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

**AUTHOR:** Michael Pignone, MD, MPH
**SECTION EDITOR:** Mason W Freeman, MD **DEPUTY EDITOR:** Nisha Parikh, MD, MPH

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

**Literature review current through:** Apr 2023.
**This topic last updated:** Nov 11, 2022.

## INTRODUCTION AND TERMINOLOGY

Lowering low-density lipoprotein cholesterol (LDL-C) via lifestyle change or pharmacologic therapy 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 observational and 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 [1-4].

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 LDLC 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 CVD risk assessment will help guide LDL-C-lowering strategies (including statin therapy) and other 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 (HDLC), and LDL-C; 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 ≤10 percent
- High – >10 percent
- Very High – ≥20 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 [5].

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 'Dietary modification for all individuals'.)

In most patients (unless they are on a diet particularly high in saturated fat such as the ketogenic diet), there is limited evidence that dietary modification alone improves cardiovascular and mortality outcomes [6,7]. Studies of specific diets (eg, Mediterranean, DASH, vegetarian, etc) that can result in lowering a person's LDL-C levels and/or 10-year cardiovascular risk are discussed separately. It is uncertain whether the CVD reduction is due to LDL-C lowering. (See "Lipid management with diet or dietary supplements", section on 'Dietary modification for all individuals'.)

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 [8]. (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. Our goal is to reduce CVD events via LDL-C lowering. Clinical trial evidence to support lowering LDL-C to a particular goal is lacking. A shared decision-making approach is very important.

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 unfavorable 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 woman with an LDL-C of 180 mg/dL (4.7 mmol/L) and a high-density lipoprotein cholesterol (HDL-C) of 40 mg/dL (1.03 mmol/L) has a 10-year risk of myocardial infarction of approximately 1 percent. This could likely be reduced by 0.2 to 0.3 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 180 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 12

percent. Use of a statin would reduce this risk to 8 to 9 percent, a three- to fourpercentage 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. (See "Familial hypercholesterolemia in adults: Overview" and "Familial hypercholesterolemia in adults: Treatment".)

If the patient does not have FH, we treat them with a high-dose statin therapy. As an example, we may start these patients on atorvastatin 40 mg daily or rosuvastatin 20 mg daily. The dose and intensity of different statin medications are described in detail separately.

A CVD risk calculation may be unnecessary 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 LDLC level alone.

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

**LDL-C lesser than or equal to 190 mg/dL** — If the patient has 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).

**High (>10 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 10 percent, we initiate statin therapy. This approach may differ in special populations such as the very old and those with diabetes. (See 'Special populations' below.)

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

  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 is that the doses that produce low to moderate LDL-C lowering were the ones studied in the vast majority of clinical trials of statin therapy in primary prevention. These moderate doses of statin were shown to reduce CVD events by 30 percent [5]. However, most trials compared a fixed dose of a single pharmacologic agent with placebo, and none of the trials have directly compared the effects of low-to-moderate- with highintensity statin therapy.

**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 CVD events and mortality [5,9-11]. 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).

A 2022 meta-analysis of 19 trials and 3 observational studies of 90,000 patients without CVD showed that patients assigned statins had reduction in the following outcomes, compared with the placebo group [12]:

- All-cause mortality – (risk ratio [RR] 0.92, 95% CI 0.87-0.98)
- Cardiovascular mortality – (RR 0.91, 95% CI 0.81-1.02)
- Stroke – (RR 0.78, 95% CI 0.68-0.90)
- Myocardial infarction – (RR 0.67, 95% CI 0.60-0.75)
- Revascularization – (RR 0.71, 95% CI 0.63-0.80)

Other prior meta-analyses examining statin therapy in primary prevention have shown similar efficacy of statin therapy on reducing CVD and mortality outcomes [9,11].

**Intermediate (5 to lesser than or equal to 10 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 10 percent, we undertake shared decision-making with the patient, including a detailed discussion of the potential benefits and costs/risks. 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 benefits are smaller and vary within this group.

A meta-analysis of 22 trials of over 39,000 participants showed that among those at intermediate CVD risk, statins were associated with a lower 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 RR 0.47 percent) given the lower observed event rates in those assigned statins and placebo (1.10 versus 1.57 percent) [9].

For patients at intermediate CVD risk, we consider the specific LDL-C level when advising them to consider statin therapy versus undergoing evaluating for other risk-enhancing factors. Risk stratification is discussed in detail separately:

- **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 10 percent, we usually suggest statin therapy.
- **LDL-C <160 mg/dL (<4.14 mmol/L)** – In these patients, the following additional tests can help us better classify patient risk (ie, into low-intermediate or high-intermediate risk categories) and help guide decisions about whether to start statin therapy. There is no consensus regarding which of these risk-enhancing factors to consider. 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 [13]. 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.
    - **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), and among females who have been pregnant, adverse pregnancy outcomes such as preeclampsia ( table 1).
    - **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. In those with CAC sore of 0, we defer statin therapy. 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** – These 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.

One meta-analysis of 22 trials of over 39,000 participants showed that among those 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 RR 0.18 percent) given the low observed event rates for those assigned statins and placebo (0.38 versus 0.56 percent) [9].

**LDL-C <70 mg/dL** — Statins have not been well studied for benefit in patients with very low baseline LDL-C levels (eg, below 70 mg/dL [1.8 mmol/L]); however, very few of these patients would be expected to have a high enough estimated absolute risk to justify statin therapy.

**Alternative approaches: Other guidelines groups** — Similar to our approach as outlined above, most society guidelines recommend evaluating future CVD risk using a risk calculator and treating those patients at higher levels of risk. For patients with modestly elevated risk, shared decision-making about treatment is warranted.

- AHA/ACC – Similar to the 2018 ACC/AHA (and others) guidelines, we recommend lifestyle modification and when appropriate, statin therapy or other LDL-lowering medications [13].

Our preferred 10-year CVD risk categories for initiation of statin therapy differ slightly from those found in the 2018 guideline from the AHA/ACC (and others) on the management of

blood cholesterol [13]. This guideline states "In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8mmol/L), at a 10-year ASCVD risk of ≥7.5 percent, start a moderate-intensity statin if a discussion of treatment options favors statin therapy."

Instead, we use low- (<5 percent), intermediate- (5 to ≤10 percent), high- (<10 percent), and very high-risk (≤20 percent) categories based on 10-year CVD risk categories to guide shared decision-making and patient therapy. (See 'CVD Risk Assessment' above.)

- ACC expert consensus update – In 2017, the ACC updated its expert consensus document on the role of nonstatin therapies [14]. Our recommendations are generally similar to those made in this consensus document.
- United States Preventive Services Task Force (USPTF) – The USPTF recommends treatment of adults aged 40 to 75 years with 10-year ASCVD risk greater than 10 percent and at least one CVD risk factor, which differs slightly from our approach [12]. The USPTF also states that providers may choose to start a low- to moderate-dose statin in such patients who have a lower (eg, 7.5 to 9.9 percent) ASCVD risk.
- National Institute for Health and Clinical Excellence (NICE) – Guidelines for lipid management for primary prevention of CVD from the United Kingdom's NICE state that patients with a 10-year risk of CVD of 10 percent or more should be offered statin therapy [15].
- European Society of Cardiology/European Atherosclerosis Society guidelines – In their 2019 guidelines for the management of dyslipidemia, these societies recommended using the SCORE system to assess the 10-year risk for fatal CVD (there is a conversion factor to obtain the risk of fatal plus nonfatal hard CVD events) [16]. SCORE-based risk charts are stratified by country-specific CVD death rates and thus may be more generalizable to European populations. For low-, moderate-, and high-risk patients, proposed LDL-C goals are <116 (3 mmol/L), <100 (2.6 mmol/L), and <70 mg/dL (1.8 mmol/L).

## SUBSEQUENT MANAGEMENT

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

**Repeat LDL-C and CVD risk assessment** — The LDL-C should be measured six to eight weeks after initiating statin therapy in order to assess LDL-C lowering and statin adherence. We also reevaluate risk factors, as this will impact our subsequent management. (See 'CVD Risk Assessment' above.)

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 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'.)

**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. (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. However, fluvastatin and pitavastatin are not commonly prescribed by nonspecialists, as other statins offer either better LDL-C lowering or are more cost effective. 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'.)

> Despite these additional interventions, some patients are statin intolerant; our management approach for such patients depends on their LCL-C level and CVD risk:

- For patients not at very high CVD risk (ie, 10-year risk <20 percent) and/or their LDL-C is ≤190 mg/dL, we do not administer other nonstatin therapy. Potential interventions for these patients include lifestyle modification and, in higher-risk patients, possible antiplatelet therapy. (See 'Lifestyle modification' above and "Aspirin in the primary prevention of cardiovascular disease and cancer".)
- If the patient has LDL-C levels substantially higher than 190 mg/dL (>4.9 mmol/L) or is

at very high CVD risk (ie 10-year risk ≥20 percent), we will try nonstatin medications. (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.

The following may be useful when assessing adherence: Atorvastatin 10 mg is expected to give a 30 to 35 percent reduction in LDL-C level, and 20 mg should give a 45 percent reduction; rosuvastatin 5 mg should give 30 percent reduction, and 10 mg should approach a 40 percent reduction; and lower doses of low-intensity statins such as lovastatin or pravastatin typically give 25 to 30 percent reduction.

The approach to the patient with suspected nonadherence is discussed separately. (See "Adherence to lipid-altering medications and recommended lifestyle changes".)

**Statin dose adjustment** — We rarely increase the intensity of the statin dose. An exception is in an adherent patient at very high 10-year risk of CVD who has not achieved an LDL-C <100 mg/dL on a moderate dose of statin.

- **Patients with very high CVD risk (≥20 percent 10-year risk) and repeat LDL-C >100 mg/dL (or 2.6 mmol/L)** – In a person with an initial ASCVD risk of >20 percent in whom the repeat LDL-C is >100 mg/dL (or 2.6 mmol/L), we switch to a high-intensity statin. After initial therapy, if the patient has a very high risk of a CVD event within 10 years and the repeat LDL-C is >100 mg/dL (2.6 mmol/L), we switch to high-intensity statin therapy; we generally do not use ezetimibe or a PCSK9 inhibitor for such patients.

- **Patients not at very high CVD risk** — For most patients who have been started on moderate-dose statin therapy, we do not intensify therapy.

  There is little evidence to suggest that intensification provides a level of (absolute) benefit that warrants more aggressive LDL-C lowering. Specifically, there have been no randomized trials comparing high- with low- or moderate-intensity statin therapy for primary prevention. In secondary prevention trials comparing high- with lowerdose statin, only a modest benefit for higher doses was observed. In addition, moderate-

intensity statin has a lower side effect profile compared with higherintensity doses and thus is likely associated with better adherence.

**Nonstatin treatment**

- **Highest CVD risk, primary prevention patients (a very high [ie, ≥20 percent] risk of a CVD event within 10 years)** – We use PCSK9 inhibitors in the highest-risk primary prevention patients who are unable to tolerate statin therapy. The effectiveness of PCSK9 inhibitors for CVD secondary prevention makes it likely that they would also be effective for primary CVD prevention. However, their high cost, requirement for injections, and the lack of long-term safety data limit their widespread use in LDL-C lowering for primary CVD prevention. Furthermore, PCSK9 inhibitors have not been adequately evaluated in patients without familial hypercholesterolemia. (see "PCSK9 inhibitors: Pharmacology, adverse effects, and use").

- **Other patients not at the highest CVD risk** – Ezetimibe can be used for LDL-C lowering if other therapies cannot be used, but it has a relatively small LDL-Clowering effect of 17 percent. Ezetimibe has not been well studied in patients without CVD. (see "Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors", section on 'Ezetimibe')

  The basis for use of ezetimibe is largely extrapolated from secondary CVD prevention trials and a metaanalysis showing efficacy for nonstatin therapies such as ezetimibe on reducing CVD events [17].

Other nonstatin treatments are not recommended in this setting. (See 'Medications we do not recommend' below.)

## 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. We believe that the risk of myocardial infarction and stroke will be significantly lowered by statin therapy in older adult patients. However, we do not consider ezetimibe as an alternative to statin therapy given limited evidence supporting its use.

- **Statins** – Our approach to LDL-C lowering with statins for patients 75 years of age

and older is similar to that in patients <75 years of age in that it is individualized and should occur after a full shared decision-making discussion of the potential benefits and costs. Patients should consider the financial cost of statin therapy, as well as the potential burdens of being on multiple medications. Among older patients, we are more inclined to recommend statin therapy if they have a high risk of CVD [18]. Although the relative CVD reduction is smaller for older compared with younger patients, the absolute CVD risk is greater in older patients [19].

Some lipid experts do not initiate statin therapy in individuals older than 85 years or in individuals with advanced comorbid disease. This is because the overall benefit from statin therapy in individuals with significant noncardiovascular conditions and limited life expectancy (less than five years) is likely small.

While studies of lipid lowering for primary prevention in patients >70 years old are somewhat limited, they suggest that older patients appear to achieve a benefit similar to younger patients. One observational study in older patients without CVD suggest a lower mortality among older patients treated with statins 0.75 (95% CI 0.740.76) [20]. 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) [21].

- Ezetimibe – We do not consider ezetimibe as an alternative to statin therapy in older patients given limited evidence supporting its use. (See "Low-density lipoprotein cholesterol lowering with drugs other than statins and PCSK9 inhibitors", section on 'Ezetimibe'.)

  Supporting data for ezetimibe for treatment of LDL-C in older adults is limited. One study reported a potential benefit of ezetimibe, but there were too many limitations to guide therapy; these included an open-label design, premature terminations due to study protocol violations, and larger-than-expected loss to follow-up. This trial evaluated monotherapy with ezetimibe in patients 75 and older [22]. 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** — The role of statin therapy in patients with diabetes is discussed separately.

(See "Overview of general medical care in nonpregnant adults with diabetes mellitus", section on '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: CKD patients without established atherosclerotic cardiovascular disease'.)

**Liver disease** — In patients with chronic liver disease, statins therapy should be approached cautiously, as these drugs can cause worsening liver dysfunction. The approach to statins in such patients 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 for a minimum of three months.

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

## MEDICATIONS WE DO NOT RECOMMEND

Primary CVD prevention trials of LDL-C lowering with clofibrate [23,24], cholestyramine [25], or gemfibrozil [26] did not show benefits for these medications on coronary mortality. Furthermore, these medications were shown to increase the risk of noncardiovascular disease mortality (with the exception of cholestyramine). Thus, we do not recommend their use for LDL-C lowering in primary CVD prevention.

## 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 lowdensity lipoprotein cholesterol (LDL-C) level and their cardiovascular disease (CVD) risk ( algorithm 1). (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.

  If the patient does not have FH, we recommend statin treatment. We use high-dose statin therapy for such individuals. (See 'LDL-C greater than or equal to 190 mg/dL' above.)

- **LDL-C <190 mg/dL (or <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. (See 'CVD Risk Assessment' above.)

  - **High-risk patients** – For patients with a high CVD risk (>10 percent 10-year risk of CVD) and LDL-C in the range of 100 to <190 mg/dL, we recommend statin therapy (**Grade 1B**). (See 'High (>10 percent 10-year) CVD risk' above.)

    For most patients, we suggest treatment with a moderate dose of a statin rather than starting at a higher dose (**Grade 2C**). However, for patients with a very high (≥20 percent 10-year risk) CVD risk and LDL-C <190 mg/dL, we usually start with high-dose statin therapy.

  - **Intermediate-risk patients** – For patients with a 5 to ≤10 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 present the potential benefits and costs/risks to patients (shared decisionmaking); if there are very high LDL-C levels (eg, >160 mg/dL [>4.14 mmol/L]), we usually suggest statin therapy (**Grade 2B**).

    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 1). (See 'Intermediate (5 to lesser than or equal to 10 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. (See 'Low (<5 percent 10-year) CVD risk' above.)

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

- **Very high-risk patients** – After follow-up, for patients with an LDL-C >100 mg/dL (2.6 mmol/L) and a ≥ 20 percent 10-year risk of a CVD event, we suggest treatment with high-intensity statin therapy (**Grade 2C**). Prior to making any medication adjustments, we ask about adherence at follow-up visits, as this can often underlie suboptimal LDL-C lowering. (See 'Statin dose adjustment' above and 'Managing side effects' above.)

- **Other patients** – In the majority of primary prevention patients who are not at very high risk and do not achieve a particular LDL-C level on statin therapy, we do not add additional nonstatin lipid-lowering medication.

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

- **Statin-intolerant patients** – In very high-risk patients (≥20 percent 10-year risk of a CVD event) with very high LDL-C levels (>160 mg/dL [>4.14 mmol/L]), if a highintensity statin is not tolerated, we suggest a nonstatin drug such as a PCSK9 inhibitor (**Grade 2B**).

  For most primary prevention patients who do not tolerate statins, we suggest not routinely administering a nonstatin lipid-lowering medication (**Grade 2C**). Potential interventions include lifestyle modification and, in higher-risk patients, antiplatelet therapy.

- **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 contraindicated in pregnant patients. 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

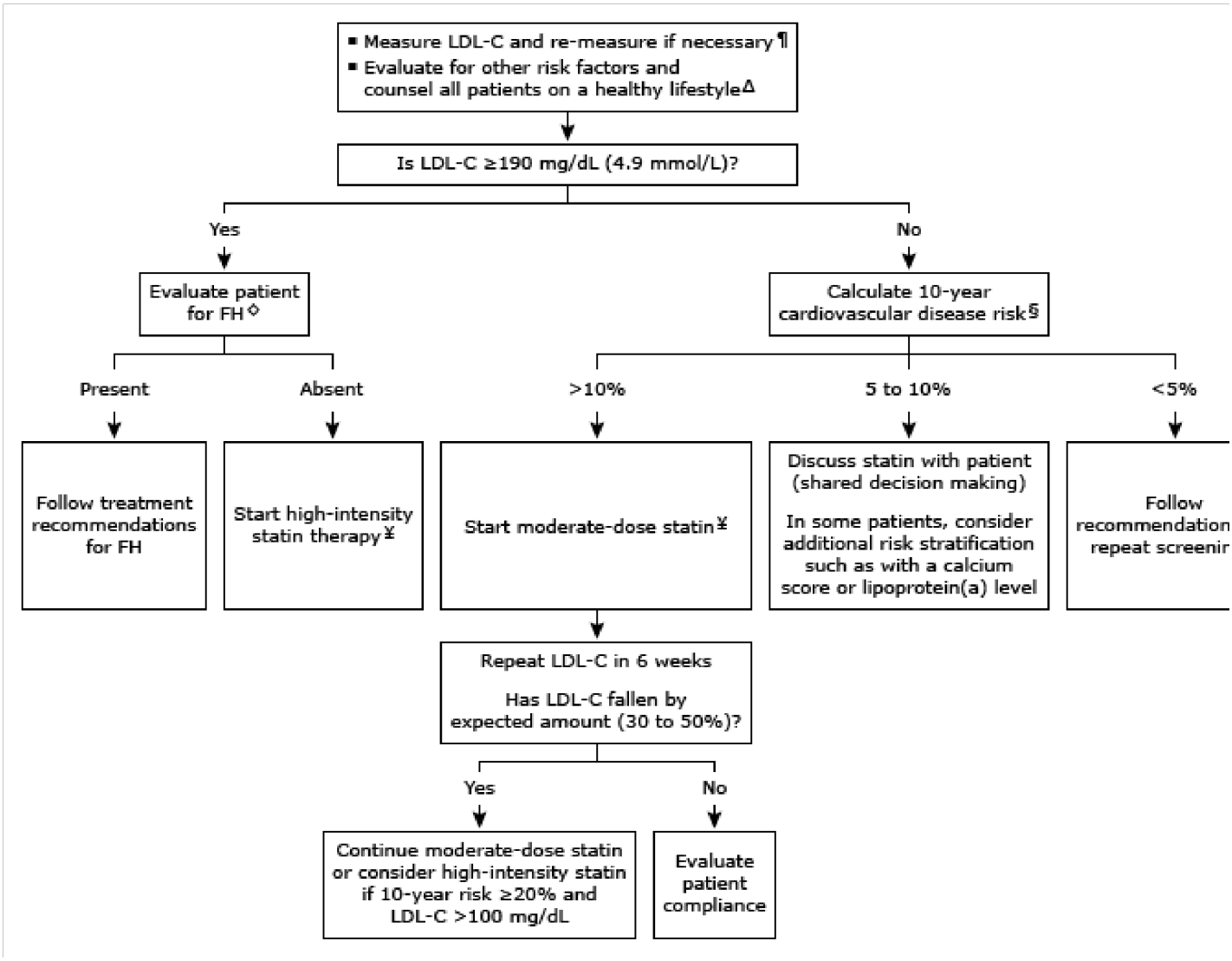
1. The Expert Panel. Second Report of the Expert Panel on Detection, Evaluation, and Tre atment of High Blood Cholesterol in Adults. NIH Publication No. 93-3095, US Governm ent Printing Office; Washington, DC 1993.
2. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1986; 256:2823.
3. Ballantyne CM, Grundy SM, Oberman A, et al. Hyperlipidemia: diagnostic and therapeutic perspectives. J Clin Endocrinol Metab 2000; 85:2089.
4. Wallis EJ, Ramsay LE, Ul Haq I, et al. Coronary and cardiovascular risk estimation for primary prevention: validation of a new Sheffield table in the 1995 Scottish health survey population. BMJ 2000; 320:671.
5. 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.
6. Multiple risk factor intervention trial. Risk factor changes and mortality results. Multiple Risk Factor Intervention Trial Research Group. JAMA 1982; 248:1465.
7. 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.
8. 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.

9. 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.
10. 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.
11. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; :CD004816.
12. US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2022; 328:746.
13. 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.
14. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017; 70:1785.
15. www.nice.org.uk/guidance/CG181/chapter/1-Recommendations (Accessed on July 02, 2015).
16. Authors/Task Force Members, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019; 290:140.
17. Silverman MG, Ference BA, Im K, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA 2016; 316:1289.

18. Ramos R, Comas-Cufí M, Martí-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. BMJ 2018; 362:k3359.
19. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet 2019; 393:407.
20. Orkaby AR, Driver JA, Ho YL, et al. Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. JAMA 2020; 324:68.
21. 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.
22. 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.
23. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Report from the Committee of Principal Investigators. Br Heart J 1978; 40:1069.
24. W.H.O. cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators. Lancet 1980; 2:379.
25. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251:365.
26. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317:1237. Topic 4549 Version 85.0

## GRAPHICS

# Algorithm for the management of elevated low density lipoprotein cholest in adults without cardiovascular disease*




The algorithm applies to all adults between the ages of 18 and 75 years. It does not apply to individual with diabetes mellitus.

---

LDL-C: low density lipoprotein cholesterol; FH: familial hypercholesterolemia.

* 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.

◇ Refer to the UpToDate topics on the evaluation of patients for familial hypercholesterolemia for mor information.

§ 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. Moderat dose statin = atorvastatin 10 to 20 mg once daily; lovastatin 40 mg once daily; pravastatin 40 mg once daily; rosuvastatin 5 to 10 mg daily; simvastatin 40 mg once daily.

Graphic 117853 Version 5.0

## 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]; nonHDL 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 (≥2.0 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 5.0

## Contributor Disclosures

**Michael Pignone, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.
**Mason W Freeman, MD** No relevant financial relationship(s) with ineligible companies to disclose.
**Nisha Parikh, MD, MPH** 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