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

Patients who have known coronary heart disease or are at high risk for CHD should aim for an LDL of <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 with treatment (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.[1]

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]

TABLE

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

Risk level	Risk factors	Goal LDL
High	Known CHD OR Noncoronary atherosclerotic disease: abdominal aortic aneurysm, peripheral arterial disease, symptomatic carotid stenosis OR Stage 5 kidney disease (GFR <15 mL/min or on dialysis) OR Diabetes OR ≥2 of the following risk factors with 10-y risk of CHD >20%: • Cigarette smoking • Hypertension (BP >140/90 mm Hg or on antihypertensive medication) • Low HDL cholesterol (<40 mg/dL) • Family history of premature CHD (in male first-degree relative <55 y; in female first-degree relative <65 y) • Age (men >45 y; women >55 y)	<100 mg/dL
Very high	Known CHD AND Multiple major risk factors: • Acute coronary syndrome • Diabetes • Metabolic syndrome • Poorly controlled or severe risk factors, especially cigarette smoking	(Optional) <70 mg/dL

BP, blood pressure; CHD, coronary heart disease; GFR,glomerular filtration rate; HDL, high-density lipoprotein; LDL,low-density lipoprotein.

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

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.[9] 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] **JFP**

A target LDL of <70 mg/dL is an option for very-high-risk patients.

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