Intensive statin therapy: a goal worth targeting

There is strong evidence that inhibition of HMG-CoA reductase with statins significantly lowers serum LDL-cholesterol (LDL-C) concentrations and improves long-term clinical outcomes among patients with both stable and unstable atherosclerotic disease [1,2]. However, there is a growing body of evidence that statin therapy is associated with improvements in outcomes that may not be fully accounted for by LDL-C lowering [3]. Moreover, while targeting LDL-C lowering is certainly important, withholding statin therapy among patients with acute coronary syndromes, stroke or stable vascular disease whose serum LDL-C concentrations are commensurate with guideline recommendations may not provide as much benefit as possible. We argue here that intensive statin therapy should be utilized unless there is a distinct contraindication in patients with established stable or unstable vascular disease.

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Alternate interpretation of results to date

In 2004, on the results of five new clinical trials, an update to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines was published [4]. In authoring this update, the panel wrote: “The trials confirm the benefit of cholesterol-lowering therapy in high-risk patients and support the ATP III treatment goal of LDL-C ≤100 mg/dl.” It should be noted that none of the five studies [1,5–8], not to mention other trials published since [2,9], actually tested a hypothesis of lipid lowering. Rather, they tested a hypothesis that statin therapy is associated with improved outcomes compared with placebo and that intensive statin therapy improved outcomes compared with moderate statin therapy.

Targeting LDL-C lowering may prevent some patients from fully benefiting from statins

Although lowering LDL-C in patients with known or suspected coronary artery disease almost certainly plays a role in improving outcomes among such patients, it was statin therapy, and not LDL lowering, that was tested in these studies. Overinterpretation of the data has important clinical consequences. Ezetimibe, fibrates and nicotinic acid may all lower LDL-C, thus achieving guideline recommendations in the absence of statin therapy, but there is no robust data from recent large-scale randomized clinical trials demonstrating a reduction in major adverse cardiovascular event rates with these medicines [10,11]. Therefore, use of arbitrary goals for LDL-C lowering may prevent some patients from receiving statin therapy when these may in fact further improve outcomes.

No clinical trial has actually tested the hypothesis that reaching these arbitrary LDL-C goals will improve outcomes

Examination of the data suggests that the goals of LDL-C less than or equal to 100 mg/dl in high-risk patients and LDL-C less than or equal to 70 mg/dl in very-high-risk patients have little prospective randomized trial data to support them. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 study, in which over 4000 patients with acute coronary syndrome were randomized to intensive statin therapy with atorvastatin 80 mg daily or moderate statin therapy with pravastatin...
Clinical trials do not suggest an association of intensive statin therapy with adverse side effects

Four major long-term clinical trials did not demonstrate an excess risk of adverse events among patients treated with intensive statin therapy versus moderate therapy. Myalgias occurred in similar numbers of patients in both arms of the TNT and PROVE IT-TIMI 22 trials [1,2], and discontinuation rates were similar in Phase 2 of the Aggrastat to Zocor (A to Z) trial [17]. Rhabdomyolysis occurred in a higher number of patients in the moderate intensity arms of both the TNT and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) studies [2,18]. Taken together, these large trials suggest that intensive statin therapy is associated with similar rates of drug discontinuation and/or muscle complaints as moderate statin therapy. Moreover, reduction in dose can frequently ameliorate these symptoms.

Statins may provide other benefits beyond lipid lowering

There is a growing body of evidence that intensive statin therapy has pleiotropic effects that go beyond their LDL-C-lowering effect. Pleiotropic effects have been speculated to include benefits in the reduction of inflammation, plaque stability and endothelial function.

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Bibliography


40 mg daily, the median LDL-C achieved in the moderate statin arm was 95 mg/dl, meaning nearly half of the patients would have been above the prior goal of 100 mg/dl or less and would therefore have been subject to intensification of their hypolipidemic regimen [1]. Likewise, in the Treating to New Targets (TNT) study, in which 10,001 patients with established but stable coronary artery disease were randomized to intensive statin therapy with atorvastatin 80 mg or moderate statin therapy with atorvastatin 10 mg, the mean LDL in the moderate statin therapy arm was 101 mg/dl, meaning that more than half of patients in the moderate statin arm had LDL-C concentrations above the current goal [2].

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Intense statin therapy reduces major adverse cardiovascular events among patients with stable and unstable vascular disease. Arbitrary targets for LDL-C lowering based on median levels achieved in randomized trials may prevent some patients with vascular disease, who have otherwise achieved these levels, from receiving statins. Therefore, we would argue that the primary goal among patients with established vascular disease should be intensive statin therapy, with LDL-C lowering as a secondary target to be achieved with supplementary therapy if levels remain elevated.
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13 Ray KK, Cannon CP: Early time to benefit with intensive statin treatment: could it be the pleiotropic effects? Am. J. Cardiol. 96(5A), F54–F60 (2005).


