An Update on Lipoprotein(a): The Latest on Testing, Treatment, and Guideline Recommendations

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Expert Analysis

Quick Takes

- Lipoprotein(a) (Lp[a]) is an independent risk factor for atherosclerotic cardiovascular disease (CVD) and calcific valvular aortic stenosis.
- Lp(a) exhibits significant race/ethnic variations, with levels highest among persons of African ancestry.
- Lp(a) levels typically do not change after 5 years of age except during times of significant inflammation, liver disease, or kidney disease; hence, levels should be interpreted cautiously during these times.
- Current guidelines support once-in-a-lifetime measurement in most individuals with increased risk of atherosclerotic CVD.
- Emerging data appear to show a strong correlation with high-sensitivity C-reactive protein levels for predicting CVD risk.
- New lines of therapy targeting lipoprotein(a) (*LPA*) gene translation are being developed.

Lipoprotein(a) (Lp[a]) is a low-density lipoprotein–like molecule with an apolipoprotein (b) moiety that is covalently attached to apolipoprotein (a) (Apo[a]), a plasminogen-like protein that confers several pathologic features to Lp(a). Produced mainly in the liver, Lp(a) has a wide spectrum of characteristics, including atherogenicity, thrombogenicity, and proinflammatory properties; hence, it may have pathologic effects on multiple systems. Its physiologic function has been a topic of debate, and it is thought to have a role in wound healing. However, many individuals have undetectable Lp(a) levels, which raises the relevance of its function. An estimated 20-25% of the world's population is believed to have elevated levels.[1]

Lp(a) levels are genetically determined, with little to no influence from environmental or lifestyle factors, and adult levels are reached in childhood, typically by 5 years of age. Studies have shown that inflammatory conditions,[2] pregnancy,[3] hypothyroidism,[4] growth hormone therapy,[5] and kidney disease[6] increase levels of Lp(a). Lp(a) levels are decreased in the settings of severe acute phase conditions,[7] postmenopausal hormone replacement,[8] hyperthyroidism, and liver disease.[9] Hence, checking levels at steady states is advised.

Lp(a) is an established independent casual risk factor for arteriosclerotic cardiovascular disease (ASCVD) and calcific aortic valve stenosis, supported by evidence from Mendelian randomization, epidemiologic studies, and numerous prospective studies. Lp(a) exhibits wide racial variations, with persons of African ancestry having significantly higher levels than do persons of Asian or Caucasian ancestry. Levels in persons of Hispanic ethnicity are comparable to those of Caucasian ancestry; among those of Hispanic ethnicity, those of Amerindian ancestry have lower levels than

do those of West African ancestry.[10] More recent studies have shown evidence of a strong association between high-sensitivity C-reactive protein (CRP) and Lp(a) levels as joint predictors of major adverse cardiovascular events, and this is an area of expanding research and a therapeutic target.

Because of Kringle IV type-2 repeat polymorphism of the lipoprotein(a) (*LPA*) gene that codes for Apo(a), there is a wide variability in Lp(a) size in the population. A high Apo(a) isoform size correlates with lower plasma concentrations of Lp(a) and vice versa. For years, this correlation posed a challenge in developing standard assays for Lp(a) quantification. Lp(a) is currently measured either in nanomoles per liter (nmol/L), which measures the number of particles, or milligrams per deciliter (mg/dL), which measures Lp(a) mass concentration; the former is in accordance with World Health Organization (WHO) laboratory measuring. The ratio of mass/molecular weight is not constant between individuals; hence, a single standard conversion between milligrams per deciliter to nanomoles per liter is not accurate.

There is no generalized consensus on Lp(a) risk thresholds:

- ≥50 mg/dL (or ≥125 nmol/L) is an accepted target in American College of Cardiology/American Heart Association (ACC/AHA) guidelines
- ≥50 mg/dL (or ≥100 nmol/L) is an accepted target in the Canadian Cardiovascular Society (CCS) guidelines
- <30 mg/dL (or <75 nmol/L) is considered normal, 30-50 mg/dL (or 50-125 nmol/L) intermediate, and >50 mg/dL (or >125 nmol/L) abnormal in the European Atherosclerotic Society (EAS) consensus statement
- >50 mg/dL (or >100 nmol/L) is accepted as a risk-enhancing cutoff in the National Lipid Association (NLA) scientific statement

Current lipid-lowering medications have not provided sufficient Lp(a) level reduction except for the proprotein convertase subtilisin/kexin 9 inhibitors. Promising results from the **ODYSSEY OUTCOMES** (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial of alirocumab indicate an approximate 23% reduction in Lp(a) levels,[11] and from the **FOURIER** (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial of evolocumab indicate an approximate 27% reduction.[12] Statins slightly increase Lp(a) levels, or levels remain stable with therapy. Ezetimibe reduces Lp(a) levels by 7.6% according to the findings of one meta-analysis;[13] however, other studies' findings revealed no change.[14] Bile acid sequestrants and fibrates do not have a significant correlation with Lp(a) levels; some studies' findings show an increase and others' show no effect. Niacin decreases Lp(a) levels by 23%; however, it is not recommended for use because it lacks mortality and morbidity benefit in patients at risk of cardiovascular disease (CVD). Additionally, its adverse effect profile limits use. Bempedoic acid is a relatively new low-density lipoprotein cholesterol (LDL-C)-lowering medication for patients intolerant of statins. Bempedoic acid appears to slightly increase Lp(a) levels by 2.4%, and some studies' findings revealed a null effect on Lp(a) levels.[15]

Several novel therapies targeting the *LPA* gene transcription rate using small interfering RNAs and gene translation with antisense oligonucleotides are in phase 2 and 3 trials (**Table 1**). The first large cardiovascular (CV) outcome study of Lp(a) from the Lp(a) HORIZON (Assessing the Impact of Lipoprotein [a] Lowering With Pelacarsen [TQJ230] on Major Cardiovascular Events in Patients With CVD) trial is projected to result in 2 years.

Table 1: Phase 2 and 3 Trials of Novel Therapies Targeting *LPA* Gene Transcription Rate Using siRNAs and Gene Translation With ASOs

Study Name, Phase (Therapy)	Therapy Mechanism	Therapy Formulation	Population	Outcome
OCEAN(a) DOSE,[a] phase 2 (olpasiran [AMG 890])	siRNA that reduces Lp(a) synthesis in the liver	SC injection of 10, 75, or 225 mg every 12 weeks, or 225 mg every 24 weeks	• 281 participants • 18-80 years of age • Lp(a) >150 nmol/L • Evidence of ASCVD	• Percent change in Lp(a) level at 36 weeks • Preliminary results: percent reduction of 70.5% to 110.5%

SLN360,[b] phase 2 (SLN360)	Double-stranded siRNA targeting *LPA* mRNA	SC injection of 30, 100, 300, or 600 mg vs. placebo	• BMI 18-32 kg/m2 • Lp(a) level >125 nmol/L • At high risk of ASCVD events	• Change of Lp(a) level from baseline
ORION-11,[c] phase 3 (inclisiran)	siRNA that inhibits PCSK9 synthesis	SC injection of 300 mg on day 1 and day 90, then every 6 months vs. placebo	• ≥18 years of age • LDL-C level ≥70 mg/dL • History of ASCVD	• Secondary outcome evaluating effect of inclisiran on Lp(a) level • Preliminary results: percent reduction of Lp(a) level by 28.5%
Lp(a)HORIZON,[d] phase 3 (pelacarsen [TQJ230])	ASO against Apo(a)	SC injection of 80 mg monthly vs. placebo	• 8,323 participants • 18-90 years of age • Lp(a) level ≥70 mg/dL • Established CVD	• Time to occurrence of MACE in 4 years
AKCEA-APO(a)-LRx,[e] phase 2 (pelacarsen [ISIS 681257])	ASO against Apo(a)	SC injection of 20, 40, or 60 mg every 4 weeks; 20 mg every 2 weeks; or 20 mg every week vs. placebo for 6-12 months	• 286 participants • 18-10 years of age • Lp(a) level ≥60 mg/dL • Diagnosed CVD • Must be on standard-of-care preventive therapy for CVD risk factors other than elevated Lp(a) levels	• Percent change from baseline Lp(a) level • Preliminary results: dose-dependent reduction ranging 35-80%
TQJ230,[f] phase 3 (pelacarsen [TQJ230])	ASO against Apo(a)	SC injection of 80 mg monthly vs. placebo	• 60 participants • Established ASCVD • Currently undergoing lipoprotein apheresis for isolated Lp(a)	• Superiority of pelacarsen over placebo in reducing the rate of lipoprotein apheresis sessions
KRAKEN,[g] phase 2 (LY3473329)	siRNA-based approach targeting Apo(a)	Daily oral dose vs. placebo	• 233 participants • Lp(a) level ≥175 nmol/L • At high risk of ASCVD	• Percent change from baseline Lp(a) level to week 12
LY3819469,[h] phase 2 (LY3819469)	siRNA-based approach targeting Apo(a)	SC injections in four different doses vs. placebo	• 254 participants • >40 years of age • Lp(a) level ≥175 nmol/L at screening	• Percent change from baseline in time-averaged Lp(a) level

Table 1: Phase 2 and 3 Trials of Novel Therapies Targeting *LPA* Gene Transcription Rate Using siRNAs and Gene Translation With ASOs. *Courtesy of Alebna PL, Mehta A.*

[a] OCEAN(a) DOSE (Olpasiran Trials of Cardiovascular Events and LipoproteiN(a) Reduction–Dose Finding Study)
[b] SLN360 (Evaluate SLN360 in Participants With Elevated Lipoprotein(a) at High Risk of Atherosclerotic Cardiovascular Disease Events)
[c] **ORION-11** (Impact of Inclisiran on LDL-C Over 18 months in Patients With ASCVD or Risk-Equivalent)
[d] Lp(a) HORIZON (Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With CVD)
[e] AKCEA-APO(a)-LRx (Phase 2 Study of ISIS 681257 [AKCEA-APO(a)-LRx] in Participants With Hyperlipoproteinemia[a]

and Cardiovascular Disease)
[f] TQJ230 (A Multicenter Trial Assessing the Impact of Lipoprotein(a) Lowering With Pelacarsen [TQJ230] on the Rate of Weekly Lipoprotein Apheresis Sessions in Patients With Hyperlipoproteinemia[a] and Established Cardiovascular Disease in Germany)
[g] KRAKEN (A Study of LY3473329 in Adult Participants With Elevated Lipoprotein(a) at High Risk for Cardiovascular Events)
[h] LY3819469 (A Study of LY3819469 in Participants With Elevated Lipoprotein[a])

Apo(a) = apolipoprotein(a); ASCVD = atherosclerotic cardiovascular disease; ASO = antisense oligonucleotide; BMI = body mass index; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); *LPA* = lipoprotein(a) gene; MACE = major adverse cardiovascular events; mRNA = messenger RNA; PCSK9 = proprotein convertase subtilisin/kexin 9; SC = subcutaneous; siRNA = small interfering RNA.

Over the years, Lp(a) has become more prominent in most guidelines around the world:

- *2022 European Atherosclerosis Society (EAS) consensus statement.* Lp(a) level measured at least once in all adults and in youth with a history of ischemic stroke or a family history of premature ASCVD or elevated Lp(a) level and no other known risk factors.
- *2021 CCS dyslipidemia guideline.* Measure once in a person's lifetime as part of initial lipid screening.
- *2019 NLA scientific statement on Lp(a).* Measure in individuals with premature ASCVD, LDL-C level ≥190 mg/dL, men <55 years of age, and women <65 years of age. Use Lp(a) level >50 mg/dL (or >100 nmol/L) as increased risk; less-than-expected LDL-C–lowering response, despite good adherence; recurrent or progressive ASCVD despite optimal lipid-lowering therapy; calcific valvular aortic stenosis; and family history of elevated Lp(a) levels.
- *2019 European Society of Cardiology (ESC)/EAS dyslipidemia guideline.* A relative indication for Lp(a) level measurement is family history of premature ASCVD; favors statin initiation in primary prevention in patients with intermediate or borderline ASCVD.
- ***2018 multisociety cholesterol guideline***. Recommends measurement in individuals with a family history of premature ASCVD.

The key questions that remain unanswered are:

- In the race to find Lp(a) level-lowering therapies, will reduced levels translate to reduced CV risk in randomized placebo-controlled trials?
- Which standardized assay(s) for measurement of Lp(a) level should be used globally?
- Should there be a threshold for risk prediction and treatment?
- Should future therapy target all persons with elevated Lp(a) levels irrespective of demographics?
- Should a subset of people with added risk (perhaps individuals in persistent inflammatory states) be started on therapy irrespective of ASCVD risk?
- In risk stratification, should there be different cutoffs for different race/ethnic groups?
- Given its bidirectional relationship with CRP, is there a role for anti-inflammatory agents in therapy?

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Clinical Topics: Diabetes and Cardiometabolic Disease, Dyslipidemia, Prevention, Advanced Lipid Testing, Lipid Metabolism

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