Editorial

Are Lower Levels of LDL-Cholesterol Really Better? Looking at the Results of IMPROVE-IT: Opinions of Three Experts – III

Theodosios D. Filippatos, Moses S. Elisaf

Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece

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Address:
Moses S. Elisaf

Department of Internal Medicine
Medical School,
University of Ioannina
45110 Ioannina, Greece
egepi@cc.uoi.gr

Cardiovascular disease (CVD) is one of the major causes of morbidity and mortality in developed countries. Current guidelines for primary or secondary CVD prevention focus on the reduction of low-density lipoprotein cholesterol (LDL-C) levels as the primary strategy for reducing CVD risk, based on the results of many randomized, placebo-controlled statin studies that have shown a significant CVD risk reduction with the use of statins.[1,2] However, it is now established that patients receiving statin treatment are still at risk for CVD events. Two meta-analyses of statin trials showed that one in seven treated patients experienced CVD events over a follow-up period of five years.[2,3] It is obvious that more aggressive treatment is needed to further reduce CVD events in patients on statin treatment.

Previous trials with the addition of niacin or cholesteryl-ester transfer protein (CETP) inhibitors to statin treatment did not demonstrate a clinical benefit in patients with low LDL-C levels.[4-6] Furthermore, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid study the addition of fenofibrate to simvastatin treatment resulted in a possible reduction of CVD events only in the subgroup of diabetic patients with high triglyceride and low high-density lipoprotein cholesterol levels.[7] These observations have brought into question the clinical benefit of hypolipidemic treatments other than statins in patients with high CVD risk. Based on these results, the recent guidelines of the American College of Cardiology/American Heart Association have emphasized the use of intensive statin therapy in patients with high CVD risk.[8]

A meta-analysis of data from 170,000 participants showed that further reductions in LDL-C concentration, below current targets, led to further reductions in vascular events.[9] This finding has led to the concept that aggressive lowering of LDL-C concentration below current targets will benefit patients with high CVD risk. Additionally, evidence from epidemiological studies supports the hypothesis that a reduction in CVD events via the lowering of LDL-C concentration may be expected, regardless of the chosen hypolipidemic treatment. However, until now evidence from trials to support these concepts was lacking.

Ezetimibe is a hypolipidemic drug that reduces intestinal cholesterol absorption by inhibiting Niemann-Pick C1-like 1 (NPC_1L_1) protein, which is located primarily on the epithelial brush border of the gastrointestinal tract. A recent study sequenced the exons of NPC_1L_1 in 7364 patients with coronary heart dis-

ease (CHD) and in 14,728 controls without CHD and identified carriers of inactivating mutations.[10] Additionally the study genotyped a specific inactivating mutation (p.Arg406x) in 22,590 patients with CHD and in 68,412 controls. It was shown that one in every 650 persons was a heterozygous carrier for one of the 15 distinct NPC_1L_1 inactivating mutations. Heterozygous carriers had reduced LDL-C levels compared with non-carriers (-12 mg/dL, p=0.04). Notably, it was shown that carrier status was associated with a reduced CHD risk (odds ratio 0.47, 95% confidence interval 0.25-0.87, p=0.008).[10] These observations show that inactivating NPC_1L_1 mutations are related to a decreased risk of CHD and provide evidence that a naturally occuring LDL-C lowering mechanism leads to reduced CHD risk.

The addition of ezetimibe to statin treatment has been shown to further reduce LDL-C concentration by approximately 20%.[11] The large randomized IMPROVE-IT trial evaluated the clinical efficacy of the combination of ezetimibe with simvastatin in 18,144 patients (mean age 64 years) who were hospitalized for ST-elevation myocardial infarction (STEMI) or non-STEMI/unstable angina and had LDL-C levels of 50-125 mg/dL (50-100 mg/dL if receiving lipid-lowering treatment).[12] At baseline, mean LDL-C levels were approximately 95 mg/dL and after one year they were reduced to 69.9 mg/dL with simvastatin 40 mg and to 53.2 mg/dL with the combination of ezetimibe and simvastatin. During the seven-year follow up, the mean LDL-C concentration was 53.7 mg/dL with ezetimibe+simvastatin and 69.5 mg/dL with simvastatin monotherapy (p<0.05). A significant reduction in the occurrence of the primary endpoint (cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization or stroke) was observed in the ezetimibe+simvastatin combination group compared with simvastatin monotherapy. Specifically, the primary endpoint occurred in 34.7% of patients receiving simvastatin monotherapy and in 32.7% of patients receiving the ezetimibe+simvastatin combination (hazard ratio 0.936, 95% CI 0.887-0.996, p=0.016). Three secondary endpoints, including the combination of all-cause death, MI, unstable angina and coronary revascularization, were also significantly reduced with the combination of ezetimibe+simvastatin compared with simvastatin monotherapy (p<0.05). Regarding the individual endpoints, myocardial infarction (hazard ratio 0.87), ischemic stroke (hazard ratio 0.79), and the combination of CVD death, myocardial infarction and stroke (hazard ratio 0.90) were also significantly reduced with the ezetimibe+simvastatin combination (p<0.05). Moreover, the further reduction in LDL-C concentration with the ezetimibe+simvastatin combination was not associated with any significant increase in cancer, or muscle- or gallbladder-related events.

The results of IMPROVE-IT show an incremental clinical benefit when a non-statin agent (ezetimibe) is added to statin therapy, resulting in a further reduction of LDL-C levels. Furthermore, these results clearly show that "lower is better" regarding LDL-C levels, at least in patients with a high CVD risk. Generally, the results of genetic analyses with NPC_1L_1-inactivating mutations and those of the IMPROVE-IT trial confirm the LDL hypothesis, meaning that a reduction in LDL-C concentration prevents cardiovascular events, independently of the LDL-C-reducing strategy.

Disclosure

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