CORRESPONDENCE

Ezetimibe plus a Statin after Acute Coronary Syndromes

TO THE EDITOR: With regard to the article by Cannon et al. (June 18 issue),[1] human serum cholesterol derives from two sources: it is either synthesized endogenously or absorbed in the intestine. Statins inhibit endogenous cholesterol synthesis, whereas ezetimibe inhibits intestinal cholesterol absorption.[2] According to findings from the Scandinavian Simvastatin Survival Study[3] and the German Diabetes and Dialysis Study,[4] patients with a high level of cholesterol absorption may receive less benefit from statin therapy than those with a low level of cholesterol absorption. However, patients with elevated absorption may particularly benefit from the addition of ezetimibe to a statin regimen.[2]

Patients with elevated intestinal cholesterol absorption can be identified with genetic testing for risk alleles in the ATP-binding cassette transporters G5 and G8 (*ABCG5/8*), Niemann–Pick C1–like 1 (*NPC1L1*), and *ABO* genes.[5,6] It remains to be investigated whether these alleles will predict whether statins will be less effective in reducing cardiovascular risk in patients harboring them than in those not harboring them. If so, testing for these alleles in addition to measuring low-density lipoprotein (LDL) cholesterol levels may be helpful in deciding when to add ezetimibe treatment to ongoing statin therapy. This would be an approach toward personalized prevention of cardiovascular disease.

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TO THE EDITOR: We discussed the article by Cannon et al. in a meeting of our internal medicine department. The rate of the primary end point was 2 percentage points lower in the simvastatin–

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ezetimibe group than in the simvastatin-monotherapy group, and the overall mortality was similar in the two groups. Of note, 42% of the participants in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), regardless of treatment assignment, discontinued the study medication prematurely.

We would like to know whether the authors conducted a per-protocol analysis, and in particular, whether there was a difference between patients who were adherent to therapy and those who were not, both within and between the assigned treatment groups, with respect to both the primary end point and mortality. It would also be interesting to know the mean LDL levels in these patients. These results could lead to a better understanding of the "lower is better" LDL hypothesis.

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TO THE EDITOR: IMPROVE-IT has aroused much enthusiasm among advocates of the concept of "lower is better," and it will undoubtedly rekindle arguments in favor of targets for LDL cholesterol levels. Although these findings make a valuable contribution to this field, the benefit of ezetimibe in this trial does not prove that the effect was mediated by the lowering of LDL cholesterol levels, nor does it provide support for the so-called LDL hypothesis (i.e., that lowering the LDL cholesterol level results in a reduction in cardiovascular events). In fact, some studies have suggested that ezetimibe may have pleiotropic effects, including amelioration of insulin resistance and antioxidant and antiinflammatory properties.[1] Furthermore, ezetimibe has been shown to have antiplatelet and antithrombotic effects that are independent of its effect on LDL cholesterol levels in patients with stable coronary artery disease.[2] These pleiotropic effects may account for at least some of the benefit of ezetimibe in further lowering the risk of cardiovascular events.

The article by Cannon and colleagues appears to offer support for this ezetimibe hypothesis, since levels of high-sensitivity C-reactive protein were significantly lower in the simvastatin–ezetimibe group than in the simvastatin-monotherapy group, and both groups consisted of patients with atherosclerotic vascular disease. Such a reduction has been shown to be independent of changes in LDL cholesterol levels.[3]

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TO THE EDITOR: The patients in IMPROVE-IT had a higher baseline risk profile than that in patients in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT–TIMI 22) study,[1] but in the IMPROVE-IT study, the incidence of cardiovascular events at 2 years was lower (19.0%, vs. 26.5%). This observation may reflect advances in the past decade in therapeutic strategies and risk-factor control after an acute coronary syndrome; it also strengthens the clinical relevance of the absolute risk reduction afforded in IMPROVE-IT by the combination of ezetimibe plus simvastatin versus simvastatin alone, since it was obtained in an overall better-treated population.

In this trial, there was an absolute reduction of 5.5 percentage points in the primary end point at 7 years with ezetimibe plus simvastatin in patients with diabetes, as compared with 0.7 percentage points in those without diabetes. Given the specific prognostic role of triglycerides in patients with diabetes,[2,3] the greater decrease in triglyceride levels at 1 year with the combination of ezetimibe plus simvastatin (to 120 mg per deciliter [1.4 mmol per liter] vs. 137 mg per deciliter [1.5 mmol per liter] in the simvastatin-monotherapy group) might in part explain this difference in outcome. Specific analyses of the data on individual participants in the trial may help in answering this question.

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TO THE EDITOR: The trial reported in the article by Cannon et al. on the effects of the combination of simvastatin and ezetimibe in patients with a previous acute coronary syndrome is a landmark study, since a clear effect on the primary end point (which includes several cardiovascular end points) was reached with a nonstatin drug that was used in addition to a statin. However, this article shows, once again, that intensive lowering of LDL cholesterol levels (in this study, with simvastatin–ezetimibe) as compared with less intensive statin therapy, although useful from the standpoint of cardiovascular disease, does not lead to a decrease in mortality.[1] This LDL-cholesterol mortality paradox, as shown in Figure 1, is a reproducible phenomenon, and the article by Cannon et al. provides further strong support for the concept. In IMPROVE-IT, lowering LDL cholesterol levels with intensive lowering of LDL cholesterol levels, as compared with the alternative therapy, did not decrease total mortality or cardiovascular mortality. This could mean that the cardiovascular events that were prevented were not severe enough to lead to the death of patients.

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TO THE EDITOR: IMPROVE-IT is interesting because it shows the difference between statistical significance and clinical relevance. In the trial, the addition of ezetimibe to simvastatin in patients with a recent acute coronary event was associated with a statistically significant reduction in the occurrence of a composite end point of death from cardiovascular disease, a major coronary

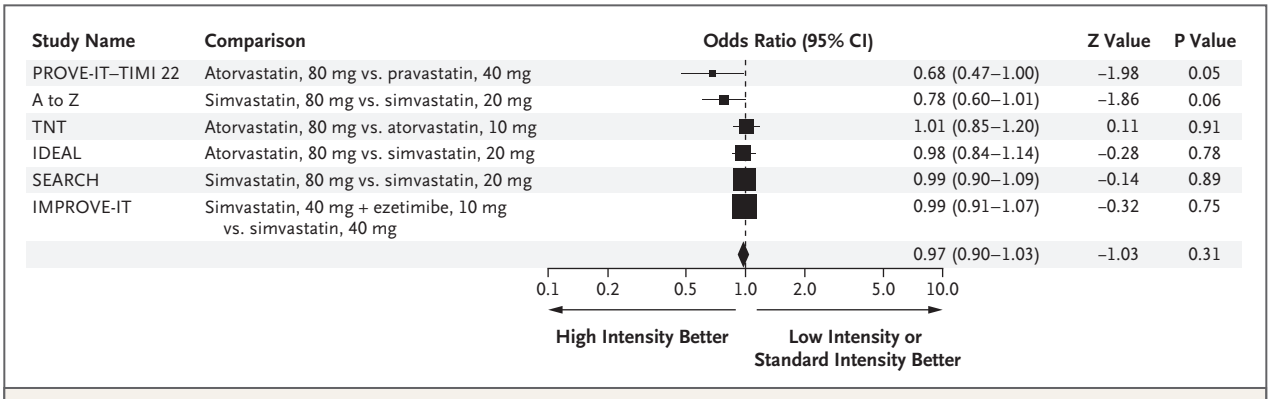

Figure 1. Odds Ratios for Mortality, According to Treatment for Cardiovascular Disease in Six Major Trials.

The meta-analysis was performed with the use of Comprehensive Meta-Analysis software, version 2.0 (Biostat). A random-effects analysis was carried out because of the heterogeneity of the data. The size of the squares corresponds to the number of patients with an event. A to Z denotes Aggrastat to Zocor, CI confidence interval, IDEAL Incremental Decrease in End Points through Aggressive Lipid Lowering, IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial, PROVE-IT–TIMI 22 Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22, SEARCH Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, and TNT Treating to New Targets. Data are from the studies listed in Nunes[1] as well as from the article by Cannon et al.

event, or nonfatal stroke after 7 years. However, the relative risk reduction was only 6%. Figure 2 of the article by Cannon et al. shows that this difference is one of the smallest effects ever observed in statin trials, even among three negative studies.[1-3] The authors also did not mention the discordant findings of the ezetimibe-based Simvastatin and Ezetimibe in Aortic Stenosis study.[4]

To show such a small difference, the investigators had to include more than 18,000 patients with a very high baseline risk (35% for the primary outcome and 15% for death), although the number of patients screened for inclusion is not available. Even in these specific conditions, the absolute risk reduction was only 2 percentage points for the primary outcome and zero for death. We conclude that the addition of ezetimibe to simvastatin has little effect on cardiovascular risk and that this effect may be partly attributable to a highly selected patient population.

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TO THE EDITOR: IMPROVE-IT shows that simvastatin–ezetimibe combination therapy is superior to simvastatin monotherapy in lowering LDL cholesterol levels and decreasing cardiovascular risk among patients after myocardial infarction. The authors also point out that lowering LDL cholesterol levels below current target levels provides additional benefit. This statement was supported by the accompanying editorial,[1] which suggests that all reductions in LDL cholesterol levels, regardless of whether they are from ezetimibe or statins, are of equivalent benefit. However, an alternative approach is the use of high-potency statins, as guidelines suggest.[2]

Our group previously compared the use of simvastatin monotherapy with simvastatin–ezetimibe combination therapy and with high-potency statins in 10,000 patients in the United Kingdom after myocardial infarction.[3] We found a trend toward lower mortality when simvastatin–ezetimibe combination therapy was compared with simvastatin monotherapy (hazard ratio, 0.93; 95% confidence interval [CI], 0.62 to 1.38). However, when high-potency statin therapy was compared with simvastatin monotherapy, there was an even greater reduction in mortality of 33% (hazard ratio, 0.67; 95% CI, 0.54 to 0.81); this effect was achieved with only modest average doses of atorvastatin (35 mg per day) and rosuvastatin (13 mg per day).

The adverse effects of statins are probably dose-related.[4] Thus, we suggest that switching to a low-dose, high-potency statin be considered before adding a nonstatin agent.

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THE AUTHORS REPLY: In response to Silbernagel and colleagues: data on the response to treat-

ment with ezetimibe with respect to levels of LDL cholesterol have been very consistent across broad subgroups.[1] Our analyses of serum samples are ongoing to test the hypothesis that patients with elevated intestinal cholesterol absorption have an enhanced response to ezetimibe, although one smaller prospective study did not provide support for this concept.[2]

In response to Couture et al.: an average of 7% of patients per year discontinued the study drug; this rate is consistent with what has been observed in other long-term trials involving patients with cardiovascular and acute coronary syndromes. We conducted an on-treatment analysis that was presented by Blazing[3] at the scientific sessions of the American Heart Association in 2014. As would be anticipated, the benefit of ezetimibe was greater across all the primary and secondary end points in this analysis.

Egom describes potential pleiotropic effects of ezetimibe. As we mentioned in the Discussion section of our article, we cannot determine whether, or to what degree, the clinical benefit seen when ezetimibe was added to simvastatin in IMPROVE-IT was mediated solely by the lowering of LDL cholesterol levels or to effects on high-sensitivity C-reactive protein, other lipoproteins such as triglycerides (as noted by Patti and Cavallari), or other potential pleiotropic effects. Given the quite striking concurrence of the IMPROVE-IT results with those of the Cholesterol Treatment Trialists meta-analysis (Fig. 2 of our article), we infer that the dominant effect of ezetimibe relates to lowering LDL cholesterol levels. The findings of recent genetic studies in which patients with polymorphisms of *NPC1L1* have both lower LDL cholesterol levels and a lower risk of coronary heart disease[4,5] support this view.

Nunes noted a lack of an effect of ezetimibe on all-cause mortality. We were not surprised, since the size of our trial was not established to detect such an effect (which would have required approximately 40,000 patients). The degree of lowering of LDL cholesterol levels, by design, was smaller in IMPROVE-IT than in placebo-controlled statin trials, only a minority of which showed such a mortality benefit. Nonetheless, the significant 13% relative reduction in the incidence of myocardial infarction and the 21% relative reduction in the incidence of ischemic stroke are important clinical benefits associated with adding ezetimibe to a statin.

In response to the comment of Richard and colleagues: a key finding of our trial is that the clinical benefit is proportional to the extent of lowering of LDL cholesterol levels. We studied patients in whom the LDL cholesterol level while receiving a statin was "at goal" (<70 mg per deciliter [1.8 mmol per liter] on average) in order to explore whether an additional benefit could be seen with an LDL cholesterol level of approximately 55 mg per deciliter (1.4 mmol per liter) or less; thus, the difference in LDL cholesterol levels was modest. Patients with higher baseline LDL cholesterol levels would be expected to have a greater decrease in LDL cholesterol levels and a greater associated benefit.

Regarding the observational data from the registries cited by Singh et al., these data are hard to interpret because of confounding. As such, we prefer to look to randomized trials for treatment effects.

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Since publication of their article, the authors report no further potential conflict of interest.

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