Which patients benefit from lowering LDL to <100 mg/dL?

**Evidence-based answer**

**A**/ Patients who have coronary heart disease (CHD) or are at high risk for CHD should aim for a low-density lipoprotein (LDL) target of <100 mg/dL. An LDL target of <70 mg/dL is an option for very-high-risk patients (strength of recommendation [SOR]: C, expert opinion).

The evidence also indicates that high-risk patients benefit from a statin—preferably in high doses—regardless of their baseline LDL or degree of LDL reduction (SOR: A, a large randomized controlled trial [RCT] and meta-analyses).

**Evidence summary**

The National Cholesterol Expert Panel (NCEP) on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults defines high-risk patients as having known CHD, diabetes, noncoronary atherosclerotic disease, or multiple risk factors for CHD.1 (Moderate- or low-risk patients are defined as having a 10-year risk of CHD <20%.) The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) also includes in the high-risk group patients with stage 5 kidney disease (glomerular filtration rate <15 mL/min or on dialysis).2

The NCEP goes on to define very-high-risk patients as those with known CHD and multiple risk factors. These risks include acute coronary syndrome, diabetes, metabolic syndrome, or poorly controlled or severe risk factors, especially cigarette smoking.3

An LDL target of <100 mg/dL for high-risk patients and an optional target of <70 mg/dL for very-high-risk patients were determined by expert interpretation of evidence from large trials and meta-analyses of a log-linear relationship between LDL levels and CHD risk (TABLE).3,4

**Lowering LDL reduces first coronary events in high-risk patients**

A large 2005 meta-analysis pooled 90,056 high-risk patients in 14 trials of statin use compared with placebo (11 studies), no treatment (1 study), very-low-dose statin use (1 study), or usual care (1 study). Primary outcomes were a change in LDL cholesterol, all-cause mortality, CHD mortality, and non-CHD mortality.5

The meta-analysis showed that high-risk patients had a 21% reduction in the 5-year incidence of first major coronary events for every 39 mg/dL decrease in LDL cholesterol (relative risk [RR]=0.79; 95% confidence interval [CI], 0.77-0.81; number needed to treat [NNT]=27). A subanalysis of 447 high-risk patients with LDL levels <100 mg/dL at baseline found that the risk of major coronary events decreased with statin therapy, but the 99% CI included 1 (RR=0.75; 99% CI, 0.56-1.01).5

**Simvastatin decreases MI and stroke regardless of baseline LDL**

One RCT included in the meta-analysis warrants special attention. This study evaluated the use of simvastatin 40 mg daily compared with placebo for 5 years in 20,536 high-risk patients who were grouped according to initial LDL level (<115 mg/dL, 115-135 mg/dL, and >135 mg/dL). Simvastatin lowered the average patient’s LDL by 39 mg/dL (no CIs provided).6
Regardless of the baseline LDL, simvastatin decreased the rate of first myocardial infarction (MI), stroke, or need for revascularization compared with placebo (RR=0.76; 95% CI, 0.72-0.81; NNT=18). Subgroup analysis of 3421 high-risk patients with LDL levels <100 mg/dL at baseline showed fewer major coronary events with simvastatin than with placebo (RR=0.78; 95% CI, 0.68-0.90).6

**High-dose statins decrease MI more than standard doses**

A 2008 meta-analysis of 29,395 high-risk patients in 7 trials examined high-dose compared with standard statin use for secondary prevention. Six trials used atorvastatin 80 mg daily as the high-dose regimen; 1 trial used simvastatin 80 mg daily. The standard regimens were 5 to 40 mg of pravastatin, simvastatin, atorvastatin, or lovastatin.

The weighted mean difference of LDL lowering between the 2 groups was 28 mg/dL (95% CI, 23-32 mg/dL), and fewer than 50% of patients achieved the treatment target (LDL <80 mg/dL). Nevertheless, intensive statin use decreased MIs compared with standard dosing (RR=0.83; 95% CI, 0.77-0.91).7

This meta-analysis included a key RCT, which enrolled 4162 high-risk patients and compared pravastatin 40 mg (standard therapy) with atorvastatin 80 mg (intensive

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TABLE

**Target LDL measurements for high-risk and very-high-risk patients**1,2,7,8

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Risk factors</th>
<th>Goal LDL</th>
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<tbody>
<tr>
<td>High</td>
<td>Known CHD OR Noncoronary atherosclerotic disease: abdominal aortic aneurysm, peripheral arterial disease, symptomatic carotid stenosis OR Stage 5 kidney disease (GFR &lt;15 mL/min or on dialysis) OR Diabetes OR ≥2 of the following risk factors with 10-y risk of CHD &gt;20%: • Cigarette smoking • Hypertension (BP &gt;140/90 mm Hg or on antihypertensive medication) • Low HDL cholesterol (&lt;40 mg/dL) • Family history of premature CHD (in male first-degree relative &lt;55 y; in female first-degree relative &lt;65 y) • Age (men &gt;45 y; women &gt;55 y)</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Very high</td>
<td>Known CHD AND Multiple major risk factors: • Acute coronary syndrome • Diabetes • Metabolic syndrome • Poorly controlled or severe risk factors, especially cigarette smoking</td>
<td>(Optional) &lt;70 mg/dL</td>
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BP, blood pressure; CHD, coronary heart disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
therapy) over an average of 24 months. The pravastatin group achieved a median LDL of 95 mg/dL and the atorvastatin group achieved a median LDL of 62 mg/dL. The atorvastatin group had fewer deaths from any cause or a major cardiovascular event (RR=0.85; 95% CI, 0.76-0.95; NNT=25).8

**Does benefit result from lower LDL, or some other statin effect?**

Since most lipid studies have been done using a statin as the sole treatment agent, it is unclear whether patients benefit more from a lower LDL or from some effect of the statin medication class.7 Statins reduce the risk of cardiovascular events in patients with an elevated C-reactive protein,10 perhaps indicating an anti-inflammatory effect. However, fibrates and niacin have also been shown to decrease coronary events in high-risk patients in a few studies.11,12

**Recommendations**

The NCEP Adult Treatment Panel III guidelines recommend treating high-risk patients to a target LDL of <100 mg/dL.1 A target LDL of <70 mg/dL is optional for very-high-risk patients (TABLE).1,3

The K/DOQI recommends that patients with stage 5 kidney disease be treated according to the NCEP guidelines for high-risk patients.2 The expected release date for the NCEP Adult Treatment Panel IV guidelines is fall 2011.13

**References**