

The IDEAL Cholesterol: Lower Is Better

Christopher P. Cannon, MD

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Three decades ago, the primary results of the Multiple Risk Factor Intervention Trial (MRFIT) were published in *JAMA*; that trial attempted to demonstrate benefits from lowering cholesterol (with diet) and managing other known risk factors for reducing cardiovascular morbidity and mortality.¹ Since then, multiple trials have shown cardiovascular benefit from lowering cholesterol, especially low-density lipoprotein cholesterol (LDL-C).^{2,3} However, as of 1993, no trial had demonstrated a clear reduction in total mortality and, thus, debate still raged as to whether it was beneficial to reduce cholesterol.³

This changed when Pedersen and colleagues⁴ reported the landmark Scandinavian Simvastatin Survival Study (4S), which demonstrated that use of simvastatin, 20 to 40 mg/d, produced a highly significant 30% reduction in total mortality, in addition to reductions in myocardial infarction (MI) and the need for coronary revascularization. Subsequent trials expanded the benefit of treating broader groups of patients with statins,⁵ including patients who had not yet had a cardiac event.⁶ One recent primary prevention study of patients with hypertension found a significant 36% reduction in the risk of death or MI with just 3 years of treatment with a standard-dose statin.⁷ The Heart Protection Study (HPS) observed benefit of a statin compared with placebo in all patients regardless of baseline LDL-C level, even in patients with an LDL-C level of less than 100 mg/dL.⁸ A line of thought then emerged that among patients with established coronary disease or diabetes, it might not even be necessary to measure cholesterol levels. Rather, physicians could simply treat high-risk patients with fixed-dose statin therapy. However, even allowing for benefits irrespective of baseline LDL-C levels, the question was still open as to whether more aggressive LDL-C lowering was an appropriate strategy.

Direct testing of varying degrees of LDL-C lowering has now been carried out in 4 large outcomes trials involving 27 548 patients, beginning with the Pravastatin or Atorvastatin Evaluation and Infection Treatment–Thrombolysis in Myocardial Infarction (PROVE IT–TIMI 22) trial. This trial compared a standard-dose statin that achieved a median LDL-C level of 95 mg/dL, meeting the current National Cholesterol Education Program (NCEP) Adult Treatment Panel III guideline target LDL-C level of less than 100 mg/dL,⁹ with a more intensive strategy using high-dose atorvastatin that achieved a median LDL-C level of 62 mg/dL.¹⁰ The trial results demonstrated a statistically significant benefit of the more intensive statin treatment, with a 16% reduction in the risk of death and major cardiovascular events, which emerged rapidly and was observed over the subsequent 2 years following an acute coronary syndrome.¹⁰

The A to Z trial showed a similar trend toward benefit, but outcomes were not statistically significant, perhaps because of a smaller-than-anticipated number of events.¹¹ The Treating to New Targets (TNT) trial, however, had a highly significant reduction in events and expanded the benefit of more intensive statin therapy to patients with stable coronary artery disease.¹² There were reductions in cardiovascular death, MI, need for revascularization, and stroke with use of high-dose vs standard-dose atorvastatin. Although the trial results were consistent with the concept that for cholesterol, “lower is better,” concerns were raised regarding a nonsignificant difference in noncardiovascular death.¹³ For this reason, many have been waiting for the results of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial for the final word on whether more intensive lipid lowering would be of benefit.

The findings from the IDEAL study, reported by Pedersen et al¹⁴ in this issue of *JAMA*, are indeed an important addition to the current pool of evidence. With use of atorvastatin, 80 mg/d, compared with simvastatin 20 to 40 mg/d (by design, the active treatment intervention of 4S), the intensive statin treatment

achieved a 23-mg/dL lower LDL-C level and led to an 11% trend in reduction in the primary end point of coronary heart disease death, MI, or cardiac arrest with resuscitation ($P = .07$).¹⁴ Thus, the primary end point was not met. However, when using the primary end point of the TNT trial, which also included stroke, there was a significant 13% reduction ($P = .02$), and when using the primary end point of the PROVE IT–TIMI 22 trial, any cardiovascular event including revascularization, there was a significant 16% reduction ($P < .001$),¹⁴ which was identical to that observed in PROVE IT–TIMI 22.¹⁰ There were no differences in all-cause, cardiovascular, or noncardiovascular mortality; the primary differences were in the nonfatal end points.

To put these data in perspective requires first considering the benefits of standard-dose statins, the control groups of these recent trials. As reported recently in the Cholesterol Treatment Trialists (CTT) meta-analysis, standard-dose statin therapy reduces the risk of coronary heart disease death or MI by 23% ($P < .001$) and the risk of any major vascular event by 21% ($P < .001$).¹⁵ The [Table](#) summarizes the 4 trials of aggressive statin therapy to date, with a synopsis of the increment of LDL-C reduction and the reduction in clinical events. As would be expected, the degree of LDL-C lowering seems to relate to the degree of clinical benefit. Taken together, these trials reaffirm the central role of lowering LDL-C as a primary means of reducing morbidity and mortality in patients with, or at risk for, cardiovascular disease.

Table. Clinical Outcome Trials Testing Intensive vs Standard Statin Therapy

Trial	Population	Number	LDL-C Reduction	Relative Risk Reduction	Relative Risk Increase
PROVE IT–TIMI 22	Acute coronary syndrome	10,825	50%	16%	0%
TNT	Stable coronary artery disease	10,000	26%	13%	0%
IMPROVE-IT	Acute coronary syndrome	17,802	24%	6%	0%
FOURIER	Acute coronary syndrome	27,395	26%	24%	0%

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At least 2 important safety concerns must be considered. First, some have noted a possible increased risk of noncardiovascular death or of cancer with the use of statins. Both the CTT meta-analysis, which included more than 90 000 patients,¹⁵ and this report of IDEAL¹⁴ show that there are no material differences over a 5-year period in the risks of development of cancer, death from cancer, or any noncardiovascular cause of death. The other major safety concern derives from well-described risks of liver and muscle toxicity, as reflected by the transient increases in liver function tests and creatine kinase levels that are seen in 1% to 3% of patients following treatment with statins at standard or high doses, compared with 1% to 2% of patients treated with placebo.^{10,12,16} Both of these findings suggest metabolic changes in either hepatic or muscle cells (but not permanent cellular damage) and are reversible with reduction in dose or stopping the medication. Rhabdomyolysis, which does involve muscle damage, is rare with most commonly prescribed statins at currently accepted doses; in the recent CTT meta-analysis, 9 (0.023%) of 39 884 patients treated with statins vs 6 (0.015%) of 39 817 patients treated with placebo reported rhabdomyolysis, for a nonsignificant excess of 3 patients (0.01%).¹⁵ Thus, although this class of drugs is safe, statin use mandates that physicians monitor patients for any adverse effects and adjust doses accordingly.

What is the mechanism by which benefits of intensive statin therapy are achieved in reducing cardiovascular morbidity and mortality? The primary reason is the greater reduction in LDL-C levels.² Multiple randomized trials of statins that lower LDL-C have shown benefit, with correlations between the degree of LDL-C reduction and the clinical benefit, as summarized in the NCEP’s national guidelines.² In addition, observational analyses of clinical trial databases have clearly demonstrated associations between lower LDL-C levels during treatment and lower risk of cardiovascular death or MI. This has been observed across many statin trials¹⁵ and, importantly, across different modes, including diet, fibrates, niacin, and statins.² Another potential mechanism of benefit relates to the additional effects of statins beyond cholesterol reduction, including lowering inflammation, as reflected by C-reactive protein (CRP) levels^{17,18} and other markers, as well as reductions in triglycerides and increases in high-density lipoprotein cholesterol (HDL-C).¹⁴ Initial analyses assessing the relative contributions of each of these factors suggest that clinical benefit may be derived from these effects.¹⁷⁻¹⁹ Ongoing trials are studying the benefits of each of these components; ie, the benefit of raising HDL-C levels, lowering CRP, and of even greater reductions in LDL-C.

So, what are the take home messages from the IDEAL trial and these decades of research? For physicians,

there are several key points. The first is that there is now considerable evidence that aggressive lowering of cholesterol reduces cardiovascular events. It is expected that the NCEP Guideline Committee will review the new evidence from the CTT meta-analysis¹⁵ and the TNT¹² and IDEAL¹⁴ trials, all published this year, to consider fully adopting as formal recommendations the therapeutic options suggested in their update from 2004,²⁰ which had been based on PROVE IT–TIMI 22,¹⁰ the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),⁷ and the HPS.⁸ Second, physicians caring for patients with vascular disease must ensure that every patient for whom statins are appropriate receives therapy at the appropriate dose. These include patients with documented coronary artery disease, especially those with recent acute events, and patients with peripheral arterial disease and cerebrovascular disease (in whom a 30% reduction in stroke has been seen with standard-dose statins and an additional 20% reduction in stroke has been seen with high-dose statins).^{12,21} Patients with diabetes also benefit from statin treatment with reductions in overall mortality, even among those who have not yet experienced a coronary event.^{22–24} More broadly, several trials with standard-dose statin treatment have shown that patients with coronary risk factors have a substantial reduction in the risk of developing their first cardiovascular event.^{7,25} Third, for patients already taking statins, these new data support monitoring LDL-C levels and aiming for new guideline-recommended low LDL-C targets.^{10,12,14,20}

What are the messages for patients from IDEAL and other statin trials? First, for the “bad” cholesterol, LDL-C, lower is better for preventing MI stroke, need for cardiac procedures, and death. Second, statins are safe overall,^{10,12,14,15} even for patients with extremely low treatment LDL-C levels.²⁶ However, patients and physicians have to work as partners to monitor for adverse effects, which can occur in up to 5% of patients but that only rarely can be life-threatening. Fortunately, these are almost always reversible and do not lead to any permanent damage. Third, patients should know their cholesterol numbers, for both LDL-C and HDL-C, to enable them to see how much lowering is needed to reach targets of an LDL-C level of less than 100 mg/dL for patients with risk factors or less than 70 mg/dL for patients with heart disease.^{20–28} And fourth, any drug treatment should be taken together with an appropriate diet and exercise program to lower cholesterol and overall vascular risk. The amount of LDL-C lowering with diet is only in the range of 7% to 12%.²⁹ Clearly, diet is a central part of the treatment, but to get the benefits of very low cholesterol levels, drug treatment is often necessary. Optimal use of diet and appropriate use of medications will dramatically reduce the risk of MI, stroke, and death from heart disease. These new data should help motivate any patients who have been hesitating about treating their cholesterol to talk with their physician to get the benefits of intensive cholesterol lowering.

Finally, the scientific community needs to continue to pursue new avenues of treatment, with approaches that may well be “beyond statins.” Even with intensive statin therapy, the current best evidence-based treatment available, many patients still will have recurrent cardiovascular events. New strategies may include development of new agents to achieve even lower target LDL-C levels, substantially increase HDL-C levels, reduce triglycerides, reduce CRP and other components of inflammation, and modify many other identified components of vascular disease.

ARTICLE INFORMATION

Corresponding Author: Christopher P. Cannon, MD, TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115 (cpcannon@partners.org).

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