MAYO CLINIC

EDITORIAL

April 2009
Volume 84
Number 4

Mayo Clinic Proceedings

Low-Density Lipoprotein Cholesterol Reduction and Prevention of Cardiovascular Disease

In this issue of *Mayo Clinic Proceedings*, 2 articles discuss lipid lowering and prevention of cardiovascular disease (CVD). Karalis[1] reviews and evaluates the evidence supporting a low-density lipoprotein cholesterol (LDL-C) target of less than 100 mg/dL for moderately high-risk individuals and concludes by saying, "The current evidence supports a strategy of early and aggressive lowering of LDL-C levels for the primary prevention of CAD [coronary artery disease]." Al Badarin et al[2] review the published literature on the effect of LDL-C by cholesterol absorption transport inhibition with ezetimibe. They conclude correctly that even though ezetimibe lowers LDL-C levels, reduces circulating inflammatory biomarkers like high-sensitivity C-reactive protein when added to statins, and has a variable effect on endothelial function based on a few small studies, no randomized controlled trial (RCT) has shown evidence of its impact on prevention of cardiovascular events.

However, the neutral results of the somewhat infamous ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) carotid artery intima-media thickness (CIMT) trial[3] has led some to question the cardiovascular benefits of ezetimibe and the LDL-C hypothesis in general. Therefore, it is important to review this controversy and LDL-C lowering in context, especially as it relates to the primary prevention of CVD.

Although reducing LDL-C levels to decrease CVD risk has come of age in the past 2 decades, in an era dominated by drugs that inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase ("statins"), it is worthwhile to recall how we arrived at current treatment guidelines because increasing evidence shows that history is being either forgotten or distorted.

The current year marks the 25th anniversary of the publication[4] of the landmark National Institutes of Health–sponsored LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial), which became the basis for the first National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP I) guideline[5] released in 1988. As Steinberg[6] points out in an excellent recent review, the reduction in LDL-C levels to decrease CVD, often referred to as *the lipid hypothesis*, had been controversial and poorly accepted by mainstream medicine for nearly 40 years, despite an extremely large body of epidemiological, animal, and genetic data and positive results from small RCTs of older, mostly minimally effective drugs. The LRC-CPPT, despite using a somewhat unpleasant-to-ingest bile acid sequestrant (cholestyramine) at a dose of 24 g/d, which achieved a moderate 12.6% greater reduction in LDL-C levels compared with placebo, provided sufficient and convincing evidence that cholestyramine reduced death due to definite coronary heart disease by a relative 24% with a relative 19% decrease in nonfatal myocardial infarction ($P<.05$ for primary end point). The LRC-CPPT and NCEP-ATP I stimulated an intensive search for and development of more effective, better tolerated, and safe agents for lowering LDL-C levels, which culminated in the approval of the first statin, lovastatin, in late 1987.[7] In the early 1990s, 3 more statins were approved, and their rapid acceptance by both clinicians and patients was evidenced by statins becoming one of the largest selling therapeutic agents by the middle of the decade. The predominant use was consistent with ATP I guidelines for the primary prevention of CVD.

See also pages 345 and 353

Dr Stein has received consulting/speaker fees and/or funding for specific clinical trials from Abbott, AstraZeneca, American Association for Clinical Chemistry, Daiichi-Sankyo, sanofi-aventis, Schering-Plough, Roche, Isis Pharmaceuticals, Takeda Pharmaceutical, Novartis Pharmaceuticals, Wyeth Pharmaceuticals, GlaxoSmithKline, US Food and Drug Administration, National Lipid Association, and Merck & Co.

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In 1994, the first RCT of this new class of agents to lower LDL-C levels was published,[8] demonstrating how effective LDL-C reduction could be in decreasing not only CVD events but also total mortality due to the disease. This secondary prevention trial also focused attention on the greater cost-effectiveness of treating patients with existing CVD, given their substantially higher absolute risk of future events. The 4S (Scandinavian Simvastatin Survival Study)[8] was followed by numerous additional successful RCTs with a variety of statins and in a variety of patient populations, such that LDL-C reduction has been well established to be the most effective intervention for reducing cardiovascular risk.[9] This includes all groups studied: primary and secondary prevention, men, women, elderly patients, diabetic patients, those with hypertension, those with moderately elevated LDL-C levels and low high-density lipoprotein cholesterol values, and most recently those with low LDL-C levels and increased levels of high-sensitivity C-reactive protein.[10] In addition, RCTs have shown that "lower LDL-C is better," and such trials have driven updated NCEP ATP guidelines in which optimal LDL-C levels in high-risk patients with CVD are now as low as 70 mg/dL.[11]

These large, global, and well-conducted RCTs of statins ensured that reducing LDL-C levels became universally accepted as the cornerstone of treatment and the basis for worldwide guidelines for the prevention of CVD.[11,12] There was little question after the first major statin trials that the reduction in CVD was related to lipid lowering and was totally consistent and supportive of the lipid hypothesis. However, stimulated by funding from the pharmaceutical industry, in which competition was fierce for market share and was driven mainly by the efficacy of lowering LDL-C levels, manufacturers of less-effective agents for lowering LDL-C levels helped propagate "beyond LDL-C" theories; these theories were that statins reduced CVD events by means other than lipid reduction, often termed *pleotropic effects*, usually shown in in vitro laboratory studies or small, poorly standardized surrogate marker trials. This belief culminated in an RCT by a pharmaceutical company that was designed to show that more LDL-C reduction with a competitor's statin achieved no greater benefit.[13] However, the results of that study clearly and convincingly showed otherwise, with additional reduction in CVD events with the drug that lowered LDL-C levels more. Even with this evidence, and perhaps with an even more powerful statin about to be approved, the investigators suggested that the reduced events were due to pleotropic effects of the more efficacious statin. However, the trial was soon followed up with results from another head-to-head RCT, with the same drug at different LDL-C lowering doses,[14] which eliminated the pleotropic potential and reinforced that lower is better. Despite the preponderance of evidence, the importance of LDL-C is being de-emphasized, and these unknown or still unproven pleotropic effects of statins are being highlighted.[15]

Within that environment, the ENHANCE study provided an opportunity for proponents of statin pleotropism or those still skeptical about the lipid hypothesis to once again question the role of LDL-C in CVD prevention. Solely on the basis of ENHANCE, a trial with a flawed design,[16] some critics proposed that the inability of ezetimibe to inhibit atherosclerosis may be due to an off-target effect that negates the benefits of LDL-C lowering, similar to that of oral estrogen and the cholesterol ester transfer protein inhibitor drug, torcetrapib. The increase in cardiovascular events observed with these last-mentioned agents is large and robust and can be explained by well-documented mechanisms—oral estrogen and progesterone are prothrombotic,[17] whereas torcetrapib increases aldosterone production and substantially raises blood pressure.[18] By comparison, the pathway by which a cholesterol absorption transport inhibitior such as ezetimibe lowers plasma LDL-C levels is similar to that of statins and bile acid sequestrants. All 3 drug classes lower LDL-C levels by up-regulation of the LDL receptor secondary to hepatic intracellular cholesterol depletion. Thus, ezetimibe is unlikely to have an off-target effect.

A more recent CIMT lipid-lowering trial with a statin alone or in combination with ezetimibe has been reported. The open-label, post hoc SANDS (Stop Atherosclerosis in Native Diabetics Study) aggressively treated patients to a LDL-C target of 70 mg/dL or lower with either high-dose statin or low-dose statin plus ezetimibe; this trial found a significant difference ($P<.0001$) in CIMT compared with those treated with low-dose statins to LDL-C levels of 100 mg/dL or lower.[19] Evidence from the 2 studies involving ezetimibe, ENHANCE (which had numerous design flaws) and SANDS (a small post hoc substudy), certainly shows no harm or trend to harm in CVD events, and both suggest a benefit associated with continued use of the drug, consistent with the well-proven LDL-C hypothesis. In response to any concerns that may have arisen on how to proceed in clinical practice, the Food and Drug Administration recently issued a statement[20] after extensive review of the ENHANCE study, reporting, in part, "Based on current available data, patients should not stop taking Vytorin or other cholesterol-lowering medications." The definitive IMPROVE-IT[21] (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), randomizing 18,000 patients with acute coronary syndrome and comparing simvastatin with or without ezetimibe, is currently under way with completion planned for 2012. The study will determine whether an LDL-C level of approximately 50

mg/dL with the combination of ezetimibe and simvastatin can reduce CVD events compared with an LDL-C level of approximately 70 mg/dL with simvastatin alone.

However, the controversy surrounding ezetimibe serves as a reminder to those focused on preventing CVD that, despite overwhelming evidence, the LDL-C hypothesis and "lower is better" are still not universally accepted. Although statins undoubtedly have antiatherosclerotic benefits, the idea of conferring pleotropic effects to statins vs reducing LDL-C levels distracts many clinicians from following current guidelines and aggressively lowering LDL-C levels. Thus far, LDL-C, or its closely associated components such as apolipoprotein B, remains the most specific and modifiable biomarker for reducing coronary heart disease, irrespective of the status of the patient's risk. Statin therapy, as low as $5 a month[22] for any dose of generic simvastatin, should therefore remain the cornerstone treatment for preventing CVD. This low price for a 40% to 45% reduction in LDL-C levels makes primary prevention, even in low-risk patients, cost-effective. Clinicians have the option, at essentially no added financial burden to patients, of dose titration to higher and more aggressive doses to achieve the appropriate LDL-C goals. However, doubling a statin dose only reduces LDL-C levels an average of 6%, and the potential for increased adverse events with higher statin doses makes clinicians reluctant to use the highest doses of any statin. Thus, combined therapy with other medications known to enhance LDL-C reduction (eg, ezetimibe, bile acid sequestrants, and niacin) remains an important option in clinical practice.

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