American Heart Association.

Lp(a):

A Toolkit for Healthcare Professionals

Novartis Pharmaceuticals Corporation supports Driving Awareness and Shared Decision Making Around Lp(a) 2026

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Professional Activities – Research Funds: Ionis; Novo Nordisk
Professional Activities – Clinical Trial: Novartis Pharmaceuticals Corporation; Eli Lilly and Company; Intellia Therapeutics

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Publisher's Note
The Lp(a): A Toolkit for Healthcare Professionals is published by Ascend Media, LLC
401 SW Ward Road, Suite 210, Lee's Summit, MO 64081
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All references and data are as of September 2026.

IN MEMORIAM



Joseph L. Witztum, MD (1943-2026)

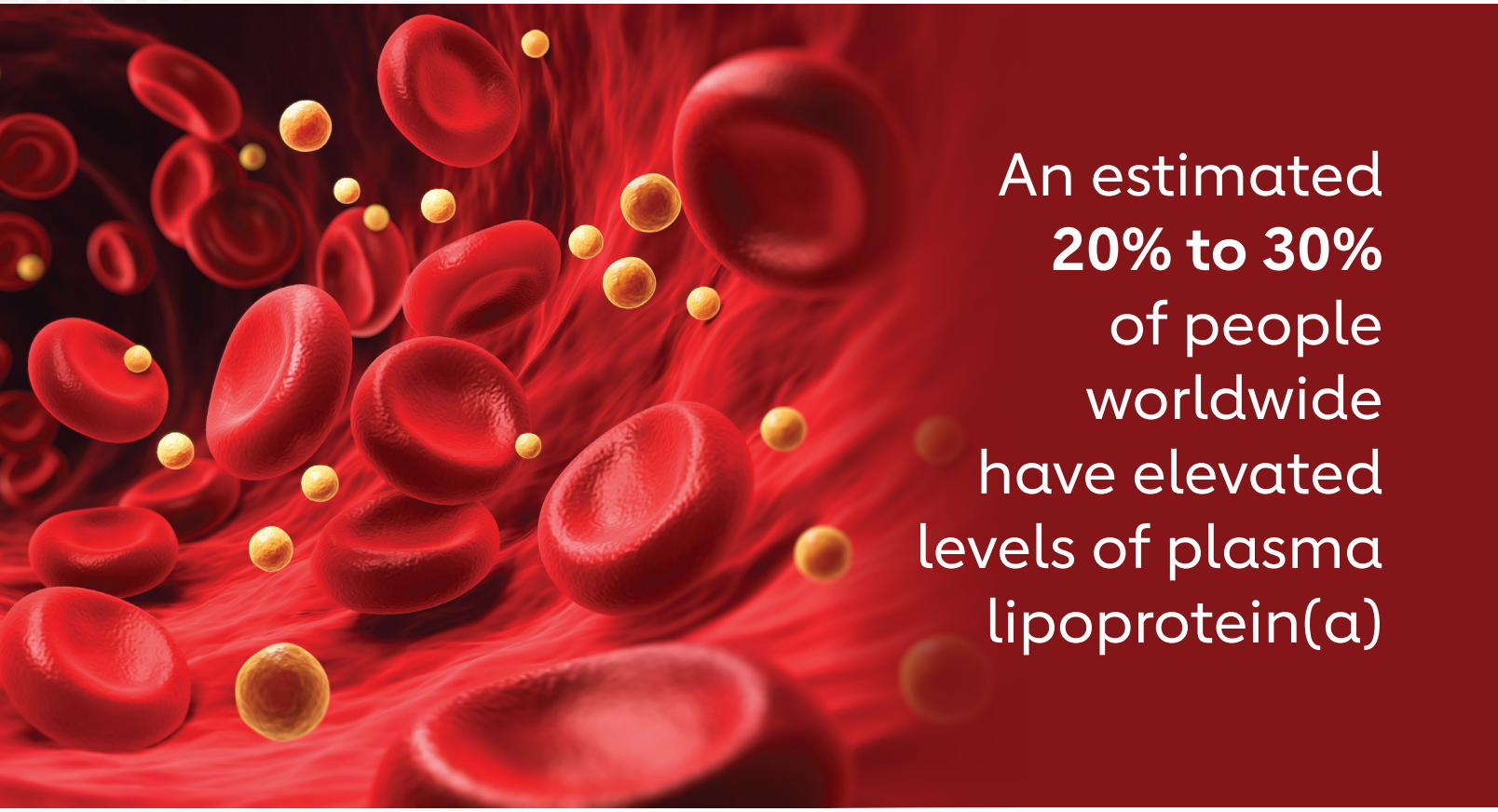
Dr. Witztum was a Distinguished Professor of Medicine in the Division of Endocrinology and Metabolism at the University of California in San Diego. For more than 40 years, Dr. Witztum made major contributions to the field of atherosclerosis and lipoprotein metabolism. He was actively involved in basic and clinical studies to develop novel therapies for unmet needs, especially in the context of hypertriglyceridemia and elevated Lp(a) levels. His research resulted in more than 500 manuscripts.

Dr. Witztum was a contributing author from this toolkit's launch in 2020 through its publication in 2025. We're grateful for his many contributions to the field.

Read more about Dr. Witztum's life and career.

Life

Career



An estimated **20% to 30%** of people worldwide have elevated levels of plasma lipoprotein(a)

An estimated 20% to 30% of people worldwide have elevated levels of plasma lipoprotein(a) [Lp(a)] which is independently associated with increased risk of cardiovascular disease (CVD) including myocardial infarction (MI), peripheral arterial disease (PAD), and stroke.[1] In addition, elevated Lp(a) is a strong predictor of the presence and progression of calcific aortic valve disease (CAVD).[1] Yet, Lp(a) gets the least attention among clinicians compared with the three other major classes of lipid disorders:

- elevated low-density-lipoprotein cholesterol (LDL-C)
- low high-density-lipoprotein cholesterol (HDL-C)
- elevated triglycerides [2,3]

It's important for clinicians to incorporate comprehensive guidelines for diagnosing, treating, and managing elevated Lp(a) into patient evaluation and risk assessment. The clinical relevance of Lp(a) as a risk-enhancing factor and the importance of patient-healthcare professional risk discussions is detailed in the **2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines.** The guideline also has implications for reducing CVD risk through cholesterol management.[4]

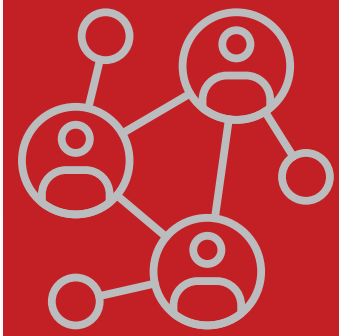
Lp(a) at a Glance

- Lp(a) is independently associated with CVD risk.
- Lp(a) levels are established in early childhood and remain relatively consistent over an individual's lifetime.
- Lp(a) is composed of apolipoprotein(a) [apo(a)] covalently bound to an apolipoprotein B (apoB)-100-containing lipoprotein particle and is the preferential carrier of proinflammatory oxidized phospholipids in plasma.
- Although definitive data are lacking, Lp(a) likely increases cardiovascular risk through multiple mechanisms, including those attributed both to its LDL-like moiety, as well as its unique apo(a) protein. The latter may confer prothrombotic and/or additional proinflammatory effects that can cause vascular cell dysfunction.[5]
- Lp(a) is approximately 6 times more atherogenic than LDL-C on a per particle basis.[6]
- Up to 90% of Lp(a) plasma concentration is determined by genetics.[5,7]
- Other factors that influence Lp(a) levels include age, sex, (pregnancy and post-menopausal status), ancestry and comorbid conditions, such as Familial Hypercholesterolemia and liver, thyroid, or kidney disease.[8,9]
- Distribution of Lp(a) levels may also vary by population-specific percentiles, due to differences in the distribution of Lp(a) levels among ancestry groups.[10]
- There is limited evidence that heart-healthy eating and regular physical activity reduce Lp(a) levels.[8] However, commitment to both will improve overall cardiovascular health.
- Although statins are a cornerstone therapy in the treatment of CVD, they are ineffective in lowering Lp(a). While some studies report that statins raise Lp(a), the increase is minimal and does not outweigh the benefit of statins in high-Lp(a) patients.[11]
- PCSK9 inhibitors can modestly lower Lp(a) levels, and patients with elevated Lp(a) may get greater cardiovascular benefit from these drugs.[12]

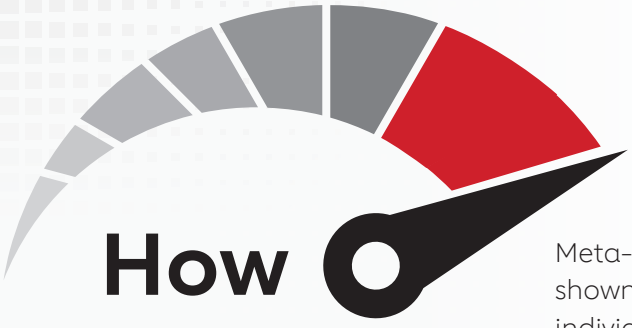


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How High Is Too High?

Meta-analyses have shown increased risk of CVD in individuals with Lp(a) levels **≥125 nmol/L (≥50 mg/dL)**.[7] According to ACC/AHA dislipidemia guideline, Lp(a) levels **≥125 nmol/L (≥50 mg/dL)** constitute a risk enhancing factor.[4]

Lp(a) increases ASCVD risk, especially at higher levels.

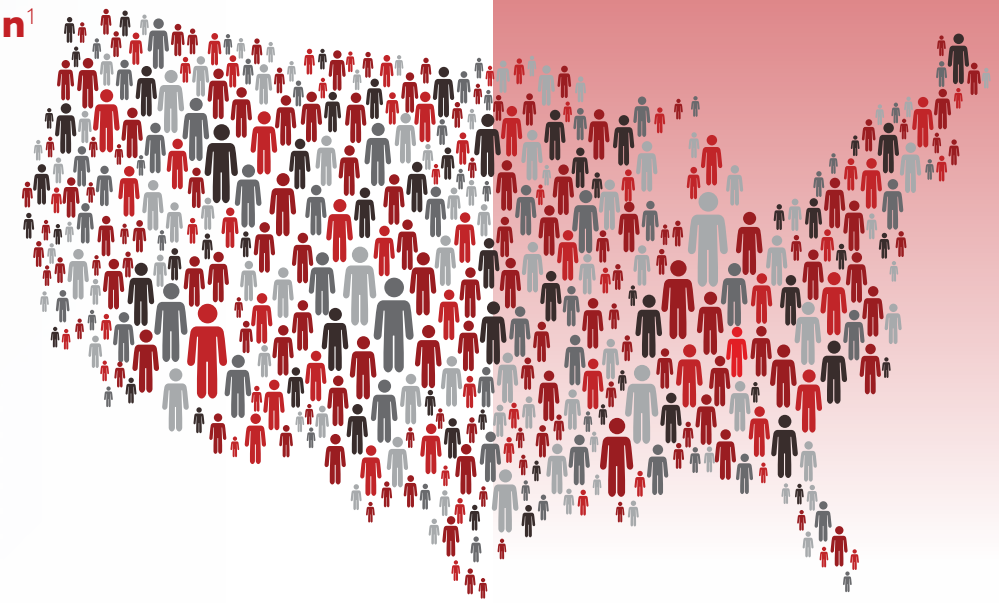
How Common Is It?

Elevated levels prevalent in

20% to 30%

of the global population[1]

- Black people have the highest median Lp(a) levels, followed by South Asian, Hispanic and East Asian peoples. Although, the impact on relative risk of ASCVD is similar regardless of ethnicity/ancestry.[13,14]
- Native American people have the lowest Lp(a) levels.[15]

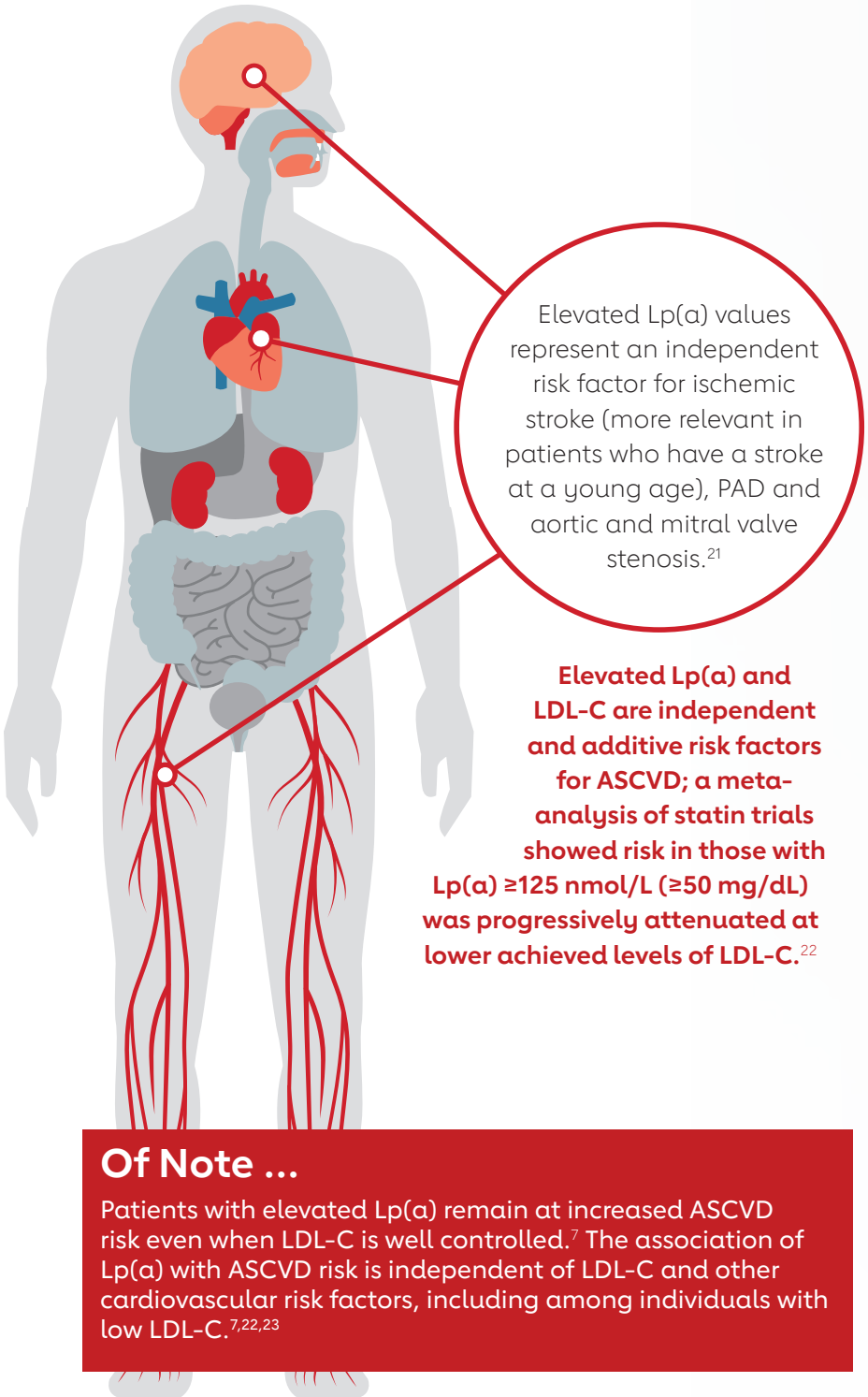


What Causes High Lp(a) Levels?



The major cause of high Lp(a) levels is genetics, mostly reflecting differences in the size of the gene encoding apo(a).[5]

Elevated Lp(a): What Are the Risks?



Elevated Lp(a) values represent an independent risk factor for ischemic stroke (more relevant in patients who have a stroke at a young age), PAD and aortic and mitral valve stenosis.[21]

Elevated Lp(a) and LDL-C are independent and additive risk factors for ASCVD; a meta-analysis of statin trials showed risk in those with Lp(a) ≥125 nmol/L (≥50 mg/dL) was progressively attenuated at lower achieved levels of LDL-C.[22]

Of Note ...

Patients with elevated Lp(a) remain at increased ASCVD risk even when LDL-C is well controlled.[7] The association of Lp(a) with ASCVD risk is independent of LDL-C and other cardiovascular risk factors, including among individuals with low LDL-C.[7,22,23]

People who have clinical CVD (including atherosclerosis-based cardiovascular diseases (ASCVD) such as acute coronary syndrome; stable angina or a history of MI or coronary or other arterial revascularization; stroke or transient ischemic attack; or PAD, including aortic aneurysm), are at higher risk for future events if Lp(a) is elevated. Elevated Lp(a) is also associated with onset[16,17] and progression[16] of CAVD, and progression to symptomatic heart failure.[18]

In the general population, Lp(a) levels **≥125 nmol/L (≥50 mg/dL)** are associated with an approximately 20% increased risk of cardiovascular events: each 3.5-fold increase in Lp(a) is associated with a 16% increase of risk of events.[14]*

People with borderline or slightly elevated LDL-C are three to four times more likely to have CVD events than those with low LDL-C.[19] Lp(a) can pose increased risk for acute coronary syndrome when LDL-C is elevated.[20]**

* ***Treatment strategy:*** *Consider implementation of aggressive LDL-C lowering strategies in patients with elevated Lp(a).*

** ***Treatment strategy:*** *Maximally manage modifiable risk factors in patients with elevated Lp(a) by including more intensive control of lipids, blood pressure, and glycemic control.*

How Does Lp(a) Work?

Despite the link between Lp(a) level and a variety of CVD events, the exact pathophysiological roles of Lp(a) are not clear. Lp(a) accumulates in the blood vessel wall, where it appears to be retained more avidly than LDL-C.[24] Recent evidence suggests that proinflammatory oxidized phospholipids present on Lp(a) promote the processes of endothelial dysfunction, inflammation and calcification in vasculature.[24] The role of Lp(a) as a prothrombotic factor is controversial, with evidence both for and against this possibility.[25]

The Challenge

- Lifestyle therapy, including heart-healthy eating and regular physical activity, has no significant effect on Lp(a) levels.[8]
- Statin therapy doesn't decrease Lp(a) levels. Patients with a history of CVD who are taking statins and have an Lp(a) **≥125 nmol/L (≥50 mg/dL)** are still at increased risk for vascular events, independent of other risk factors.[7, 22]
- Niacin lowers Lp(a); yet, to date, there are no randomized trials in people with high Lp(a) to determine if this is beneficial or not. Randomized Clinical Trials do not support use of niacin as an add-on drug to statin therapy as it has been associated with enhanced side effects and even adverse events.[4,7]
- It is suggested by post hoc analyses that PCSK9 inhibitors lower Lp(a) to a modest degree, but the specific contribution of Lp(a) reduction in lowering CVD risk in treated patients remains unclear.
- Lipoprotein apheresis (LA) is currently the only FDA approved treatment for lowering Lp(a). FDA approved for Lp(a) lowering when:
  - Clinically diagnosed familial hypercholesterolemic heterozygotes

  and
  - Either documented coronary artery disease or documented peripheral artery disease

  and
  - Lp(a) ≥130 nmol/L (≥60mg/dL) [4]

In Whom Should Lp(a) Be Measured?

Because the majority of Lp(a) plasma concentration (up to 90%) is influenced by genetics through the *LPA* gene[5], relative indications for its measurements are:

- Family history of premature CVD (men, age <55 years; women, age <65 years).
- A personal history of premature CVD.
- Individuals with Familial Hypercholesterolemia.
- Individuals with family history of elevated Lp(a).

Lp(a) should be measured at least once in adulthood to identify individuals at increased ASCVD risk. An Lp(a) level **≥125 nmol/L (≥50 mg/dL)** is considered a risk-enhancing factor, which is associated with about a 1.4-fold increased ASCVD risk, and values ≥250 nmol/L (100 mg/dL) are associated with ≥2-fold higher estimated risk. Elevated Lp(a) should prompt more intensive management of LDL-C and other modifiable cardiovascular risk factors. Cascade measurement in first-degree relatives of individuals with elevated Lp(a) is recommended. However, despite recent guidelines suggesting measurement of Lp(a) in all adults, the testing rate for Lp(a) remains very low.[4,26]

If a decision is made to measure Lp(a), an Lp(a) **≥125 nmol/L (≥50 mg/dL)** may be considered a risk-enhancing factor for CVD events.[4]



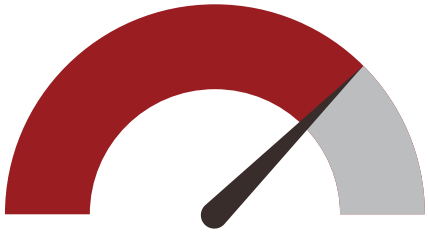
What to Know When Managing Your Patients' Lp(a) Risk



- In patients already on statin therapy, high Lp(a) is still associated with residual CVD risk.
- In primary prevention for adults ages 30 to 79 with an intermediate PREVENT-ASCVD 10-year risk and with LDL-C of 70 to 189 mg/dL, LDL-C–lowering therapy with a statin is recommended after a clinician–patient discussion.[4] If measured, an Lp(a) **≥125 nmol/L (≥50 mg/dL)** may be considered a risk-enhancing factor.
- In all individuals with elevated Lp(a) (**≥125 nmol/L or ≥50 mg/dL**), optimal early control of modifiable cardiovascular risk factors is recommended to reduce ASCVD risk.[1–4]
- In individuals with clinical ASCVD and elevated Lp(a) who have not achieved LDL-C and nonHDL-C treatment goals on maximally tolerated statin therapy, the addition of a PCSK9 mAb with proven cardiovascular benefit is recommended to achieve treatment goals and reduce ASCVD risk.[4–7]
- The presence of an elevated Lp(a) in patients with very-high-CVD risk and baseline LDL-C ≥70 mg/dL or non–HDL-C ≥100 mg/dL despite maximally tolerated statin and ezetimibe therapies may be used as a factor favoring a PCSK9 inhibitor.
- Although niacin and hormone replacement therapy can reduce Lp(a) levels, these drugs are **not** recommended because they haven't demonstrated benefit and may be **harmful,** according to the 2024 focused update to the 2019 NLA scientific statement on Lp(a).[7]
- Maximize treatment of modifiable risk factors.







- Good adherence to various LDL-C-lowering diets will reduce LDL-C levels by 10% to >15%. Moderate-intensity statins can be expected to reduce LDL-C levels by an additional 30% to 49%, and high-intensity statins by ≥50%. Adding ezetimibe or bempedoic acid to statin therapy typically provides an additional 13% to 30% reduction in LDL-C. Much greater additive reductions occur by adding a PCSK9 inhibitor to statin plus ezetimibe, providing a 43% to 64% reduction.[4]
- In clinical practice, lifestyle modifications and statin therapy are commonly introduced together. The maximum percentage change will occur by four to 12 weeks after starting a statin or combined therapy.[4]
- Review the need for lifestyle adjustments in eating habits and level of physical activity to maintain a healthy weight or body mass index, and the elimination of tobacco use. Promote a heart healthy lifestyle and provide relevant advice, educational materials or referrals as needed.[4]



The **2026 ACC/AHA Multisociety Dyslipidemia Guidelines** recommends assessing PREVENT-ASCVD 10-year risk and treating to LDL-C goals of < 100 mg/dL (< 10% risk) and < 70 mg/dL (≥ 10% risk). Statins recommended as first-line lipid-lowering therapy.[4]

Access the American Heart Association's Life's Essential 8™
heart.org/lifes8

Recent Approaches to Lowering Lp(a): What the Studies Show

Approaches that result in lowering of both Lp(a) and LDL

Lipoprotein Apheresis (LA): Moriarty and colleagues reported that lipoprotein apheresis (LA) therapy can effectively reduce both LDL and Lp(a), with a significant reduction in future CVD events (94% reduction in major adverse cardiovascular events over a mean treatment period of 48 months).[27] In the Pro(a)LiFe-Study (Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization)[28], it was shown that LA has a lasting effect on prevention of cardiovascular events in patients with Lp(a)-hyperlipidemia. Mean Lp(a) concentration was reduced in a single LA treatment by 68.1% on average and a significant decline of the mean annual cardiovascular event rate was observed from 0.58±0.53 2 years before regular LA to 0.11±0.15 thereafter.

PCSK9 inhibitors reduce LDL-C by 43% to 64% and lower Lp(a) by 20% to 30%. Analysis of the ODYSSEY OUTCOMES and FOURIER outcomes trials showed enhanced benefit from PCSK9 inhibitor therapy in patients with elevated Lp(a) despite more modest (16-22%) Lp(a) percent lowering in this group.[12]

Inclisiran, a small interfering RNA molecule that targets PCSK9 messenger RNA, has been evaluated in people with high risk for CVD and elevated LDL-C. Compared with placebo, inclisiran reduced Lp(a) by 21.9% in the ORION-10 trial evaluating inclisiran in patients with ASCVD and by 18.6% in the ORION-11 trial that enrolled subjects with an ASCVD equivalent.[29]

Enlicitide, the first FDA-approved oral PCSK9 inhibitor, was approved in 2026 as an adjunct to diet and exercise to reduce LDL-C in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia. In CORALreef Lipids, enlicitide also produced a modest reduction in Lp(a) (approximately 28% versus placebo at 24 weeks). Cardiovascular outcomes data for enlicitide are not yet available.[30]

Emerging Therapies that specifically and effectively lower Lp(a)

There are three compounds (pelacarsen, olpasiran and lepodisiran) that are in Phase 3 clinical trials.

Pelacarsen is an antisense oligonucleotide (ASO) that targets apo(a) messenger RNA and lowers Lp(a) by ~80%. This compound is currently being tested in a Phase 3 cardiovascular outcomes trial (Lp(a) HORIZON; NCT04023552).

- 8323 participants; randomized, double-blind, placebo-controlled trial
- Key inclusion criteria: Lp(a) ≥ 70 mg/dL; pre-existing ASCVD
- Primary endpoint: time to expanded major adverse cardiovascular event (Lp(a) ≥ 70 mg/dL or ≥ 90 mg/dL)
- Study has been completed and the primary end point was not met

Olpasiran is a silencing RNA compound (siRNA) that targets apo(a) messenger RNA and lowers Lp(a) by >90%. This compound is currently being tested in a Phase 3 cardiovascular outcomes trial (OCEAN(a); NCT05581303)

- 7297 participants; randomized, double-blind, placebo-controlled trial
- Key inclusion criteria: Lp(a) ≥ 200 nmol/L; history of ASCVD
- Primary endpoint: time to CHD death, myocardial infarction, or urgent coronary revascularization
- Anticipated study completion date is **December 2026**
- OCEAN(a)-PreEvent (NCT07136012) is enrolling participants with Lp(a)≥ 200 nmol/L at risk for a first major cardiovascular events, with a completion date of **October 2031**



Three RNA-targeting drugs that lower Lp(a) >80% are in Phase 3 cardiovascular outcomes trials.

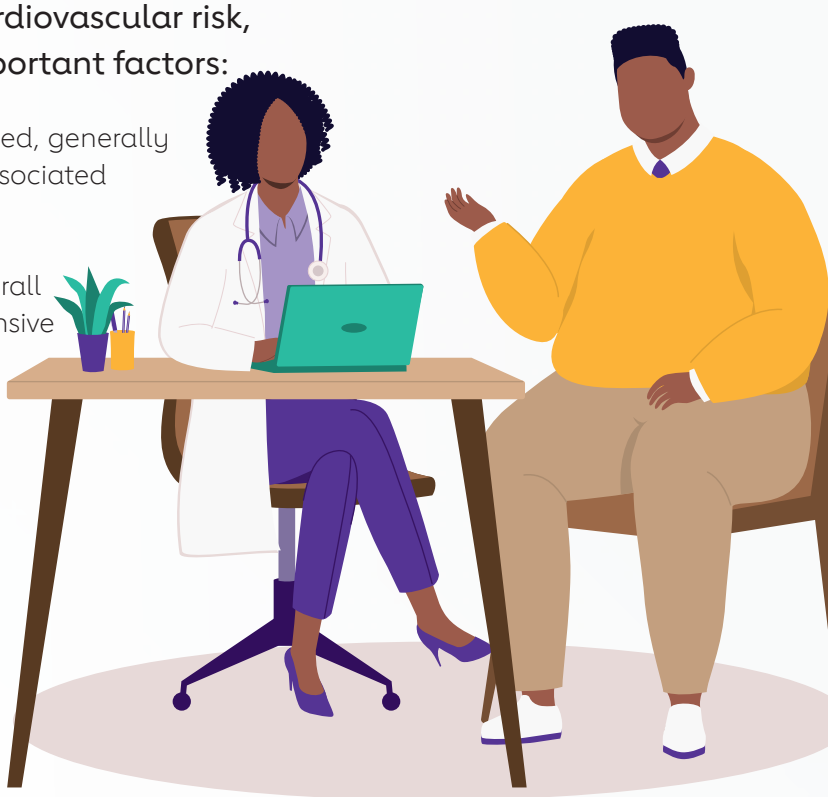
Lepodisiran is a silencing RNA compound that targets apo(a) messenger RNA. It is being tested in a Phase 3 cardiovascular outcomes trial (ACCLAIM-Lp(a); NCT06292013) with an anticipated study completion date of **March 2029**. The trial recruited both secondary prevention and high-risk primary prevention subjects.

Other Lp(a)-specific lowering drugs in the pipeline: There are several additional compounds that are in development.[31] These include **zerlasiran**, another siRNA compound against apo(a) mRNA (Phase 2 completed; up to 96% Lp(a) lowering), and a small molecule (**muvalaplin**) that disrupts Lp(a) formation (Phase 2 completed; up to 86% lowering) and is in a Phase 3 cardiovascular outcomes trial (NCT07157774). Gene editing approaches targeting LPA for permanent lowering of Lp(a) have shown promise in preclinical studies[32,33] and CTX320, a Cas9-based gene editor in lipid nanoparticles, is being tested in Phase 1 trails.[34]



The Importance of Shared Decision-Making

Clinicians and patients should work together to make informed decisions based on the patient's overall cardiovascular risk, values and preferences. Consider these important factors:



- Explain that Lp(a) is largely genetically determined, generally stable over the life course, and independently associated with ASCVD risk.
- Discuss how the patient's Lp(a) level modifies overall ASCVD risk and may support earlier or more intensive LDL-C lowering and management of other modifiable cardiovascular risk factors.
- Review treatment options and goals, distinguishing therapies used to reduce overall ASCVD risk from Lp(a)-specific therapies that remain under investigation.
- Discuss the implications of elevated Lp(a) for family members and the role of cascade testing in first-degree relatives.
- Encourage patients to discuss their values, preferences, concerns and personal goals, including medication burden, cost and potential adverse effects.
- Use a guide to facilitate shared decision-making with the patient.[4]

Access to the American Heart Association's Lp(a) Discussion Guide at **heart.org/lpa**

Of Note...

Evidence indicates that measuring Lp(a) may reclassify CVD risk and aid in pharmacotherapy decision-making. Lp(a) levels are predominantly genetically determined and generally stable over time; therefore, a single measurement is usually sufficient. Repeat measurement may be considered in selected circumstances.[4]



What Does the Future Hold?

Much is now known about Lp(a) and its role in CVD. But more evidence is needed to inform future recommendations for clinical practice. For Lp(a) to be accepted as a risk factor for intervention, randomized outcome trials of specific Lp(a) lowering that demonstrate reduction in CVD risk are required. The results of these trials will provide the initial answers as to the benefits of Lp(a) lowering but many important unanswered questions are likely to remain, requiring further investigation.



- Will earlier measurement of Lp(a) and effective interventions to lower it help to improve outcomes?
- How will Lp(a) screening inform clinical decision-making for more aggressive management of cardiovascular risk in high Lp(a) patients?
- What will be the benefit of medical interventions that target Lp(a) lowering, and how will such therapies change outcomes of people at risk and those currently affected by CVD?
- Will Lp(a)-lowering therapy be effective in people with low LDL-C, in light of new promising LDL-C–lowering therapies beyond statins, ezetimibe, bempedoic acid and PCSK9 inhibitors?
- What role will lipoprotein apheresis continue to play in reduction of LDL and Lp(a) in people with FH?
- What part will artificial intelligence and machine learning play in risk assessment that will expedite patient diagnosis and treatment?

To answer these and a myriad of other questions, it's encouraging that randomized, placebo-controlled, double blind cardiovascular outcomes trials of **pelacarsen, olpasiran, lepodisaran** and **muvalaplin** that specifically and effectively reduce Lp(a), are ongoing and due to report between 2026 and 2031. In addition, there are several other potential therapies in earlier stages of development.

This underscores an urgent need for better standardization of Lp(a) measurement and an improved understanding of Lp(a) metabolism, physiology and the pathologic mechanisms by which Lp(a) and oxidized phospholipids on Lp(a) lead to CVD.

Finally, the knowledge gaps for unique populations need to be addressed, including the possible relationship of high Lp(a) with stroke in children and to better define the unmet medical needs for Lp(a) reduction in people of all ancestries.

2026 ACC/AHA Multisociety Dyslipidemia Guidelines

Top 10 Takeaways

Currently, there is no treatment specific for elevated Lp(a), but clinicians can make sure their patients' LDL-C levels and other modifiable risk factors are well controlled according to the current guideline.[4]

1 **Treat dyslipidemia earlier** to reduce lifelong exposure to atherogenic lipoproteins. Health-behavior counseling should start in youth, with early pharmacotherapy considered in youth with familial hypercholesterolemia (FH) and in young adults with **LDL-C ≥160 mg/dL** or a strong family history of premature ASCVD.

2 **Use the PREVENT equations instead of the Pooled Cohort Equations** for 10- and 30-year risk assessment in primary prevention (ages 30–79), applying the **"CPR" model**: **C**alculate 10-year ASCVD risk, **P**ersonalize the estimate with factors outside PREVENT, and possibly **R**eclassify with selective coronary artery calcium (CAC) and **R**eassess treatment.

3 **LDL-lowering therapy** can be considered at a 10-year PREVENT-ASCVD risk of **3% to <5%** (**borderline**) and should be considered at **5% to <10%** (**intermediate**) after a clinician–patient discussion.

4 **LDL-C and non–HDL-C treatment goals are back** to guide therapy, with **percentage LDL-C reduction** remaining a priority and the goal depending on risk level.

5 **ApoB testing** can be useful to refine risk and guide therapy once LDL-C and non–HDL-C goals are met, particularly with **triglycerides ≥150 mg/dL**, diabetes, or low achieved LDL-C (<70 mg/dL).

6 **Lipoprotein(a) should be measured at least once.** It is a risk enhancer at **≥125 nmol/L (50 mg/dL)** (~1.4-fold risk) and confers ≥2-fold risk at **≥250 nmol/L (100 mg/dL)**, prompting more intensified LDL-C lowering.

7 **CAC scoring** (men ≥40, women ≥45) can improve risk assessment and guide LDL-C/non–HDL-C goals, with both absolute score and standardized percentile carrying prognostic value.

8 **LDL-lowering therapy is recommended** in adults 40–75 years with **diabetes, CKD stage 3 or 4, or HIV**, regardless of LDL-C level; after age 75, pharmacotherapy can be considered alongside lifestyle interventions.

9 In **secondary prevention**, a goal of **LDL-C <55 mg/dL and non–HDL-C <85 mg/dL** is recommended for those at very high risk; most patients with prior ASCVD events will qualify for the <55 mg/dL goal.

10 In patients with **persistently elevated triglycerides**, statin therapy remains the foundation of pharmacotherapy as an adjunct to lifestyle intervention.



Check Out Patient Education Resources at **heart.org/lpa**



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