Response by Takase and Matoba to Letter Regarding Article, “Ezetimibe in Combination With Statins Ameliorates Endothelial Dysfunction in Coronary Arteries After Stenting: The CuVIC Trial (Effect of Cholesterol Absorption Inhibitor Usage on Target Vessel Dysfunction After Coronary Stenting), a Multicenter Randomized Controlled Trial”

In Response:

We appreciate the letter regarding our recently published CuVIC trial (Effect of Cholesterol Absorption Inhibitor Usage on Target Vessel Dysfunction After Coronary Stenting). As pointed out, our notion is that the improvement of coronary endothelial function in the ezetimibe plus statin treatment arm compared with statin alone arm might owe to the reductions in oxysterols was based on a post hoc analysis. In the analysis, we generated subgroups (n=62 each) by matching on-treatment low-density lipoprotein cholesterol (LDL-C) levels from the 2 treatment arms; therefore, it was important to assess baseline characteristics of the subgroups. Between the 2 on-treatment LDL-C-matched subgroups, there were no significant differences at the baseline, in background characteristics (sex, age, systolic blood pressure, and ejection fraction) and coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, family history, smoking habits, and metabolic syndrome). There were also no differences in laboratory data (total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDL-C, apolipoprotein A1, apolipoprotein B, and high-sensitive C-reactive protein) at the baseline. Changes in lipids during study treatment were analyzed using ANCOVA to correct baseline LDL-C values, and a significant decrease of the total oxysterol level was observed in ezetimibe plus statin arm, as shown in Figure III in the online-only Data Supplement. Although there might have been unmeasured confounders in the post hoc analysis, the decreases in oxysterols seem to be substantial by the treatment with ezetimibe and were associated with an improvement of coronary endothelial function.

It is also interesting to discuss the mechanisms of vasculo-protective effects of lipid-lowering therapy, namely the reduction in LDL-C, pleiotropic effects by statins, or now reductions in oxysterols by ezetimibe. In the PANACEA study (Postprandial Endothelial Function After Combination of Ezetimibe and Simvastatin), there were negligible effects of either simvastatin 80 mg or simvastatin 10 mg plus ezetimibe 10 mg on peripheral endothelial function among patients with metabolic syndrome. About the authors of the PANACEA study argument against the effects on endothelial function beyond LDL-C reduction of statins or ezetimibe, here we raise some notions that might explain at least in part the different findings between the CuVIC trial and the PANACEA study. First, the CuVIC trial enrolled patients after coronary stenting, most of which showed coronary endothelial dysfunction as evidenced by the acetylcholine-induced contractions of coronary arteries. Endothelial dysfunction at the baseline might uncover the beneficial effects of ezetimibe. Second, to our knowledge, the correlation between coronary endothelial function and peripheral endothelial function, both of which are considered as good surrogate markers of cardiovascular events, is significant but limited.

In the previous study, the correlation of coronary responses to ACh (acetylcholine) and brachial dilator response to reactive hyperemia ($R^2=0.13$) and the change of coronary blood flow and reactive hyperemia peripheral arterial tonometry index measured by EndoPAT ($R^2=0.16$) were less than sufficient to estimate the effects of drug therapies on coronary endothelial function by these peripheral endothelial function studies. Third, the difference of treatment period, 7 months in the CuVIC trial and 6 weeks in the PANACEA study, might also affect the findings. Because of these notions, we had better not simply dismiss the pleiotropic effects of statins or ezetimibe beyond LDL-C-lowering effect on the results of the PANACEA study. Rather, it is time to reconsider the mechanisms of lipid-lowering therapy, including the oxysterol-lowering effect of ezetimibe, on coronary endothelial function, which apparently requires further investigations by the use of lipid-lowering agents with different mechanisms.

Disclosures

Dr Matoba has received honoraria as a speaker from MSD. The other author reports no conflicts.

Susumu Takase
Tetsuya Matoba

Department of Cardiovascular Medicine
Kyushu University Graduate School of Medical Sciences
Higashi-ku, Fukuoka, Japan

References


(Arterioscler Thromb Vasc Biol. 2017;37:e54. DOI: 10.1161/ATVBAHA.117.309301.)

© 2017 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org

DOI: 10.1161/ATVBAHA.117.309301
Response by Takase and Matoba to Letter Regarding Article, "Ezetimibe in Combination With Statins Ameliorates Endothelial Dysfunction in Coronary Arteries After Stenting: The CuVIC Trial (Effect of Cholesterol Absorption Inhibitor Usage on Target Vessel Dysfunction After Coronary Stenting), a Multicenter Randomized Controlled Trial"
Susumu Takase and Tetsuya Matoba

Arterioscler Thromb Vasc Biol. 2017;37:e54
doi: 10.1161/ATVBAHA.117.309301
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/37/5/e54

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology 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 Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/