Association Between Hospitalization for Heart Failure and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes: An Observational Study

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Diabetes Care 2016;39:726–734 | DOI: 10.2337/dc15-0764

OBJECTIVE

To examine, among patients with type 2 diabetes, the association between hospitalization for heart failure (hHF) and treatment with dipeptidyl peptidase 4 inhibitors (DPP-4is) versus sulfonylureas (SUs), and treatment with saxagliptin versus sitagliptin.

RESEARCH DESIGN AND METHODS

This was a retrospective, observational study using a U.S. insurance claims database. Patients initiated treatment between 1 August 2010 and 30 August 2013, and had no use of the comparator treatments in the prior 12 months (baseline). Each comparison consisted of patients matched 1:1 on a propensity score. Time to each outcome was compared between matched groups using Cox models. Analyses were stratified by the presence of baseline cardiovascular disease (CVD). Secondary analyses examined associations between comparator treatments and other selected cardiovascular events.

RESULTS

After matching, the study included 218,556 patients in comparisons of DPP-4i and SU, and 112,888 in comparisons of saxagliptin and sitagliptin. The hazard ratios (HRs) of hHF were as follows: DPP-4i versus SU (reference): HR 0.95 (95% CI 0.78–1.15), *P* = 0.580 for patients with baseline CVD; HR 0.59 (95% CI 0.38–0.89), *P* = 0.013 for patients without baseline CVD; saxagliptin versus sitagliptin (reference): HR 0.95 (95% CI 0.70–1.28), *P* = 0.712 for patients with baseline CVD; HR 0.99 (95% CI 0.56–1.75), *P* = 0.972 for patients without baseline CVD. Comparisons of the individual secondary and composite cardiovascular outcomes followed a similar pattern.

CONCLUSIONS

In patients with type 2 diabetes, there was no association between hHF, or other selected cardiovascular outcomes, and treatment with a DPP-4i relative to SU or treatment with saxagliptin relative to sitagliptin.

The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI) 53 trial, and Trial Evaluating Cardiovascular Outcomes with Sitagliptin

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Received 12 April 2015 and accepted 5 December 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0764/-/DC1.

See accompanying articles, pp. 664, 668, 677, 686, 694, 701, 709, 717, 735, and 738.

(TECOS) are complete (1–4). Whereas the EXAMINE trial and the TECOS showed no statistically significant impact of alogliptin or sitagliptin, respectively, on hospitalization for heart failure (hHF), in the SAVOR-TIMI 53 trial unexpectedly more patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (1–4). These findings prompt uncertainty regarding whether the risk of hHF differs across the class of dipeptidyl peptidase 4 inhibitors (DPP-4is), or whether the risk of hHF differs between the DPP-4i class and other classes of antihyperglycemic medications. Until the completion of the Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes (CAROLINA) trial, no cardiovascular outcomes trials (CVOTs) will provide insight into the cardiovascular safety of DPP-4 inhibition compared with another class of antihyperglycemic medications (5). Moreover, none of the current CVOTs will provide head-to-head data within the DPP-4i class, and, to our knowledge, no published observational studies have provided comparisons of the risk of heart failure within the DPP-4i class.

The current study offers observational data to address the current uncertainties regarding within–DPP-4i and across-class differences in the association between hHF and antihyperglycemic treatments among patients with type 2 diabetes by *1*) examining the association between hHF and treatment with DPP-4is versus sulfonylureas (SUs), and *2*) examining the association between hHF and treatment with saxagliptin versus sitagliptin. Secondary analyses compared the aforementioned groups with respect to other cardiovascular outcomes, including hospitalization for acute myocardial infarction (AMI), hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all outcomes together, including hHF.

RESEARCH DESIGN AND METHODS

Prior to data analysis, the protocol of this study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (http://www.encepp.eu/encepp/viewResource.htm?id=8696). Analyses comparing saxagliptin with linagliptin or alogliptin were not undertaken due to a failure to meet prespecified sample size criteria, as described below. This study used a retrospective, observational cohort design. The study used as its methodological foundation, as closely as possible, the approach that is outlined in the U.S. Food and Drug Administration (FDA) document *Mini-Sentinel Protocol for Active Surveillance of Acute Myocardial Infarction in Association with Use of Antidiabetes Agents* by Selby et al. (6).

Data Source

The study used U.S. administrative insurance claims data drawn from the Truven Health MarketScan Commercial and Medicare Supplemental databases. These databases comprise enrollment information; demographic information; and inpatient medical, outpatient medical, and outpatient pharmacy claims data collected from >300 large self-insured U.S. employers and >25 U.S. health plans.

The Truven Health MarketScan Commercial database includes information for individuals who are under the age of 65 years and are the primary individual insured or are a spouse or dependent of that individual. The Truven Health MarketScan Medicare Supplemental database includes both the Medicare-paid and supplemental insurance–paid components of reimbursed insurance claims for individuals who are eligible for Medicare and have supplemental insurance paid for by their current or former employer.

The study databases that were used satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the Health Insurance Portability and Accountability Act of 1996 privacy rule regarding the determination and documentation of statistically deidentified data.

Patient Selection

Generic names of all study medications and all codes used in this study are available in Supplementary Table 1. Within the DPP-4i versus SU comparison, patients were required to have one or more outpatient prescription claims for a DPP-4i or an SU between 1 August 2010 (1 May 2012 for linagliptin because of later FDA approval) and 30 August 2013. Within the saxagliptin versus sitagliptin comparison, patients were required to have one or more outpatient prescription claims for saxagliptin (including saxagliptin/metformin fixed-dose combination) or sitagliptin (including sitagliptin/metformin and sitagliptin/simvastatin fixed-dose combinations) between 1 August 2010 and 30 August 2013. For each comparison, the date of the first of such claims was designated as the "index date," and the medication to which that claim corresponded was designated as the "index therapy."

The medication-specific beginning dates for the period of patient selection (1 August 2010 for saxagliptin and sitagliptin, and 1 May 2012 for linagliptin) were chosen to be at least 1 year after the approval of a given medication in order to mitigate any bias that may arise from early prescribing patterns or initial limited market access for the medication. The end date for the period of patient selection (30 August 2013), which also served as the end date for follow-up, was chosen because this is the date on which the results of the SAVOR-TIMI 53 and EXAMINE trials were initially presented, and physicians may have altered their prescribing patterns or heart failure ascertainment for DPP-4is after reports of the hHF results in those trials.

All patients in each of the two comparisons were further required to meet all of the following inclusion criteria: ≥1 day of follow-up; ≥18 years of age on the index date; 365 days of continuous enrollment (no gaps >31 days) in medical and pharmacy benefits immediately prior to the index date (this period is designated as the "baseline period"); ≥1 outpatient prescription claims for an antihyperglycemic medication or one or more medical claims with an ICD-9-CM diagnosis code for type 2 diabetes during the baseline period.

We excluded patients from the comparison if they had more than one type of DPP-4i (both comparisons), more than one type of SU (DPP-4i vs. SU comparison only), or both a DPP-4i and an SU on the index date (DPP-4i vs. SU comparison only); one or more outpatient prescription claims for any DPP-4i (both comparisons) or any SU (DPP-4i vs. SU comparison only) during the baseline period; hHF in the 60-day period before the index date; one or more medical claims with ICD-9-CM, Current Procedural Terminology, 4th edition, or Healthcare Common Procedure Coding System codes (where applicable) indicative of type 1 diabetes, pregnancy, or gestational diabetes during the

baseline period, or from the index date through the earlier of the end of continuous enrollment or the end of available data.

All analyses were stratified by the presence of baseline cardiovascular disease (CVD), which was defined as having one or more medical claims with any CVD codes, as outlined in Supplementary Table 1, during the baseline period.

Follow-up Period

For all analyses, the follow-up period was of variable length, began on the day after the index date, and ended at the first occurrence of one of the following censoring events: cessation of index therapy (defined per the Mini-Sentinel protocol and described in detail within the footnote of Supplementary Table 6); filling an outpatient prescription claim for an SU (DPP-4i cohort), a DPP-4i (SU cohort), or a nonindex DPP-4i (saxagliptin and sitagliptin cohorts); beginning of a >31-day gap in continuous enrollment in health insurance benefits; inpatient death; or reaching the study end date of 30 August 2013. Information on deaths occurring outside of the inpatient setting was not available in the study database.

For the DPP-4i versus SU comparison only, individual agents within the class of the index therapy were considered to be interchangeable; thus, within-class switches did not terminate follow-up.

Measurement of Study Outcomes

The primary outcome was hHF during the follow-up period. An hHF event was defined as an inpatient hospital admission with a principal discharge diagnosis of heart failure (7). Time to hHF was defined as the number of days from the index date until the date of hospital admission for the first occurrence of an hHF event.

The secondary outcomes were hospitalization for AMI, hospitalization for stroke, hospitalization for unstable angina, coronary revascularization, and a composite of all outcomes together, including hHF, during the follow-up period (8–10). The secondary outcomes were separately measured and analyzed as time-to-event variables, with times to each event being measured independently from one another, regardless of the occurrence of other events. Finally, although inpatient death was treated as a reason for censoring, hHF or secondary outcome events resulting in inpatient death were treated as events as opposed to being a cause for censoring.

Measurement of Covariables

Covariables measured for this study included demographics measured as of the index date based on enrollment information, as well as healthcare use measures, general comorbidities, cardiovascular risk factors, and antihyperglycemic and other medications measured during the baseline period, based on medical and pharmacy insurance claims. These variables were largely drawn from the aforementioned Mini-Sentinel protocol. Supplementary Tables 2 and 3 provide a comprehensive listing of all covariables measured for this study.

Statistical Analyses

The primary method of statistical adjustment in this study was propensity score matching using the nearest-neighbor technique and enforcing a caliper of 0.01 on the probability scale. A total of four propensity score matches were completed for the primary analyses, as follows: DPP-4i versus SU stratified by baseline CVD; and saxagliptin versus sitagliptin stratified by baseline CVD. For each comparison, a propensity score was obtained from a logistic regression in which the dependent variable was a binary variable for being in the DPP-4i or saxagliptin cohort, as appropriate to the comparison. All logistic regressions used an independent variable specification that was selected a priori and included all variables (i.e., selection techniques such as stepwise variable selection were not used) listed in Supplementary Tables 1 and 2, with the exception that "CVD-related conditions" variables were omitted from the analyses among patients with no baseline CVD. The balance achieved by the propensity score was assessed via the standardized difference.

The primary analyses of study outcomes were conducted through bivariate Cox proportional hazards models and applied to the propensity score–matched samples. For these and all models described below, the Schoenfeld test was used to assess whether the independent variable of the models met the proportionality assumption of the Cox proportional hazards modeling approach (11). No multiplicity adjustments were made for hypothesis testing. In all analyses, $P \leq 0.05$ was considered the threshold for statistical significance when testing hypotheses.

Power calculations based on published rates of hHF indicated that 12,869 patients with baseline CVD and 77,209 patients with no baseline CVD would be needed to have 80% power to detect a hazard ratio (HR) of 1.33 (per the Mini-Sentinel protocol sequential analysis plan) (1,12). Any analyses with combined comparator samples that did not meet these prespecified sample size and power criteria were not conducted.

Sensitivity Analyses

For the primary outcome of hHF, the following prespecified sensitivity analyses were conducted. First, analyses were conducted through multivariable, as opposed to bivariate, Cox proportional hazards models using the population of individuals meeting the patient selection criteria of the study before matching. Second, analyses were subset to patients who were ≥65 years of age. Third, analyses were subset to patients who had no baseline or follow-up use of thiazolidinediones. Fourth, analyses were subset to patients who had no baseline use of loop diuretics. Fifth, analyses were conducted when extending the period during which hHF was identified to up to 30 days beyond the last point at which hHF was identified for the primary analyses. Sixth, analyses were conducted when uniformly allowing a gap in days' supply of ≤45 days before triggering the cessation of therapy. Seventh, analyses were subset to patients who met criteria that approximated the cardiovascular risk criteria of the SAVOR-TIMI 53 trial (see the last row of Supplementary Table 1). Finally, in a post hoc sensitivity analysis, the primary outcome of hHF, as well as all secondary outcomes, was analyzed when stratifying patients by the presence versus absence of baseline heart failure. These post hoc sensitivity analyses were not subjected to the prespecified sample size and power criteria described above. Propensity score matches were reconducted for any sensitivity analyses involving a subset of the overall study cohorts.

RESULTS

Patient Characteristics

After applying the propensity score match, the study included the following numbers of patients among patients with no baseline CVD: 82,019 DPP-4i and 82,019 SU; 43,402 saxagliptin and 43,402 sitagliptin; among patients with baseline CVD: 27,259 DPP-4i and 27,259 SU; 13,042 saxagliptin and 13,042 sitagliptin (Supplementary Tables 4 and 5).

The proportions of DPP-4i patients who were successfully matched to an SU patient were 89.2% among patients with no baseline CVD and 92.3% among patients with baseline CVD; these proportions for saxagliptin patients were 100.0% (only one patient was not matched) and 99.9%. Summary statistics for the postmatch distributions of a selected subset of study covariables are displayed in Table 1; corresponding information is provided for all study covariables in Supplementary Tables 2 and 3. Information on the duration of study follow-up by cohort, which on average was ~6 months, is provided in Supplementary Table 6.

hHF

Kaplan-Meier plots visually depicting the distribution of time to hHF for the primary analyses, along with information on HRs for hHF, are provided in Fig. 1. As indicated by 95% CIs crossing 1, there was no statistically significant difference in the hazards of hHF between DPP-4i patients and SU-treated patients with baseline CVD (HR 0.95 [95% CI 0.78–1.15], $P = 0.580$) (Fig. 1*A*) or between saxagliptin-treated patients and sitagliptin-treated patients in either CVD stratification (patients with baseline CVD: HR 0.95 [95% CI 0.70–1.28], $P = 0.712$ [Fig. 1*B*]; patients with no baseline CVD: HR 0.99 [95% CI 0.56–1.75], $P = 0.972$ [Fig. 1*D*]). Among patients with no baseline CVD, those treated with DPP-4is had statistically significant lower hazards of hHF (HR 0.59 [95% CI 0.38–0.89], $P = 0.013$ [Fig. 1*C*]) compared with those treated with SUs.

Consistent with the primary analysis results, among patients with no baseline CVD, those treated with a DPP-4i had statistically significant lower hazards of hHF compared with those treated with an SU in every performed sensitivity analysis (all $P < 0.05$) (Table 2). All other prespecified sensitivity analysis comparisons yielded statistically insignificant differences between the compared cohorts (Tables 2 and 3). The post hoc analyses stratifying patients by the presence versus the absence of baseline heart failure yielded results that were directionally similar to the primary analyses, but with no statistically significant differences found for hHF (Supplementary Table 7).

Secondary Outcomes

There was no statistically significant difference in the hazards of the composite cardiovascular outcome between saxagliptin-treated patients and sitagliptin-treated patients in either CVD stratification (patients with baseline CVD: HR 0.90 [95% CI 0.78–1.05], $P = 0.183$ [Table 3]; patients with no baseline CVD: HR 1.04 [95% CI 0.86–1.25], $P = 0.687$ [Table 3]). Those treated with a DPP-4i had statistically significant lower hazards of the composite cardiovascular outcome compared with those treated with an SU, in both CVD strata (among patients with no baseline CVD: HR 0.70 [95% CI 0.61–0.81], $P < 0.001$; among patients with baseline CVD: HR 0.87 [95% CI 0.78–0.96], $P = 0.007$ [Table 2]).

Consistent with the primary analysis results, those treated with a DPP-4i often had statistically significant lower hazards of the secondary outcomes compared with those treated with an SU ($P < 0.05$) in the prespecified sensitivity analyses (Table 2). The comparisons between saxagliptin and sitagliptin yielded statistically insignificant differences in the hazards of all secondary outcomes in the prespecified sensitivity analyses (Table 3). The post hoc analyses stratifying patients by the presence versus the absence of baseline heart failure yielded results that were generally similar to the primary analyses (Supplementary Table 7).

CONCLUSIONS

This real-world observational study was motivated by the unexpected finding that saxagliptin increased the risk of hHF relative to placebo within the SAVOR-TIMI 53 trial, and by the incongruence of these findings with those of the EXAMINE and TECOS trials, which showed no statistically significant impact of alogliptin or sitagliptin, respectively, on hHF (2–4). In the absence of head-to-head trials, any data providing an understanding of within–DPP-4i class differences in cardiovascular safety would currently have to be based upon indirect comparisons of the various clinical trials that have been completed or are underway. Such comparisons may be complicated by substantial differences with respect to many design features, as follows: enrollment criteria, geographic regions, follow-up time, sample size, adjudication and assessment, and order of hierarchical testing (13). Thus, this study addresses a present need for evidence regarding the comparative safety of DPP-4is relative to other antihyperglycemic medications, and of saxagliptin relative to sitagliptin.

To our knowledge, this is the first study comparing cardiovascular outcomes between saxagliptin and sitagliptin. Prior observational studies (12,14–23) that assessed the association between hHF and either the DPP-4i agents as a class or specific DPP-4i agents (i.e., sitagliptin) have used a wide variety of designs and patient populations with mixed results. Two studies (12,18) identified that DPP-4i treatment is associated with a reduced rate of hHF relative to other oral antihyperglycemic medications, two studies (14,16) suggested a neutral association relative to other oral antihyperglycemic medications and/or insulin, and two studies (19,20) suggested an increased rate of hHF with DPP-4i treatment relative to matched control subjects not otherwise initiating a new antihyperglycemic medication but rather in the midst of treatment with any of a range of potential antihyperglycemic medications. Notably, the designs used by the two studies that found an association between the DPP-4i treatment and an increased rate of heart failure may have created a risk of residual bias in favor of the matched control subjects; all else being equal, the matched patients did not necessarily require new pharmacotherapy to manage their diabetes.

It is possible, in accordance with the results of DPP-4i CVOTs and our analysis, that DPP-4is may increase the risk of heart failure compared with placebo, but do not increase the risk compared with an alternative active treatment that itself possesses some risk of hHF. In support of this possibility, none of the observational studies that

Table 1—Selected subset of characteristics of DPP-4i and SU cohorts after propensity score matching and of saxagliptin and sitagliptin cohorts after propensity score matching

	Baseline CVD*		No baseline CVD*		Baseline CVD†		No baseline CVD†	
	DPP-4i (*N* = 27,259)	SU (*N* = 27,259)	DPP-4i (*N* = 82,019)	SU (*N* = 82,019)	Saxagliptin (*N* = 13,042)	Sitagliptin (*N* = 13,042)	Saxagliptin (*N* = 43,402)	Sitagliptin (*N* = 43,402)
Age (years), mean (SD)	63.9 (11.8)	63.9 (12.0)	54.7 (10.9)	54.8 (11.1)	63.2 (11.3)	63.3 (11.4)	54.8 (10.7)	54.9 (10.8)
Male sex	60.1	59.9	52.9	52.7	61.4	61.2	54.1	54.1
Hospitalization in 30 days preindex	8.8	9.1	1.4	1.5	3.9	3.6	0.7	0.6
Hospitalization in 31–365 days preindex	23.1	23.2	4.2	4.3	20.7	20.1	3.9	3.9
Cardiologist visit during baseline	64.3	65.0	9.1	9.1	64.1	64.4	8.5	8.5
Chronic kidney disease (excluding ESRD)	6.8	6.9	1.9	1.9	6.2	6.4	1.9	1.9
ESRD	7.2	7.1	1.2	1.2	5.2	5.2	0.9	0.9
Hyperlipidemia or lipid disorder	57.7	58.0	44.3	44.2	58.1	57.8	45.4	45.3
Hypertension	75.5	75.5	53.7	53.8	75.9	76.2	55.9	55.7
Microvascular complications of diabetes								
Nephropathy	4.4	4.5	2.2	2.2	4.4	4.4	2.2	2.2
Peripheral neuropathy	14.0	14.2	6.9	7.0	14.5	14.1	7.2	7.3
Retinopathy	7.7	7.6	5.0	4.9	9.5	9.2	6.2	6.2
Heart failure	13.9	14.2	0.0	0.0	12.0	11.9	0.0	0.0
Hospitalized heart failure	1.0	1.1	0.0	0.0	1.0	1.1	0.0	0.0
AMI	4.8	5.0	0.0	0.0	3.6	3.5	0.0	0.0
Other ischemic heart disease	53.6	53.6	0.0	0.0	54.3	54.6	0.0	0.0
Other heart disease	59.6	59.7	0.0	0.0	57.2	57.5	0.0	0.0
Stroke (narrow)	1.7	1.8	0.0	0.0	1.2	1.1	0.0	0.0
Stroke (broad)	18.1	18.2	0.0	0.0	16.9	16.5	0.0	0.0
Peripheral artery disease	10.6	10.7	0.0	0.0	10.5	10.5	0.0	0.0
Coronary revascularization procedures								
Coronary artery bypass graft	2.1	2.1	0.0	0.0	1.3	1.2	0.0	0.0
Percutaneous coronary intervention	4.5	4.6	0.0	0.0	4.3	4.2	0.0	0.0
Medication use (180 days preindex)								
Any antihyperglycemic medication	71.2	72.3	75.0	75.5	83.6	83.7	81.6	81.4
Number of antihyperglycemic medication classes, mean (SD)	2.0 (0.7)	2.0 (0.8)	2.1 (0.6)	2.1 (0.7)	2.5 (0.9)	2.5 (0.9)	2.5 (0.8)	2.5 (0.8)
Any antihypertensive medication	86.6	86.6	68.6	68.8	88.1	88.1	71.4	71.8
Lipid-lowering medications	73.6	73.7	57.7	57.9	76.5	76.6	60.7	60.7
Digoxin (cardiac glycoside)	5.5	5.4	0.2	0.2	5.0	5.2	0.3	0.3

Values are reported as %, unless otherwise indicated. CVD, cardiovascular disease; ESRD, end-stage renal disease. Information is provided for all study covariables in Supplementary Table 2 (DPP-4i and SU cohorts) and Supplementary Table 3 (saxagliptin and sitagliptin cohorts). *In the DPP-4i and SU cohorts, the mean (SD, range) of the absolute value of standardized differences for all covariables was as follows: 0.51% (0.46%, 0–2.30%) for patients with baseline CVD; 0.32% (0.34%, 0–1.60%) for patients with no baseline CVD. †In the saxagliptin and sitagliptin cohorts, the mean (SD, range) of the absolute value of standardized differences for all covariables was: 0.48% (0.36%, 0–1.50%) for patients with baseline CVD; 0.34% (0.26%, 0–1.20%) for patients with no baseline CVD.

compared patients initiated on a DPP-4i treatment to patients initiated on an alternative antihyperglycemic therapy found a statistically significant association between the DPP-4i treatment and hHF, whereas some found a benefit (12,18).

Our study provides observational insight regarding the association between hHF and DPP-4i treatment compared with SU treatment; however, the risk of heart failure with SU treatment remains uncertain. The Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) study compared cardiovascular safety among patients receiving dual therapy of rosiglitazone with metformin or SU to that among patients receiving dual therapy of metformin and SU (24). Although the primary composite end

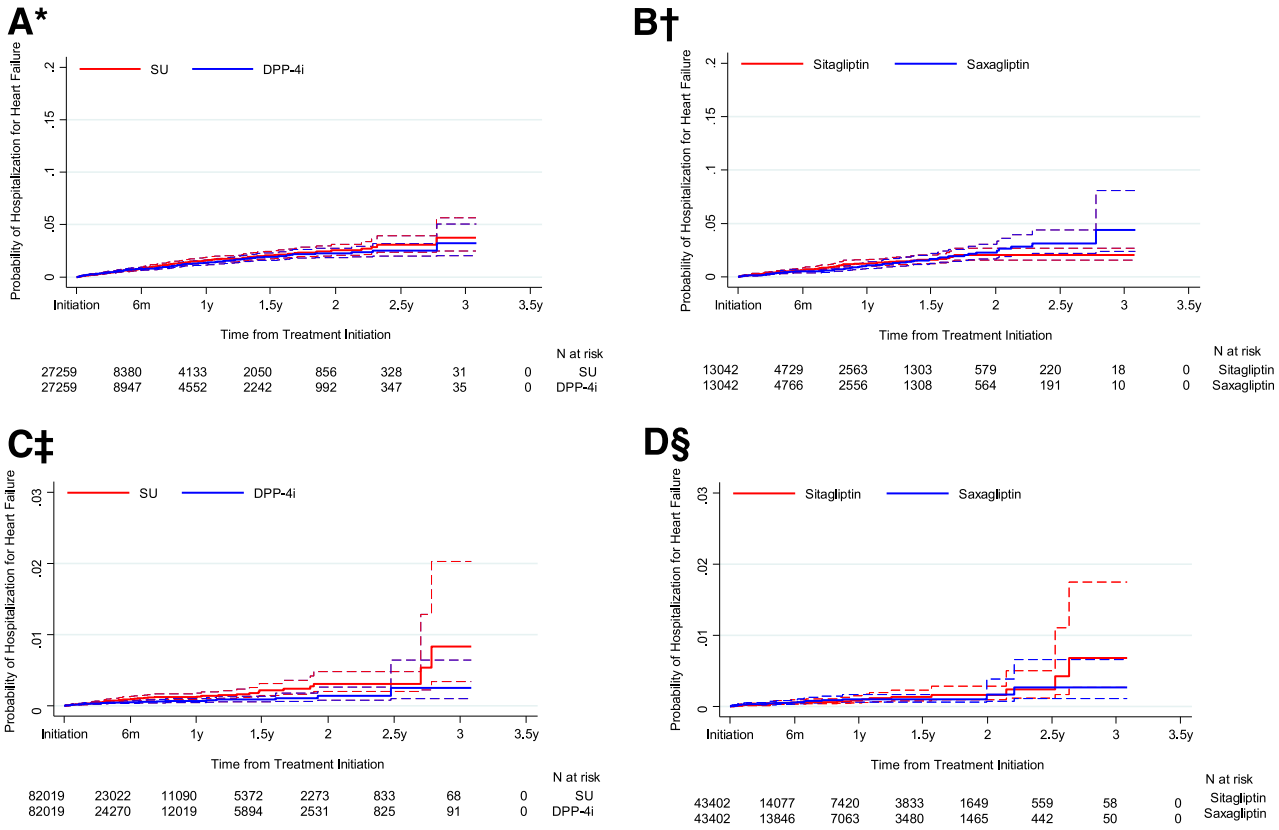

Figure 1—Kaplan-Meier plots of hHF: DPP-4i and SU cohort with baseline CVD (panel *A*); saxagliptin and sitagliptin cohorts with baseline CVD (panel *B*); DPP-4i and SU cohort with no baseline CVD (panel *C*); saxagliptin and sitagliptin cohorts with no baseline CVD (panel *D*). *HR treating SUs as reference (HR < 1 indicates a lower rate for DPP-4i) 0.946 (95% CI 0.778–1.151), *P* = 0.580. †HR treating sitagliptin as reference (HR < 1 indicates a lower rate for saxagliptin) 0.945 (95% CI 0.699–1.278), *P* = 0.712. ‡HR treating SUs as reference (HR < 1 indicates a lower rate for DPP-4i) 0.585 (95% CI 0.384–0.892), *P* = 0.013. §HR treating sitagliptin as reference (HR < 1 indicates a lower rate for saxagliptin) 0.990 (95% CI 0.560–1.749), *P* = 0.972. Dotted lines around the survival curve point estimates represent 95% confidence bands.

point was balanced between the two study arms, rosiglitazone therapy resulted in an increased risk of heart failure with an HR of 2.10, which is consistent with known effects of thiazolidinediones on fluid balance. Observational data regarding the rate of heart failure with the use of SUs has been mixed, with two studies (25,26) finding an association between SU treatment and an increased rate of heart failure compared with metformin treatment, and one study (27) finding no association between SU treatment and heart failure in the context of a case-control analysis compared with no SU exposure. Beyond heart failure, the increased risk of other cardiovascular events with SU therapy is better established in clinical trials (28) and observational studies (29,30). In agreement with our results, these prior studies found that DPP-4i therapy was often associated with a reduced rate of cardiovascular events compared with SU therapy. Ultimately, the findings related to DPP-4i versus SU therapy in our study are unexplained and should be interpreted with caution in light of the study limitations discussed below. The CAROLINA study, which uses an SU as an active comparator, may provide further insight into these questions.

Our study findings should be viewed in light of some limitations. First, we specifically attempted to address our primary objective by following the approach of one of the U.S. FDA Mini-Sentinel protocols for cardiovascular surveillance; this protocol did not involve the assessment of mortality. A chief reason for this is that many electronic health insurance claims databases, including the one used for the current study, lack complete information on mortality. In the EXAMINE, SAVOR-TIMI 53, and TECOS trials, alogliptin, saxagliptin, and sitagliptin did not increase or decrease the rate of cardiovascular or all-cause death. Thus, although we would not expect, based on trial data, alogliptin, saxagliptin, or sitagliptin to increase the risk of these outcomes, the present analyses leave unaddressed questions regarding whether the risk of cardiovascular or all-cause mortality differs between the studied groups (or alogliptin) in a real-world setting. Future research to address these questions is needed.

Second, due to an observational study design, we cannot rule out the possibility of residual confounding. The following aspects of the design and methods counter this limitation: *1*) selection bias specific to heart failure was likely minimal, as during the study period none of the medications used here were known to pose a risk of heart failure, and clinicians likely preferred using both DPP-4is and SUs to thiazolidinediones among patients at heightened risk for heart failure; *2*) the propensity score match performed extremely well, as evidenced by mean absolute values of the standardized differences ranging from 0.32% to

Table 2—Summary of results for all prespecified study analyses for DPP-4i and SU cohorts

	Sample *N*	Schoenfeld test	Events, *N*	HR	Lower 95% CI	Upper 95% CI	*P* value
No baseline CVD							
Primary and secondary analyses							
hHF	164,038	0.100	93	0.585	0.384	0.892	0.013
Coronary artery bypass graft	164,038	0.381	149	0.690	0.498	0.956	0.026
Hospitalization for AMI	164,038	0.400	247	0.738	0.574	0.949	0.018
Hospitalization for stroke	164,038	0.929	142	0.525	0.372	0.741	<0.001
Hospitalization for UA	164,038	0.072	6	0.489	0.089	2.702	0.412
Coronary revascularization	164,038	0.257	543	0.788	0.665	0.933	0.006
Composite outcome	164,038	0.189	808	0.702	0.610	0.807	<0.001
Sensitivity analyses							
Multivariable Cox	237,232	<0.001	143	0.599	0.402	0.894	0.012
Age ≥65 years	23,862		Prespecified sample criteria not met (*N* = 23,862)				
No baseline or follow-up TZDs	128,324	0.600	68	0.416	0.247	0.701	0.001
No baseline loop diuretics	156,132	0.007	63	0.558	0.333	0.934	0.026
SAVOR-TIMI 53–like patients	50,026		Prespecified sample criteria not met (*N* = 50,026)				
30-day extension	164,038	0.110	108	0.598	0.405	0.883	0.010
45-day gap allowance	164,038	0.094	113	0.617	0.422	0.901	0.012
Baseline CVD							
Primary and secondary analyses							
hHF	54,518	0.163	402	0.946	0.778	1.151	0.580
Coronary artery bypass graft	54,518	0.431	198	0.766	0.579	1.015	0.063
Hospitalization for AMI	54,518	0.849	232	0.843	0.651	1.091	0.195
Hospitalization for stroke	54,518	0.051	185	0.865	0.649	1.155	0.326
Hospitalization for UA	54,518	0.491	10	2.187	0.563	8.496	0.258
Coronary revascularization	54,518	0.036	817	0.785	0.684	0.901	0.001
Composite outcome	54,518	0.054	1,470	0.869	0.784	0.963	0.007
Sensitivity analyses							
Multivariable Cox	78,964	0.069	650	0.950	0.796	1.135	0.573
Age ≥65 years	23,036	0.232	278	0.976	0.771	1.235	0.839
No baseline or follow-up TZDs	42,758	0.413	322	1.065	0.856	1.326	0.570
No baseline loop diuretics	42,082	0.429	122	0.833	0.583	1.189	0.314
SAVOR-TIMI 53–like patients	41,238	0.161	366	1.007	0.820	1.236	0.948
30-day extension	54,518	0.139	458	0.928	0.772	1.114	0.421
45-day gap allowance	54,518	0.134	480	0.863	0.721	1.032	0.106

TZD, thiazolidinedione; UA, unstable angina.

0.51% across the four comparisons, and a maximum value of 2.3% (a standardized difference of <10% is generally considered to be indicative of adequate balance) across a sum total of 442 covariables that are likely to be correlated with severity and duration of diabetes included in the four models (e.g., the proportions of patients with baseline metformin use, which has been suggested to be of benefit with respect to the risk of heart failure [31,32], differed across groups by only a few tenths of a percentage point); *3*) the high proportion of matched subjects likely reflects the clinical similarity of the cohorts we compared; and *4*) the new-user cohort design is the recommended default design for comparative studies by the Agency for Healthcare Research and Quality (33). An important implication of the new-user cohort design, however, is that in order to increase internal validity it specifically excludes patients who used a comparator treatment in the prior 12 months and therefore is generalizable only to this set of patients. Many real-world users of DPP-4is may have prior exposure to SUs or vice versa, and the current study does not include such patients. This design may have also resulted in selection bias if DPP-4i users who used SUs differed systematically from those who did not. Consequently, the study results corresponding to the DPP-4i and SU comparison may not be generalizable to DPP-4i users with prior exposure to SUs or vice versa.

Third, the study database comprised insurance claims data from individuals with commercial or Medicare plus supplemental health insurance and may not be generalizable to individuals with other insurance or without health insurance coverage. These data are not collected for research purposes; they lack some potentially important demographic measures, such as patients' race, socioeconomic status, or education; and the diagnostic and procedure coding in the data may be subject to errors.

Fourth, the average and median durations of patient follow-up were relatively short at ~6 months and 3 months, respectively, across the study cohorts. The short duration of follow-up was primarily driven by a high censoring rate due to strict rules regarding the cessation of index therapy. Across the analyses, the cessation of index therapy was the most common reason for the end of follow-up, generally being the reason for end of follow-up in >60% of patients. In two separate prespecified sensitivity analyses, we relaxed the Mini-Sentinel approach of using strict criteria for censoring, resulting in follow-up times that were 25–97% longer than in the primary analysis. Importantly, these sensitivity analyses yielded results that were similar to those of the primary analyses.

Table 3—Summary of results for all prespecified study analyses for saxagliptin and sitagliptin cohorts

	Sample *N*	Schoenfeld test	Events, *N*	HR	Lower 95% CI	Upper 95% CI	*P* value
No baseline CVD							
Primary and secondary analyses							
hHF	86,804	0.155	47	0.990	0.560	1.749	0.972
Coronary artery bypass graft	86,804	0.253	94	0.986	0.657	1.480	0.946
Hospitalization for AMI	86,804	0.389	127	1.013	0.714	1.437	0.942
Hospitalization for stroke	86,804	0.124	82	0.892	0.578	1.376	0.606
Hospitalization for UA	86,804	0.045	5	1.548	0.266	9.028	0.627
Coronary revascularization	86,804	0.158	312	1.055	0.844	1.317	0.639
Composite outcome	86,804	0.491	458	1.038	0.864	1.247	0.687
Sensitivity analyses							
Multivariable Cox	152,038	<0.001	86	1.149	0.696	1.898	0.588
Age ≥65 years	11,854		Prespecified sample criteria not met (*N* = 11,854)				
No baseline or follow-up TZDs	64,202		Prespecified sample criteria not met (*N* = 64,202)				
No baseline loop diuretics	82,520	0.345	31	1.226	0.604	2.490	0.573
SAVOR-TIMI 53–like patients	26,686		Prespecified sample criteria not met (*N* = 26,686)				
30-day extension	86,804	0.111	58	0.895	0.535	1.495	0.671
45-day gap allowance	86,804	0.120	63	1.029	0.629	1.683	0.909
Baseline CVD							
Primary and secondary analyses							
hHF	26,084	0.166	169	0.945	0.699	1.278	0.712
Coronary artery bypass graft	26,084	0.546	94	0.744	0.494	1.119	0.155
Hospitalization for AMI	26,084	0.422	107	0.784	0.535	1.148	0.211
Hospitalization for stroke	26,084	0.879	75	0.744	0.471	1.175	0.205
Hospitalization for UA	26,084	0.904	3	1.999	0.181	22.085	0.572
Coronary revascularization	26,084	0.061	412	0.983	0.810	1.192	0.862
Composite outcome	26,084	0.248	680	0.903	0.777	1.050	0.183
Sensitivity analyses							
Multivariable Cox	52,647	0.060	466	0.823	0.642	1.054	0.122
Age ≥65 years	10,108		Prespecified sample criteria not met (*N* = 10,108)				
No baseline or follow-up TZDs	18,996	0.227	142	0.860	0.618	1.198	0.372
No baseline loop diuretics	20,740	0.086	63	0.863	0.526	1.418	0.562
SAVOR-TIMI 53–like patients	19,334	0.295	157	0.811	0.592	1.111	0.192
30-day extension	26,084	0.177	188	0.940	0.706	1.251	0.670
45-day gap allowance	26,084	0.082	191	0.971	0.731	1.289	0.839

TZD, thiazolidinedione; UA, unstable angina.

Furthermore, within the SAVOR-TIMI 53 trial, the increased risk of hHF was the greatest at the first time point (i.e., 6 months) of follow-up (34).

Finally, the approach to censoring upon the cessation of therapy could have been a potential source of bias when ascertaining outcomes if the cessation of therapy was informative (e.g., if physicians systematically ceased patients' treatment in anticipation of hHF or another cardiovascular outcome). Although the two aforementioned sensitivity analyses in which we extended the period during which hHF was identified were used to address this matter, and we have no reason to believe that there would be differential informative censoring across the compared groups, the potential for informative censoring cannot be completely ruled out in the analysis.

In summary, heart failure is not uncommon among patients with type 2 diabetes, and the selection of pharmacotherapy can affect that risk. It is an important part of current medical practice to monitor all patients with type 2 diabetes for heart failure symptoms, such as shortness of breath and edema. In this observational study of patients with type 2 diabetes, we found no association between hHF, or other selected cardiovascular outcomes, and treatment with a DPP-4i relative to SU or treatment with saxagliptin relative to sitagliptin.

Acknowledgments. The authors thank Kate Higgins, Research Assistant at Truven Health Analytics, for her support.

Funding and Duality of Interest. This study was sponsored by AstraZeneca.

A.Z.F. was a paid consultant to Truven Health Analytics, which was paid by the study sponsor AstraZeneca to conduct this study. S.S.J., K.C., R.F., E.R., and A.L.C. are employees of Truven Health Analytics, which was paid by the study sponsor AstraZeneca to conduct this study. A.G. and I.K. were employees of AstraZeneca at the time that this research was conducted. K.T. is an employee of MedImmune/AstraZeneca. J.S. is an employee of AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.Z.F., S.S.J., A.G., I.K., and J.S. contributed to the study concept and design, researched the data, and wrote the article. K.T., K.C., R.F., E.R., and A.L.C. contributed to the study concept and design, researched the data, and reviewed and edited the article. S.S.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 75th Scientific Sessions of the American Diabetes Association, Boston, MA, 5–9 June 2015.

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