Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease

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INTRODUCTION

Patients with cardiovascular disease (CVD) are at high risk for future CVD events. Therapy to reduce the risk of subsequent events in such patients is referred to as secondary prevention. Secondary prevention interventions are aimed at known modifiable risk factors for CVD events such as smoking, hypertension, diabetes, and elevated levels of low density lipoprotein cholesterol (LDL-C). LDL-C plays a key role in the pathogenesis and perpetuation of atherosclerotic CVD, and LDL-C lowering has been shown in large clinical trials to reduce the risk of CVD events and, in some populations, to reduce all-cause mortality.

This topic will review the evidence for the benefit from lowering LDL-C in secondary prevention as well as our treatment approach. The approach to lipid lowering therapy for the subgroup of very high-risk patients with an acute coronary syndrome is discussed separately. (See "Low-density lipoprotein-cholesterol (LDL-C) lowering after an acute coronary syndrome".)

The mechanisms by which statins are beneficial are presented separately. (See "Mechanisms of benefit of lipid-lowering drugs in patients with coronary heart disease", section on 'Timing and mechanisms of benefit'.)

Our approach to patients with familial hypercholesterolemia, who have very high LDL-C levels, is discussed separately. (See "Familial hypercholesterolemia in adults: Treatment".)

DEFINITIONS

Risk groups — Patients with established atherosclerotic cardiovascular disease (ASCVD) include those with stable or unstable coronary artery disease, ischemic stroke of atherosclerotic origin, transient ischemic attack, or peripheral arterial disease. These individuals are at high risk of a cardiovascular disease (CVD) event.

There is a spectrum of risk among these individuals. Unfortunately, a validated and accurate CVD risk calculator for those with known CVD has yet to be developed.

- **Average-risk** patients are those without any high-risk or very-high-risk factors.
- **High-risk** patients are those with a prior CVD event or those with other uncontrolled CVD risk factors. (See "Overview of established risk factors for cardiovascular disease", section on 'Established risk factors for atherosclerotic CVD'.)
- **Very-high-risk** patient groups are discussed below.

Some patients **without** established CVD have combinations of risk factors that result in a 10-year risk of CVD events of more than 20 percent. These individuals begin to approach yearly CVD event rates of those with established CVD, but fall into the “primary prevention” category. The approach to these patients is discussed elsewhere. (See "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease", section on 'Summary and recommendations'.)

Intensity of statin therapy — Moderate-intensity statin therapy (30 to 50 percent LDL-C reduction) includes daily treatment with [1]:

- Lovastatin 40 to 80 mg
- Pravastatin 40 to 80 mg
- Simvastatin 20 to 40 mg

- Atorvastatin 10 to 20 mg
- Rosuvastatin 5 to 10 mg
- Pitavastatin 2 to 4 mg

High-intensity statin therapy (≥50 percent LDL-C reduction) includes daily treatment with [1]:

- Atorvastatin 40 to 80 mg
- Rosuvastatin 20 to 40 mg.

OUR APPROACH

We treat all patients with known cardiovascular disease (CVD) with proven lifestyle interventions (see 'Initial therapy' below) and high-intensity statin therapy, irrespective of baseline low density lipoprotein cholesterol (LDL-C) (algorithm 1) [2].

The evidence to support this approach is presented below. (See 'Benefits of LDL-C lowering' below.)

After successful initiation of high-intensity statin therapy, we remeasure LDL-C within six to eight weeks. For patients who have not achieved the expected 50 percent reduction in LDL-C or who in whom the LDL-C is ≥70 mg/dL (1.8 mmol/L), possible nonadherence should be considered, given that nonadherence to statin therapy is frequent.

For some patients with CVD in whom the LDL-C remains ≥70 mg/dL (1.8 mmol/L) after high-intensity statin therapy, we consider adding a second drug to further lower LDL-C. The decision to add a second LDL-C lowering drug should take into account the potential magnitude of benefit from additional therapy: the higher the residual risk, the more likely we are to add a second drug (or even a third). (See 'Magnitude of benefit and baseline risk' below and 'Treatment goal' below.)

In most cases, when we add a second agent, we usually choose ezetimibe before a PCSK9 inhibitor for reasons of cost and convenience. After treatment with statin plus ezetimibe, we remeasure LDL-C within six to eight weeks. For many higher-risk patients whose LDL-C remains significantly ≥70 mg/dL (1.8 mmol/L), we consider adding a PCSK9 inhibitor. The higher the degree of CVD risk, the more likely we are to add a PCSK9 inhibitor.

This approach of adding a second (or even a third) agent should involve shared decision-making between the patient and the provider. Shared decision making means discussing the potential benefits and risks of a new drug with the patient. As discussed below, this discussion is often brief if the chosen drug is ezetimibe, as it is low cost and well tolerated. When suggesting that patients start a PCSK9 inhibitor, the discussion is often longer given the higher cost, need for periodic injection, and less robust long-term safety data. In addition, health care providers should assess the potential negative impact on medication compliance of adding another medication. Finally and to the extent possible, we teach the patient about the nature of the disease, including the potential for early atherosclerotic CVD events.

Initial therapy — All patients with CVD should be recommended lifestyle (modification) interventions associated with improved clinical outcomes and treated with a high intensity statin. (See "Prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Lifestyle modifications' and 'Intensity of statin therapy' above.)

Statins, ezetimibe, and PCSK9 inhibitors have been shown to reduce the risk of adverse cardiovascular events. Among these three, statins are the best studied. High-intensity statin therapy lowers LDL-C by 50 to 60 percent. They are more effective than ezetimibe and significantly less costly and easier to use than PCSK9 inhibitors. In addition, they have been used with an excellent safety profile for over 30 years. Thus, statins are the first choice in virtually all patients with elevated LDL-C.

In stable patients (outpatients), we attempt to treat with high intensity statin (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily) and we prefer the highest approved dose in most cases. In patients with intolerance to a high-intensity statin, we recommend moderate-intensity statin plus ezetimibe. Possible dose adjustment in special populations is discussed below. (See 'Special populations' below.)

In patients who do not tolerate one statin because of myopathy, clinicians should to try another statin that may be better tolerated or to try alternative dosing regimens, such as giving the drug every other day, often using low doses of rosuvastatin. (See "Statin muscle-related adverse events".)

Failure of a patient to achieve the expected LDL-C lowering with maximal doses of either atorvastatin or rosuvastatin may be due to poor adherence to therapy and life style

recommendations or a variable response to the therapy.

For patients who cannot tolerate statin therapy, we start ezetimibe. For those patients whose LDL-C remains ≥70 mg/dL (1.8 mmol/L), we consider adding a PCSK9 antibody [3]. (See 'Additional therapy' below.)

Specific comments regarding the administration of these drugs are found elsewhere. (See "Statins: Actions, side effects, and administration".)

Additional therapy — After the patient has been treated with a maximally tolerated dose of a high-intensity statin, we take the following approach to therapy:

- For **average-risk** (see 'Risk groups' above) patients whose on-statin treatment LDL-C ≥70 mg/dL (1.8 mmol/L), we consider adding ezetimibe. The decision to add ezetimibe should involve a discussion with the patient that explains a small benefit and a small risk/cost. Our contributors have differing thresholds for adding ezetimibe. We rarely add PCSK9 inhibitor in these patients.

- For **high-risk** (see 'Risk groups' above) patients whose on-statin treatment LDL-C is above 70 mg/dL (1.8 mmol/L), we treat with a second drug and usually start with ezetimibe for reasons of cost and convenience. If the LDL-C on statin monotherapy is <70 mg/dL (1.8 mmol/L), we usually do not add a second drug.

  If the LDL-C remains above 70 mg/dL (1.8 mmol/L) on statin plus ezetimibe, we consider adding a PCSK9 inhibitor.

- For **very high risk** patients (see 'Risk groups' above), whose on-statin treatment LDL-C is ≥70 mg/dL (1.8 mmol/L), we treat with a second drug and usually start with ezetimibe for reasons of cost and convenience. If the LDL-C on statin plus ezetimibe is ≥50 mg/dL (1.3 mmol/L), we consider adding a PCSK9 inhibitor.

  If after statin monotherapy, the LDL-C is <70 mg/dL (1.8 mmol/L), we consider adding ezetimibe. In most cases, this will lower the LDL-C to about 50 mg/dL (1.29 mmol/L), and we usually would not consider adding a PCSK9 inhibitor.

The decision to add ezetimibe or PCSK9 inhibitor to statin should take into account the predicted magnitude of benefit and the patient's preferences (see 'Benefits of LDL-C lowering' below) [4]. If a second drug is added, we choose ezetimibe before PCSK9

inhibitor in most cases for reasons of cost and convenience [3].

As mentioned above, the absolute benefit (see 'Magnitude of benefit and baseline risk' below) will be greatest in the highest-risk CVD patients (see 'Risk groups' above). If the patient is able to receive PCSK9 inhibitor therapy, the clinician can then re-evaluate the value of using ezetimibe in a three-drug regimen compared with discontinuing ezetimibe and employing the two-drug regimen of a statin plus PCSK9 inhibitor. Inconvenience of three compared with two LDL-C lowering drugs is one reason to consider stopping ezetimibe. Whether ezetimibe is needed for patients who require addition of PCSK9 inhibitor, and who likely have very low LDL-C after treatment with statin plus PCSK9 inhibitor, has not been well studied.

Other possible therapies — Patients who have not achieved their LDL-C goal using ezetimibe or PCSK9 inhibitor should be referred to a clinician who specializes in the treatment of complex lipid disorders.

For patients with homozygous familial hypercholesterolemia (HoFH), lomitapide is potentially of value, but its cost and side-effect profile may prevent it from being prescribed. LDL apheresis may be considered for patients with homozygous or heterozygous FH, but the time and limited availability of LDL apheresis centers present challenges for most patients. (See "Treatment of drug-resistant hypercholesterolemia", section on 'Potential future approaches'.)

Bempedoic acid has modest efficacy on LDL-C. Its most valuable use may be around the same point in the care pathway as ezetimibe, that is when the maximum recommended or tolerated statin dose has failed to achieve the appropriate LDL-C goal, and PCSK9 inhibition is not possible (due to cost or patient preference). Its efficacy in lowering LDL-C is probably a little less than ezetimibe, but the two in combination provide the possibility of substantial LDL-C reduction in the utterly statin-intolerant patient. (See "Treatment of drug-resistant hypercholesterolemia".)

Monitoring therapy — We believe it is reasonable to remeasure LDL-C after initiation of lipid lowering therapy. The principal reasons for monitoring LDL-C are to evaluate compliance with therapy and to potentially help motivate patients to remain compliant. Evaluation of drug efficacy or screening for adverse effects is not necessary with LDL-C lowering therapies. While no high-quality evidence exists to support a specific laboratory test or a specific time interval, we suggest that the LDL-C be checked approximately six to

eight weeks after the initiation or change of treatment [5]. If LDL-C reduction is substantially less than expected, possible non-tolerance or nonadherence to treatment should be carefully explored, or escalation of therapy considered. Thereafter, measurement every 12 months is reasonable in patients who seem adherent to lifestyle modifications and pharmacotherapy to evaluate adherence or to comply with insurer specifications. More frequent lipid monitoring is reasonable if the patient has elevated risk of medication nonadherence.

BENEFITS OF LDL-C LOWERING

Across a broad range of baseline cardiovascular disease (CVD) risk and LDL-C baseline levels, most therapies that lower LDL-C lead to a clinically important reduction in the risk of myocardial infarction (MI) and ischemic stroke.

While a mortality benefit has been more difficult to consistently demonstrate, intense LDL-C lowering lowers the risk of all-cause death in those at very high risk. Whatever the reason for the difficulty in consistently demonstrating a mortality benefit, we believe that most patients will accept a recommendation for LDL-C lowering in order to achieve a reduction in ischemic events (eg, MI or ischemic stroke), even in the absence of a demonstrated mortality benefit, since these events degrade quality of life in part through disability, drive up health care costs, and likely portend additional ischemic events.

A 2018 meta-analysis of 34 randomized trials (n = 270,788) comparing more with less intense LDL-C lowering for both secondary and primary prevention evaluated all-cause and cardiovascular mortality [6]. All-cause mortality was lower for more compared with less intensive therapy (rate ratio 0.92, 95% CI 0.88-0.96) but varied by baseline LDL-C level. More intensive LDL-C lowering led to a significantly lower risk of all-cause death when the baseline LDL-C was greater than 100 mg/dL ($p<0.001$ for the interaction).

Statin therapy — There have been several meta-analyses of clinical trials with statins in patients with CVD that have evaluated hard clinical end points [2,7,8]. A 2011 meta-analysis of randomized trials comparing intensive with moderate statin therapy that included patients with both stable coronary heart disease (CHD) and acute coronary syndrome (ACS) (n = 41,778) found that intensive therapy lowered the risk of non-fatal MI (RR 0.82, 95% CI 0.76-0.89) and a composite of fatal and non-fatal strokes reported in 10 randomized controlled trials (RR 0.86, 95% CI 0.77-0.96). In this meta-analysis, there was

no statistically significant reduction in all-cause mortality (relative risk [RR] 0.92, 95% CI 0.83-1.03) or cardiovascular mortality (RR 0.89, CI 0.78-1.01). There was moderate heterogeneity of results across the included trials [2]. In the subgroup of trials of patients with ACS, intensive therapy reduced both all-cause mortality (RR 0.75, CI 0.61-0.91) and cardiovascular mortality (RR 0.74, CI 0.59-0.94) and there was no heterogeneity.

Combination therapies

- Ezetimibe **plus statin combination therapy** – The addition of ezetimibe to statin therapy was evaluated in two separate trials, IMPROVE-IT and RACING [9,10]. In IMPROVE-IT, 18,144 patients with an acute coronary syndrome in the preceding 10 days and an LDL-C of 50 to 100 mg/dL (1.3 to 2.6 mmol/L) if on lipid-lowering therapy, or an LDL-C of 50 to 125 mg/dL (1.3 to 3.2 mmol/L) if not on lipid-lowering therapy, were randomly assigned simvastatin 40 mg/day plus ezetimibe 10 mg/day, or simvastatin 40 mg/day plus placebo [9]. The median time-weighted average achieved LDL-C was lower in the ezetimibe/simvastatin arm (53.7 versus 69.5 mg/dL [1.4 versus 1.8 mmol/L]). After a median follow-up of six years, there was a reduction in the primary composite end point (cardiovascular death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization more than 29 days after randomization, nonfatal stroke) in the ezetimibe/simvastatin arm (hazard ratio [HR] 0.94, 95% CI 0.89-0.99). This resulted in an absolute reduction in the rate of the primary end point at seven years (32.7 versus 34.7 percent). There was no reduction in all-cause mortality (HR 0.99, CI 0.91-1.07) or cardiovascular mortality (HR 1.00, CI 0.89-1.13); however, MI (HR 0.87, CI 0.80-0.95) and stroke (HR 0.86, CI 0.73-1.00) were reduced. (See 'Acute coronary syndrome patients' below.)

  The open-label, randomized RACING trial from South Korea compared moderate-dose statin (rosuvastatin 10 mg) plus ezetimibe with high-dose statin therapy (rosuvastatin 20 mg) in 3780 patients with atherosclerotic cardiovascular disease (ASCVD) [10]. After three years, rates of the primary outcome (a composite of cardiovascular death, major cardiovascular events, non-fatal stroke) were similar (noninferior) in the treatment groups (9.1 versus 9.9 percent; absolute difference -0.78 percent, 90% CI -2.39 to 0.83). At each year of follow-up, LDL-C concentrations <70 mg/dL were more frequently observed in patients assigned to combination therapy compared with high-dose statin monotherapy; for example, at study year 3, LDL-C was <70 mg/dL in 72 versus 58 percent. Discontinuation or dose reduction of

the study drug due to statin intolerance that can develop at moderate to high doses were less frequent with combination therapy compared with high-dose statin monotherapy group (4.8 versus 8.2 percent, p<0.0001).

- **PCSK9-antibodies plus statins** – Initial meta-analyses of fairly short-term trials of intensifying therapy with PCSK9-antibodies suggested reductions in cardiovascular events [11]. (See "PCSK9 inhibitors: Pharmacology, adverse effects, and use".)

  In the FOURIER trial, 27,564 patients with CVD, defined as a history of myocardial infarction, nonhemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher than average cardiovascular risk, were randomly assigned to receive evolocumab or placebo. Patients were already receiving high-intensity statin therapy if they could tolerate it, and were required to be receiving at least moderate-intensity statin therapy (70 percent of patients were on high-intensity therapy), and on this therapy were required to have a minimum LDL-C of at least 70 mg/dL (1.8 mmol/L) [12]. After a median follow-up of 2.2 years, treatment with evolocumab reduced the risk of a composite end point of cardiovascular death, MI, stroke, revascularization, or unstable angina (9.8 percent versus 11.3 percent; HR 0.85; 95% CI 0.79-0.92). This included a reduced risk of non-fatal MI (RR 0.73, 95% CI 0.65-0.82) and non-fatal stroke (RR 0.79, CI 0.66-0.95), but no decrease in cardiovascular mortality (RR 1.05, CI 0.88-1.25) or all-cause mortality (RR 1.04, CI 0.91-1.19). The benefits of evolocumab continued to accrue with increasing exposure to the study medication as has been shown with other cholesterol lowering therapies.

  A beneficial effect of PCSK9 inhibition with alirocumab in patients with an acute coronary syndrome was found in the ODYSSEY OUTCOMES trial [13]. (See "Low-density lipoprotein-cholesterol (LDL-C) lowering after an acute coronary syndrome", section on 'PCSK9 inhibitors'.)

Magnitude of benefit and baseline risk — In all patients with ASCVD, LDL-C lowering decreases the risk of CVD death, myocardial infarction (MI), ischemic stroke, and recurrent ischemic events. With treatment, the magnitude in reduction in risk is related to the baseline risk, as well as the potency of the LDL-C lowering drug. (See 'Risk groups' above.)

As the reduction in relative risk is constant at all pretreatment levels, the absolute reduction in risk with an LDL-C lowering drug is greater at higher baseline risk [7]. ASCVD

patients without higher than average risk features (see 'Risk groups' above) may have a 10-year risk in the range of 20 to 25 percent. LDL-C lowering, across all subgroups of patients with ASCVD, reduces the risk by about 21 to 22 percent (1 to 3 percentage points, NNT = 33 to 100 for 10-years treated) for each 38.7 mg/dL (1 mmol/L) reduction in LDL-C [14,15]. Thus, a potent intervention (such as high-intensity statin therapy) decreases absolute risk to greater extent than a weaker intervention (such as ezetimibe) in patients with similar baseline risk.

With regard to additional therapy on top of statin therapy (see 'Additional therapy' above), a patient case may help to illustrate the magnitude of benefit. A 60-year-old man had an MI five years ago and has done well for years on high-intensity statin therapy (and other appropriate CVD risk-reducing interventions). His stable LDL-C has been about 75 mg/dL (1.9 mmol/L). His 10-year risk for a CVD event is around 20 percent. The addition of PCSK9 inhibitor, which would lower the LDL-C to about 35 mg/dL (0.9), would lower the risk by about 20 percent to about 16 percent (0.8 x 20), or lower the absolute risk about 4 percent. The addition of ezetimibe would lower the risk to about 18 percent or lower the absolute risk about 2 percent. We believe that many patients will accept the potential burdens associated with additional therapy for this magnitude of benefit.

The practitioner's ability to precisely define baseline risk in the individual patient leads to imprecision in the ability to explain to the patient (to predict) the magnitude of benefit from a specific LDL-C lowering intervention. This is partially explained by the fact that baseline risk is explained by factors other than LDL-C such as the presence of other risk factors. There are no validated tools to precisely define baseline risk.

TREATMENT GOAL

Many experts interpret the evidence presented above (see 'Our approach' above) as supporting the concept that "lower is better," that the reduction in major vascular events is directly proportional to the absolute reduction in LDL-C, and that every reasonable attempt should be made to significantly lower LDL-C [7,8,16,17]. One randomized trial (Treat Stroke to Target [TST]) specifically compared treating to a target LDL-C <100 mg/dL with <70 mg/dL and found a significant reduction in major cardiovascular events when treating to the lower treatment [18] (see "Overview of secondary prevention of ischemic stroke", section on 'LDL-C lowering therapy'). Others have argued that LDL-C lowering

therapies proven effective in randomized trials should only be prescribed as they were in the trials.

Our approach (see 'Our approach' above) incorporates both of these ideas. In addition, our recommendations acknowledge that not all patients with CVD are at equal risk of CVD events.

With regard to formulating recommendations for the goal of treatment, we broadly interpret the evidence as follows:

- Higher-risk patients derive a greater absolute risk reduction with therapy compared with lower-risk patients
- The more potent the lipid lowering therapy in reducing LDL-C, the greater the CVD relative risk reduction.

While the evidence does not clearly identify a threshold below which further LDL-C lowering leads to little benefit, we believe that efforts to lower the LDL-C <70 mg/dL (1.8 mmol/L) should be made in most patients with CVD. We also believe that in those at highest risk (see 'Risk groups' above), a lower target may be considered. There is no single study that evaluated 70 mg/dL (1.8 mmol/L) as a target for therapy. This value has been adopted by a broad range of experts and consensus groups as a reasonable goal based on numerous well performed studies of LDL-C lowering.

All trials of LDL-C lowering therapy have demonstrated better outcomes in the group that has received more aggressive LDL-C lowering (whether the comparator is placebo or a lower intensity of statin therapy). Many trials have achieved LDL-C levels below 70 mg/dL (1.8 mmol/L) [19,20]. This has been true for high-dose statins (JUPITER), statin plus ezetimibe (IMPROVE-IT) [21], and PCSK9 inhibitors (FOURIER). High-dose statins (see 'Intensity of statin therapy' above) were used in the important PROVE IT [17], TNT [8], SATURN [22], JUPITER [23], and IDEAL [24] trials.

Most [25,26], but not all [27], analyses have suggested a continuous log-linear benefit with LDL-C lowering. In a 2010 meta-analysis of 26 trials (nearly 170,000 patients) of statin therapy in a broad range of patients and baseline LDL-C levels, there was an approximate 22 percent reduction in the rate of major vascular events per 40 mg/dL (1.0 mmol/L) decrease in LDL-C.

There was no evidence of any threshold within the LDL-C range studied, suggesting that reduction of LDL–C by 80-120 mg/dL (2 to 3 mmol/L) would reduce risk by about 40 to 50 percent [7].

Finally, the use of two classes of LDL-C lowering drugs in statin-treated patients has been shown to lead to an additional reduction in CVD events in study populations that achieved a mean LDL-C below 55 mg/dL:

- In the FOURIER trial (PCSK9 inhibitor): start LDL-C of 90 mg/dL; final LDL-C of 30 mg/dL. (See 'Benefits of LDL-C lowering' above.)
- In the IMPROVE IT trial (ezetimibe): start LDL-C of 69 mg/dL; final LDL-C of 54 mg/dL. (See 'Benefits of LDL-C lowering' above.)

SPECIAL POPULATIONS

Women of childbearing age — Statin therapy is currently contraindicated during pregnancy [28]. However, there are more recent data suggesting that statins may not be uniformly teratogenic. Ezetimibe has not been extensively studied in pregnancy and therefore may have risks associated with its use. No data are available about use of PCSK9 inhibitors in pregnancy.

Older patients — The benefit from LDL-C-lowering therapy extends to healthy individuals 75 years of age or older. We recommend statins and will occasionally consider PCSK9 therapy for these individuals with established cardiovascular disease (CVD).

Although fewer patients in this age group were enrolled in clinical trials, a benefit has been seen in virtually every subgroup analysis [7]. The absolute CVD risk is much higher in older individuals, so the number of events potentially prevented is greater.

However, the decision whether to treat an elevated LDL-C in an older individual should be individualized based on both chronological and biologic age. A patient with a limited life span from a concomitant illness (eg, advanced cancer) is probably not a candidate for drug therapy. On the other hand, an otherwise healthy older individual should not be denied drug therapy simply on the basis of age alone.

Some experts initiate statin therapy in these individuals with a moderate- rather than

high-intensity statin based on a concern for a greater likelihood of side effects (see 'Initial therapy' above and 'Intensity of statin therapy' above). Age-related reduction in the efficacy of some metabolic pathways (particularly in the liver) may be a possible mechanism. In addition, older individuals receive a greater number of medications, some of which may compete for hepatic detoxification.

For older individuals not started on high-intensity statin, consideration can be given to up-titrating to high-intensity statin within three months if they have tolerated the moderate dose. The recommendation to consider high-intensity statin is based on the comparable event reduction seen in randomized clinical trials comparing older and younger individuals presenting with and acute coronary syndrome or a prior CVD event.

A benefit from the use of PCSK9 inhibitor (alirocumab) in older patients was found in a prespecified analysis of the ODYSSEY OUTCOMES trial of patients with an acute coronary syndrome [29] (see "Low-density lipoprotein-cholesterol (LDL-C) lowering after an acute coronary syndrome", section on 'PCSK9 inhibitors'). In this subgroup analysis, the relative risk reduction for all-cause mortality was similar for patients ≥65 versus <65 years of age (hazard ratio 0.77 in both groups). As expected, the three-year absolute reduction in death with alirocumab was significantly greater in the older group (2.1 versus 0.1 percent).

Very-high-risk patients — Patients may fall into the very-high-risk category by having one or more of the following diagnoses or characteristics.

Familial hypercholesterolemia — The approach to patients with familial hypercholesterolemia (FH) is presented separately. (See "Familial hypercholesterolemia in adults: Treatment", section on 'Heterozygous individuals'.)

Acute coronary syndrome patients — The detailed discussion of our approach to these very-high-risk patients is presented elsewhere. (See "Low-density lipoprotein-cholesterol (LDL-C) lowering after an acute coronary syndrome".)

Chronic kidney disease patients — For most patients with CVD and chronic kidney disease (CKD), including stage 4 or 5 disease (table 1), we attempt to lower the LDL-C with statin therapy. The studies supporting this approach are discussed in detail elsewhere. (See "Lipid management in patients with nondialysis chronic kidney disease", section on 'Treatment' and "Secondary prevention of cardiovascular disease in end-stage kidney disease (dialysis)", section on 'Lipid modification' and "Definition and staging of

chronic kidney disease in adults", section on 'Definition and staging of chronic kidney disease' and "Chronic kidney disease and coronary heart disease", section on 'Chronic kidney disease as an independent risk factor for CHD'.)

For non-dialysis CKD patients with known CVD, our approach is similar to that in the general population (see 'Our approach' above) with the following caveats:

- When a patient's renal function becomes severely decreased (stage 4 or 5) (table 1), the potential benefits and risks from long-term LDL-C lowering with statin therapy are less well defined. When statin therapy is chosen, maximal dose atorvastatin is preferred for most of these patients as it is not dependent on renal function for its metabolism and excretion. With other statins, we use a low to moderate dose due to some level of renal excretion.

- Concerning second line therapy, we add ezetimibe for patients who have not met their LDL-C goal.

- PCSK9 inhibitors are used in some patients without CKD whose LDL-C cannot be sufficiently lowered with statin and ezetimibe (see 'Additional therapy' above). Subgroup analyses of large, randomized trials show that this class of drugs is also effective in patients with stage 3 CKD [30,31]. Data in patients with higher stages of CKD (ie, lower estimated glomerular filtration rate) are more scant, although one study included 208 patients with stage 4 CKD [31]. The role of PCSK9 in the management of lipids and cardiovascular diseases or risks in advanced CKD is currently unclear.

For patients receiving dialysis, benefit from statin therapy has been harder to demonstrate [32], although the risk continues to be low. After a discussion of this issue with the patient, we consider low- to moderate-dose atorvastatin.

Other very high-risk patients — Other very high-risk groups include those with known CVD and diabetes, recurrent cardiovascular disease events, or polyvascular disease (atherosclerosis in multiple) circulatory beds [33]. (See 'Risk groups' above.)

For patients with established ASCVD plus diabetes, recurrent cardiovascular disease events, or polyvascular disease, we have a much lower threshold for adding ezetimibe or PCSK9 to statin therapy than in patients without these very high-risk features. Our contributors have somewhat differing approaches here, with some recommending a

second or a third agent if LDL ≥50mg/dL (1.3 mmol/L) on maximum tolerated statin and others much less likely to use additional therapy in this setting.

There are other markers of significantly elevated risk, including an elevated level of C-reactive protein or lipoprotein(a). In addition, patients who have poorly controlled atherosclerotic CVD risk factors constitute a high-risk group for recurrent events. (See "Lipoprotein(a)" and "C-reactive protein in cardiovascular disease".)

Japanese patients — High-intensity statin therapy for the secondary prevention of CVD is not widely used in Asian populations, and in particular in Japanese patients [34]. Potential reasons include the absence of randomized trials of this therapy in Asian populations and a concern that the response to statin therapy might differ across ethnicities, particularly in populations with differing baseline risk factors or a lower baseline risk of CVD [35].

The REAL-CAD study randomly assigned 13,054 Japanese patients with stable coronary artery disease to pitavastatin 4 or 1 mg daily [36]. The mean LDL-C level before enrollment was 93 mg/dL. After a median follow-up of 3.9 years, the achieved LDL-C was 76.6 and 91.0 mg/dL in the two groups, respectively. The group treated with high-dose pitavastatin had a lower risk of the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, or unstable angina (4.3 versus 5.4 percent; hazard ratio 0.81, 95% CI 0.69-0.95). There was no difference between the two groups in the risk of adverse side effects. In addition, all-cause mortality was reduced with high- versus low-intensity pitavastatin (3.7 versus 4.2 percent; p = 0.03). This trial supports the concept that high-intensity statin is more effective than low-intensity statin for reducing cardiovascular events.

SAFETY

Low density lipoprotein cholesterol (LDL-C) lowering, including to values rarely seen in the general population, has not been associated with any significant adverse outcomes. A meta-analysis of 19 randomized trials of primary and secondary prevention found no increase in noncardiovascular mortality associated with cholesterol-lowering therapy overall or with the administration of a statin [7,37].

An increase of new onset diabetes cases was observed in the JUPITER and other trials and seems to be related with higher doses of statins [38]. However, this excess of diabetes is

largely compensated by the benefit of the therapy on cardiovascular morbidity and mortality in diabetic patients [39].

Minimum LDL-C — While there are theoretical concerns about lowering LDL-C to territory uncommonly seen naturally, the preponderance of evidence suggests that doing so has no adverse effects over a 5- to 10-year period.

Analyses from the JUPITER trial evaluated adverse event rates in patients taking rosuvastatin who attained an LDL-C below 50 or 30 mg/dL (1.3 or 0.78 mmol/L) [23,40]:

- In an adjusted analysis that used logistic regression, patients on rosuvastatin who attained an LDL-C below 50 mg/dL (1.3 mmol/L) had a slightly higher rate of adverse events than those who did not [23]. This higher rate of overall adverse events was not driven by any particular class of adverse event and, in particular, musculoskeletal and neurologic event rates were similar in the two groups.

- In an analysis that used propensity score adjustment, patients on rosuvastatin who attained an LDL-C below 30 mg/dL (0.78 mmol/L) also had a slightly higher rate of adverse events than those who did not (relative risk 1.10, 95% CI 1.01-1.21) [40]. Particular adverse events were more common in the low cholesterol group, including diabetes, hepatobiliary disorders, and psychiatric disorders (particularly insomnia). However, the study looked at many possible adverse events, and so these particular events may simply reflect chance variation.

With regard to ezetimibe therapy, a prespecified analysis of the IMPROVE-IT trial found that patients achieving an LDL-C less than 30 mg/dL at one month had a similar safety profile over six years, compared with patients achieving higher LDL-C concentrations [21].

Trials of PCSK9 inhibitors suggest that very low levels of LDL-C have no significant major adverse events over a two- to four-year period [41-44]. A study of over 3000 patients taking alirocumab found that individuals with on-therapy LDL-C levels of <25 mg/dL did not have a significantly increased rate of adverse events compared with those with higher levels during a median drug exposure of about 1.5 years [41]. In a randomized trial of the PCSK9-ab alirocumab, 575 patients on therapy had two successive LDL-C levels below 25 mg/dL (0.65 mmol/L), and adverse events were no greater than in patients on placebo [44]. In the FOURIER trial, the LDL-C was lowered to 30 mg/dL in the treatment group [12].

In addition, there are rare reports of patients with total deficiency of PCSK9 with LDL-C

levels in the range of 15 mg/dL (0.39 mmol/L), and these patients do not seem to have any adverse clinical effects from these extremely low LDL-C levels [43].

REFERRAL TO A LIPID SPECIALIST

Primary care physicians should consider referral of any patient for whom decision making has become difficult.

RECOMMENDATIONS OF OTHERS

Each year, new studies are published that inform recommendations for the management of elevated LDL-C. Over the past 10 years, and likely longer, societal recommendations for management have become more aggressive with regard to intensity of therapy. Thus, guidelines that do not take into account newer relevant studies may be out of date in important ways.

While our approach is similar to that presented in many societal guidelines, the most recent recommendations from the European Society of Cardiology are somewhat more aggressive for the highest-risk patients [45-47].

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 lipids (Beyond the Basics)" and "Patient education: High cholesterol and lipid treatment options (Beyond the Basics)")

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: Secondary prevention of cardiovascular disease".)

SUMMARY AND RECOMMENDATIONS

- **General approach** – Patients with cardiovascular disease (CVD), all of whom are at high risk of a CVD event, should be recommended lifestyle (modification) interventions that are associated with improved clinical outcomes as well as lifelong statin therapy. (See "Prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Lifestyle modifications'.)

  - **Initial therapy** – For patients with CVD, independent of the baseline low density lipoprotein cholesterol (LDL-C) level, we recommend lifelong high-intensity statin therapy (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg) rather than moderate intensity statin or no LDL-C lowering therapy (**Grade 1A**). For patients who do not tolerate these doses, the maximally tolerated dose of a statin should be used. (See 'Our approach' above.)

  - **Statin intolerance** – For patients with CVD who do not tolerate a high-intensity statin, we recommend a moderate-intensity statin plus ezetimibe (**Grade 1B**).

    For those patients with CVD who do not tolerate any statin regimen, we start ezetimibe. In patients whose LDL-C remains above 70 mg/dL (1.8 mmol/L), we consider adding a PCSK9 inhibitor. (See 'Initial therapy' above.)

- **Monitoring therapy** – After the patient's highest tolerated statin dose has been identified, the LDL-C should be reevaluated and statin adherence/tolerance should

be explored if the degree of LDL-C reduction is less than expected. (See 'Our approach' above.)

- **Additional therapy** – Our subsequent approach is based on patient risk category (see 'Risk groups' above).

  - **Average-risk patients** – If LDL-C is ≥70 mg/dL (1.8 mmol/L) after treatment with statin, we consider adding ezetimibe. Our contributors have differing thresholds for adding this drug in this population. (See 'Risk groups' above and 'Additional therapy' above.)

  - **High-** or **very-high-risk patients** – If the LDL-C is ≥70 mg/dL (1.8 mmol/L) on high-intensity statin therapy, we recommend adding ezetimibe or a PCSK9 inhibitor to statin therapy (**Grade 1A**). In most cases, this second drug will be ezetimibe for reasons of cost and convenience. (See 'Our approach' above and 'Additional therapy' above and 'Risk groups' above.)

    - For **high-risk** patients if the LDL-C is <70 mg/dL (1.8 mmol/L) on statin monotherapy, we usually do not add a second drug. For **very-high-risk patients**, some of our expert contributors consider adding ezetimibe.

    - For **high-risk** patients whose LDL-C is ≥70 mg/dL (1.8 mmol/L) on statin plus ezetimibe, some of our expert contributors consider adding a PCSK9 inhibitor. If the LDL-C is <70 mg/dL (1.8 mmol/L) on statin plus ezetimibe, we rarely add a PCSK9 inhibitor.

    - For **very-high-risk** patients (see 'Definitions' above) whose LDL-C is ≥70 mg/dL (1.8 mmol/L) on statin plus ezetimibe, we recommend adding a PCSK9 inhibitor (**Grade 1A**). For these patients whose LDL-C is ≥50 mg/dL (1.3 mmol/L), after treatment with statin plus ezetimibe, some of our expert contributors consider adding a PCSK9 inhibitor.

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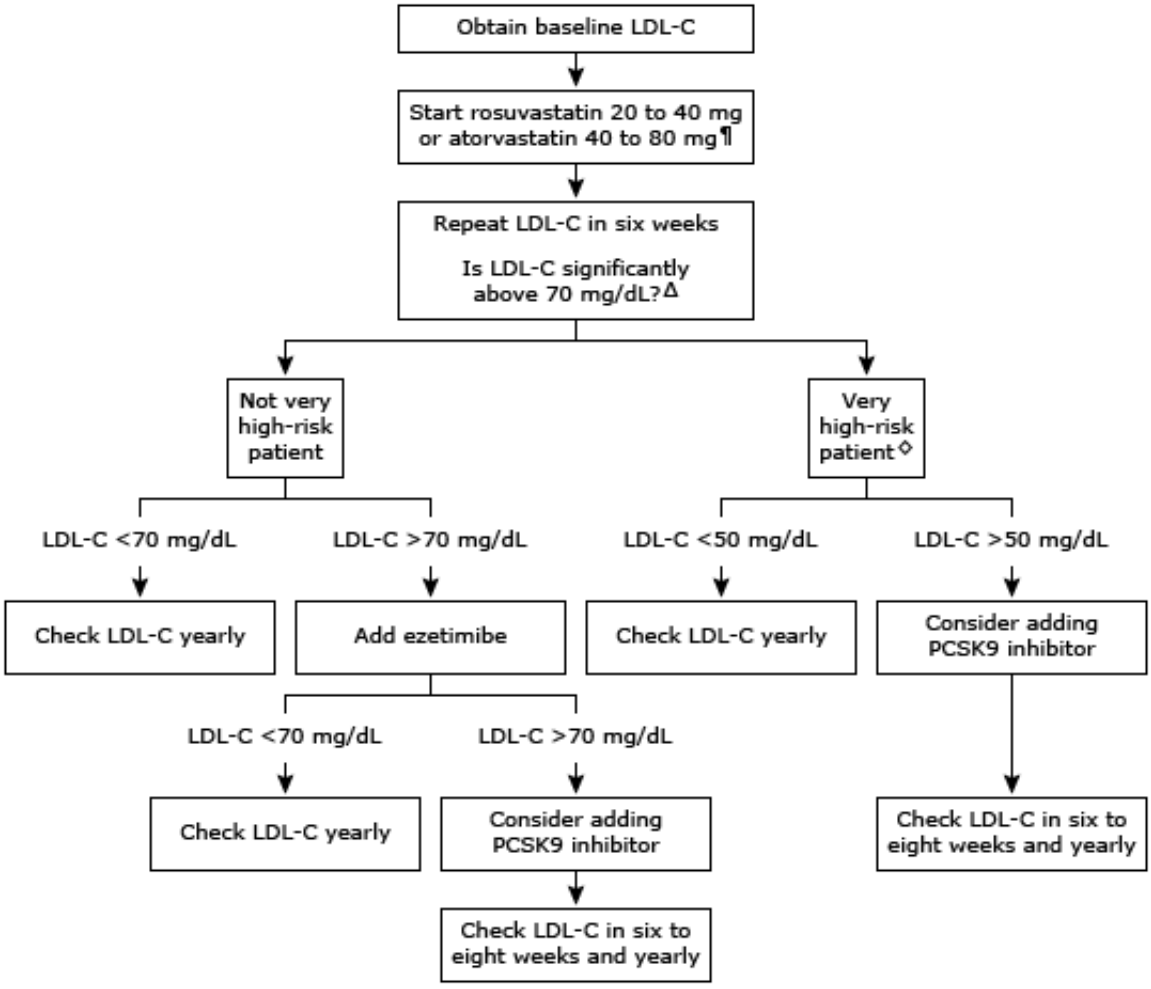
GRAPHICS

Low density lipoprotein cholesterol (LDL-C) lowering with drugs in patient with cardiovascular disease (secondary prevention)*



* Secondary prevention patients include those with coronary artery carotid, aorta, or peripheral artery disease.
¶ In some cases it may be appropriate to start at a lower dose and uptitrate.
Δ The clinician is expected to use his or her independent medical judgment in the context of individual circumstances to make adjustments, as necessary. "Significant" will vary from patient to patient and depends on many factors such as overall cardiovascular risk, likely compliance with a recommendation for additional therapy, or co-morbidities. Refer to relevant UpToDate topic reviews.
◇ High-risk secondary prevention patients include those with acute coronary syndrome in the past year, familial hypercholesterolemia, diabetes, chronic kidney disease (stage 3 or 4), repeat atherosclerotic cardiovascular disease event, or the need for revascularization while on statin.

Graphic 114470 Version 3.0

Chronic kidney disease classification based upon glomerular filtration rate and albuminuria

GFR stages	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60 to 89	Mildly decreased
G3a	45 to 59	Mildly to moderately decreased
G3b	30 to 44	Moderately to severely decreased
G4	15 to 29	Severely decreased
G5	<15	Kidney failure (add D if treated by dialysis)
Albuminuria stages	**AER (mg/day)**	**Terms**
A1	<30	Normal to mildly increased (may be subdivided for risk prediction)
A2	30 to 300	Moderately increased
A3	>300	Severely increased (may be subdivided into nephrotic and nonnephrotic for differential diagnosis, management, and risk prediction)

The cause of CKD is also included in the KDIGO revised classification but is not included in this table.

GFR: glomerular filtration rate; AER: albumin excretion rate; CKD: chronic kidney disease; KDIGO: Kidney Disease Improving Global Outcomes.

Data from:

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Graphic 70597 Version 17.0

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Conflict of interest policy

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