JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 69, NO. 5, 2017

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.11.036

EDITORIAL COMMENT

Low-Density Lipoprotein Cholesterol and the On-Target Effects of Therapy

How Low Is Too Low?*

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Reducing low-density lipoprotein cholesterol (LDL-C) is the cornerstone of cardiovascular disease prevention. The widespread use of statin therapy for LDL-C reduction is believed to underlie important changes in the incidence, prevalence, and mortality associated with myocardial infarction and cardiovascular disease in the parts of the world where the drugs are widely available and widely used. Indeed, the cardiovascular benefits of statin therapy so substantially outweigh the risks that statins have largely replaced aspirin as the "go to" therapy for the primary prevention of cardiovascular events.

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For most patients, high-intensity statin therapy can lead to substantial reductions in LDL-C, but on-treatment LDL-C concentrations are almost always higher than 25 mg/dl, even when patients with relatively low LDL-C concentrations at baseline take high-intensity statins (1). The advent of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, however, has meant that reducing LDL-C concentrations to <25 mg/dl is feasible in a significant minority of patients. Because cholesterol plays an important role in human physiology, there has been concern that maintaining LDL-C concentrations at very low levels may have direct adverse consequences.

In this issue of the *Journal*, Robinson et al. (2) present a detailed look at the adverse effects of alirocumab collected in the 14 randomized trials included in the ODYSSEY phase 2 and 3 development program. The investigators compared alirocumab-treated patients who achieved LDL-C <25 or <15 mg/dl with alirocumab-treated patients with LDL-C ≥25 mg/dl, as well as those on placebo. Approximately 25% of subjects achieved LDL-C <25 mg/dl, and 9% achieved LDL-C <15 mg/dl. In the whole development program, there were 4,029 patient-years of exposure to alirocumab, compared with 2,114 patient-years of exposure to placebo or ezetimibe. Although the exact number of patient-years of follow-up for patients with LDL-C <25 or <15 mg/dl is not detailed in the paper, the investigators make some important and clinically relevant observations about the safety of very low LDL-C.

First, the incidence of cataracts was 2.0 per 100 patient-years among those with LDL-C <25 mg/dl, compared with 0.6 per 100 patient-years for those with LDL-C ≥25 mg/dl, a finding that remained statistically significant after adjusting for the propensity to achieve LDL-C <25 mg/dl (hazard ratio: 3.4; 95% confidence interval: 1.6 to 7.4; $p = 0.0018$). As the investigators note, these results are consistent with the results from the recently published HOPE 3 (Heart Outcomes Prevention Evaluation 3) trial, in which patients randomly allocated to rosuvastatin 10 mg/day had a significantly higher rate of cataract surgery (3.8% vs. 3.1%; $p = 0.02$) (3). Although the pathophysiologic mechanism for this relationship is not clear, older studies have noted that the ocular lens must synthesize cholesterol locally to maintain lens structure and clarity and that genetic defects in cholesterol metabolism can lead to cataracts (4). The possibility that potent inhibitors to cholesterol synthesis might lead to cataract formation was noted in

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humans during early trials of lovastatin (5). However, the mechanisms by which very low plasma LDL-C concentrations induced by the combination of statin therapy and PCSK9 inhibitors might alter local lens cholesterol biosynthesis are not clear.

Statins accelerate the progression to diabetes among those who are at risk for, but do not have, diabetes at baseline (6,7). Because the association between statin use and type 2 diabetes was first observed in JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), it has been replicated in trials comparing statins with placebo and in trials comparing more intense with less intense statins (6,8,9). Genetic studies have reported that common variants in PCSK9 and 3-hydroxy-3-methylglutaryl-CoA reductase that are associated with lower LDL-C are also related to an increased risk for type 2 diabetes (10,11). These findings raise the possibility that the effects of statins and PCSK9 inhibitors on diabetes may be biologically intertwined with the LDL-C-reducing effects of the medications (12).

In the ODYSSEY program, among those without diabetes at baseline, the incidence of diabetes or complications of diabetes was higher among those with LDL-C <25 versus ≥25 mg/dl (1.8 vs. 1.4 per 100 patient-years, respectively). Although the higher rate among patients with LDL-C <25 mg/dl may be due to confounding, the investigators do not present a propensity-adjusted risk estimate for the occurrence of diabetes or its complications among those without diabetes at baseline, so we cannot be sure. Of note, no relationship between alirocumab and type 2 diabetes among those with pre-diabetes was noted in a recently published report from the ODYSSEY program, although the results were not stratified by achieved LDL-C (13).

Finally, there has been particular interest in the neurocognitive effects of very low LDL-C. Recently published results from the OSLER (Open Label Study of Long Term Evaluation Against LDL-C) development program for evolocumab reported a rate of neurocognitive adverse events that was 3 times higher in the active than placebo arm (14). In the ODYSSEY LONG TERM (Long-Term Safety and Tolerability of Alirocumab [SAR236553/REGN727] Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia) results, which include a subset of the patients in this work, neurocognitive adverse effects were seen in 18 of 1,550 patients (1.2%) in the alirocumab arm and 4 of 788 (0.5%) in the placebo arm ($p = 0.17$) (15). In the data published here, no significant differences in the rate of neurocognitive effects between alirocumab and placebo or ezetimibe, or across different achieved LDL-C concentrations, were seen (2). These data are encouraging, but longer term follow-up with more total patient-years of observation, as well as structured (rather than spontaneous) collection of this class of adverse events is required to be certain of the neurocognitive safety of very low LDL-C concentrations.

The data from the ODYSSEY program represent an important first step in understanding the risks of achieving very low LDL-C concentrations with this novel class of medications. In 2007, the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial (10), with 4,001 patient-years of follow-up, reported an increased risk for cancer with ezetimibe therapy. As is the case for alirocumab today, ezetimibe was approved for LDL-C reduction but had not yet been shown to reduce cardiovascular events. Luckily, investigators were quickly able to determine that ezetimibe was not associated with an increased risk for cancer by analyzing data from 2 other clinical trials with a total of more than 18,000 patient-years of follow-up (12). Compared with that experience with ezetimibe, alirocumab seems reassuringly safe, although understanding the possible "on-target" physiological effects of lowering LDL-C to <25 or <15 mg/dl will require more patients to receive the drug, each for a more extended period of time. In that context, the data presented here, although reassuring, represent only the beginning of our understanding of the safety of this novel class of medications. The ongoing cardiovascular endpoint trials of alirocumab should provide not only a sense of the true cardiovascular benefit of these drugs but also a more accurate and nuanced understanding of their risks.

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KEY WORDS adverse effects, LDL cholesterol, lipids, PCSK9 inhibitors