To the Editor:

I read with interest the placebo-control study by Walker et al. about the effect of fenofibrate on vascular endothelial function in 22 healthy normo-lipidemic older adults. The authors concluded that short-term treatment with fenofibrate improved vascular endothelial function in adults by reducing oxidative stress and by inducing an increase in endothelial nitric oxide synthase. Repeat measurement of flow-mediated dilatation (FMD) has a potential advantage as a biomarker of vascular disease, and I agree with their final conclusion, as long as the statistical analysis is valid.

I have 3 statistical concerns on the study of Walker et al. First, distributions of triglyceride, insulin-related indicators, and C-reactive protein are normal in general after logarithmic transformation. Among several insulin-related biomarkers, they used indices of insulin resistance, named the homeostasis model assessment-insulin resistance. If Walker et al. included homeostasis model assessment-insulin resistance, C-reactive protein, and triglyceride as independent variables of multivariable linear regression analysis, logarithmic transformation of these variables is recommended for the analysis. Empirically, non-normally distributed variables in a regression can often lead to the residuals themselves being non-normally distributed. The result of multiple linear regression analysis was not summarized as a table, including $\beta$ and its significance of each confounding variable, and significant contribution of fenofibrate treatment on the change in brachial artery FMD was simply described.

Second, the authors mentioned that the improvements in brachial artery FMD were independent of changes in blood pressure. Does this mean that there is no significant contribution of blood pressure on the change in brachial artery FMD? To clearly demonstrate the effect of each independent variable on the change in brachial artery FMD, additional information is required. Because there is a multicollinearity between systolic and diastolic blood pressures, I recommend not including both the blood pressures simultaneously as independent variables.

Finally, coefficient of determination (adjusted $R^2$) by independent variables to predict the change in brachial artery FMD was not presented in their study. Furthermore, only 22 individuals are available to be included in the multiple regression analysis. Multiple regression analysis requires ≥20 individuals per variable, and there are some pitfalls of fitting their data to the proposed regression model and creating highly unstable estimates.

The result of multivariate analysis is a key outcome in their study, and negative data with lack of significance on blood pressure should have been presented. Nevertheless, many more samples are needed for multiple regression analysis for stable estimates. Such concerns warrant comment from the authors.

Disclosures

None.

Tomoyuki Kawada
Department of Hygiene and Public Health
Nippon Medical School
Tokyo, Japan

Effect of Fenofibrate on Vascular Endothelial Function: Statistical Appraisal and its Validity
Tomoyuki Kawada

Hypertension. published online April 15, 2013;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2013/04/15/HYPERTENSIONAHA.113.01227.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension 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 Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/