Evaluation and Management of Lipid Disorders

Bridgette A. Christopher, MD, PhD
Fellow, Division of Cardiology
Sarah W. Stedman Nutrition and Metabolism Center
and Duke Molecular Physiology Institute
Duke University School of Medicine
Durham, North Carolina

Neha J. Pagidipati, MD, MPH
Assistant Professor of Medicine
Division of Cardiology and Duke Clinical Research Institute
Duke University School of Medicine
Durham, North Carolina
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409 12th Street, SW
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Evaluation and Management of Lipid Disorders
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This monograph is designed to enable the obstetrician–gynecologist to do the following:

- Understand the underlying pathophysiology of lipid disorders
- Appropriately screen for and diagnose lipid disorders in women
- Evaluate women with lipid disorders and initiate management
- Manage lipid disorders in women when appropriate and refer when indicated
- Counsel women about lifestyle changes and other interventions that decrease the risk of lipid disorders and their sequelae

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Heart disease remains the leading cause of mortality in women despite scientific evidence that altering risk factors can significantly affect the morbidity and mortality of this disease. Dyslipidemia is one of these modifiable risk factors. Because obstetrician–gynecologists play a prominent role in providing preventive health care to women, they should be proactive in identifying women with abnormal lipid profiles and providing the best initial evidence-based management for these patients.

This monograph was written by Bridgette Christopher, MD, PhD, and Neha Pagidipati, MD, MPH. Dr. Christopher is currently completing her final year of cardiology fellowship at Duke University and plans to practice general cardiology with an emphasis on prevention. Dr. Pagidipati is a cardiovascular prevention specialist at Duke University who is focusing on lipid, obesity, and diabetes management in patients at high risk of cardiovascular disease. The authors have synthesized numerous recommendations from multiple resources and organizations into a single easy-to-follow guide on screening, diagnosis, and management that focuses on women with dyslipidemia across the entire spectrum of their health care. Obstetrician–gynecologists should find this monograph, along with the included tables, boxes, and figures, useful in the office setting.

Russell R. Snyder, MD
Editor
ABSTRACT: Cardiovascular disease (CVD) remains the leading cause of mortality for women, and only a small percentage of women have optimally managed risk factors. One of the strongest risk factors for CVD is an increased lipid level. Many women seek primary care from obstetrician–gynecologists who often identify and provide initial management of dyslipidemia in these women. Thus, it is imperative that obstetrician–gynecologists become familiar with the identification and treatment of women with dyslipidemia to minimize their future risk of CVD. This monograph provides a brief primer on the epidemiology, pathophysiology, diagnosis, and management of dyslipidemia in women, as it pertains to CVD risk.

It is estimated that 16.5 million U.S. individuals have cardiovascular disease (CVD) (1), and CVD remains the major cause of death among U.S. women (2). Despite continuing advances in the treatment of CVD, heart disease is responsible for nearly 25% of all deaths in women older than 65 years (2). Although treating established CVD remains a focus of clinical research, identifying and managing the at-risk population continues to be one of the ultimate goals of cardiovascular (CV) care. Prevention of CVD in at-risk populations would decrease overall mortality and the significant cost of treatment of progressive CVD in the total population (3, 4).

Multiple modifiable risk factors for CVD have been identified, including the following seven factors (1):

1. Dyslipidemia
2. Hypertension
3. Poor diet
4. Sedentary behavior
5. Obesity
6. Tobacco use
7. Dysglycemia

Attaining an increased rate of optimal control of these risk factors is associated with a decreased rate of overall and CV mortality (5). However, a study in the National Health and Nutrition Examination Survey III cohort showed that less than 7.5% of adults met the goal for at least six of the seven factors (5). A large meta-analysis from multiple U.S. studies also noted poor management of risk factors, with less than 3% of the participants achieving optimal management (6). Particularly, women appear to have poor control of CVD risk factors (7).

Dyslipidemia, or increased lipid levels associated with an increased risk of disease, affects approximately 53% (105.3 million) of U.S. adults (8). Among reproductive-aged women, 25% have a low-density lipoprotein (LDL) cholesterol level of 130 mg/dL or greater (9).
The high prevalence of dyslipidemia in the United States is concerning because of its strong relationship with CVD risk. Dyslipidemia has been estimated to account for 49% of the population-attributable risk of a first myocardial infarction (MI)\(^{(10)}\). Clinical trials and observational studies have consistently shown a log-linear relationship between LDL cholesterol level and coronary heart disease, without a clear threshold below which the risk is zero \(^{(11)}\). Thus, dyslipidemia (specifically, an increase in the LDL cholesterol level) is a critical risk factor to control in the general population.

Because most women predominantly seek care from obstetrician–gynecologists throughout early and mid-adulthood \(^{(12)}\), these clinicians have an important role in screening for and managing dyslipidemia in women. This monograph provides information regarding the current approaches for the screening, diagnosis, and management of women with dyslipidemia. Referral to a cardiologist or a lipid specialist also is addressed (Box 1). The ultimate goal of this monograph is to outline an evidence-based approach to the management of women with dyslipidemia to reduce the overwhelming burden of CVD.

**Anatomy, Physiology, and Pathophysiology**

The importance of lipids in the development of atherosclerosis and ultimately clinical CVD has been well established. Some of the earliest studies showed the clear association between increased LDL cholesterol levels and CV events, such as MI \(^{(13)}\). Conversely, studies focused on mitigating increased LDL cholesterol levels have shown a reduction in CVD mortality \(^{(14)}\). Understanding the pathophysiology of dyslipidemia is crucial to properly identifying and treating patients at risk of CVD.

**Box 1. Indications for Referral to a Cardiologist or a Lipid Specialist**

- History of clinical atherosclerotic cardiovascular disease (CVD)
- Low-density lipoprotein cholesterol level of 190 mg/dL or greater
- Fasting triglyceride level of 500 mg/dL or greater
- Familial hypercholesterolemia (homozygous and heterozygous)
- Family history of premature atherosclerotic CVD
- Findings on physical examination concerning for hypercholesterolemia (eg, xanthoma, arcus cornealis, and xanthelasma)
- Failure of statin therapy to achieve appropriate low-density lipoprotein cholesterol level
- Statin intolerance or history of rhabdomyolysis with statin therapy
- Additional concerns by the clinician regarding family history or personal risk factors for CVD
Lipids are abundant in the plasma, but a carrier system is required to transport hydrophobic lipids through primarily aqueous plasma. Lipids are packaged in complex structures involving lipoproteins, and the structure of these lipoproteins facilitates the constituent lipids within the molecules and the ultimate destination of the lipoprotein in the body. Lipoprotein molecules are commonly classified by their density in plasma. However, although “LDL” and “high-density lipoprotein (HDL)” are commonly used terms in clinical practice, it is important to realize that lipoprotein particles occur on a spectrum. There is no clear cutoff in density or size for each molecule, and particles, such as LDL, can vary from small, dense, highly atherogenic particles to larger, less dense, less atherogenic particles (15). The laboratory value of the LDL cholesterol level is expressed as concentration in milligrams per deciliter, which does not indicate the size or number of individual lipoprotein particles. Also, it is important to note that the composition of apolipoproteins (carrier proteins that bind lipids) varies across the spectrum of these molecules. The study of certain apolipoproteins, such as apo AI found in HDL particles and apo B100 found in LDL particles, has identified the unique roles of these different proteins (16). However, many of the apolipoproteins found in these complex transport molecules remain incompletely understood.

The overall role of lipoproteins is to transport lipids between structures, such as the gastrointestinal tract, liver, plasma, muscle, and peripheral tissues. This is a bidirectional system: 1) one subset of lipoproteins ferries lipids from the digestive system into circulation and ultimately to tissues for uptake and use (Fig. 1 and Fig. 2) and 2) the reverse system moves lipoproteins from peripheral tissues back to the liver (Fig. 3). Both arms of this transport system can play a role in clinical dyslipidemia (17).

Lipoproteins play a key role in the body’s ability to uptake lipids from the diet and transport them to tissues. When fats and cholesterol are ingested in the diet, they are hydrolyzed by lipases in the digestive system into smaller components of free fatty acids and small glyceride particles. These smaller lipid components encounter bile salts in the intestines, and these complexes are transported into intestinal cells. Within the intestinal cells, lipids are packaged into chylomicrons and moved into the portal circulation and then plasma. Peripheral tissues, such as muscles, can extract free fatty acids from chylomicrons, and chylomicrons also are transported to the liver for further processing. Chylomicrons are processed into very low-density lipoprotein (VLDL) within the liver and excreted back into circulation. Once in circulation, VLDL can be used by peripheral tissues to extract lipids, and they also can interact with other lipoprotein particles, such as HDL, to exchange contents. It is this cycle of exchanging contents and lipoproteins that exemplifies the concept of a lipoprotein spectrum: shedding triglycerides moves VLDL to intermediate-density lipoprotein (IDL) and ultimately allows for repackaging to LDL in the liver, whereas the addition and subtraction of various apolipoproteins in the transport molecule determines the trafficking of the molecule and its lipid contents.
Figure 1. Cholesterol transport exogenous pathway.

Figure 2. Cholesterol transport endogenous pathway. Abbreviations: IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.
The transport of cholesterol is key to its role in atherogenesis. Circulating LDL cholesterol can move from the plasma into the walls of arteries. Enzymes found within the intima of arteries lead to cholesterol modifications, such as oxidation and glycation, and modified cholesterol triggers a cascade of events that leads to monocyte recruitment. Once monocytes engulf modified cholesterol, they become lipid-laden macrophages known as foam cells. Inflammatory molecules released by foam cells trigger migration of smooth muscle cells into the arterial intima, and ultimately remodeling and fibrosis of the foam cell–smooth muscle cell milieu leads to formation of intimal atheroma covered by a fibrous cap (16). If a fibrous cap ruptures, the inflammatory and thrombotic components of the atheroma are exposed to circulating platelets and coagulation factors. Clinically, acute coronary syndrome results from an acute plaque rupture that triggers thrombosis and blockage of coronary flow, leading to ischemia of heart muscle. Studies of medications that can lead to atheroma regression and stabilization are ongoing to lessen the risk of acute plaque rupture and thrombosis, but previous studies have shown that decreasing circulating levels of LDL cholesterol also are associated with decreased rates of acute coronary syndrome (11).

Cholesterol can be synthesized de novo in the liver, which is the basis for mechanism of action of statin medications. Statins act by inhibiting hydroxymethylglutaryl-CoA reductase, the rate limiting enzyme of cholesterol synthesis. Many clinical trials have demonstrated that statins not only decrease LDL cholesterol concentration in plasma but also significantly decrease CV events and mortality (17–19). Another key step in lipid
metabolism is LDL particle uptake by the liver, which has been a major target of pharmacologic intervention. The importance of the LDL receptor in the uptake and processing of the LDL particle was noted in studies of familial hypercholesterolemia (20–22). Mutations in the LDL receptor that led to decreased uptake of LDL particles from plasma and, consequently, increased plasma LDL cholesterol concentration are associated with increasing rates of atherosclerosis and MI. More recent studies have identified mutations in LDL receptor-associated proteins that can either increase or decrease LDL transport depending on the mutation. One such protein is proprotein convertase subtilisin/kexin type 9 (PCSK9), which binds to LDL receptors and inhibits their recycling, preventing them from returning to the cell surface to remove LDL particles from the plasma (23–25). New monoclonal antibody therapies targeted at blocking interaction of PCSK9 with the LDL receptor have shown promise in decreasing plasma concentrations of LDL cholesterol, with decreases in CV mortality (26). Research is ongoing into other key components of the regulation and uptake of LDL particles.

The proportion of lipids within lipoproteins influences the pathogenicity of the particles in atherosclerosis. The absolute concentration of LDL cholesterol in plasma (which is reported on a typical lipid panel) is important, but so are particle number and particle size (15). Expert lipidologists will use these variables in patients whose LDL cholesterol concentrations do not fully explain an individual’s risk of CVD.

Although the role of LDL cholesterol in CVD has been established clinically, the role of HDL cholesterol in atherosclerosis is less well understood. Research has shown that higher plasma HDL cholesterol concentrations are associated with lower rates of atherosclerosis and coronary artery disease (CAD) (27); however, increasing the HDL cholesterol level in clinical trials has not been shown to improve CV outcomes. For example, niacin and cholesterol ester transfer protein inhibitors, which increase plasma HDL cholesterol concentrations, have not been shown to improve CV mortality (28–31). It is possible that HDL cholesterol is a marker of CV risk but is not directly involved in the pathophysiology of CVD. Currently, decreasing the LDL cholesterol level rather than increasing the HDL cholesterol level is the mainstay of lipid management.

Much of the understanding of the role of LDL cholesterol in atherosclerosis comes from the study of familial hypercholesterolemia. Familial hypercholesterolemia encompasses multiple mutations, but the most common mutations affect the LDL receptor. Patients who carry a mutation that decreases the function of LDL receptors cannot clear LDL cholesterol from the bloodstream. Therefore, they have lifetime high exposure to LDL cholesterol, which leads to premature and severe atherosclerosis (32). The most common type of familial hypercholesterolemia is inherited in an autosomal dominant fashion. Homozygous patients with familial hypercholesterolemia have the most severe phenotypes (20), and overall prevalence is predicted to be approximately 1 in 250,000 patients (33). Heterozygous individuals with familial hypercholesterolemia are more common, and recent estimates predict that between 2% and 4% of the general population may
have this disorder (33). The long-term risk of increased LDL cholesterol exposure underscores the need to identify and treat patients with familial hypercholesterolemia as early as possible (34).

**Screening for Dyslipidemia and Assessment of Cardiovascular Risk**

The rationale for screening for lipid disorders is based on the following evidence:

- Dyslipidemia is common (35).
- Testing is quick, easy, inexpensive, and reliable.
- Level of LDL cholesterol is directly related to the risk of CVD (12).
- Treatment of dyslipidemia in patients with established CVD or at high risk of CVD decreases the risk of CV events (17).

Controversy exists regarding the appropriate candidates and timing of screening (36). However, cardiologists in the United States generally use the American College of Cardiology (ACC) and American Heart Association (AHA)’s 2013 blood cholesterol guidelines as a reference for screening (19). These guidelines suggest that all adults aged 21 years or older be screened for dyslipidemia with a fasting lipid panel (and have their overall CVD risk assessed) every 4–6 years (19). A fasting lipid panel is preferred to a nonfasting panel because LDL cholesterol is calculated using the triglyceride level, which may be increased after eating. If the nonfasting triglyceride level is greater than 500 mg/dL, a fasting lipid panel is required to calculate LDL cholesterol level.

Screening for dyslipidemia should not be performed during pregnancy because lipid levels increase dramatically throughout pregnancy (37) and do not completely normalize until approximately 1 year postpartum (38). Lipid levels begin to decrease in the early postpartum period; therefore, if women have not been screened previously, a fasting lipid panel at the 6-week postpartum visit is an acceptable initial test (38). If lipid levels are increased, lifestyle counseling and future testing can be planned.

Once the fasting lipid panel results are obtained, subsequent management and assessment of CV risk should follow the 2013 ACC/AHA blood cholesterol guidelines (19). These guidelines are based on the strength of evidence available to support each treatment pathway. It is important to understand the strength of each recommendation, as delineated by classification of recommendation and level of evidence (Table 1). When the recommendation is very strong (such as classification of recommendation I and level of evidence A), the patient should be informed that a significant body of evidence demonstrates benefit with treatment. However, if the patient has a condition for which treatment is associated with a weaker recommendation, it is important to discuss this with the patient. Familiarity with the strength of recommendations for each patient group will assist the clinician in providing appropriate counseling for shared decision making.
The 2013 ACC/AHA blood cholesterol guidelines define four patient groups that will likely benefit from lipid therapy (Fig. 4) (19). The first group with potential treatment benefit includes individuals aged 21 years or older with clinical CVD, including CAD (history of MI, stable or unstable angina, or coronary revascularization), peripheral arterial disease, or cerebrovascular disease (stroke or transient ischemic accident). For secondary prevention, the recommendation calls for high-intensity statin therapy in patients aged 21–75 years (classification of recommendation I and level of evidence A), and it is reasonable to discuss moderate-intensity statin therapy in patients older than 75 years (classification of recommendation I and level of evidence A) (Table 2). Specific recommendations for initiating statin therapy are outlined in the next section.

The second group with potential treatment benefit includes individuals aged 21 years or older without known CVD but with an LDL cholesterol level of 190 mg/dL or greater. These patients should receive high-intensity statin therapy (classification of recommendation I and level of evidence B) (19). Given the lifetime high risk of CVD in this group and the need to evaluate for possible secondary causes of dyslipidemia (Table 3) and for genetic causes, such as familial hypercholesterolemia, these patients should be referred to a cardiologist or lipid specialist (39). In this patient population, the need to achieve at least a 50% reduction in the LDL cholesterol level (classification of recommendation IIa and level of evidence B) may require additional nonstatin therapy (classification of recommendation IIb and level of evidence C).
Patients aged 21 years or older
• Perform screening lipid panel
• Counsel regarding healthy diet, exercise, and tobacco abstinence

Clinical atherosclerotic CVD

Low-density lipoprotein level of 190 mg/dL or greater

Diabetes mellitus

Atherosclerotic CVD risk score
• Clinician–patient shared decision making

Questions remain

75 years and younger
High-intensity statin

Older than 75 years (or safety concerns)
Moderate-intensity statin

Atherosclerotic CVD 10-year risk of 7.5% or greater
High-intensity statin

Atherosclerotic CVD 10-year risk less than 7.5%
Moderate-intensity statin

Atherosclerotic CVD 10-year risk between 5% and 7.5%
Moderate-intensity statin

Additional risk stratification
Consider statin therapy in the following situations:
• Low-density lipoprotein level of 160 mg/dL or greater
• Family history of premature atherosclerotic CVD
• High-sensitivity C-reactive protein level of 2 mg/L
• Coronary artery calcium score of 300 Agatston units or greater
• Ankle–brachial index of less than 0.9
• Increased lifetime atherosclerotic CVD risk

Figure 4. Algorithm for identification and management of statin benefit groups. This is a general decision algorithm for patients who may benefit from statin treatment. The algorithm is based on the American College of Cardiology/American Heart Association’s guidelines, which specifically identify patients with diabetes mellitus aged 40–75 years with a low-density lipoprotein cholesterol level of 70–189 mg/dL (a previous step in the algorithm that is not shown in this figure identifies patients with a low-density lipoprotein cholesterol level greater than 190 mg/dL). Abbreviation: CVD, cardiovascular disease. (Data from Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published errata appear in J Am Coll Cardiol 2015;66:2812; J Am Coll Cardiol 2014;63:3024]. J Am Coll Cardiol 2014;63:2889–934.)
### Table 2. Statin Therapy Intensity and Dosages

<table>
<thead>
<tr>
<th>Expected LDL Cholesterol Decrease</th>
<th>High-Intensity</th>
<th>Moderate-Intensity</th>
<th>Low-Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% or More</td>
<td>Atorvastatin, 40–80 mg</td>
<td>Atorvastatin, 10–20 mg</td>
<td>Simvastatin, 10 mg</td>
</tr>
<tr>
<td>30–50%</td>
<td>Rosuvastatin, 20–40 mg</td>
<td>Rosuvastatin, 5–10 mg</td>
<td>Pravastatin, 10–20 mg</td>
</tr>
<tr>
<td>Less Than 30%</td>
<td>Simvastatin, 20–40 mg</td>
<td>Lovastatin, 20 mg</td>
<td>Fluvastatin, 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin, 40–80 mg</td>
<td>Lovastatin, 40 mg</td>
<td>Pitavastatin, 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin, extended release, 80 mg</td>
<td>Fluvastatin, twice daily, 40 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin, 2–4 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Table 3. Important Causes of Secondary Dyslipidemia

<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Testing Indicated</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus and insulin</td>
<td>Fasting glucose and hemoglobin A$_1c$ level measurement</td>
<td>Control blood sugar</td>
</tr>
<tr>
<td>resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>Consider further evaluation if patient fits clinical picture</td>
<td>Lifestyle modifications and treatment with contraceptives</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Liver function tests</td>
<td>Treatment of an underlying disorder</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Urine protein test</td>
<td>Treatment of an underlying disorder</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Creatinine clearance</td>
<td>Control of risk factors</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Thyroid function tests</td>
<td>Thyroid hormone replacement</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index and waist-to-hip ratio calculation</td>
<td>Counseling regarding nutrition, exercise, and weight loss</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>Clinical history</td>
<td>Tobacco cessation counseling</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>Clinical history</td>
<td>Moderation or cessation of alcohol use</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>Clinical history</td>
<td>Referral for treatment of eating disorder</td>
</tr>
<tr>
<td>Medications</td>
<td>Review prescription and over-the-counter medication use</td>
<td>Identify estrogens, tamoxifen, raloxifene, protease inhibitors, antipsychotic and anticonvulsant medications, corticosteroids, oral retinoids, immunosuppressants, thiazide diuretics, and beta blockers</td>
</tr>
</tbody>
</table>
The third group are patients aged 40–75 years with type 1 diabetes mellitus or type 2 diabetes mellitus. Diabetes mellitus is an independent risk factor for CVD (40). Although optimal glucose control is important in modifying risk of microvascular complications (41), intensive glucose control has not been consistently shown to improve CVD mortality (42). Because CVD mortality cannot be mitigated by glucose control alone, it is important to optimize the CVD risk of patients with diabetes mellitus with the use of statins. In patients with diabetes mellitus aged 40–75 years with an LDL cholesterol level of 70–189 mg/dL, the 2013 ACC/AHA blood cholesterol guidelines recommend treatment with a statin (19). The dosage of statin therapy depends on the patient’s 10-year risk of developing atherosclerotic CVD. This risk can be calculated using the Pooled Cohort Equations; calculators are available online (http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate) and in the form of a free smartphone application (ASCVD Risk Estimator Plus from the ACC). Several commonly assessed criteria are used for calculating a patient’s atherosclerotic CVD risk (Box 2). For patients with diabetes mellitus, a high-intensity statin should be used if a 10-year atherosclerotic CVD risk is 7.5% or greater (classification of recommendation IIa and level of evidence B); otherwise, a moderate-intensity statin should be used (classification of recommendations I and level of evidence A). In patients with diabetes mellitus who are younger than 40 years or older than 75 years, the patient and health care provider should discuss the risks and benefits of statin treatment on an individualized basis (classification of recommendation IIa and level of evidence C) (19).

**Box 2. Clinical Factors Used in Calculation of Atherosclerotic Cardiovascular Disease Risk**

- Age
- Gender
- Ethnicity
- Total cholesterol level
- High-density lipoprotein cholesterol level
- Low-density lipoprotein cholesterol level
- Systolic blood pressure
- History of diabetes mellitus
- Hypertension treatment
- Smoking status
- History of statin therapy
- History of aspirin therapy

The final treatment benefit group includes patients who do not qualify for one of the previous categories, but who are aged 40–75 years and have an LDL cholesterol level of 70–189 mg/dL and a 10-year atherosclerotic CVD risk of 7.5% or greater. These patients benefit from moderate-intensity to high-intensity statin therapy (classification of recommendation I and level of evidence A). Also, it is reasonable to discuss treatment with a moderate-intensity statin in patients with a 10-year atherosclerotic CVD risk between 5% and 7.5% (classification of recommendation IIa and level of evidence B). In patients who choose not to initiate statin therapy, the risk should be reassessed every 4–6 years with the Pooled Cohort Equation (classification of recommendation I and level of evidence B). If questions remain about treatment, additional risk stratification factors may be used, such as LDL cholesterol level of 160 mg/dL or greater, family history of premature atherosclerotic CVD, high sensitivity C-reactive protein level of 2 mg/dL or greater, coronary artery calcium score of 300 Agatston units or greater, ankle–brachial index of less than 0.9, or increased lifetime atherosclerotic CVD risk (classification of recommendation IIb and level of evidence C) (19).

Although significant clinical evidence exists for benefit of statin treatment in the previously mentioned four patient groups, situations may occur in which a patient’s CVD risk is not fully captured with the algorithm in Figure 4. Therefore, health care providers have the flexibility to treat patients beyond the scope of the guidelines. Patients not otherwise identified in a statin benefit group but with additional CVD risk factors may be considered for primary prevention statin therapy after evaluating potential risk reduction benefits (classification of recommendation IIb and level of evidence C) (19). The decision to treat these patients should involve a thorough discussion of risks versus benefits of statin treatment, and the patient’s preferences should be respected.

Other societies have published different lipid guidelines. For example, the American Association of Clinical Endocrinologists and American College of Endocrinology guidelines released in 2017 include additional risk factors, recommend the use of risk calculators other than the Pooled Cohort Equation, and advocate for different lipid targets (43). Although the premise behind identification and treatment of at-risk patients is similar between the ACC/AHA guidelines and the American Association of Clinical Endocrinologists and American College of Endocrinology guidelines, the risk stratification and treatment goals differ between the groups. Similarly, the joint European Society of Cardiology and European Atherosclerosis Society guidelines (44) and the National Lipid Association guidelines (45, 46) present other, slightly modified approaches to lipid management. The United States Preventive Services Task Force has not updated its screening recommendations since 2008 (47), but treatment benefit groups generally are identified in a similar manner to the 2013 ACC/AHA blood cholesterol guidelines (48).

Broad lipid screening of the adult population should identify at-risk individuals who may not exhibit clinical signs or symptoms of atherosclerotic CVD. However, there are certain factors in a patient’s history or examination that should prompt further investigation into the possibility of a lipid disorder, especially familial hypercholesterolemia.
Physical examination findings of cholesterol deposition, such as tendon xanthomas, arcus cornealis (found in patients younger than 45 years, not to be confused with arcus senilis), xanthelasma, and planar xanthomas, are rare but are specific for hypercholesterolemia. The Dutch Lipid Clinic Network has integrated a list of clinical signs and medical and family history factors into a risk calculator (49). The Dutch Lipid Clinic Network risk score is highly correlated with the risk of CV mortality in a general population (50). If these risk factors are identified in a patient, the patient should undergo lipid screening and be referred to a lipid specialist.

**CASE NO. 1.** A 21-year-old woman (gravida 0) seeks contraceptive counseling. She has a strong family history of heart disease; her father had an MI at age 45 years.

This woman’s family history is concerning for a risk of early CVD, defined as a first CV event occurring in a male first-degree relative who is younger than 55 years or in a female first-degree relative who is younger than 65 years. In addition to obtaining a thorough family history, a detailed physical examination should be performed in this patient, including accurate blood pressure (BP), height, and weight measurements; a thorough CV examination; and a skin and eye examination to identify corneal arcus and xanthomas of the eyelid and tendons. Also, it is important to perform a screening lipid panel at this time because an increased LDL cholesterol level (ie, 190 mg/dL or greater) would point to a hereditary syndrome, such as heterozygous familial hypercholesterolemia (and would require referral to a lipid specialist). Once this patient’s lipid panel is evaluated, recommendations regarding contraception can be given. If a fasting lipid panel demonstrates an increased triglyceride level (ie, greater than 500 mg/dL), contraceptives containing exogenous estrogen would not be recommended given the risk of increasing triglyceride levels further and increasing the risk of triglyceride-induced pancreatitis. Based on the results of the lipid panel, this patient may qualify for treatment with a statin if her LDL cholesterol level is increased. If her LDL cholesterol level is not increased, a referral to a cardiologist or lipid specialist is still warranted because of her significant family history of early CVD. Given the contraindication of statin therapy in pregnancy, she should be counseled regarding contraception options that do not increase her CV risk. The strongest recommendation would be for a copper-containing intrauterine device, and progestin-only contraceptives would be an acceptable alternative (Table 4). If she desires pregnancy in the future, she should be instructed to discontinue statin therapy before pregnancy.

**Therapeutic Options for Women With Dyslipidemia**

Lifestyle change is recommended for all patients with dyslipidemia. Smoking cessation, regular physical activity, healthy diet, and weight management provide significant benefits over a woman’s lifetime and come with minimal to no risk (6, 51). The American Heart Association recommends that adults perform 150 minutes or more per week of moderate-intensity exercise or 75 minutes or more per week of vigorous exercise to optimize CV health (52). Examples of moderate-intensity exercise include brisk walking, bicycling (less than 16 km/h [10 miles per hour] pace), and doubles tennis. Generally, moderate activity should allow the participant to speak while exercising, but not sing.
Vigorous-intensity exercise includes jogging or running, swimming laps, and bicycling at a fast pace. If a patient can speak no more than a few words at a time before needing to pause for breath, then the activity level is likely vigorous (53). Ideally, exercise should be spread into multiple sessions throughout the week, but the total amount of weekly activity should remain at the goal as recommended by the AHA.

Less guidance exists regarding optimal dietary choices, and customized dietary counseling should be based on the patient’s CVD risk factors. For example, patients with hypertension may benefit from a salt-restricted diet, patients with obesity may benefit

Table 4. Hormonal Agents, Lipid Effects, and Cardiovascular Risk Considerations

<table>
<thead>
<tr>
<th>Medication</th>
<th>Lipid Effect</th>
<th>Risk Factors for Atherosclerotic Cardiovascular Disease</th>
<th>Current or Previous Atherosclerotic or Ischemic Cardiovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraceptive Formulations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper-containing intrauterine device</td>
<td>None</td>
<td>Appropriate to use</td>
<td>Appropriate to use</td>
</tr>
<tr>
<td>Levonorgestrel-releasing intrauterine device</td>
<td>Theoretic effects</td>
<td>Likely appropriate to use (benefits outweigh risks)</td>
<td>*Initiation: Likely appropriate to use (benefits outweigh risks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>†Continuation: Not recommended (risks outweigh benefits)</td>
</tr>
<tr>
<td>Etonogestrel implant</td>
<td>Minimal effect on LDL and triglyceride levels; decrease in HDL levels</td>
<td>Likely appropriate to use (benefits outweigh risks)</td>
<td>Initiation*: Likely appropriate to use (benefits outweigh risks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuation†: Not recommended (risks outweigh benefits)</td>
</tr>
<tr>
<td>Progestin-only injectable contraceptive</td>
<td>Minimal effect on LDL and triglyceride levels; decrease in HDL levels</td>
<td>Not recommended (risks outweigh benefits)</td>
<td>Not recommended (risks outweigh benefits)</td>
</tr>
<tr>
<td>Progestin-only pills</td>
<td>Minimal effect on LDL and triglyceride levels; decrease in HDL levels</td>
<td>Likely appropriate to use (benefits outweigh risks)</td>
<td>Initiation*: Likely appropriate to use (benefits outweigh risks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continuation†: Not recommended (risks outweigh benefits)</td>
</tr>
<tr>
<td>Combined hormonal contraceptives</td>
<td>Varies, but generally increased LDL and triglyceride levels</td>
<td>Contraindicated use</td>
<td>Contraindicated use</td>
</tr>
<tr>
<td><strong>Menopausal Estrogen Formulations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral estrogen</td>
<td>Decrease in LDL level, increase in HDL level, and increase in triglyceride level</td>
<td>Contraindicated use</td>
<td>Contraindicated use</td>
</tr>
<tr>
<td>Transdermal estrogen</td>
<td>Decrease in LDL level, increase in HDL level, and increase in triglyceride level</td>
<td>Contraindicated use</td>
<td>Contraindicated use</td>
</tr>
<tr>
<td>Vaginal (topical) estrogen</td>
<td>None</td>
<td>No documented lipid effect; theoretic concern for systemic estrogen effect</td>
<td>No documented lipid effect; theoretic concern for systemic estrogen effect</td>
</tr>
</tbody>
</table>

*Initiation refers to starting a method in a patient with the condition.
†Continuation refers to continuing a method if the condition first occurred during use of the method.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
from calorie restriction, and patients with diabetes mellitus or insulin resistance may require a low carbohydrate diet. For patients with mild-to-moderately increased triglyceride levels (less than 500 mg/dL), dietary guidance should emphasize weight loss and avoidance of food with a high glycemic index. For patients with high levels of fasting triglycerides (greater than 500 mg/dL), dietary restriction of fat is necessary, and fasting triglyceride levels should be decreased significantly before attempted weight loss given the risk of pancreatitis after rebound increases of triglyceride levels with postdiet refeeding syndrome. Referral to smoking cessation counselors, dieticians, exercise physiologists, and weight loss clinicians should be considered in all patients, if indicated. Lifestyle changes generally are not easy for patients, and routine encouragement should be offered at follow-up visits. Identifying barriers to change and eliciting the patient’s motivators should be addressed to provide the best chance for success.

Many women will be unable to minimize their CVD risk to an acceptable level with lifestyle changes alone (17). For patients with a normal LDL cholesterol level but an increased fasting triglyceride level, pharmacologic management can be complex and should be directed by a lipid specialist (Box 1). Statin therapy is the next step of treatment in patients with increased LDL cholesterol levels (19). Recommendations for the starting dosage are dictated by the patient’s CV risk, as outlined in Figure 4. When initiating statin therapy, the health care provider and the patient should have an informed discussion about the potential risks of statins (54). Overall, statins are well tolerated, but risks, such as musculoskeletal pain or weakness, new onset diabetes mellitus, neurocognitive decline, and major organ damage (rarely), should be reviewed. Commonly, patients are aware of the risk of myalgias with statins. Although these effects can occur in approximately 5–10% of patients, they are rarely life threatening (55). An overview of the evaluation and treatment of muscle problems with statin therapy is reviewed later in this section. In patients with risk factors for diabetes mellitus (metabolic syndrome, impaired fasting glucose level, and obesity), statin initiation has been associated with an increased rate of diabetes diagnosis (56). However, patients in the statin treatment group in this study received a diabetes mellitus diagnosis approximately 5 weeks earlier than those in similar nonstatin groups, and it is likely that statin initiation simply unmasks impending diabetes mellitus in these at-risk patients. Cognitive decline with statin therapy was initially a concern given a small number of case reports, but multiple studies and systematic reviews have shown no difference in cognitive function for patients who receive statins (57). Rare events of severe liver and kidney damage have been reported with statin use. The largest risk for serious organ injury is medication interaction, which emphasizes the need to evaluate a patient’s current medication list for the risk of interaction with a chosen statin. Overall serious injury is exceedingly rare, and large randomized control trials and meta-analyses have not shown statin therapy to be a significant independent risk factor for these events (58).

At the initiation of therapy, a baseline liver transaminase level should be assessed. Contrary to previous guidelines, liver function tests do not need to be routinely monitored after the initiation of statin therapy; however, if concerns for liver dysfunction
arise, the baseline transaminase level can be helpful in determining the potential role of the statin (19). There is no requirement to measure a baseline creatine kinase level. It should be assessed only in patients with symptoms concerning for statin myopathy. For patients at high risk of myopathy (such as those previously intolerant of other statins, those with a family history of statin intolerance or muscle disease, or those taking concomitant medications that may increase the risk of myopathy), a baseline creatine kinase level can be assessed (19). Also, it is useful to evaluate and document the patient’s baseline musculoskeletal problems before the initiation of statin therapy, which will assist in determining whether muscle symptoms have changed once the patient starts taking statins. Patients starting statin therapy should undergo a screening test for diabetes mellitus if it has not already been performed. Also, women should use reliable contraception while taking statins given the contraindication to statin use in pregnancy (Table 5).

A lipid panel should be performed 4–12 weeks after the statin therapy is initiated (19). Although the guidelines no longer recommend modifying the LDL cholesterol level to achieve the target for patients in the primary prevention group, a repeat lipid panel is important to confirm the patient’s response to therapy. The intensity of statin therapy is classified by the expected change in LDL cholesterol level with treatment, but not every patient will have the same response to therapy. If the LDL cholesterol response is significantly below the expected amount, nonadherence to therapy should be considered. If adherence is not an issue, then statin dosage intensification may be considered. After the initial lipid panel for patients undergoing statin treatment, lipid levels can be assessed every 3–12 months based on the clinical scenario. Assessment at 3 months may be appropriate if the statin dosage is changed, whereas assessment at 12 months is appropriate for patients who have been maintained on a stable statin regimen. For patients in the secondary prevention group, it is important to achieve an LDL cholesterol level decrease of at least 50% (and a goal of less than 100 mg/dL could be considered) (59). If this target is not met, the patient should be referred to a cardiologist or lipid specialist for further

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Pregnancy Class†</th>
<th>Breastfeeding Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Category X</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>Category D</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>Category D</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>Category C</td>
<td>Avoid if possible</td>
</tr>
</tbody>
</table>

*Patients taking these medications should use long-acting contraception, and the medications should be discontinued if the patients plan pregnancy or are found to be pregnant.
†Based on the 1979 letter category system. In 2014, the U.S. Food and Drug Administration published Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling, also referred to as “Pregnancy and Lactation Labeling Rule” or PLLR. The new labeling system replaces the 1979 letter category system (ie, pregnancy categories A, B, C, D, and X) and provides the prescriber with relevant safety information for critical decision making when treating pregnant or lactating women. The Pregnancy and Lactation Labeling Rule mandates that, for all drugs and biologic agents submitted for approval after June 30, 2015, manufacturers include a complete statement of the known risks based on available data in the medication package insert. If animal and human data are available, they should be presented. Labeling for prescription drugs approved on or after June 30, 2001, will be phased gradually. The Pregnancy and Lactation Labeling Final Rule is available at https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for
management. Also, there is no lower limit of LDL cholesterol level that requires deintensi-
fication or cessation of statin therapy. Recent trials have shown that patients with lifelong
LDL cholesterol at extremely low levels do not have negative clinical phenotypes (24);therefore, achieving low LDL cholesterol levels is a safe and acceptable result of statin
therapy.

Some patients may develop muscle symptoms while using statins. It is important to
determine if the symptoms are truly related to the statin therapy. Differentiating common
causes of muscle pain from statin myopathy will prevent unnecessary discontinuation of
statin therapy. Statin myopathy (ie, weakness) and myalgia (ie, pain and soreness) are
most commonly seen in proximal muscle groups and are usually bilateral and symmetric.
Muscles may or may not be sore to palpation on examination. Patients may describe
difficulty rising from a seated position, leg fatigue while climbing stairs, or difficulty
reaching for items above their heads. If these symptoms are new since the initiation of
statin therapy, further investigation is warranted (Fig. 5). A creatine kinase level should
be assessed, although an increased creatine kinase level is not mandatory for a diagnosis
of statin myopathy (19). If the clinical suspicion for statin intolerance is high, the statin
should be discontinued. Also, the patient should undergo thyroid function studies and a
vitamin D level test, if not performed previously, because hypothyroidism and vitamin D
deficiency are associated with statin intolerance. The clinician also should evaluate the
patient’s medication list thoroughly for potential drug interactions, especially for medica-
tions that interact with the cytochrome \textit{P}450 enzyme specific to a particular statin.

If muscle symptoms disappear within days to weeks after statin cessation, it is reason-
able to restart the same statin at the original or lower dosage to determine the causal
relationship of the symptoms to the statin. If symptoms do not recur, statin therapy can
be continued. If muscle symptoms do recur with challenge, statin therapy should be
discontinued to allow symptoms to resolve fully, and a trial of a different statin should
be initiated (19). Generally, pravastatin, fluvastatin, and pitavastatin are associated with
fewer muscle events and are a good choice in patients who have been unable to tolerate
other statins (55, 60). Alternate day regimens also can be tried, if daily regimens result in
muscle symptoms.

Rarely, statin therapy is associated with rhabdomyolysis, a severe myopathy with
muscle tissue breakdown. This injury releases intracellular muscle proteins, such as cre-
tine kinase and myoglobin, into the circulation, which can lead to acute kidney injury
in serious cases. The rate of rhabdomyolysis is reported to be 2–3 cases per 100,000
statin-treated patients (61), and it is important to promptly diagnose and manage these
rare cases (Fig. 5). In patients with muscle pain, weakness, or dark urine, statin therapy
should be discontinued, and a renal function panel, creatine kinase measurement, and
urinalysis should be performed. Increases in creatine kinase levels at 10 times the upper
limit of normal are concerning for rhabdomyolysis. Treatment is supportive and may
include administration of intravenous fluids, hospitalization, or both, if there is a concern
for acute kidney injury. Patients with documented rhabdomyolysis should not receive another statin, and they should be referred to a lipid specialist for alternative treatment options (62).

Figure 5. Algorithm for management of presumed statin myopathy. Patients with a history of rhabdomyolysis or multiple statin intolerances should be referred to a lipid specialist for additional management.
Although other therapies exist for the treatment of dyslipidemia, the 2013 ACC/AHA guidelines recommend statins as the mainstay of pharmacologic treatment. Agents, such as fibrates, niacin, fish oil, and ezetimibe, are not recommended as first-line therapy (19). They may be used as adjunctive therapies with statins in certain populations of patients, but an increased risk of adverse effects has been documented with some of these combinations (63). There is no evidence that complementary and alternative agents, such as red yeast rice or coenzyme Q10, have long-term CV benefits. If patients cannot tolerate statins, or if the treatment does not result in the expected improvement in LDL cholesterol levels, the next step would be to refer these patients to a lipid specialist who can further evaluate their treatment options (Box 1). Many new therapies recently have been approved by the FDA, such as PCSK9 inhibitors. Additional agents are being tested in ongoing clinical trials that may change lipid management in special populations in the coming years. A lipid specialist will be able to help patients navigate the constantly changing landscape of dyslipidemia therapy.

**Cardiovascular Risk Management Across the Spectrum of Women’s Health Care**

Beyond lipid management, it is crucial for health care providers to manage risk factors, such as tobacco use, obesity, poor exercise and diet, hypertension, and impaired glucose tolerance or diabetes mellitus, in their patients (49). A future risk of CVD appears to be associated with additional factors that are specific to women. For example, risk factors for polycystic ovary syndrome (PCOS) overlap with many traditional risk factors for lipid disorders (such as those listed earlier in this section), and it is important to educate women with PCOS that management of their condition also will affect their dyslipidemia and CVD risk (64–67). Similarly, women with preeclampsia (68–72), gestational hypertension (73–77), and gestational diabetes mellitus (78–81) are known to have an increased risk of CVD later in life. These women would benefit from a discussion regarding primary prevention of CVD directed at management of modifiable lifestyle factors, including diet, exercise, and weight loss, if indicated (82–84). If these women qualify for one of the treatment groups based on ACC/AHA guidelines, it is important to counsel them regarding the recommendations. High-risk women who do not wish to have children in the future may wish to start pharmacotherapy even if their atherosclerotic CVD risk is only 5% instead of waiting for their risk to increase with age. Other women, especially those planning to become pregnant in the future, may wish to avoid medications and instead focus on lifestyle management.

**CASE NO. 2.** A 30-year-old woman presents with irregular menses (oligomenorrhea), bothersome facial hair, and acne. She has a body mass index (BMI) of 36 (calculated as weight in kilograms divided by height in meters squared) with an increased waist–hip ratio. Laboratory test results are notable for high LDL cholesterol level, low HDL cholesterol level, and increased triglyceride and hemoglobin (Hb) A1c levels.
This woman has multiple factors concerning for metabolic syndrome (i.e., increased Hb A₁c level, dyslipidemia, and obesity). Her irregular menses also suggest possible PCOS. The first step in her evaluation is to perform a fasting lipid panel to determine if her LDL cholesterol level is 190 mg/dL or greater, which would place her in a statin benefit group. If she starts statin therapy, she should also use contraception because statin therapy is contraindicated in pregnancy. If her LDL cholesterol level is not 190 mg/dL or greater, the intervention should focus on lifestyle modifications, such as exercise, healthy diet, and weight loss. If she meets diagnostic criteria for diabetes mellitus, based on her Hb A₁c or fasting glucose level, this problem also should be addressed. If her symptoms and risk factors remain unchanged after lifestyle modification, treatment options for PCOS and CVD risk should be discussed. This patient may benefit from progestin-containing contraceptives to manage oligomenorrhea. Progestin-only contraceptives should have minimal effect on her LDL cholesterol and triglyceride levels. A referral to a lipid specialist for additional evaluation regarding possible statin therapy is appropriate.

Obstetrician–gynecologists provide care to a wide age range of women and are uniquely positioned to address CVD risk early and often (38). For example, prepregnancy counseling is an ideal opportunity to establish a lipid baseline level and provide counseling regarding lifetime habits that promote heart health, such as avoidance of tobacco use, healthy diet, optimal weight management, and routine exercise. Also, it provides an opportunity to identify high-risk individuals, such as those with LDL cholesterol levels of 190 mg/dL or greater, who may be asymptomatic and otherwise not identified. Women with initial LDL cholesterol values of 190 mg/dL or greater without clear secondary causes of dyslipidemia should be referred to a lipid specialist because they may have a genetic mutation causing hereditary hypercholesterolemia. Young women with both traditional risk factors and risk-associated conditions (such as PCOS, preeclampsia, gestational diabetes mellitus, or gestational hypertension) can be identified and counseled regarding lifestyle management of CVD risk potentially decades before they would develop symptomatic CVD (85, 86). Focusing on a healthy lifestyle, avoidance of tobacco use, control of associated medical conditions, and statin treatment in appropriate groups allows for optimal CVD prevention strategies in women.

In women with known CVD who wish to become pregnant, the risks of teratogenicity of key CV medications should be addressed. Women taking statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists should discontinue these medications before pregnancy (Table 5) (87). The management of all CV medications during pregnancy is beyond the scope of this monograph, but it is important to note that women with known CVD should be monitored by a cardiologist during pregnancy. For women who use statins for primary prevention, interruption of treatment for the duration of pregnancy and breastfeeding is expected to have minimal effect on long-term CVD prevention. Women with very high lipid levels, such as those with familial hypercholesterolemia, may require changes to treatment during pregnancy (88), and a lipid specialist should assist with their prenatal care. All women
Using teratogenic CVD medications (Table 5) should be counseled on the importance of contraception between pregnancies, and once women have completed childbearing, long-term contraception is ideal to avoid the risk of unintended pregnancy (Table 4).

**CASE NO. 3.** A 26-year-old patient comes to the office for prepregnancy counseling. She has a normal BMI. She incorporates healthy diet and regular exercise into her lifestyle. She is a non-smoker and does not have diabetes mellitus. Two years ago, she had chest pain while working out at the gym, followed by cardiac arrest. After resuscitation, electrocardiography showed ST-segment increases. Emergent cardiac catheterization showed a 100% left anterior descending artery stenosis with no dissection, with luminal irregularities seen in other coronary vessels. She was treated with a drug-eluting stent to the left anterior descending artery, 80 mg of atorvastatin, aspirin, clopidogrel, a beta-blocker, and an ACE inhibitor. Her lipid panel indicated an LDL level of 250 mg/dL at the time of cardiac arrest and her medical history review revealed an extensive family history of early CVD. She is interested in becoming pregnant in the near future and would like to discuss her medications.

This is a complicated case that hinges on the patient’s beliefs and priorities, and the best course is to provide the patient with as much information as she needs to make an educated decision. This woman’s presentation is consistent with hereditary dyslipidemia, particularly heterozygous familial hypercholesterolemia. Given her history, she should be referred to a cardiologist for management and possible genetic testing. The most common mutations in familial hypercholesterolemia are autosomal dominant, giving a 50% chance of inheritance to her offspring. Thus, a referral to a genetic counselor would be appropriate. She should avoid pregnancy while she uses a statin or ACE inhibitor; clopidogrel has been categorized as a pregnancy category B drug by the U.S. Food and Drug Administration (package insert should be checked for additional safety details), but dual antiplatelet therapy (aspirin and clopidogrel) could increase her general risk of bleeding. Given her prior stent placement and the need for dual antiplatelet therapy, she should be referred to a cardiologist who can help the patient weigh her need for dual antiplatelet therapy and her desire for pregnancy. A limited body of research is available regarding pregnancy in women with prior MI, but the fact that she has already had an MI and cardiac arrest would suggest she has a high risk for another cardiac event. If she desires to become pregnant, she could consider in vitro fertilization with genetic screening of embryos before implantation. She should be monitored by a cardiologist and a high-risk obstetric team throughout her pregnancy. If she is amenable, she could also undergo in vitro fertilization, embryo screening, and use of a gestational carrier for the pregnancy.

Generally, combined oral contraceptives (OCs) containing estrogen are not recommended for women with known CAD or ischemic heart disease given the increased risk of thromboembolism (89). Combined OCs also are contraindicated in patients with other CV conditions that are beyond the scope of this publication (90). However, for women whose only CVD risk factor is dyslipidemia, the recommendations regarding the use of combined OCs are unclear (91). Although a theoretical risk of thromboembolism does exist, management with combined OCs may be beneficial in certain populations. In patients with PCOS, combined OCs decrease androgen levels and increase sex hormone-binding globulin levels, thus improving androgen balance (92). Specific effects of combined OCs
on lipids depend on the formulation and combination of the estrogen–progestin components of the pill, and the benefit and risk to an individual patient should be evaluated before prescription. Overall, a decision regarding optimal contraception should be a shared decision between the patient and the clinician, balancing long-term versus short-term contraception, method of delivery, and risks and benefit of each treatment option. The Centers for Disease Control and Prevention outlines recommendations for contraception based on a women’s CV risk in *U.S. Medical Eligibility Criteria for Contraceptive Use, 2016* (89).

Women’s health care providers are the primary providers of hormone therapy (HT). The understanding of how HT agents relate to CVD continues to evolve. Clinical trials have shown that premenopausal women develop CVD at a lower rate than men (93), and young women who have undergone oophorectomy develop CAD sooner than their age-matched female counterparts who have not undergone oophorectomy (94). This led to the idea that estrogen may be protective in the development of CVD. However, studies that evaluated the effects of HT in the prevention of CVD failed to demonstrate a benefit, and, in some cases, the trials were halted early because of noncardiac events, such as increased rates of breast cancer (95). Although additional HT studies are ongoing, concern remains regarding the increased association of oral HT with thromboembolism, including venous thromboembolism, stroke, and MI (95, 96). Given the lack of evidence for an improvement of CVD with HT and the concern for increased risk of thromboembolism, oral HT is not recommended for CVD prevention. Safety of HT use depends on the profile of the specific patient. The patient’s risks should be weighed against the benefits of the potential HT use, and the ultimate decision should be shared between the patient and her clinician. Transdermal estrogen therapy has not been associated with worsening dyslipidemia or increased venous thromboembolism, and this may be a reasonable option in women with CV risk factors (97). Women should weigh the risks and benefits of transdermal estrogen therapy with their clinician and come to a shared decision regarding the best option for potential HT.

**CASE NO. 4.** A 50-year-old menopausal woman presents with bothersome vasomotor symptoms. She is a former smoker, who quit more than 5 years ago. Her brother had an MI at the age of 60 years. Her BMI is 32 and her BP is 155 mm Hg, systolic, and 88 mm Hg, diastolic. Her lipid panel reveals a total cholesterol level of 250 mg/dL, LDL cholesterol level of 170 mg/dL, and HDL cholesterol level of 40 mg/dL. Currently, she takes no medications.

Although this patient is concerned about vasomotor symptoms, her CV risk needs to be addressed before discussing management of menopausal symptoms. She is a former smoker and has obesity and hypertension. Her LDL cholesterol level is increased, and her HDL cholesterol level is low, which is consistent with dyslipidemia. In addition to lifestyle counseling regarding diet, exercise, and weight loss, she should have an evaluation for secondary causes of dyslipidemia. Thyroid function, Hb A$_1c$ level, and kidney function should be evaluated. Her 10-year atherosclerotic CVD risk, as calculated by the Pooled Cohort Equation, is 7.7%. Based on ACC/AHA guidelines, her 10-year risk
potentially places her in the treatment group with a moderate- to high-intensity statin in addition to lifestyle changes. Also, she may require medical treatment for high BP if it remains increased on additional evaluation. One advantage of the Pooled Cohort Equation is the ability to demonstrate how changes in risk factors can affect her calculated risk. For instance, if lifestyle changes and hypertension management result in a BP of 125 mm Hg, systolic, and 80 mm Hg, diastolic, and a total cholesterol level of 220 mg/dL, LDL cholesterol level of 160 mg/dL, and HDL cholesterol level of 45 mg/dL, her 10-year atherosclerotic CVD risk becomes 4.5%. However, family history does not factor into this specific risk equation, and her projected risk will increase as she ages. It is important to have a risk–benefit discussion regarding statin treatment based on the patient’s concerns and priorities. Given this patient’s risk factors, it is also important to discuss nonhormonal treatment of her vasomotor symptoms. If her CVD risk factors are optimized with diet, medical therapy, or both, the use of transdermal estrogen HT could be considered because transdermal preparations are lipid neutral and are not known to increase a risk of thromboembolism in observational studies (96, 97).

Medication management becomes complex when multiple health conditions require several classes of pharmacotherapy. Statins have unique properties based on their water solubility and metabolism (Table 6) (98) and it is crucial to be aware of important interactions between statins and other medications (99). For example, statin myopathy has been shown to be more common in patients taking multiple medications with potential interactions than in patients taking statins alone (98). However, patients who cannot take a particular statin either because of intolerance or because of drug interaction may be

<table>
<thead>
<tr>
<th>Statin Medication</th>
<th>Dose Range</th>
<th>Type</th>
<th>Metabolism</th>
<th>Medications With Increased Risk of Statin Toxicity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10–80 mg</td>
<td>Lipophilic</td>
<td>CYP 3A4</td>
<td>Fibrates, macrolide antibiotics, azole antifungals, diltiazem, verapamil, warfarin, digoxin, protease inhibitors, cyclosporine, and tacrolimus</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5–40 mg</td>
<td>Hydrophilic</td>
<td>Minimal CYP metabolism (2C9 and 2C19)</td>
<td>Fibrates, cyclosporine, diclofenac, phenytoin, warfarin, diazepam, and ibuprofen</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10–40 mg</td>
<td>Lipophilic</td>
<td>CYP 3A4 and 3A5</td>
<td>Fibrates, macrolide antibiotics, azole antifungals, diltiazem, verapamil, warfarin, digoxin, protease inhibitors, cyclosporine, tacrolimus, amiodarone, amlodipine, and colchicine</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10–80 mg</td>
<td>Hydrophilic</td>
<td>Renal clearance</td>
<td>Fibrates, cyclosporine, and colchicine</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>20–40 mg</td>
<td>Lipophilic</td>
<td>CYP 3A4</td>
<td>Fibrates, macrolide antibiotics, azole antifungals, diltiazem, verapamil, warfarin, digoxin, protease inhibitors, cyclosporine, tacrolimus, amiodarone, and colchicine</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>20–80 mg</td>
<td>Lipophilic</td>
<td>CYP 2C9</td>
<td>Diclofenac, phenytoin, warfarin, and colchicine</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1 mg</td>
<td>Lipophilic</td>
<td>Minimal CYP metabolism (2C9 and 2C8)</td>
<td>Fibrates, colchicine</td>
</tr>
</tbody>
</table>

*This is only a partial drug interaction list; it is important to investigate for drug interactions whenever prescribing a new medication to a patient.

Abbreviation: CYP, cytochrome P450 enzyme.
able to take a statin that undergoes a different drug metabolism pathway. If patients have multiple potential drug interactions or cannot take several different families of statins, a referral to a lipid specialist is recommended (Box 1).

Decisions about medical therapy also become complex as women age. In addition to managing polypharmacy concerns, women need to consider lifetime risk-to-benefit ratios of statin therapy. Most recommendations do not include primary prevention lipid therapy in patients older than 75 years. It is uncertain what exposure time is required for primary prevention statins to demonstrate significant mortality benefits; however, given that the life expectancy for elderly women varies widely after age 75 years, it is crucial to make a shared decision with the older patient regarding statin therapy for primary prevention. For instance, unlike an active 75-year-old woman who is generally healthy and whose life expectancy is 10 years or longer, a woman with life-limiting cancer is unlikely to benefit from primary prevention statin therapy. The patient’s preferences, CV risk factors, potential medication interactions, and opportunity for long-term statin benefit should be discussed on a case-by-case basis. Intensity of statin therapy should be discussed even in women with a known atherosclerotic CVD. The ACC/AHA guidelines suggest changing from a high-intensity to a moderate-intensity statin after age 75 years (19), but this should be a shared decision between the patient and the clinician.

Key Points

Cardiovascular disease remains the leading cause of death in women (5). Assessing CV risk in women is crucial to identifying at-risk patients, and managing dyslipidemia is a primary goal in CVD risk factor modification. Lifestyle factors should be addressed, but many women at moderate-to-high risk of CVD mortality also require statin treatment for optimal CVD prevention. Currently, the ACC/AHA guidelines outline stratification of patients into groups that will likely benefit from statin therapy (19). The goal is not to manage a specific LDL cholesterol level but rather to achieve an overall reduction of CVD risk over the patient’s lifetime. Women who have a high risk, including an LDL cholesterol level of 190 mg/dL or greater, significant family history of early heart disease, or a personal history of CVD, or who do not respond to or do not tolerate statin therapy should be referred to a cardiologist or lipid specialist for further evaluation and management. Women’s health care providers are crucial in managing CVD risk by diagnosing and treating dyslipidemia. The most poignant diagnostic and management points for obstetrician–gynecologists include the following:

- Patients should be screened beginning at age 21 years. Screening should be repeated every 4–6 years. Lipid levels can change significantly in pregnancy, especially during the second and third trimesters, so screening at this time should be avoided, if possible.
- For all patients with a risk of CVD, lifestyle modifications are crucial. Patients should avoid tobacco use, eat a healthy diet, exercise, and maintain a normal weight.
• Comorbid conditions, such as diabetes mellitus, hypertension, obesity, chronic kidney disease, and thyroid disease, should be managed optimally.

• Four main lipid treatment benefit groups were described in the 2013 ACC/AHA guidelines (19):
  1. Patients with known atherosclerotic CVD
  2. Patients with an LDL cholesterol level of 190 mg/dL or greater
  3. Patients with diabetes mellitus with an LDL cholesterol level of 70–189 mg/dL aged 40–75 years
  4. Patients with a calculated 10-year atherosclerotic CVD risk of 7.5% or greater by the Pooled Cohort Equation

• Statins are the mainstay of pharmacologic treatment in the ACC/AHA risk groups. For each treatment benefit group, an intensity of statin therapy is recommended based on expected LDL cholesterol response to treatment.

• After initiation of a statin, a lipid panel should be performed to evaluate a patient’s response to treatment. Also, patients should be monitored for adverse effects of statin therapy.

• Women should not take statins, ACE inhibitors, angiotensin receptor blockers, or aldosterone antagonists during pregnancy or breastfeeding.

• Women’s health care providers are crucial in the evaluation of risks and benefits of combined OCs and HT in women at risk of CVD.
The following list is for information purposes only. Referral to these sources and websites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or website does not reflect the quality of that source or website. Please note that websites are subject to change without notice.

Professional Organizations


Professional Clinical Tool


Patient Resources


Complete the answer sheet at www.clinicalupdates.org under “Test Your Clinical Skills” and receive 5 continuing medical education credits. The answers appear on page 34.

Directions: Select the one best answer or completion.

1. What percentage of reproductive-aged women has an LDL cholesterol level greater than 130 mg/dL?
   A. 7.5
   B. 25
   C. 49
   D. 53

2. Chylomicrons are converted to VLDL in
   A. blood vessels
   B. intestine
   C. liver
   D. muscle

3. According to the authors, the mainstay of lipid management is
   A. decreasing LDL cholesterol level
   B. decreasing total cholesterol level
   C. decreasing triglyceride level
   D. increasing HDL cholesterol level

4. After pregnancy, what is the amount of time required for blood lipid levels to normalize?
   A. 4 weeks
   B. 6 weeks
   C. 12 weeks
   D. 52 weeks

5. For which of the following patients do ACC/AHA guidelines recommend moderate-intensity statin therapy?
   A. A 50-year-old patient with CAD and a history of a transient ischemic accident
   B. A 50-year-old patient with an LDL cholesterol level of 200 mg/dL
   C. A 50-year-old patient with type 2 diabetes mellitus, an LDL cholesterol level of 150 mg/dL, and an atherosclerotic CVD risk of 6%
   D. A 76-year-old patient with type 2 diabetes mellitus with an LDL cholesterol level of 150 mg/dL

6. Which of the following physical findings in a 60-year-old woman would not be an indication of increased cholesterol levels?
   A. Arcus senilis
   B. Planar xanthomas
   C. Tendon xanthoma
   D. Xanthelasma

7. Which of the following activities is characteristic of moderate-intensity exercise?
   A. Bicycling at 12 miles per hour
   B. Singing during exercise
   C. Speaking during exercise
   D. Swimming laps
8. Which of the following laboratory test results is recommended before initiation of statin therapy?
   A. Creatinine level
   B. Creatine kinase level
   C. Glucose level
   D. Liver transaminase level

9. Which percentage of reduction of LDL cholesterol level is recommended as minimum for patients who are taking statins for secondary prevention?
   A. 10%
   B. 25%
   C. 40%
   D. 50%

10. A patient receiving statin therapy reports pain in her upper thighs. Which of the following laboratory tests is least indicated for her assessment?
    A. Creatine kinase level measurement
    B. Liver transaminase level measurement
    C. Thyroid function test
    D. Vitamin D level measurement

11. The mechanism of inheritance of familial hypercholesterolemia is most likely
    A. autosomal dominant
    B. autosomal recessive
    C. sex-linked dominant
    D. sex-linked recessive

12. Which route of administration of estrogen for postmenopausal women is considered lipid neutral by authors?
    A. Oral
    B. Subcutaneous pellets
    C. Transdermal
    D. Vaginal

13. Screening of women is advised to begin at
    A. age 21 years
    B. age 25 years
    C. age 35 years
    D. first pregnancy

14. According to the 2013 ACC/AHA guidelines, which of the following patients would not require lipid therapy?
    A. A 55-year-old diabetic patient with an LDL cholesterol level of 100 mg/dL
    B. A patient with a 10-year atherosclerotic CVD risk of 5% by Pooled Cohort Equation
    C. A patient with a known atherosclerotic CVD
    D. A patient with an LDL cholesterol level of 200 mg/dL.


65. Gunning MN, Fauser, BC. Are women with polycystic ovary syndrome at increased cardiovascular disease risk later in life? Climacteric 2017;20:222–7. (Level III)


Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I  Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Answers

Each monograph in *Clinical Updates in Women’s Health Care* is an overview of a topic of importance to obstetrician–gynecologists in practice. Upcoming titles include the following:

- Acute Cough
- Migraine and Other Headache Disorders

If not previously completed, earn CME credits for back issues of *Clinical Updates in Women’s Health Care*. Listed are updates and all current titles by publication date. Online access to the complete title list is available at www.clinicalupdates.org.

**Updates**

Also available at www.clinicalupdates.org are the following content updates:

- *Anorectal Disorders* (May 2015)
- *Care of Aging Women* (January 2018)
- *Common Dermatologic Conditions* (January 2018)
- *Complementary and Alternative Medicine* (June 2015)
- *Memory Loss and Dementia* (January 2019)
- *Obesity* (October 2013)
- *Obesity* (August 2017)
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- *Sleep Disorders* (September 2015)
- *Upper Gastrointestinal Tract, Biliary, and Pancreatic Disorders* (June 2017)

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- *Incidental Radiologic Findings* (Vol. XVII, No. 4, July 2018)
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Reliable Take-Home Information for Your Patients

The American College of Obstetricians and Gynecologists’ Patient Education Pamphlets are designed to complement and supplement the information and advice you provide in the office. After you talk to your patients about evaluation and management of lipid disorders, ensure they have accurate information they can refer to and share with their families and friends when they are at home.

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