Letter by McGuire and Aguilar Regarding Article, “Effect of Torcetrapib on Glucose, Insulin, and Hemoglobin A1c in Subjects in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) Trial”

To the Editor:

The improved glucose metrics associated with torcetrapib reported by Barter et al.1 are interesting and unexpected and raise a series of questions regarding the possible mediators of such effects. Beyond potential effects related to the torcetrapib mechanism of action, off-target effects, or changes in serum lipids, another possibility not addressed in the report relates to potential differences in treatments between the study groups that may have directly influenced glucose metabolism beyond the reported incidence of diabetes drug initiation. This is an important consideration in that the validity of randomized comparisons hinges on the premise that, beyond study treatment assignment, patients are treated similarly throughout the study.

Given the influence of torcetrapib on blood pressure and serum potassium via aldosterone modulation, key imbalances in treatments between the groups may have occurred as a direct result of torcetrapib exposure, many of which are known to influence indexes of glucose metabolism. For example, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and oral potassium supplementation all have favorable glycometabolic effects.2–4 In addition, thiazide diuretics with known adverse effects on glucose metabolism may have been preferentially discontinued or avoided in the torcetrapib arm as a result of declining serum potassium. Finally, in the placebo group, absent the favorable effects of torcetrapib on both high- and low-density lipoprotein cholesterol, the placebo group may have been exposed to higher-intensity statin therapy or the addition of niacin, each of which adversely affects glucose metabolism.5

In the absence of a cogent mechanistic explanation for the improved glucose metrics observed with torcetrapib, the reporting and analysis of concomitant treatments during the study that individually and in aggregate may have materially influenced glucose metabolism in the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE) trial are imperative to aid in the interpretation of these most interesting findings.

Disclosures

Dr McGuire reports receiving honoraria for consulting services for Genentech, F. Hoffmann LaRoche, Daiichi Sankyo, Novo Nordisk, Tethys Bioscience, Boehringer Ingelheim, and Sanofi-aventis. Dr Aguilar reports receiving honoraria for consulting services for Sanofi-aventis and Amylin.

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Circulation. 2012;125:e427
doi: 10.1161/CIRCULATIONAHA.111.057844

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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