Circulation

LETTER TO THE EDITOR

Letter by Donzelli et al Regarding Article, "Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)"

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To the Editor:

The authors[1] conclude that "in IMPROVE-IT the benefit of adding ezetimibe to statin was enhanced in patients with DM and in high-risk nondiabetics" (in other words "≥75 years-old"). Conversely, the analysis shows (Figure III in the online-only Data Supplement) that, in patients <75 years without diabetes mellitus, all the efficacy of composite end points was in tendency worse (or indifferent) in the ezetimibe group: primary end point hazard ratio, 1.02; secondary end point I, 1.00; secondary end point II, 1.02; secondary end point III, 1.03; and tertiary end point, 1.02.

It is notable that patients ≥75 years, although showing more favorable end points in the ezetimibe/simvastatin group versus the simvastatin monotherapy group, are the age group with low evidence from randomized controlled trials to support the initiation of statin therapy in primary prevention, and even the initiation of high-intensity statin therapy in secondary prevention.[2]

Diabetics patients, however, show a disturbing tendency to accumulate more deaths at 7 years (Table IV in the online-only Data Supplement)[1]: for cardiovascular deaths, Kaplan-Meier event rates were indeed 11.15% with simvastatin alone and 11.68% with ezetimibe/simvastatin; any deaths were 21.79% with simvastatin alone and 23.46% with ezetimibe/simvastatin. Therefore, a completely informed patient would face a dilemma. On the one hand, he or she can expect a significant reduction of myocardial infarction (0.76; 95% CI, 0.66–0.88), stroke (0.73; 0.56–0.95), and composite primary end points (0.85; 0.78–0.94). On the other hand, a nonsignificant increase of hospitalization for unstable angina (1.04; 0.72–1.52) and a possible nonsignificant increase of cardiovascular deaths and all-cause deaths can be expected. Simvastatin alone (without ezetimibe) might offer a slightly better chance to be alive at 7 years.

The inconsistency of the nonfatal and fatal end points should be emphasized and caution interpretation of softer end points, in this and in all randomized controlled trials. An obvious interpretation is that such nonfatal end points could not be very serious, if neither the all-cause mortality nor even the cardiovascular mortality shows a significant difference; rather, they tend to go in in the unwanted direction.

Undoubtedly, the outcome least subject to bias is all-cause mortality, and in 5 previous randomized comparisons such an outcome has always counted some more deaths in ezetimibe/simvastatin than in the simvastatin-only or the placebo comparators.[3]

In the patients at very high risk in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)[4] there was no inconsistency between cardiovascular mortality and all-cause mortality (both showed no benefit). Instead, in the Cholesterol Treatment Trialists' meta-analysis,[5] the cardiovascular mortality of patients at low risk appeared decreased, whereas the noncardiovascular mortality increased. Indeed, Figure 3 of this seminal meta-analysis[5] reported that participants without car-

*The views expressed by Dr Donzelli are his own and do not necessarily represent those of his organization.

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diovascular diseases with a baseline 5-year risk of major vascular events <5% had 31+98 vascular+nonvascular deaths with statins, and 40+87 deaths, respectively, in the control groups, with a similar (and balanced for other features) overall number of participants.

These analyses require a careful report of a sum of the serious adverse events that capture overall mortality and all serious morbidity including major vascular events. Only if serious adverse events also include the major vascular events selected as trial end points, can one achieve a fair balance of the outcomes and evaluate if a cholesterol-lowering treatment is worthwhile. Unfortunately, many trials omit these data, or adopt a serious adverse events reporting limited to the commonly accepted adverse effects of cholesterol-lowering drugs.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, Park JG, White JA, Bohula E, Braunwald E; on behalf of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2018;137:1571–1582.
2. Stone NJ, Robinson J, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S1–S45.
3. Donzelli A, Battaggia A. The efficacy of ezetimibe does not seem a credible real effect. *Intern J Cardiol*. 2016;222:795–796.
4. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489
5. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590.