Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease

AUTHORS: Michael Pignone, MD, MPH, MACP, Christopher P Cannon, MD
SECTION EDITOR: Mason W Freeman, MD
DEPUTY EDITOR: Sara Swenson, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Apr 2024.**
This topic last updated: **Apr 25, 2024.**

INTRODUCTION AND TERMINOLOGY

Lowering low-density lipoprotein cholesterol (LDL-C) can reduce the risk of atherosclerotic cardiovascular disease (ASCVD) in people without established CVD. This approach to CVD prevention is called primary prevention. The rationale for LDL-C reduction is based upon clinical trial evidence that lowering of LDL-C in patients across a broad range of LDL-C levels reduces a patient's risk of CVD [1].

CVD in this context refers to fatal or nonfatal myocardial infarction, acute coronary syndrome, sudden cardiac death, coronary artery revascularization, stroke, and peripheral arterial disease.

The decision about whether to lower LDL-C with pharmacotherapy incorporates both LDL-C level and a patient's estimated 10-year CVD risk. These factors help guide shared decision-making (ie, risk and benefit) discussions between patients and their providers.

This topic reviews the management and evidence for LDL-C lowering in patients for the purpose of primary CVD prevention. Such management and evidence in patients with established disease is discussed separately. (See "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease".)

CVD RISK ASSESSMENT

We conduct CVD risk evaluation and discussion with our patients when they reach 20 years of age or at their first encounter with the health care system if they are older than 20 years of age. A 10-year CVD risk assessment (for patients who are 40 years of age or older) can help guide LDL-C-lowering strategies (including statin therapy) and a 10-year or lifetime CVD risk assessment can guide preventive care. (See "Atherosclerotic cardiovascular disease risk assessment for primary prevention in adults: Our approach", section on 'Our approach to ASCVD risk assessment'.)

As an initial step, we measure total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and LDL-C (often calculated, but measured directly if triglycerides are >400); measurement methods are discussed in detail separately. (See "Measurement of blood lipids and lipoproteins", section on 'LDL cholesterol'.)

We also determine a patient's CVD risk using risk assessment tools that estimate the patient's 10-year risk of CVD based upon their baseline LDL-C and other risk factors (eg, blood pressure, smoking). Recommendations for the use of risk calculators are discussed in detail separately. (See "Cardiovascular disease risk assessment for primary prevention: Risk calculators".)

We define the following risk categories based on a person's estimated 10-year risk of CVD:

- Low – <5 percent
- Intermediate – 5 to 7.4 percent
- High – 7.5 to 19.9 percent
- Very high – ≥20 percent

  The ACC/AHA uses similar categories of risk but labels intermediate (5 to 7.4 percent) as “borderline” risk, high risk (7.5 to 20 percent) as “intermediate” risk, and very high risk (≥20 percent) as “high” risk. We prefer the labels outlined above because we (and the ACC/AHA) believe that statin therapy is indicated in patients with a 10-year ASCVD risk of 7.5 to 19.9 percent.

Based on their estimated 10-year CVD risk, the patient and their provider(s) can decide whether a 30 percent relative risk reduction, which is a reasonable expectation for statin therapy, translates into an absolute risk reduction large enough to be worth the cost, burdens, and potential side effects of daily therapy [1].

Irrespective of their LDL-C, patients who have other modifiable risk factors for CVD (ie, hypertension, diabetes, smoking) should be treated with aggressive risk factor reduction, including lifestyle changes and pharmacotherapy, as indicated. (See "Overview of primary prevention of cardiovascular disease".)

LIFESTYLE MODIFICATION

We obtain a dietary history in patients with high LDL-C to identify specific dietary patterns that can raise LDL-C (eg, ketogenic or paleolithic diets). If the patient is on such a diet, we recommend lifestyle changes, remeasure LDL-C, and then treat with statin as necessary to further reduce LDL-C.

In all patients, a healthy diet, physical activity, and maintaining a healthy weight are all important for overall health and should be pursued apart from whether they reduce LDL-C. Therefore, we recommend that all patients with high LDL-C undergo lifestyle modifications of aerobic exercise and consuming a healthy diet. For patients with a body mass index in the overweight or more adiposity category, we also suggest weight loss. Specific recommendations are provided separately.

- (See "Exercise and fitness in the prevention of atherosclerotic cardiovascular disease".)
- (See "Healthy diet in adults".)
- (See "Obesity in adults: Prevalence, screening, and evaluation".)
- (See "Lipid management with diet or dietary supplements", section on 'Our approach'.)

In most patients (unless they are on a diet particularly high in saturated fat such as the ketogenic diet), there is reasonable evidence that dietary modification alone improves cardiovascular risk, but prior trials have not shown material decreases in cardiovascular events and mortality [2]. One explanation is that some prior trials have only achieved modest decreases (eg, 3.5 and 6.6 mg/dL decreases) in LDL-C with dietary intervention aimed at lowering dietary fat [2,3]. The Mediterranean [4], DASH, vegetarian, and vegan [5] diets have been shown to lower a person's LDL-C levels and/or 10-year cardiovascular risk [6]. Whereas the Mediterranean diet lowers the risk of incident CVD, this does not appear to be mediated though lower levels of LDL-C; the lower CVD risk may be mediated through lower blood pressure and improvements in dysglycemia [7]. Both the vegan [5] and lacto-ovo vegetarian [8] diets were associated with lower LDL-C. This is discussed in detail separately. (See "Lipid management with diet or dietary supplements", section on 'Our approach'.)

Concomitant exercise and dietary modification have been shown in one study to lower LDL-C levels compared with either exercise or dietary modification alone or compared with no lifestyle changes [9]. (See "Exercise and fitness in the prevention of atherosclerotic cardiovascular disease".)

Weight reduction has the added benefit of lowering other CVD risk factors such as blood pressure in patients with hypertension and hyperglycemia in patients with diabetes. This is discussed separately. (See "Overweight, obesity, and weight reduction in hypertension" and "Initial management of hyperglycemia in adults with type 2 diabetes mellitus", section on 'Weight management'.)

INDICATIONS FOR STATIN THERAPY

Rationale for our approach and treatment goals — Our recommendations for statin therapy are based upon the LDL-C level and baseline CVD risk as discussed in the sections that follow (algorithm 1). Our goal is to reduce CVD events via LDL-C lowering. A shared decision-making approach is very important; in particular, in those at intermediate 10-year risk for atherosclerotic cardiovascular disease (ASCVD), patient preferences are very important. (See 'CVD risk assessment' above.)

Although lipid-lowering therapy with statins reduces **relative** CVD risk by approximately 30 percent regardless of baseline LDL-C, the **absolute** benefit of treatment will be proportional to the patient's underlying absolute risk of CVD. Thus, patients with a low baseline CVD risk will have a lower absolute benefit from treatment than a patient with high baseline CVD risk. In contrast, the adverse effects and burdens of treatment will be experienced equally by high- and low-risk patients. Thus, the risk-benefit calculation for treatment may be more favorable for patients with high baseline CVD risk and less favorable for those at low baseline CVD risk.

The following are two patient examples for which the decision to start statin therapy may differ despite both patients having the same baseline LDL-C:

- **A patient with lower absolute risk reduction –** A 45-year-old nonsmoking normotensive white woman with an LDL-C of 140 mg/dL (3.62 mmol/L) and a high-density lipoprotein cholesterol (HDL-C) of 40 mg/dL (1.03 mmol/L) has a 10-year risk of ASCVD events of approximately 1 percent. This could result in a 30 percent relative risk reduction likely be reduced from 1 to 0.7 percentage points if she were treated with a statin daily for 10 years.

- **A patient with higher absolute risk reduction –** A 60-year-old nonsmoking normotensive man with an LDL-C of 140 mg/dL (4.7 mmol/L) and an HDL-C of 40 mg/dL (1.03 mmol/L) has a 10-year risk of a myocardial infarction of approximately 9 percent. Use of a statin would reduce this risk to 6 percent, a 3 percentage-point reduction if he were treated with a statin daily for 10 years.

LDL-C greater than or equal to 190 mg/dL — For all patients with LDL-C ≥190 mg/dL (≥4.9 mmol/L), we do a work-up for familial hypercholesterolemia (FH) and, if present, treat accordingly. The work-up and management of FH are discussed separately but include intensive lipid lowering. (See "Familial hypercholesterolemia in adults: Overview" and "Familial hypercholesterolemia in adults: Treatment".)

Whether or not patients have FH, we treat them with a high-dose statin therapy (algorithm 1). As an example, we may start these patients on atorvastatin 40 (or 80) mg daily or rosuvastatin 20 mg daily.

A CVD risk calculation is not needed prior to treatment for individuals with an LDL-C ≥190 mg/dL (≥4.9 mmol/L), because we usually prescribe statin therapy for them based on the elevated LDL-C level alone. It is useful to estimate anticipated absolute benefit for the patient.

There are unique and important considerations of statin therapy in women of childbearing age. (See 'Childbearing potential' below.)

LDL-C less than 190 mg/dL — For patients without diabetes who have LDL-C <190 mg/dL (or <4.9 mmol/L), the indication for statin therapy is guided by the patient's 10-year estimated CVD risk group (ie, low, intermediate, or high). Our approach to patients with this level of LDL-C and diabetes is described below (algorithm 1). (See 'Diabetes' below.)

High (7.5 to 20 percent) and very high (greater than or equal to 20 percent) 10-year CVD risk — For most patients with an LDL-C >100 mg/dL (>2.59 mmol/L) and a predicted 10-year CVD risk of greater than 7.5 percent, we initiate statin therapy (algorithm 1). Note that we label these risk groups as “high” and “very high,” while the ACC/AHA labels them as “intermediate” and “high” risk; however, our approach to management is consistent with ACC/AHA guidelines [10]. This approach may differ in special populations. (See 'Special populations' below.)

- **Dosing –** We usually choose a moderate-dose statin as initial therapy. Examples of a moderate dose of a statin are 10 to 20 mg of atorvastatin or 5 to 10 mg of rosuvastatin (table 1).

  However, it is reasonable to start with high-intensity statin therapy for patients found to be at particularly high CVD risk, such as those with a 10-year risk of 20 percent or higher.

  The reason we most commonly use moderate-intensity statin therapy to initiate therapy is that these doses were the ones studied in a majority of clinical trials of statin therapy in primary prevention. These moderate doses of statin were shown to reduce CVD events by

30 percent [1]. However, most trials compared a fixed dose of a single pharmacologic agent with placebo, and none of the trials in primary prevention have directly compared the effects of low-to-moderate- with high-intensity statin therapy; these comparisons were done in patients with ASCVD.

In patients in these high- and very high-risk categories, we will subsequently adjust treatment if the patient has not achieved adequate LDL-C lowering. (See 'Medication adjustment' below.)

- **Supporting evidence** – Several individual randomized trials and meta-analyses of clinical trials of statin therapy for LDL-C lowering (or total cholesterol lowering) have shown a benefit of statins in preventing the combined outcomes of CVD events and CVD mortality [1,11-13]. In these studies, the benefits of reducing CVD and mortality were shown regardless of the patient's baseline LDL-C levels (ie, there was even a benefit seen at low baseline LDL-C levels). In these studies, statin therapy was especially effective at reducing the risk of myocardial infarction (as compared with other types of CVD events). In general, there are stronger data supporting that LDL-C lowering reduces CVD and mortality in secondary compared with primary prevention.

  The Cholesterol Treatment Trialists' collaboration used pooled data from 27 trials in over 175,000 patients examining statin therapy in primary and secondary prevention patients [11,13]. This study demonstrated that statins can reduce CVD outcomes in both primary and secondary prevention patients [11,13]. Per each 1 mmol reduction in LDL-C, the following rate ratios (RRs) were observed.

  - Major coronary event – (RR 0.79, 95% CI 0.77–0.81)
  - Stroke – (RR 0.85, 95% CI 0.80-0.89)
  - Coronary revascularization – (RR 0.76, 95% CI 0.73-0.79)
  - Major vascular event – (RR 0.79, 95% CI 0.77-0.81)

Intermediate (5 to 7.4 percent) 10-year CVD risk — For patients with LDL-C <190 mg/dL (4.9 mmol/dL) and a 10-year risk between 5 and 7.5 percent, we undertake shared decision-making with the patient, including a detailed discussion of the potential benefits and costs/risks (algorithm 1). The reason that we do not uniformly recommend statins in such patients is because they may have a similar relative risk compared with high-risk patients, but their absolute risk is lower; therefore, the absolute benefits are smaller and vary within this group. Note that we label this risk group as “intermediate,” while the ACC/AHA labels it as “borderline”; however, our approach to management is consistent with ACC/AHA guidelines [10].

The Cholesterol Treatment Trialists' meta-analysis of 22 trials of over 175,000 participants showed that among the 28,362 patients at intermediate CVD risk, statins reduced the relative risk of vascular events compared with the placebo group (RR 0.62 95% CI 0.60-0.79); however, the absolute risk reduction for any vascular event was more modest (absolute risk reduction 0.47 percent over five-year period given the lower observed event rates in those assigned statins versus placebo [1.10 versus 1.57 percent]) [11].

For patients at intermediate CVD risk, we consider additional factors that if elevated will lead us to suggest statin and lipid-lowering therapy:

- **LDL-C >160 mg/dL (>4.14 mmol/L) –** In patients with LDL-C levels >160 mg/dL and a calculated 10-year atherosclerotic CVD (ASCVD) risk of 5 to 7.4 percent, we recommend statin therapy.

- **Presence of other risk-enhancing factors –** We agree with the 2018 American College of Cardiology/American Heart Association (ACC/AHA; and others) guideline on management of blood cholesterol, which states that other risk-enhancing factors may favor initiation of statin therapy (table 2) [10]. It is reasonable to gather relevant history of risk-enhancing factors during the medical encounter; coronary artery calcium (CAC) and other tests may also provide useful information to help guide treatment decisions. If any of these factors are present, we would discuss treatment with statin with the patient.

  - **Factors from patient history –** These factors include a family history of premature CVD, chronic kidney disease, a chronic inflammatory disorder (such as chronic human immunodeficiency viral infection [14]), and among females who have been pregnant, adverse pregnancy outcomes such as preeclampsia (table 2).

  - **CAC –** In intermediate CVD risk patients with LDL-C <160 mg/dL (<4.14 mmol/dL), particularly those who are reluctant to start statin therapy, we consider additional risk stratification with CAC. (See "Coronary artery calcium scoring (CAC): Overview and clinical utilization".)

    In patients with a CAC score suggesting atherosclerosis (100 Agatston units or higher), we usually recommend statin therapy. The interpretation of a CAC score also depends on the expected versus observed distribution in a given population. Many preventive cardiologists will treat for any CAC >0. In those with a CAC score of 0, one can defer statin therapy if the patient prefers. This recommendation and the supporting evidence are discussed separately. (See "Coronary artery calcium scoring (CAC): Overview and clinical utilization", section on 'CAC score greater than or equal to 100 or >75 percentile for age, sex, and race'.)

- **Other risk-enhancing factors –** Elevations of other factors include blood tests such as hsCRP and Lp(a), which are discussed in detail separately. (See "Lipoprotein(a)", section on 'Disease associations' and "Overview of established risk factors for cardiovascular disease", section on 'C-reactive protein'.)

Low (<5 percent) 10-year CVD risk — For most patients with LDL-C <190 mg/dL (4.9 mmol/dL) and a 10-year risk less than 5 percent, we do not start statin therapy.

The Cholesterol Treatment Trialists' meta-analysis of 22 trials of over 175,000 participants showed that among the 24,790 at low CVD risk, statins were associated with a lower relative risk of vascular events compared with the placebo group (RR 0.62; 95% CI 0.47-0.81); however, the absolute risk reduction for any vascular event was very modest (absolute risk reduction 0.18 percent over five years) given the low observed event rates for those assigned statins and placebo (0.38 versus 0.56 percent) [11].

As noted above, use of calcium scoring can help identify higher-risk patients with evidence of ASCVD (which would then merit treatment).

SUBSEQUENT MANAGEMENT

Our approach to LDL-C lowering is summarized in an algorithm (algorithm 1).

Repeat LDL-C and CVD risk assessment — The LDL-C should be measured four to six weeks after initiating statin therapy in order to assess LDL-C lowering and statin adherence. Some physicians also check creatinine phosphokinase and liver function tests to confirm safety. We also reevaluate risk factors, as this will impact our subsequent management. (See 'CVD risk assessment' above.)

If LDL-C reduction has not been achieved, we assess adherence and consider adjusting therapy. (See 'Medication adjustment' below.)

If there is a change in health status, a repeat LDL-C level and CVD risk assessment may be warranted. For example, the LDL-C increases in some females during menopause. Such changes in the LDL-C may warrant change in management.

Conversely, in some patients with severe illness, the LDL-C can drop to very low levels. In this case, we generally continue the statin therapy.

For patients taking statins who have had no major change to their health status or adherence, LDL-C does not need to be repeated.

In those who do not start a statin, we usually reassess their atherosclerotic cardiovascular disease (ASCVD) risk on a routine and periodic basis. This approach is discussed in detail separately. (See "Atherosclerotic cardiovascular disease risk assessment for primary prevention in adults: Our approach", section on 'Our approach to ASCVD risk assessment'.)

Monitoring and managing side effects — Side effects can vary somewhat among the different statins and are discussed in detail separately. The most major adverse reaction limiting statin use is the development of muscle symptoms. Statins can increase the risk of new-onset diabetes in a dose-dependent fashion. (See "Statins: Actions, side effects, and administration", section on 'Diabetes mellitus'.)

Although changes in cognitive function are listed as a possible side effect in the label of statins, large randomized trials have demonstrated no effect on cognition, and thus this is not a side effect that patients should be concerned with. (See "Statins: Actions, side effects, and administration", section on 'Side effects' and "Statin muscle-related adverse events".)

Some patients will not tolerate first-line statins (eg, atorvastatin, rosuvastatin, pravastatin, or simvastatin). In this case, some lipid specialists prescribe fluvastatin or pitavastatin. Additionally, use of alternate-day regimens of low doses of statins is a common approach (eg, rosuvastatin 2.5 mg three times per week). These and other options for adjusting statin regimens in patients with adverse effects are discussed in detail separately. (See "Statins: Actions, side effects, and administration", section on 'Management considerations'.)

> If a patient does not tolerate statins, then four other classes of drugs are options: ezetimibe, bempedoic acid, bile-acid sequestrants (eg, colesevelam), and PCSK9 inhibitors. At present, PCSK9 inhibitor use is generally limited to those with ASCVD or familial hypercholesterolemia, but one agent, inclisiran, did get FDA approval for use in primary prevention. (See 'Nonstatin treatment' below.)

Assessing and managing nonadherence — Adherence is important and needs to be checked periodically. Some patients do not achieve appropriate LDL-C reduction due to nonadherence. More frequent testing is reasonable when adherence is in doubt. Thus, it is important to ask about adherence at follow-up visits. In current electronic health records, it is often possible to check if the patient has been filling the prescriptions from the pharmacy. That can then allow a discussion of adherence.

The approach to the patient with suspected nonadherence is discussed separately. We engage in shared decision making; this may include discussion of a patient's hesitancy to take lipid-lowering medication and their fear of side effects. Sharing results from randomized trials on

efficacy and safety is often helpful. (See "Adherence to lipid-altering medications and recommended lifestyle changes".)

Medication adjustment — For primary prevention, a general target for LDL-C is <100 mg/dL. Thus, if LDL-C therapy does not result in LDL-C <100 mg/dL (2.6 mmol/L) in patients at high and very high risk, we intensify lipid lowering, usually first increasing the dose of statin to intensive statin therapy (table 1), sometimes adding a nonstatin LDL-C-lowering medication, as noted below (algorithm 1). (See 'Nonstatin treatment' below.)

We choose this target because this matches the achieved LDLs of many of the primary prevention trials. In addition, analyses of achieved LDL versus outcomes show that the lower the achieved LDL, the lower the event rate. However, there have not been specific treat-to-target trials in primary prevention.

For patients with higher ASCVD risk score, the benefit will be greater, and thus we recommend a more intensive treatment approach for those higher-risk patients. In some patients, intensifying statin therapy or using dual therapy with a statin and nonstatin medication (eg, ezetimibe, bempedoic acid) is appropriate.

Nonstatin treatment

Indications — In the setting of primary prevention, indications for nonstatin treatment include the following:

- For patients who are statin intolerant, or those who are unwilling to start a statin due to fear of side effects, use of nonstatin agents can be an alternative. Two agents have been specifically tested and shown to reduce cardiovascular events in primary prevention: ezetimibe in the EWTOPIA 75 trial [15] and bempedoic acid in the CLEAR OUTCOMES trial [16].

- For patients at high or very high risk of ASCVD who do not achieve adequate LDL-C lowering on statin therapy alone, we first add oral ezetimibe 10 mg daily. If after four to six weeks the LDL-C remains greater than or equal to 100 mg/dL, we consider adding another nonstatin medication, particularly for people who are at high risk and/or continue to have elevated LDL-C levels. Nonstatin agents include oral bempedoic acid and/or bile-acid sequestrants (eg, colesevelam) (table 3).

Available agents

- Ezetimibe – First line is ezetimibe since it is available as a low-cost generic (table 3). It will lead to approximately 20 to 25 percent reduction in LDL. This agent has been shown to

not have any effect on muscle symptoms and has no effect on development of diabetes, the two side effects of statins. As such, it can be a good option for patients unwilling or unable to take statins.

EWTOPIA 75 evaluated monotherapy with ezetimibe in patients 75 and older [15]. More than 3700 patients were randomly assigned to ezetimibe or usual care. At a median follow-up of 4.1 years, patients assigned to ezetimibe had a lower risk of the composite outcome of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke (hazard ratio 0.66, 95% CI 0.50-0.86). There are several other trials showing clinical benefit of adding ezetimibe to statin therapy in other patient populations (ie, in those with existing ASCVD). (See "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease".)

- Bempedoic acid – This drug reduces LDL by 20 to 25 percent and recently has been shown to reduce cardiovascular events in a large trial involving patients in primary and secondary prevention cohorts (table 3) [16]. There was a significant reduction in events in the primary prevention subgroup alone [17,18].

  In a trial of 13,970 patients who were unable or unwilling to take statins due to adverse effects and had or were at high risk for cardiovascular disease, patients were assigned either bempedoic acid 180 mg daily or placebo and followed for 40 months [17]. Among the subgroup of 4206 primary prevention patients, those assigned bempedoic acid compared with placebo had lower rates of these outcomes:

  - Composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization was lower (5.3 versus 7.6 percent; HR 0.70 95% CI, 0.55-0.89).

  - Composite of death from cardiovascular causes, nonfatal stroke, or nonfatal myocardial infarction (4 versus 6.4 percent); fatal or nonfatal myocardial infarction (1.4 versus 2.2 percent); and cardiovascular death (1.8 versus 3.1 percent).

  People assigned bempedoic acid had similar rates of stroke or coronary revascularization compared with placebo. Those assigned bempedoic acid had higher rates of gout (2.6 versus 2 percent), cholelithiasis (2.5 versus 1.1 percent), and renal impairment (10.3 percent) versus (8.1 percent). Rates of serum creatinine, uric acid, and hepatic-enzyme levels were also modestly higher in those assigned bempedoic acid.

- Colesevelam – This is also an option for LDL lowering, but it has slightly less LDL lowering (in the range of 15 to 20 percent). It is available generically but requires six tablets daily,

which can be a barrier to use. There is not an outcomes trial of this agent (table 3).

- **PCSK9 inhibitors –** These medications have previously been approved for use for primary prevention only in patients with familial hypercholesterolemia (ie, those with baseline LDL >190 mg/dL and a family history of severe hypercholesterolemia). Recently, one of the agents, inclisiran, did get approval for use in primary prevention. However, the much higher costs of drugs in this class compared with less expensive, generically available ones make this drug option more challenging for many patients (table 3).

SPECIAL POPULATIONS

Age >75 years — We start statin therapy for older-aged patients in whom LDL-C lowering is deemed appropriate by the above-outlined criteria. Statin therapy lowers the risk of stroke and myocardial infarction in older adult patients; the relative risk reduction may be smaller, but the absolute risk reduction is larger because of the high absolute risk among older versus younger patients.

Studies of lipid lowering for primary prevention in patients >70 years old suggest that older patients appear to achieve a similar benefit compared with younger patients. In older patients, the relative risk reduction may be smaller compared with younger patients, but the absolute risk reduction is larger because of the high absolute risk of ASCVD in older individuals. A meta-analysis of patients ≥75 years of age included in primary and secondary prevention trials found that statins reduced risk of major vascular events by 26 percent per 1 mmol/L reduction in LDL-C (risk ratio 0.74, 95% CI 0.61-0.89) [19].

With ezetimibe, one study evaluated monotherapy with ezetimibe in patients 75 and older [15]. More than 3700 patients were randomly assigned to ezetimibe or usual care. At a median follow-up of 4.1 years, patients assigned to ezetimibe had a lower risk of the composite outcome of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke (hazard ratio 0.66, 95% CI 0.50-0.86).

Diabetes — For patients with diabetes and an LDL-C ≥190 mg/dL (≥4.9 mmol/L), our approach is the same as for patients without diabetes who have an LDL-C in this range. (See 'LDL-C greater than or equal to 190 mg/dL' above.)

For patients with diabetes, age ≥40 years, and an LDL-C <190 mg/Dl (<4.9 mmol/L), we start a moderate intensity statin. The majority of patients with diabetes who are ≥40 years of age will be in the intermediate or high risk atherosclerotic cardiovascular disease (ASCVD) category [20].

For adults with diabetes aged 20 to 39 years with one or more additional risk factors, we have a shared decision-making discussion of the benefits and risks of starting moderate-intensity statin [21].

Prior randomized studies of moderate-intensity statins in patients with diabetes have shown that statins are efficacious at reducing primary ASCVD events [22-25]. A meta-analysis of these four primary prevention trials of over 10,000 participants with diabetes showed that those assigned statins versus placebo had lower cardiovascular and cerebrovascular events (RR 0.75, 95% CI 0.67–0.85); fatal/non-fatal stroke (RR 0.69, 95% CI 0.51–0.92); and fatal/non-fatal myocardial infarction (RR 0.70, 95% CI 0.54–0.90) [26]. There was a non-significant RR reduction in all-cause mortality with statin use versus placebo (RR 0.84, 95% CI 0.65–1.09).

In patients with diabetes, age ≥40 years, and who have a high ASCVD risk score ≥20 percent, we consider starting a high-intensity statin and set a lower LDL-C goal of <70 mg/dL (<1.8 mmol/L). Although no trials of high-intensity statin therapy have been conducted in patients with diabetes, the benefit from statins is greater in those patients who have a higher baseline ASCVD risk. (See 'Rationale for our approach and treatment goals' above.)

Persons living with HIV — HIV infection is associated with excess risk of ASCVD. The role of statin therapy in such patients is discussed separately. (See "Management of cardiovascular risk (including dyslipidemia) in patients with HIV", section on 'Recognizing and managing dyslipidemia'.)

Chronic kidney disease — The role of statins in these patients is discussed separately. (See "Lipid management in patients with nondialysis chronic kidney disease", section on 'Primary prevention: Patients with CKD without established atherosclerotic cardiovascular disease'.)

Liver disease — The approach to the use of statins in patients with liver disease is discussed separately. (See "Statins: Actions, side effects, and administration", section on 'Chronic liver disease'.)

Childbearing potential — Prior to initiating statin therapy in females of childbearing age, we engage in shared decision-making discussions regarding the following:

- Statins are contraindicated in pregnancy due to potential harmful effects on the fetus.
- The need for effective contraception when a statin is initiated. (See "Contraception: Counseling and selection".)

If the patient is already on a statin and actively trying to conceive, we withdraw the statin. The FDA recently updated the statin labels to include a new analysis of risk that found **no increase**

in risk if a patient was on statin at the time they found they were pregnant, so long as it is stopped when the pregnancy is noted. As such, this can be reassuring to women who are on statins and do become pregnant.

Pregnancy — Statins are contraindicated during pregnancy. (See "Statins: Actions, side effects, and administration", section on 'Risks in pregnancy and breastfeeding'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Lipid disorders in adults" and "Society guideline links: Primary prevention of cardiovascular disease" and "Society guideline links: Assessment of cardiovascular risk".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: High cholesterol and lipid treatment options (Beyond the Basics)")
- Basics topics (see "Patient education: High cholesterol (The Basics)" and "Patient education: Can foods or supplements lower cholesterol? (The Basics)" and "Patient education: High triglycerides (The Basics)")

SUMMARY AND RECOMMENDATIONS

Overview of approach – Our approach to statin therapy is guided by a patient's low-density lipoprotein cholesterol (LDL-C) level and their cardiovascular disease (CVD) risk. (See 'CVD risk assessment' above.)

- **Lifestyle modification –** We counsel all patients with an elevated LDL-C to exercise and adopt a healthy diet. (See 'Lifestyle modification' above.)

- **LDL-C ≥190 mg/dL (or ≥4.9 mmol/L) –** For all such patients, we perform a work-up for familial hypercholesterolemia (FH) and, if present, we treat accordingly. Whether or not the patient has FH, we recommend statin treatment. We use high-dose statin therapy for such individuals (table 1). (See 'LDL-C greater than or equal to 190 mg/dL' above.)

- **LDL-C 100 to <190 mg/dL (or 2.6 to <4.9 mmol/L) –** In such patients, the indication for a statin therapy is guided by the patient's 10-year estimated CVD risk group (algorithm 1 and table 1). (See 'CVD risk assessment' above.)

  - **High-risk and very high-risk patients –** For patients with a high or very high CVD risk (>7.5 percent 10-year risk of CVD) and LDL-C in the range of 100 to <190 mg/dL, we recommend statin therapy (**Grade 1A**). Clinical trials have consistently shown that statin use reduces the risk of major cardiac events. The higher the ASCVD score, the higher the risk of serious cardiac events and the greater the absolute benefit of statin therapy. (See 'High (7.5 to 20 percent) and very high (greater than or equal to 20 percent) 10-year CVD risk' above.)

    In the context of primary prevention, we typically use moderate-intensity statin therapy as initial therapy. It is also reasonable to consider high-intensity statin therapy in patients at very high risk (>20 percent 10-year risk of CVD).

  - **Intermediate-risk patients –** For patients with a 5 to 7.4 percent 10-year risk of CVD and an LDL-C in the range of 100 to <190 mg/dL (2.6 to <4.9 mmol/L), we suggest statin therapy (**Grade 2A**). We present the potential benefits and costs/risks to patients using shared decision-making. While the absolute benefit is small in patients with ASCVD scores near the threshold of 5 percent, the treatment is generally safe and well tolerated. We are particularly likely to encourage statin use if there are very high LDL-C levels (eg, >160 mg/dL [>4.14 mmol/L]).

    For other intermediate-risk patients, a coronary artery calcium score, lipoprotein(a) level, high-sensitivity C reactive protein level, or presence of other risk enhancer can help guide decision-making (table 2). (See 'Intermediate (5 to 7.4 percent) 10-year CVD risk' above.)

- **Low-risk patients –** For most patients with a low (<5 percent 10-year) CVD risk, we do not start statin therapy but consider further risk stratification. (See 'Low (<5 percent) 10-year CVD risk' above.)

- **Repeat LDL-C and CVD risk assessment –** We measure LDL-C response at four to six weeks after initiating therapy and every 12 months thereafter to assess adherence, efficacy, and if there is a change in patient health status.

  Our goal LDL-C is <100 mg/dL. In high-risk patients, if the LDL-C remains above this level, we consider intensifying the dose of statin and/or dual therapy with ezetimibe. Other options include adding bempedoic acid and/or a bile acid sequestrant. (See 'Subsequent management' above.)

- **Managing side effects –** Adverse effects can vary among the statins. Management options in patients with side effects are discussed separately. (See 'Monitoring and managing side effects' above and "Statins: Actions, side effects, and administration".)

- **Statin-intolerant patients –** In patients in the above risk categories, if statin is not tolerated, both ezetimibe and bempedoic acid are reasonable effective alternatives to statins. We prefer ezetimibe due to its lower side effect profile. Alternative therapy includes bile acid sequestrants.

- **Special populations –** In people >75 years of age, we use the same approach to guide therapy as we do for patients <75 years old. (See 'Age >75 years' above.)

  Statins are stopped in pregnant patients due to higher potential risk versus benefits. Therefore, we counsel some of our female patients of childbearing age who are on statin therapy to also use contraceptive therapy. (See 'Pregnancy' above and 'Childbearing potential' above.) Other special populations are discussed above. (See 'Special populations' above.)

ACKNOWLEDGMENT

Michael Pignone, MD, MPH, was recently a member of the United States Preventive Services Task Force. The expressed opinions herein are those of Dr. Pignone and do not necessarily represent those of the United States Preventive Services Task Force.

REFERENCES

1. Chou R, Dana T, Blazina I, et al. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2016; 316:2008.
2. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006; 295:655.
3. Caggiula AW, Christakis G, Farrand M, et al. The multiple risk intervention trial (MRFIT). IV. Intervention on blood lipids. Prev Med 1981; 10:443.
4. Estruch R, Ros E, Salas-Salvadó J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 2018; 378:e34.
5. Barnard ND, Alwarith J, Rembert E, et al. A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Cross-over Trial. J Am Nutr Assoc 2022; 41:127.
6. Gardner CD, Vadiveloo MK, Petersen KS, et al. Popular Dietary Patterns: Alignment With American Heart Association 2021 Dietary Guidance: A Scientific Statement From the American Heart Association. Circulation 2023; 147:1715.
7. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al. Effect of a Lifestyle Intervention Program With Energy-Restricted Mediterranean Diet and Exercise on Weight Loss and Cardiovascular Risk Factors: One-Year Results of the PREDIMED-Plus Trial. Diabetes Care 2019; 42:777.
8. Sofi F, Dinu M, Pagliai G, et al. Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). Circulation 2018; 137:1103.
9. Stefanick ML, Mackey S, Sheehan M, et al. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. N Engl J Med 1998; 339:12.
10. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 73:e285.
11. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular

disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380:581.

12. Ray KK, Seshasai SR, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 2010; 170:1024.
13. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; :CD004816.
14. Grinspoon SK, Fitch KV, Zanni MV, et al. Pitavastatin to Prevent Cardiovascular Disease in HIV Infection. N Engl J Med 2023; 389:687.
15. Ouchi Y, Sasaki J, Arai H, et al. Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized, Controlled Trial. Circulation 2019; 140:992.
16. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med 2023; 388:1353.
17. Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic Acid for Primary Prevention of Cardiovascular Events in Statin-Intolerant Patients. JAMA 2023; 330:131.
18. Ray KK, Nicholls SJ, Li N, et al. Efficacy and safety of bempedoic acid among patients with and without diabetes: prespecified analysis of the CLEAR Outcomes randomised trial. Lancet Diabetes Endocrinol 2024; 12:19.
19. Gencer B, Marston NA, Im K, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. Lancet 2020; 396:1637.
20. Wong ND, Glovaci D, Wong K, et al. Global cardiovascular disease risk assessment in United States adults with diabetes. Diab Vasc Dis Res 2012; 9:146.
21. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care 2024; 47:S179.
22. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364:685.
23. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; 361:2005.
24. Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin

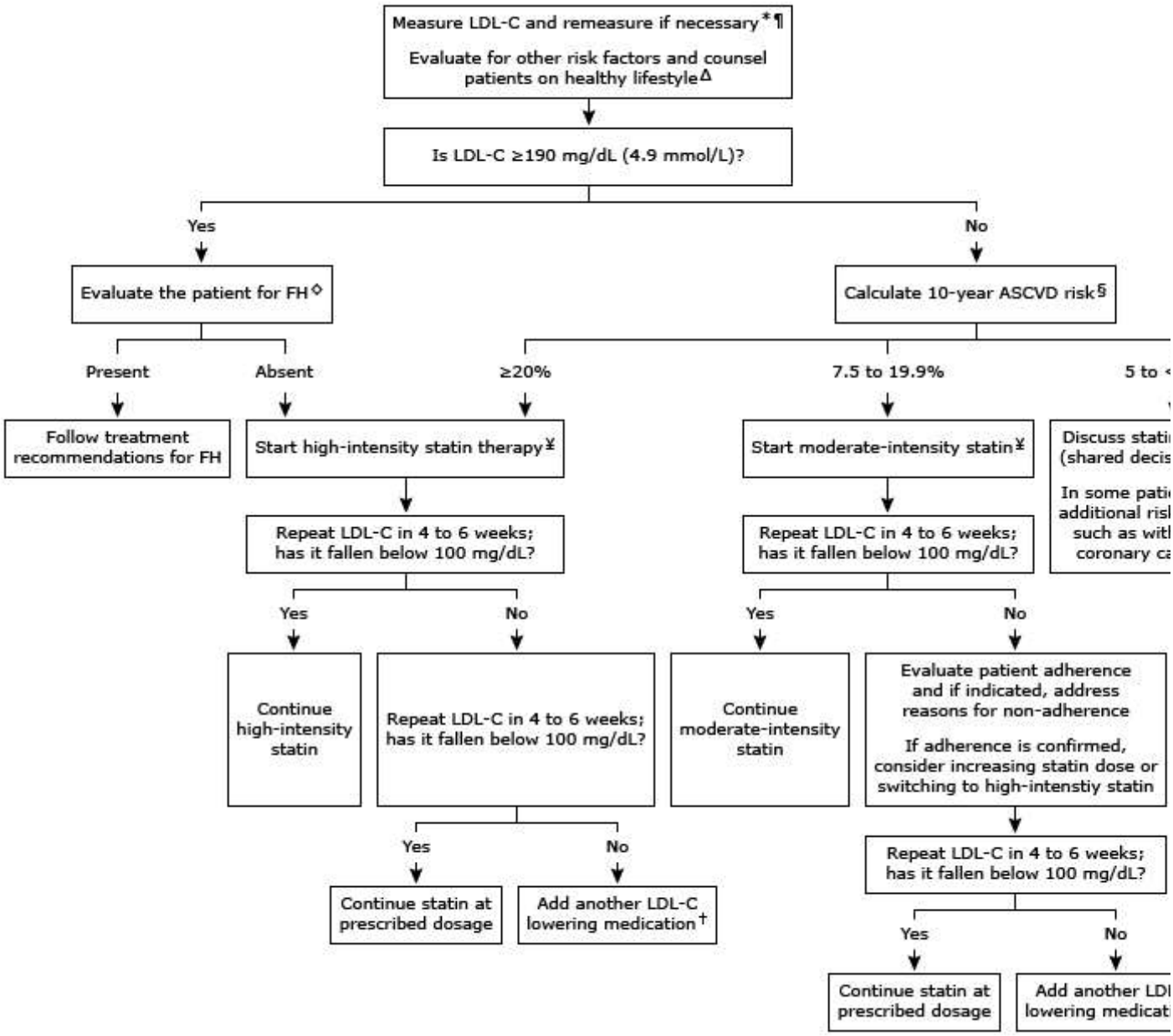
Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care 2006; 29:1478.

25. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005; 28:1151.
26. de Vries FM, Denig P, Pouwels KB, et al. Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis. Drugs 2012; 72:2365.

Topic 4549 Version 92.0

GRAPHICS

Algorithm for the management of elevated low-density lipoprotein cholesterol in adults without cardiovascular disease and diabetes



The algorithm applies to all adults over the age of 18. It does not apply to individuals with diabetes mellitus or established cardiovascular disease.

ASCVD: atherosclerotic cardiovascular disease; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol.

* Recommendations for screening are found elsewhere.

¶ We recommend that decisions regarding the initiation of LDL-C interventions be made only after two baseline values have been recorded.

Δ All adults, irrespective of LDL-C, should receive counseling on the benefits of a healthy lifestyle and should be evaluated for the presence of diabetes, hypertension, and smoking.

◇ For more information, refer to the UpToDate topics on the evaluation of patients for familial hypercholesterolemia.

§ Recommendations for the use of risk calculators are found elsewhere.

¥ High-dose statin: atorvastatin 40 to 80 mg once daily; rosuvastatin 20 to 40 mg once daily. For patients who are statin intolerant, or those who are unwilling to start a statin due to fear of side effects, use of non-statin agents can be an alternative. Two agents have been specifically tested and shown to reduce cardiovascular events in primary prevention are ezetimibe and bempedoic acid.

Moderate-dose statin: atorvastatin 10 to 20 mg once daily; fluvastatin 40 mg twice daily; lovastatin 40 to 50 mg once daily; pitavastatin 1 to 4 mg once daily; pravastatin 40 to 80 mg once daily; rosuvastatin 5 to 10 mg daily; simvastatin 20 to 40 mg once daily.

‡ For patients with 5 to 7.4% 10-year ASCVD risk and who have LDL-C ≥160 mg/dL, we usually suggest statin therapy.

† In general, we take this step for patients on their highest-tolerated statin dosage. We first add oral ezetimibe 10 mg daily. If LDL-C is still ≥100 mg/dL, we add bempedoic acid (or a fibrate such as colesevelam). Refer to UpToDate for further information.

Graphic 143459 Version 3.0

Statin doses and intensities

	Daily dose range	Low intensity	Moderate intensity	High intensity
Amount of LDL-C lowering		**<30%**	**30 to 49%**	**≥50%**
Lovastatin	20 to 80 mg	20 mg	40 to 80 mg	–
Pravastatin	10 to 80 mg	10 to 20 mg	40 to 80 mg	–
Simvastatin	10 to 40 mg*	10 mg	20 to 40 mg	–
Fluvastatin	20 to 80 mg	20 to 40 mg	40 mg twice daily (or XL 80 mg once daily)	–
Pitavastatin	1 to 4 mg	–	1 to 4 mg	–
Atorvastatin	10 to 80 mg	–	10 to 20 mg	40 to 80 mg
Rosuvastatin	5 to 40 mg	–	5 to 10 mg	20 to 40 mg

- Doses are intended for adult patients with normal organ (ie, kidney, liver) function and are administered once daily, unless otherwise noted.
- Coadministration of drugs that alter CYP metabolism or drug transporters (eg, OATP, BCRP) often requires statin dose limitations or avoidance. When initiating or altering drug therapy, use of a drug interactions database, such as the drug interactions program within UpToDate, is advised.

LCL-C: low-density lipoprotein cholesterol; XL: extended-release 24-hour preparation.

* Although simvastatin has been used at higher doses (ie, up to 80 mg/day), we do not recommend doses >40 mg/day as there is a higher risk of myopathy, including rhabdomyolysis.

Data from: Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 73:e285.

Graphic 140458 Version 7.0

Risk-enhancing factors for clinician-patient risk discussion

Risk-enhancing factors

- Family history of premature ASCVD (males, age <55 years; females, age <65 years)
- Primary hypercholesterolemia (LDL cholesterol, 160 to 189 mg/dL [4.1 to 4.8 mmol/L]; non-HDL cholesterol 190 to 219 mg/dL [4.9 to 5.6 mmol/L])*
- Metabolic syndrome (increased waist circumference [by ethnically appropriate cutpoints], elevated triglycerides [>150 mg/dL, nonfasting], elevated blood pressure, elevated glucose, and low HDL cholesterol [<40 mg/dL in males; <50 mg/dL in females] are factors; a tally of 3 makes the diagnosis)
- Chronic kidney disease (eGFR 15 to 59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- Chronic inflammatory conditions, such as psoriasis, RA, lupus, or HIV/AIDS
- History of premature menopause (before age 40 years) and history of pregnancy-associated conditions that increase later ASCVD risk, such as preeclampsia
- High-risk race/ethnicity (eg, South Asian ancestry)
- Lipids/biomarkers associated with increased ASCVD risk
  - Persistently elevated* primary hypertriglyceridemia (≥175 mg/dL, nonfasting)
  - If measured:
    - Elevated high-sensitivity C-reactive protein (≥2 mg/L).
    - Elevated Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
    - Elevated apoB (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL cholesterol >160 mg/dL and constitutes a risk-enhancing factor.
    - ABI (<0.9).

ABI: ankle-brachial index; AIDS: acquired immunodeficiency syndrome; apoB: apolipoprotein B; ASCVD: atherosclerotic cardiovascular disease; eGFR: estimated glomerular filtration rate; HDL cholesterol: high-density lipoprotein cholesterol; HIV: human immunodeficiency virus; LDL cholesterol: low-density lipoprotein cholesterol; Lp(a): lipoprotein (a); RA: rheumatoid arthritis.

* Optimally, 3 determinations.

Graphic 131708 Version 8.0

Adult dosing, major side effects, and drug interaction potential of lipid-lowering drugs

Drug class	Dose range*	Administration	Major side effects and drug interaction potentials
Statins			
Atorvastatin	10 to 80 mg/day	Take any time	Muscle-related (eg, myalgia, myopathy, myositis, rhabdomyolysis) headache; gastrointestinal (eg, nausea, constipation, dyspepsia, diarrhea); sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Statins are dependent on CYP metabolism and/or transmembrane transporters (eg, OATP, BCRP) for clearance, subjecting them to a significant number of clinically relevant drug interactions. Coadministration of drugs that alter CYP metabolism or drug transporters often requires dose limitations or avoidance. The patient's medication list should be analyzed using a drug interaction program whenever therapy is adjusted.
Fluvastatin	IR: 20 to 80 mg/day	IR: Take in the evening Divide dose twice per day (morning and evening) if dose >40 mg/day	
	XR: 80 mg/day	XR: Take any time	
Lovastatin	IR: 20 to 80 mg/day	IR: Take once daily with evening meal	
	XR: 20 to 60 mg/day	XR: Take in the evening	
Pitavastatin	1 to 4 mg/day	Take any time	
Pravastatin	10 to 80 mg/day	Take in the evening¶	
Rosuvastatin	5 to 40 mg/day	Take any time	
Simvastatin	10 to 40 mg/day	Take in the evening	
Cholesterol absorption inhibitor			
Ezetimibe	10 mg/day	Take any time	Generally well tolerated; low risk for potential drug interactions. Increased transaminases may be observed with concurrent statin use; however, coadministration is common.
PCSK9 inhibitors			
Alirocumab	75 to 150 mg every 2 weeks or 300 mg every 4 weeks	Administer by subcutaneous injection into thigh, abdomen, or upper arm	Injection site reactions. Low risk for potential drug interactions.
Evolocumab	140 mg every 2 weeks or 420 mg every		

	month Homozygous familial hypercholesterolemia: 420 mg every month to 420 mg every 2 weeks		
Adenosine triphosphate citrate lyase inhibitor			
Bempedoic acid	180 mg daily	Take any time	Hyperuricemia, acute gouty arthritis; myalgia, muscle spasms, arthralgias; tendon rupture; increased aspartate aminotransferase. Potential for significant drug interactions; dose limitations for some statins are recommended during concurrent use. The patient's medication list should be analyzed using a drug interaction program whenever therapy is adjusted.
Fibric acid derivatives			
Fenofibrate	Nanocrystal: 145 mg/day Micronized: 90 to 200 mg/day Nonmicronized: 120 to 160 mg/day Fenofibric acid: 105 to 135 mg/day	Multiple formulations exist with varying dosing and administration Some formulations must be administered with food	Increased serum transaminases, muscle-related (eg, myalgia, myositis, rhabdomyolysis), gastrointestinal (eg dyspepsia, nausea, bloating, cramping). Potential for significant drug interactions; eg, increased risk of myopathy with statins, enhanced anticoagulant effect of warfarin. Gemfibrozil use with statins is not recommended. The patient's medication list should be analyzed using a drug interaction program whenever therapy is adjusted.
Gemfibrozil	600 mg twice per day	Take 30 minutes before meals	
Bezafibrate (not available in the United States)	Sustained release: 400 mg once daily	Take with or after meals	
Bile acid sequestrants			
Cholestyramine	Powder: 4 to 24 g/day	Take within 30 minutes of a meal Administer granules or powder as	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase. Impaired absorption of fat soluble vitamins and coadministered
Colestipol	Granules: 5 to 30 g/day		

	Tablet: 2 to 16 g/day	prepared suspension Do not hold cholestyramine in mouth for prolonged periods (may cause tooth discoloration or enamel decay) Administer other oral medications ≥1 hour before or 4 to 6 hours after bile acid sequestrants	medications. The patient's medication list should be analyzed using a drug interaction program whenever therapy is adjusted.
Colesevelam	Granules or tablet: 3.75 g/day		
Nicotinic acid (niacin)	IR: 250 mg to 6 g/day	Take with meals	Not recommended for use in most patients due to poor tolerability and lack of efficacy for clinical endpoints. Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; hyperpigmentation (particularly in intertriginous regions) acanthosis nigricans, and dry skin; nausea, vomiting, diarrhea; myositis; hyperglycemia, hyperuricemia; hypotension; increased risk of infection. Low risk for potential drug interactions.
	XR (Niaspan): 0.5 to 2 g/day	Take at bedtime after a low-fat snack or evening meal	

IR: immediate release; LDL-C: low density lipoprotein cholesterol; PCSK9 inhibitors: proprotein convertase subtilisin kexin type 9 inhibitors; XR: extended release.

* Dose ranges provided are total daily doses for oral administration (except PCSK9 inhibitors) in adult patients with normal organ function. Statin dose ranges include low-, moderate-, and/or high-intensity LDL-C-lowering therapy, depending on specific statin. For indications and doses, refer to the relevant clinical topic reviews and drug information monographs included within UpToDate.

¶ Per United States labeling, may be taken any time of day; however, UpToDate contributors prefer evening administration due to pravastatin's short half-life.

Graphic 77498 Version 25.0

Contributor Disclosures

Michael Pignone, MD, MPH, MACP No relevant financial relationship(s) with ineligible companies to disclose. **Christopher P Cannon, MD** Grant/Research/Clinical Trial Support: Amgen [Lipids (Salary support from Colorado Prevention Center (CPC) Clinical Research)]; Bayer [CKD (Salary support from Colorado Prevention Center (CPC) Clinical Research)]; Better therapeutics [Diabetes]; Boehringer-Ingelheim [AF, DM, HF, CKD]; Cleerly [Imaging (Salary support from Colorado Prevention Center (CPC) Clinical Research)]; Esperion [Lipids (Salary support from Colorado Prevention Center (CPC) Clinical Research)]; Lexicon [DM (Salary support from Colorado Prevention Center (CPC) Clinical Research)]; Novo Nordisk [DM]; Silence [Lipids (Salary support from Colorado Prevention Center (CPC) Clinical Research)]. Consultant/Advisory Boards: Amarin [Lipids]; Amgen [Lipids]; Amryt/Chiesi [Lipids]; Areteia [Data and Safety Monitoring Board – Pulmonary]; Ascendia [ACS]; BI [AF, DM, HF, CKD]; Biogen [Alzheimers]; Bristol-Myers Squibb [AF, ACS]; CSL Behring [Lipids]; Eli Lilly [DM, ACS]; Janssen [AF, DM, ACS/CAD]; Lexicon [DM, CKD, HF]; Milestone [SVT]; Novo Nordisk [Data and Safety Monitoring Board – DM]; Pfizer [AF, DM, lipids]; Rhoshan [ACS]; ROMTherapy, Inc [Data and Safety Monitoring Board – Cardiac Rehab]; Veterans Administration [Data and Safety Monitoring Board]. All of the relevant financial relationships listed have been mitigated. **Mason W Freeman, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sara Swenson, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy