RESPONSE TO COMMENT ON MITA ET AL.

Sitagliptin Attenuates the Progression of Carotid Intima-Media Thickening in Insulin-Treated Patients With Type 2 Diabetes: The Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE): A Randomized Controlled Trial. Diabetes Care 2016;39:455–464

Tomoya Mita,[1,2] Naoto Katakami,[3,4] Iichiro Shimomura,[3] and Hirotaka Watada[1,2,5]

Diabetes Care 2016;39:e104–e105 | DOI: 10.2337/dci16-0012

We appreciate the thoughtful comments raised by Maiorino et al. (1) on our recent articles on attenuation of progression of carotid intima-media thickness (IMT) by dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes mellitus (T2DM) free of apparent cardiovascular disease (CVD), the SPIKE and SPEAD-A studies (the Sitagliptin Preventive Study of Intima-Media Thickness Evaluation and the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis, respectively) (2,3). As pointed out by Maiorino et al., comparison of baseline data of the two studies showed that carotid artery IMT at baseline was not thicker in patients with longer duration of T2DM, those with higher baseline HbA_{1c}, or those using insulin. Although the reasons for this finding remain unclear, the unexpected results may relate to the different frequency of use of drugs for prevention of CVD between the two studies, such as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and statin and antiplatelet agents, which could potentially prevent the progression of carotid IMT or occasionally reduce carotid IMT in patients with T2DM.

Intriguingly, Maiorino et al. suggested further analysis of IMT progression and regression. Accordingly, we defined IMT progression as worsening of IMT relative to baseline and IMT regression as improvement or no change in IMT relative to baseline. To characterize patients with IMT regression and IMT progression, we conducted subgroup analysis of the combined data of SPEAD-A and SPIKE studies based on IMT changes. With regard to the effect of improved glycemic control on carotid IMT in these studies, we agreed with the comment that a beneficial effect of improved glycemic control on carotid IMT could not be completely ruled out even after adjusting for differences in HbA_{1c} between the dipeptidyl peptidase 4 inhibitor groups and the conventional treatment groups. We concluded that the observed difference in IMT between the two treatment groups was due to the effects of alogliptin and sitagliptin, including their blood glucose–lowering effects as mentioned in the CONCLUSIONS sections of our articles (2,3). The glucose-lowering effects in particular were probably achieved at least by lessening fluctuations in blood glucose levels, which were unfortunately not evaluated in our studies. This conclusion was made on the basis of the fact that alogliptin and sitagliptin produced only a modest reduction in fasting blood glucose levels. Thus, we speculate that this effect may attenuate the progression of atherosclerosis, as already reported by Barbieri et al. (4) in a subanalysis of a small number T2DM patients without a control group.

Funding. Financial support for this study was provided by the Japan Society for Patients Reported Outcome research fund from Mitsubishi Tanabe, Ono, and Novo Nordisk.

Duality of Interest. T.M., N.K., I.S., and H.W. received research funds and lecture fees from several companies as described in the original study (2). No other potential conflicts of interest relevant to this article were reported.

References

1. Maiorino MI, Bellastella G, Giugliano D, Esposito K. Comment on Mita et al. Sitagliptin attenuates the progression of carotid intima-media thickening in insulin-treated patients with type 2 diabetes: the Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE): a randomized controlled trial. Diabetes Care 2016;39:455–464 (Letter). Diabetes Care 2016;39:e102–e103

[1]*Department of Metabolism & Endocrinology, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan*
[2]*Center for Molecular Diabetology, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan*
[3]*Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan*
[4]*Department of Atherosclerosis and Metabolism, Osaka University Graduate School of Medicine, Suita, Osaka, Japan*
[5]*Center for Therapeutic Innovations in Diabetes, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan*

Corresponding author: Tomoya Mita, tom-m@juntendo.ac.jp.

2. Mita T, Katakami N, Shiraiwa T, et al.; Collaborators on the Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE) Trial. Sitagliptin attenuates the progression of carotid intima-media thickening in insulin-treated patients with type 2 diabetes: the Sitagliptin Preventive Study of Intima-Media Thickness Evaluation (SPIKE): a randomized controlled trial. Diabetes Care 2016;39:455–464
3. Mita T, Katakami N, Yoshii H, et al.; Collaborators on the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A) Trial. Alogliptin, a dipeptidyl peptidase 4 inhibitor, prevents the progression of carotid atherosclerosis in patients with type 2 diabetes: the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A). Diabetes Care 2016; 39:139–148
4. Barbieri M, Rizzo MR, Marfella R, et al. Decreased carotid atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-IV inhibitors. Atherosclerosis 2013;227:349–354