp(a) levels were measured; patients were categorized by Lp(a) level (eg, 105-150 nmol/L, 150-190 nmol/L, 190-215 nmol/L, and 215-260 nmol/L) and results were compared with those of patients with Lp(a) less than 105 nmol/L. The study population was nearly 55% female and the mean age of patients at the time of enrollment was 56.5 years.<sup>3</sup> Approximately 98% of patients were classified as “White” and less than 2% of patients were classified as “Black” or “Black British.” Mean total cholesterol and triglycerides were approximately 222 mg/dL and 154 mg/dL, respectively, among the cohort. Patients had an average body mass index of 27 kg/m<sup>2</sup> and a mean systolic blood pressure of nearly 140 mm Hg. Across Lp(a) categories, incidence rates (IRs) of MACE and nonfatal myocardial infarction (MI) (evaluated as a component of MACE) were computed per 100 person-years.<sup>3</sup> Associations between Lp(a) level and time until occurrence of first MACE and MI were analyzed using Cox proportional hazard models adjusted for age, sex, and ethnicity, with stratification based on ASCVD 10-year risk score categories (categorized as low, intermediate, and high risk).<sup>2,3</sup>

Results showed that IRs of MACE and MI per 100 person-years increased corresponding with the patient’s 10-year ASCVD risk score.<sup>2,3</sup> However, a substantially significant increase was seen among those in the high-risk category (IRs, 1.52 and

0.75, respectively; n = 27,733) compared with the those in the intermediate- (IRs, 0.72 and 0.38; n = 121,272) and low-risk (.14 and .09; n = 161,183) categories.<sup>3</sup> Furthermore, within each risk category, Lp(a) levels exceeding 105 nmol/L were associated with an 82% increase in the IRs of MACE and MI.

Across and within all ASCVD 10-year risk categories, elevated Lp(a) (>105 nmol/L) was associated with a notable rise in the risk of both MACE and MI when compared with lower levels of Lp(a) (<105 nmol/L) as evidenced by adjusted hazard ratios (HRs). For patients in the low-risk category, HRs ranged from 1.15 to 1.55 for MACE and 1.32 to 1.72 for MI. For patients in the intermediate-risk category, HRs ranged from 1.19 to 1.51 for MACE and 1.37 to 1.77 for MI. Finally, for patients in the high-risk category, HRs ranged from 1.12 to 1.55 for MACE and 1.14 to 1.76 for MI.<sup>2,3</sup>

Overall, higher Lp(a) levels (>105 nmol/L) were associated with a substantial increase in the risk of MACE (range, 12%-55%); and of MI (range, 14%-75%) when compared with levels below 105 nmol/L in this primary prevention population.<sup>3</sup>

### Current Gaps in Knowledge and Study Limitations

Although Lp(a) is becoming more recognized as a risk factor for ASCVD, gaps in knowledge exist which must be addressed to further clinician understanding of its pathogenesis. For example, the causes of variation in plasma levels across different ethnicities are not fully understood. In addition, a complete understanding of apolipoprotein(a) synthesis, Lp(a) particle assembly, and the mechanism of clearance from circulation has not been achieved.<sup>4</sup> The current study results provide insights on the observed impact of Lp(a) on MACE across ASCVD risk categories; however, certain limitations were acknowledged by the investigators. For instance, the applicability of the 10-year ASCVD risk calculator is restricted to patients of Black or White ethnicities, reducing the ability to generalize study design and results to other ethnicities. Also, the authors note the existence of healthy volunteer bias in the study population from the UK Biobank, further limiting generalizability.<sup>3</sup>

### Spotlight on Screening of Lp(a)

Screening of Lp(a) levels is uncommon. It is not included in routine blood panels and thus the majority of patients are not screened.<sup>4</sup> The results of a large observational study of 6 academic health systems in California from 2012 to 2021 revealed that only 0.3% of adults had been tested for Lp(a). Among patients with a personal or family history of CVD, Lp(a) testing was extremely low (< 4% and 3.3%, respectively).<sup>1</sup> The American College of Cardiology and American Heart Association guidelines recommend measurement of Lp(a) levels as a risk-enhancing factor for the primary prevention of ASCVD, especially if individuals have

a known personal or family history of heart disease.<sup>4,5</sup> Nearly a quarter of people worldwide are estimated to have elevated Lp(a)—defined as greater than 50 mg/dL or 125 nmol/L.<sup>1,5</sup> Many of these patients are asymptomatic, remaining unaware of their condition.

### Conclusions

Patients with elevated Lp(a) are at significantly higher risk of composite MACE and MI, regardless of their ASCVD 10-year risk score. In the study by Benbow et al, in all 3 ASCVD risk categories (low, intermediate, high), Lp(a) levels were the primary determinant of MACE or MI. Further understanding of its pathogenesis and awareness of Lp(a) levels is important to inform decision-making regarding treatment and risk management among clinicians. The underutilization of Lp(a) screening may be a missed opportunity to improve cardiovascular outcomes for patients. Screening of family members of individuals with elevated Lp(a) levels may also prove beneficial in identifying additional patients due to its genetic nature. Incorporating elevated Lp(a)

levels into an individual's ASCVD risk assessment during routine clinical practice could enhance risk prediction and provide more informed guidance for follow-up disease management. ●

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## Elevated Lipoprotein(a) Increases Cardiovascular Risk Independently of SMuRFs

AMANDA MEYER, MS

**H**ow lipoprotein(a) (Lp[a]) affects cardiovascular (CV) risk, particularly in the context of major adverse CV events (MACE) among patients based on the baseline atherosclerotic CV disease (ASCVD) status, was recently presented as, “The Association of Lipoprotein(a) With MACE Among Individuals With and Without Baseline ASCVD: the Mass General Brigham Lp(a) Registry” during the American Heart Association Scientific Sessions 2023, which ran from November 11 to 13, 2023, in Philadelphia, Pennsylvania.<sup>1,2</sup>

Lp(a) has been recognized as an independent and causal risk factor for coronary heart disease (CHD).<sup>3</sup> In a retrospective study of the Mass General Brigham Lp(a) Registry, Shiyovach and colleagues examined the relationship between elevated Lp(a) and standard modifiable risk factors (SMuRFs) in the context of MACE.<sup>1</sup> Identified risk factors included diabetes mellitus, hyperlipidemia, hypertension, and smoking. MACE was defined as nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or CV mortality.<sup>2</sup>

The investigators used a large dataset provided by the MGB Lp(a) Registry, a repository of Lp(a) measurements covering approximately 2 decades (2000-2019).<sup>1,3</sup> The cohort, consisting of more than 16,000 patients aged at least 18 years, offered a diverse representation of individuals who underwent Lp(a) testing between 2000 and 2019.<sup>1,2</sup> Among the total patient cohort (N = 16,419), 10,181 patients (62%) had baseline ASCVD,

whereas 6238 patients (38%) did not have baseline ASCVD.<sup>2</sup> Compared with patients without baseline ASCVD, patients with baseline ASCVD were older (54 vs 64 years), more likely to be male (55% vs 62%), and showed a higher prevalence of traditional CV risk factors.

The 4 pillars of SMuRFs—diabetes, hyperlipidemia, hypertension, and smoking—were used to evaluate the impact of elevated Lp(a).<sup>1</sup> These factors may influence CV risk and can be evaluated to understand the relationship between Lp(a) levels and MACE.<sup>4</sup>

Analysis of the distribution of SMuRFs within the cohort showed that 23.7% of patients had no SMuRFs, revealing the inherent diversity in CV risk profiles. In contrast, 17.8% of patients had 3 or more SMuRFs and presented a heightened risk of MACE. Patients with severe kidney dysfunction and malignant neoplasm were excluded from the study to avoid the influence of complicating variables.<sup>1</sup>

The median follow-up of 11.9 years enabled comprehensive examination of the incidence of MACE with respect to the number of SMuRFs and Lp(a) levels.<sup>1</sup> A larger number of SMuRFs led to an increased risk of MACE among patients with Lp(a) levels that were high (log-rank  $P = .031$ ) and low (log-rank  $P = .001$ ). High Lp(a) emerged as an independent predictor of the primary outcome of fatal or nonfatal MI, challenging the conventional hierarchy of risk factors.<sup>1,5</sup>

This finding is supported by those of Nordestgaard and colleagues, who observed a strong association between elevated Lp(a) and an increased risk of CV events.<sup>6</sup> They described that Lp(a) was established as a potent and independent predictor of ASCVD in meta-analyses of large cohorts. Furthermore, Berman described that in the registry study, patients with baseline ASCVD showed a relatively stable rate of MACE regardless of Lp(a) levels.<sup>2</sup> In contrast, patients without baseline ASCVD showed an increased rate of MACE with increasing Lp(a) levels.

The Framingham Risk Score, a standard metric in CV risk estimation, primarily factors in age, sex, total cholesterol, high-density lipoprotein cholesterol, blood pressure, and smoking status.<sup>7</sup> However, the unique contribution of Lp(a) to CV risk, as highlighted by Shiyovach and colleagues, challenges the reliance on traditional risk factors.

The risk imposed by Lp(a) surpasses that associated with individual SMuRFs and approximates the risk conferred by having 2 SMuRFs.<sup>1</sup> These findings echo those of a meta-analysis performed through the Emerging Risk Factors Collaboration, which demonstrated the incremental predictive value of Lp(a) in assessing CV risk beyond traditional risk factors.<sup>8</sup> The independence of Lp(a) as a predictor of MACE supports its contribution to CV risk.<sup>1</sup>

The investigators demonstrated that Lp(a) affects CV risk, particularly in the context of MACE among patients regardless of baseline ASCVD status independently of the number of SMuRFs.<sup>1</sup> Baseline ASCVD increases the absolute risk of MACE, with the

association between Lp(a) levels and CV events plateauing at Lp(a) levels of 150 to 200 nmol/L.<sup>2</sup> Patients without baseline ASCVD show a decreased absolute risk of MACE, with a linear association between Lp(a) levels and CV events. Integration of Lp(a) into risk assessment models may change how CV risk is considered and managed. ●

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## Examining Low Rates of Real-World Lp(a) Testing: Insights From a Decade-Long Cohort Study in a Diverse Health System

DOROTHY COOPERSON VIEWEG

The results of a recent retrospective cohort study found low rates of real-world lipoprotein(a) (Lp[a]) testing within a large, diverse health system between 2010 and 2021. Furthermore, certain patient characteristics were associated with disparities in testing rates.<sup>1</sup> The findings were presented as a poster, “Predictors of Lp(a) Testing Among Multiethnic Individuals” during a session at the American Heart Association Scientific Sessions 2023, which ran from November 11 to 13, 2023, in Philadelphia, Pennsylvania.<sup>1</sup>

Lp(a) is an apolipoprotein B–containing lipoprotein with atherogenic potential.<sup>2,3</sup> A high concentration of Lp(a) in the blood is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD).<sup>4</sup>

Investigators from Stanford Cardiovascular Institute, Stanford Medicine, and other institutions analyzed data from Sutter Health, a Northern California health system treating over 3 million patients,

to determine the prevalence of Lp(a) testing, as well as to identify any specific patient characteristics that were associated with those patients who received testing. Patients who were 18 years or older and who had at least 2 primary care visits between 2010 and 2021 were included in the study. Those patients who had at least 1 Lp(a) laboratory test ordered were defined as Lp(a) cases. Incident density matching was used to select controls matched with Lp(a) cases by visit date at a ratio of 5:1. The investigators used conditional logistic regression to assess associations between Lp(a) testing and individual patient demographics, including age, gender, race and ethnicity, and certain clinical characteristics.<sup>1</sup>

A total of 1,484,410 patients were included in the cohort. Of this total, only 1% of patients (n = 14,818) underwent Lp(a) testing during the study period. In the tested cohort, the mean age was 54.3 years and 48.1% of the population was female,

while in the untested cohort, the mean age was 51.6 years and 59.3% of the population was female. Additionally, among those who underwent Lp(a) testing, there was a lower prevalence of Hispanic ethnicity, and a higher prevalence of patients who identified as non-Hispanic Asian, and specifically as South Asian. The prevalence of ASCVD was more than doubled in the tested cohort compared with the untested cohort (17.5% vs 8.6%). However, in patients without a diagnosis of ASCVD, the mean 10-year ASCVD risk was higher among those who were not tested (9.70%) than those who underwent testing for Lp(a) (6.30%), and a greater proportion of patients in the untested cohort had a 10-year ASCVD risk of greater than 20%. Preferred provider organization or fee-for-service was the primary insurance coverage for 55.6% of those tested and for 49.6% of those who were not tested, and the prevalence of Medicaid/Medi-Cal or Medicare coverage was lower among tested patients. Furthermore, a greater proportion of patients who underwent Lp(a) testing had cardiology visits and statin prescriptions.<sup>1</sup>

Among those who were assessed, the median concentration of Lp(a) was 35 mg/dL. Investigators emphasized differences in testing rates associated with patient race and ethnicity: compared with non-Hispanic White patients, South Asian patients were 3 times more likely to have undergone Lp(a) testing (odds ratio [OR], 3.19; 95% CI, 2.98-3.41) whereas non-Hispanic Black and Hispanic patients were less likely to have undergone testing (OR, 0.70; 95% CI, 0.62-0.80; and OR, 0.64; 95% CI, 0.59-0.69; respectively). Additionally, having history of ASCVD was noted to be associated with over twice the likelihood of undergoing testing (OR, 2.14; 95% CI, 1.99-2.29).<sup>1</sup>

According to the 2019 clinical practice guidelines released by the American College of Cardiology and American Heart Association Task Force, an Lp(a) of at least 50 mg/dL is a risk-enhancing factor for CVD, and the National Lipid Association notes that Lp(a) levels above 30 mg/dL are associated with coronary heart disease and emphasizes that elevated Lp(a) is an independent, causal risk factor for both cardiovascular and all-cause mortality.<sup>2,4</sup>

The American Association of Clinical Endocrinologists/American College of Endocrinology Guidelines for Management of

Dyslipidemia and Prevention of Cardiovascular Disease note that Lp(a) testing should be considered in certain patients, including patients with clinical ASCVD, a family history of premature ASCVD or increased Lp(a), a 10-year ASCVD risk of at least 10%, and South Asian or African ancestry.<sup>5</sup> Furthermore, elevated Lp(a) levels may inform appropriate pharmacotherapeutic treatment decision-making.<sup>2,4</sup>

These study results provide real-world data on implementation of Lp(a) testing in Northern California, showing consistently low testing rates between 2010 and 2021, as well as differences in testing rates by patient race and ethnicity. Certain findings indicate that clinical practice aligns with guideline recommendations, including higher testing rates among South Asian patients and those with a history of ASCVD; yet, low rates of testing among Black patients and those at highest risk of ASCVD indicate inconsistencies in aligning to testing guidelines.<sup>1</sup> For example, Black patients have an approximately 3-fold higher median concentration of Lp(a) than do White patients, but results of the analysis showed that Black patients were 30% less likely to undergo Lp(a) testing than were White patients.<sup>1,3,4</sup> Study investigators asserted that expanding Lp(a) testing access may help reduce disparities in ASCVD risk assessment and treatment.<sup>1</sup> ●

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## Prospective Atherosclerosis Risk in Communities (ARIC) Study Connects Differences in Lipoprotein(a) With Racial Disparities in Atherosclerotic Cardiovascular Disease

ERIN GARROW, PHD

**I**n a prospective study of 9519 adults with no baseline atherosclerotic cardiovascular disease (ASCVD), investigators concluded that differences in plasma lipoprotein(a) (Lp(a)) distributions between White and Black participants probably contribute to racial disparities in ASCVD.<sup>1,2</sup> Study authors added

that investigational therapies aimed at lowering Lp(a) could help to address these disparities.<sup>2</sup>

The findings were presented as a poster, “Assessing the Contribution of Racial Difference in Elevated Lipoprotein(a) Levels to Disparities in Atherosclerotic Cardiovascular Disease:

The Atherosclerosis Risk in Communities (ARIC) Study,” at the American Heart Association (AHA) Scientific Sessions 2023, which convened from November 11 to 13, 2023, in Philadelphia, Pennsylvania.<sup>2</sup> Acknowledging that higher levels of Lp(a) had been reported in Black adults relative to White adults, investigators sought to compare the relative risk of higher Lp(a) levels on incident ASCVD in these 2 populations and to estimate the percentage of cases of ASCVD in each population attributable to higher Lp(a) levels.<sup>1</sup> The investigation used data from the Atherosclerosis Risk in Communities (ARIC) study, which in 1987 recruited 15,792 Black and White adults aged 45 to 64 years from 4 US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland).<sup>2,3</sup> The ARIC study has followed active participants to the present by means of regular clinical exams and telephone follow-ups.<sup>4</sup>

Authors of the present study measured Lp(a) levels in stored plasma samples drawn between 1996 and 1999 from participants during the fourth clinical visit of the ARIC study (baseline). Samples were classified into the following categories based on Lp(a) levels: below 30 mg/dL, at least 30 mg/dL to 50 mg/dL, at least 50 mg/dL to 100 mg/dL, or at least 100 mg/dL. Using follow-up clinical data from the subsequent 20 to 25 years, the investigators assessed associations between higher Lp(a) levels ( $\geq 30$  mg/dL) and incident ASCVD (defined as coronary heart disease or ischemic stroke) both overall and by race and assessed whether differences by race were significant. Finally, the investigators estimated the percentage of incident (post-baseline) ASCVD attributable to higher Lp(a) levels—the population-attributable fraction (PAF)—for the study population and for Black and White subpopulations.<sup>1,2</sup>

The mean (SD) age of study participants at baseline was 63.1 (5.6) years.<sup>2</sup> Overall, patients were mostly White (77.5%) and female (58.8%). Of White patients, 24% had plasma Lp(a) levels of at least 30 mg/dL; of Black patients, 53.5% had elevated plasma Lp(a) levels. When adjusted for biologic and social cofounders (age, sex, race, education, smoking, alcohol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, antihypertensive medications, diabetes mellitus, and body mass index), higher Lp(a) levels were associated with higher risk of ASCVD among all participants; **patients with plasma Lp(a)**

**of at least 100 mg/dL were 1.7 times more likely to have a subsequent ASCVD event (95% CI, 1.4-2.1).**<sup>1,2</sup>

Associations between Lp(a) level and ASCVD risk did not differ significantly by race.<sup>1,2</sup> Among White participants, 4.7% of all incident ASCVD was estimated to be attributable to higher Lp(a) levels (95% CI, 2.3%-7.0%); among Black participants, the estimate was 10.7% (95% CI, 5.8-15.4%).<sup>2</sup>

“Patients with plasma Lp(a) of at least 100 mg/dL were 1.7 times more likely to have a subsequent ASCVD event (95% CI, 1.4-2.1),”

The study expands the limited body of literature and data estimating how differences in Lp(a) contribute to race-based disparities in ASCVD. Also, use of the PAF enabled evaluation of higher Lp(a) levels upon ASCVD at the population level. Investigators noted several limitations to the study. The patient population was limited to only Black and White participants, excluding patients of other races and ethnicities (and Asian, Hispanic, or Native American patients). Moreover, the analysis did not include genetic data related to Lp(a).<sup>2</sup>

According to the investigators, genetic heritage may inform health disparities associated with race. Future research examining the role that biology plays in ASCVD could inform public health solutions addressing the racial disparities associated with this disease.<sup>2</sup> ●

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