The Safety of Dipeptidyl Peptidase 4 Inhibitors and the Risk for Heart Failure

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In 2008, the Food and Drug Administration proposed a 2-step process for the approval of oral glucose-lowering therapies for type 2 diabetes that included an initial approval contingent on effective hemoglobin A1c reduction and then a postmarketing cardiovascular outcomes trial with predefined end points, longer follow-up, and a higher risk population to demonstrate “noninferiority” to placebo. Incretin-based therapies were the first drugs to be evaluated under the new guidance policy. Glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide are incretin hormones secreted from the small intestine after meals and lower glucose levels by increasing β-cell insulin secretion, decreasing glucagon release, improving satiety, and slowing gut motility. Glucagon-like peptide-1 is rapidly de-activated by the enzyme dipeptidyl peptidase 4 (DPP4). The incretin axis can be pharmacologically enhanced either through injections of GLP-1 mimetics to achieve supraphysiologic levels or by inhibition of DPP4, which prolongs the half-life of physiologic levels of GLP-1, thus prolonging its action, although to a lesser extent than exogenous GLP-1 agonist. In preclinical experiments, both GLP-1 agonists and DPP4 inhibitors promoted nonglycemic-mediated cardioprotective actions. There were no signals of any cardiovascular harm in any of the incretin-based clinical development programs and, in fact, there were data to suggest direct cardioprotective and vasculoprotective benefits.

To date, 3 DPP4 inhibitors (saxagliptin,3 alogliptin,4 and sitagliptin5) and 1 GLP-1 agonist (lixisenatide6) have published the primary results of their cardiovascular outcomes trials. On balance, the studies were more similar than different. Two studies enrolled patients following an acute coronary syndrome,4,6 while the other 2 enrolled stable patients of whom most had established cardiovascular disease.3,5 The primary results of the trials were also similar. Each easily met the noninferiority boundary with an upper bound of the 95% CI well below 1.3 for their primary and secondary composite end points. In fact, the event curves of each trial seemed to intertwine and the hazard ratios all fell within a few hundredths of a decimal point of 1.00. These safety data alone in almost 43,000 patients with type 2 diabetes are an important advance in understanding the cardiovascular risk profile of drugs to treat diabetes.

Among the different trial results, the most unexpected finding was a 27% increased relative risk of hospitalization for heart failure in patients assigned to saxagliptin compared with placebo in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) Study (N = 289; 3.5% vs 228; 2.8% over 2 years; P = .007).7 Despite extensive analysis, no mechanism of action to explain this observation could be found.7 The results from the Examination of Cardiovascular Outcomes With Alogliptin vs Standard of Care (EXAMINE) Study, where there was a numerically but not statistically higher rate of hospitalizations for heart failure in patients treated with alogliptin compared with placebo (n = 106, 3.9% vs n = 89, 3.3%; hazard ratio, 1.19; 95% CI, 0.90-1.58; P = .22),8 further raised the suspicion of a possible class effect of the DPP4 inhibitors on the risk of hospitalization for heart failure.

The Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) Study, which compared sitagliptin vs placebo in 14,671 stable patients with type 2 diabetes and established cardiovascular disease, was the third DPP4 study to report results and provides valuable, although discordant, data regarding the risk for heart failure. In contrast to the SAVOR-TIMI 53 and EXAMINE trials, the rates of hospitalization for heart failure in TECOS were exactly the same between sitagliptin and placebo (3.1% vs 3.1%; hazard ratio, 1.00; 95% CI, 0.83-1.20; P = .98).9 This report by McGuire et al9 in JAMA Cardiology provides a detailed assessment of the hospitalization for heart failure end point in TECOS. Regardless of how it was analyzed and using similar analytic methods to SAVOR-TIMI 53 and EXAMINE, there was no signal of any increased risk of hospitalization for heart failure or the total hospitalizations for heart failure, nor evidence of any heterogeneity in the risk of hospitalization for heart failure by time or in different subgroups. This contrasts to saxagliptin, where the greatest risk of hospitalization for heart failure was observed just during the first year after randomization.7 Overall, this is very reassuring data for sitagliptin.

There are several potential explanations for the discordant findings. The patient populations in the 3 trials were more similar than different, but there were some distinctions. The EXAMINE Study enrolled patients following acute coronary syndromes. Most patients in SAVOR-TIMI 53 had established cardiovascular disease, but a significant proportion of patients did not have manifest cardiovascular disease. More than 15% of patients in SAVOR-TIMI 53 had an estimated glomerular filtration rate less than 50 mL/min/1.73 m² compared with 9.3% in TECOS. However, the subtle differences in patient population are unlikely to explain the differences in
outcomes. Moreover, all 3 studies used a similar well-defined heart failure end point adjudicated by a blinded committee. While there could be differential ascertainment of clinical events between studies, blinded adjudication and treatment randomization should protect against any actual bias.

Another possibility is that the different DPP4 inhibitors have different pharmacologic properties. Dipeptidyl peptidase 4 is a ubiquitous enzyme with multiple substrates in addition to GLP-1, including brain natriuretic peptide, neuropeptide Y, substance P, and stromal cell–derived factor-1. The physiologic effects on DPP4 inhibition on most of these substrates in animals, let alone humans, are largely unknown. While there are biochemical differences between the different DPP4 inhibitors, the physiologic effects on glucose, weight, and adverse effects are generally similar. Because there was no heart failure signal observed with the GLP-1 agonist lixisenatide, one would have to hypothesize that there is a differential selectivity between DPP4 inhibitors for non–GLP-1 substrates that somehow tips the balance and worsens the risk of hospitalization for heart failure. More investigation into potential mechanisms to explain these observations could paradoxically identify a new therapeutic target to treat or prevent heart failure. It is also unlikely that glucose lowering by itself worsens heart failure as there is no association between the degree of hemoglobin A1c lowering and heart failure, so any potential mechanism would likely be “off target” of glycemic control.

Hospitalization for heart failure was one of many prespecified end points and, therefore, it is possible that one of these findings is due to chance. But one cannot prove or disprove “chance.” Several large claims-based studies have failed to identify any association between DPP4 inhibitors and hospitalization for heart failure, although owing to residual confounding and bias, real-world data are unlikely to disentangle the confusion.

Two smaller randomized studies provide additional data regarding the association between incretin therapy and cardiac function. In one trial of 254 patients with reduced left ventricular function, vildagliptin increased ventricular end-diastolic volume compared with placebo. In another study of 300 patients recently hospitalized for heart failure, the GLP-1 agonist liraglutide increased the rate of death or hospitalization for heart failure (hazard ratio, 1.30; 95% CI, 0.92-1.83; P = .14), despite modest reductions in weight and blood pressure.

The debate over heart failure and incretin therapy has at least renewed interest in understanding the association between diabetes and heart failure. Not only are patients with diabetes at higher risk of developing heart failure—with patients with both heart failure and diabetes at highest risk—but the combination of both diseases limits treatment options. Many diabetes drugs are unappealing, or even contraindicated, in patients with heart failure owing to weight gain, edema, hypoglycemia, or the presence of concurrent renal insufficiency. Thus, the identification of drugs that are effective at glycemic control and have documented cardiovascular safety in patients with heart failure is an important clinical need.

No class of diabetes drug agents has now been as thoroughly evaluated as the DPP4 inhibitors. Overall, they are safe without any increase in cardiovascular death, myocardial infarction, or stroke. Of the 3 DPP4 inhibitors, sitagliptin appears to have the safest cardiovascular profile. These trials also highlight the importance of well-powered trials with hard clinical end points. Without them, we would not have detected a potential heart failure risk with saxagliptin and might have been left with the impression that this class of agents was cardioprotective, when in fact, and despite preclinical data, there does not appear to be any nonglycemic-mediated cardioprotection.

The overall safety, but lack of efficacy, of the incretin-based therapies must also be taken in the context of the EMPA-REG Outcomes Study. The sodium-glucose cotransporter type 2 inhibitor empagliflozin was associated with a significant reduction in cardiovascular death, overall mortality, and hospitalization for heart failure in a population similar to TECOS. These data, which require confirmation from the other ongoing sodium-glucose cotransporter type 2 cardiovascular outcome trials, are the first definitive demonstration that a diabetes drug can improve cardiovascular outcomes, mostly likely unrelated to glycemic control and owing to effects on blood pressure, weight, and sympathetic tone. The sodium-glucose cotransporter type 2 inhibitors have now “raised the bar” on expectations of new diabetes therapies. The recent reports of improved cardiovascular outcomes with pioglitazone further highlight the possibilities of improving long-term macrovascular outcomes.

Owing to the well-documented microvascular benefit of improved glycemic control, the identification of cardiovascular-safe diabetes drugs that effectively lower glucose remains an important clinical need. The incretin therapies thus fulfill this goal. Ultimately, we need diabetes drugs that also reduce cardiovascular risk, and that will only be demonstrated through a continued commitment to long-term outcome studies.

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