American Heart Association.

Lp(a): A Toolkit for Health Care Professionals

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Contents:

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

An estimated 20% to 30% of people worldwide have high levels of plasma lipoprotein(a), which are independently associated with atherosclerotic cardiovascular disease (ASCVD) and increased risk of myocardial infarction and stroke, among other conditions. Yet, elevated Lp(a) calcific aortic valve disease gets the least clinical attention among health care professionals[1] compared to the three other major classes of lipid disorders: elevated low-density-lipoprotein cholesterol (LDL-C); low high-density-lipoprotein cholesterol (HDL-C); and elevated triglycerides.[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 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 atherosclerotic cardiovascular disease risk through cholesterol management.[3]

Lp(a) at a Glance

- Lp(a) is independently associated with ASCVD.
- 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 some evidence is conflicting, Lp(a) seems to increase cardiovascular risk through multiple mechanisms, including those attributable to both 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.[4]
- Elevated Lp(a) is associated with heightened risk for myocardial infarction, ischemic stroke and enhanced peripheral artery disease.[5]
- Other factors that influence Lp(a) levels include age, sex, ethnicity[12] and comorbid conditions, such as familial hypercholesterolemia[8] 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. It's also affected by certain disease conditions.[6]
- Despite the positive effects of diet and exercise in preventing cardiovascular disease, the two don't reduce Lp(a) levels.[9]
- Statins are ineffective in reducing Lp(a). To the contrary, although not well appreciated, research shows statins can increase Lp(a) levels, on average, by approximately 10%-50%.[10]

Up to 90%

of Lp(a) plasma concentration is determined by genetics[6,7]

Other factors that influence Lp(a) levels include age, sex, ethnicity[12] **and comorbid conditions, such as familial hypercholesterolemia**[8] **and liver or kidney disease.**

How High Is Too High?

Meta-analyses have shown increased risk of coronary heart disease and myocardial infarction with Lp(a) levels above 30 mg/dL and increased risk of ischemic stroke with levels above 50 mg/dL. According to AHA/ACC cholesterol guidelines, Lp(a) ≥ 50mg/dL constitutes a risk-enhancing factor. Relative indication for its measurement is family history of premature ASCVD.[6]

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

How Common Is It?

Elevated levels prevalent in

20% to 30%

of the global population[6]

Black people have the highest Lp(a) levels

American Indians have the lowest.[11]

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
- lifestyle
- comorbid conditions, such as familial hypercholesterolemia, diabetes or kidney disease.

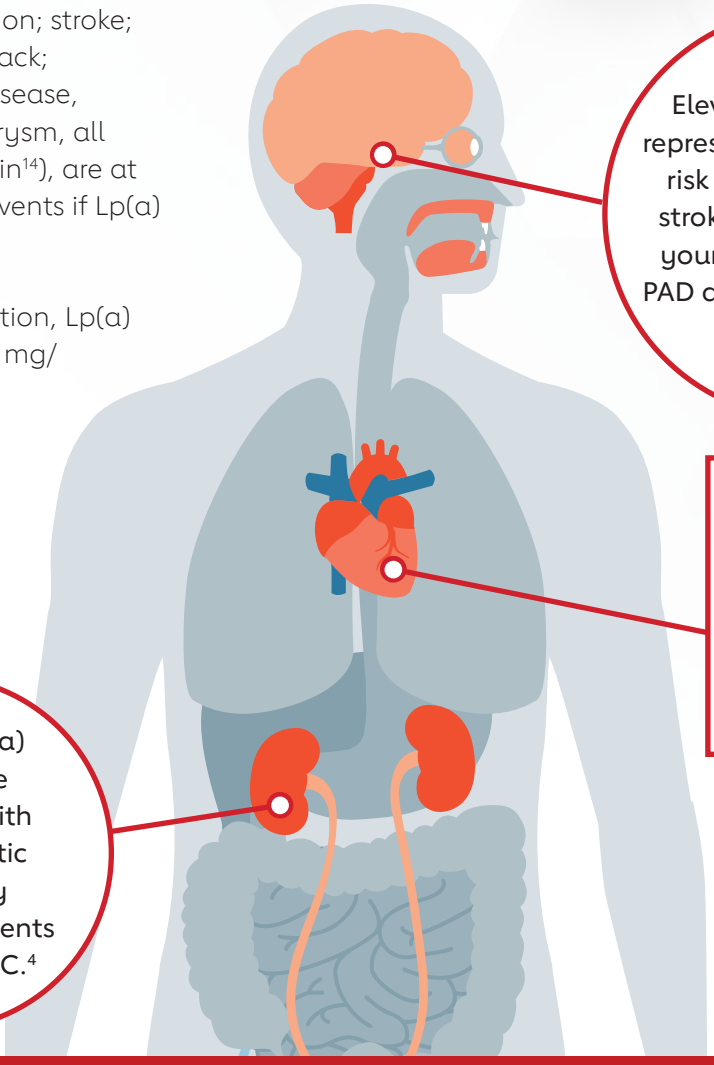
Lp(a) concentration levels may vary by population-specific percentiles. This is because the distribution of Lp(a) levels differs among ethnic groups.[6]

Elevated Lp(a): What Are the Risks?

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; transient ischemic attack; or peripheral artery disease, including aortic aneurysm, all of atherosclerotic origin[14]), 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.[15]*

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.[12]* Lp(a) can pose greater risk for acute coronary syndrome when LDL-C is elevated.[13]



Elevated Lp(a) values represent an independent risk factor for ischemic stroke (more relevant in young stroke patients), PAD and aortic and mitral valve stenosis.

In people with established CHD, elevated Lp(a) levels increase the risk of coronary heart disease and general cardiovascular events, particularly in those with LDL-C ≥ 130 mg/dL.[4,25]

Elevated Lp(a) seems to be associated with atherosclerotic renal artery stenosis in patients with low LDL-C.[4]

** 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.[16] 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.[17] Lipoprotein apheresis is currently the only FDA approved treatment (April 2020) for elevated Lp(a) in those with Functional Hypercholesterolemic Heterozygotes with LDL-C ≥ 100 mg/dl and lipoprotein(a) [Lp(a)] ≥ 60 mg/dL, and either documented coronary artery disease and/or documented peripheral artery disease.[18]

How Does Lp(a) Work?

Lp(a) is pro-inflammatory.

Despite the link between Lp(a) level and both ASCVD and calcific aortic valve disease, the exact pathophysiologic mechanism isn't clear. Recent evidence suggests that oxidized phospholipids present on Lp(a) promote endothelial dysfunction, inflammation and calcification in vasculature.[19] Lp(a) has also been detected in the blood vessel wall, where it appears to be retained more avidly than LDL.[20] Similarly, growing evidence links elevated Lp(a) to calcific aortic stenosis.[21]

The Challenge

- Lifestyle therapy, including diet and physical exercise, has no significant effect on Lp(a) levels.[6]
- Statin therapy doesn't decrease Lp(a) levels. Patients with a history of ASCVD who are taking statins and have an Lp(a) ≥50 mg/dL are at increased risk for ASCVD 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 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.
- Lipoprotein apheresis is the only FDA-approved treatment for lowering Lp(a) and can be used for those with elevated Lp(a) and recurrent ASCVD events.[6]

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,[5] relative indications of its measurement are:

- Family history of premature ASCVD (men, age <55 years; women, age <65 years) not explained by major risk factors
- A personal history of premature ASCVD not explained by major risk factors

If a decision is made to measure Lp(a), an Lp(a) ≥50 mg/dL or ≥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 ASCVD.
- 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) ≥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 ASCVD risk.[19]
- The presence of an elevated Lp(a) in patients with very-high-risk ASCVD 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 ASCVD benefit and may be harmful, according to the NLA scientific statement.[6]
- Maximize treatment of modifiable cardiovascular 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 ≥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.

- 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.[14]

- Review lifestyle habits such as diet, physical activity, weight or body mass index and tobacco use. Promote a healthy lifestyle and provide relevant advice, educational materials or referrals.[14]

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.[22]

Recent Approaches to Lowering Lp(a): What the Studies Show[14]

- According to the Lipoprotein Apheresis study by Moriarty, Gray and Gorby, lipoprotein apheresis 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.[23]

- 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. Patients clinically selected by progressive cardiovascular disease were characterized by a highly frequent expression of small apo(a) isoforms. The incidence rates of cardiovascular events 2 years before (y-2 and y-1) and prospectively 2 years during LA treatment (y+1, y+2) were compared. The mean age of patients was 51 years at the first cardiovascular event and 57 years at the first LA. Before LA, mean low-density lipoprotein cholesterol and Lp(a) were 2.56±1.04 mmol·L(-1) (99.0±40.1 mg·dL(-1)) and Lp(a) 3.74±1.63 µmol·L(-1) (104.9±45.7 mg·dL(-1)), respectively. Mean annual rates for Major Adverse Coronary Events (MACE) declined from 0.41 for 2 years before LA to 0.09 for 2 years during LA (P<0.0001 and Number Need to Treat (NNT) was 3 after 2 years. Event rates including all vascular beds declined from 0.61 to 0.16 (P<0.0001). Analysis of single

years revealed increasing major adverse coronary event rates from 0.30 to 0.54 (P=0.001) for y-2 to y-1 before LA, decline to 0.14 from y-1 to y+1 (P<0.0001) and to 0.05 from y+1 to y+2 (P=0.014). In patients with Lp(a)-hyperlipoproteinemia, progressive cardiovascular disease 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.[24]

- PCSK9 inhibitors reduce LDL-C by 43% to 64% and also lower Lp(a) by 20% to 30%. Post-hoc analyses of the FOURIER (evolocumab) and ODYSSEY Outcome (alirocumab) trials demonstrated that independent of LDL-C reduction, evolocumab reduced risk of major adverse cardiovascular events (MACE) by 16%, and alirocumab lowered MACE risk by 0.6% for each 1 mg/dL improvement in Lp(a) levels. Neither the AHA/ACC nor

ESC/EAS guidelines incorporate treatment algorithms for Lp(a) reduction. However, clinicians should be apprised of PCSK9 inhibitors' effect on serum Lp(a).

- Inclisiran, a small interfering RNA molecule that targets PCSK9 messenger RNA, has been evaluated in people with high risk for cardiovascular disease 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 people with ASCVD and by 18.6% in the ORION-11 trial that enrolled people with an ASCVD equivalent.

- AKCEA-APO(a)-LRX (APO(a)-L_{RX}), a second-generation ASO targeting messenger RNA of the LPA gene, 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 APO(a)-L_{RX} 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 APO(a)-L_{RX} (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 of APO(a)-L_{RX} 20 mg weekly. At six months, 23% of the group taking the lowest dose and 98% of the highest dose of APO(a)-L_{RX} achieved Lp(a) concentrations ≤50 mg/dL. APO(a)-L_{RX} was also associated with reductions in LDL-C and apolipoprotein B.

The average Lp(a) reduction was 80% for patients taking APO(a)-LRX 20 mg weekly.

The Importance of Shared Decision-Making

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

- Because cholesterol-lowering therapy is for a lifetime, involve patients in decision-making 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 your patient 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 checklist to facilitate shared decision-making with the patient.[14]

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.[6]

AHA/ACC guidelines characterize Lp(a) >50 mg/dL (≥125 nmol/L), if measured, as a risk-enhancing factor, with assessment of Lp(a) indicated in women with hypercholesteremia and in people with a family history of premature ASCVD.[14]

What Does the Future Hold?

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

Much is now known about Lp(a) and its role in ASCVD and aortic valve disease. 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:

- Is it reasonable to recommend universal testing of Lp(a) in everyone, regardless of family history or health status, to encourage healthy habits and inform clinical decision-making?
- Will earlier testing and effective interventions help to improve outcomes?
- 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 Lipoprotein apheresis continue to play in reduction of LDL and Lp(a) in people with FH and anginal symptoms?
- What part will artificial intelligence and machine learning play in risk assessment that will expedite patient diagnosis and treatment? AI has the potential to address disparities in medical resources and expedite patient diagnosis and treatment.[4] It may also improve cardiovascular disease risk prediction and facilitate personalized medicine.[16]

To answer these and a myriad other questions, it's encouraging that a randomized, placebo-controlled, double blind trial of Lp(a) reduction-Lp(a) Horizon, using antisense oligonucleotides to block the production of Lp(a), is currently being conducted worldwide and results of outcome studies may be available in 2024.

Pharmaceutical companies are developing other promising Lp(a)-lowering therapies such as small interfering RNA inhibitor technology. If these early studies continue to show safety and efficacy, it's likely that more randomized trials will be conducted with the aim to reduce ASCVD and possibly AVS progression through novel targeted Lp(a) reduction.

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 AVS.

Finally, we need to address the knowledge gaps for unique populations, 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 people who are Black, South Asian or of Hispanic descent. The AHA/ACC guidelines are designed to stimulate a thoughtful, global discussion that will result in improved health and outcomes for those entrusted to our care.[6]

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 ≥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 lipoprotein apheresis 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 lipoprotein apheresis 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 cigarette smokers, 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 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 ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

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