



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

*Diabetes Care* 2016;39:e102–e103 | DOI: 10.2337/dc16-0475

Maria Ida Maiorino,<sup>1</sup>  
Giuseppe Bellastella,<sup>1</sup>  
Dario Giugliano,<sup>1</sup> and  
Katherine Esposito<sup>2</sup>

We read with interest the article by Mita et al. (1) in *Diabetes Care* reporting a beneficial effect of sitagliptin on the progression of carotid intima-media thickening in Japanese patients with type 2 diabetes. This article parallels another article highlighting the prevention of the progression of carotid atherosclerosis by alogliptin in patients with type 2 diabetes (2). The two articles appeared in the same journal (*Diabetes Care*) in 2016, were conducted by the same group, had the same first author, and had the same (almost identical) baseline values of carotid intima-media thickness (IMT) among the patients with diabetes. The two studies also had important differences concerning duration of diabetes (17.2 years sitagliptin vs. 9 years alogliptin), baseline HbA<sub>1c</sub> (8.1% vs. 7.3%), and insulin use (all sitagliptin patients vs. no alogliptin patients). So, at least in Japanese people, three of the main clinical aspects that characterize type 2 diabetes—duration of disease, baseline HbA<sub>1c</sub>, and insulin use—are not associated with baseline IMT. Moreover, the amelioration of HbA<sub>1c</sub> after treatment with either sitagliptin or alogliptin was not associated with changes in IMT, suggesting a largely independent effect of the glucose-lowering

capacity of these drugs from their beneficial effect on carotid atherosclerosis.

Throughout the articles, the authors state that sitagliptin “attenuated the progression of carotid IMT” or alogliptin caused “substantial regression of IMT.” The terms progression and regression are used without a clear definition of their meaning. Intuitively, progression may indicate increased IMT versus baseline and regression decreased IMT versus baseline. If so, as we believe, the authors would have conducted an analysis based on the categorization of the changes in IMT into two outcomes: decreased/no change of IMT versus baseline (regression) and increased IMT values versus baseline (progression). Next, they would have calculated, in percentage terms, how many patients progressed or regressed in the intervention groups as compared with the control groups. More specifically, they would also have defined regression as a decrease of  $\geq 0.020$  mm in mean IMT at the end of follow-up. With this definition, for example, a regression of IMT was observed by Esposito et al. (3) in 52% of 88 patients with diabetes randomly assigned to repaglinide and in 18% of 87 patients with diabetes assigned to glyburide

over a period of 12 months at the same level of glycemic control as evidenced by the quite identical reduction in post-treatment HbA<sub>1c</sub>. Although Mita et al. (1,2) adjusted for the differences in HbA<sub>1c</sub> between intervention and control groups, a beneficial effect of improved glycemic control on IMT cannot be totally excluded.

As large randomized trials did not demonstrate beneficial effects of either sitagliptin or alogliptin on cardiovascular events among patients with type 2 diabetes at high cardiovascular risk, Mita et al. (1,2) suggest an earlier treatment with dipeptidyl peptidase 4 inhibitors for primary prevention of cardiovascular disease in type 2 diabetes without apparent cardiovascular disease. This hope, however, is already a reality in people with type 2 diabetes, as demonstrated by the results of dietary interventional trials with a Mediterranean diet (4,5).

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

### References

1. 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

<sup>1</sup>Division of Endocrinology and Metabolic Diseases, Department of Medical, Surgical, Neurological, Metabolic Sciences and Aging, Second University of Naples, Naples, Italy

<sup>2</sup>Diabetes Unit, Department of Clinical and Experimental Medicine, Second University of Naples, Naples, Italy

Corresponding author: Maria Ida Maiorino, mariaida.maiorino@unina2.it.

© 2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

- 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
- 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
  - Esposito K, Giugliano D, Nappo F, Marfella R; Campanian Postprandial Hyperglycemia Study Group. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 2004;110:214–219
  - Estruch R, Ros E, Salas-Salvadó J, et al.; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279–1290
  - Esposito K, Giugliano D. Mediterranean diet for primary prevention of cardiovascular disease. *N Engl J Med* 2013;369:674–675