JAMA Insights

Lipoprotein(a)

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Lipoprotein(a) is a low-density lipoprotein-like particle that carries oxidized phospholipids and has proinflammatory and proatherogenic properties. In prospective studies, higher levels of lipoprotein(a) are associated with significantly higher risk of atherosclerotic cardiovascular disease (ASCVD) and all-cause mortality.[1] In a meta-analysis of 29 069 patients, the incidence of ASCVD events per 1000 person-years was 80.0 (95% CI, 75.3-84.9) among people with lipoprotein(a) greater than or equal to 50 mg/dL and 55.3 (95% CI, 53.4-57.3) for people with lipoprotein(a) less than 15 mg/dL (adjusted hazard ratio, 1.35 [95% CI, 1.11-1.66]).[2] A similar association of elevated lipoprotein(a) with ASCVD was observed among 460 506 participants from the UK Biobank study.[3] Medications such as pelacarsen, olpasiran, and lepodisiran reduce lipoprotein(a) production in the liver and lower plasma lipoprotein(a) by up to 99%, and are currently undergoing testing in randomized clinical trials to determine whether they reduce rates of ASCVD in people with elevated lipoprotein(a).[4]

Supplemental content

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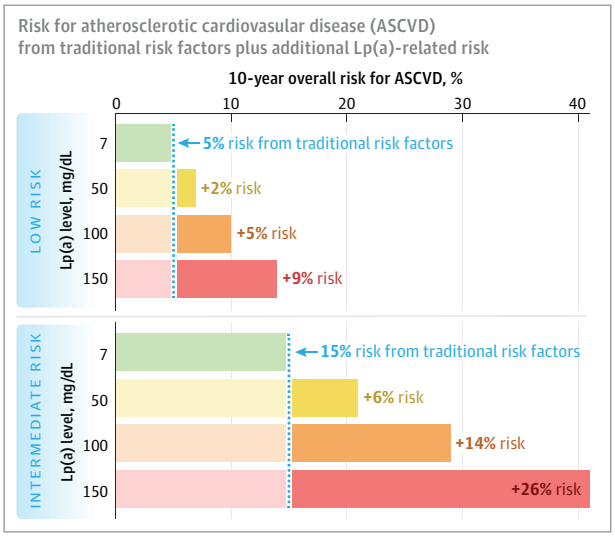

Additional risk caused by lipoprotein(a) [Lp(a)] is multiplied with the 10-year (or lifetime) ASCVD risk for a personalized assessment. For example, if a patient has no or few traditional risk factors, an estimated absolute 10-year ASCVD risk for that person of 5% increases 2.72-fold to approximately 14% in case of lipoprotein(a) of 150 mg/dL vs a patient with lipoprotein(a) of 7 mg/dL. If the same patient has multiple traditional risk factors, the baseline absolute ASCVD risk of 15% increases to >40% or lipoprotein(a) of 50 mg/dL, the relative risk increase is 1.4-fold compared with lipoprotein(a) of 7 mg/dL. For lipoprotein(a) of 100 mg/dL, the relative risk increase is approximately 2-fold. Data are based on the UK Biobank including >400 000 individuals.[1]

Factors Associated With Elevated Lipoprotein(a)

Lipoprotein(a) levels are primarily determined genetically by the *LPA* gene, remain mostly stable throughout life, and are not substantially modified by lifestyle factors. Therefore, measuring lipoprotein(a) once in a lifetime should be sufficient in most individuals.[1,4] Smoking cessation, physical activity, fasting, and diet have minimal, if any, effect on lipoprotein(a) levels.[1] Levels of lipoprotein(a) are approximately 20% higher in postmenopausal females than in age-matched males. Lipoprotein(a) levels typically range from less than 0.1 mg/dL to greater than 300 mg/dL, but variation in levels is observed by race and ethnicity due to genetic variants in the *LPA* locus and potentially other unknown factors. For example, the median (IQR) lipoprotein(a) value is 7 (3-29) mg/dL in White individuals, compared with approximately 30 (18-54) mg/dL in Black individuals. In a 2020 UK Biobank study, Chinese individuals had approximately 15% lower and South Asian individuals had approximately 60% higher lipoprotein(a) levels than White individuals (median lipoprotein(a): 16 nmol/L for Chinese individuals, 75 nmol/L for Black individuals, 31 nmol/L for South Asian individuals, and 19 nmol/L for White individuals).[1,3] Some health conditions appear to influence lipoprotein(a) levels. For example, chronic kidney disease is associated with increased lipoprotein(a) levels, while severe liver disease is associated with lower lipoprotein(a) levels.[1]

Lipoprotein(a) and ASCVD Risk

ASCVD risk increases continuously with increasing lipoprotein(a) levels, without evidence of a threshold effect, and associations of higher lipoprotein(a) with greater risk of ASCVD are independent of traditional cardiovascular risk factors such as low-density lipoprotein (LDL) cholesterol and blood pressure. The relative risk increase for incident ASCVD over an 11-year period was 1.11 (95% CI, 1.10-1.12) per approximately each 20-mg/dL increment in lipoprotein(a). The association was not meaningfully affected by ancestry, cardiovascular disease risk factors including LDL cholesterol, or various cardiovascular risk scores.[3] Guidelines consider lipoprotein(a) level of 50 mg/dL or greater as "high,"[1,3,5] representing approximately the top 20th population percentile. A lipoprotein(a) level of 50 mg/dL is associated with an approximately 40% relative risk increase in ASCVD, compared with 7 mg/dL (median in a reference population; **Figure**).

Mendelian randomization studies are consistent with observational data and support a causal association for lipoprotein(a) with ASCVD outcomes: common genetic variants in the *LPA* gene that cause lifelong higher lipoprotein(a) levels are more frequent in persons who develop ASCVD. In contrast, people with rare loss of function or common splice site variants associated with low lipoprotein(a) levels also have lower rates of ASCVD.[1]

Guideline Recommendations for Lipoprotein(a) Testing

The American Heart Association/American College of Cardiology 2018 cholesterol and 2019 prevention guidelines stated that elevated levels of lipoprotein(a) may be clinically useful for shared decision-making regarding statin initiation or increasing statin dose

or intensity.[5] The European (class IIa; level of evidence, C [indicating that this therapy is reasonable, but based on limited or weak evidence]) and Canadian guidelines (strong recommendation; high-quality evidence) recommend measuring lipoprotein(a) in all adults at least once in their lifetime,[1,6] an approach also recommended by recent scientific statements from the American Heart Association (2022) and National Lipid Association, but not based on high-quality evidence (2024; class I; level of evidence, B-NR [indicating evidence ranging from moderate to no evidence supporting the recommendation]).[4,7] To date, no randomized trials have been completed to demonstrate that measuring lipoprotein(a) improves outcomes and no clinical trials have demonstrated that lowering lipoprotein(a) with drug therapy improves cardiovascular outcomes.

Management of High Lipoprotein(a)

Because lipoprotein(a) is associated with increased rates of ASCVD events, individuals with lipoprotein(a) levels of 50 mg/dL or higher should be advised to modify risk factors for cardiovascular events, including with lifestyle interventions (eg, smoking cessation, weight loss, healthy diet, physical activity) and treatments to lower LDL cholesterol, blood pressure, glucose, and other risk factors as recommended by guidelines (eTable in the Supplement).

Statins do not lower lipoprotein(a) and may slightly increase lipoprotein(a) in some individuals, though not enough to justify discontinuing the statin given high-quality evidence from randomized clinical trials that statins significantly and meaningfully reduce ASCVD events.[1] Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors lower LDL cholesterol by 50% to 60% and lipoprotein(a) by 15% to 30%.[1] However, no randomized clinical trials have assessed PCSK9 inhibitors in patients selected for high lipoprotein(a) and these medications are not currently indicated for lipoprotein(a) lowering.[2] Weekly lipoprotein apheresis lowers lipoprotein(a) by approximately 30% to 35% and is approved by the US Food and Drug Administration for patients with familial hypercholesterolemia and documented coronary or peripheral artery disease who have lipoprotein(a) greater than or equal to 60 mg/dL (or ≥130 nmol/L). Registry-based data showed a meaningful lowering of ASCVD events in patients with lipoprotein(a) values greater than 60 mg/dL who were treated with apheresis, but these studies did not include a control group, eg, sham apheresis.

Low-dose aspirin may be considered for high lipoprotein(a) among individuals who are not at increased risk of bleeding.[1,4,7] Post hoc analyses in 2 primary prevention randomized placebo-controlled trials found that aspirin lowered risk of ASCVD events in patients with genetically high lipoprotein(a), consistent with several observational studies. However, no randomized clinical trials have studied aspirin in patients selected for high lipoprotein(a) levels.

Specific lipoprotein(a) lowering has become possible with the recent development of novel mRNA therapies such as subcutaneously injected pelacarsen, olpasiran, lepodisiran, and zerlasiran that degrade apolipoprotein(a) mRNA[8] or the oral small molecule inhibitor muvalaplin that inhibits lipoprotein(a) formation in the liver.[9] These drugs reduce lipoprotein(a) in a dose-dependent manner by up to 99%. Currently, there is no randomized clinical trial evidence that these lipoprotein(a)-lowering drugs reduce rates of ASCVD events.[2]

Conclusions

High lipoprotein(a) levels, defined as 50 mg/dL or greater, are associated with increased rates of ASCVD events. Patients with elevated levels of lipoprotein(a) should be treated with lifestyle management such smoking cessation, physical activity, and Mediterranean diet; cholesterol-lowering therapy; and blood pressure control. Whether lipoprotein(a) itself is a modifiable risk factor that should be lowered for ASCVD prevention currently remains unknown.

ARTICLE INFORMATION

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Published Online: April 24, 2025. doi:10.1001/jama.2025.2373

Conflict of Interest Disclosures: Dr Mora reported being a co-inventor on a patent examining glycoprotein acetylation in relation to colorectal cancer risk issued to LabCorp and on a patent examining glycoprotein acetylation in relation to cardiovascular disease risk pending for Genos Inc. Dr Kronenberg reported receiving personal fees from Novartis, Amgen, Silence Therapeutics, CRISPR Therapeutics, and Roche during the conduct of the study.

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