Letter by Westerink and Visseren 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”

To the Editor:

We read with great interest the study of Takase et al on the addition of ezetimibe to lipid-lowering therapy (simvastatin) on coronary artery endothelial function. It shows that addition of ezetimibe not only lowers low-density lipoprotein cholesterol (Table 2) but also lowers important oxysterols (Table 3) and is associated with an improvement in coronary endothelial dysfunction.

The main conclusions from the article (the presumed relation between a decrease in oxysterols and an improvement of coronary endothelial function), however, hinge on a post hoc analysis from the study. In Figure 5, the authors compare both treatment arms in patients who have reached equivalent post-treatment low-density lipoprotein cholesterol levels and find that in patients who have been treated with the simvastatin/ezetimibe combination, there is less endothelial dysfunction. However, the potential important role of higher pretreatment low-density lipoprotein cholesterol levels in this treatment arm is not discussed, and the authors thus presume a strict linear relation between low-density lipoprotein cholesterol levels, with or without treatment, and coronary endothelial function.

In this regard, it is interesting to look at data from peripheral endothelial function studies because peripheral endothelial function has a strong correlation with coronary endothelial function. For example, in patients with the metabolic syndrome, the differences between low-dose simvastatin in combination with ezetimibe and high-dose simvastatin on fasting and postfat load endothelial function were studied. Although this is a different population, we think that based on the conclusions from the here published CuVIC trial, similar results would have been expected. In the PANACEA study, however, no differences were observed in endothelial function between both treatment arms, in both the fasting and postfat load state, using 2 different methods of endothelial function test (FMD [flow-mediated dilatation] and EndoPAT [peripheral arterial tone]), while reaching exactly the same lipid levels under all circumstances, singling out the nonlipid-lowering effect of ezetimibe. Because there were no differences in peripheral endothelial function under all studied conditions, the possibility of an (pleiotropic) effect of ezetimibe on endothelial function was dismissed, may it be mediated by oxysterols or by something else. Because one of the main differences between the PANACEA and CuVIC is the attained lipid levels, we suspect that the observed differences in endothelial function in the CuVIC study are dependent on differences in changes in or attained lipid levels. Although there are differences between the methods in measurement of endothelial function and the study populations, we are very much interested in the opinions of the authors on why their results are different from our results and whether the PANACEA study does not undermine the presumed causal relation between oxysterol lowering and improvements in endothelial function.

Disclosures

None.

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References


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