

in the clinic Dyslipidemia

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Dyslipidemia affects 1 of every 2 American adults and is a major risk factor for cardiovascular disease (CVD), cardiovascular death, and all-cause mortality. Large observational studies have found 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 coronary artery disease (CAD) events (1, 2). Long-term prospective epidemiologic studies have consistently shown that persons with healthier lifestyles and fewer coronary risk factors, particularly those with normal lipid profiles, have an overall lower incidence of CVD. Prevention and sensible management of dyslipidemia can markedly alter cardiovascular morbidity and mortality.

Prevention and Screening

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. Clinicians should routinely encourage all patients to adopt the following habits (3, 4):

- Attain and maintain normal body weight.
- Follow a diet containing less than 25%–35% of calories from fat, less than 7% of calories from saturated fat, and fewer than 200 mg of cholesterol per day.
- Emphasize a plant-based diet (vegetables, fruits, and high-fiber foods), with the goal of consuming at least 2 grams per day of plant sterols and 10–25 grams per day of viscous (soluble) fiber.
- Exercise aerobically for at least 30 minutes on most and preferably all days of the week.
- Avoid all forms of tobacco.
- Consume no more than 1–2 alcoholic beverages per day.

Regardless of the presence of pre-existing CVD, patients who adopt these habits will have healthier lipid profiles, placing them in lower risk strata for cardiovascular events. Because of their higher baseline risk, patients with preexisting

disease may see the most marked alteration in risk for poor health outcomes. Ultimately, increasing healthy lifestyles should reduce population-wide lipid levels and 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 of age and women older than 45 (5). Clinicians should also screen younger adults (men aged 20–35 years or women aged 20–45 years) who have other risk factors for CVD, whose family history suggests a heritable familial lipid disorder, or who have evidence of hyperlipidemia on physical examination. Of note, the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) recommends beginning screening of all adults at age 20, regardless of cardiovascular risk profile (4). The rationale is that screening promotes healthy behaviors and increases public awareness of cholesterol, in addition to identifying very high-risk patients (6, 7). However, the incremental yield and cost-effectiveness of earlier universal screening as opposed

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2. Goldbourt U, Yaari S. Cholesterol and coronary heart disease mortality. A 23-year follow-up study of 9902 men in Israel. *Arteriosclerosis*. 1990;10:512-9. [PMID: 2369362]
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4. National Cholesterol Education Program. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Institutes of Health: Bethesda, MD 2002. NIH No. 02-5215 accessed at www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf on 11 July 2007.
5. Screening for Lipid Disorders in Adults. U.S. Preventive Services Task Force: Rockville, MD; 2001. Accessed at [www.ahrq.gov/clinic/uspstf/uspstf.htm](http://www.ahrq.gov/clinic/uspstf/uspstf/uspstf.htm) on 11 July 2007.

to risk factor–based screening in young adults is unclear.

Moderate-quality evidence supports screening adults older than 65 years. Total cholesterol predicts CVD in the elderly, and persons older than 65 have a higher baseline risk for CVD, increasing their potential absolute benefit from interventions to manage dyslipidemia (8). Regardless of age, all patients with known CVD should have lipid levels measured.

How and how often should clinicians screen for dyslipidemia?

It is acceptable to screen for dyslipidemia with nonfasting serum total cholesterol and HDL cholesterol levels since these measures can identify persons at increased risk for CVD as well as other lipid measures.

A study that compared fasting and nonfasting total cholesterol values in 181 general internal medicine outpatients found no clinically important difference in fasting and nonfasting results for total and HDL cholesterol levels (9).

The NCEP–ATP III advocates initial screening with a fasting lipid profile that includes measurement of triglycerides and indirect calculation of LDL cholesterol level (4). The U.S. Preventive Services Task Force does not recommend the inclusion of triglyceride measurement as part of lipid profile evaluation

(5). LDL cholesterol and triglyceride measurements are useful for guiding treatment, but do not improve risk prediction better than measurement of total and HDL cholesterol only.

When screening for dyslipidemia, clinicians should confirm abnormalities with 2 measurements at least a week apart before initiating therapy (10). The average of the 2 measures should be considered the baseline when lipid control interventions are instituted. Clinicians should measure LDL cholesterol in patients with unfavorable total and HDL cholesterol levels to guide management decisions after screening. Measurement of LDL cholesterol requires a fasting sample. Direct measurement of LDL does not require fasting, but it is not offered in all laboratories, may be expensive, and does not improve risk prediction. However, it is necessary when triglyceride levels are > 400 mg/dL.

In the absence of data to support a specific screening interval, screening every 5 years seems reasonable in low-risk patients since 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 dyslipidemia. Evidence best supports routine screening for dyslipidemia in men aged > 35 years and women > 45 years. However, the NCEP–ATP III advocates that screening for dyslipidemia begin at age 20 as a way to increase awareness of dyslipidemia and promote healthy behaviors. Screening at earlier ages is warranted for patients with cardiovascular risk factors or a clinical history suggestive of familial hyperlipidemia. Nonfasting total and HDL cholesterol levels are sufficient for initial screening, but abnormal values should be confirmed with a second test and LDL levels are warranted for guiding treatment decisions. Some authors also advocate routine measurement of triglycerides. In the absence of good data to guide screening frequency, screening every 5 years seems reasonable unless patients are near a threshold for therapy or develop new risk factors.

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. Calculation of risk using specific risk equations appears 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 screening maneuvers, including lipid measures alone and algorithms based on expert guidelines (11).

Electronic tools for calculating risk are publicly available (12). Patients and clinicians can also calculate risk using **Figure 1**. The Framingham risk equation allows the clinician to classify patients by their respective level of risk, including the following: CAD or CAD risk equivalent (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 tests should clinicians obtain before starting therapy for dyslipidemia?

Epidemiologic studies have associated high levels of LDL cholesterol with particularly high absolute risk for CAD in the presence of 2 or more CAD risk factors (13). Prospective studies consistently show > 20% 10-year risk for myocardial infarction or CAD death in patients in this risk subgroup. Therefore, the clinician must first focus on identifying elevated LDL cholesterol.

In addition to obtaining 2 measures of LDL cholesterol to confirm diagnosis, it is important for clinicians to set thresholds before initiating potential lifelong therapy and to identify causes of LDL > 130 mg/dL so that they can target diet and drug therapy to the lipid transport abnormality that is elevating the LDL cholesterol (Table 1). Randomized clinical trials of various lipid-lowering drugs have found that efficacy in lowering LDL cholesterol is related to the abnormality in lipid metabolism (14).

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

HDL Cholesterol

Clinicians should pay close attention to HDL cholesterol and potential causes of levels < 40 mg/dL (Table 2), which include elevated triglycerides, obesity, physical inactivity, type 2 diabetes, tobacco, very high carbohydrate intake (> 60% of calories), and certain drugs (β -blockers, anabolic steroids, progestational agents). Identification of the specific disorder of low HDL cholesterol allows institution of therapies to raise HDL cholesterol.

Triglycerides

Triglyceride levels are another secondary target for therapy. Many prospective epidemiologic studies have shown increased triglycerides to be related to increased risk for CAD (15). Meta-analyses of prospective studies indicate that elevated triglycerides are an independent risk factor for CAD (16). In men, adjustment for other risk factors (e.g., diabetes, HDL cholesterol, obesity) often removes the association. Despite evidence suggesting a stronger association of elevated triglyceride levels with CAD in women than in men (17), there are no trials examining the benefit of triglyceride lowering in

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12. National Cholesterol Education Program. Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death). National Institutes of Health: Bethesda, MD; 2002. Accessed at <http://hp2010.nhlbi-hin.net/atpiiii/calculator.asp?usertype=prof> on 11 July 2007.

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Step 1: Determine the patient's Framingham point scores

Risk Factor	Points					
Age						
	Men (Women)					
20-34	-9 (-7)					
35-39	-4 (-3)					
40-44	0 (0)					
45-49	3 (3)					
50-54	6 (6)					
55-59	8 (8)					
60-64	10 (10)					
65-69	11 (12)					
70-74	12 (14)					
75-79	13 (16)					
HDL Cholesterol						
	Men and Women					
≥60	-1					
50-59	0					
40-49	1					
<40	2					
Systolic BP (mm Hg)						
	Untreated Men (Women)	Treated Men (Women)				
<120	0 (0)	0 (0)				
120-129	0 (1)	1 (3)				
130-139	1 (2)	2 (4)				
140-159	1 (3)	2 (5)				
≥160	2 (4)	3 (6)				
Total Cholesterol		Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
	Men (Women)	Men (Women)	Men (Women)	Men (Women)	Men (Women)	Men (Women)
<160	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
160-199	4 (4)	3 (3)	2 (2)	1 (1)	0 (1)	0 (1)
200-239	7 (8)	5 (6)	3 (4)	1 (2)	0 (1)	0 (1)
240-279	9 (11)	6 (8)	4 (5)	2 (3)	1 (2)	1 (2)
≥280	11 (13)	8 (10)	5 (7)	3 (4)	1 (2)	1 (2)
Tobacco						
	Men (Women)	Men (Women)	Men (Women)	Men (Women)	Men (Women)	Men (Women)
Nonsmoker	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoker	8 (9)	5 (7)	3 (4)	1 (2)	1 (1)	1 (1)

Step 2: Add points from above to estimate patient's 10-year risk of a cardiovascular event

Total Points	Men		Total Points	Women	
	Total Points	10-Year Risk (%)		Total Points	10-Year Risk (%)
<0	<0	<1	<9	<1	<1
0	0	1	9	1	1
1	1	1	10	1	1
2	2	1	11	1	1
3	3	1	12	1	1
4	4	1	13	2	2
5	5	2	14	2	2
6	6	2	15	3	3
7	7	3	16	4	4
8	8	4	17	5	5
9	9	5	18	6	6
10	10	6	19	8	8
11	11	8	20	11	11
12	12	10	21	14	14
13	13	12	22	17	17
14	14	16	23	22	22
15	15	20	24	27	27
16	16	25	≥25	≥30	≥30
≥17	≥17	≥30			

Figure 1. Tool to estimate 10-year risk of cardiovascular event using Framingham point scores

women. The clinician should stratify patients, based on fasting triglyceride levels as follows: normal, <150 mg/dL; borderline high, 150 to 199 mg/dL; high, 200 to 499 mg/dL; and very high, > 500 mg/dL. Borderline

high triglyceride levels suggest specific familial abnormalities of triglyceride-rich lipoprotein metabolism in which the liver overproduced triglyceride-rich lipoproteins. Persons with elevated triglyceride

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Table 1. Differential Diagnosis of Elevated LDL Cholesterol*

<i>Disease</i>	<i>Characteristics</i>	<i>Notes</i>
Heterozygous familial hypercholesterolemia (Frederickson-Levy type IIa)	<ul style="list-style-type: none"> LDL cholesterol >220 mg/dL Xanthomas, elevated total or LDL cholesterol in childhood confirm diagnosis Autosomal-dominant inheritance with 1/500 prevalence in United States First-degree relative with early-onset CAD and/or familial hypercholesterolemia 	<ul style="list-style-type: none"> Identifies persons with deficiency of LDL receptors best treated with HMG-CoA reductase inhibitors and/or bile acid-binding resins
Familial combined hyperlipidemia (Frederickson-Levy type IIb)	<ul style="list-style-type: none"> Elevated LDL cholesterol and/or elevated triglycerides Elevated apolipoprotein B levels First-degree relative with early-onset CAD and/or lipid disorder Autosomal-dominant inheritance with incomplete penetrance; gene prevalence as high as 25% in United States Associated with the metabolic syndrome 	<ul style="list-style-type: none"> Identifies persons with hepatic overproduction of B-containing lipoproteins who may benefit from niacin therapy
Dysbetalipoproteinemia (Frederickson-Levy type III)	<ul style="list-style-type: none"> Elevated LDL cholesterol and triglycerides Family history of early-onset CAD and/or hyperlipidemia Low prevalence of xanthomas Associated with apolipoprotein E₂ homozygosity Prevalence of 1/1750 in patients with CAD Associated with atherosclerotic disease, especially peripheral vascular disease 	<ul style="list-style-type: none"> Broad beta band on lipoprotein electrophoresis, but best confirmed by apolipoprotein E₂-E₂ genotype Responsive to fibric acids, HMG-CoA reductase inhibitors
Polygenic hypercholesterolemia	<ul style="list-style-type: none"> Elevated LDL cholesterol Variable family history of early-onset CAD and/or hyperlipidemia Unclear inheritance pattern 	<ul style="list-style-type: none"> Most common pattern in hypercholesterolemia
Secondary hypercholesterolemia	<ul style="list-style-type: none"> Elevated LDL cholesterol with or without high triglycerides Associated with signs and symptoms of the underlying condition 	<ul style="list-style-type: none"> Diet and drug therapies often ineffective Correction of underlying secondary cause may normalize lipid profile

* CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

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

levels are more likely to have the metabolic syndrome. High triglyceride levels may also be due to reduced clearance of triglyceride-rich lipoprotein or may identify persons with other metabolic problems in need of intervention (e.g., diabetes, alcoholism, chronic renal failure, and the nephrotic syndrome). Triglyceride levels > 500 mg/dL are associated with pancreatitis and warrant treatment.

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 detection of

secondary causes of dyslipidemia. Physical examination should include measurement of body mass index and blood pressure; peripheral vascular examination with measurement of ankle-brachial index and evaluation for bruits to assess cardiovascular risk; and evaluation of the liver and thyroid to identify evidence of secondary causes of dyslipidemia, skin for xanthomas, and eyes for xanthelasmas and hypertensive changes.

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

Secondary causes of dyslipidemia include hypothyroidism, obstructive

Table 2. Differential Diagnosis of Low HDL Cholesterol* (< 40 mg/dL)

<i>Disease</i>	<i>Characteristics</i>
Familial hypoalphalipoproteinemia	<ul style="list-style-type: none">• HDL cholesterol levels may be very low (<10 mg/dL)• Many rare genetic defects have been identified (Tangier disease, Fisheye disease, apolipoprotein A₁ Milano)• Not all cases are high risk, but family history of early-onset atherosclerosis is associated with deleterious forms• Usually low apolipoprotein A₁ levels
Familial combined hyperlipidemia	<ul style="list-style-type: none">• HDL cholesterol levels inversely related to triglyceride levels, except in cases of alcoholism and estrogen use• Part of the metabolic syndrome• May respond to weight loss and drug therapies that reduce triglyceride levels
Low HDL cholesterol in the presence of low total cholesterol	<ul style="list-style-type: none">• Populations with low total cholesterol and triglyceride levels (triglyceride <150 mg/dL) may have low HDL cholesterol but normal apolipoprotein A₁ levels• Probably not related to CAD risk• Reassure patient if apolipoprotein A₁ levels are normal
Secondary hypoalphalipoproteinemia	<ul style="list-style-type: none">• May be secondary to drug therapy (progestogens, anabolic steroids, and β-blockers without intrinsic sympathetic activity), chronic renal failure, cigarette smoking, or obesity

* CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

liver disease, the nephrotic syndrome, renal failure, uncontrolled diabetes mellitus, and tobacco or alcohol use. Various drugs can also cause dyslipidemia.

It is important to control secondary causes before starting drug therapy to modify lipids because the lipid abnormality may disappear with correction of the secondary cause and drug therapy can be ineffective in the presence of these conditions. If a drug is suspected to be the cause of the lipid abnormality, consider the

benefits vs. the risks before discontinuing therapy.

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

Clinicians should consider apolipoprotein evaluation and referral to a lipid specialist when they suspect the patient might have genetic familial hypercholesterolemia. These persons may have difficulty controlling lipids and are at a high risk for early CVD. Screening first-degree relatives is warranted.

Drugs That Can Cause Dyslipidemia

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

Diagnosis... Clinicians should obtain 2 measures of LDL 1 week apart in patients found to have unfavorable total and HDL cholesterol levels on screening examination. LDL levels should be interpreted in light of cardiovascular risk using the Framingham risk equation. Measurement of HDL cholesterol and triglycerides can help to identify the causes of dyslipidemia and further target intervention. Focus history and physical examination on the identification of CVD, cardiovascular risk factors, and potential secondary causes of dyslipidemia. Specialized testing and specialty referral may be useful if familial hypercholesterolemia is suspected.

CLINICAL BOTTOM LINE

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When should clinicians consider therapeutic interventions for patients with dyslipidemia?

Once dyslipidemia has been confirmed and the patient's coronary risk status has been evaluated, the NCEP-ATP III advocates intervention as summarized in the following discussion (4).

What should clinicians advise patients with dyslipidemia about lifestyle changes?

All patients with lipid disorders should be advised about the importance of therapeutic lifestyle changes. Patients should institute these changes regardless of whether drug therapy is also prescribed. Use of the NCEP-ATP III Therapeutic Lifestyle Change Diet (Table 3) can result in a 5% to 15% reduction in LDL cholesterol. According to the National Health and Nutrition Examination Survey (NHANES) III, a 15% reduction in LDL cholesterol could reduce the need for cholesterol-lowering drugs from 14% to 5%, if applied to the entire U.S. population (18). A diet rich in fruits, vegetables, nuts, and whole grains with use of monounsaturated oils (olive oil, canola oil) and low in red meat and animal fat seems to substantially reduce risk, independent of serum lipid levels (19).

Increased soy consumption can increase HDL cholesterol.

Patients with dyslipidemia should attain and maintain a normal body weight. Overweight patients should reduce their caloric intake from fat 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 (e.g., running, walking, cycling, or swimming) will greatly enhance weight reduction programs. Studies of weight loss with or without exercise suggest that exercise facilitates optimizing lipids (20).

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 for weight reduction.

When should clinicians recommend drug therapy?

Decisions regarding when to add drug therapy to dietary modifications depend on underlying risk factors and the individual clinical situation. Strong evidence supports drug therapy for high-risk patients when LDL cholesterol levels are

Table 3. Diet for Therapeutic Lifestyle Changes

Nutrient	Recommended Intake
Saturated fat*	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%–35% of total calories
Carbohydrate (especially complex)	50%–60% of total calories
Fiber	20–30 g/d
Protein	Approximately 15% of total calories [†]
Cholesterol	<200 mg/d

*Trans fatty acids also raise low-density lipoprotein cholesterol, and intake should be kept to a minimum.

[†]Balance energy intake and expenditure to maintain desirable body weight.

above NCEP-ATP III LDL cholesterol goals. Low-risk patients should complete a 6-month trial of lifestyle changes before considering drugs. A lower threshold for starting drugs is reasonable when LDL cholesterol levels are > 15% above threshold. In patients with CAD or a CAD equivalent, LDL cholesterol level > 100 mg/dL is a threshold for initiation of therapy. In high-risk patients with evidence of CVD progression, some clinicians begin therapy at lower LDL cholesterol levels (> 70 mg/dL). For patients hospitalized with CAD, many experts initiate LDL cholesterol-lowering drugs before discharge if LDL cholesterol > 130 mg/dL (21). Reduction in LDL cholesterol levels will reduce the risk for clinical coronary disease and stroke in diverse settings, including primary prevention, secondary prevention, and diabetes. The recommendations on when to start therapy are based on the evidence for the effectiveness of drug therapy for reducing cardiovascular events by improving lipid levels.

In a primary prevention trial that randomly assigned 6595 men 45 to 64 years of age to pravastatin or placebo, the relative risk reduction of coronary events with pravastatin was 31% (95% CI, 17% to 43%) with no excess death from noncardiovascular causes (22). In another analysis, pravastatin therapy reduced hospital admissions for CVD without adverse effects on noncardiovascular hospitalization (23).

In a trial comparing lovastatin with placebo for primary prevention in adults with average total cholesterol and LDL cholesterol levels and below-average HDL cholesterol levels, lovastatin reduced the incidence of first acute major coronary events (relative risk, 0.63 [CI, 0.50 to 0.79] (24).

A trial evaluated the effect of simvastatin vs. placebo on mortality and morbidity in 4444 patients with CAD and found that the relative risk for death in patients receiving simvastatin vs. those receiving placebo was 0.70 [CI, 0.58 to 0.85] (25).

In a secondary analysis of a randomized, controlled trial, pravastatin reduced the

rate of recurrent cardiovascular events in patients aged 65 to 75 years (26).

A trial compared the secondary prevention effects of pravastatin with those of a placebo over 6.1 years in 9014 patients who were 31 to 75 years of age. The study found that the relative risk reductions for pravastatin vs. placebo were 24% (CI, 12% to 35%) for CAD death and 22% (CI, 13% to 31%) for overall mortality (27).

What options are available for drug therapy?

There are various lipid-lowering agents that can be used alone or combined to achieve the patient's individual NCEP-ATP III cholesterol goals (Table 4). A good 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, attempt to increase HDL cholesterol to > 40 mg/dL and reduce triglycerides to < 150 mg/dL by selection or combination of drugs with effects on multiple lipoproteins.

When is combination drug therapy for dyslipidemia warranted?

Combination therapy should be considered in patients with severely elevated lipids that are unresponsive to monotherapy. In some disorders, such as familial hypercholesterolemia, up to 3 or 4 drugs may be required. It is also important to realize that specific agents are more effective when used in combination as they act synergistically to treat certain lipid abnormalities where single-drug therapy has been ineffective in normalizing the lipid profile.

Numerous randomized trials of short duration (3 to 6 months) have compared single and combination drug regimens for their effects on serum lipid levels. Combination drug regimens are often superior in their ability to lower LDL cholesterol and concomitantly lower triglyceride levels and raise HDL

Implementation of Interventions for Dyslipidemia

Patients with 0–1 cardiac risk factor:

- If LDL cholesterol \geq 160 mg/dL, institute lifestyle changes.
- If LDL cholesterol \geq 190 mg/dL, add drug therapy.
- If LDL cholesterol 160–189 mg/dL, consider adding drug therapy based on patient preferences.

Patients with 2 or more risk factors and 10-year risk <10%:

- If LDL cholesterol > 130 mg/dL, institute lifestyle changes.
- If LDL cholesterol \geq 160 mg/dL, consider adding drug therapy.

Patients with 10-year risk 10–20%:

- If LDL cholesterol >130 mg/dL, strongly consider adding drug therapy to lifestyle changes.
- If LDL cholesterol 100–129 mg/dL, consider adding drug therapy to lifestyle changes based on patient preferences.

Patients with 10-year risk > 20%, CAD, or CAD risk equivalents:

- If LDL cholesterol > 100 mg/dL, initiate drug therapy and lifestyle changes.
- If LDL cholesterol 70–100 mg/dL, initiate lifestyle changes and consider drug therapy.

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26. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med*. 1998;129:681-9. [PMID: 9841599]
27. The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-57. [PMID: 9841303]

Table 4. Drug Treatment for Lipid Disorders*

Drug Class	Mechanism of Action	Dosage	Benefits	Side Effects	Notes
Statins (HMG-CoA reductase inhibitors)	Partially inhibit HMG-CoA reductase, the rate-limiting step of cholesterol synthesis; this induces LDL-receptor formation and removal of LDL cholesterol from blood	Atorvastatin (10–80 mg QD)	Well-studied for safety and efficacy in many trials	Abnormal liver function tests (less common than previously thought); myositis/myalgias (use with fibrates increases risk); rosuvastatin should not be given with warfarin or gemfibrozil	Drug of choice 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 in combination with niacin and fibrates in patients with combined hyperlipidemia. Rosuvastatin is newest and not as thoroughly studied as the other statins.
		Fluvastatin (20–40 mg every night or 80 mg XL every night)			
		Lovastatin (20–80 mg every night)			
		Pravastatin (10–40 mg every night)			
		Rosuvastatin (5–40 mg every night)			
Bile acid sequestrants	Interrupt bile acid reabsorption requiring bile acid synthesis from cholesterol	Colestipol (2 scoops bid or tid)	Nonabsorbed with long-term safety established; LDL cholesterol lowering 10%–15%	Taste/texture, bloating, heartburn, constipation, drug interaction (avoidable by administration of drugs 1 hour before or 4 hours after meals); triglyceride increase	First-line drug to lower LDL cholesterol in children and in women with child-bearing potential. Second-line drug with statins to synergistically induce LDL receptors. Do not use if triglycerides levels are >300 mg/dL or if the patient has a gastrointestinal motility disorder.
		Colesevelam hydrochloride (three 625-mg tablets bid [3.8 g total])			
Fibrates	Reduce VLDL synthesis and induces lipoprotein lipase	Gemfibrozil (600 mg bid)	Best triglyceride-reducing drugs, lowers 50% or more in many patients; increases HDL 15%	Nausea, skin rash; use with caution if renal insufficiency or gallbladder disease	Does not reliably reduce (and may increase) LDL cholesterol. Use cautiously with statins due to myositis/myalgia. Use with repaglinide may cause severe hypoglycemia.
		Fenofibrate (43–200 mg/day depending on brand)			
Ezetimibe	Selectively inhibits intestinal absorption of cholesterol and related phytosterols	10 mg once daily	Reduces LDL by 18%, triglycerides by 8%, and apolipoprotein B by 16%	Well tolerated, but contraindicated in patients with liver disease or elevated liver enzymes	Can use in combination with statins to yield further LDL reduction, increase in HDL, and triglyceride reduction. Do not combine with resins, fibrates, or cyclosporine.
Niacin	Largely unknown; reduces hepatic production of B-containing lipoproteins, increases HDL cholesterol production	Niacin (500 mg–1 g tid or 500 mg–2 g every night of extended-release niacin)	Lowers LDL cholesterol and triglycerides 10%–30%; most effective drug at raising HDL cholesterol (25%–35%)	Flushing, nausea, glucose intolerance, gout, liver function test abnormalities, and elevated uric acid levels; may increase homocysteine levels	Drug of choice for combined hyperlipidemia and in patients with low HDL cholesterol. Extended-release preparations limit flushing and liver function test abnormalities. Long-acting OTC niacin preparations are not recommended, as they increase the incidence of hepatotoxicity. Lowers lipoprotein (a). Used in combination with statins or bile acid-binding resins in patients with combined hyperlipidemia.
Omega-3 polyunsaturated fatty acids	Inhibit hepatic triglyceride synthesis and augment chylomicron triglyceride clearance secondary to increased activity of lipoprotein lipase	4 g/day	Effective in controlling triglyceride levels up to 45%; raises HDL 13%	Dyspepsia, nausea; may increase bleeding time; use cautiously in patients receiving anticoagulant therapy	Can increase LDL in some patients with increased triglycerides.
Ezetimibe and simvastatin (combination drug)	Both selectively inhibit the intestinal absorption of cholesterol and partially inhibit HMG-CoA reductase	Ezetimibe: 10 mg/simvastatin: 10, 20, 40, or 80 mg every night	Combination therapy fosters patient adherence; synergistic benefits	Abnormal liver function tests, myositis/myalgia	Contraindicated in liver disease, pregnant or nursing women. Avoid use with fibrates, >1 g niacin, amiodarone, or verapamil due to increased risk for myopathy.

* *bid* = twice daily; *CAD* = coronary artery disease; *HDL* = high-density lipoprotein; *LDL* = low-density lipoprotein; *OTC* = over the counter; *tid* = three times daily; *VLDL* = very-low-density lipoprotein.

cholesterol levels—both secondary goals in lipid management (28, 29).

A community-based, randomized trial involving over 3000 patients found that LDL cholesterol levels can be significantly reduced by another 25.8% with the addition of ezetimibe (10 mg) to statin therapy (30).

When prescribing combination therapy, be vigilant for drug interactions, such as those between P-450-metabolized drugs, like statins, and fibrates; this interaction may induce rhabdomyolysis.

What are the 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, noncoronary vascular disease, and other risk factors (Table 5).

How should therapy for dyslipidemia be monitored?

Most interventions for dyslipidemia require 6 months or more to affect clinical event rates, and all treatments are usually life-long. Regular follow-up is important after initiation of drug therapy for dyslipidemia. In the absence of direct

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 routine monitoring of liver function tests before each follow-up visit, statin-induced hepatotoxicity seems to be less common than previously believed, and the American College of Physicians' guideline on treatment for dyslipidemia in type 2 diabetes does not advocate routine measurement of liver function tests in patients receiving statins (31, 32).

More frequent visits may be necessary to deliver counseling about therapeutic lifestyle changes, which require much support from the clinician in fostering adherence. New agents that are used as monotherapy or combination therapy should be added one drug at a time because if adverse reactions occur, the clinician will be better able to determine

Selection of Drugs for Lipid Control

- In patients with high LDL only, consider statins first, resins or an intestinal absorption blocker second, and niacin third.
- In patients with high LDL and low HDL, consider statins first and niacin second.
- In patients with high LDL, low HDL, and high triglycerides, consider niacin and statins first and fibrates second.
- In patients with high triglycerides, with or without low HDL, consider fibrates first, niacin second, and statins third.
- In patients with low HDL only, consider niacin first and fibrates second.

Table 5. Goals and Thresholds for Therapy according to LDL Cholesterol Levels

Risk Group	Low-Density Lipoprotein Cholesterol Goal (mg/dL)	Initiate Lifestyle Change (mg/dL)	Consider Drug Therapy (mg/dL)
High risk: CAD* or CAD risk equivalents† (10-year risk >20%)	<100 (optional goal <70)	≥100‡	≥100 (or >70)
Moderately high risk: ≥2 risk factors‡ (10-year risk 10%–20%)	<130 (optional goal <100)	≥130‡	≥130 (or 100–129)
Moderate risk: ≥2 risk factors‡ (10-year risk <10%)	<130	≥130	≥160
Lower risk: 0–1 risk factor	<160	≥160	≥190

* Coronary artery disease (CAD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

† CAD risk equivalents include clinical manifestations of noncoronary forms of atherosclerosis (peripheral vascular disease, abdominal aortic aneurysm, and carotid disease; diabetes, and ≥2 risk factors with 10-year risk for CAD >20%).

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

28. Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. *Circulation*. 2003;107:2409-15. [PMID: 12719279]
29. Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol*. 2002;90:1084-91. [PMID: 12423708]
30. Pearson TA, Denke MA, McBride PE, et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clin Proc*. 2005;80:587-95. [PMID: 15887425]

which agent is causing the effects. Consensus recommendations advocate 6-week follow-up with lipid measurement after each new agent is started.

What are the side effects of drug therapy for dyslipidemia?

Statins (HMG-CoA reductase inhibitors) can cause myalgia, myositis, and elevated liver enzymes. Fibrates can cause nausea and skin rashes 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, although generally they are otherwise well-tolerated. Niacin is valuable and efficacious but is probably the least tolerated lipid lowering agent. It can cause flushing, nausea, headache, glucose intolerance, and gout. Some of these untoward 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.

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 1 to 65 months, the authors concluded that statin therapy is associated with a small excess risk for aminotransferase elevations (risk difference/1000 patients [RD, 4.2 [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]). Trial findings may differ from what occurs in practice (33).

Clinicians should be vigilant for side effects when prescribing drugs for dyslipidemia. Unfortunately, there is insufficient evidence to

establish clear recommendations for the monitoring for 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 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, stanol-ester-containing margarines or foods (34), flaxseed (35), and garlic (36) show some effectiveness. Other nontraditional therapies that have possible evidence of some effect on lipids are green tea extract, commiphora wightii (guggul or guggulipid), and pomegranate juice. However, these 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 considered in this category may include patients with familial hypercholesterolemia, type III dyslipoproteinemia, very low HDL cholesterol syndromes (HDL cholesterol < 20 mg/dL), and resistant hypertriglyceridemia (triglycerides > 1000 mg/dL). Also, patients who are at a very high risk for a vascular event, such as very young patients with vascular disease before the age of 45 and those with

31. American College of Physicians. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. *Ann Intern Med.* 2004;140:650-8. [PMID: 15096337]

32. Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Lipid control in the management of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2004;140:644-9. [PMID: 15096336]

33. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation.* 2006;114:2788-97. [PMID: 17159064]

evidence of disease progression despite treatment, should be considered as candidates for referral to a lipid specialist. Patients at very high risk may need multiple interventions to lower their LDL cholesterol substantially below the usual goal, to raise HDL cholesterol, or to identify and treat

other lipid and nonlipid risk factors. Current treatments to lower LDL cholesterol are very efficacious; however, a poor response may prompt an examination of secondary causes, such as unusual lipid and lipoprotein disorders, lack of compliance, or other causes.

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

CLINICAL BOTTOM LINE

Practice Improvement

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

In April 2005, The Ambulatory Care Quality Alliance released a set of 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 (Table 6). In addition, a voluntary program within Medicare, the 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 (37) and includes a measure related to lipid control in patients with diabetes.

Table 6. Ambulatory Care Quality Alliance Dyslipidemia-Related Quality Indicators*

Indicator	Description	Notes
Lipid measurement	Percentage of patients with diabetes with ≥ 1 LDL cholesterol test or 1 all-component test	The all-component test is a lipid panel that includes LDL cholesterol, HDL cholesterol, and triglycerides separately Measurement interval is the past 15 mo
LDL cholesterol level measurement	Percentage of patients with diabetes with ≥ 1 LDL cholesterol level < 100 mg/dL or < 130 mg/dL	Actually 2 measures reflecting moderately successful (< 130 mg/dL) and optimal (< 100 mg/dL) treatment outcomes Measurement interval is the past 15 mo
Drug therapy for lowering LDL cholesterol	Percentage of patients with CAD who were prescribed a lipid-lowering therapy	Based on current ACC/AHA guidelines

*ACC/AHA = American College of Cardiology/American Heart Association; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

34. Miettinen TA, Puska P, Gylling H, et al. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med*. 1995;333:1308-12. [PMID: 7566021]
35. Jenkins DJ, Kendall CW, Vidgen E, et al. Health aspects of partially defatted flaxseed, including effects on serum lipids, oxidative measures, and ex vivo androgen and progestin activity: a controlled crossover trial. *Am J Clin Nutr*. 1999;69:395-402. [PMID: 10075322]
36. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. *Ann Intern Med*. 2000;133:420-9. [PMID: 10975959]
37. American College of Physicians. Medicare Pay-for-Reporting Program: Physicians Quality Reporting Initiative (PQRI) Resources Physicians Quality Report Initiative (PQRI) Overview. Accessed at www.acponline.org/pmc/pqri.htm on 11 July 2007.

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

As noted earlier, several organizations offer recommendations about dyslipidemia screening and these recommendations differ with respect to the age at which screening should be started and which screening tests should be used (4, 5). In addition, evidence-based guidelines are available to guide clinicians in the care of patients with the disorder and include an

American College of Physicians guideline on lipid control in patients with type 2 diabetes (32). 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 the National Heart Lung and Blood Institute's NCEP-ATP III document, which is available at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm (4).

in the clinic Tool Kit

Dyslipidemia

PIER Modules

<http://PIER.acponline.org>

Access the following PIER modules: Screening for Dyslipidemia, Lipid Disorders.

Practice Guidelines

www.abrq.gov/clinic/uspstf/uspschol.htm

Access the U.S. Preventive Services Task Force recommendations on screening for dyslipidemia (update anticipated in late 2007).

www.nhlbi.nih.gov/guidelines/cholesterol/index.htm

Access the National Cholesterol education Program Adult Treatment Panel III recommendations on detection, evaluation, and treatment of high cholesterol.

www.annals.org/cgi/reprint/140/8/644.pdf

Access the American College of Physicians' guideline on pharmacologic treatment of dyslipidemia in patients with type 2 diabetes.

Framingham Risk Calculator

<http://bp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof>

Use this calculator to estimate a person's risk for cardiovascular events.

LDL Calculator

<http://cpsc.acponline.org/enhancements/ldlCalc.html>

Use this calculator to determine a patient's LDL from total cholesterol, HDL cholesterol and triglyceride levels.

Patient Information

www.annals/intbeclinic/tools

Download a copy of the patient information sheet that appears on the following page for duplication and distribution to your patients.

www.doctorsforadults.com/images/healthpdfs/cholesterol_report.pdf

Obtain the patient information pamphlet, "Managing Your Cholesterol," developed by the American College of Physicians.

in the clinic

THINGS PEOPLE SHOULD KNOW ABOUT LIPIDS (CHOLESTEROL)

In the Clinic
Annals of Internal Medicine

Lipids (cholesterol) are fatty substances in the blood. Lipids can build up inside arteries and lead to heart attack, stroke, or other forms of heart disease. There are several types of lipids that affect health.

Ideal lipid levels and the need for treatment to control lipids depend on whether a person has diabetes, high blood pressure, tobacco use, family history of heart disease, or other factors that make them high risk for heart attack and stroke. Discuss your lipid levels with your doctor.

Lipids and Their Role in Health

<i>Lipid Type</i>	<i>Description</i>	<i>Normal and Abnormal Levels, mg/dL</i>
LDL (low-density lipoprotein cholesterol)	"Bad" cholesterol: High levels increase buildup of lipids and blockages in arteries	Below 100 (very good) 100–129 (OK) 130–159 (borderline bad) 160–189 (bad) 190 or above (very bad)
HDL (high-density lipoprotein cholesterol)	"Good" cholesterol: High levels protect arteries from buildup of lipids and blockages in arteries	Below 40 (bad) 40–60 (OK) 60 or above (good)
Total cholesterol	Combination of different types of cholesterol	Below 200 (good) 200–239 (borderline bad) 240 or above (bad)
Triglycerides	Another type of fat in the blood; high levels can block arteries	Below 150 mg/dL (good) 150–199 (borderline bad) 200–499 (bad) 500 or above (very bad)

Things You Can Do to Control Lipids

- Keep body weight normal.
- Follow a diet containing less than 25% to 35% of calories from fat, less than 7% of 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.
- Consume no more than 1 to 2 alcoholic beverages per day.

Web Sites with Good Information about Lipids

MedlinePLUS

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

American Heart Association

www.americanheart.org/presenter.jhtml?identifier=4488

National Heart, Lung, and Blood Institute

www.nhlbi.nih.gov/chd/why.htm

1. A 45-year-old man with a history of coronary artery disease is evaluated for a lipid disorder. He has been taking simvastatin, 40 mg/d, for the past year with no significant side effects; however, his coronary artery disease has continued to progress. He exercises regularly and is following the therapeutic lifestyle change diet. A lipid profile demonstrates the following results: serum total cholesterol, 200 mg/dL; triglycerides, 150 mg/dL; high-density lipoprotein (HDL) cholesterol, 41 mg/dL; and low-density lipoprotein (LDL) cholesterol, 125 mg/dL. Thyroid function and liver function are normal.

What is the most appropriate therapy for this patient?

- A. Increase the dosage of simvastatin to 80 mg/d
 - B. No further lipid-lowering therapy
 - C. Add a bile acid sequestrant or ezetimibe
 - D. Add gemfibrozil, 150 mg twice daily
2. A 57-year-old man with established coronary artery disease is being treated with atorvastatin, 40 mg/d. His current lipid profile is as follows: total cholesterol, 202 mg/dL; LDL cholesterol, 98 mg/dL; HDL cholesterol, 41 mg/dL; triglycerides, 315 mg/dL; non-HDL cholesterol, 161 mg/dL; very-low-density lipoprotein cholesterol, 63 mg/dL.
- The next step in the management of this patient should focus on which of the following target values?
- A. Serum total cholesterol <200 mg/dL
 - B. Serum triglycerides <200 mg/dL
 - C. Serum HDL cholesterol > 45 mg/dL
 - D. Serum non-HDL cholesterol <130 mg/dL
 - E. High-sensitivity C-reactive protein <0.5 mg/L

3. A 65-year-old man is referred for elevated blood pressure (165/95 mm Hg). He is 170 cm (67 in) tall and weighs 86.5 kg (190 lb). Waist circumference is 106.5 cm (42 in). Fasting lipid profile yields the following results: serum total cholesterol, 284 mg/dL; triglycerides, 300 mg/dL; HDL cholesterol, 34 mg/dL; and LDL cholesterol, 190 mg/dL. He smokes a pack of cigarettes per day, eats a typical American diet with frequent consumption of fast food, and has a sedentary lifestyle. He has no symptoms of coronary artery disease, and his electrocardiogram is normal. The patient's calculated Framingham risk is > 30% for coronary artery disease within the next 10 years.

What is the most appropriate management for this patient?

- A. Begin a therapeutic lifestyle change diet and exercise program with a follow-up appointment in 6 months.
 - B. Begin therapy with a statin with the goal of lowering LDL cholesterol to 130 mg/dL.
 - C. Begin therapy with a statin with the goal of lowering LDL cholesterol to <100 mg/dL and non-HDL cholesterol to <130 mg/dL.
 - D. Begin therapy with a bile acid sequestrant.
 - E. Begin therapy with an insulin sensitizer.
4. A 66-year-old woman presents for a second opinion. During a recent visit to the gynecologist, the patient's total cholesterol level was 300 mg/dL. The gynecologist prescribed a statin, but the patient is reluctant to take medication. She has no other risk factors, has a healthy lifestyle, and does not have coronary artery disease.

What is the appropriate recommendation for this patient?

- A. Initiation of statin therapy
 - B. Initiation of therapy with a bile acid sequestrant
 - C. Measurement of fasting lipid profile
 - D. Initiation of therapy with ezetimibe
5. A 62-year-old woman is having an annual physical. She has had well-controlled type 2 diabetes mellitus for 7 years that is currently managed with metformin and glipizide. Her recent hemoglobin A_{1c} was 6.8%, and almost all of her home glucose measurements are within the targeted range. She adheres to a "heart-healthy" diet and has maintained a stable body weight since diagnosis (BMI 28.7). Her blood pressure has been well controlled on lisinopril, 5 mg/d. A recent fasting lipid profile shows the following: total cholesterol, 194 mg/dL; LDL cholesterol, 107 mg/dL; HDL-cholesterol, 52 mg/dL; triglycerides, 176 mg/dL. LDL cholesterol levels have ranged between 103 and 116 mg/dL over the past 3 years.

Which of the following is the most appropriate therapy to reduce this patient's cardiovascular risk?

- A. Diet only
- B. Atorvastatin
- C. Niacin
- D. Fenofibrate
- E. Ezetimibe

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.