Sitagliptin and Cardiovascular Outcomes in Type 2 Diabetes

TO THE EDITOR: Although the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) reported by Green et al. (July 16 issue)[1] provides valuable data, we have concerns about within-trial differences in glycemic control and medication that could have biased the results in favor of sitagliptin. In this trial, patients who received placebo, as compared with patients who received sitagliptin, received a greater number of conventional therapies for diabetes.[1] Thiazolidinediones may cause heart failure, and insulin and sulfonylureas may not be without risk.[2] Therefore, the lack of a heart-failure signal could be falsely reassuring. Can the authors describe the use of medications for diabetes during the trial and, if possible, make statistical adjustments of outcome risks for these variables?

TECOS provided a signal for acute pancreatitis. Since the current and previous trials such as the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial[3] and the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial[4] were underpowered for this outcome, we performed a meta-analysis of large trials showing that dipeptidyl peptidase 4 (DPP-4) inhibitors, as compared with usual care, were associated with a 78% higher risk of "acute"[1,3] or "definite acute"[4,5] pancreatitis. The absolute risk may be small, since sample-size–weighted event rates suggest that the use of DPP-4 inhibitors in approximately 834 patients for 2.4 years might lead to one additional episode. It would be helpful if continued surveillance of trial findings and large, adequately powered, population-based studies could assess longer-term risks of pancreatitis associated with DPP-4 inhibitors.

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TO THE EDITOR: I disagree with the findings with respect to heart failure in TECOS for the following reasons. First, the use of sitagliptin resulted in hospitalization for heart failure in 3.1% of patients; this rate is similar to that reported in the SAVOR-TIMI 53 trial (3.5% with saxagliptin) and the EXAMINE trial (3.1% with alogliptin). Second, the heart-failure data in TECOS were adjusted for a history of heart failure at baseline, whereas the SAVOR-TIMI 53 trial showed unadjusted data that revealed higher rates of hospitalization among patients with a history of heart failure at baseline. Third, in both groups in TECOS, no data were provided regarding the use of angiotensin-converting–enzyme (ACE) inhibitors, which could have affected the rate of hospitalization for heart failure.

A previous study has suggested that the combination of ACE inhibitors with DPP-4 inhibitors ("gliptins") resulted in excess heart failure due to an elevation in levels of substance P.[1] The use of open-label agents except for the study drug in TECOS could have led to the modification in the prescription after the availability of the SAVOR-TIMI 53 results.

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TO THE EDITOR: In TECOS, although sitagliptin, as compared with placebo, modestly reduced the glycated hemoglobin level, there was no difference in cardiovascular outcomes, survival, or hospitalization for congestive heart failure over a period of 4 years in a population with type 2 diabetes and established cardiovascular disease. The authors concluded by stating, "sitagliptin may be used in a diverse group of patients with type 2 diabetes who are at high cardiovascular risk without increasing rates of cardiovascular complications."

Although these findings are touted as a big win for DPP-4 inhibitors, why should clinicians prescribe an expensive drug that provides no discernible benefit? Would a placebo not be a much cheaper alternative? It seems that sitagliptin and similar drugs that lower the mean plasma glucose level but either cause harm or, at best, cause no harm, are not providing meaningful benefit to patients with type 2 diabetes. Should clinical outcome not be the criterion for their approval and clinical use? Would insurers not do better by providing a gym membership for patients with diabetes rather than covering these drugs?

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THE AUTHORS REPLY: The concerns raised by Rutter et al. with respect to possible unequal open-label drop-in of glucose-lowering agents were considered in the risk-assessment component of our trial design. Rosiglitazone was not permitted at enrollment in our trial, and its use was discouraged during the trial because of ongoing concerns about its cardiovascular safety profile. The protocol mandated the inclusion of a minimum of 2000 patients who were receiving pioglitazone. However, the protocol was amended because so few patients who were receiving that agent could be identified; only 396 of the 14,735 patients who underwent randomization (2.7%) were receiving pioglitazone. Baseline use of a thiazolidinedione did not have an effect on the risk of hospitalization for heart failure. Post-baseline use of thiazolidinediones increased marginally to 3.6% in the sitagliptin group and 4.2% in the placebo group.

There appears to be a small signal for an increased risk of acute pancreatitis across the SAVOR-TIMI 53, EXAMINE, and TECOS trials, with a signal in the opposite direction for rates of pancreatic cancer in trials that included such events (SAVOR-TIMI 53 and TECOS). It is important to look not only at the number of patients with events but also at the total number of events and the outcomes in patients who had events. A more detailed analysis of acute pancreatitis and pancreatic-cancer events and patient-level data and outcomes from TECOS is under way. Reporting a "78% higher risk" of acute pancreatitis would seem unduly alarming, given the low absolute rates, but we agree that continued long-term vigilance is essential.

To address Kumar's concerns: differences in the populations studied may influence the risk of participants being hospitalized for heart failure, but in a randomized, double-blind comparison with placebo, our trial showed that the use of sitagliptin does not affect this risk. The result is the same with or without adjustment for previous heart failure. Post-baseline use of ACE inhibitors was similar in the sitagliptin and placebo groups (58.2% vs. 58.1%). With no difference seen in rates of hospitalization for heart failure, there is no evidence of a putative increased risk associated with the combined use of an ACE inhibitor and a DPP-4 inhibitor in the TECOS cohort.

In reply to Kay: TECOS was a cardiovascular safety study that showed unequivocally that sitagliptin can be used for its primary purpose. In other words, it can help to control glucose levels in people with type 2 diabetes, without affecting their risk of cardiovascular disease.

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

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