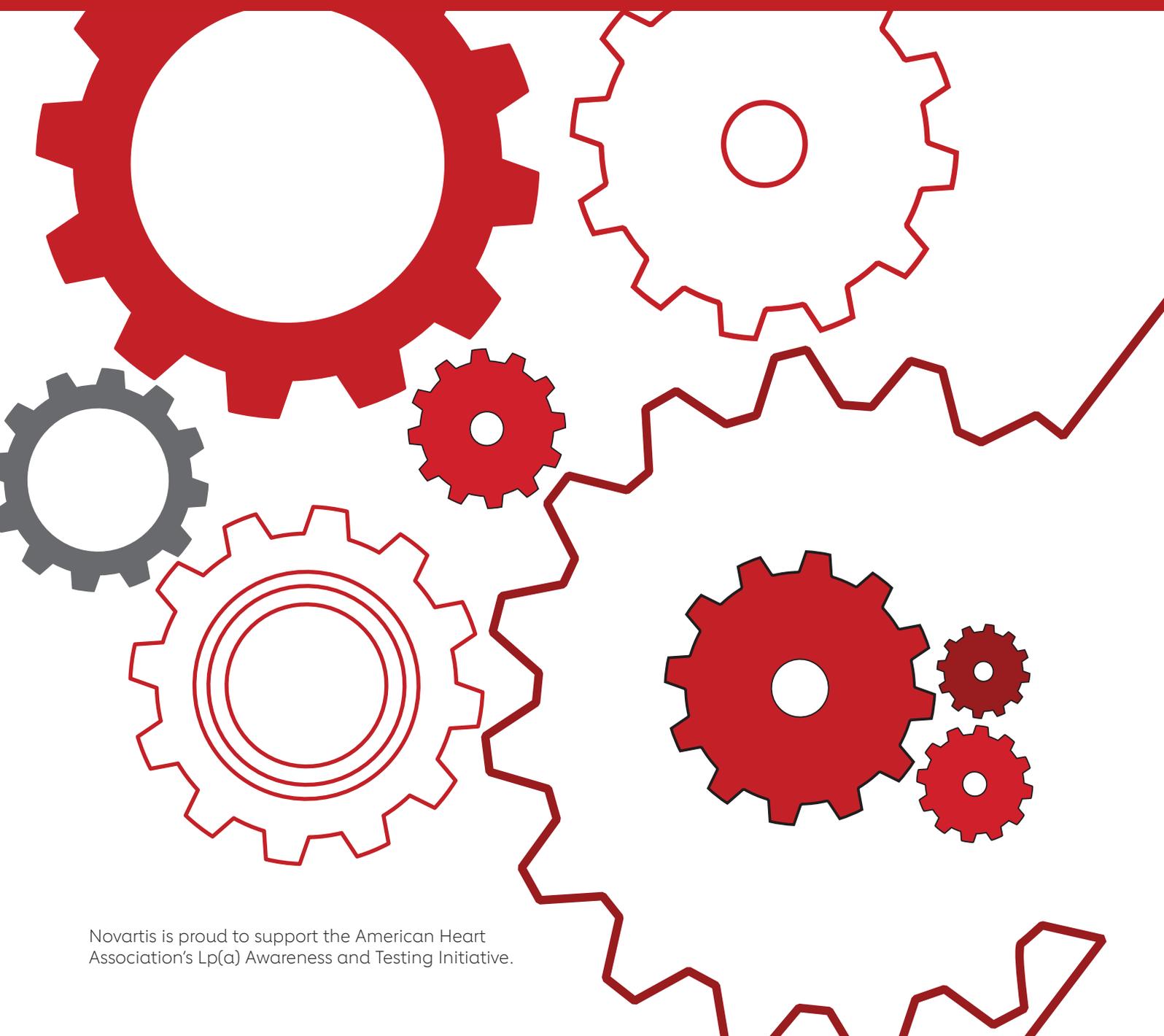




American  
Heart  
Association.

# Lp(a): A Toolkit for Health Care Professionals



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

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## Disclosures

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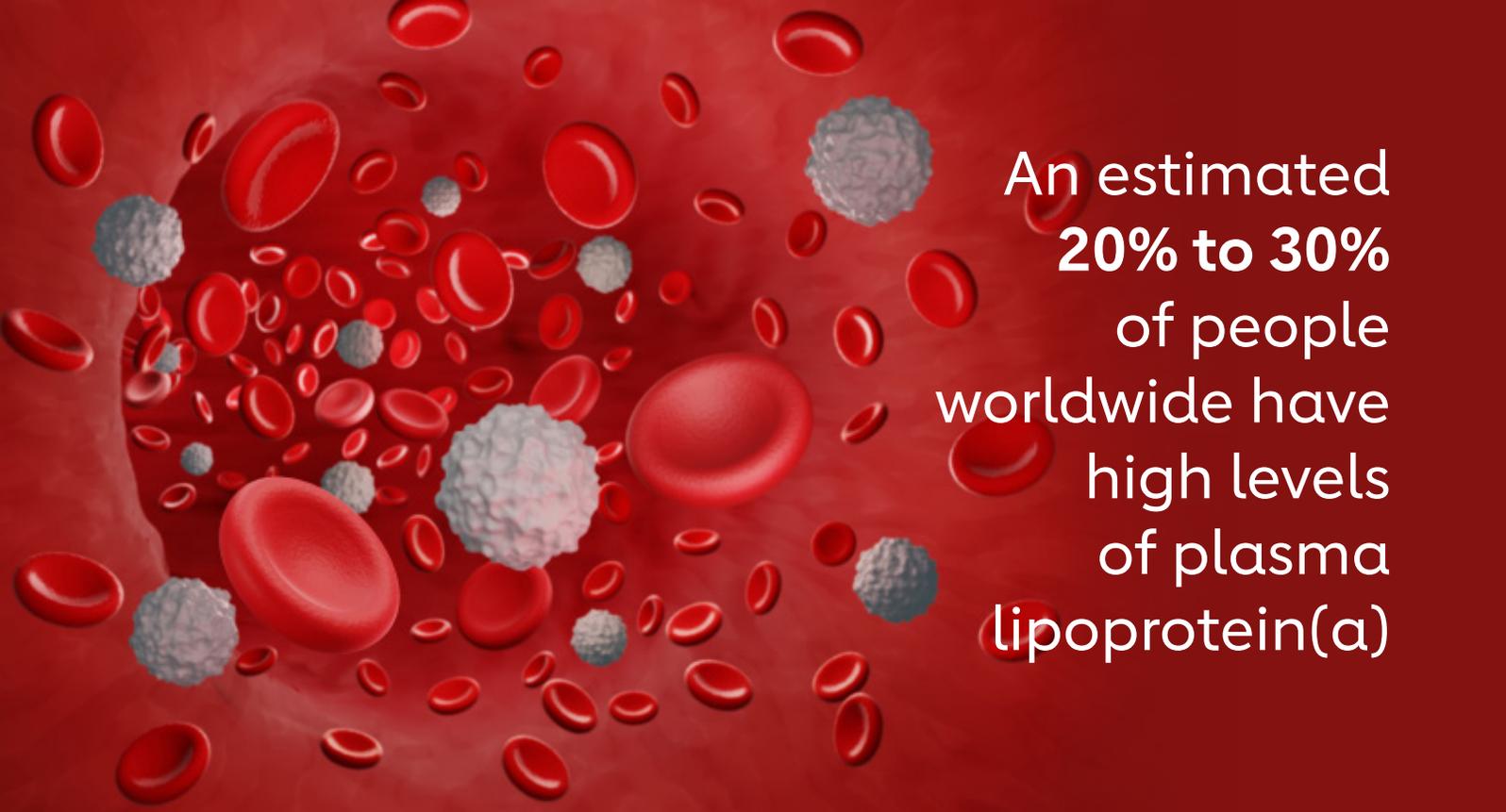
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An estimated 20% to 30% of people worldwide have high levels of plasma lipoprotein(a), which is independently associated with atherosclerotic cardiovascular disease (ASCVD) and increased risk of myocardial infarction (MI), peripheral arterial disease (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 clinical attention among clinicians compared to the **three other major classes of lipid disorders**:

- elevated low-density-lipoprotein cholesterol (LDL-C)
- low high-density-lipoprotein cholesterol (HDL-C)
- elevated triglycerides<sup>1</sup>

**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 discussion 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 ASCVD risk through cholesterol management.<sup>2</sup>

An illustration of a blood vessel with red blood cells and lipoprotein(a) particles. The red blood cells are shown as red, biconcave discs, and the lipoprotein(a) particles are shown as grey, spherical structures with a textured surface. The background is a deep red color, representing the blood.

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



**Up to 90%**  
of Lp(a) plasma  
concentration is  
determined  
by genetics<sup>4</sup>



Other factors that  
influence Lp(a)  
levels include age,  
sex, ethnicity<sup>5</sup> and  
comorbid conditions,  
such as familial  
hypercholesterolemia<sup>6</sup>  
and liver or kidney  
disease.

# Lp(a) at a Glance

- Lp(a) is independently associated with ASCVD and CAVD.
- 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.
- Although definitive data are lacking, Lp(a) likely increases cardiovascular risk through multiple mechanisms, including those attributed to its LDL-like moiety as well as the unique apo(a) protein. The latter may confer prothrombotic and additional proinflammatory effects that can cause vascular cell dysfunction.<sup>3</sup>
- Elevated Lp(a) is associated with heightened risk for myocardial infarction, peripheral arterial disease, stroke, and calcific aortic valve disease.<sup>3</sup>
- Up to 90% of Lp(a) plasma concentration is determined by genetics.<sup>4</sup>
- Other factors that influence Lp(a) levels include age, sex, ethnicity<sup>5</sup> and comorbid conditions, such as familial hypercholesterolemia<sup>6</sup> and liver or kidney disease.
- Distribution of Lp(a) levels may vary by population-specific percentiles, due to differences in the distribution of Lp(a) levels among ethnic groups.
- Despite the positive effects of diet and exercise in preventing cardiovascular disease, the two don't reduce Lp(a) levels.<sup>5</sup>
- Statins are ineffective in reducing Lp(a). To the contrary, research shows statins can modestly increase Lp(a) levels, on average, approximately 10-15%.<sup>7</sup> The mechanism is not understood and is inconsequential with respect to CAD incidence.

# How High Is Too High?

Meta-analyses have shown increased risk of myocardial infarction, peripheral arterial disease, stroke, and CAVD with Lp(a) levels above 50 mg/dL. According to AHA/ACC cholesterol guidelines, Lp(a) greater than/equal to 50 mg/dL constitutes a risk-enhancing factor.<sup>2</sup>

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

# What Causes High Lp(a) Levels?

The major cause of high Lp(a) levels is genetics.



Additional factors that can affect Lp(a) levels include:

- age
- sex
- ethnicity
- comorbid conditions, such as familial hypercholesterolemia, diabetes or kidney disease

# How Common Is It?



Elevated levels prevalent in

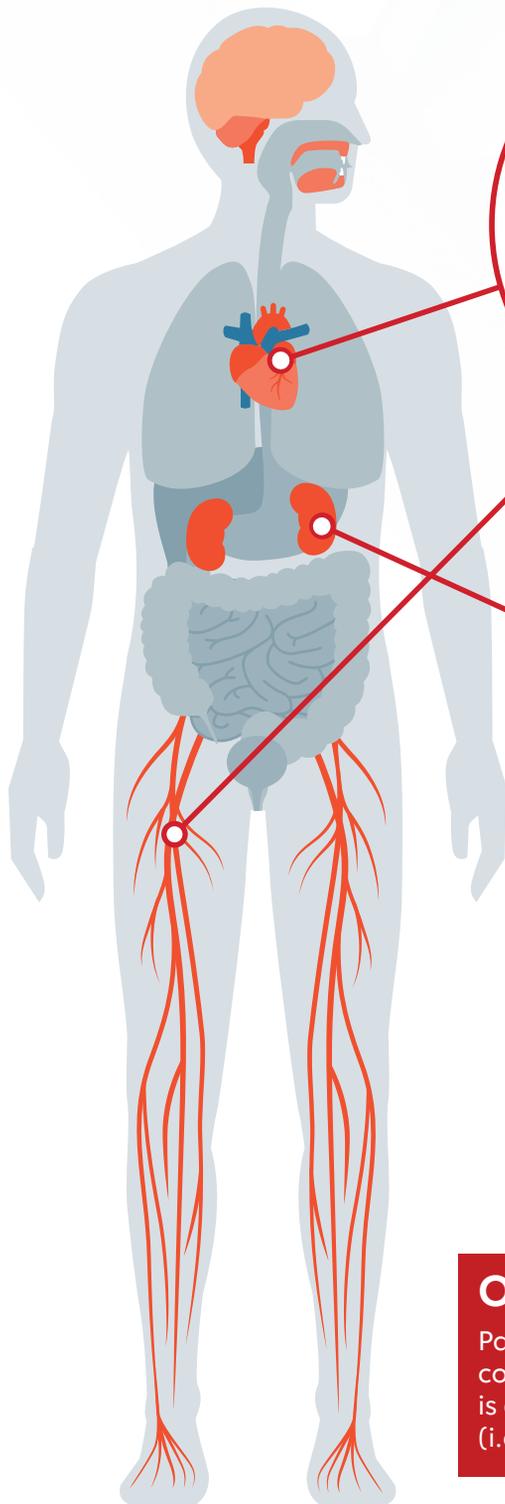
**20% to 30%**  
of the global population<sup>4</sup>

Black people have the highest Lp(a) levels, followed by South Asians, Hispanics and East Asians. American Indians have the lowest.<sup>11</sup>



Lp(a) concentration levels may vary by population-specific percentiles. This is because the distribution of Lp(a) levels differs among ethnic groups.<sup>4</sup>

# Elevated Lp(a): What Are the Risks?



Elevated Lp(a) values represent an independent risk factor for ischemic stroke and coronary heart disease, including aortic, mitral valve stenosis and peripheral arterial disease.<sup>10</sup>

Elevated Lp(a) seems to be associated with atherosclerotic renal artery stenosis in patients with low LDL-C.<sup>9</sup>

**In people with established coronary heart disease, elevated Lp(a) levels increase the risk of CHD and general cardiovascular events, particularly in those with LDL-C  $\geq$ 130 mg/dL.<sup>11</sup>**

People who have clinical ASCVD (including acute coronary syndrome; those with stable angina or a history of myocardial infarction or coronary or other arterial revascularization; stroke or transient ischemic attack; or peripheral arterial disease, including aortic aneurysm, all of atherosclerotic origin<sup>2</sup>), are at higher risk for future events if Lp(a) is elevated.

In the general population, Lp(a) levels greater than 50 mg/dL (~ 125 nmol/L) are associated with an approximately 20% increased risk of CHD events: each 3.5-fold increase in Lp(a) is associated with a 16% increase of risk of CHD events.<sup>12\*</sup>

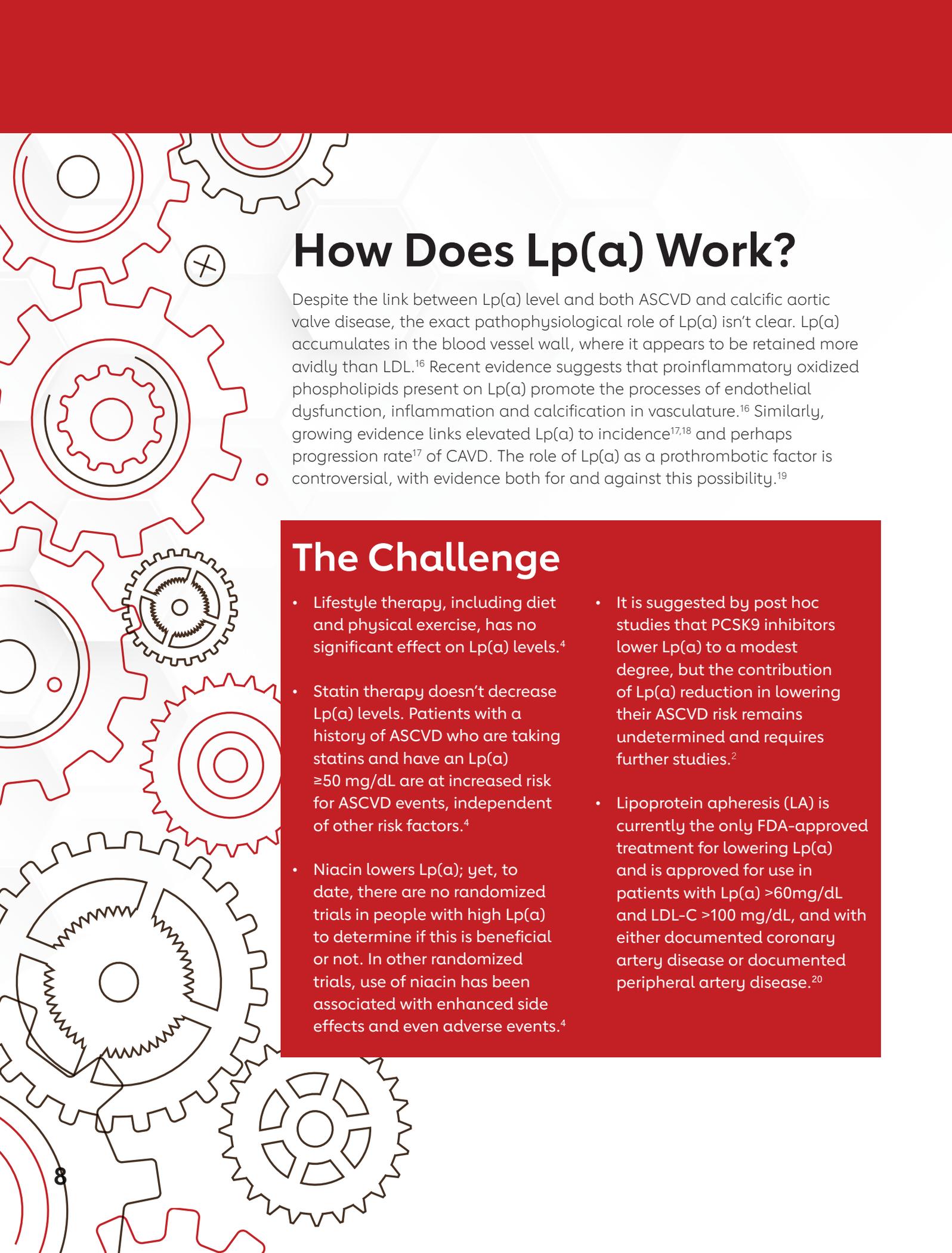
People with borderline or slightly elevated LDL-C are three to four times more likely to have ASCVD events than those with low LDL-C.<sup>13\*\*</sup> Lp(a) can pose greater risk for acute coronary syndrome when LDL-C is elevated.<sup>14</sup>

\* *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.<sup>4</sup> In particular, residual risk 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.<sup>15</sup>



# How Does Lp(a) Work?

Despite the link between Lp(a) level and both ASCVD and calcific aortic valve disease, the exact pathophysiological role of Lp(a) isn't clear. Lp(a) accumulates in the blood vessel wall, where it appears to be retained more avidly than LDL.<sup>16</sup> Recent evidence suggests that proinflammatory oxidized phospholipids present on Lp(a) promote the processes of endothelial dysfunction, inflammation and calcification in vasculature.<sup>16</sup> Similarly, growing evidence links elevated Lp(a) to incidence<sup>17,18</sup> and perhaps progression rate<sup>17</sup> of CAVD. The role of Lp(a) as a prothrombotic factor is controversial, with evidence both for and against this possibility.<sup>19</sup>

## The Challenge

- Lifestyle therapy, including diet and physical exercise, has no significant effect on Lp(a) levels.<sup>4</sup>
- Statin therapy doesn't decrease Lp(a) levels. Patients with a history of ASCVD who are taking statins and have an Lp(a)  $\geq 50$  mg/dL are at increased risk for ASCVD events, independent of other risk factors.<sup>4</sup>
- 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.<sup>4</sup>
- It is suggested by post hoc studies that PCSK9 inhibitors lower Lp(a) to a modest degree, but the contribution of Lp(a) reduction in lowering their ASCVD risk remains undetermined and requires further studies.<sup>2</sup>
- Lipoprotein apheresis (LA) is currently the only FDA-approved treatment for lowering Lp(a) and is approved for use in patients with Lp(a)  $> 60$  mg/dL and LDL-C  $> 100$  mg/dL, and with either documented coronary artery disease or documented peripheral artery disease.<sup>20</sup>

## To Screen or Not to Screen

Because the majority of Lp(a) plasma concentration (up to 90%) is influenced by genetics through the *LPA* gene,<sup>4</sup> relative indications of its measurement are:

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

Although the 2018 ACC/AHA guidelines<sup>2</sup> and the 2019 NLA statement on Lp(a)<sup>4</sup> have not recommended measurement of Lp(a) in all individuals, subsequent guidelines do contain recommendations for Lp(a) screening in all individuals at least once in a lifetime.<sup>21,22</sup>

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



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



- In statin-treated patients, high Lp(a) is associated with residual ASCVD risk.<sup>25</sup>
- In primary prevention for adults ages 40–75 with a 10-year ASCVD risk of 7.5% to 19.9%, risk-enhancing factors favor initiation of statin therapy. If measured, an Lp(a)  $\geq 50$  mg/dL or  $\geq 125$  nmol/L may be considered a risk-enhancing factor.<sup>4</sup>
- In high-risk or very-high-risk patients with LDL-C  $\geq 70$  mg/dL (non-HDL-C  $\geq 100$  mg/dL) and a Lp(a)  $\geq 50$  mg/dL or  $\geq 100$  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 ASCVD risk.<sup>4</sup>
- The presence of an elevated Lp(a) in patients with very-high-risk ASCVD and baseline LDL-C  $\geq 70$  mg/dL or non-HDL-C  $\geq 100$  mg/dL despite maximally tolerated statin and ezetimibe therapies may be used as a factor favoring a PCSK9 inhibitor.<sup>4</sup>
- Although niacin and hormone replacement therapy can reduce Lp(a) levels, these drugs are not recommended because they haven't demonstrated ASCVD benefit and may be **harmful**, according to the NLA scientific statement.<sup>4</sup>
- 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 another 30% to 49%, and high-intensity statins by  $\geq 50\%$ . 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.<sup>2</sup>

- 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.<sup>2</sup>
- Review lifestyle habits such as a heart healthy eating plan, physical activity, weight or body mass index and tobacco use. Promote a healthy lifestyle and provide relevant advice, educational materials or referrals.<sup>2</sup>  
**Access the American Heart Association's Life's Essential 8™ at [heart.org/lifes](https://heart.org/lifes)**<sup>8</sup>

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.<sup>2</sup>



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

- According to a study of Lipoprotein Apheresis (LA) by Moriarty, Gray and Gorby, LA should be considered for patients in the United States suffering from an elevated Lp(a) and progressive CVD. Moriarty and colleagues report that LA therapy has demonstrated a reduction of LDL cholesterol and Lp(a) as well as a significant reduction in future CVD events. In their study of patients with near normal LDL-C and elevated Lp(a) they report a percent reduction of 64% and 63% for LDL-C and Lp(a), respectively, with a mean LDL-C to 29 mg/dL and Lp(a) to 51 mg/dL, with a 94% reduction in major adverse cardiovascular events over a mean treatment period of 48 months.<sup>23</sup>
- In the Pro(a)LiFe-Study, Lipoprotein Apheresis for Lipoprotein(a)-Associated Cardiovascular Disease: Prospective 5 Years of Follow-Up and Apolipoprotein(a) Characterization, results confirm that LA has a lasting effect on prevention of cardiovascular events in patients with Lp(a)-hyperlipidemia. Mean Lp(a) concentration before commencing regular LA was 108.1 mg/dL. This was reduced by a single LA treatment by 68.1% on average. 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 (P<0.0001). In patients with Lp(a)-hyperlipoproteinemia, progressive CVD and maximally tolerated lipid-lowering medication, LA effectively lowered the incidence rate of cardiovascular events, but only Lp(a) concentration appeared to comprehensively reflect Lp(a)-associated cardiovascular risk.<sup>24</sup>
- PCSK9 inhibitors reduce LDL-C by 50% to 60% and also modestly lower Lp(a) by 25% to 30%.<sup>2</sup> Post-hoc analyses of the FOURIER (evolocumab) and ODYSSEY Outcome (alirocumab) trials demonstrated a greater benefit

with respect to cardiovascular events in patients with elevated baseline Lp(a).<sup>4</sup>

The 2022 EAS consensus statement on Lp(a) incorporates treatment algorithms for Lp(a) reduction.<sup>25</sup>

- 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. In the phase 2 ORION-1 study, a single dose of inclisiran 500 mg lowered LDL-C by 41.9% and Lp(a) by 18.2% at 180 days compared to baseline in this patient population. People

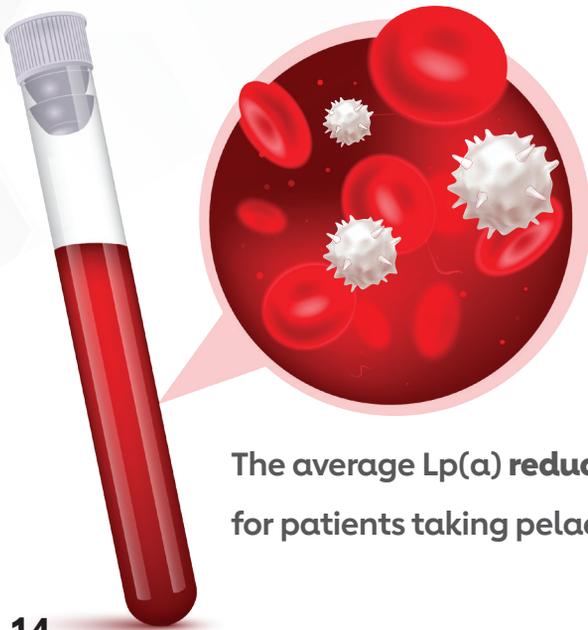
randomized to the placebo arm had LDL-C rise by 2.1% and Lp(a) by 0.5%. A two-dose regimen of inclisiran 300 mg reduced LDL-C by 52.6% and Lp(a) by 25.6% at 180 days from baseline. LDL-C rose by 1.8%, and Lp(a) was unchanged in the control group. Compared to placebo, inclisiran reduced Lp(a) by 25.6% in the ORION-10 trial evaluating inclisiran in patients with ASCVD and by 18.6% in the ORION-11 trial that enrolled people with an ASCVD equivalent.<sup>26</sup>



- Pelacarsen (formerly AKCEA-APO(a)-L<sub>RX</sub>), a second-generation ASO targeting apo(a) messenger RNA, has been evaluated in a multicenter, double-blind phase 2 study of people with established CVD and Lp(a) levels >60 mg/dL (150 nmol/L). Patients (N=286) were randomized to one of five pelacarsen groups or placebo. The primary endpoint was Lp(a) percentage change from baseline at six months. Researchers found a dose-dependent reduction in Lp(a). Compared to baseline, the lowest dose of pelacarsen (20 mg every four weeks) reduced Lp(a) by 38.4 mg/dL at six months while the highest dose (20 mg every week) lowered Lp(a) by 75.1 mg/dL at six months. The average Lp(a) reduction was 80% for patients taking pelacarsen 20 mg weekly.

At six months, 23% of the group taking the lowest dose and 98% of the highest dose of pelacarsen achieved Lp(a) concentrations ≤50 mg/dL and was also associated with reductions in LDL-C and apolipoprotein B.<sup>26</sup> Pelacarsen, is currently in phase 3 cardiovascular outcomes trials in secondary prevention patients with a baseline Lp(a)>70mg/dL. (<https://www.clinicaltrials.gov/study/NCT04023552>)

- A silencing RNA targeting apo(a) messenger RNA, olpasiran, is also in phase 3 cardiovascular outcomes trials (<https://www.clinicaltrials.gov/study/NCT05581303>) based on effective Lp(a) lowering of over 90% in early phase trials.<sup>26</sup>

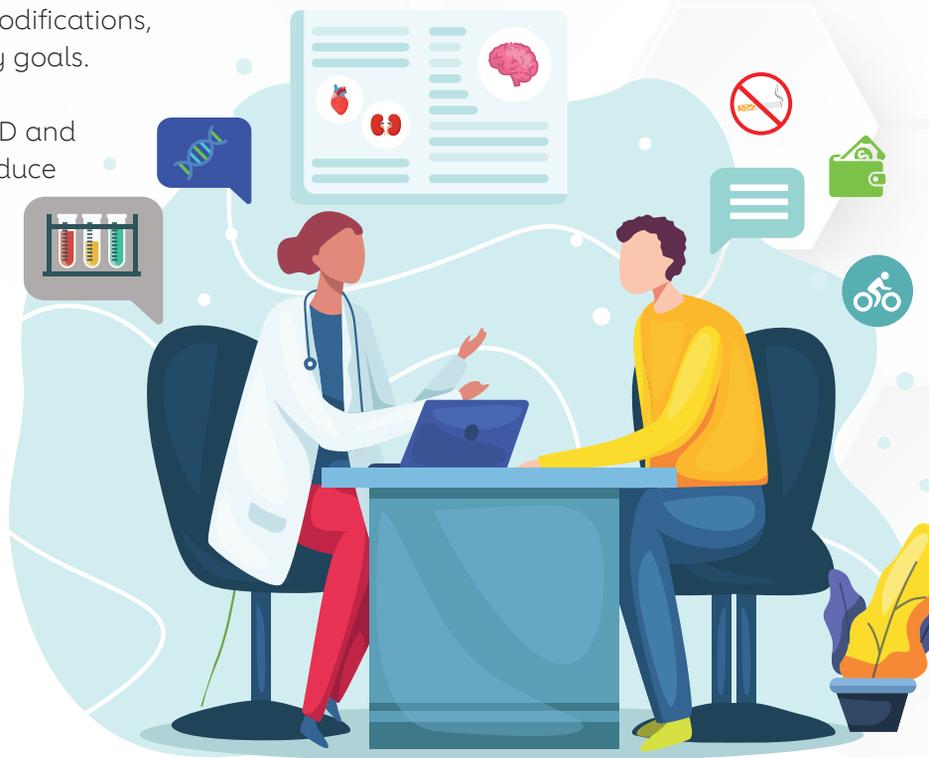


The average Lp(a) reduction was **80%** for patients taking pelacarsen 20 mg weekly.

# The Importance of 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 ASCVD and how the treatment recommendations reduce ASCVD 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.<sup>2</sup>  
**Access to the American Heart Association's Lp(a) Discussion Guide at [heart.org/lpa](https://heart.org/lpa)**



## Of Note...

Evidence indicates that measuring Lp(a) may reclassify ASCVD 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.<sup>4</sup>

AHA/ACC guidelines characterize Lp(a)  $\geq 50$  mg/dL ( $\geq 125$  nmol/L), if measured, as a risk-enhancing factor, with assessment of Lp(a) indicated in women with hypercholesterolemia and in people with a family history of premature ASCVD.<sup>2</sup>



# What Does the Future Hold?

Much is now known about Lp(a) and its role in ASCVD and CAVD. But more evidence is needed to inform future recommendations for clinical practice. For Lp(a) to be accepted as a risk factor for intervention, a randomized clinical trial of specific Lp(a) lowering in those at risk is required. Until we have the results of such a trial, several important unanswered questions remain.



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 ASCVD?
- 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 trials of **pelacarsen** and **olpasiran**, therapies that specifically reduce Lp(a), are ongoing and due to report in 2025-2026.

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 ASCVD and CAVD.

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 ethnicities. Additional data are urgently needed in individuals who are Black, South Asian and of Hispanic descent.

## 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 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 $\geq 50\%$ .

### **3** In very-high-risk ASCVD, use an LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statin 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  $\geq 70$  mg/dL ( $\geq 1.8$  mmol/L). In patients at very high risk whose LDL-C level remains  $\geq 70$  mg/dL ( $\geq 1.8$  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  $\geq 190$  mg/dL [ $\geq 4.9$  mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy. If the LDL-C level remains  $\geq 100$  mg/dL ( $\geq 2.6$  mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains  $\geq 100$  mg/dL ( $\geq 2.6$  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  $\geq 70$  mg/dL ( $\geq 1.8$  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  $\geq 50\%$ .

**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  $\geq 70$  mg/dL ( $\geq 1.8$  mmol/L), at a 10-year ASCVD risk of  $\geq 7.5\%$ , 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  $\geq 30\%$ , and if 10-year risk is  $\geq 20\%$ , reduce LDL-C levels by  $\geq 50\%$ .



**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  $\geq 160$  mg/dL ( $\geq 4.1$  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  $\geq 175$  mg/dL ( $\geq 1.97$  mmol/L); and, if measured in selected individuals, apolipoprotein B  $\geq 130$  mg/dL, high-sensitivity C-reactive protein  $\geq 2.0$  mg/L, ankle-brachial index  $< 0.9$  and lipoprotein (a)  $\geq 50$  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  $\geq 70$  mg/dL to 189 mg/dL ( $\geq 1.8$ -4.9 mmol/L), at a 10-year ASCVD risk of  $\geq 7.5\%$  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  $\geq 55$  years old. For any patient, if the CAC score is  $\geq 100$  Agatston units or  $\geq 75^{\text{th}}$  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 changes 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  $\geq 70$  mg/dL ( $\geq 1.8$  mmol/L) on maximal statin therapy (see No. 3).



Check Out Patient Education Resources at [heart.org/lpa](http://heart.org/lpa)

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