posterior heel pain and stiffness that improves with rest. On examination, there is usually tenderness of the Achilles tendon approximately 2 to 6 cm above the calcaneal insertion. Treatment includes activity modification, eccentric exercises (muscle lengthening in response to external resistance), and use of appropriate footwear. NSAIDs can be used for pain control.

Achilles tendon rupture commonly occurs during strenuous activities, although it may occur spontaneously in the elderly or rarely with fluoroquinolone use. Patients usually have heel pain and may report hearing a "pop." On examination, a tendon defect may be palpable; a lack of plantar flexion with calf squeezing suggests complete rupture (sensitivity, 93%; specificity, 96%) (**Figure 21**). Treatment is controversial and consists of surgery with immobilization or immobilization alone.

Plantar fasciitis classically causes sharp, medial-inferior heel pain with the first morning steps and after prolonged rest. Pain usually improves with further walking but may persist in severe cases. On examination, the medial calcaneal tubercle is frequently tender. Passive toe dorsiflexion with standing may reproduce pain (sensitivity, 32%; specificity, 100%). Treatment includes weight loss, rest, calf/heel stretching, and arch supports (if pes planus is present). NSAIDs may be helpful for pain control. Patients should be counseled that resolution can be expected but may take months. For recalcitrant cases, ultrasonography, extracorporeal shockwave therapy, night splints, and glucocorticoid injections can be considered. Surgery is reserved for patients who do not respond to these measures.

Midfoot Pain

Tarsal tunnel syndrome (posterior tibial nerve compression as it passes through the tarsal tunnel) causes posteromedial heel paresthesia that radiates distally into the plantar foot surface. On examination, pain may be reproduced with nerve tapping and with provocative measures that compress the nerve (plantar flexion-inversion and dorsiflexion-eversion tests). First-line treatment consists of activity modification, orthotics, NSAIDs, and neuromodulators.

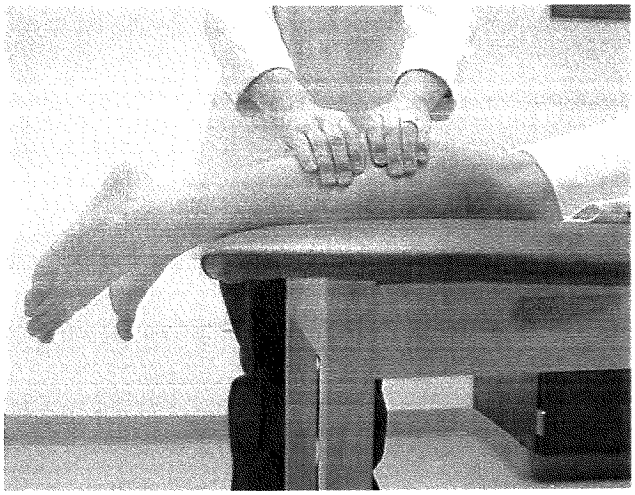

FIGURE 21. Thompson test. The patient is positioned in the prone position. The examiner squeezes mid-calf and observes for plantar flexion of the foot. When the patient has an intact Achilles tendon, plantar flexion will occur. When there is a complete Achilles tendon rupture, no plantar flexion is observed.

Reproduced with permission from Davis MF, Davis PF, Ross DS. Expert Guide to Sports Medicine. Philadelphia, PA: American College of Physicians; 2005:401. ©2005, American College of Physicians.

Forefoot Pain

Morton neuroma (interdigital nerve injury) causes pain between the metatarsal heads and the sensation of walking on a pebble. First-line therapy consists of footwear modification and padding. Glucocorticoid injections may provide temporary relief. Interdigital nerve resection is reserved for those who do not respond to conservative measures.

Hammertoe deformities (proximal interphalangeal joint flexion deformity with distal interphalangeal joint extension and extended or neutral position of the metatarsophalangeal joint) occur with constricting footwear and increasing age. Treatment includes footwear modification, padding, and possibly surgery.

Hallux or bunion deformity (lateral deviation of great toe with medial bony deformity of uncertain etiology) can lead to pain, osteoarthritis of the first metatarsophalangeal joint, and overlying bursitis. Treatment includes orthotic devices, NSAIDs, and possibly surgery.

KEY POINTS

- Treatment of acute ankle sprain includes intermittent cryotherapy, a lace-up support or air stirrup brace combined with elastic compression wrapping, early mobilization with weight bearing as tolerated, and acetaminophen and oral or topical NSAIDs.
- Stress fracture most commonly occurs in the metatarsals, tarsals, and calcaneus and is suggested by pain with percussion or pain with hopping on a single leg; radiography is first-line diagnostic testing but may fail to reveal a fracture line.
- Plantar fasciitis classically causes sharp, medial-inferior heel pain with the first morning steps and after prolonged rest; the medial calcaneal tubercle is frequently tender.

Dyslipidemia

Evaluation of Lipid Levels

Major guidelines differ in their recommendations regarding when to initiate screening for lipid disease in adults. The U.S. Preventive Services Task Force (USPSTF) recommends universal lipid screening in adults aged 40 to 75 years to calculate risk for atherosclerotic cardiovascular disease (ASCVD) using the American Heart Association (AHA)/American College of Cardiology (ACC) Pooled Cohort Equations (https://tools.acc.org/ASCVD-Risk-Estimator-Plus). The 2018 AHA/ACC Guideline

on the Management of Blood Cholesterol assigns a high priority to the estimation of lifetime ASCVD risk in children, adolescents, and young adults and promotion of lifestyle risk reduction across the age spectrum.

Lipid measurement also may be indicated to investigate for familial hypercholesterolemia; to determine adherence to and effectiveness of therapy; and to evaluate for dyslipidemia in the presence of potential complications, such as pancreatitis.

LDL Cholesterol

The association between high LDL cholesterol levels and increased risk for ASCVD is widely accepted. Historically, cholesterol treatment targeted specific LDL cholesterol goals because LDL cholesterol is the most atherogenic lipoprotein. The AHA/ACC cholesterol management guideline, however, recommends initiation of fixed-dose statin therapy in patients with ASCVD regardless of LDL cholesterol level, with subsequent lipid monitoring. The primary utility of LDL cholesterol measurement is therefore to identify patients without known ASCVD who will benefit from treatment with statin therapy and to assess response to therapy.

In patients with elevated LDL cholesterol levels, secondary causes, including hypothyroidism, poorly controlled diabetes mellitus, nephrotic syndrome, and medications (e.g., glucocorticoids, diuretics, amiodarone), should be considered. In patients without a secondary cause, genetic testing for familial hypercholesterolemia is appropriate in patients with an LDL cholesterol level of 250 mg/dL or higher (≥6.47 mmol/L) and in those who have an LDL cholesterol level of 190 mg/dL or higher (≥4.92 mmol/L) as well as a first-degree relative with a similar LDL cholesterol elevation or premature coronary artery disease.

Triglycerides

Elevated triglyceride levels (>150 mg/dL [1.69 mmol/L]) are independently associated with increased ASCVD risk; however, it is uncertain whether reducing triglyceride levels decreases risk. Causes of hypertriglyceridemia include diabetes; excessive alcohol intake; hypothyroidism; and medications, such as glucocorticoids, protease inhibitors, and estrogens. Lifestyle factors, including obesity and concentrated sugar intake, are also implicated. Patients with triglyceride levels of 500 mg/dL or higher (≥5.65 mmol/L) without an identifiable cause should be evaluated for familial hypertriglyceridemia.

Acute pancreatitis can be induced by triglyceride levels greater than 500 to 1000 mg/dL (>5.6-11.3 mmol/L). Triglyceride levels should be measured in selected patients with pancreatitis, especially in cases of pancreatitis without a clear cause (such as alcohol use or biliary disease).

HDL Cholesterol

HDL cholesterol is a protective factor against the development of ASCVD and is an important component in assessment of ASCVD risk. However, a causative link between low HDL cholesterol levels and ASCVD has not been established. Pharmacologic treatment to raise HDL cholesterol levels is not recommended.

KEY POINTS

- The U.S. Preventive Services Task Force recommends universal lipid screening in adults aged 40 to 75 years to calculate risk for atherosclerotic cardiovascular disease.
- The primary utility of LDL cholesterol measurement is to identify patients who will benefit from treatment with statin therapy and to assess response to therapy.

Management of Dyslipidemias

Treatment with therapeutic lifestyle changes and pharmacologic therapy may be indicated after assessment of ASCVD risk.

Therapeutic Lifestyle Changes

All patients at increased cardiovascular risk should be counseled regarding therapeutic lifestyle changes, including dietary modification, regular physical activity, weight loss, and smoking cessation.

Patients should be encouraged to adhere to a diet that focuses on consumption of fruits, vegetables, fiber, and monounsaturated fats and minimizes intake of saturated and *trans* fats, simple carbohydrates, and red meats. Examples of heart-healthy diets include the DASH (Dietary Approaches to Stop Hypertension) and Mediterranean diets. The AHA/ACC additionally recommend reducing the percentage of calories from saturated fat (<7% of calories from saturated fat; <6% of calories from saturated fat in patients at high cardiovascular risk) and the percentage of calories from *trans* fats. Replacing saturated fats with polyunsaturated fats has been shown to reduce LDL cholesterol levels and cardiovascular mortality. To facilitate these changes, clinicians should provide patients with educational resources and, when appropriate, refer them to a dietitian. Behavioral support programs may increase adherence to appropriate diets, and referral should be considered.

The AHA/ACC also recommends that patients, including those with chronic medical conditions, engage in moderate to vigorous physical activity for a minimum of 150 min/wk. Adults should perform muscle-strengthening exercises two to three times per week as well.

KEY POINT

- All patients at increased cardiovascular risk should be counseled regarding therapeutic lifestyle changes, including dietary modification, regular physical activity, weight loss, and smoking cessation. **HVC**

Pharmacologic Therapy

Statins are the mainstay of pharmacologic therapy for dyslipidemia and the primary and secondary prevention of ASCVD. Statin dosages for high- and moderate-intensity therapy are presented in **Table 40**.

TABLE 40. High- and Moderate-Intensity Statin Therapy

Therapy Intensity	Drug and Dosage
High intensity	Atorvastatin, 40-80 mg/d
	Rosuvastatin, 20-40 mg/d
Moderate intensity	Atorvastatin, 10 mg/d
	Rosuvastatin, 10 mg/d
	Simvastatin, 20-40 mg/d
	Pravastatin, 40 mg/d
	Lovastatin, 40 mg/d
	Fluvastatin, 40 mg twice daily

Effective adjunctive LDL cholesterol-lowering drugs include ezetimibe, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (**Table 41**). Fibrates and niacin are not recommended as adjuncts to statin therapy to reduce LDL cholesterol levels.

Primary Prevention of Atherosclerotic Cardiovascular Disease

The AHA/ACC recommendations for primary prevention of ASCVD are summarized in **Figure 22**. Regardless of risk category, physicians should engage all patients in a discussion that considers risk factors, healthy lifestyle, benefits and risks of drug therapy, and patient preferences.

Adults aged 40 to 75 years without diabetes and with an LDL cholesterol level of 70 mg/dL to 189 mg/dL (1.81-4.90 mmol/L) should undergo risk assessment for the primary prevention of ASCVD using the Pooled Cohort Equations. The 10-year risk for ASCVD can be categorized as high (≥20%), intermediate (≥7.5% to <20%), borderline (5% to <7.5%), or low (<5%). In adults aged 40 to 75 years at high risk for ASCVD, high-intensity statin therapy should be initiated to reduce the LDL cholesterol level by 50% or more. The AHA/ACC cholesterol management guideline identifies two other major categories of higher-risk patients that benefit from primary prevention statin therapy without calculating the 10-year ASCVD risk. Adults of any age with an LDL cholesterol level of 190 mg/dL or higher (≥4.92 mmol/L) should be started on high-intensity statin therapy, and adults aged 40 to 75 years with diabetes should be started on moderate-intensity statin therapy. In patients with diabetes and additional ASCVD risk factors, the 10-year ASCVD risk can be calculated to determine whether high-intensity statin therapy is indicated.

In adults at intermediate risk according to the Pooled Cohort Equations, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy (**Table 42**). When the decision about initiating statin therapy remains uncertain, it is reasonable to obtain a coronary artery calcium (CAC) score to guide therapeutic decisions (see MKSAP 19 Cardiovascular Medicine). If the CAC score is 0, it is appropriate to withhold statin therapy and reassess in 5 to 10 years as long as higher-risk conditions (e.g., family history of premature ASCVD, cigarette smoking) are absent. If the CAC score is 1 to 99, it is reasonable to initiate statin therapy for most patients aged 55 years or older. In patients with a CAC score of 100 or higher or at the 75th percentile or higher, it is reasonable to initiate statin therapy regardless of age. Patients at borderline or low risk generally do not require statin therapy, but therapy can be discussed with patients at borderline risk when additional risk-enhancing factors are present.

Nonstatin drugs to lower LDL cholesterol should be considered alone or in combination with statins in patients who do not achieve adequate LDL cholesterol reduction with statin therapy or cannot tolerate statins, especially high-risk patients. Before nonstatin drugs are initiated, patient preferences as

TABLE 41. Characteristics of Lipid-Lowering Nonstatin Drugs

Medication	LDL Cholesterol Lowering	ASCVD Risk Reduction	Adverse Effects	Approximate Cost
PCSK9 inhibitors	↓↓↓↓	↓↓↓	Nasopharyngitis, injection-site reactions, possible cognitive effects	$$$$
Ezetimibe	↓↓	↓↓↓	Diarrhea, arthralgia, abdominal pain, myositis, elevated liver aminotransferase levels when combined with statins	$$-$$$
Bile acid sequestrants	↓↓	↓ (cholestyramine)	Constipation, bloating, nausea, elevated liver aminotransferase levels, interference with drug absorption	$$
			Increased triglyceride levels only if baseline levels are elevated	
Fibrates	↓	Not well determined	Myositis (especially if combined with statins), nausea, abdominal pain	$$
Phytosterols	↓	Not well determined	Mild bloating; diarrhea or constipation	$-$$
Icosapent ethyl	–	↓↓	Pneumonia, atrial fibrillation	$$

ASCVD = atherosclerotic cardiovascular disease; PCSK9 = proprotein convertase subtilisin/kexin type 9.

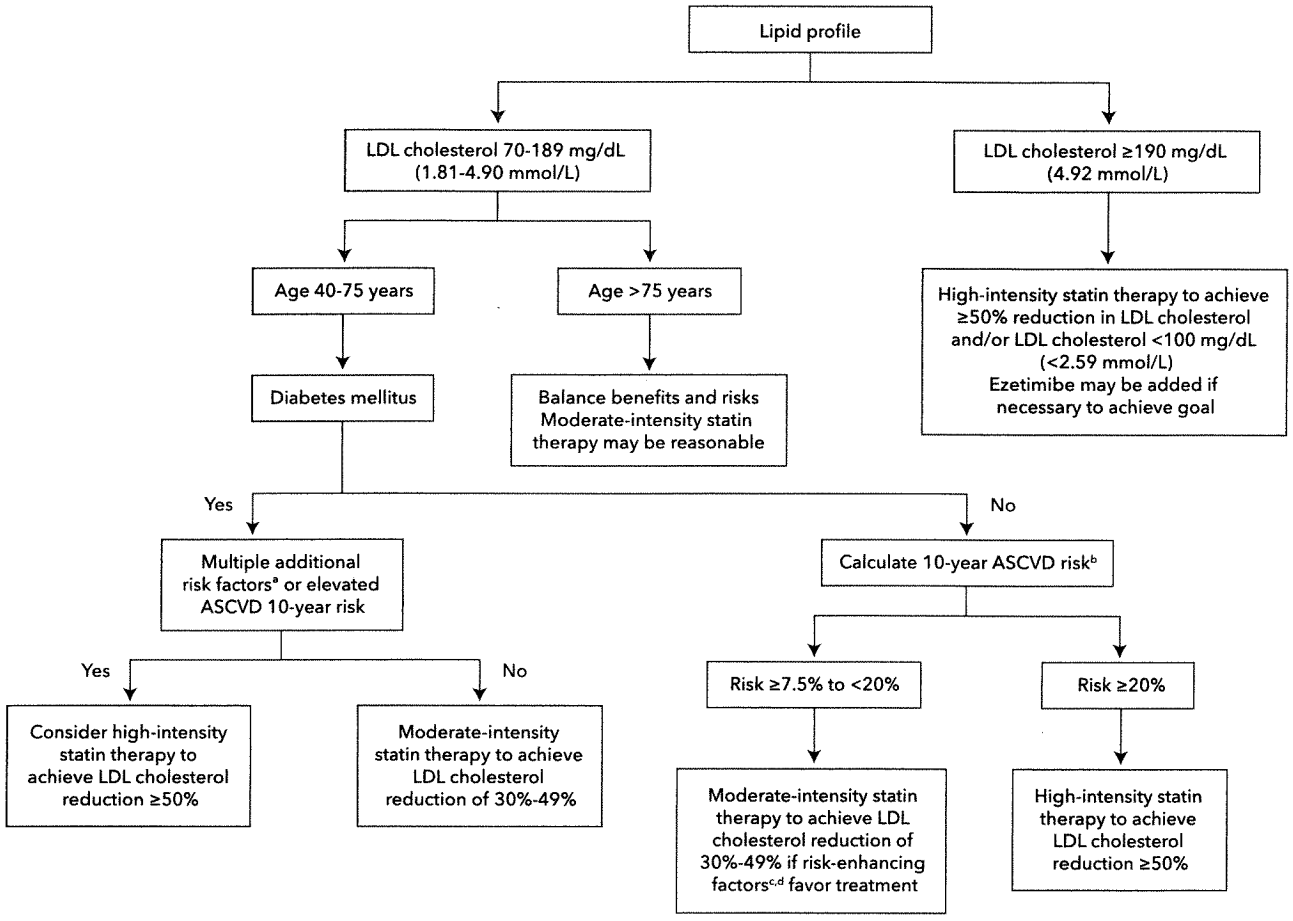

FIGURE 22. Recommendations for statin therapy in the primary prevention of ASCVD. ASCVD = atherosclerotic cardiovascular disease.

[a]Additional risk factors include long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus), albuminuria (30 mg of albumin/g creatinine), estimated glomerular filtration rate less than 60 mL/min/1.73 m^2, retinopathy, neuropathy, and ankle-brachial index less than 0.9.

[b]Risk for fatal and nonfatal myocardial infarction or stroke. An ASCVD risk calculator is available at http://tools.acc.org/ASCVD-Risk-Estimator-Plus?#!/calculate/estimate/.

[c]See Table 42 for a list of ASCVD risk-enhancing factors.

[d]If the decision about initiating statin therapy remains uncertain, it is reasonable to obtain a coronary artery calcium score to guide therapeutic decisions.

Recommendations from Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082-43. [PMID:.30586774] doi:10.1161/CIR.0000000000000625

well as anticipated ASCVD risk reduction and adverse effects should be discussed. Ezetimibe can be used for primary prevention of ASCVD in patients with an initial LDL cholesterol level of 190 mg/dL or higher (≥4.92 mmol/L) who do not achieve a 50% reduction in LDL cholesterol while taking maximally tolerated statin therapy or who have an LDL cholesterol level of 100 mg/dL or higher (≥2.59 mmol/L).

The USPSTF recommendations for primary prevention statin therapy differ from those of the AHA/ACC. In asymptomatic adults aged 40 to 75 years without ASCVD who have at least one ASCVD risk factor (dyslipidemia, diabetes, hypertension, or smoking), the USPSTF recommends low- to moderate-intensity statin therapy in those with a calculated 10-year ASCVD event risk of 10% or higher (grade B recommendation) and selective consideration of low- to moderate-intensity statin therapy in those with a calculated 10-year ASCVD event risk of 7.5% to 10% (grade C recommendation).

The U.S. Department of Veterans Affairs and U.S. Department of Defense, in their 2020 joint clinical practice guideline on managing dyslipidemia to reduce cardiovascular disease risk, recommend moderate-intensity statin therapy for primary prevention in patients with a 10-year cardiovascular risk of 12% or higher, an LDL cholesterol level of 190 mg/dL or higher (≥4.92 mmol/L), or diabetes. A summary of the guideline recommendations is provided in **Table 43**.

Secondary Prevention of Atherosclerotic Cardiovascular Disease

Patients eligible for secondary prevention therapy include those with acute coronary syndrome (ACS); history of myocardial infarction (MI); stable or unstable angina; coronary or other arterial revascularization; stroke; transient ischemic attack; or peripheral artery disease, including aortic aneurysm. According to AHA/ACC guidelines, high-intensity statin

TABLE 42. Risk-Enhancing Factors for Clinician-Patient Risk Discussion

Family history of premature ASCVD (males, age <55 y; females, age <65 y)

Primary hypercholesterolemia (LDL cholesterol 160-189 mg/dL [4.14-4.90 mmol/L]; non-HDL cholesterol 190-219 mg/dL [4.92-5.67 mmol/L])[a]

Metabolic syndrome (increased waist circumference, elevated triglycerides [>150 mg/dL {1.69 mmol/L}], elevated blood pressure, elevated glucose, and low HDL cholesterol [<40 mg/dL {1.04 mmol/L} in men; <50 mg/dL {1.29 mmol/L} in women] are factors; tally of three makes the diagnosis)

Chronic kidney disease (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)

Chronic inflammatory conditions, such as psoriasis, RA, or HIV/AIDS

History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia

High-risk race/ethnicities (e.g., South Asian ancestry)

Lipid/biomarkers: Associated with increased ASCVD risk

Persistently[a] elevated, primary hypertriglyceridemia (≥175 mg/dL [1.98 mmol/L])

If measured:

1. Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
2. Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL (0.50 g/L) or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)
3. Elevated apoB ≥130 mg/dL (1.3 g/L): A relative indication for its measurement would be triglycerides ≥200 mg/dL (2.26 mmol/L). A level ≥130 mg/dL (1.3 g/L) corresponds to an LDL cholesterol >160 mg/dL (4.14 mmol/L) and constitutes a risk-enhancing factor
4. ABI <0.9

ABI = ankle-brachial index; apoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; eGFR = estimated glomerular filtration rate; Lp(a) = lipoprotein(a); RA = rheumatoid arthritis.

[a]Optimally, three determinations.

Reproduced with permission from Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082-143. [PMID: 30586774] doi:10.1161/CIR.0000000000000625. ©2018, American Heart Association, Inc.

therapy should be initiated in patients aged 75 years or younger with ASCVD to achieve a reduction in LDL cholesterol of 50% or greater. If high-intensity statin therapy is contraindicated or not tolerated, moderate-intensity statin therapy should be initiated to achieve a reduction in LDL cholesterol of 30% to 49%.

Patients with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions are considered to be at very high risk. These patients may benefit from the addition of nonstatin drug therapy to maximally tolerated statin therapy when the LDL cholesterol level remains 70 mg/dL or higher (≥1.81 mmol/L). Ezetimibe is the preferred nonstatin option when further lowering of LDL cholesterol is necessary.

The PCSK9 inhibitors are monoclonal antibodies that bind to serine protease PCSK9, a liver enzyme that degrades hepatocyte LDL receptors. Treatment with PCSK9 inhibitors produces an additional 43% to 64% reduction in LDL cholesterol when added to statin therapy. Barriers to the use of PCSK9 inhibitors include high cost and subcutaneous administration. Adding a PCSK9 inhibitor can be considered for secondary prevention in very high-risk patients if the LDL cholesterol level remains 70 mg/dL or higher (≥1.81 mmol/L) or the non-HDL cholesterol level is 100 mg/dL or higher (≥2.59 mmol/L) despite maximally tolerated lipid-lowering therapy, which includes a statin plus ezetimibe. The long-term safety of PCSK9 inhibitors is unknown, and cost-effectiveness is low.

For secondary prevention, the 2020 U.S. Department of Veterans Affairs and U.S. Department of Defense cholesterol guideline recommends at least moderate-intensity statin therapy and, in higher-risk patients, high-intensity statin therapy (see Table 43). Higher-risk patients include those with MI or ACS in the past 12 months; recurrent ACS, MI, or stroke; or established cardiovascular disease with additional risk factors.

Statin Monitoring, Safety, and Intolerance

A lipid panel should be obtained 4 to 12 weeks after initiation of lipid-lowering therapy to assess treatment adherence and response. Patients who do not achieve adequate reduction in LDL cholesterol (≥50% reduction with high-intensity statin therapy, 30%-49% reduction with moderate-intensity statin therapy) should be assessed for medication adherence and intensify lifestyle modifications. Once treatment goals have been achieved, lipid levels should be measured every 3 to 12 months as indicated.

Statins are generally safe and well tolerated. They can cause asymptomatic, dose-related elevations in aminotransferase levels in approximately 1% of patients, but liver injury occurs in less than 0.001% of patients. Although observational studies have suggested higher rates, data from randomized trials show that the incidence of statin-associated muscle symptoms is no greater than 1%, and the incidence of myopathy and rhabdomyolysis is less than 0.1%. Before statin therapy is started, liver chemistry tests should be obtained at baseline; however, liver chemistry tests and muscle enzyme studies should not be obtained during therapy in the absence of symptoms. Statin therapy also increases the risk for newly diagnosed type 2 diabetes by approximately 0.2% per year, although the risk appears to be restricted to patients with other risk factors for diabetes. In patients with prior cerebrovascular disease, statins may increase the risk for hemorrhagic stroke, but these drugs also reduce total stroke risk in this population.

Most statin-related adverse effects can be reversed by stopping treatment. In patients with statin intolerance, switching to another statin is reasonable. Other options include decreasing the dosage and/or dosing frequency and, less preferably, discontinuing statin therapy and initiating nonstatin drugs.

Statins have the potential to cause drug-drug interactions that predominantly increase the plasma concentrations of

TABLE 43. Summary of the U.S. Department of Veterans Affairs/U.S. Department of Defense Dyslipidemia Pharmacotherapy Recommendations

Recommendation Topic	Conclusion
Primary Prevention	
Moderate-intensity statin therapy for patients with a 10-year CVD risk ≥12%, an LDL cholesterol level ≥190 mg/dL (4.92 mmol/L), or diabetes mellitus	Recommended
Moderate-intensity statin therapy for patients with a 10-year CVD risk between 6% and 12%	Suggested
PCSK9 inhibitors	Recommended against
Ezetimibe	No recommendation
Secondary Prevention	
At least moderate-intensity statin therapy	Recommended
High-intensity statin therapy for higher-risk patients[a,b]	Suggested
Adding ezetimibe to statin therapy for higher-risk patients[a,b]	Suggested
PCSK9 inhibitor for higher-risk patients[b,c]	Suggested
Other Medications, Supplements, and Nutraceuticals	
Adding icosapent ethyl to statin therapy for secondary prevention in patients with persistently elevated fasting triglyceride levels >150 mg/dL (1.69 mmol/L)	Suggested
Niacin for primary or secondary prevention	Recommended against
Adding fibrates to statin therapy for primary or secondary prevention	Suggested against
Omega-3 fatty acids as dietary supplements for primary or secondary prevention	Suggested against
Adding icosapent ethyl to statin therapy for primary prevention in patients with persistently elevated fasting triglyceride levels >150 mg/dL (1.69 mmol/L)	No recommendation
Monitoring	
Routine monitoring of lipid levels in patients receiving statin therapy	Suggested against

CVD = cardiovascular disease; PCSK9 = proprotein convertase subtilisin/kexin type 9.

[a]In patients who are willing to intensify treatment after discussing the risk of high-intensity statin therapy.

[b]Higher-risk patients include those with a myocardial infarction or acute coronary syndrome in the past 12 months; recurrent acute coronary syndrome, myocardial infarction, or stroke; or established CVD with additional risk factors (e.g., currently smoking, diabetes, peripheral artery disease, or coronary revascularization).

[c]In patients who are willing to intensify treatment after discussing the uncertain long-term safety and benefits.

Information from O'Malley PG, Arnold MJ, Kelley C, et al. Management of dyslipidemia for cardiovascular disease risk reduction: synopsis of the 2020 updated U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. Ann Intern Med. 2020;173:822-9. [PMID: 32956597] doi:10.7326/M20-4648

statins, thereby increasing the risk for myopathy and rhabdomyolysis. There are some interactions with common nonstatin cardiac medications (e.g., fibrates, dabigatran), and statins can potentiate warfarin, resulting in higher than expected INR values. All statins are contraindicated in pregnancy.

KEY POINTS

- For primary prevention of atherosclerotic cardiovascular disease (ASCVD), the American Heart Association and American College of Cardiology recommend (1) high-intensity statin therapy for patients with 10-year ASCVD risk of 20% or higher, (2) high-intensity statin therapy for an LDL cholesterol level of 190 mg/dL or higher (≥4.92 mmol/L), (3) moderate-intensity statin therapy in patients aged 40 to 75 years with diabetes mellitus, and (4) moderate-intensity statin therapy for patients aged 40 to 75 years with risk-enhancing factors and 10-year ASCVD risk of 7.5% to less than 20%.

(Continued)

KEY POINTS *(continued)*

- The American Heart Association and American College of Cardiology recommend secondary prevention of atherosclerotic cardiovascular disease with high-intensity statin therapy.
- A lipid panel should be obtained 4 to 12 weeks after statin therapy initiation to determine treatment adherence and response to therapy.
- In patients treated with statin therapy, liver chemistry tests and muscle enzyme studies should not be routinely obtained in the absence of symptoms of liver dysfunction or myopathy.

HVC

Management of Hypertriglyceridemia

Therapeutic lifestyle changes are the cornerstone of management of elevated triglyceride levels. Medications that increase triglyceride levels, such as estrogens, β-blockers, and glucocorticoids, should be avoided if possible. Omega-3 fatty acids,

which are found in many types of fish, reduce triglyceride levels and should be incorporated into the diet; however, omega-3 fatty acid supplements do not reduce heart disease, stroke, or death.

In most patients, the value of pharmacologic treatment of hypertriglyceridemia for preventing cardiovascular events has not been established. In adults with a 10-year ASCVD risk of 7.5% or higher and a triglyceride level of 175 mg/dL or higher (≥1.98 mmol/L), initiating or intensifying statin therapy can be considered for a persistently elevated triglyceride level despite lifestyle interventions and addressing reversible factors. In patients with persistently elevated triglyceride levels despite statin therapy and either established cardiovascular disease or diabetes and multiple other risk factors, the addition of icosapent ethyl, a highly purified fish oil, may decrease the risk for cardiovascular events, an effect lacking for other omega-3 fatty acids. Fibrates are the most effective pharmacotherapy for hypertriglyceridemia, resulting in a 30% to 50% reduction in triglyceride level; these agents are indicated in patients with severe hypertriglyceridemia to prevent acute pancreatitis. Pharmacologic doses (4 g/d) of omega-3 fatty acid preparations are also effective at decreasing triglyceride levels.

KEY POINTS

HVC
- Therapeutic lifestyle changes are the cornerstone of management of hypertriglyceridemia.
- Statin therapy can be considered in patients with a 10-year risk for atherosclerotic cardiovascular disease of 7.5% or higher and a persistently elevated triglyceride level (≥175 mg/dL [1.98 mmol/L]) despite lifestyle interventions and addressing reversible factors.

Management of Dyslipidemia in Special Populations

Patients older than 75 years without known ASCVD and an LDL cholesterol level of 70 mg/dL to 189 mg/dL (1.81-4.90 mmol/L) can be engaged in a discussion of the potential benefits of statin therapy for primary prevention. If statin therapy is selected, a moderate-intensity statin is recommended, but the benefit in this population is less robust than in other higher-risk groups. If the decision to initiate statin therapy is uncertain, measuring the CAC score can be helpful. Statin therapy can be avoided if the CAC score is 0. It is reasonable to forgo initiating a statin or to stop statin therapy in the face of functional decline, multiple comorbid conditions, frailty, or reduced life expectancy.

For secondary prevention of ASCVD in patients older than 75 years, it is reasonable to continue statins in those who are already tolerating therapy; moderate-intensity therapy is beneficial and is preferable to high-intensity therapy in these patients.

Initiation of statin therapy is not recommended in adults on dialysis for end-stage kidney disease, but it may be reasonable to continue a statin in patients already receiving therapy.

When discussing the benefits of statin therapy and lifestyle modification with women, clinicians should specifically consider premature menopause and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes), which increase ASCVD risk. The available evidence does not indicate that statins are hazardous during pregnancy, but they have not been proved safe and are currently contraindicated in pregnant women. Women of childbearing age should be counseled to use reliable contraception while taking a statin and to discontinue statin therapy 1 to 2 months before pregnancy is attempted.

Xanthomas

Xanthomas are lipid deposits in the connective tissue of the skin, tendons, or fasciae that manifest as yellow, orange, reddish, or yellow-brown papules, plaques, or nodules. They are associated with primary and secondary hyperlipidemias, and the type of xanthoma closely correlates with the type of lipoprotein that is elevated. The most common xanthoma types include eruptive, plane, xanthelasma, tuberous, and tendinous.

Eruptive xanthomas present as clusters of small erythematous papules, typically on the extensor surfaces of the arms, legs, and buttocks. Diagnosis is made by skin biopsy that shows lipid-laden macrophages in the dermis. Eruptive xanthomas are pathognomonic of hypertriglyceridemia, with a vast number of patients also having a diagnosis of diabetes. Lesions typically resolve with control of carbohydrate and lipid metabolism. Plane xanthomas are yellow-to-red plaques found in the skin folds of the neck and trunk. They can be associated with familial dyslipidemias and various hematologic cancers. Xanthelasma is a type of plane xanthoma localized to the periorbital area, most commonly on the upper medial eyelid (**Figure 23**), and is characterized by soft, nontender, nonpruritic plaques. Xanthelasma can occur without hyperlipidemia, particularly in older persons, but is often associated with familial dyslipidemias when present in a younger person. These lesions are a classic feature of primary biliary cholangitis, a condition often associated with marked hypercholesterolemia. Tendon xanthomas are subcutaneous

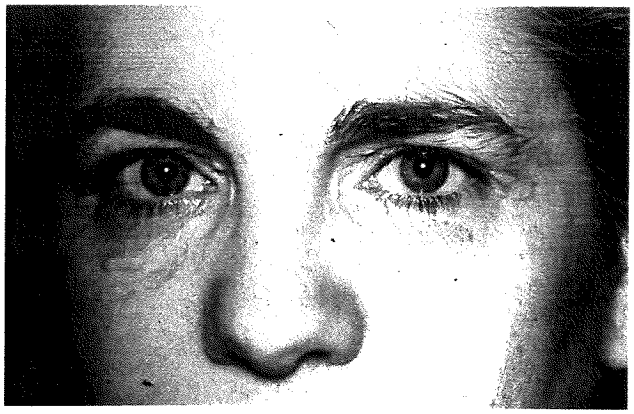

FIGURE 23. Xanthelasma. This type of plane xanthoma presents as asymptomatic, flat, yellow-to-orange papules or plaques around the eyelids and can be associated with familial dyslipidemia in young adults.

nodules occurring on the extensor tendons, especially on the hands and the Achilles tendon; they are associated with familial hypercholesterolemia.

Metabolic Syndrome

Epidemiology and Pathophysiology

Metabolic syndrome, also referred to as insulin resistance syndrome, comprises a constellation of risk factors for cardiovascular disease and type 2 diabetes. It is a common condition, occurring in 20% to 35% of U.S. adults.

TABLE 44. Diagnostic Criteria for Metabolic Syndrome

Measure (Any Three of Five Constitute Diagnosis of Metabolic Syndrome)	Categorical Cut Points
Elevated waist circumference[a,b]	≥102 cm [40 in] in men; ≥88 cm [35 in] in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L)
	or
	On drug treatment for elevated triglycerides
Reduced HDL cholesterol	<40 mg/dL (1.03 mmol/L) in men; <50 mg/dL (1.30 mmol/L) in women
	or
	On drug treatment for reduced HDL cholesterol[c]
Elevated blood pressure	≥130 mm Hg systolic blood pressure
	or
	≥85 mm Hg diastolic blood pressure
	or
	On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL (5.6 mmol/L)
	or
	On drug treatment for elevated glucose

[a]To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

[b]Some U.S. adults of non-Asian origin (e.g., White, Black, Hispanic) with marginally increased waist circumference (e.g., 94-101 cm [37-39 inches] in men and 80-87 cm [31-34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cut point (e.g., ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

[c]Fibrates and nicotinic acid are the most commonly used drugs for elevated triglycerides and reduced HDL cholesterol. Patients taking one of these drugs are presumed to have high triglycerides and low HDL cholesterol.

Although there are several definitions for metabolic syndrome, the diagnostic criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (with minor modifications by the AHA/National Heart, Lung, and Blood Institute) are the most widely used (**Table 44**). The presence of a pathophysiologic link between the components of the metabolic syndrome is controversial; however, insulin resistance and adipocyte cytokines associated with metabolic syndrome appear to play a central role in inducing inflammatory changes that contribute to ASCVD.

Management

Treatment of metabolic syndrome focuses on addressing each of the component risk factors. Lifestyle modifications, particularly weight loss and exercise, are the most important treatment interventions. Routine pharmacotherapy is not recommended in patients who do not meet treatment criteria for the individual risk factors. In some studies, metformin has been shown to prevent progression to diabetes; however, it is inferior to lifestyle modifications, and its role in treating metabolic syndrome has not been established.

Mental and Behavioral Health

Mood Disorders

Mood disorders are characterized by elevated or depressed mood associated with psychomotor, cognitive, and/or vegetative symptoms that cause significant functional impairment. The two main groups of mood disorders are depressive disorders and bipolar disorder.

Depressive Disorders

The lifetime prevalence of depressive disorders in developed countries is approximately 20%. Women are affected almost twice as often as are men. Peak onset is in the fifth decade of life, and incidence decreases in the elderly population. Depression is the leading cause of disability in the United States among individuals aged 15 to 44 years and is a major risk factor for suicide.

Depressive disorders often initially present in the primary care setting but are underdiagnosed because screening is underperformed. Depressive symptoms are frequently encountered in patients with chronic medical disease, either as a direct result of the illness or as a response to illness-related disability. Depression commonly accompanies thyroid disease, cancer, neurologic diseases (Parkinson disease), heart failure, HIV infection, inflammatory bowel disease, and diabetes mellitus. Medications, including glucocorticoids and interferon, may also trigger depressive symptoms. During evaluation for depression, clinicians must assess for these secondary causes.