Dyslipidemia

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CME Objective: To review current evidence for the prevention and screening, diagnosis, and treatment of dyslipidemia.

The information contained herein should never be used as a substitute for clinical judgment.

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More than 15% of U.S. adults have high serum cholesterol levels. Hypercholesterolemia is a major risk factor for cardiovascular disease (CVD), cardiovascular death, and all-cause mortality (1). Large observational studies have reported a strong, graded relationship between increasing levels of low-density lipoprotein (LDL) cholesterol or decreasing levels of high-density lipoprotein (HDL) cholesterol and increasing risk for atherosclerotic coronary heart disease (CHD) events (2, 3). Long-term, prospective epidemiologic studies have consistently shown that persons with healthier lifestyles and fewer CHD risk factors, and particularly persons with favorable lipid profiles, have lower incidences of CHD. Prevention and sensible management of dyslipidemia can markedly alter cardiovascular morbidity and mortality.

**Prevention and Screening**

### Coronary Artery Disease Equivalents

- Diabetes mellitus
- Aortic aneurysm
- Peripheral vascular disease (claudication, ankle–brachial index <0.9)
- Symptomatic carotid artery disease (transient ischemic attack, stroke)
- 10-year risk for coronary artery disease >20% using Framingham risk equation

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

Lifestyle changes can favorably affect total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels. The American Heart Association (AHA) recommends that all adults consume a healthy diet, exercise regularly, and avoid tobacco smoke. 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 (4, 5).

Regardless of the presence of pre-existing CHD, patients who adopt these habits will have healthier lipid profiles, reducing their CHD risk. Because of their higher baseline risk, patients with CHD or coronary artery disease (CAD) risk–equivalent conditions (Box) may see the most marked reduction 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 for dyslipidemia?**

No direct evidence links lipid screening and subsequent treatment with reduced adverse outcomes from CVD or stroke. However, moderate-quality indirect evidence supports routine dyslipidemia screening for men older than 35 years and women older than 45 years (6). According to the USPSTF, clinicians should also screen younger adults (men aged 20 to 35 years or women aged 20 to 45 years) who have other risk factors for CVD, whose family history of premature CHD or history of lipid abnormalities suggests a heritable familial lipid disorder, or who have evidence of hyperlipidemia on physical examination. In contrast, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) recommends beginning screening of all adults at age 20 years, regardless of their CHD risk profile (5). This recommendation is based on the rationale that screening promotes healthy behaviors, increases public awareness of cholesterol, and identifies patients with a high risk for CHD (7, 8). However, the incremental yield and cost-effectiveness of earlier universal screening versus risk factor–based screening in young adults is unclear.

In 2007, the USPSTF concluded that the evidence was insufficient to recommend for or against routine screening for lipid disorders in children or adolescents (aged ≤20 years) (9). But, in 2010, the USPSTF recommended routine screening for overweight and
obesity in persons younger than 20 years (10). The American Association of Pediatrics (AAP) recommends a more aggressive screening policy: targeted screening of children and adolescents aged 2 years or older for abnormal blood lipid levels based on family history and other CVD–related risk factors (11). 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 (10). This lifestyle counseling is particularly important for young persons with 1 or more CVD risk factors and high LDL cholesterol levels or who are overweight or obese with low HDL cholesterol levels or high triglyceride levels. The AAP recommends considering pharmacologic intervention to treat children whose LDL cholesterol level remains persistently high even after therapeutic lifestyle counseling (10).

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 (12). Regardless of age, all patients with known CHD or CAD risk equivalent conditions should have lipid levels measured.

How and how often should clinicians screen for dyslipidemia? The AHA and the National Cholesterol Education Program (NCEP) recommends that every adult age 20 years or older have their fasting lipid profile measured every 5 years (4, 5). However, the USPSTF recommendations are more restrictive than those of the AHA and NCEP. The USPSTF recommends lipid screening for men older than 35 years and women older than 45 years who have an increased risk for CHD. Furthermore, the USPSTF recommends measurement of only total cholesterol and HDL cholesterol instead of a complete lipid profile and accepts lipid profiles from both fasting and nonfasting subjects (6).

A study of fasting versus nonfasting total cholesterol values in 181 general internal medicine outpatients found no clinically important differences between fasting and nonfasting results for total and HDL cholesterol levels (13). Another large cross-sectional population study that compared fasting and nonfasting lipid profiles for 33,391 persons aged 20 to 95 years reported that lipid profiles changed minimally in response to normal food intake in persons in the general population (14).

The NCEP-ATP III advocates initial screening with a fasting lipid profile that includes measurement of triglycerides and indirect calculation of LDL cholesterol level (5). The USPSTF does not recommend triglyceride measurement as part of a lipid profile evaluation (6). Measurements of LDL cholesterol and triglyceride levels are useful for guiding treatment, but do not improve on risk prediction as with total and HDL cholesterol values.

The primary treatment target is LDL cholesterol level. Once the LDL cholesterol goal has been attained, attention should turn to other lipid risk factors when present. If triglycerides are high (≥2.26 mmol/L [≥200 mg/dL]), the secondary target of treatment becomes non–HDL cholesterol level. Non–HDL cholesterol level is the difference between the total and HDL cholesterol levels and includes the cholesterol carried on all potentially proatherogenic apolipoprotein B–containing particles, such as very low-density lipoprotein (VLDL) cholesterol, intermediate-density lipoprotein cholesterol, and LDL cholesterol as well as chylomicrons (triglyceride-rich) and lipoprotein(a). If

the LDL cholesterol goal has been attained but the non-HDL cholesterol goal has not, there are 2 alternative approaches: Increase the dose of the LDL-lowering drug to reduce both LDL and VLDL cholesterol levels, or consider adding a triglyceride-lowering drug (fibrates or nicotinic acid) to LDL cholesterol-lowering therapy, which will mainly lower VLDL cholesterol levels. Thereafter, persons can be monitored for response to therapy every 4 or 6 months, or more often if considered necessary (5). Calculation of LDL cholesterol level is best performed on a lipid profile obtained after the patient has fasted for at least 8 to 10 hours. Direct measurement of LDL cholesterol level does not require the patient to be fasting, but it may be expensive and does not improve on risk prediction. However, direct measurement is necessary when triglyceride levels are greater than 4.52 mmol/L (>400 mg/dL).

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

Prevention and Screening... Healthy diet, regular exercise, and avoidance of tobacco can help patients avoid or reduce dyslipidemia. Evidence supports routine screening for dyslipidemia in men aged 35 years or older and women aged 45 years or older. However, the NCEP-ATP III advocates that screening for dyslipidemia begin at age 20 years, in part, to increase awareness of dyslipidemia and promote healthy behaviors. 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 values to measure and at what age to begin testing, AHA and NCEP guidelines recommend measuring a fasting lipid profile on all adults age 20 years or older every 5 years (5).

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. Calculation of risk using specific risk equations seems to be more accurate than using lipid levels alone or simply counting risk factors.

Data from the Lipid Research Clinic Prevalence and Follow-up Studies, which included 3678 men and women aged 35 to 74 years, suggest that a Framingham-based coronary risk model (area under the receiver-operating characteristic curve, 0.85) was superior to all other forms of risk assessment, including lipid measures alone and algorithms based on expert guidelines (15).

An electronic tool for calculating risk is publicly available at a National Heart Lung and Blood Disease Web site (http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof) (16). The Framingham risk equation allows the clinician to classify patients by their level of risk: CHD or CAD risk equivalent (Box) (including >20% 10-year risk for a cardiovascular event), moderate risk (10% to 20% risk), or low risk (<10%). These assessments of risk should guide treatment strategies and goals.

What laboratory test results should clinicians obtain before starting therapy for dyslipidemia?

High levels of LDL cholesterol in persons with 2 or more CAD risk...
factors have been associated in prospective studies with an absolute 10-year risk of more than 20% for myocardial infarction or CAD death (17). Furthermore, clinical trials show that therapy targeted at reducing LDL cholesterol levels decreases the risk for CHD death. Therefore, the clinician must first focus on identifying and treating elevated LDL cholesterol levels.

Before initiating potentially lifelong therapy, clinicians need to risk-stratify patients and set appropriate LDL cholesterol goals. It is important to identify causes of elevated LDL cholesterol levels to appropriately target diet and drug therapy. The efficacy in lowering LDL cholesterol level depends on how high it is at baseline (18).

**How should clinicians measure and interpret triglyceride and HDL cholesterol levels?**

**Triglyceride levels**
Triglyceride levels are a secondary target for therapy. Numerous prospective epidemiologic studies have shown that increased triglyceride levels are related to increased risk for CAD (19), and a metanalysis of prospective studies shows that high triglyceride levels are an independent risk factor for CAD (20).

The association of elevated triglyceride levels with CAD seems to be stronger for women than men (20), because, in men, adjustment for other risk factors (for example, diabetes, HDL cholesterol level, obesity) seems to explain this association (21). The clinician should stratify patients based on fasting triglyceride levels as follows: normal, less than 1.70 mmol/L (<150 mg/dL); borderline high, 1.70 to 2.25 mmol/L (150 to 199 mg/dL); high, 2.26 to 5.64 mmol/L (200 to 499 mg/dL); and very high, greater than 5.65 mmol/L (>500 mg/dL). Borderline high triglyceride levels suggest specific familial abnormalities of triglyceride-rich lipoprotein metabolism in which the liver overproduces triglyceride-rich lipoproteins. In persons with high triglyceride levels (>2.26 mmol/L [>200 mg/dL]), the Adult Treatment Panel (ATP) III suggests that non-HDL cholesterol is a secondary target for lipid-lowering therapies (5). However, it is important to note that LDL cholesterol level is the primary target for all patients with hyperlipidemia.

Persons with elevated triglyceride levels are more likely to have the metabolic syndrome. High triglyceride levels may also result from reduced clearance of triglyceride-rich lipoproteins or may identify persons with other clinical problems that require intervention (for example, diabetes, alcoholism, chronic renal failure, and the nephrotic syndrome). Triglyceride levels greater than 5.65 mmol/L (>500 mg/dL) are associated with pancreatitis and warrant treatment.

**HDL cholesterol level**
HDL cholesterol levels are 1 of 5 factors used in Framingham risk scoring and are inversely associated with CHD. coronary events decrease 2% for every 1% increase in HDL cholesterol level (22). An HDL cholesterol level greater than 1.6 mmol/L (>60 mg/dL) has been associated with a decreased risk for coronary events, whereas an HDL cholesterol level less than 1.0 mmol/L (<40 mg/dL) predicts an increase in coronary events. Low HDL cholesterol levels are caused most commonly by acquired conditions, such as smoking tobacco, obesity, inactivity, hypertriglyceridemia, type 2 diabetes mellitus, and a high-carbohydrate diet. Low HDL cholesterol levels can also be caused by drugs, such as β-blockers or androgenic steroids. Genetic abnormalities, including mutations in genes encoding apoA-I, LCAT, and ABC1, can also decrease HDL cholesterol levels.
Before initiating drug therapy in a patient with an HDL cholesterol level less than 1.0 mmol/L (<40 mg/dL), it is important to rule out other possible contributing factors, such as smoking tobacco; some medications (Box); and lifestyle habits, such as being sedentary. When patients have CHD or an equivalent condition and an HDL cholesterol level less than 1.0 mmol/L (<40 mg/dL), they should receive nicotinic acid or fibrate therapy (23); however, better–tolerated and more effective therapeutic agents are in development (19).

What should clinicians look for in the history and physical examination of a patient with dyslipidemia?

History and physical examination should focus on identifying coronary risk factors and detecting secondary causes of dyslipidemia. A thorough health history, including a detailed reconciliation of all medications, should be performed, because some medications may affect lipid levels, such as thiazide diuretics, β-blockers, anabolic steroids, and estrogens/progestins (Box). The Framingham Risk Calculation should be performed to risk-stratify the patient (16). The physical examination should include measuring the body mass index (BMI), checking the blood pressure, and examining peripheral pulses as well as checking carotids and other vessels for bruits. An examination of the liver and thyroid may also identify secondary causes of dyslipidemia.

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. The clinician should review the patient’s medications for those that can cause dyslipidemia (Box).

It is important to address secondary causes before starting drug therapy to reduce lipids, because the abnormality may resolve after addressing these factors and because drug therapy may 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 when they suspect the patient has a genetic familial hypercholesterolemia. Apolipoproteins are proteins in lipid particles, and their measurement can be helpful for 2 reasons. First, direct measurement of apolipoproteins can be more accurate than measurement of lipid levels in the setting of massively elevated lipids. Second, measurement of apolipoproteins can provide clues about the cause of some dyslipemias. An assessment of particle size may be warranted in these patients, along with levels of apolipoprotein A and B to provide a more detailed characterization of the given 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, a lipoprotein(a) level can serve as a
risk marker for future atherothrombotic events (24). Screening first-degree relatives should be strongly considered. It can be very difficult to control lipid levels in these patients, and they have an increased risk for early CHD.

Diagnosis... Low-density lipoprotein cholesterol levels should be interpreted in light of cardiovascular risk based on the Framingham risk equation. Measurement of high-density lipoprotein cholesterol and triglyceride levels can help identify the causes of dyslipidemia and further target interventions. History and physical examination should focus on the identification of coronary heart disease, 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?
All patients with lipid disorders should be advised about the importance of behavioral lifestyle changes. Patients should adopt these changes regardless of whether or not drug therapy is being prescribed. Use of the NCEP-ATP III Therapeutic Lifestyle Change Diet can result in a 5% to 15% reduction in LDL cholesterol level. According to the National Health and Nutrition Examination Survey (NHANES) III, a 15% reduction in LDL cholesterol can reduce the need for cholesterol-lowering drugs from 14% to 5% of the population, if adopted by everyone (25). A diet rich in fruits, vegetables, nuts, and whole grains with use of mono-unsaturated oils (for example, olive oil and canola oil) and low in red meat and animal fat seems to substantially reduce risk, independent of serum lipid levels (26). Increased soy consumption can increase HDL cholesterol level.

Patients with dyslipidemia and a normal BMI of 18.5 to 24.9 kg/m² should focus on healthy eating and regular exercise in order to maintain a normal body weight and reduce their lipid levels (4).

Overweight patients (BMI, 25 to 29.9 kg/m²) and obese patients (BMI, >30 kg/m²), 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) will greatly enhance weight reduction programs. Studies of weight loss with or without exercise suggest that exercise facilitates achieving optimum lipid levels (27).

The clinician and patient should set goals and select treatment strategies for weight loss and risk factor control and should 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?
Decisions about adding drug therapy to dietary modifications depend on underlying risk factors and on the patient’s clinical situation. Strong evidence supports drug therapy for high-risk patients when LDL cholesterol levels exceed NCEP-ATP III goals (Box). In

patients with none or 1 CHD risk factor, a 6-month trial of lifestyle changes should be completed before initiating treatment. When LDL cholesterol levels are more than 15% above threshold, starting drugs earlier may be reasonable. In patients with CAD or a CAD equivalent, an LDL cholesterol level greater than 2.59 mmol/L (>100 mg/dL) should prompt initiation of drug therapy. In high-risk patients who show CVD progression, some clinicians begin therapy at lower LDL cholesterol levels (that is, >1.8 mmol/L [>70 mg/dL]). In patients who are hospitalized with a cardiovascular event, even though cholesterol levels can change during hospitalization, LDL cholesterol-lowering drugs should be initiated before discharge when the LDL cholesterol level is 3.35 mmol or greater (≥130 mg/dL). Clinical judgment should be used when the cholesterol level is 2.59 to 3.34 mmol/L (100 to 129 mg/dL) (28). Reduction in LDL cholesterol levels will reduce the risk for clinical coronary disease and stroke in diverse situations, including primary prevention, secondary prevention, and persons with diabetes. The recommendations about when to start therapy are based on the data supporting the effectiveness of drug therapy for reducing cardiovascular events by improving lipid levels.

**What options are available for drug therapy?**

There are various lipid-lowering agents to use alone or in combination to achieve NCEP-ATP III cholesterol goals (Table 1). A strong knowledge of drug actions and interactions allows the clinician to adapt drug therapy to meet the specific lipid abnormality. After LDL cholesterol goals are attained, reduce triglyceride levels to less than 1.7 mmol/L (<150 mg/dL) and then attempt to increase HDL cholesterol levels to greater than 1.0 mmol/L (>40 mg/dL) by selection or combination of drugs with effects on multiple lipoproteins. The selection of the agent depends on the type of dyslipidemia (Box).

**When is combination drug therapy for dyslipidemia warranted?**

Combination therapy should be considered in patients with severely elevated lipid levels that are unresponsive to monotherapy. In some disorders, such as familial hypercholesterolemia, up to 3 or 4 drugs may be required. Many randomized trials of short duration (3 to 6 months) have compared single and combination drug regimens for their effects on serum.
Selection of Drugs for Lipid Control

- For high LDL cholesterol level only, consider statins first, resins or an intestinal absorption-blocker second, and niacin third.
- For high LDL cholesterol and low HDL cholesterol levels, consider statins first and niacin second.
- For high LDL cholesterol, low HDL cholesterol, and high triglyceride levels, consider niacin and statins first and fibrates second.
- For high triglyceride levels, with or without low HDL cholesterol levels, consider fibrates first and niacin second.
- For low HDL cholesterol levels only, consider niacin first and fibrates second.

<table>
<thead>
<tr>
<th>Table 1. Goals for Therapy Using LDL Cholesterol Levels</th>
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<tr>
<td>Risk Group</td>
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<td></td>
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<tr>
<td>High risk</td>
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<tr>
<td>CHD or CHD risk equivalents (10-year risk &gt;20%)*</td>
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<tr>
<td>Moderately high risk</td>
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<tr>
<td>Moderate risk</td>
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<tr>
<td>Lower risk</td>
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CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

* CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerosis (peripheral vascular disease, abdominal aortic aneurysm, carotid disease, and stroke; diabetes, and ≥2 risk factors with 10-year risk for CHD >20%).

† Any person at high risk or moderately high risk who has lifestyle-related risk factors (obesity, physical inactivity, elevated triglyceride levels, low HDL cholesterol levels, or the metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL cholesterol levels.

‡ If baseline LDL cholesterol level is <2.59 mmol/L (<100 mg/dL), an LDL cholesterol-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglyceride levels and low HDL cholesterol levels, combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug can be considered.

§ Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on medication), low HDL cholesterol level (<1.03 mmol/L [<40 mg/dL]), family history of premature CHD (<55 years of first-degree male relative and <65 years of first-degree female relative), and age (men, ≥45 years; women, ≥55 years).

∥ For moderately high-risk persons, when LDL cholesterol levels are 2.59 to 3.34 mmol/L (100 to 129 mg/dL), at baseline or with lifestyle therapy, using an LDL cholesterol-lowering drug to achieve an LDL cholesterol level <2.59 mmol/L (<100 mg/dL) is a therapeutic option on the basis of available clinical trial results.
lipid levels. It is also important to realize that specific agents may be more effective when used in combination, because they act synergistically to treat certain lipid abnormalities. Combination therapy can lower LDL cholesterol level but can also lower triglyceride levels and raise HDL cholesterol levels, both secondary goals in lipid management (29–31). Ezetimibe decreases LDL cholesterol levels by blocking absorption through the intestine (30). Although ezetimibe decreases LDL cholesterol levels, clinical trials show that it does not reduce coronary events (30, 31).

Two major studies released in 2008 showed no survival benefit of ezetimibe when used in combination with statin therapy (32, 33). Because no clinical trial has shown that ezetimibe decreases coronary events, it is not recommended as primary therapy for patients with elevated LDL cholesterol levels.

The lipid-lowering medications that are combined most frequently include statins, bile acid–binding resins, fibrates, and nicotinic acid. However, 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 (34). Nicotinic acid, either crystalline or the extended-release niacin preparation (Niaspan), can be effective with statins because it is complementary by raising HDL cholesterol levels and lowering triglyceride levels. Clinicians should avoid using long-acting, nonflushing, over-the-counter niacin preparations, because they can cause hepatotoxicity. A systematic review found that high-dose statin monotherapy seems to be superior to combination therapy (35).

What are the therapeutic goals of treatment?
Just like therapeutic decisions, treatment goals are individually determined according to the patient’s level of risk based on the presence or absence of CAD, CAD risk equivalents, non–coronary vascular disease, and other risk factors (Box).

How should therapy for dyslipidemia be monitored?
Most interventions to treat dyslipidemia require at least 6 months to reduce the risk for CVD event rates (5), 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 schedule follow-up 6 weeks after the initiation of any new lipid-lowering agent with a fasting lipid profile. During this follow-up visit, 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. Although some authors advocate routinely monitoring liver function tests before each follow-up visit, statin-induced hepatotoxicity seems much less common than previously believed, so the American College of Physicians’ guideline on treatment for dyslipidemia in type 2 diabetes does not recommend routine liver function tests in patients treated with statins (36, 37).

More frequent visits may be required to provide counseling about behavioral lifestyle changes, which generally require much support from the clinician to foster adherence. Overall, only 39% of patients receiving drug therapy and only 34% of patients receiving dietary therapy reach their NCEP goal (38). New or additional drugs should be added one at a time because, if adverse reactions occur, it is easier to determine which drug

References:
34. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97:52C-60C. [PMID: 16581329]
## Table 2. Drug Treatment for Lipid Disorders

<table>
<thead>
<tr>
<th>Drug Class and Mechanism of Action</th>
<th>Dose</th>
<th>Benefits</th>
<th>Side Effects</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Statins (HMG-CoA reductase)</strong></td>
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<td>Partially inhibit HMG-CoA reductase, the rate-limiting step of cholesterol synthesis. This induces LDL receptor formation and the removal of LDL cholesterol from blood.</td>
<td><strong>Atorvastatin</strong> (10–80 mg/d)</td>
<td>Well-studied for safety and efficacy in many trials; LDL cholesterol-lowering ranges from 22% to 63% depending on drug.</td>
<td>Abnormal liver function tests (relatively uncommon). Myositis/myalgias (use with fibrates increases risk). Rosuvastatin should not be given with warfarin or gemfibrozil.</td>
<td>Choice of drug for elevated LDL cholesterol based on efficacy and safety. The 6 statins are metabolized differently, allowing substitution if side effects occur. Used in combination with bile acid–binding resins to synergistically reduce LDL cholesterol. Use with niacin and fibrates in patients combined hyperlipidemia. Rosuvastatin is newest and as well studied as the other statins. Do not use in pregnant or nursing women. Avoid with active liver disease. 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 &gt;3.39 mmol/L (&gt;300 mg/dL) or in gastrointestinal motility disorder. Does not reliably reduce (and can increase) LDL cholesterol level. Use cautiously with statins due to myositis/myalgia. Use with repaglinide may cause severe hypoglycemia.</td>
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<td><strong>Fluvastatin</strong> (20–40 mg every night or 80 mg XL every night)</td>
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<td><strong>Lovastatin</strong> (10–40 mg evening meal or 10–60 XL every night)</td>
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<td></td>
<td><strong>Pravastatin</strong> (10–80 mg at bedtime)</td>
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<td></td>
<td><strong>Rosuvastatin</strong> (5–40 mg/d)</td>
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<td></td>
<td><strong>Simvastatin</strong> (5–80 mg at evening meal)</td>
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<td><strong>Bile acid sequestrants</strong></td>
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<td>Interrupt bile acid reabsorption requiring bile acid synthesis from cholesterol.</td>
<td><strong>Colestipol</strong> (2 scoops 2 or 3 times per day)</td>
<td>Nonabsorbed with long-term safety established. LDL cholesterol-lowering by 10% to 15%.</td>
<td>Unpleasant taste/texture, bloating, heartburn, constipation, drug interaction (avoidable by administering drugs 1 h before or 4 h after meals). Triglyceride levels increase.</td>
<td>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 &gt;3.39 mmol/L (&gt;300 mg/dL) or in gastrointestinal motility disorder. Does not reliably reduce (and can increase) LDL cholesterol level. Use cautiously with statins due to myositis/myalgia. Use with repaglinide may cause severe hypoglycemia.</td>
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<tr>
<td></td>
<td><strong>Colestyramine</strong> (3.8 g total)</td>
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<td><strong>Fibrates</strong></td>
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<td>Reduce VLDL synthesis and lipoprotein lipase.</td>
<td><strong>Gemfibrozil</strong> (600 mg 2 times per day)</td>
<td>Best triglyceride level-reducing drugs, lowers by 50% or more in many patients. Increases HDL cholesterol level by 15%.</td>
<td>Nausea, skin rash. Use with caution if renal insufficiency or gallbladder disease.</td>
<td>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. 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–binding resins in patients with combined hyperlipidemia. Do not use in pregnant or nursing women. Can increase LDL cholesterol level in some patients with increased triglyceride levels.</td>
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<td></td>
<td><strong>Fenofibrate</strong> (45–145 mg/d depending on brand)</td>
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<td><strong>Ezetimibe</strong></td>
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<td>Selectively inhibits intestinal absorption of cholesterol and related phytosterols.</td>
<td>10 mg once per day</td>
<td>Reduces LDL cholesterol level by 18%, triglyceride level by 8%, and apolipoprotein B by 16%.</td>
<td>Well-tolerated, but contraindicated in patients with liver disease or elevated liver enzyme levels.</td>
<td>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. 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–binding resins in patients with combined hyperlipidemia. Do not use in pregnant or nursing women. Can increase LDL cholesterol level in some patients with increased triglyceride levels.</td>
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<td><strong>Niacin</strong></td>
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<td>Largely unknown; reduces hepatic production of B-containing lipoproteins. Increases HDL cholesterol.</td>
<td><strong>Niacin</strong> (500–750 mg to 1–2 g every night of extended-release niacin)</td>
<td>Lowers LDL cholesterol and triglyceride levels 10% to 30%. Most effective drug to raise HDL cholesterol level (25% to 35%).</td>
<td>Flushing, nausea, glucose intolerance, gout, liver function test abnormalities, and elevated uric acid. May increase homocysteine.</td>
<td>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. 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–binding resins in patients with combined hyperlipidemia. Do not use in pregnant or nursing women. Can increase LDL cholesterol level in some patients with increased triglyceride levels.</td>
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<td><strong>Omega-3</strong></td>
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<td>Polyunsaturated fatty acids inhibit hepatic triglyceride synthesis and augment chylomicron triglyceride clearance secondary to increased activity of lipoprotein lipase.</td>
<td>4–6 g/d with higher dosing for OTC formulations</td>
<td>Effective in controlling triglyceride levels up to 45%. Raises HDL cholesterol level 13%.</td>
<td>Dyspepsia, nausea. May increase bleeding time. Use cautiously in patients receiving anticoagulant therapy.</td>
<td>Can increase LDL cholesterol level in some patients with increased triglyceride levels.</td>
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<td><strong>Ezetimibe and simvastatin</strong> (combination drug)</td>
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<td>Both selectively inhibit the intestinal absorption of cholesterol and partially inhibit HMG-CoA reductase.</td>
<td><strong>Ezetimibe</strong>, 10 mg every night; <strong>Simvastatin</strong>, 10–80 mg every night</td>
<td>Combination therapy may improve patient adherence. Synergistic benefits.</td>
<td>Abnormal liver function tests. Myositis, myalgia.</td>
<td>Avoid use with fibrates, &gt;1 g; niacin; amiodarone; or verapamil due to increased risk for myopathy. Contraindicated in liver disease and in pregnant or nursing women.</td>
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HDL = high-density lipoprotein; LDL = low-density lipoprotein; OTC = over-the-counter; VLDL = very-low-density lipoprotein.
caused the problem. The NCEP ATP III recommends that after treatment with the initial lipid-lowering agent is started, the clinician should reassess the fasting lipid profile in 6 weeks to assess the response to therapy. If the LDL cholesterol goal is still not achieved, further intensification of therapy should be considered, with re-evaluation in another 6 weeks (5).

What are the side effects of drug therapy for dyslipidemia?
The most common side effect of statins (HMG-CoA reductase inhibitors) are myalgias, myositis, and elevated liver enzyme levels; however, 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 (39). A study discovered that variations in a gene encoding a transporter protein are linked to many cases of statin-induced myopathy (36).

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 statin therapy is associated with a small excess risk for aminotransferase elevations (risk difference per 1000 patients [RD], 4.2 [95% CI, 1.5 to 6.9]) but not for myalgias (RD, 2.7 [CI, −3.2 to 8.7]), creatine kinase elevations (RD, 0.2 [CI, −0.6 to 0.9]), rhabdomyolysis (RD, 0.4 [CI, −0.1 to 0.9]), or withdrawal of therapy compared with placebo (RD, −0.5 [CI, −4.3 to 3.3]) (40).

However, trial findings may differ from the experience in actual clinical practice.

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 myalgias. The intestinal cholesterol absorption-blocking drugs and the bile acid–binding drugs tend to cause abdominal bloating and constipation; otherwise, they are generally well-tolerated. Niacin is valuable and efficacious but probably the least well-tolerated lipid-lowering agent. However, community-based studies revealed higher rates of muscle symptoms.

Niacin can cause flushing, nausea, headache, glucose intolerance, and gout. Some of these effects can be minimized with proper drug administration. To minimize flushing, a nonenteric-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 a niacin dose.

Clinicians should be vigilant for side effects when prescribing drugs for dyslipidemia. Unfortunately, evidence is insufficient to establish clear recommendations regarding monitoring and management of 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 differ, it may be reasonable to substitute one statin for another when side effects occur.

What should clinicians advise patients about the use of complementary–alternative therapies for dyslipidemia?
Among commonly used alternative therapies for controlling lipids, plant–based diets have shown some effectiveness (42), including stanol ester–containing margarines or foods, oat bran (43), and nuts in moderation (44). 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 for help in managing patients with dyslipidemia?**

The clinician should consider consulting a lipid specialist for patients with lipid disorders that are rare or resistant to treatment. These include those patients with specific rare disorders that 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 III dyslipoproteinemia, very low HDL cholesterol syndromes (HDL cholesterol level <0.5 mmol/L [<20 mg/dL]), and resistant hypertriglyceridemia (triglyceride level >11.3 mmol/L [>1000 mg/dL]). Also, patients with a high risk for a vascular event, such as young patients with vascular disease before the age of 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 lower their LDL cholesterol level substantially below the usual LDL cholesterol goal, to raise their HDL cholesterol level, or to identify and treat other lipid and nonlipid risk factors. Current treatments to lower LDL cholesterol level are very efficacious; however, a poor response may prompt an examination of secondary causes, such as unusual lipid and lipoprotein disorders or poor adherence to medication.

**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 from 1 July through 31 December 2007 (45) 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 earlier, 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 (5, 6). In addition, evidence-based guidelines include an American College of Physicians’ guideline on lipid control in patients with type 2 diabetes (46). A comprehensive

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

**CLINICAL BOTTOM LINE**

**Practice Improvement**


Dyslipidemia

PIER Modules
http://PIER.acponline.org
Access the following PIER modules: Screening for Dyslipidemia, Lipid Disorders. PIER modules provide an evidence-based, electronic resource for clinical recommendations and links to patient information materials at the point of care.

Practice Guidelines
www.ahrq.gov/clinic/uspstf/uspschol.htm
Access the U.S. Preventive Services Task Force recommendations on screening for dyslipidemia (update anticipated in late 2007).
Access the National Cholesterol education Program Adult Treatment Panel III recommendations on detection, evaluation, and treatment of high cholesterol.
www.annals.org/cgi/reprint/140/9/644.pdf
Access the American College of Physicians’ guideline on pharmacologic treatment of dyslipidemia in patients with type 2 diabetes.

Framingham Risk Calculator
Use this calculator to estimate a person’s risk for cardiovascular events.

Patient Information
www.annals.org/intheclinic/toolkit-dyslipidemia.html
Download a copy of the patient information sheet that appears on the following page for duplication and distribution to your patients.
Obtain the patient information pamphlet, “Managing Your Cholesterol,” developed by the American College of Physicians.

Figure. Treatment of dyslipidemia helps prevent this disease. Low magnification micrograph of the distal right coronary artery with complex atherosclerosis and luminal narrowing.
THINGS YOU SHOULD KNOW ABOUT LIPIDS (CHOLESTEROL)

Lipids (cholesterol) are fatty substances in the blood. Lipids can build up and clog blood vessels, which contributes to heart attack, stroke, or other forms of heart disease. There are several types of lipids that affect health: Your LDL cholesterol is a bad type of cholesterol, whereas the HDL cholesterol is a good type that removes cholesterol build up.

Ideal lipid levels and the need to control lipid levels depend on whether a person is at greater risk for heart attacks or strokes. This risk is increased for diabetes, high blood pressure, tobacco use, family history of heart disease, or other factors that increase risk for heart attack and stroke. Talk about your lipid levels with your doctor.

Things You Can Do to Control Lipids

- Keep body weight normal (BMI, 18.5 to 24.9 kg/m²).
- Get fewer than 25% to 35% of your daily calories from fat, less than 7% of your calories from saturated fat, and less than 200 mg of cholesterol per day.
- Eat a diet that contains more plant-based foods (vegetables, fruits, grains) than animal-based foods (meat, dairy, eggs).
- Exercise at least 30 minutes on most days of the week.
- Avoid all forms of tobacco.
- Drink no more than 1 to 2 alcoholic beverages per day.

For More Information

Web Sites With Good Information About Lipids

www.nlm.nih.gov/medlineplus/cholesterol.html
MedlinePLUS

www.americanheart.org/presenter.jhtml?identifier=4488
American Heart Association

www.nhlbi.nih.gov/cholesterol
www.nhlbisupport.com/chd1/52Tipsheets/foodgroup.htm
National Heart, Lung, and Blood Institute
1. A 57-year-old woman is seen after a stenting procedure of the left main coronary artery. The patient has type 2 diabetes mellitus. Her father had a myocardial infarction at age 62 years. Current medications are rosuvastatin, 40 mg/d; aspirin, 81 mg/d; and glipizide, 10 mg/d.

On physical examination, blood pressure is 152/92 mm Hg. Lungs are clear. Cardiac examination reveals no murmurs, and the point of maximal impulse is not displaced. Fasting lipid levels are as follows: total cholesterol level, 5.18 mmol/L (200 mg/dL); HDL cholesterol level, 1.09 mmol/L (42 mg/dL); LDL cholesterol level, 3.13 mmol/L (121 mg/dL); triglyceride levels, 2.07 mmol/L (183 mg/dL). Hemoglobin A\(^1c\) level is 6.9%.

Which is the most appropriate treatment for this patient?
A. Add a second lipid-lowering drug
B. Increase the dose of rosuvastatin
C. Substitute fenofibrate for rosuvastatin
D. Substitute metformin for glipizide

2. A 63-year-old man is evaluated during a follow-up appointment. One month ago, he had a transient ischemic attack. Carotid ultrasonography revealed a 60% left internal carotid artery stenosis, and transthoracic echocardiogram revealed left ventricular hypertrophy. He is currently asymptomatic. He has hypertension and quit smoking 10 years ago. He has no history of coronary artery disease and no family history of premature coronary artery disease. Current medications are hydrochlorothiazide and aspirin. His LDL cholesterol level 6 months ago was 3.57 mmol/L (138 mg/dL), and he has adhered to recommended lifestyle modifications, including diet and exercise.

On physical examination, blood pressure is 125/85 mm Hg, the BMI is 30 kg/m\(^2\), waist circumference 38 inches, and the remainder of the examination is unremarkable. Fasting lipid levels are as follows: serum total cholesterol, 4.63 mmol/L (184 mg/dL); serum triglyceride level, 2.26 mmol/L (226 mg/dL); serum HDL cholesterol level, 1.01 mmol/L (39 mg/dL); serum LDL cholesterol level, 2.59 mmol/L (100 mg/dL).

Which is the most appropriate next step in the management of this patient?
A. Statin therapy
B. Fibric acid derivative
C. Serum LDL cholesterol particle-size measurement
D. Diet and exercise

3. A 65-year-old man is evaluated during a routine visit. His medical history includes hypertension controlled with hydrochlorothiazide. He is otherwise healthy, however, he admits to a sedentary lifestyle and no regular exercise program.

On physical examination, the blood pressure is 125/85 mm Hg, the BMI is 30 kg/m\(^2\), waist circumference 38 inches, and the remainder of the examination is unremarkable. Fasting lipid levels are as follows: total cholesterol level, 5.34 mmol/L (206 mg/dL); HDL cholesterol level, 1.3 mmol/L (50 mg/dL); LDL cholesterol level, 3.32 mmol/L (128 mg/dL); triglyceride level, 1.63 mmol/L (144 mg/dL).

In addition to continuing therapeutic lifestyle changes, which is the most appropriate management option for this patient?
A. Add atorvastatin
B. Add nicotinic acid
C. Change hydrochlorothiazide to amlodipine
D. Change hydrochlorothiazide to carvedilol

4. A 50-year-old man has a routine evaluation. He has type 2 diabetes mellitus, diagnosed 5 years ago. He reports measuring his plasma glucose level in the morning and sporadically throughout the day and has noted no foot or eye problems. Medical history is also significant for hypertension, hyperlipidemia, and coronary artery disease treated with stenting 3 years ago. He reports rare episodes of chest pain. Medications include metformin, 1000 mg twice daily; aspirin, 81 mg/d; lovastatin, 80 mg/d; lisinopril, 20 mg/d; and atenolol, 25 mg/d.

Physical examination findings, including blood pressure of 120/80 mm Hg, are unremarkable. Lipid levels are as follows: hemoglobin A\(^1c\) 6.9%; serum creatinine, normal; serum potassium, normal; serum total cholesterol level, 4.78 mmol/L (185 mg/dL); serum triglyceride level, 1.69 mmol/L (150 mg/dL); serum HDL cholesterol level, 1.16 mmol/L (45 mg/dL); serum LDL cholesterol level, 2.84 mmol/L (110 mg/dL).

Which is the most appropriate next step in the management of this patient?
A. Increase lovastatin dose
B. Continue periodic monitoring of serum cholesterol level
C. Substitute a higher-potency statin, such as atorvastatin or rosuvastatin
D. Add gemfibrozil