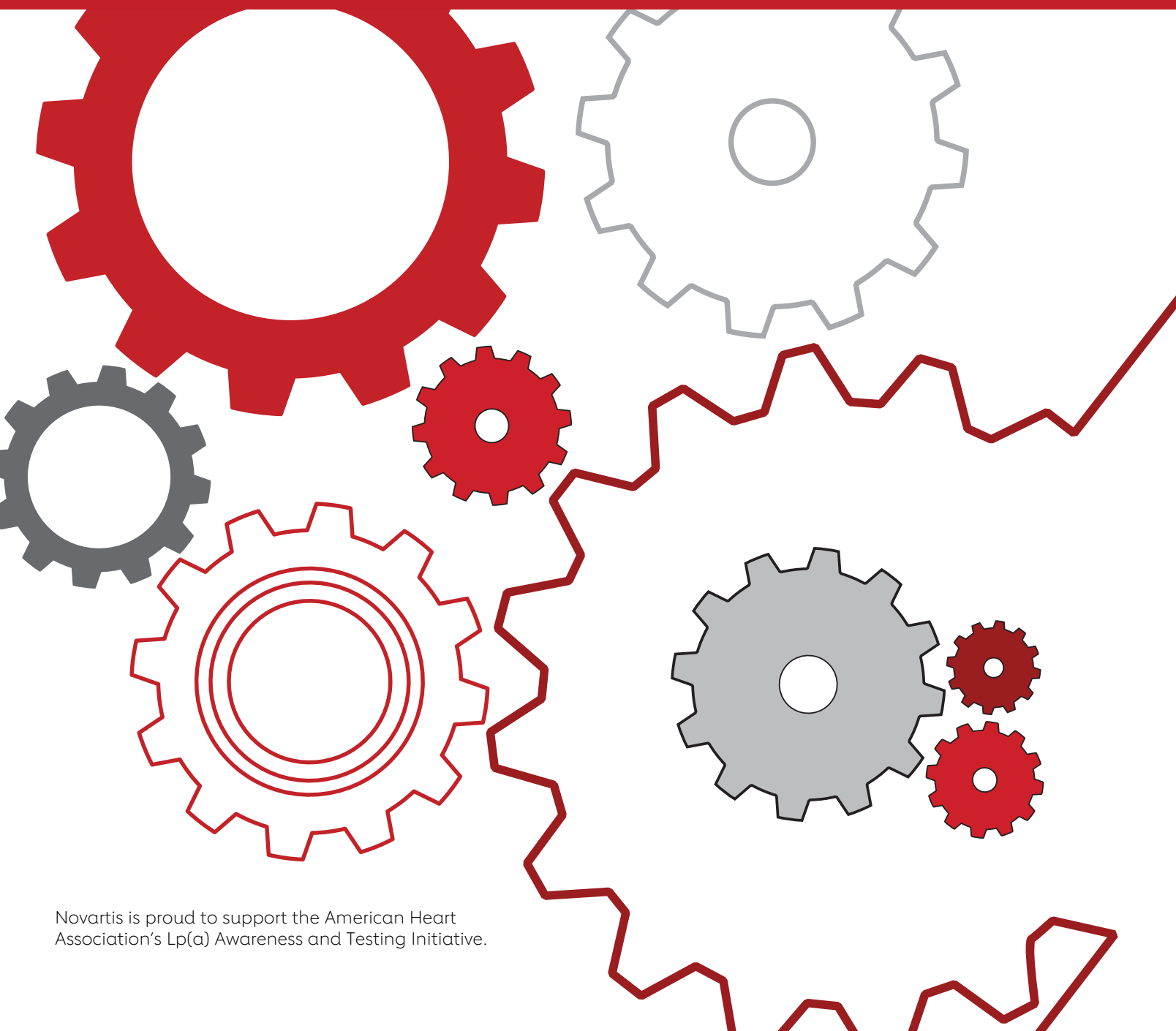
American Heart Association.

Lp(a): A Toolkit for Health Care Professionals



Novartis is proud to support the American Heart Association's Lp(a) Awareness and Testing Initiative.

Contents:

Contributing Authors

Marlys Koschinsky PhD, FAHA, is professor, physiology and pharmacology, and scientist at Robarts Research Institute, Schulich School of Medicine & Dentistry at Western University in Ontario, Canada. She is a recognized leader in the Lp(a) field and has unraveled many mysteries of this unique lipoprotein. She has national and international collaborations with many stakeholder groups and has helped translate knowledge from the basic biochemistry of Lp(a) to preclinical, clinical and R&D applications.

Joseph L. Witztum, MD, is 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 has made major contributions to the field of atherosclerosis and lipoprotein metabolism. He has been 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 has resulted in more than 500 manuscripts.

Cindy Lamendola, MSN, ANP, FAHA, FPCNA, is an adult nurse practitioner and clinical research nurse manager at Stanford University School of Medicine in Stanford, California. She has focused on risk management of cardiovascular disease and type 2 diabetes. Areas of research include insulin resistance, type 2 diabetes and relationship to cardiovascular disease and lipid abnormalities, including Lpa. She is a founding member of the Preventive Cardiovascular Nurses Association, and member and fellow of AHA.

Leslie L. Davis, PhD, APRN, FAAN, FAANP, FACC, FAHA, FPCNA, is an associate professor at the University of North Carolina at Chapel Hill. She also maintains a part-time nurse practitioner practice with the Division of Cardiology at the UNC Chapel Hill School of Medicine. A cardiovascular expert, Dr. Davis is a certified hypertension clinician and a fellow in the American Academy of Nursing, the American Association of Nurse Practitioners, the American College of Cardiology, the American Heart Association and the Preventive Cardiovascular Nurses Association.

Disclosures

Marlys Koschinsky PhD, FAHA
Professional Services and Activities – Employment: University of Western Ontario
Professional Services and Activities – Other Professional Activities: Amgen; Eli Lilly and Company; Novartis

Joseph L. Witztum, MD
Professional Services and Activities – Other Professional Activities: Ionis
Financial Stake – Other Business: Oxitope, Kleanthi Diagnostic
Intellectual Property – Patent: Patents and patent applications

Cindy Lamendola, MSN, ANP, FAHA, FPCNA
Professional Services and Activities – Employment: School of Medicine, Stanford University
Professional Services and Activities – Other Professional Activities: Alnylam Pharmaceuticals, Inc.; Novo Nordisk; Novartis Pharmaceuticals Corporation; Novartis

Leslie L. Davis, PhD, APRN, FAAN, FAANP, FACC, FAHA, FPCNA
Professional Services and Activities – Employment: University of North Carolina at Chapel Hill

Professional Services and Activities – Other Professional Activities: American Association of Nurse Practitioners; American College of Cardiology; Kentucky Association of Nurse Practitioners and Nurse Midwives; Nurse Practitioners Associates for Continuing Education; Preventive Cardiovascular Nurses Association; Skin, Bones, Hearts, and Private Parts; University of North Carolina at Chapel Hill

Intellectual Property – Copyright: Journal for Nurse Practitioners

Intellectual Property – Other Intellectual Property: Nursing Clinics of North America

Publisher's Note
The Lp(a): A Toolkit for Health Care Professionals is published by Ascend Media, LLC
401 SW Ward Road, Suite 210, Lee's Summit, MO 64081

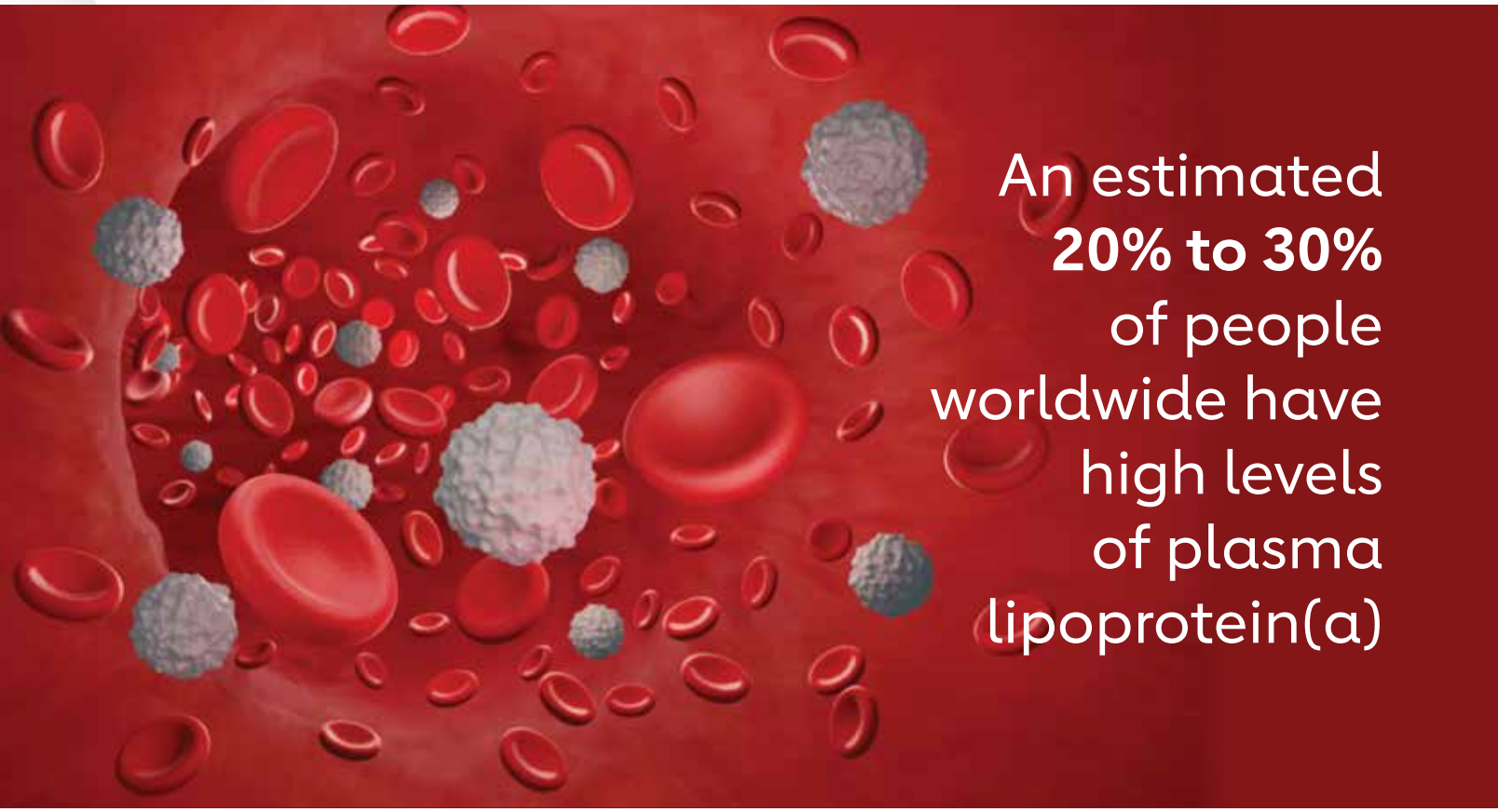
All references and data are as of September 2024

Scan to view a video on the impact of Lp(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. In addition, elevated Lp(a) is a strong predictor of the presence and progression of calcific aortic valve disease (CAVD). 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[1,2]

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-health care professional risk discussions is detailed in the **2018 Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.** The guidelines also have implications for reducing CVD risk through cholesterol management.[3]



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.[4]
- Lp(a) is approximately 6 times more atherogenic than LDL on a per particle basis.[5]
- Up to 90% of Lp(a) plasma concentration is determined by genetics.[4,6]
- Other factors that influence Lp(a) levels include age, sex, ethnicity[7] and comorbid conditions, such as Familial Hypercholesterolemia[8] and liver or kidney disease.[7]
- Lp(a) levels are approximately 10-15% higher in women than men.[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. However, commitment to both will improve overall cardiovascular health.[7]
- Statins are ineffective in lowering Lp(a). To the contrary, research shows statins can modestly increase Lp(a) levels by, on average, approximately 10-15%.[11] The mechanism is not understood.
- PCSK9 inhibitors can modestly lower Lp(a) levels.[12]

Up to 90%

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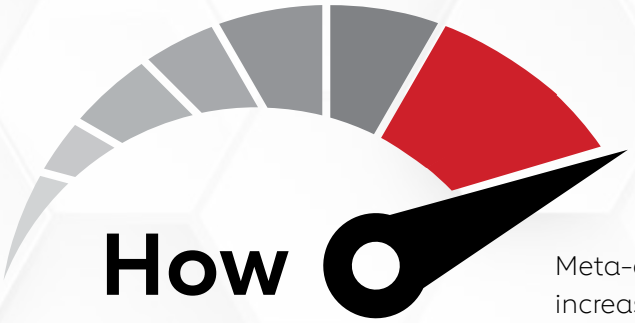
Scan to view a video on Lp(a) at a glance.

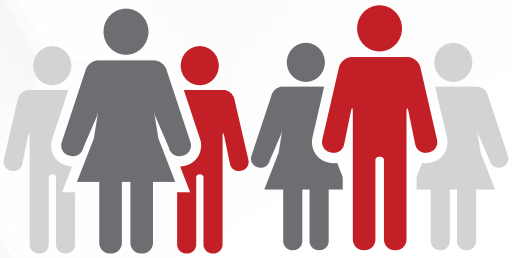


How High Is Too High?

Meta-analyses have shown increased risk of CVD in individuals with Lp(a) levels above 50 mg/dL. According to AHA/ACC cholesterol guidelines, Lp(a) levels greater than/equal to 50 mg/dL constitute a risk enhancing factor.[3]

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

How Common Is It?



Elevated levels prevalent in

20% to 30%

of the global population[10]

Black people have the highest median Lp(a) levels,

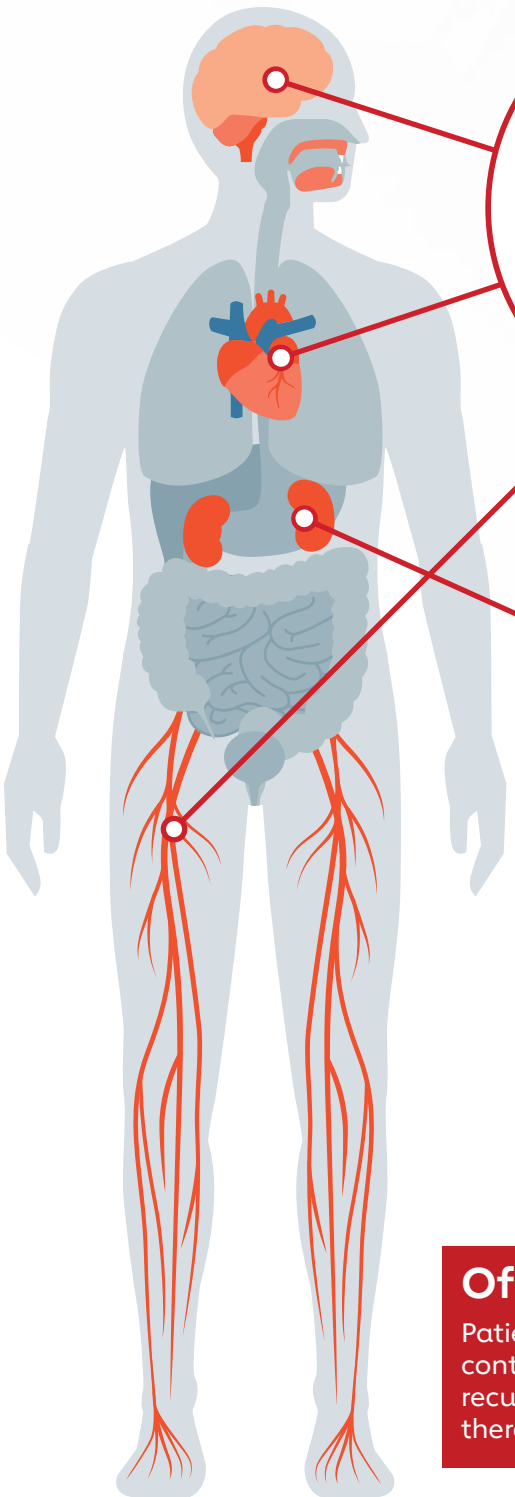
followed by South Asian, Hispanic and East Asian peoples.

Native American people have the lowest Lp(a) levels.[13]

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).[4]

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.[18]

Elevated Lp(a) seems to be associated with atherosclerotic renal artery stenosis in hypertensive patients with low LDL-C.[17]

In people with established CVD, elevated Lp(a) levels significantly increase the risk of future cardiovascular events, particularly in those with LDL-C ≥ 130 mg/dL.[19]

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[14,15] and progression[14] of CAVD, and progression to symptomatic heart failure.[16]

In the general population, Lp(a) levels greater than 50 mg/dL (~125 nmol/L) 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.[20*]

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.[21] Lp(a) can pose increased risk for acute coronary syndrome when LDL-C is elevated.[22**]

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

*** Treatment strategy: Maximally manage treatable risk factors in patients with elevated Lp(a).*

Of Note ...

Patients with elevated Lp(a) are at risk even if their LDL-C is optimally controlled by statins.[6] In particular, residual risk conferred by Lp(a) for a recurrent event is about 10% even when statins and other lipid-lowering therapies (i.e., PCSK9 inhibitors) are used to lower LDL-C.[23]

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.[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.[7]
- Statin therapy doesn't decrease Lp(a) levels. Patients with a history of CVD who are taking statins and have an Lp(a) ≥50 mg/dL are at increased risk for vascular events, independent of other risk factors.[6]
- 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. In other randomized trials, use of niacin has been associated with enhanced side effects and even adverse events.[6]

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:
  - Patient has heterozygous familial hypercholesterolemia

  and
  - LDL-C > 100mg/dL

  and
  - Patient has established coronary artery disease or peripheral artery disease

  and
  - Lp(a) > 60 mg/dL[26]

In Whom Should Lp(a) Be Measured?

Scan to view a video on Lp(a) measurement.

Because the majority of Lp(a) plasma concentration (up to 90%) is influenced by genetics through the *LPA* gene[4], relative indications for its measurements are:

- Family history of premature CVD (men, age <45 years; women, age <55 years).
- A personal history of premature CVD.
- Individuals with Familial Hypercholesterolemia.
- Individuals with family history of elevated Lp(a).

Although the 2018 ACC/AHA guidelines[3] and the 2019 NLA statement on Lp(a)[6] have not recommended measurement of Lp(a) in all individuals, most[27-30] but not all[31,32], subsequent statements/guidelines contain recommendations for Lp(a) screening in all individuals at least once in a lifetime. However, despite recent guidelines suggesting measurement of Lp(a) in all adults, the testing rate for Lp(a) remains very low.

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

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

- In patients already on statin therapy, high Lp(a) is associated with residual CVD risk.
- In primary prevention for adults ages 40-75 with a 10-year CVD risk of 7.5% to 19.9%, risk-enhancing factors favor initiation of statin therapy. If measured, an Lp(a) ≥50 mg/dL or ≥125 nmol/L may be considered a risk-enhancing factor.
- In high-risk or very-high-risk patients with LDL-C ≥70 mg/dL (non–HDL-C ≥100 mg/dL) and a Lp(a) ≥50 mg/dL or ≥100 nmol/L on maximally tolerated statin treatment, it's reasonable to consider more intensive therapies (such as ezetimibe and/or PCSK9 inhibitors) to lower LDL-C (and non–HDL-C) to better reduce CVD risk.[6]
- 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 NLA scientific statement.[6]
- Maximize treatment of modifiable risk factors.
- Good adherence to various LDL-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 bile acid sequestrants 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.[3]

- 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.[3]

- 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.[3] **Access the American Heart Association's Life's Essential 8™ heart.org/lifes8**

The **AHA/ACC 2018 Guideline on the Management of Blood Cholesterol** recommends assessing 10-year ASCVD risk and focusing on reducing LDL-C, primarily through the use of statin therapy. It advocates for more aggressive lowering of LDL-C on a percentage basis, (e.g., <50%). The AHA/ACC guidelines include a value statement regarding cost considerations for PCSK9 inhibitors.[3]

Scan to view a video on Life's Essential 8 and Lp(a).

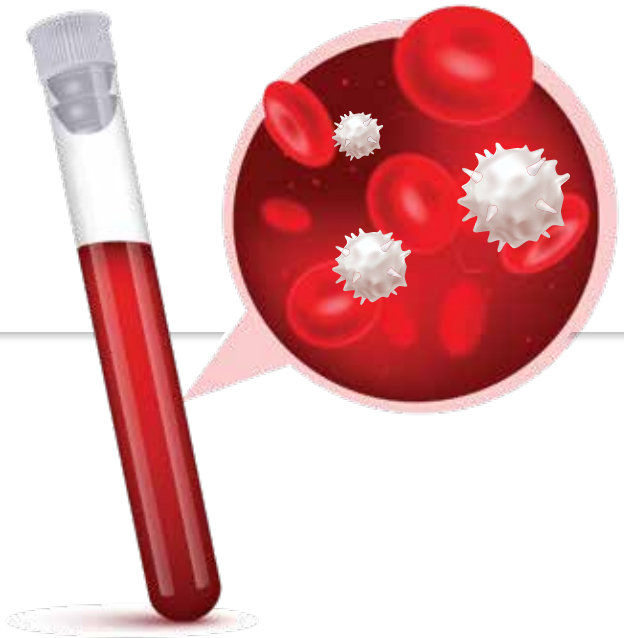
Recent Approaches to Lowering Lp(a): What the Studies Show

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).[33] In the Pro(a)LiFe-Study (Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization)[34], 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 25.6% 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.[35]



Scan to view a video on what the future holds for Lp(a).

Emerging Therapies that specifically and effectively lower Lp(a)

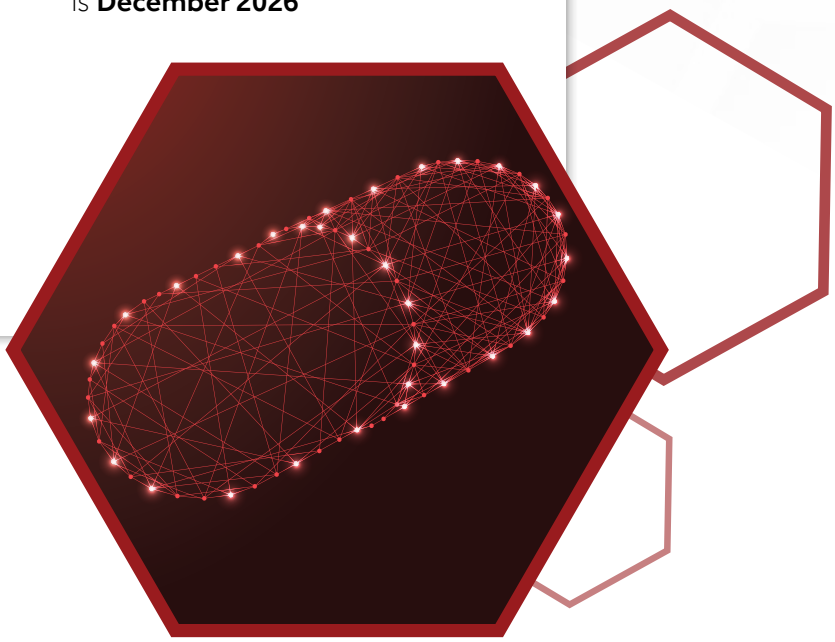
There are three compounds (pelacarsen, olpasiran and lepodisiran) that are in Phase 3 clinical trials.

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 MACE (Lp(a) ≥ 70 mg/dL or ≥ 90 mg/dL)
- Anticipated study completion date is **May 2025**

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**



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

Lepodisaran 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 (currently recruiting)) with an anticipated study completion date of **March 2029**.

Other Lp(a)-specific lowering drugs in the pipeline: There are several additional compounds that are in earlier stages of development.[36] 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 and is in Phase 2 (NCT05563246), with up to 65% Lp(a) reduction observed in Phase 1.

The Importance of Shared Decision-Making

Scan to view a video on shared decision-making.

Clinicians and patients should work in tandem to arrive at an informed treatment decision. Consider these important factors:

- Because cholesterol-lowering therapy is intended to be prescribed for a lifetime, patients should be involved in shared decision-making about treatment options to encourage better health outcomes, better health care experiences and lower costs.
- Discuss recommendations for lifestyle modifications, pharmacological treatment and therapy goals.
- Explain the patient's risk of clinical CVD and how the treatment recommendations reduce CVD risk.
- Encourage patients to verbalize values, attitudes, abilities, concerns, and personal goals for making lifestyle changes and taking medications, including concerns about cost or side effects.
- Use a guide to facilitate shared decision-making with the patient.[3] **Access to the American Heart Association's Lp(a) Discussion Guide at heart.org/lpa**

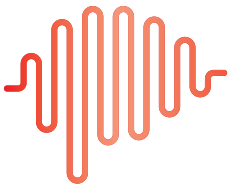
Of Note...

Evidence indicates that measuring Lp(a) may reclassify CVD risk and aid in pharmacotherapy decision-making. Repeat measurement of Lp(a) isn't recommended as the clinical value of serial measurements hasn't been established.[6]

AHA/ACC guidelines characterize Lp(a) >50 mg/dL (≥125 nmol/L) as a risk-enhancing factor, with assessment of Lp(a) indicated in women with hypercholesteremia and in people with a family history of premature CVD.[3]

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.



What part will artificial intelligence and machine learning play in risk assessment that will expedite patient diagnosis and treatment?

- Will earlier measurement of Lp(a) and effective interventions to lower it help to improve outcomes?
- Is it reasonable to recommend universal testing of Lp(a) in all individuals in early adulthood regardless of family history or health status?
- 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 and PCSK9 inhibitors?
- What role will LA 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 myriad other questions, it's encouraging that randomized, placebo-controlled, double blind cardiovascular outcomes trials of **pelacarsen**, **olpasiran** and **lepodisaran** that specifically and effectively reduce Lp(a), are ongoing and due to report between 2025 and 2029. 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.

2018 AHA/ACC Cholesterol Guidelines

Top 10 Takeaways

Currently, there is no treatment for elevated Lp(a), but clinicians can make sure their patients' LDL levels and triglycerides are well controlled according to the current guidelines.

1 **For all people, emphasize a heart-healthy lifestyle,** which reduces ASCVD risk at all ages. In younger people, a heart-healthy lifestyle can lower risk of developing factors and is the foundation of ASCVD risk reduction. In young adults 20 to 39 years of age, assessing lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

2 **In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.** The more LDL-C is reduced on statin therapy, the greater subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by ≥50%.

3 **In very-high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy.** Very high risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions. In very-high-risk ASCVD patients, it's reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices. It is reasonable to consider LA when other measures are insufficient to reach LDL threshold.

4 **In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.** If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered. However, the long-term safety (>3 years) is uncertain, and economic value is uncertain at mid-2018 list prices. It is reasonable to consider LA when other measures are insufficient to reach LDL threshold.

5 **In patients 40 to 75 years old with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.** In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years old, it's reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.

6 **In adults 40 to 75 years old evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.** Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD); the presence of risk-enhancing factors (see No. 8); the potential benefits of lifestyle and statin therapies; the potential for adverse effects and drug–drug interactions; consideration of costs of statin therapy; and patient preferences and values in shared decision-making.

7 **In adults 40 to 75 years old without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.** Risk-enhancing factors favor statin therapy (see No. 8). If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.

8 **In adults 40 to 75 years old without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiating statin therapy (see No. 7).** Risk-enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of preeclampsia or premature menopause (age <40 years); chronic inflammatory disorders (eg, rheumatoid arthritis, psoriasis or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5 to 7.5% (borderline risk).

9 **In adults 40 to 75 years old without diabetes mellitus and with LDL-C levels ≥70 mg/dL to 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring coronary artery calcium.** If CAC is zero, treatment with statin therapy may be withheld or delayed, except in persons who smoke tobacco, people with diabetes mellitus and those with a strong family history of premature ASCVD. A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years old. For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

10 **Assess adherence and percentage response to LDL-C–lowering medications and lifestyle modifications with repeat lipid measurement four to 12 weeks after statin initiation or dose adjustment, repeated every three to 12 months as needed.** Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. In very-high-risk ASCVD patients, triggers for adding non-statin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

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

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