Response to Letter Regarding Article, “Achievement of Dual Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein Targets More Frequent With the Addition of Ezetimibe to Simvastatin and Associated With Better Outcomes in IMPROVE-IT”

In response to Dr Robinson, we have made clear throughout our article that the data presented are observational and therefore support the idea that low-low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein levels are associated with low rates of cardiovascular events.1 Given the observational nature of the present analysis, limitations exist, which have been acknowledged in our article and in the editorial.

With regard to our observation that lower on-treatment high-sensitivity C-reactive protein levels are associated with lower residual risk, we note that the data from IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) are directionally consistent with prior data from the Cholesterol and Recurrent Events (CARE), Air Force Coronary Artherosclerosis Prevention Study (AFCAPS)/Texas Coronary Atherosclerosis Prevention Study (TexCAPS), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT-TIMI 22), Aggrastat-to-Zocor (A-to-Z), and Justification for the Use of Statins in the Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trials.2

Dr Robinson (and the 2013 American College of Cardiology/American Heart Association cholesterol guideline) claims that there has not been a trial of “treat to target” to support the concept that lower LDL reduces cardiovascular events. The objection appears to be a lack of trials designed specifically to treat each patient to a target of <X mg/dL, as has been recommended in the prior National Cholesterol Education Program (and most other) guidelines.3

However, the IMPROVE-IT trial was prospectively designed to compare, in a randomized fashion, 2 groups with a mean LDL-C that we estimated to be on average ≈50 and 65 mg/dL and thus to explore if “even lower is even better.”4 The mean LDL-C levels at 1 year in the 2 groups were very close to our estimate: 53.2 versus 69.9 mg/dL. However, the medians and interquartile range more fully describe the groups: the simvastatin group had a median LDL-C of 67 mg/dL and an interquartile range of 55.0 to 81.0 mg/dL, and the ezetimibe/simvastatin group had a median of 50.0 mg/dL and an interquartile range of 39.0 to 62.0 mg/dL. Thus, in simpler terms, IMPROVE-IT found, in a randomized comparison, that a 2-drug regimen that achieved an LDL-C range of ≈40 to 60 mg/dL had significantly fewer cardiovascular events than the statin-only strategy that achieved a range of between 40 and 60 mg/dL and thus to explore if “even lower is even better.”

References

Disclosures
Dr Bohula reports personal fees from Merck and Co. Dr Giugliano reports grant support from Merck during the conduct of the study; grant support and personal fees from Amgen; and personal fees from Merck, Daiichi-Sankyo, Pfizer, CVS Caremark, Regeneron, and Sanofi outside the submitted work. Dr Cannon reports grant support from Accunetronics, Arisaph, and Janssen; grant support and personal fees from Takeda; and personal fees from Bristol-Myers Squibb, CSL Behring, Essentialis, Kowa, Lipimedix, Pfizer, Regeneron, Boehringer Ingelheim, GlaxoSmithKline, Merck & Co, Inc, and Sanofi outside the submitted work. S.A. Murphy reports consulting fees from Merck and Co. Dr Blazing reports other support from Merck during the conduct of the study and personal fees from Merck, Sanofi, Amgen, Novartis, AstraZeneca, and Pfizer outside the submitted work. Dr Tershakovec is an employee of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, and may hold stock/stock options in the company. Dr Braunwald reports other support from Merck during the conduct of the study and personal fees from Daiichi-Sankyo, Sanofi Aventis, The Medicines Company, Menarini International, Bayer, and Medscop outside the submitted work. The other authors report no disclosures.

Erin A. Bohula, MD, DPhil
Robert P. Giugliano, MD, SM
Christopher P. Cannon, MD
Jing Zhou, MS
Sabina A. Murphy, MPH
TIMI Study Group
Cardiovascular Division
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
Boston, MA

Jennifer White, MS
Duke Clinical Research Institute
Durham, NC

Andrew M. Tershakovec, MD MPH
Merck
Kenilworth, NJ

Michael A. Blazing, MD
Duke Clinical Research Institute
Durham, NC

Eugene Braunwald, MD
TIMI Study Group
Cardiovascular Division
Department of Medicine
Brigham and Women’s Hospital
Harvard Medical School
Boston, MA

(Circulation. 2016;133:e463. DOI: 10.1161/CIRCULATIONAHA.116.020947.)
© 2016 American Heart Association, Inc.
Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.116.020947
Response to Letter Regarding Article, "Achievement of Dual Low-Density Lipoprotein Cholesterol and High-Sensitivity C-Reactive Protein Targets More Frequent With the Addition of Ezetimibe to Simvastatin and Associated With Better Outcomes in IMPROVE-IT"

Erin A. Bohula, Robert P. Giugliano, Christopher P. Cannon, Jing Zhou, Sabina A. Murphy, Jennifer White, Andrew M. Tershakovec, Michael A. Blazing and Eugene Braunwald

Circulation. 2016;133:e463
doi: 10.1161/CIRCULATIONAHA.116.020947

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/133/13/e463

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/