DPP-4 Inhibitors and Heart Failure: Some Reassurance, Some Uncertainty
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# DPP-4 Inhibitors and Heart Failure: Some Reassurance, Some Uncertainty

*Kristian B. Filion and Samy Suissa*

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The American Diabetes Association's *Standards of Medical Care in Diabetes—2016* recommends the use of dipeptidyl peptidase 4 (DPP-4) inhibitors in combination with metformin as a second- or third-line treatment for type 2 diabetes (1). Owing to their relatively high costs, many jurisdictions restrict their use to patients whose glycemia remains poorly controlled on metformin–sulfonylurea combination therapy. By inhibiting DPP-4 activity, these agents increase postprandial incretin concentrations, thereby increasing insulin secretion and decreasing glucagon secretion (1). With intermediate efficacy, a low risk of hypoglycemia, neutral effects on body weight, and relatively rare adverse effects (1), their use has increased considerably since their 2006 entry into the U.S. market (2). Nevertheless, concerns remain regarding their potential association with serious adverse effects including acute pancreatitis (3), pancreatic cancer (3), and heart failure (HF) (4).

The potential increased risk of HF with DPP-4 inhibitors was reported in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, which randomized 16,492 patients with type 2 diabetes and either a history of cardiovascular disease (CVD) or multiple CVD risk factors to saxagliptin (Onglyza) or placebo (5) (Table 1). Patients randomly assigned to saxagliptin unexpectedly had a significantly higher risk of hospitalization for HF (hazard ratio [HR] 1.27 [95% CI 1.07–1.51]), a prespecified component of the secondary composite end point. This increased risk was clustered in the first year of follow-up (HR 1.46 [95% CI 1.15–1.88]) with no increase thereafter (6).

The increased HF risk in SAVOR-TIMI 53 was not observed in subsequent trials (Table 1). In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, 5,380 patients with type 2 diabetes and a recent hospitalization for acute coronary syndrome were randomly assigned to alogliptin (Nesina in the U.S. and Vipidia in Europe) or placebo (7). Overall, alogliptin was not associated with an increased risk of hospitalization for HF (HR 1.19 [95% CI 0.90–1.58]), but the risk differed among patients with (HR 1.00 [95% CI 0.71–1.42]) and without (HR 1.76 [95% CI 1.07–2.90]) a history of HF (*P* for interaction = 0.068) (8). Most recently, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized 14,671 patients to sitagliptin (Januvia) or placebo and observed no difference in the risk of hospitalization for HF (adjusted HR 1.00 [95% CI 0.83–1.20]) (9). Pooling data across all three cardiovascular outcome trials results in an HR of 1.15 (95% CI 0.98–1.34) (Fig. 1).

The safety signal raised by the SAVOR-TIMI 53 trial has led to several observational studies that produced somewhat conflicting results (10–17). In this issue of *Diabetes Care*, Fu et al. (18) report the results of a retrospective cohort study that compared the risk of hospitalization for HF with DPP-4 inhibitors to that of sulfonylureas and, in secondary analyses, directly compared the HF risks of saxagliptin and sitagliptin. Exposure was defined using an as-treated approach, in which patients were censored upon discontinuation of their cohort entry therapy or switching to the other drug. Using propensity score matching, the authors found no evidence of an increased risk of hospitalization for HF with DPP-4 inhibitors among patients with CVD history at baseline (HR 0.95 [95% CI 0.78–1.15]) and with no CVD history (HR 0.59 [95% CI 0.38–0.89]). Similarly, no difference was observed when comparing saxagliptin to sitagliptin (HR 0.95 [95% CI 0.70–1.28] and HR 0.99 [95% CI 0.56–1.75], respectively).

The study by Fu et al. (18) has several strengths. These include a large sample size of 218,556 patients and the use of propensity scores to minimize confounding. Furthermore, the head-to-head

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**See accompanying articles, pp. 664, 668, 677, 686, 694, 701, 709, 717, 726, and 738.**

**Table 1—Data from randomized placebo-controlled trials of DPP-4 inhibitors and the risk of HF**

| | | | | | | Hospitalization for HF | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Rate (no. per 100 PYs) | | |
| Study | Year | DPP-4 inhibitor | Population | Sample size | Median follow-up (years) | DPP-4 inhibitor | Placebo | HR (95% CI) |
| SAVOR-TIMI 53 (5,6) | 2013, 2014 | Saxagliptin | CVD or multiple CVD risk factors | 16,492 | 2.1 | 1.71* | 1.36* | 1.27 (1.07–1.51) |
| EXAMINE (7,8) | 2013, 2015 | Alogliptin | Post-ACS | 5,380 | 1.5 | 2.69† | 2.28† | 1.19 (0.90–1.58) |
| | | | With history of HF | 1,533 | | 5.60† | 5.85† | 1.00 (0.71–1.42) |
| | | | With no history of HF | 3,847 | | 1.53† | 0.86† | 1.76 (1.07–2.90) |
| TECOS (9) | 2015 | Sitagliptin | CVD | 14,671 | 3.0 | 1.07 | 1.09 | 1.00 (0.83–1.20)‡ |

ACS, acute coronary syndrome; PYs, person-years. *Estimated using the total person-years of follow-up reported for each group (16,884 for saxagliptin and 16,761 for placebo). †Estimated using the median duration of follow-up for the trial. ‡Adjusted for baseline history of HF.

comparison of saxagliptin and sitagliptin represents an important addition to the literature particularly in light of the conflicting trial evidence on this issue. In addition, given the inherent differences between patients who participate in clinical trials and those seen in everyday clinical practice (19,20), these data should provide some reassurance to practicing clinicians and patients with type 2 diabetes.

This study also has important limitations, many of which are acknowledged by the authors. With a mean follow-up of only 6 months (median 3 months), the duration of follow-up may have been inadequate to fully assess the HF risk of DPP-4 inhibitors. Concerns regarding this limitation are partially mitigated by the early risk identified in SAVOR-TIMI 53 (6), but it remains important in interpreting these data. Informative censoring upon discontinuation of study medication must also be considered; the inclusion of an analysis analogous to an intention-to-treat approach where exposure is defined at cohort entry and patients are followed for a fixed duration of follow-up (e.g., 6 or 12 months) could shed light on this potential issue. In addition, despite matching on propensity score, the potential for confounding remains, particularly from formulary restrictions with DPP-4 inhibitors in place in many jurisdictions, which can result in important bias in pharmacoepidemiologic research (21). Finally, although the study restricted the cohort to new users of the study drugs, the recommended approach to avoid bias from the inclusion of prevalent users (22), the exclusion of patients who previously used sulfonylureas can be highly restrictive, even more so than many randomized trials. This is a potential major limitation of this approach; its scope can be far removed from the real-world data expected from such studies. Moreover, given the progressive nature of type 2 diabetes and its multistep treatment, the study of antidiabetes drugs is a challenging area in pharmacoepidemiology that is particularly ripe for selection and time-related biases (23). Despite these limitations, this study (18) joins several observational studies that have found no evidence of an increased HF risk with DPP-4 inhibitors (13–17).

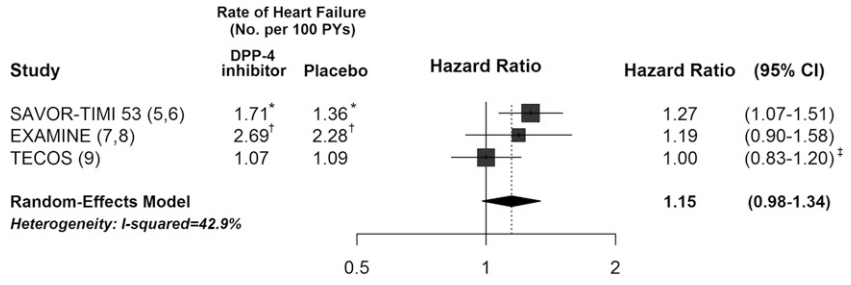


**Figure 1—**Meta-analysis of the cardiovascular outcome trials reporting the risk of HF with DPP-4 inhibitors. The box size is proportional to the weight in the meta-analysis. *Estimated using the total person-years of follow-up reported for each group (16,884 for saxagliptin and 16,761 for placebo). †Estimated using the median duration of follow-up for the trial. ‡Adjusted for baseline history of HF.

There are several potential explanations for the discordance in data from trials and observational studies regarding DPP-4 inhibitors and the risk of HF. First, it is possible that the safety signal observed in SAVOR-TIMI 53 (5,6) and in the post hoc subgroup analyses of EXAMINE (8) are chance findings due to multiple testing. Second, it is possible that the increased risk of HF is specific to saxagliptin, the DPP-4 inhibitor examined in SAVOR-TIMI 53. Although Fu et al. compared the HF risks of saxagliptin and sitagliptin, with a mean follow-up of 6 months, their analysis in patients with a history of CVD (the population studied in SAVOR-TIMI 53) was underpowered, as they only ruled out HRs above 1.75 (18). Finally, the heterogeneity in comparators and their corresponding HF risks must be considered. All three trials were placebo-controlled but encouraged the use of nonstudy medications to maintain glycemic control; differences in the distribution of use of these drugs (and their HF risks) may explain some heterogeneity in risk estimates. On the other hand, many of the observational studies used sulfonylureas as the comparator, a drug class that has been associated with increased cardiovascular risk (24).

The observational study by Fu et al. (18) provides some welcome reassurance regarding the HF risk of DPP-4 inhibitors. However, to impart actual real-world data, such observational studies should ideally strive to evaluate the full spectrum of users of these drugs, not only the treatment-naïve ones. As the signals of this association from the large randomized trials remain largely unexplained, there is certainly room for broader observational studies that use different innovative approaches accounting for the complexity

of pharmacoepidemiologic studies in type 2 diabetes.

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