Correspondence

Response to Letter Regarding Article, "Achievement of Dual Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein Targets More Frequent With the Addition of Ezetimibe to Simvastatin and Associated With Better Outcomes in IMPROVE-IT"

In response to Dr Robinson, we have made clear throughout our article that the data presented are observational and therefore support the idea that low low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein levels are associated with low rates of cardiovascular events.[1] Given the observational nature of the present analysis, limitations exist, which have been acknowledged in our article and in the editorial.

With regard to our observation that lower on-treatment high-sensitivity C-reactive protein levels are associated with lower residual risk, we note that the data from IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) are directionally consistent with prior data from the Cholesterol and Recurrent Events (CARE), Air Force Coronary Arteriosclerosis Prevention Study (AFCAPS)/Texas Coronary Atherosclerosis Prevention Study (TexCAPS), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT-TIMI 22), Aggrastat-to-Zocor (A-to-Z), and Justification for the Use of Statins in the Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trials.[2]

Dr Robinson (and the 2013 American College of Cardiology/American Heart Association cholesterol guideline) claims that there has not been a trial of "treat to target" to support the concept that lower LDL reduces cardiovascular events. The objection appears to be a lack of trials designed specifically to treat each patient to a target of <X mg/dL, as has been recommended in the prior National Cholesterol Education Program (and most other) guidelines.[3]

However, the IMPROVE-IT trial was prospectively designed to compare, in a randomized fashion, 2 groups with a mean LDL-C that we estimated to be on average ≈50 and 65 mg/dL and thus to explore if "even lower is even better."[4] The mean LDL-C levels at 1 year in the 2 groups were very close to our estimate: 53.2 versus 69.9 mg/dL. However, the medians and interquartile range more fully describe the groups: The simvastatin group had a median LDL-C of 67 mg/dL and an interquartile range of 55.0 to 81.0 mg/dL, and the ezetimibe/simvastatin group had a median of 50.0 mg/dL and an interquartile range of 39.0 to 62.0 mg/dL. Thus, in simpler terms, IMPROVE-IT found, in a randomized comparison, that a 2-drug regimen that achieved an LDL-C range of ≈40 to 60 mg/dL had significantly fewer cardiovascular events than the statin-only strategy that achieved an LDL-C level of ≈55 to 80 mg/dL. The consistent nature of the ezetimibe effect on events in IMPROVE-IT compared with the effect of statins observed in the Cholesterol Treatment Trialists (CTT) meta-analyses supports the comparison of these 2 treatment regimens in this manner. Thus, the trial does provide randomized data to demonstrate the clinical benefit of lower LDL-C levels. Therefore, a guideline committee could incorporate these data and propose titrating a patient to a target range (as in previous US and current non-US guidelines). In this case, we believe a range of between 40 and 60 mg/dL is supported by our data.

Disclosures

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