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Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

TO THE EDITOR: In reporting the results of the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), Marso et al. (Nov. 10 issue)[1] describe a lower rate of cardiovascular events among patients with type 2 diabetes mellitus who received the glucagon-like peptide 1 (GLP-1) analogue semaglutide than among patients who received placebo. Their results are consistent with those in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial,[2] which assessed the effects of another GLP-1 analogue, liraglutide.

In SUSTAIN-6, the use of insulin at trial entry was similar between the two groups. However, during the LEADER trial, the use of insulin was approximately two times higher in the placebo group than in the liraglutide group, and during SUSTAIN-6, the use of insulin was approximately three times higher in the placebo group than in the semaglutide group. The significantly greater use of insulin in the placebo groups in these two trials may, at least in part, explain the increase in the risk of death from any cause as well as the increase in the risks of heart failure, cardiovascular events, renal failure, and hypoglycemia in these two groups. Hazard ratios for these events associated with increased use of insulin range from 1.23 to 4.57, as shown in two cohort studies in primary care.[3,4] Thus, we wonder whether the greater use of insulin in the placebo groups than in the liraglutide and semaglutide groups during these trials may have amplified the beneficial effects of liraglutide and semaglutide.

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TO THE EDITOR: Marso et al. report diabetic retinopathy complications in patients with type 2 diabetes who received semaglutide; this raises the possibility that GLP-1–receptor agonists could cause progression of diabetic retinopathy. The authors cite seminal studies involving patients with type 1 diabetes and suggest that progression of diabetic retinopathy is due to the glucose-lowering effect of treatment.[1] Studies involving patients with type 2 diabetes,[2,3] albeit smaller and retrospective, also have shown similar find-

ings: diabetic retinopathy progressed after the initiation of either intensive diabetes case management (the use of medications and other interventions to improve glucose control)[2] or insulin therapy.[3] Furthermore, such studies suggest that decrements of more than 2% in glycated hemoglobin levels are associated with progression of diabetic retinopathy.[2,4]

In SUSTAIN-6, among patients who had an initial decrease in the glycated hemoglobin level, it is very likely that many patients had a greater than 2% decrease in the glycated hemoglobin level. Did progression of diabetic retinopathy occur predominantly in that group? Addressing the relationship between the decrease in the glycated hemoglobin level and progression of retinopathy might provide further guidance to clinicians treating patients with diabetic retinopathy and glycated hemoglobin levels that are high enough to permit a greater than 2% decrease with effective therapies. It also might help to address a potential causal relationship between GLP-1–receptor agonists and the progression of diabetic retinopathy.

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TO THE EDITOR: Marso et al. state that with the exception of the complications of retinopathy, semaglutide had a safety profile that was similar to that of other GLP-1 agonists, such as liraglutide, in patients with type 2 diabetes. However, the authors do not report the causes of death for the 18 patients in the intervention group (as compared with 14 in the placebo group) who died from noncardiovascular causes.

They cite the LEADER trial[1] to establish the safety of liraglutide. The LEADER trial showed that liraglutide was associated with a significant reduction not only in the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, but also in death from any cause (hazard ratio, 0.85; 95% confidence interval, 0.74 to 0.97; P=0.02).

Given that SUSTAIN-6 was designed to establish the safety of a new agent, will the authors comment on the noncardiovascular causes of death in the participants? Also, why was the rate of death from any cause lower among patients who received liraglutide than among those who received placebo in the LEADER trial but not lower among those who received semaglutide than among those who received placebo in SUSTAIN-6?

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1. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.

THE AUTHORS REPLY: Cosmi et al. cite observational studies that associate insulin use with increased cardiovascular risk, and they suggest that the greater new use of insulin in the placebo group than in the semaglutide group may have contributed to the difference in cardiovascular risk observed with semaglutide. However, the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial,[1] a large-scale, randomized, controlled trial evaluating a potential cardiovascular effect of insulin, showed that insulin glargine, as compared with placebo, was not associated with an increased cardiovascular risk. We therefore do not think that the use of

Table 1. Deaths from Noncardiovascular Causes in SUSTAIN-6.*

Variable	Semaglutide (N = 1648)	Placebo (N = 1649)
	number of patients (percent)	
Deaths from noncardiovascular causes	18 (1.1)	14 (0.8)
Cause of death		
Cancer	8 (0.5)	6 (0.4)
Infection, including sepsis	5 (0.3)	4 (0.2)
Gastrointestinal disorder	2 (0.1)	0
Pulmonary disorder	0	2 (0.1)
Hemorrhage not attributable to cardiovascular bleeding or stroke	0	1 (0.1)
Noncardiovascular neurologic disorder	1 (0.1)	0
Noncardiovascular procedure or surgery	1 (0.1)	0
Renal disorder	1 (0.1)	0
Trauma	0	1 (0.1)

* SUSTAIN-6 denotes Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

insulin contributed to the effect seen in our trial. However, exploratory analyses have been designed to address this question and other hypotheses regarding cardiovascular benefit.

Ipp et al. inquire about the increased rates of diabetic retinopathy complications among patients who received semaglutide as compared with those who received placebo, and they mention additional studies that indicate an effect of rapid glucose lowering on progression of retinopathy in patients with type 2 diabetes. They suggest the evaluation of patients with large initial decreases in blood glucose levels (reflected by decreases in glycated hemoglobin levels) in our trial. We agree that a rapid decrease in blood glucose levels may be a possible contributor to observed differences in diabetic retinopathy complications in the two groups in our trial.

Williams and Stewart inquire about noncardiovascular causes of death. Rates of noncardiovascular death were low and causes of noncardiovascular death were balanced between the trial groups (Table 1). The LEADER trial showed an effect of liraglutide on the rate of death from cardiovascular causes, but not on the rate of death from noncardiovascular causes. In our trial, we saw no effect on the rate of death from cardiovascular causes, possibly because semaglutide had no true effect, or because a true effect was not identified, given the limited number of events and short duration of follow-up. The duration of follow-up was approximately two times as long in the LEADER trial as in SUSTAIN-6, and the sample size was approximately three times as large.

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Since publication of their article, the authors report no further potential conflict of interest.

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