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Dyslipidemia

Prevention and Screening

Diagnosis

Treatment

Practice Improvement

Dyslipidemia is an important risk factor for coronary artery disease and stroke. Long-term, prospective epidemiologic studies have consistently shown that persons with healthier lifestyles and fewer risk factors for coronary heart disease, and particularly those with favorable lipid profiles, have reduced incidence of coronary heart disease. Prevention and sensible management of dyslipidemia can markedly alter cardiovascular morbidity and mortality.

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Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease (CVD). According to data from 2009–2012, more than 100 million U.S. adults aged 20 years or older have total cholesterol levels of 200 mg/dL (5.17 mmol/L) or greater, and almost 31 million have levels of 240 mg/dL (6.20 mmol/L) or greater. In 2016 alone, approximately 660 000 persons in the United States had a new coronary event and approximately 305 000 had a recurrent event (1). Epidemiologic data suggest that dyslipidemia can contribute to the risk for an ischemic cerebrovascular accident (2). Further, evidence is increasing that insulin resistance, which is associated with the metabolic syndrome, is a major risk factor for atherosclerotic CVD, cerebrovascular accident, and peripheral arterial disease (3) because it tends to increase levels of plasma triglycerides and low-density lipoprotein cholesterol (LDL-C) and reduce levels of high-density lipoprotein cholesterol (HDL-C) (4).

Large observational studies have reported a strong, graded relationship between higher levels of LDL-C, or lower levels of HDL-C, and increasing risk for atherosclerotic coronary heart disease (CHD) events (5, 6).

Prevention and Screening

What preventive lifestyle measures should clinicians recommend to reduce risk for dyslipidemia?

Lifestyle changes can favorably affect total cholesterol, HDL-C, LDL-C, and triglyceride levels. The American Heart Association (AHA) recommends that all adults consume a healthy diet, exercise regularly, and avoid tobacco smoke (7). However, the U.S. Preventive Services Task Force (USPSTF) points out that lifestyle modifications, such as diet and physical activity, are unlikely to substantially reduce lipid levels and that many patients with hyperlipidemia require drugs to reach therapeutic goals (8).

Regardless of the presence of preexisting CHD, patients who adopt these habits will have healthier lipid profiles and reduce CHD risk. Because of their higher baseline risk, patients with CHD or CHD risk–equivalent conditions (see the **Box:** Risk-Equivalent Conditions) may have the most improvement in risk for poor health outcomes.

Ultimately, increasing healthy lifestyles should reduce population-wide lipid levels and, consequently, reduce the need for drug therapy.

Who should be screened?

The age at which screening for dyslipidemia should start is controversial. No direct evidence links lipid screening and subsequent treatment with reduced adverse outcomes from CVD or stroke. In fact, in 2013 the American College of Cardiology (ACC) and the AHA concluded that evidence does not support LDL-C or non–HDL-C levels as treatment targets (7). According to the USPSTF, clinicians should screen all men aged 35 years or older for lipid disorders and those aged 20–35 years if they are at increased risk for CHD. It strongly recommends screening women aged 45 years or older and recommends screening women aged 20–45 years if they are at increased risk for CHD (9). Persons with risk factors for CVD (see the **Box:** Coronary Risk Factors), whose family history of premature CHD or lipid abnor-

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3. Wild SH, Byrne CD, Tzoulaki I, Lee AJ, Rumley A, Lowe GD, et al. Metabolic syndrome, haemostatic and inflammatory markers, cerebrovascular and peripheral arterial disease: The Edinburgh Artery Study. Atherosclerosis. 2009;203:604-9. [PMID: 18804759]
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8. Moyer VA; U.S. Preventive Services Task Force. Behavioral counseling interventions to promote a healthful diet and physical activity for cardiovascular disease prevention in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:367-71. [PMID: 22733153]

malities suggests a heritable lipid disorder or who have evidence of hyperlipidemia on physical examination are considered to have increased risk for CHD. The USPSTF makes no recommendation for or against routine screening for lipid disorders in men aged 20–35 years or in women aged 20 years or older who are not at increased risk for CHD (9). In contrast, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) recommends beginning screening all adults at age 20 years, regardless of CHD risk profile (10). This recommendation is based on the rationale that screening promotes healthy behaviors, increases public awareness of cholesterol, and identifies patients at high risk for CHD (11). However, the incremental yield and cost-effectiveness of earlier universal screening versus risk factor–based screening in young adults is unclear.

The USPSTF recommends routine screening for overweight and obese persons younger than 20 years (12). The National Heart, Lung, and Blood Institute (NHLBI) recommends a more aggressive screening policy that is also endorsed by the American Academy of Pediatrics: No screening for children younger than 1 year; targeted screening of children aged 1–8 years if there is a family history of heart disease or high cholesterol or if the child has other risk factors or a high-risk medical condition; targeted screening of adolescents aged 9–16 years if there is a family history of heart disease or high cholesterol or the child has other risk factors or a high-risk medical condition; and universal screening of young adults aged 17 years or older (13). Untreated abnormal lipid levels in children and adolescents are linked to increased risk for CHD in adulthood, so behavioral lifestyle counseling is an important first step to prevent or reduce abnormal lipid levels in youths (12, 14). Lifestyle counseling is particularly important for young persons with 1 or more CVD risk factors and high LDL-C levels or who are overweight or obese with low HDL-C levels or high triglyceride levels. The American Academy of Pediatrics recommends considering pharmacologic intervention to treat children whose LDL-C level remains persistently high even after therapeutic lifestyle counseling (15).

Moderate-quality evidence supports screening adults older than 65 years. Total cholesterol level predicts CHD in elderly persons. Persons older than 65 years have a higher baseline risk for CHD, increasing their potential absolute benefit from interventions to manage dyslipidemia (16). Regardless of age, lipid levels should be measured in patients with known CHD or CHD risk–equivalent conditions (see the **Box:** Risk-Equivalent Conditions).

How and how often should clinicians screen for dyslipidemia?

Most U.S. organizations recommend screening all adults for dyslipidemia at least every 5 years. The ACC/AHA recommends that all adults aged 20–78 years have a fasting lipid profile measured every 4–6 years if there is no atherosclerotic CVD and more often if this condition is present (7). The NCEP (ATP-III) recommends measurement of the fasting lipid profile in adults aged 20 years or older every 5 years (10). However, the USPSTF recommendations are more restrictive than those of the ACC/AHA and NCEP-ATP III—it recom-

Risk-Equivalent Conditions

- Acute coronary syndromes
- History of myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization
- Stroke
- Transient ischemic attack
- Peripheral arterial disease of atherosclerotic origin

Coronary Risk Factors

Nonmodifiable risk factors: Age, sex, family history, genetic predisposition

Modifiable risk factors: Smoking, atherogenic diet, alcohol intake, physical activity, dyslipidemias, hypertension, obesity, diabetes, metabolic syndrome

Emerging risk factors: Elevation in C-reactive protein; fibrinogen; coronary artery calcification; homocysteine; lipoprotein(a); small, dense LDL-C

9. U.S. Preventive Services Task Force. Final Update Summary: Lipid Disorders in Adults (Cholesterol, Dyslipidemia): Screening. July 2015. Accessed at www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening on 19 October 2017.
10. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143-421. [PMID: 12485966]
11. Cleeman JI, Grundy SM. National Cholesterol Education Program recommendations for cholesterol testing in young adults. A science-based approach. Circulation. 1997;95:1646-50. [PMID: 9118536]

mends universal lipid screening for men older than 35 years every 5 years, with shorter intervals for persons with a history of elevated lipid levels and longer intervals for those not at increased risk with normal lipid levels; men aged 20–34 years at increased risk for CHD should be screened more often and women aged 20 years or older should be screened if they are at increased risk for CHD. Furthermore, the USPSTF accepts lipid profiles from both fasting and nonfasting persons (9).

A study of fasting versus nonfasting total cholesterol levels in 181 general internal medicine outpatients found no clinically important differences between fasting and nonfasting results for total and HDL-C levels (16). Another large cross-sectional population study that compared fasting and nonfasting lipid profiles for 33 391 persons aged 20–95 years reported that lipid profiles changed minimally in response to normal food intake in persons in the general population and that nonfasting levels also predicted cardiovascular events (17).

The NCEP-ATP III advocates initial screening with a fasting lipid profile that includes measurement of triglycerides and indirect calculation of LDL-C level (10). The USPSTF does not recommend triglyceride measurement as part of a lipid profile evaluation (9). Measurements of LDL-C and triglyceride levels are useful for guiding treatment but do not improve on risk prediction with total and HDL-C levels (9).

The updated 2013 ACC/AHA guidelines concluded that the evidence does not support LDL-C or non–HDL-C levels as treatment targets (7). The new guidelines identify 4 groups of patients needing primary or secondary prevention in whom the focus is now to reduce CVD events by maximizing statin therapy to achieve the appropriate reduction of LDL-C. The clinical guidelines emphasize the use of high-intensity statins for patients with atherosclerotic CVD to achieve at least a 50% reduction in LDL-C unless otherwise contraindicated or if the patient has an adverse reaction to statins. In cases of adverse reactions, a moderate-intensity statin should be used (7).

In the absence of data to support a specific interval, screening every 5 years seems to be reasonable in low-risk patients, because lipid levels do not vary greatly from year to year (7). Clinicians might consider more frequent screening for patients who have lipid levels near treatment thresholds or who develop new cardiovascular risk factors.

Prevention and Screening... Healthy diet, regular exercise, and avoidance of tobacco can help patients preclude or reduce dyslipidemia. Evidence supports routine screening for dyslipidemia in men aged 35 years or older and women aged 45 years or older. Screening at earlier ages is warranted for children and adolescents with cardiovascular risk factors or a clinical history suggestive of familial hyperlipidemia. Although authorities disagree on which cholesterol levels to measure and at what age to begin testing, ACC/AHA and NCEP-ATP III guidelines recommend measuring a fasting lipid profile in all adults aged 20 years or older every 5 years.

CLINICAL BOTTOM LINE

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How should clinicians interpret results of lipid screening in relation to evaluating overall cardiovascular risk?

When diagnosing dyslipidemia, clinicians should estimate a patient's cardiovascular risk. Risk assessment guides clinicians' decisions on treatment for primary prevention. Treatment is most beneficial for patients with the highest risk. Calculation of risk using specific equations is more accurate than using lipid levels alone or simply counting risk factors. Several algorithms are used in the United States, including the Framingham Risk Score, the ACC/AHA Arteriosclerotic Cardiovascular Disease Risk Estimator, and the Reynolds Risk Score. Some experts believe that cardiovascular risk scores to predict CVD lack validation, especially in populations outside the United States (18). Also, their use to identify patients who will benefit from pharmacologic agents and to guide management of those with lipid disorders lacks predictive value because the current risk calculators may overestimate risk (19). Many people believe that this can lead to overprescribing and escalating doses of statins and combinations of drugs that may result in adverse effects without known beneficial outcomes.

An electronic tool for calculating cardiovascular risk is publicly available through the ACC/AHA (www.cvriskcalculator.com/). It calculates the 10-year risk for heart disease or stroke using the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (7). In 2016, the calculator incorporated the USPSTF guidelines for initiating aspirin therapy. Also, in 2015 and in 2014 it incorporated the updates from Joint National Committee-8 guidelines for hypertension. The incorporation of these guidelines enhances the tool's ability to accurately calculate cardiovascular risk.

If whether to treat based on risk is uncertain after quantitative assessment, family history, high-sensitivity C-reactive protein levels, coronary artery calcium score, and ankle–brachial index can be considered. There is no recommendation for or against adding any of the following to assess risk for the first atherosclerotic CVD event: apolipoprotein B levels, chronic kidney disease, albuminuria, or cardiorespiratory fitness (7).

What laboratory test results should clinicians obtain before starting therapy?

The absolute benefit of beginning medical therapy depends on the patient's level of risk for CVD. Therefore, it is imperative to risk-stratify the patient because potentially life-long therapy is being initiated. It is also important to identify causes of elevated cholesterol levels to appropriately target diet and drug therapy. Therefore, shared decision making between the clinician and the patient is recommended before beginning any treatment plan.

Dyslipidemia includes a large range of lipid abnormalities and may involve a combination of increased total cholesterol (≥240 mg/dL [6.20 mmol/L]), LDL-C (>160 mg/dL [4.13 mmol/L]), and triglyceride levels (>200 mg/dL [2.25 mmol/L]) or decreased HDL-C (<40 mg/dL [1.03 mmol/L]). Although the screening recommendations and the timing of testing vary by the given organization, it is generally agreed that laboratory tests should include baseline measurement of total

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20. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: a cross-sectional study. Arch Intern Med. 2012;172:1707-10. [PMID: 23147400]

cholesterol, LDL-C, HDL-C, and triglyceride levels. For patients with a history of CVD or those with a very high level of risk, tests that may be considered in addition to the baseline lipid profile include measurement of lipoprotein(a), apolipoprotein B, and apolipoprotein A1.

The blood sample should be obtained under fasting conditions (12 hours) if possible; however, a nonfasting sample provides measures of total cholesterol and HDL-C levels that vary little with fasting (20). The only exception is if triglycerides exceed 400 mg/dL (4.52 mmol/L) in which case a fasting lipid profile is indicated. Thus, in the vast majority of the cases, a nonfasting lipid profile provides acceptably accurate measures for risk calculation. As mentioned, it is important that the patient and provider make a joint decision on whether to begin pharmacologic treatment because the benefits can outweigh the harms. For patients with a 10-year risk greater than 12%, clinical trials indicate that CVD risk can be decreased by 20% to 30% with the use of a moderate-dose statin over a 5-year period (7, 21).

How should clinicians measure and interpret triglyceride and HDL-C levels?

Triglyceride levels

Triglyceride levels are a secondary target for therapy. Numerous prospective epidemiologic studies have shown that increased triglyceride levels are related to an increased risk for CAD (22), and a meta-analysis of prospective studies found that high triglyceride levels are an independent risk factor for CAD (23). Triglyceride levels must be tested in a fasting state to be accurate because they can increase by as much as 20% in a nonfasting state. If triglyceride levels exceed 400 mg/dL (4.52 mmol/L), follow-up assessment of fasting lipid levels should be considered (20).

The association of elevated triglyceride levels with CAD seems to be stronger for women than for men (23) because adjustment for other risk factors in men (for example, diabetes, HDL-C level, obesity) seems to explain this association. The clinician should stratify patients based on fasting triglyceride levels as follows: normal, less than 150 mg/dL (1.70 mmol/L); borderline high, 150–199 mg/dL (1.70–2.24 mmol/L); high, 200–499 mg/dL (2.26–5.64 mmol/L); and very high, greater than 500 mg/dL (5.65 mmol/L).

Persons with elevated triglyceride levels are more likely to be predisposed to the metabolic syndrome. Elevated levels may also result from reduced clearance of triglyceride-rich lipoproteins or may identify persons with other metabolic problems or deleterious lifestyle habits in need of intervention (for example, diabetes, chronic renal failure, nephrotic syndrome, or alcohol use disorder). Triglyceride levels greater than 5.65 mmol/L (500 mg/dL) are associated with pancreatitis and warrant treatment.

HDL-C levels

HDL-C level is used to calculate cardiovascular risk and is inversely associated with CVD and coronary death, independently from other traditional risk factors (24). An HDL-C level less than 40 mg/dL (1.03 mmol/L) predicts an increase in atherosclerotic events and for each 1-mg/dL (0.02-mmol/L) reduction it is estimated that coronary risk increases by 2%–3% (25). In addition, results from a meta-analysis showed a 30% reduction in mortality when an in-

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crease (about 13 mg/dL [0.33 mmol/L]) in HDL-C occurred (26). Low HDL-C levels are caused most commonly by acquired conditions, such as smoking tobacco, obesity, inactivity, hypertriglyceridemia, type 2 diabetes, and a high-carbohydrate diet. Low HDL-C levels can also be caused by such drugs as β-blockers or androgenic steroids. Genetic abnormalities, including mutations in genes encoding apoA-I, LCAT, and ABC1, can also decrease HDL-C levels.

Before initiating drug therapy in patients with an HDL-C level less than 40 mg/dL (1.03 mmoL/L), it is important to rule out other possible contributing factors, such as smoking tobacco; medications (see the **Box:** Drugs That Can Cause Dyslipidemia); and lifestyle habits, such as being sedentary. Most treatment guidelines do not recommend medications to specifically increase HDL-C levels and prefer to advise lifestyle changes, which include weight loss, aerobic exercise, and smoking cessation (7, 24).

What should clinicians look for in the history and physical examination?

History and physical examination should focus on identifying coronary risk factors and detecting secondary causes of dyslipidemia. The history should be thorough and include a detailed reconciliation of all medications because some medications may affect lipid levels (**Box:** Drugs That Can Cause Dyslipidemia). The physical examination should include measuring body mass index (BMI) and blood pressure, examining peripheral pulses, and checking carotids and other vessels for bruits. Liver and thyroid examination may also identify secondary causes of dyslipidemia. In addition to the physical examination and health history, it is important to risk-stratify patients with the use of risk algorithms, such as the ACC/AHA Arteriosclerotic Cardiovascular Disease Risk Estimator and the Reynolds Risk Score. Risk algorithms include lipid levels with some combination of other traditional risk factors, including age, sex, family history of premature coronary disease, smoking, hypertension, diabetes mellitus, obesity, and a sedentary lifestyle.

What are the causes of secondary dyslipidemia, and how should clinicians diagnose them?

Secondary causes of dyslipidemia include hypothyroidism, obstructive liver disease, the nephrotic syndrome, renal failure, uncontrolled diabetes mellitus, and tobacco or alcohol use. Various drugs can also cause dyslipidemia (**Box:** Drugs That Can Cause Dyslipidemia).

It is important to address secondary causes before starting drug therapy, because treatment of the secondary cause may render lipid-lowering therapy unnecessary. Lipid-lowering drugs may also be ineffective in persons with these conditions. If a drug is suspected as the cause of the lipid abnormality, consider the benefits versus the risks before discontinuing therapy.

When should clinicians consider specialized lipid tests or referral to a specialist?

Clinicians should consider an apolipoprotein evaluation and referral to a lipid specialist if they suspect familial hypercholesterolemia, which is an inherited disorder characterized by very high LDL-C levels that lead to premature atherosclerotic CVD. Early detection and treatment are important to prevent premature heart disease. Apolipoproteins

Drugs That Can Cause Dyslipidemia

- Corticosteroids
- Androgenic steroids
- Progestogens
- Thiazide diuretics
- β-blockers
- Retinoic acid derivatives
- Oral estrogens

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are proteins in lipid particles, and measurement can be helpful because direct measurement can be more accurate than measuring lipid levels in the setting of massively elevated levels and it can provide clues about the cause of some dyslipidemias. An assessment of particle size may be warranted in these patients, along with measurement of apolipoprotein A and B levels to provide a more detailed characterization of the lipid disorder. Accurate typing can help guide the choice of therapeutic pharmacologic agents. When a genetic disorder of lipid metabolism is suspected, especially in conjunction with a history of premature atherosclerotic disease, lipoprotein(a) level can serve as a risk marker for future atherothrombotic events (27). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been recently approved and are effective in decreasing lipoprotein(a) levels (28). Screening first-degree relatives should be strongly considered. Lipid control in these patients can be very difficult, but it is also very important because they have increased risk for early CHD.

Diagnosis... LDL-C levels should be interpreted based on calculation of cardiovascular risk. Measurement of HDL-C and triglyceride levels can help identify the causes of dyslipidemia, enhance risk assessment, and further target interventions. History and physical examination should focus on identifying CHD, cardiovascular risk factors, and potential secondary causes of dyslipidemia. Specialized testing and specialty referral may be useful when familial hypercholesterolemia is suspected.

CLINICAL BOTTOM LINE

Treatment

What should clinicians advise patients with dyslipidemia about lifestyle changes?

Patients with lipid disorders should be informed of the importance of behavioral lifestyle changes and should adopt these changes regardless of whether drug therapy is being prescribed. Use of the NCEP-ATP III Therapeutic Lifestyle Change Diet can result in a 5%–15% reduction in LDL-C level (10). According to the National Health and Nutrition Examination Survey, a 15% reduction in LDL-C could reduce the need for cholesterol-lowering drugs from 14% to 5% of the population. The 2013 ACC/AHA Guideline on Lifestyle Management to Reduce Cardiovascular Risk emphasizes a diet rich in fruits, vegetables, nuts, and whole grains and use of monounsaturated oils (for example, olive oil and canola oil) as well as low-fat dairy products, poultry, and fish rather than animal products (29). The diet limits sweets, sugar-sweetened beverages, and red meat. A diet low in red meat and animal fat seems to substantially reduce risk, independent of serum lipid levels (30). Moderate alcohol consumption, smoking cessation, weight reduction, and regular exercise can increase HDL-C by up to 10% (29).

Patients with dyslipidemia and a normal BMI (18.5–24.9 kg/m^2) should focus on healthy eating and regular exercise to maintain

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a healthy body weight and reduce lipid levels (12). Overweight (BMI, 25–29.9 kg/m^2) and obese (BMI, ≥30 kg/m^2) patients should reduce their caloric intake from fats and simple carbohydrates and aim for at least 30 minutes of physical activity on most days. A structured aerobic exercise program using large-muscle groups (for example, running, walking, cycling, or swimming) greatly enhances weight reduction. Studies of weight loss with or without exercise suggest that exercise can optimize lipid levels (31).

The clinician and patient should set goals and select treatment strategies for weight loss and risk factor control and schedule periodic weight checks and maintenance counseling. Obese patients may require more intensive interventions and counseling for weight reduction.

When should clinicians recommend drug therapy?

Recent guidelines have emphasized evidence-based treatment according to risk as opposed to LDL targets. The 2013 ACC/AHA guidelines align recommendations with evidence from clinical trials, and most clinical trials included patients based on clinical risk, not absolute levels of cholesterol (7).

The first step is for clinicians to encourage a healthy lifestyle. Lifestyle modifications include adhering to a heart healthy diet, regular exercise, avoidance of tobacco, and maintaining a healthy weight.

The second step is to determine the patient's atherosclerotic CVD risk. The 2013 ACC/AHA guidelines propose use of the Pooled Cohort Equations, a risk calculator based on several large clinical trials (7).

The third step is for the clinician and patient to share in the decision regarding lipid treatment, discussing the risks and benefits as well as the costs of lipid-lowering medications.

The fourth step is to start treatment. A secondary prevention strategy is applied to patients with clinical atherosclerotic CVD. For secondary prevention, high-intensity statin therapy is recommended.

A primary prevention strategy is used for patients at high risk for cardiac events who do not have clinical atherosclerotic CVD (7). These patients fall into 3 categories: primary elevation of LDL-C to 190 mg/dL (4.91 mmol/L) or greater; diabetes mellitus of either type, aged 40–75 years, and an LDL-C level of 70–189 mg/dL (1.81–4.88 mmol/L); or 10-year risk for atherosclerotic CVD 7.5% or greater, aged 40–75 years, and an LDL-C level of 70–189 mg/dL (1.81–4.88 mmol/L).

Lipid-lowering therapy should be offered to all patients who need secondary prevention. Treatment should not be delayed by management of modifiable risk factors. Beginning treatment with high-intensity statins is recommended for adults with clinical evidence of CVD. The decision to use high-intensity statins should take into consideration informed consent of the patient and shared decision making. Comorbidities, multiple drug therapy, and the benefits and risks of treatment should be considered (7).

What options are available for drug therapy?

The options for drug treatment are listed in the **Table**. The 2013 guidelines from the ACC/AHA indicate that statins are the preferred drugs to lower lipids (7). Many large-scale, high-quality clinical trials show that statins not only decrease LDL-C levels but also decrease cardiovascular

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Table. **Drug Treatment for Lipid Disorders**

Drug Class and Mechanism of Action	*Dose*	*Benefits*	*Side Effects*	*Notes*
Statins (HMG-CoA reductases) Partially inhibits HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This induces LDL-receptor formation and the removal of LDL cholesterol from blood.	Atorvastatin (10–80 mg/d) Fluvastatin (20–40 mg every night or 80 mg extended-release every night) Lovastatin (10–40 mg evening meal or 10–60 extended-release every night) Pravastatin (10–80 mg at bedtime) Rosuvastatin (5–40 mg/d) Simvastatin (5–80 mg evening meal) Pitavastatin (2-4 mg/d)	Well-studied for safety and efficacy in many trials: LDL cholesterol–lowering ranges from 22% to 63% depending on drug.	Abnormal liver function tests (relatively uncommon). Myositis/myalgias (use with fibrates increases risk). Rosuvastatin should not be given with warfarin or gemfibrozil.	Choice of drug for elevated LDL cholesterol based on efficacy and safety. The 7 statins are metabolized differently, allowing substitution if side effects occur. Sometimes used in combination with bile acid sequestrants to synergistically reduce LDL cholesterol. If combined with a fibrate, monitor for transaminase elevations. Do not use in pregnant or nursing women. Contraindicated in active liver disease.
Bile acid sequestrants Interrupt bile acid reabsorption requiring bile acid synthesis from cholesterol.	Colestipol (2 scoops 2 or 3 times per day) Colsevelam hydrochloride (three 625 mg tablets 2 times per day [3.8 g total])	Not absorbed. Long-term safety established. LDL cholesterol–lowering by 10% to 15%.	Unpleasant taste/texture, bloating, heartburn, constipation, drug interaction (decreased by administrating drugs 1 h before or 4 h after meals). Triglyceride levels increase.	First-line drug to lower cholesterol in children and in women with child-bearing potential. Second-line drug with statins to synergistically induce LDL cholesterol receptors. Do not use if triglyceride levels >3.39 mmol/L (>300 mg/dL) or in gastrointestinal motility disorder.
Fibrates Reduce VLDL synthesis and lipoprotein lipase.	Gemfibrozil (600 mg 2 times per day) Fenofibrate (45–145 mg/d depending on brand)	Best drugs for reducing triglyceride levels, lowers by 50% or more in many patients. Increases HDL cholesterol level by 15%.	Nausea, skin rash. Use with caution if renal insufficiency or gallbladder disease.	Does not reliably reduce (and can increase) LDL cholesterol level. Use cautiously with statins due to the possibility of myositis/myalgia. Use with repaglinide may cause severe hypoglycemia.
Ezetimibe Selectively inhibits intestinal absorption of cholesterol and related phytosterols.	10 mg once per day	Reduces LDL cholesterol level by 18%, triglyceride level by 8%, and apoB by 16%.	Well-tolerated, but contraindicated in patients with liver disease or elevated liver enzyme levels.	Can use with statins for further LDL cholesterol and triglyceride level reduction and to increase HDL cholesterol level. Do not combine with resins, fibrates, or cyclosporine.

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Table–Continued

Drug Class and Mechanism of Action	*Dose*	*Benefits*	*Side Effects*	*Notes*
Niacin Largely unknown; reduces hepatic production of B-containing lipoproteins. Increases HDL cholesterol.	Niacin (500–750 mg to 1–2 g every night of extended-release niacin)	Lowers LDL cholesterol and triglyceride levels 10% to 30%. Most effective drug to raise HDL cholesterol level (25% to 35%).	Flushing of the skin, nausea, glucose intolerance, gout, liver function test abnormalities, and elevated uric acid. May increase homocysteine.	Drug of choice for combined hyperlipidemia and in patients with low HDL cholesterol level. Extended-release preparations limit flushing and liver function test abnormalities. Long-acting OTC niacin preparations not recommended, because they increase the incidence of hepatotoxicity. Lowers lipoprotein(a). Used in combination with statins or bile acid sequestrants in patients with combined hyperlipidemia. Do not use in pregnant or nursing women.
Omega-3 fatty acids Polyunsaturated fatty acids inhibit hepatic triglyceride synthesis and augment chylomicron triglyceride clearance secondary to increased activity of lipoprotein lipase.	Lovaza 4 g/d Omtryg 4.8 g/d Vascazen 4 g/d Epanova 2–4 g/d Vascepa (icosapent) 2 g/d every 12 h with food	Effective in controlling triglyceride levels up to 45%. Raises HDL cholesterol level 13%. Used as an adjunct to diet when triglycerides are greater than or equal to 500 mg/dL.	Dyspepsia, nausea. May increase bleeding time. Use cautiously in patients receiving anticoagulant therapy.	Can increase LDL cholesterol level in some patients with increased triglyceride levels. Swallow capsule whole; do not break open, dissolve, crush or chew. Safety and efficacy not established in patients <18 y.
ApoB antisense oligonucleotide	Mipomersen (Kynamro) 200 mg/mL SQ once weekly	Indicated as an adjunct to lipid-lowering medications and diet to reduce LDL cholesterol, apoB, TC, and non-HDL cholesterol in patients with homozygous familial hypercholesterolemia.	Measure baseline liver function. Can cause elevated transaminases. Check bilirubin, aspartate transaminase, and alanine transaminase if nausea, vomiting, abdominal pain, fever, jaundice, lethargy or flu-like symptoms develop. If greater than 2x ULN, consider withholding. If greater than 5x the ULN, withhold dose. Recheck in 1 wk.	Administer on the same day each week; if dose is missed, the injection should be given at least 3 d from the next weekly dose. Inject SQ into abdomen, thigh, or outer area of upper arm. Do no inject in areas of active skin disease or injury such as sunburn, rashes, inflammation, infections, or psoriasis. Avoid tattooed or scarred areas. Requires refrigeration (36–46 degrees F) Allow to reach room temperature for at least 30 min prior to administration.

Continued on following page

Table–Continued

Drug Class and Mechanism of Action	*Dose*	*Benefits*	*Side Effects*	*Notes*
Ezetimibe and simvastatin (combination drug) Both selectively inhibit the intestinal absorption of cholesterol and partially inhibit HMG-CoA reductase.	Ezetimibe, 10 mg every night Simvastatin, 10–80 mg every night	Combination therapy may improve patient adherence. Synergistic benefits.	Abnormal liver function tests. Myositis, myalgia.	Avoid use with fibrates, >1 g; niacin; amiodarone; or verapamil due to increased risk for myopathy. Contraindicated in liver disease and in pregnant or nursing women.
PCSK9 inhibitors Indicated as an adjunct to diet and other LDL-lowering therapies for treatment of patients with homozygous familial hypercholesterolemia who require additional lowering of LDL cholesterol	Evolocumab (Repatha) 140 mg/mL SQ every 2 weeks or 420 mg SQ once monthly Alirocumab (Praluent) 75 mg/mL SQ every 2 wk or 300 mg SQ every 4 wk	Used as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults who have heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD, who require additional lowering of LDL cholesterol. For those with homozygous familial hypercholesterolemia who require additional lowering of LDL cholesterol after other agents such as statins, ezetimibe, and LDL apheresis.	Mild or moderate hepatic impairment. Mild or moderate renal impairment. Severe impairment has not been studied.	Safety and efficacy not established in children with heterozygous familial hypercholesterolemia. In children younger than 13 y, safety and efficacy is not established. In young adults aged 13–17 y, administer as a single dose of 420 mg SQ monthly. Measure LDL cholesterol levels 4–8 wk after initiating, since response to therapy depends on the degree of LDL-receptor function. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen.
Microsomal triglyceride transport protein inhibitor	Lomitapide (Juxtapid) 5 mg–60 mg daily	Indicated for those with homozygous familial hypercholesterolemia to be used as an adjunct with other lipid lowering agents and LDL apheresis to reduce LDL cholesterol, TC, apoB, and non-HDL cholesterol.		Available only through restrictive access programs due to the potential for hepatotoxicity risk. Administer with daily supplements that contain vitamin E 400 IU, linoleic acid 200 mg, α-linolenic acid 210 mg. Take once per day with a glass of water, without food, at least 2 h after the evening meal as food increases gastrointestinal adverse effects. Swallow whole, do not crush, chew, open, or dissolve.

apoB = apolipoprotein B; CVD = cardiovascular disease; HDL = high-density lipoprotein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; OTC = over-the-counter; PCSK9 = proprotein convertase subtilisin/kexin type 9; SQ = subcutaneous; TC = total cholesterol; ULN = upper limit of normal; VLDL = very low-density lipoprotein.

events in patients with preexisting atherosclerotic CVD and in patients at high risk for atherosclerotic CVD.

Additional drugs have emerged as agents to decrease lipids. However, these drugs alone do not decrease the risk for atherosclerotic disease. For example, ezetimibe decreases LDL-C by targeting the Niemann-Pick C1-like 1 (NPC1L1) protein; however, no clinical trial has shown that it alone

can decrease cardiovascular events (32), a finding also noted with PCSK9 inhibitors (33–35). Niacin, which was used by many clinicians to increase HDL-C and decrease triglyceride levels, is no longer recommended for routine dyslipidemia treatment. The HPS2-THRIVE (Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events) showed that niacin has no clinical benefit (36) and causes such adverse reactions as glucose intolerance, gastrointestinal upset, musculoskeletal discomfort, skin-related disorders (such as rash and flushing), headache, gout, and serious infections (36).

Pharmacologic interventions that are *not* recommended for primary prevention include fibrates, bile acid–binding resins, omega-3 fatty acid supplements, plant sterols or stanols, and niacin.

When is combination drug therapy warranted?

Combination therapy should be considered in patients with severely elevated lipid levels that do not respond to maximum statin monotherapy. Recent trials show that adding specific agents to statins can decrease LDL-C and cardiovascular events more than statins alone. For example, IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) showed that adding ezetimibe to existing statin therapy improves a combined cardiovascular end point (37). However, the benefits of adding ezetimibe were small; therefore, in 2016 the U.S. Food and Drug Administration decided that the results of IMPROVE-IT were not sufficient to recommend ezetimibe for patients at high risk for atherosclerotic CVD. HPS2-THRIVE showed that niacin has no clinical benefit and causes adverse reactions (36). The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial showed that adding a PCSK9 inhibitor to existing moderate or high-dose statin therapy improved a combined cardiovascular outcome (38). However, these drugs are expensive; therefore, patients and clinicians should discuss the cost–benefit ratio.

When prescribing combination therapy, the clinician needs to be vigilant for drug interactions. Fibrates should be used with caution when combined with statins, particularly gemfibrozil, because they compete with the statin for metabolism via the cytochrome P450 system. This interaction may induce rhabdomyolysis (39).

What are the therapeutic goals of treatment?

The first therapeutic goal is to improve the patient's lifestyle. The second goal is to decrease the risk for cardiovascular events. Reducing absolute levels of LDL-C is no longer a therapeutic goal. The 2013 ACC/AHA guidelines no longer base treatment decisions on these values; instead, they focus on identifying high- and medium-risk subgroups who would benefit from treatment aimed at reducing cardiovascular risk (7).

How should therapy be monitored?

Most interventions to treat dyslipidemia require at least 6 months to reduce the risk for CVD event rates (7), and treatment is usually lifelong. Regular follow-up is important after initiation, but in the absence of strong evidence to support a specific monitoring interval, it seems reasonable to perform a fasting lipid profile 6 weeks after initiation of any new lipid-lowering agent. During all follow-up visits, the clinician should discuss adherence, identify side effects, and encourage lifestyle changes. The frequency of follow-up visits should depend on the patient's progress. Some authors advocate routine liver function tests before each follow-up visit, but statin-induced hepatotoxicity seems much less common than previously believed, so the American College of Physicians' guideline on treatment for dyslipidemia does not recommend these tests in patients treated with statins (7). However, when statin therapy is begun and during the first year of treatment, liver function (aminotransferase levels) should be measured at baseline, 3 months, and 12 months. Creatine kinase levels should also be measured at baseline for interpretation of future test results. Although the absolute benefit of statin therapy depends on the patient's level of risk for CVD, there is potential for harm as well. Risk for serious liver injury is quite small if the statin dose is moderate, but patients with aminotransferase levels greater than 3 times the normal levels should be evaluated for the net benefit of continuing statin therapy versus adjusting or discontinuing treatment (40, 41). In 2012, the U.S. Food and Drug Administration concluded that serious liver injury with statins is rare and unpredictable in patients and, therefore, recommended that routine periodic measurement of liver enzymes does not seem to be effective in detecting or preventing liver dysfunction or myopathy.

More frequent visits may be required to counsel about behavioral lifestyle changes, which generally require extensive support from the clinician to foster adherence. Overall, only 39% of patients on drug therapy and 34% of patients on dietary therapy reach their NCEP-ATP III goal (42). New or additional drugs should be added one at a time because if adverse reactions occur, this method makes it easier to determine which drug caused the problem. The recommendation is

that after the initial lipid-lowering agent is started, the clinician should reassess the fasting lipid profile in 6 weeks to assess adherence (7). If lipids do not decrease as expected, in addition to addressing adherence the clinician should reinforce lifestyle modifications and consider referral to a lipid specialist (7).

What are the side effects of drug therapy?

The most common side effects of statins are myalgia, myositis, and elevated liver enzyme levels; however, the frequency of serious events is low, and rhabdomyolysis is rare. The incidence of myopathy due to statins is 1 per 10 000 patients per year (43). A recent study discovered that variations in a gene encoding a transporter protein are linked to many cases of statin-induced myopathy (44). Fibrates can cause nausea and skin rash and must be used cautiously with statins, because the combination tends to increase the incidence of myositis and myalgia. The intestinal cholesterol absorption-blocking drugs and the bile acid–binding resins tend to cause abdominal bloating and constipation, although otherwise they are generally well tolerated. Niacin, which is still prescribed by some clinicians although not recommended for routine treatment of dyslipidemia, is the least well-tolerated lipid-lowering agent. It can cause flushing, nausea, headache, glucose intolerance, and gout. Some of these effects can be minimized with proper drug administration. To minimize flushing, a non–enteric-coated aspirin can be taken 1 hour before the evening dose along with a low-fat snack. Patients should also avoid hot beverages, baths, or showers around the time of niacin dosing.

A systematic review quantified the risks for musculoskeletal, renal, and hepatic complications associated with statin therapy. After examining data from 74 102 persons enrolled in 35 trials and followed for up to 65 months, the authors concluded that, compared with placebo, statin therapy is associated with a small excess risk for elevated aminotransferase levels (risk difference [RD] per 1000 patients, 4.2 [95% CI, 1.5 to 6.9]) but not for myalgia (RD, 2.7 [CI, −3.2 to 8.7]), elevated creatine kinase levels (RD, 0.2 [CI, −0.6 to 0.9]), rhabdomyolysis (RD, 0.4 [CI, −0.1 to 0.9]), or therapy withdrawal (RD, −0.5 [CI, −4.3 to 3.3]) (44). However, trial findings may differ from the experience in actual clinical practice.

In a prospective, observational cohort (PRIMO [Pexelizumab for Reduction in Infarction and Mortality] study) of nearly 8000 French patients aged 18 to 75 years who received high-dose statins for at least 3 months, 10.1% developed muscular pain, with 24.2% of these reporting pain "all over" that often caused a disruption in daily activities. The median time to developing muscular symptoms was 1 month, but 80% of those who developed symptoms did so within 3 months of initiating or intensifying statin therapy (45).

Clinicians should be vigilant for side effects when prescribing drugs for dyslipidemia. However, evidence is insufficient to establish clear recommendations with regard to monitoring and managing side effects. When severe side effects occur, discontinuation may be the only option. Clinicians and patients need to weigh the risks and benefits of therapy with minor side effects. Because metabolism of the various statins differs, it may be reasonable to substitute one statin for another if side effects occur.

What should clinicians advise patients about the use of complementary–alternative therapies?

Among commonly used alternative therapies for controlling lipids, plant-based diets have been shown to have some effectiveness (46), as have nuts in moderation (47, 48). Some dietary changes might affect serum lipid levels merely by replacing fatty foods with healthier choices. However, complementary–alternative therapies should not substitute for drug therapy in high-risk patients.

When should clinicians consult a lipid specialist?

The clinician should consider consulting a lipid specialist for patients with lipid disorders that are rare or resistant to treatment. These specific rare disorders require either special monitoring or complex regimens that are difficult to initiate in a routine practice setting. Patients in this category may include those with familial hypercholesterolemia, type 3 dyslipoproteinemia, very low HDL-C syndromes (HDL-C level 20 mg/dL [<0.5 mmol/L]), and resistant hypertriglyceridemia (triglyceride level 1000 mg/dL [>11.3 mmol/L]). Also, patients at high risk for a vascular event, such as those with vascular disease before age 45 years and patients with evidence of disease progression despite treatment, are candidates for referral to a lipid specialist. Patients at very high risk may need multiple interventions to reduce LDL-C levels substantially below the usual goals, to increase HDL-C levels, or to identify and treat other lipid and nonlipid risk factors. Current treatments to reduce LDL-C level are very efficacious; however, a poor response may prompt an examination for secondary causes, such as unusual lipid and lipoprotein disorders, lack of adherence, or other causes. If lipids do not decrease as expected, then adherence issues and lifestyle modifications should be addressed and referral to a lipid specialist should be considered (7).

Treatment... Treatment of dyslipidemia should always include modification of diet and exercise to optimize lipid levels. Clinicians should base drug therapy decisions on the individual patient's risk for cardiovascular events and should select drugs that reduce that risk. Strong evidence supports statin therapy for high-risk patients.

CLINICAL BOTTOM LINE

What measures do U.S. stakeholders use to evaluate the quality of care for patients with dyslipidemia?

In April 2005, the Ambulatory Care Quality Alliance released 26 health care quality indicators for clinicians, consumers, and health care purchasers to use in quality improvement efforts, public reporting, and pay-for-performance programs at www.aqaalliance.org. In May 2005, the Centers for Medicare & Medicaid Services endorsed the development of these indicators. Of the 26 indicators, 3 focus on dyslipidemia. In addition, the voluntary Medicare Physicians Quality Reporting Initiative pays physicians a bonus for reporting on quality measures that apply to their patients and includes a measure related to lipid control in patients with diabetes.

What do professional organizations recommend regarding the care of patients with dyslipidemia?

As noted, several organizations offer recommendations about dyslipidemia screening that differ with respect to the age at which screening should be started and which screening tests should be used (7, 10). In addition, evidence-based guidelines include a guideline from the American College of Physicians on lipid control in patients with type 2 diabetes (46). A comprehensive listing of guidelines is available through the National Guideline Clearinghouse at www.guidelines.gov. However, the most widely used lipid guideline in the United States is the 2013 ACC/AHA guideline on blood cholesterol treatment (http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a).

In the Clinic

Tool Kit

Dyslipidemia

Practice Guidelines

www.aace.com/files/lipid-guidelines.pdf
Guidelines for prevention of cardiovascular disease by the American Association of Clinical Endocrinologists and the American College of Endocrinology.

www.healthquality.va.gov/guidelines/CD/lipids/
Guidelines from the U.S. Department of Veterans Affairs.

www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Dyslipidaemias-Management-of
Guidelines from the European Society of Cardiology.

Patient Information

www.lipid.org/practicetools/tools/tearsheets
Information and tear sheets on dyslipidemia and other lipid disorders from the National Lipid Association.

http://pcna.net/clinical-tools/education-for-your-patients/cholesterol
Information available in both English and Spanish from the Preventive Cardiovascular Nurses Association.

https://medlineplus.gov/cholesterol.html
Information about cholesterol management from Medline.

In the Clinic

WHAT YOU SHOULD KNOW ABOUT DYSLIPIDEMIA

What Is Dyslipidemia (High Cholesterol)?

- Lipids are fatty substances in your blood. These substances are called cholesterol and triglycerides. It is normal to have some fats in your blood.
- Sometimes the levels of fats in your blood can get too high. This is called dyslipidemia or high cholesterol.
- When you have too many fats in your blood, they can build up and clog the blood vessels in your heart. This can cause heart attack, stroke, and other diseases.

What Are the Risk Factors?

You may be at higher risk for dyslipidemia if you:

- Are older than 65 years of age
- Have a family history of dyslipidemia
- Are a smoker
- Eat an unhealthy diet
- Drink alcohol very frequently
- Do not exercise
- Are a person with high blood pressure, obesity, or diabetes

How Is It Diagnosed?

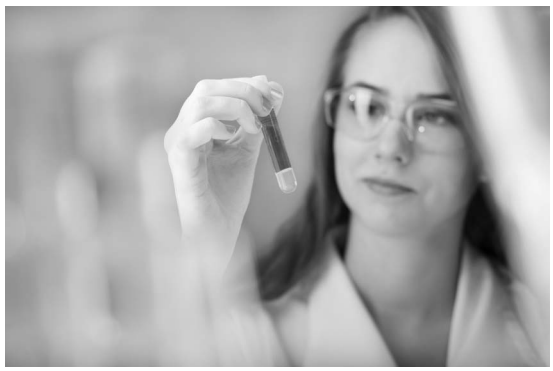
Your doctor will ask you questions about your current health and health history.

- You may also get a physical exam.
- Your health care provider will give you a blood test to check fat levels in your blood. This test may require you to not eat for a few hours.

How Is It Treated?

Your doctor will work with you to create a plan for your treatment. One part of your treatment will include making healthy changes, such as:

- Eating a heart-healthy diet
- Getting regular exercise
- Quitting smoking
- Losing weight if needed



Sometimes lifestyle changes aren't enough. There are several medicines available that help lower the fat levels in your blood. Many people are prescribed one of several medicines called statins. You and your doctor should work together to decide what medicine is right for you.

Should I Be Screened?

- In general, women 45 years or older and men 35 years or older should be screened regularly.
- You may be screened at a younger age if you have certain risk factors or family history of dyslipidemia.

Questions for My Doctor

- Do I need to be screened for dyslipidemia?
- What is the healthiest diet for me to eat?
- Are there foods that I should not eat?
- What is the best form of exercise for me?
- What is the best medicine for me?
- Does the medicine have side effects?
- Will this medicine interact with my other medicines?

For More Information

ACP[SM]
American College of Physicians
Leading Internal Medicine, Improving Lives

National Heart, Lung, and Blood Institute
www.nhlbi.nih.gov/health/resources/heart/heart-cholesterol-hbc-what-html

Medline Plus
https://medlineplus.gov/ency/article/000403.htm

Patient Information