RESPONSE TO 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

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Diabetes Care 2018;41:e145–e146 | https://doi.org/10.2337/dci18-0028

We thank Donzelli et al. (1) for their interest in our article (2). The report of the EMPATHY study (2) showed no significant difference between the intensive group and the standard group for the primary end point, but the difference was significant for cerebral events, which was one of the secondary end points. Our study did not adjust for multiplicity of secondary end points. We thus agree with the authors of the letter (1) that these results do not provide substantial evidence that aggressive LDL cholesterol (LDL-C)–lowering therapy prevents cerebral events. This is why we identified our investigation of cerebral events as an exploratory analysis.

Our study focused particularly on the assessment of effects of stains on atherosclerotic events. Thus, we established the secondary end point of stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage) and assessed the data within that context. We believe that our findings support those of previous studies (3) that statins do not contribute to increases in hemorrhagic stroke.

Just as for the primary end point, we found no statistically significant difference in deaths from any cause or in serious adverse drug reactions between the intensive and standard treatment groups. Because we did not find statistical significance, we feel that it is probably premature to discuss risks and benefits from our current data based on numerical differences in the actual values between the two groups.

Donzelli et al. (1) pointed to a J-curve association between LDL-C and total mortality, citing the Japan Lipid Intervention Trial (J-LIT) study (4) as an example. However, because J-LIT is a cohort study, it includes potential risks such as reversal of cause and effect (5). We feel that direct comparison of the J-LIT findings with those from randomized controlled trials such as the EMPATHY study may be problematic and would like to point out that meta-analysis has shown no increase in mortality from statin intervention to aggressively lower LDL-C (6).

The EMPATHY study was designed to evaluate the effects of a treat-to-target approach to lipid management. As such, the study was not blinded but instead used prospective randomized open-label blinded end point (PROBE) methodology. This imposes a number of limitations on the study, which of course means that care must be taken when interpreting the results. For example, as the authors of the letter point out, the unblinded nature of the study raises the potential issue of soft end points (7). However, in this study if we look at the cardiac events that were included within the primary end point, the intergroup results were comparable to those for the hard end point of myocardial infarction. Among the soft end points, unstable angina was more common in the intensive group, coronary angioplasty was more common in the standard group, and the incidence of coronary artery bypass grafting was nearly the same in both groups. Based on these findings, we discounted the likelihood of overestimation of event incidence due to overdiagnosis in the standard group.

We appreciate this opportunity to discuss the implications of our findings.

Acknowledgments. EDIT, Inc. (Tokyo, Japan) provided medical writing and editing.

Funding and Duality of Interest. The EMPATHY study was supported by Shionogi & Co., Ltd. H.I. reports grants and personal fees from Shionogi & Co., Ltd. during the conduct of the study and grants and personal fees from Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Company, Limited, MSD K.K., Mitsubishi Tanabe Pharma Corporation, Shionogi & Co., Ltd., and Taisho Toyama Pharmaceutical Co., Ltd.; grants from Sumitomo Dainippon Pharma Co., Ltd., Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd., Teijin Pharma Limited, Mochida Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Eli Lilly Japan K.K.; and personal fees from Nipro Corporation and SBI Pharmaceuticals Co., Ltd. outside the submitted work. K.U. reports other (contracted work) from Shionogi & Co., Ltd. during the conduct of the study and personal fees from Shionogi & Co., Ltd. outside the submitted work. I.K. reports personal fees from Shionogi & Co., Ltd. during the conduct of the study and grants and

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personal fees from Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd., Astellas Pharma Inc., Daiichi Sankyo Company, Limited, and Otsuka Pharmaceutical Co., Ltd. and grants from MSD K.K., Shionogi & Co., Ltd., GlaxoSmithKline K.K., Sanofi K.K., Genzyme Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., Mitsubishi Tanabe Pharma Corporation, and Bristol-Myers Squibb outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

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