Q/What does the evidence tell us about treating very-high-risk patients to an LDL <70 mg/dL?

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EVIDENCE-BASED ANSWER

A/ **NOT MUCH.** No studies directly compare low-density lipoprotein (LDL) levels <70 mg/dL to levels of 71 to 100 mg/dL in very-high-risk patients. However, no evidence suggests a "floor" for LDL cholesterol levels beyond which further reductions of heart disease risk can't be achieved (strength of recommendation [SOR]: **A**, systematic reviews of randomized controlled trials [RCTs]). The target LDL cholesterol of <70 mg/dL is based on data extrapolated from RCTs (SOR: **B**).

Comparing larger (80 mg) with smaller doses of atorvastatin shows that larger doses reduce LDL and major cardiac events more than smaller doses. No studies report patient-oriented outcomes of treatments for patients who fail to reach target LDL levels <100 mg/dL.

CLINICAL COMMENTARY

Treatment benefits—and potential barriers

As this review demonstrates, patients at very high risk of coronary artery disease may derive benefit from lowering LDL cholesterol to <70 mg/dL. Attempting to reach this goal for such patients seems to be a "no-brainer." In reality, however, several possible barriers to treatment exist, including:

- *The goal may be unachievable, even with the highest dose of statins, combination therapy, and lifestyle changes.*
- *The risk of myopathy (which is rare) or adverse side effects (less rare) is proportional to the statin dose and may prevent certain patients from achieving the goal.*
- *For most statins, cost increases with dosage.*
- *For patients with multiple comorbidities, the incremental health benefit of intensive LDL lowering may not be significant.*

As with any medical intervention, you should explain all risks and benefits to the patient, who should participate actively in the decision to pursue the goal of intensively lowering LDL cholesterol.

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Evidence summary

The National Cholesterol Education Program's definition of "very high risk" for coronary heart disease (CHD) encompasses established CHD and CHD equivalents, including diabetes, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, and multiple cardiac risk factors that confer a 10-year calculated cardiac risk greater than 20%.[1]

Statin dosage: Bigger is better

The Treating to New Targets (TNT) study showed that in patients with stable CHD, intensive lipid lowering with atorvastatin 80 mg daily delivered significant clinical

benefit beyond that provided by atorvastatin 10 mg daily.[2] The mean LDL achieved in TNT was 77 mg/dL on 80 mg atorvastatin, compared with 101 mg/dL on 10 mg.

Patients with diabetes who took 80 mg had a 2.26% absolute risk reduction for major cardiovascular events (number needed to treat=43). Secondary outcomes—including all cardiovascular events, cerebrovascular events, and congestive heart failure with hospitalization—also improved on 80 mg atorvastatin.

Although this study enrolled a total of 10,001 patients with clinically evident CHD, it was not sufficiently powered to demonstrate differences in overall mortality between the 2 groups. While it is clear that patients in the 80-mg group had better outcomes than patients in the lower-dose group, the exact role of LDL lowering cannot be easily separated from other potentially beneficial effects of the higher dose of atorvastatin.

No evidence points to a "floor" for LDL cholesterol levels beyond which further reductions of heart disease risk can't be achieved.

How low should LDL go?

What the studies show

In the Heart Protection Study, patients with CHD, other occlusive arterial disease, or diabetes were randomized to 40 mg simvastatin or placebo.[3] Simvastatin reduced relative risk of CHD—regardless of baseline LDL—even in patients with a baseline LDL <116 mg/dL.

Further analysis showed that among the many types of high-risk patients, 5 years of simvastatin at 40 mg daily would prevent about 70 to 100 people in 1000 from suffering at least 1 major vascular event (myocardial infarction, stroke, or the need for revascularization). Interestingly, patients with relatively smaller reductions in LDL (those in the lowest third) showed the same decrease in CHD events as patients in the highest third—although the overall difference in LDL wasn't large.

A meta-analysis of these and other studies concluded that intensive lipid lowering with high-dose statin therapy confers a significant benefit over standard-dose therapy for preventing predominantly nonfatal cardiovascular events.[4] The safety and tolerability of higher and standard statin doses are similar.[2] Two additional meta-analyses supported the use of intensive statin regimens to reduce cardiovascular risk, but didn't find evidence for lowering LDL to a particular target level.[5,6]

Meta-analysis: The lower the LDL, the lower the risk of CHD

The ENHANCE study, a double-blind, randomized trial conducted over a period of 24 months, compared the effects of 80 mg per day of simvastatin with either placebo or 10 mg per day of ezetimibe in 720 patients with familial hypercholesterolemia. The primary outcome measure was a change in intima-media thickness of the walls of the carotid and femoral arteries. The results of the study have raised the question of whether it is appropriate to target LDL cholesterol primarily to reduce CHD risk, because ezetimibe did not affect carotid artery intima-media thickness, despite its effectiveness in reducing LDL cholesterol.[7]

However, an earlier 19-trial meta-regression analysis (81,859 patients with stable CHD) demonstrated that each 1% reduction in LDL cholesterol corresponded to a 1% decrease in risk for CHD. This result held true regardless of different approaches to treatment, which included diet, bile-acid sequestrant, statins, or ileal bypass surgery.[8]

Recommendations

The Adult Treatment Panel (ATP) III guidelines recommend an LDL level <100 mg/dL for high-risk patients (CHD or a CHD risk equivalent).[9] An update to the ATP III guidelines states that the LDL goal of <100 mg/dL was as low as could be supported by clinical trial evidence at the time of publication and was also the practical limit of LDL reduction that could be achieved with standard treatment in most high-risk patients.[1] The ATP III update offers the option of treating high-risk patients to a target LDL <70 mg/dL and clarifies that recent trials have shown no significant side effects associated with very low LDL levels.

Recent American Diabetes Association guidelines state that the LDL target should be <100 mg/dL in patients with diabetes, with the option of treating patients with both overt CHD and diabetes to an LDL of <70 mg/dL.[10] JFP

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ADA guidelines recommend an LDL target of <100 mg/dL in patients with diabetes.