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EDITORIAL



Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT

John A. Jarcho, M.D., and John F. Keaney, Jr., M.D.

The so-called LDL hypothesis is the concept that excess low-density lipoprotein (LDL) cholesterol is a causal factor in the development of atherosclerotic vascular disease. By extension, this hypothesis also assumes that reducing LDL cholesterol levels, regardless of the means, should produce a corresponding reduction in cardiovascular events. Considerable evidence supports the LDL hypothesis, including animal studies and epidemiologic studies involving humans, as well as clinical trials of both statins and nonstatin lipid-modifying agents. In a meta-analysis that included more than 90,000 participants in 14 randomized trials of statins, the Cholesterol Treatment Trialists' (CTT) collaborators found that, on average, a reduction of 1 mmol per liter (38.7 mg per deciliter) in LDL cholesterol levels yields a consistent 23% reduction in the risk of major coronary events over 5 years.¹

Despite this body of evidence, there has been a long-standing argument that the beneficial effects of statins are not adequately explained by their effects on LDL cholesterol. Statins have a complex array of biologic effects — including amelioration of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, and inhibition of inflammation — that are unrelated to their lipid-lowering effect and that are sometimes called “pleiotropic effects.”² It has been argued that such effects may account for at least some of the benefit of statin therapy in preventing cardiovascular events. This alternative theory is sometimes referred to as the “statin hypothesis” — the idea that statins have a unique efficacy in atherosclerotic vascular disease that is not shared by other lipid-modifying agents and that reduction in LDL cholesterol

levels is not the only basis for the beneficial effect of statins (Fig. 1).

Several recent negative clinical trials have seemed to offer support for the statin hypothesis. In each of these trials, the addition of a nonstatin lipid-modifying agent to statin therapy conferred no significant increment in cardiovascular benefit over that seen with a statin alone.³⁻⁶ In addition, in a clinical trial of rosuvastatin,⁷ the beneficial effect of this statin was found to correlate not only with its effect on LDL cholesterol levels but also independently with its ability to reduce the level of high-sensitivity C-reactive protein, a marker of inflammation.⁸ Given these findings, the 2013 cholesterol treatment guidelines of the American College of Cardiology and the American Heart Association heavily emphasized statin therapy as the preferred treatment option for patients with established cardiovascular disease or hyperlipidemia.⁹

With this background, the report by Cannon et al. of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),¹⁰ now published in the *Journal*, offers important new evidence in favor of the LDL hypothesis. In IMPROVE-IT, 18,144 patients who had had an acute coronary syndrome were randomly assigned to either simvastatin (40 mg) plus ezetimibe (10 mg) or to simvastatin (40 mg) plus placebo. At 1 year, the mean LDL cholesterol level was 53.2 mg per deciliter (1.4 mmol per liter) in the simvastatin-plus-ezetimibe group, and 69.9 mg per deciliter (1.8 mmol per liter) in the simvastatin-monotherapy group. The primary end point was a composite of cardiovascular death, major coronary event (nonfatal myocardial infarction, unstable angina, or coronary revascularization),

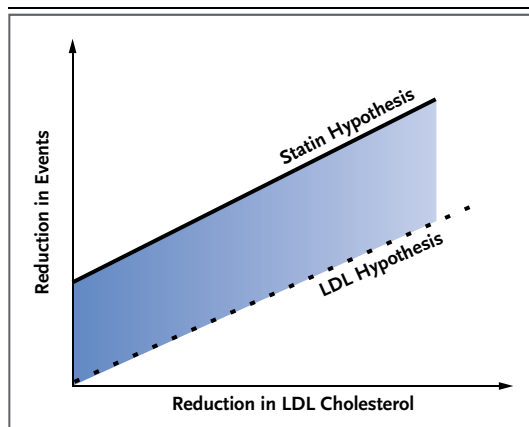


Figure 1. Schematic Depiction of the Statin Hypothesis.

The reduction in low-density lipoprotein (LDL) cholesterol with lipid-modifying agents is plotted against the reduction in cardiovascular events under either the LDL hypothesis or the statin hypothesis. The putative added “pleiotropic” effects of statins (effects that are unrelated to their lipid-lowering effects) are represented by the shaded area. The IMPROVE-IT trial provides important new evidence in favor of the LDL hypothesis.

or nonfatal stroke. At 7 years, the rate of the primary end point was significantly lower, by 2.0 percentage points, in the simvastatin-plus-ezetimibe group than in the simvastatin-monotherapy group (32.7% vs. 34.7%). No significant differences in rates of adverse events were seen between the two study groups.

IMPROVE-IT is a landmark study in that it is the first clinical trial to show a benefit of adding a nonstatin lipid-modifying agent to statin therapy. Ezetimibe, the added agent in this trial, works by reducing the intestinal absorption of cholesterol, a distinct mechanism that is unrelated to that of statins. And yet, the event-rate reduction with the addition of ezetimibe was precisely the same as that predicted by the CTT analysis of statin trials described above (see Fig. 2 in the article by Cannon et al.),¹⁰ which suggests that reduction of LDL cholesterol levels per se explains the effect of statins on coronary heart disease.

These results offer important hope to patients who have unacceptable side effects from statin therapy and to those who may not achieve adequate LDL reduction with statins. The 2013 guidelines do not recommend the use of specific targets for LDL cholesterol levels, but they do acknowledge that some patients may have an

“insufficient response to statin therapy” and that in such patients the addition of a nonstatin agent may be considered.⁹ The results of IMPROVE-IT should, at a minimum, reinforce such a recommendation and will undoubtedly rekindle arguments in favor of targets for LDL cholesterol levels.

The results of IMPROVE-IT also imply that other interventions to reduce LDL cholesterol levels may prove to be beneficial. In this regard, the recent development of PCSK9 inhibitors is of note. These agents reduce LDL-receptor degradation, thereby enhancing LDL clearance from the circulation, and they have been shown to reduce LDL cholesterol levels by as much as 60%.^{11,12} Definitive clinical outcomes trials with these agents are ongoing.

IMPROVE-IT should not be interpreted as showing anything uniquely beneficial about the use of ezetimibe. Indeed, the real implication of IMPROVE-IT is to suggest that all reductions in LDL levels, regardless of mechanism, are of equivalent benefit. Thus, a patient who is currently being treated with 40 mg of simvastatin would be expected to benefit just as much from a higher-intensity statin regimen (e.g., 40 to 80 mg of atorvastatin or 20 to 40 mg of rosuvastatin) as from the addition of ezetimibe, assuming equivalent reductions in LDL cholesterol levels.

A sobering observation was that 42% of the participants in IMPROVE-IT, regardless of treatment assignment, discontinued the study medication prematurely. As noted by the authors, this discontinuation rate is approximately 7% per year, which closely mirrors that seen in other trials. Since lipid-lowering is presumably intended to be a lifelong goal, this diminishment in long-term use is an important practical clinical concern, and one that suggests that treatment adherence to lipid-lowering therapy needs to be an ongoing focus of practitioner attention. It also raises questions about the practicality of long-term use of PCSK9 inhibitors, since all these agents are currently given by subcutaneous injection once every 2 to 4 weeks.

Overall, IMPROVE-IT provides us with important information on the value of lowering LDL cholesterol levels, regardless of the agent used. These data help emphasize the primacy of LDL cholesterol lowering as a strategy to prevent coronary heart disease. Perhaps the LDL hypothesis should now be considered the “LDL principle.”

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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