COMMENT ON ITOH ET AL.

Intensive Treat-to-Target Statin Therapy in High-Risk Japanese Patients With Hypercholesterolemia and Diabetic Retinopathy: Report of a Randomized Study. Diabetes Care 2018;41:1275–1284

Alberto Donzelli,[1] *Alessandro Schivalocchi,*[2] *Giulia Giudicatti,*[2] *and Alessandro Battaggia*[3]

Diabetes Care 2018;41:e143–e144 | https://doi.org/10.2337/dc18-1358

The commercially funded randomized study by Itoh et al. (1), comparing treat-to-target approaches in patients with diabetic retinopathy with hypercholesterolemia (baseline LDL cholesterol [LDL-C] ~106 mg/dL), "found no significant decrease in CV [cardiovascular] events or CV-associated deaths with intensive therapy." The authors speculated about a nonsignificant decrease "possibly because the between-group difference of LDL-C was lower than expected (27.7 mg/dL at 36 months of treatment)." The intensive statin therapy targeted LDL-C <70 mg/dL, while the standard one targeted 100–120 mg/dL.

The primary outcome, a composite of CV events, tended to occur less often in the intensive group: in 129 patients versus 153 in the standard group (hazard ratio [HR] 0.84, 95% CI 0.67–1.07). An exploratory finding also showed fewer cerebral events (HR 0.52, 0.31–0.88; $P = 0.01$). However, a Yekutieli correction for multiple comparisons shows that none of the results reach the cutoff for statistical significance ($P = 0.00437956$). Moreover, "fewer cerebral events" may lead one to think "fewer strokes," but the article's Supplementary Table 3*A* and *B* (1) show that cerebral events included only cerebral infarction (not cerebral or subarachnoid hemorrhage) and revascularization. Instead, the difference in total strokes, including the hemorrhagic ones, is not statistically significant (HR 0.64, 0.40–1.01), even without correction for multiple comparisons.

Moreover, and disappointingly, all-cause deaths tended to increase in the intensive group (41 vs. 34; HR 1.21, 95% CI 0.77–1.91), as did serious adverse drug reactions (41 vs. 28), and it is doubtful whether a fully informed patient would choose an intensive cholesterol-lowering therapy to prevent 24 CV events at the price of an excess of 13 serious adverse drug reactions and 7 deaths.

This is not the first randomized controlled trial in which CV events and mortality diverge. For example, the Japan Lipid Intervention Trial (J-LIT) (2), with 47,294 hypercholesterolemic patients treated with simvastatin 5–10 mg/day followed for 6 years showed a J-curve association between LDL-C and total mortality. The mortality nadir was between in-treatment average LDL-C 120 and 129 mg/dL; the large subgroup between 80 and 119 mg/dL showed a clear tendency to harm, and the subgroup <80 mg/dL a significant mortality excess (relative risk 1.72, 95% CI 1.17–2.53).

However, the seriousness of many CV events is debatable, because they are not associated with fewer deaths, as expected, but with more. A possible interpretation of this inconsistency is that events such as coronary revascularization, nonfatal myocardial infarction, and nonfatal ischemic stroke can be "discretionary" to some extent. Loss of blinding to treatment allocation probably occurs in lipid-lowering trials because drugs predictably lower LDL-C and physicians managing the patients over time become aware of lipid values. Loss of blinding might bias decisions about revascularizations, resulting in more procedures (and some more periprocedural infarctions) in less intensively treated patients (3).

This could lead also to greater recourse to electrocardiograms, computed tomography scans, and MRIs, resulting in finding more silent myocardial infactions or strokes in the less intensively treated. The outcome least subject to bias is all-cause mortality.

Consistently, the claimed enhanced CV benefits (without any mortality reduction) of adding ezetimibe to statin in patients with diabetes and in seniors (4) could merely be due to the increased incidence and prevalence of CV events in those with diabetes and the elderly and to the consequent objective overdiagnosis in these subgroups (5).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

[1]*Unit of Appropriateness in Primary Care, Health Protection Agency, Metropolitan City of Milan, Italy*
[2]*Hygiene, Public Health and Preventive Medicine, University of Milan-Bicocca, Milan, Italy*
[3]*Unità Locale Socio-Sanitaria 20, Verona, Italy*

Corresponding author: Alberto Donzelli, adonzelli@ats-milano.it.

The views expressed by A.D. are his own and do not necessarily represent those of his organization.

References

1. Itoh H, Komuro I, Takeuchi M, et al.; EMPATHY Investigators. Intensive treat-to-target statin therapy in high-risk Japanese patients with hypercholesterolemia and diabetic retinopathy: report of a randomized study. Diabetes Care 2018;41:1275–1284

2. Matsuzaki M, Kita T, Mabuchi H, et al.; J-LIT Study Group. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia. Circ J 2002;66:1087–1095

3. Alberto D, Alessandro B. The efficacy of ezetimibe does not seem a credible real effect. Int J Cardiol 2016;222:795–796

4. Giugliano RP, Cannon CP, Blazing MA, et al.; IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of adding ezetimibe to statin on cardiovascular outcomes and safety in patients with vs. without diabetes: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation 2018;137:1571–1582

5. Donzelli A, Schivalocchi A, Giudicatti G. Ezetimibe in diabetics: why all-cause mortality does not improve at all? Circulation. In press