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Integrating Lipoprotein(a) Into Clinical Assessments and Encounters

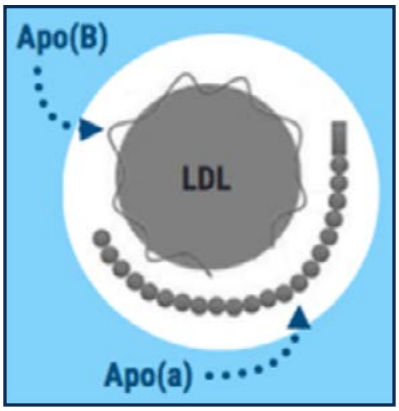
Another piece of the puzzle in assessing and managing ASCVD

When we consider dyslipidemia along with hypertension, diabetes, age, sex, race, tobacco use and other factors to gauge and lower atherosclerotic cardiovascular disease (ASCVD) risk and events, we have historically been focused on identifying and managing high low-density-lipoprotein cholesterol (LDL-C).

But a growing body of research shows that elevated levels of lipoprotein(a), also known as Lp(a), can pack a powerful punch – above and beyond traditional risk factors. High Lp(a) has been causally implicated in both ASCVD and aortic valve disease. Moreover, elevated Lp(a) is linked to a greater risk of future events among people with established ASCVD.

While Lp(a) is not universally screened for, it is becoming more widely addressed in clinical guidelines and, in turn, there will be more opportunities to discuss Lp(a) and its potential role in CVD with our patients.

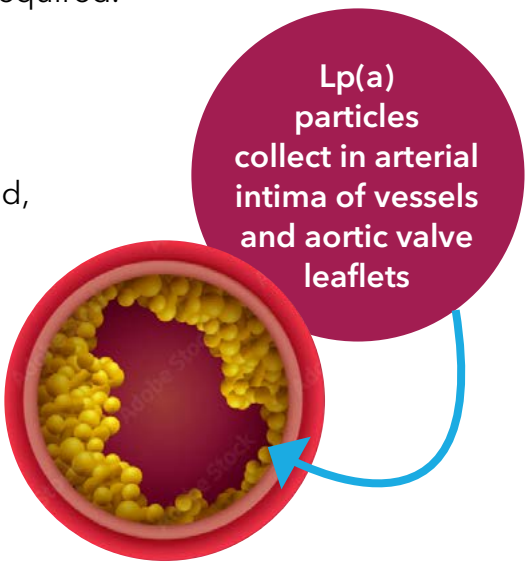
There is an urgent need to heighten awareness of Lp(a) among clinicians and patients alike. Elevated Lp(a) levels, which are largely inherited, are now recognized as an independent and robust risk factor for myocardial infarction, ischemic stroke, peripheral artery disease, and calcific aortic valve disease. Lp(a) may be useful in improving ASCVD risk stratification and risk prediction in high-risk groups, especially.



One thing that sets Lp(a) apart is its structure. Lp(a) consists of an LDL-like particle attached to apolipoprotein(a) [apo(a)] covalently bound to apolipoprotein (b). There are variable and heterogeneous Kringle repeats that then lead to different sizes of Lp(a). The large size heterogeneity poses a challenge for measurement of Lp(a) and the clinical relevance is that isoform independent assays are required.

While the exact function of Lp(a) has yet to be elucidated, Lp(a) particles have been shown to be:

- Proatherogenic
- Prothrombotic
- Proinflammatory



Its effects also promote calcified vasculature and endothelial dysfunction, and may also accelerate ASCVD and be a more potent risk factor than LDL-C.

The relevance of Lp(a) as a risk-enhancing factor is included 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. And yet Lp(a) often isn't part of clinical lipid discussions, leaving open potential missed opportunities to more comprehensively assess and reduce ASCVD risk.

By the Numbers

1 out of 5 U.S. adults have a high Lp(a) **≥50 mg/dL OR ≥125 nmol/L**

1 in 3 people with FH have elevated Lp(a)

3-fold increase in aortic stenosis with elevated Lp(a) level

Up to **90%** of Lp(a) is determined by autosomal co-dominant inheritance, but other factors may come into play

There is a need for increased awareness of and discussions about Lp(a) in clinical practice.

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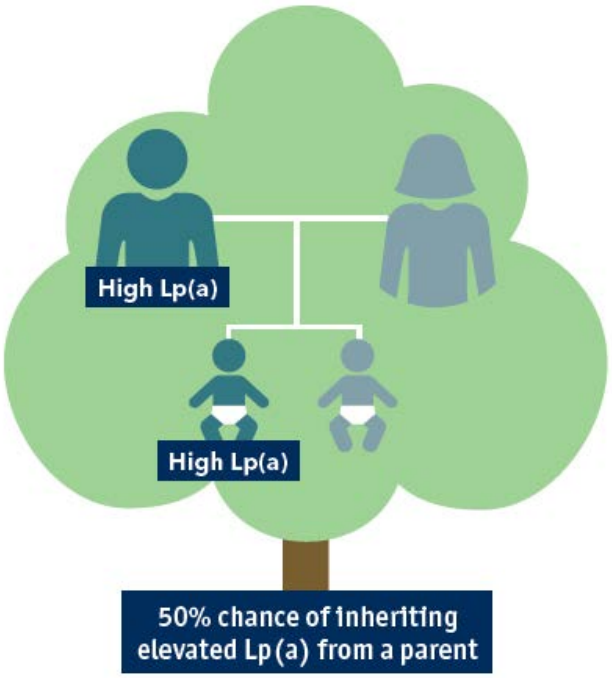
Key Highlights, Things to Know

- **Lp(a) is almost entirely genetically determined** – up to 90% of Lp(a) plasma concentration is controlled by genetics; it's one of the strongest indicators of genetic risk for ASCVD. Still, although common, the way Lp(a) manifests can be variable and individual.



Other factors that play a role:

- Age
- Sex
- People of certain racial/ethnic backgrounds – significant variations are seen in Lp(a) plasma levels across racial/ethnic groups, with the highest levels seen among those of African ancestry, though cardiovascular risk with Lp(a) is fairly consistent
- Comorbid conditions, such as familial hypercholesterolemia (FH), liver, kidney and thyroid diseases
- Certain medications, including statins, PCSK9 inhibitors, hormone replacement therapy

- **Unlike LDL-C, an individual's lifetime Lp(a) levels are usually reached by childhood and tend not to change a lot**; as research quickly accumulates, it's important to note, however, that some factors may influence Lp(a) over time.
- **High Lp(a) is harmful even in the setting of well-controlled LDL-C.**
- **Lp(a) is unaffected by environmental or lifestyle factors**, such as diet and physical activity.
- **Research is ongoing** to determine whether and to what extent novel Lp(a) lowering therapies lower ASCVD events or improve outcomes.

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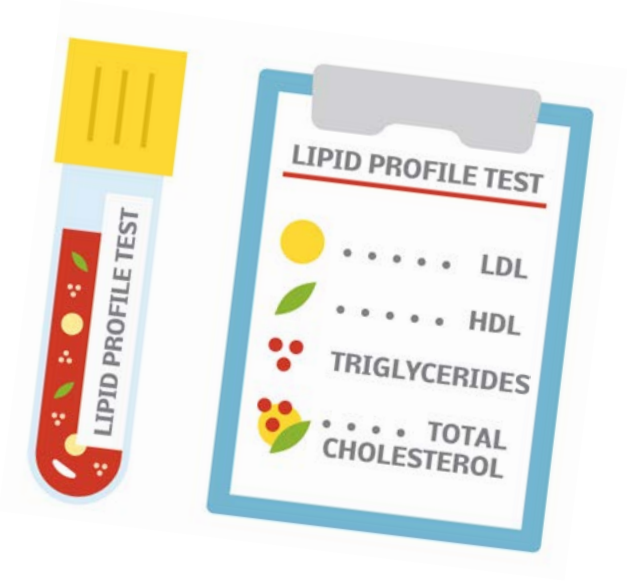
When to Screen for Lp(a)



Lp(a) is not part of standard lipid testing. And, as of now, there is no universal screening recommendation to assess Lp(a). However, **there are specific reasons when Lp(a) testing is warranted and should be discussed with patients.** For example, in individuals with:

- High LDL-cholesterol, despite talking optimal statin therapy or other cholesterol-lowering therapies
- A personal history of revascularization, peripheral artery disease, myocardial infarction, or stroke at a younger revascularization age
- LDL-C ≥ 190 mg/dL or confirmed familial hypercholesterolemia
- A first-degree relative with early onset heart disease, myocardial infarction, or stroke (before age 55 for males, and 65 for females)
- A family history of elevated Lp(a)

Black people are more likely to have higher levels of Lp(a) than other racial/ethnic groups.

Experts say it is reasonable to measure Lp(a) in most individuals with an increased risk of ASCVD and in preparation for discussions around preventive risk reduction therapy. For those without clearly established risk factors or for whom a baseline lipid panel leave open questions, shared decision-making is important to consider Lp(a) testing for comprehensive risk assessment. It's also important to take a thorough family history and ask about any personal history of premature ASCVD.

> **It is reasonable to consider adding an Lp(a) test the next time someone is having a standard lipid panel, especially if they have a suspected heightened risk of ASCVD. It can be explained to patients as another test to better understand the impact of cholesterol on their body and any genetic predisposition to cardiovascular disease.**

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Lp(a) Risk Thresholds – How High is Too High?

High Lp(a) may raise one's chance of a heart attack or stroke by 2-4 fold.

Broad consensus on Lp(a) risk thresholds is lacking. However, according to ACC/AHA guidance, an Lp(a) of **≥50 mg/dL OR ≥125 nmol/L** is considered high and should be considered an ASCVD risk-enhancing factor. As with LDL-C, higher plasma concentrations of Lp(a) confer increased ASCVD risk.

Note that Lp(a) is measured in two ways depending on the laboratory used, so care needs to be taken to accurately interpret the results and educate patients to avoid any confusion.

Serial Lp(a) Testing May Be Needed for Some Patients

In most cases, patients may only need one Lp(a) test as levels are fairly fixed by youth. However, we are learning that certain things can influence Lp(a) and may affect test results. For example, menopause, certain medications (such as estrogen supplements, hormone replacement or fertility treatments), kidney or thyroid diseases, and PCSK9 inhibitors. In these cases, repeat Lp(a) testing may be useful.

Moreover, Lp(a) increases significantly during pregnancy and can double between 10 and 35 weeks. This may be clinically relevant for those who have known baseline elevated Lp(a) levels.

Non-genetic influences that can increase Lp(a)

- Hypothyroidism
- Menopause, growth hormones
- Kidney disease or transplantation
- Pregnancy

Non-genetic influences that can lower Lp(a)

- High saturated fat diet
- Hyperthyroidism
- Hormone replacement therapy
- Liver disease

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Treating High Lp(a)

Currently, the only FDA-approved therapy to treat high Lp(a) levels is lipoprotein apheresis for patients with Lp(a) >60mg/dL + LDL-C >100 mg/dL + documented FH or coronary artery disease.

Several large cardiovascular outcome trials are now underway that are testing therapies targeting the *LPA* gene transcription rate using small interfering RNAs and gene translation with antisense oligonucleotides. Two that are looking at effect on outcomes include:

- Assessing the Impact of Lipoprotein(a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With CVD (Lp(a)HORIZON)
- Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction (OCEAN(a))

Until more targeted therapies are available, high Lp(a) levels should provide an opportunity to:

- **Drive conversations about ASCVD risk reduction and cascade Lp(a) screening for first-degree relatives** who might also benefit from a more aggressive lifestyle modification and strategies to lower LDL-cholesterol.
- **Be more aggressive about lifestyle modification strategies** – take the time to reassess a patient's lifestyle habits and offer additional support for heart-healthy eating, losing weight or smoking cessation.
- **Intensify LDL-C lowering therapies**, including adding ezetimibe and/or PCSK9 inhibitors.
- **Monitor and maximally control other CVD risk factors**, such as hypertension, diabetes, body weight, among others; talk to patients about how high Lp(a) may change other health goals and discuss how help prioritize and make a plan that is realistic and aligns with their goals.

A mixed story emerges in terms of existing cholesterol-lowering medications and Lp(a).

Statin therapy doesn't lower Lp(a) and, in fact, may raise Lp(a) slightly. However, statins for LDL-C lowering should be continued given their role in preventing heart attacks and stroke. Undetermined is the potential (favorable) effect of niacin and PCSK9 inhibitors on Lp(a).

> **We are especially concerned about preventing related heart attacks, strokes, and calcific aortic valve disease, and although we can't directly treat Lp(a) at the moment, knowing if a patient has elevated levels can drive intensified lifestyle and risk factor modification that could help prevent cardiovascular events.**

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5 Talking Points to Share With Patients About Lp(a)

As Lp(a) and the associated risks of elevated levels gains more attention, patients may ask about what it is and how it might affect their health. It's also an opportunity for ongoing conversations with patients about ASCVD risk reduction.

Here are some talking points you can use to help educate patients as appropriate.

1. **Lp(a) is a particle in your blood that carries cholesterol and fat. Similar to LDL cholesterol, often called the "bad" cholesterol, Lp(a) can attach to the walls of your arteries.** Knowing your Lp(a) can give us a more complete picture and better understanding of how likely you are to develop heart disease or have a heart attack or stroke in the future.

   You can think of Lp(a) as one more piece of the lipid (cholesterol) puzzle. High Lp(a) can serve as a red flag to step up efforts to live heart healthy and manage other factors that make heart disease, heart attack and strokes more likely – even if your cholesterol is otherwise healthy (within normal range).

2. **It's fairly common. In fact, 1 in 5 adults have high Lp(a).** Most people don't know their Lp(a) because it's not included in your usual cholesterol blood test. But a simple blood test can check your Lp(a).

3. **Your Lp(a) is mostly determined by your genes – the ones you inherit or get from your birth parents.** If your parent has high Lp(a), you have a 50/50 chance of also having elevated Lp(a). But there are additional factors that can play a role and affect Lp(a) levels. In most cases, people only need to have their Lp(s) checked once. That's because blood Lp(a) levels generally remain fairly constant over time and are often decided by the time someone is in childhood. Some people may need repeat testing.

4. Lp(a) is considered high if it is **equal to or greater than 50 mg/dL OR equal to or greater than 125 nmol/L** (different laboratories use one of these two measurements, so be sure you understand your test result). High Lp(a) can be harmful even if LDL-cholesterol is normal.

5. **Lp(a) levels aren't impacted by what you eat, how much you exercise or other lifestyle choices.** But knowing you have high Lp(a) can help to drive more intense lifestyle modification and knowing and managing other risk factors to help prevent cardiovascular events like heart attacks and strokes.

Although we can't directly treat high Lp(a) at the moment, there are clinical trials underway to test medications that can lower Lp(a) and to see if any related Lp(a) lowering can reduce heart or blood vessel disease or events.

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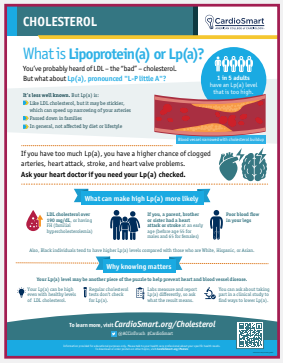
For Further Discussion

Many questions remain to be answered. Yet to be determined is:

- Whether initial successes of targeted Lp(a) lowering therapies will translate into better outcomes and reduce CV events as is being studies in randomized placebo-controlled trials.
- Gaining consensus about ongoing risk assessments to account for non-genetic influences on Lp(a) over a lifetime, as well as a standard assay for measuring Lp(a) and whether different thresholds are needed for predicting individual risk and treatment or for different race/ethnic groups based on evolving epidemiological data.
- Best approach to treatment in the setting of high Lp(a) with otherwise normal lipid levels and low ASCVD risk.
- The role of additional testing such as imaging (CAC) in individuals with elevated Lp(a).

Additional Patient Resources

For more information, visit *CardioSmart.org/Cholesterol*. You'll find tools for your patients including:



What is Lipoprotein(a) or Lp(a)? *(infographic)*

Understanding High Lipoprotein(a) *(handout)*