COMMENTARY

Glucagon-Like Peptide 1 Receptor Agonists, Carotid Atherosclerosis, and Cardiovascular Outcomes

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Glucagon-like peptide 1 receptor agonists (GLP-1 RA) represent an integral part of the arsenal used in clinical practice to improve cardiovascular outcomes in patients with diabetes. Large-scale randomized controlled trials have shown that liraglutide, dulaglutide, albiglutide, and semaglutide all reduce the risk of cardiovascular events in patients with diabetes and either established atherosclerotic cardiovascular disease (ASCVD) or high-risk characteristics (1–4). In contrast, exenatide and lixisenatide improved glycemic control but did not have a sizable impact on cardiovascular events in clinical trials (5,6), suggesting that glycemic control and cardiovascular outcomes are at least partly uncoupled. A meta-analysis including 42,920 participants from five randomized trials demonstrated that GLP-1 RA as a drug class are associated with a significant 13% reduction in the risk of the composite of myocardial infarction, stroke, or cardiovascular death in patients with diabetes and established ASCVD (7). GLP-1 RA are recommended in patients with diabetes and established ASCVD or at high risk of ASCVD (8). They are also indicated as second-line therapy in patients without ASCVD (or without indicators of high risk) who do not meet treatment goals with lifestyle modifications and metformin alone, and they are preferred to insulin if injectable therapy is needed (8).

Although the impact of GLP-1RA on cardiovascular outcomes has been shown to be directly correlated with the reduction in glycated hemoglobin (9), pleiotropic effects of agents from this class have been documented, including reduction of systolic and diastolic blood pressure (10), body weight (11), and vascular inflammation (12), in addition to improvement of endothelial function (13). However, the impact of GLP-1 RA on atherosclerotic plaque volume and composition had not yet been investigated.

As reported in this issue of *Diabetes Care*, Koska et al. (14) examined whether the GLP-1 RA exenatide modifies carotid plaque volume and composition in patients with type 2 diabetes. They conducted a placebo-controlled, double-blind, pragmatic randomized trial in which 163 participants were randomly allocated to receive either exenatide 2 mg ($n = 109$) or placebo ($n = 54$) subcutaneously once weekly. Patients with a high carotid atherosclerosis burden at baseline were enrolled, with the majority presenting calcified plaques and lipid-rich necrotic cores. Plaque volume and composition were measured using serial carotid MRI at baseline, 9 months, and 18 months of follow-up. Despite a mean reduction in glycated hemoglobin of 0.55% with once-weekly exenatide compared with placebo, there was no significant difference in the change over time in plaque volume between study groups. Plaque composition was also not modified by once-weekly exenatide, without significant differences detected in changes over time in the dimensions of calcified plaques, lipid-rich necrotic core plaques, and fibrous caps between the two treatment arms. Results were consistent among key prespecified subgroups and after excluding participants not completely adhering to the protocol.

The lack of benefit of once-weekly exenatide on carotid plaque volume and composition observed in this study is consistent with its modest effect on the primary composite end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) trial of 14,752 patients followed for a median of 3.2 years (hazard ratio 0.91, 95% CI 0.83–1.00, $P = 0.06$). Whether other GLP-1 RA associated with more marked cardiovascular benefits (liraglutide, dulaglutide, albiglutide, and semaglutide) would yield different results on carotid MRI is not known. Nevertheless, a previous study without a placebo group found that liraglutide, a GLP-1 RA that demonstrated cardiovascular benefits (1), significantly reduced carotid intima-media thickness (15). In the Harmony Outcomes trial, the reduction of cardiovascular risk with albiglutide was

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greater than would have been expected given the degree of glycated hemoglobin reduction, suggesting that the cardioprotective effects are not exclusively linked to glycemic control (3,9). In the current study, a correlation was observed between reductions of glycated hemoglobin and plaque volume in the exenatide group, but the significance of this observation is uncertain given the lack of overall effect on changes in carotid MRI end points compared with placebo.

The increase in heart rate of 9 bpm at 3 months of treatment with once-weekly exenatide compared with placebo was more marked than that reported in clinical trials of GLP-1 RA associated with greater reductions in cardiovascular event rates (1,4,11). In light of the prognostic value of resting heart rate on cardiovascular outcomes and its link with experimental atherosclerosis (16), the heart rate–elevating effect of once-weekly exenatide might explain in part the disappointing carotid imaging results in the current study.

The study by Koska et al. (14) needs to be carefully interpreted in light of the relatively small sample size and the high rate (25%) of incomplete imaging procedures at 18 months of follow-up. The latter may be of importance given that patients who withdrew early had lower BMI and triglyceride values than those who completed the study. Given that some clinical trials of GLP-1 RA have shown limited differences in outcomes within the first 2 years but greater separation of cumulative cardiovascular event curves thereafter, the 18-month follow-up duration in the current study might also have represented a limitation. Finally, the lack of effect of once-weekly exenatide on carotid plaque volume and composition observed in this study does not exclude a potential effect on coronary atherosclerosis. Notwithstanding these limitations, the study by Koska et al. suggests that the cardiovascular benefits of GLP-1 RA might not be entirely due to structural changes in atherosclerotic plaques. In order to definitely answer that question, additional placebo-controlled randomized trials involving imaging of carotid and coronary arteries should be conducted with those GLP-1 RA that have shown more pronounced benefits on cardiovascular outcomes.

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