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Risk for Hospitalized Heart Failure Among New Users of Saxagliptin, Sitagliptin, and Other Antihyperglycemic Drugs

A Retrospective Cohort Study

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Background: Recent postmarketing trials produced conflicting results about the risk for hospitalized heart failure (hHF) associated with dipeptidyl peptidase-4 (DPP-4) inhibitors, creating uncertainty about the safety of these antihyperglycemic agents.

Objective: To examine the associations of hHF with saxagliptin and sitagliptin.

Design: Population-based, retrospective, new-user cohort study.

Setting: 18 health insurance and health system data partners in the U.S. Food and Drug Administration's Mini-Sentinel program.

Patients: Patients aged 18 years or older with type 2 diabetes who initiated therapy with saxagliptin, sitagliptin, pioglitazone, second-generation sulfonylureas, or long-acting insulin products from 2006 to 2013.

Measurements: Hospitalized HF, identified by International Classification of Diseases, Ninth Revision, Clinical Modification codes 402.x1, 404.x1, 404.x3, and 428.xx recorded as the principal discharge diagnosis.

Results: 78 553 saxagliptin users and 298 124 sitagliptin users contributed an average of 7 to 9 months of follow-up data to 1 or more pairwise comparisons. The risk for hHF was not higher with DPP-4 inhibitors than with the other study drugs. The hazard ratios from the disease risk score (DRS)–stratified analyses were 0.83 (95% CI, 0.70 to 0.99) for saxagliptin versus sitagliptin, 0.63 (CI, 0.47 to 0.85) for saxagliptin versus pioglitazone, 0.69 (CI, 0.54 to 0.87) for saxagliptin versus sulfonylureas, and 0.61 (CI, 0.50 to 0.73) for saxagliptin versus insulin. The DRS-stratified hazard ratios were 0.74 (CI, 0.64 to 0.85) for sitagliptin versus pioglitazone, 0.86 (CI, 0.77 to 0.95) for sitagliptin versus sulfonylureas, and 0.71 (CI, 0.64 to 0.78) for sitagliptin versus insulin. Results from the 1:1 propensity score–matched analyses were similar. Results were also similar in subgroups of patients with and without prior cardiovascular disease and in a subgroup defined by the 2 highest DRS deciles.

Limitation: Residual confounding and short follow-up.

Conclusion: In this large cohort study, a higher risk for hHF was not observed in users of saxagliptin or sitagliptin compared with other selected antihyperglycemic agents.

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Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral antihyperglycemic medications that work by slowing the inactivation of the incretin hormones by the DPP-4 enzyme (1). The resulting increase and prolongation of incretin levels reduces both fasting and postprandial glucose concentrations in a glucose-dependent manner. The cardiovascular safety of DPP-4 inhibitors has recently become a subject of considerable debate due to the conflicting findings from several large postmarketing trials (2–4). The SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) trial unexpectedly showed a higher incidence of hospitalized heart failure (hHF) in the saxagliptin group than the placebo group (2). In contrast, 2 other postmarketing trials—the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) trial (3) and TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) (4)—did not find a statistically significant difference in the risk for hHF among patients receiving alogliptin or sitagliptin versus placebo.

Based on these clinical trials, it remains unclear whether the increased hHF risk observed with saxagliptin but not sitagliptin is due to properties of the drugs, different patient characteristics between the trials, or random error related to multiple hypothesis testing. Patients with diabetes have a higher hHF risk than those without (5, 6), so any antihyperglycemic agent that modifies the risk warrants further examination. Thus, we assessed the associations of hHF with the 2 most commonly used DPP-4 inhibitors, saxagliptin and sitagliptin, in a large population-based cohort of patients with type 2 diabetes mellitus (T2DM) treated with antihyperglycemic agents in routine clinical settings.

Methods

Study Design

This study was part of a larger, ongoing active surveillance project designed to complement SAVOR-TIMI 53. The primary goal of the project was to compare the risk for acute myocardial infarction (AMI) between saxa-

See also:

Editorial comment 771

EDITORS' NOTES

Context

Postmarketing placebo-controlled trials and observational studies have provided conflicting results about the risk for hospitalized heart failure (hHF) among patients using dipeptidyl peptidase-4 (DPP-4) inhibitors.

Contribution

This large cohort study compared new users of 2 DPP-4 inhibitors (saxagliptin or sitagliptin) and new users of second-generation sulfonylureas, pioglitazone, or long-acting insulin products. The investigators did not find an increased risk for hHF among DPP-4 inhibitor users.

Caution

The average follow-up was less than 1 year.

Implication

This observational study provides additional evidence on the risk for hHF among users of DPP-4 inhibitors compared with other antihyperglycemic drugs used in routine clinical practice.

gliptin and selected antihyperglycemic agents among patients with T2DM. A detailed protocol has been published previously (7, 8). The AMI surveillance project uses a sequential design with updated analyses as new data accrue. Within this larger project, we conducted the hHF analysis as a 1-time assessment, which allowed us to provide timely information about the safety of DPP-4 inhibitors while maintaining the scientific rigor of the analysis. Both the AMI and hHF analyses used a new-user cohort design (Figure 1) (9) to compare saxagliptin with sitagliptin and each with pioglitazone, second-generation sulfonylureas, and long-acting insulin products. These comparators were chosen because they were common alternatives to saxagliptin in clinical practice at the time of the protocol development (10). Therefore, this study included 7 head-to-head comparisons: saxagliptin versus sitagliptin, saxagliptin versus pioglitazone, saxagliptin versus sulfonylureas, saxagliptin versus insulin, sitagliptin versus pioglitazone, sitagliptin versus sulfonylureas, and sitagliptin versus insulin.

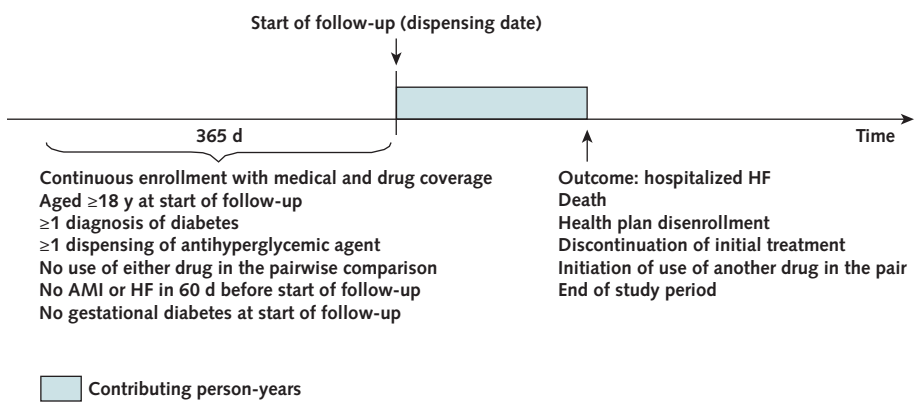
Data Source

This study was conducted within Mini-Sentinel, a pilot program created to assist the U.S. Food and Drug Administration (FDA) in developing a national active safety surveillance system of FDA-regulated medical products (11, 12). Mini-Sentinel uses a distributed data system that allows data to be stored locally under the control of the participating data partners (13). At the time of this assessment (August 2014), the Mini-Sentinel Distributed Database comprised quality-checked data covering 178 million persons and 358 million person-years of longitudinal observation time between 2000 and 2014 from 18 administrative claims and clinical data partners (a complete list of data partners is provided in the Acknowledgment). Mini-Sentinel is a public health surveillance activity that is not under the purview of institutional review boards (14, 15).

Study Cohort

For each pairwise comparison (for example, saxagliptin vs. sulfonylureas), we identified new users of the DPP-4 inhibitor of interest or the comparator drug among patients aged 18 years or older with T2DM beginning on 1 August 2009 (for saxagliptin) or 1 October 2006 (for sitagliptin). We defined T2DM as having at least 1 prescription for an oral antihyperglycemic medication other than metformin or at least 1 diagnosis of diabetes plus at least 1 prescription for metformin. We considered metformin differently from other antihyperglycemic agents because it is also used to treat conditions other than T2DM, including polycystic ovary syndrome (16). We defined new use of the DPP-4 inhibitor or the comparator drug as no prior dispensing of either drug during 365 days of continuous health plan enrollment, and we defined the dispensing date of the first eligible prescription of either drug as the index date. Use of other study drugs did not disqualify patients but

Figure 1. Study design for each of the 7 pairwise comparisons.



AMI = acute myocardial infarction; HF = heart failure.

was adjusted for in the analysis. For example, past use of pioglitazone disqualified saxagliptin users from the comparisons of saxagliptin versus pioglitazone but not from the comparisons of saxagliptin versus sulfonylureas.

We excluded patients who had a principal discharge diagnosis of AMI (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 410.x0 and 410.x1) or HF (ICD-9-CM codes 402.x1, 404.x1, 404.x3, and 428.xx) in the 60 days before the index date because of their high risk for recurrence and the high potential for unmeasured confounding. As a reference, SAVOR-TIMI 53 also excluded patients who had an acute vascular (cardiac or stroke) event within 2 months before randomization. In the comparisons with pioglitazone, we further excluded patients with an outpatient or inpatient diagnosis of HF during the 365-day baseline period because the condition is a contraindication to the use of pioglitazone. We divided all remaining patients into those with and those without a history of cardiovascular disease (CVD) (see Appendix Table 1, available at www.annals.org, for specific diagnoses and procedures) during the baseline period.

Outcome

Hospitalized HF was identified by ICD-9-CM codes 402.x1, 404.x1, 404.x3, and 428.xx recorded as the principal discharge diagnosis. The algorithm has a positive predictive value greater than 90% based on prior validation studies (17).

Follow-up

Each pairwise comparison followed eligible new users of the DPP-4 inhibitor or comparator drug of interest from the index date until the earliest occurrence of an hHF event, discontinuation of the initiated therapy (for example, new users of saxagliptin discontinuing its use), initiation of therapy with the other drug in the pair (for example, new users of saxagliptin adding or switching to a sulfonylurea in the comparisons of saxagliptin vs. sulfonylureas), health plan disenrollment, death, or the end of the study period (which varied by data partner from 30 June 2012 to 31 December 2013). Discontinuation of use occurred when the days' supply seemed to have been exhausted for a period of 10 days or one third of the days' supply of the most recent dispensing, whichever was greater.

Adjustment for Confounders

We used 2 complementary approaches—disease risk score (DRS) stratification (18) and 1:1 exposure propensity score (PS) matching (19)—to adjust for prespecified confounders, including patient demographic characteristics, medical history, medication use, risk factors for hHF and other cardiovascular events, other antihyperglycemic treatments, and health services utilization measures (Table 1 and Appendix Table 2, available at www.annals.org). The protocol provides algorithms used to identify these covariates (7).

DRS Stratification

The DRS-stratified analysis was a 2-step process (Appendix Figure, available at www.annals.org) (18). We first used a larger, earlier T2DM population from the same data partners to estimate the relative hazard for hHF events associated with the baseline covariates using a multivariable Cox regression model. For the saxagliptin analysis, we created a cohort of patients with T2DM in 2007 to 2008 within each data partner and followed them through the end of 2009 for occurrence of hHF events. We required 12 months of baseline data to measure all potential confounders needed to estimate the DRS. The corresponding periods were 2004 to 2005 and 2006 for the sitagliptin analysis. Next, we assigned to each new user in our pairwise comparisons a DRS equal to $\chi\beta$, where χ was the new user's covariate profile and β was the vector of the log of the hazard ratio (HR) estimates for the covariates from the Cox model fitted to the larger T2DM population. The resulting DRS was the new user's estimated hazard of hHF at baseline, conditional on their covariate profile, relative to a patient with a reference covariate profile (that is, a profile with all covariates set to zero). Within each CVD stratum at each data partner, we ordered patients from lowest to highest and divided them into deciles based on their DRSs.

1:1 PS Matching

We estimated the PSs by data partner and within subgroups defined by CVD history for each pairwise comparison. The PS model estimated the probability of initiating therapy with saxagliptin (or sitagliptin) versus the comparator drug and included all potential confounders as predictors. We then used a greedy matching procedure (20) to identify the nearest possible match within a caliper of 0.01 (on the probability scale) between a randomly selected saxagliptin (or sitagliptin) user and a comparator user within the same quarter of cohort entry.

Statistical Analysis

For both DRS stratification and PS matching in each pairwise comparison, we used a stratified Cox proportional hazards model to estimate the HR and 95% CI for hHF. We stratified the analyses by data partner, quarter of cohort entry, and CVD history. The DRS-adjusted analyses were further stratified by DRS decile. We examined the HRs separately for patients with and without a history of CVD. We also conducted DRS-adjusted pairwise comparisons in high-risk subgroups (patients with a history of CVD who were also within the 2 highest deciles of DRS) in an attempt to match the high baseline risk for hHF among the SAVOR-TIMI 53 participants. Finally, we examined possible heterogeneity of the adjusted HRs by data partner, time receiving the study drug, and calendar time. All analyses were performed with SAS, version 9.3 (SAS Institute).

Role of the Funding Source

The FDA was involved in the design, conduct, and reporting of the study.

Table 1. Selected Baseline Patient Characteristics, by Study Drug: Saxagliptin Analysis

Covariate	Saxagliptin*	Sitagliptin	Pioglitazone	Sulfonylureas	Long-Acting Insulin
New users, *n*†	78 553	210 178	144 266	432 351	247 863
Demographic characteristics					
Mean age, *y*	57.2	59.1	58.3	58.8	59.4
Male, %	56.1	54.8	57.9	55.1	53.8
Comorbid conditions, %‡					
Asthma	6.5	7.2	6.6	7.9	9.2
Cancer	6.4	7.3	6.2	7.3	9.1
Chronic obstructive pulmonary disease	6.1	7.5	6.2	8.4	10.7
Chronic kidney disease	5.7	7.4	7.4	8.7	13.2
Dementia	1.4	2.5	1.9	2.7	3.9
Depression	9.0	10.1	9.2	11.1	14.0
End-stage renal disease	0.5	0.9	0.8	1.0	1.9
Fracture	2.8	3.3	3.0	3.3	4.3
Heart failure (>60 d)§	5.1	7.1	4.4	7.3	11.1
HIV/AIDS	0.2	0.2	0.2	0.2	0.3
Hyperlipidemia	79.2	77.5	76.6	71.3	76.2
Hypertension	77.9	77.9	75.9	74.1	79.4
Hypoglycemia	4.1	5.1	5.2	5.6	9.7
Obesity or weight gain	18.5	19.0	16.7	19.7	23.6
Osteoporosis	4.3	4.8	4.2	4.4	4.6
Peripheral neuropathy	14.4	15.8	15.4	14.8	22.6
Tobacco use	7.1	7.5	7.0	10.2	12.1
Concurrent antihyperglycemic drug use, %					
Any	100.0	100.0	100.0	100.0	100.0
α-Glucosidase inhibitor	0.3	0.4	0.4	0.2	0.6
Long-acting insulin	8.1	8.6	9.2	7.0	100.0
Short-acting insulin	1.8	2.4	2.8	2.0	13.8
Meglitinide	1.2	1.1	1.1	0.6	1.5
Metformin	68.5	67.6	61.7	58.9	56.3
Pioglitazone	10.5	11.4	100.0	6.9	11.7
Saxagliptin	100.0	0.7	1.7	1.4	2.4
Sitagliptin	6.5	100.0	11.7	7.5	13.1
Second-generation sulfonylurea	32.4	35.3	40.8	100.0	51.9
Other DPP-4 inhibitor	0.2	0.1	0.5	0.3	0.6
Other thiazolidinedione	1.2	1.4	6.6	0.8	0.9
Other	1.8	1.3	3.4	1.7	5.2
CVD in prior year, %‡					
AMI (>60 d)	0.5	0.6	0.4	0.5	0.8
Carotid revascularization	0.1	0.2	0.1	0.2	0.2
Coronary revascularization	4.6	5.8	4.3	5.6	8.0
Coronary artery bypass graft surgery	2.2	3.0	2.1	2.9	4.4
Percutaneous coronary intervention	3.0	3.7	2.7	3.6	5.1
Lower-extremity revascularization	0.4	0.5	0.5	0.6	1.1
Other ischemic heart disease	16.5	19.4	15.5	17.5	22.7
Other heart disease	18.5	21.9	17.2	20.6	26.5
Peripheral arterial disease	4.5	5.2	4.1	5.3	7.6
Stroke	5.5	6.8	5.4	6.1	8.3

AMI = acute myocardial infarction; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4.
* Includes users who contributed to ≥1 pairwise comparison.
† New use with respect to the drug itself, before conducting pairwise comparisons that excluded patients who used either drug in each comparison during the baseline period.
‡ Recorded in inpatient or outpatient encounter unless otherwise specified.
§ Excluded from comparisons involving pioglitazone.

RESULTS

The age and sex distributions of new users of the study drugs were similar, with a mean age near 60 years and about 55% men (Tables 1 and 2; complete profiles are shown in Appendix Tables 2 and 3, available at www.annals.org). The proportion with a prior HF diagnosis was 5% for saxagliptin users, 7% for sitagliptin users, 7% for sulfonylurea users, and 11% for insulin users.

A total of 78 553 new users of saxagliptin contributed to 1 or more of the 4 pairwise comparisons. The average follow-up was about 7 months for saxagliptin users and 7 to 8 months for users of sitagliptin, pioglitazone, and sulfonylureas. For users of insulin, the mean follow-up was about 4 months. The incidence rate of hHF per 1000 person-years ranged from 2 to 4 for saxagliptin users across the 4 pairwise comparisons and was about 7 for sitagliptin users, 4 for pioglitazone

users, 9 for sulfonylurea users, and 16 for insulin users.

A total of 298 124 new users of sitagliptin contributed to 1 of the 3 pairwise comparisons. The mean follow-up was 8 to 9 months for both sitagliptin users and users of pioglitazone and sulfonylureas. New users of insulin had a shorter follow-up of approximately 4 months. The incidence rate of hHF per 1000 person-years was between 3 and 5 for sitagliptin users across the pairwise comparisons and was about 4 for pioglitazone users, 9 for sulfonylurea users, and 16 for insulin users.

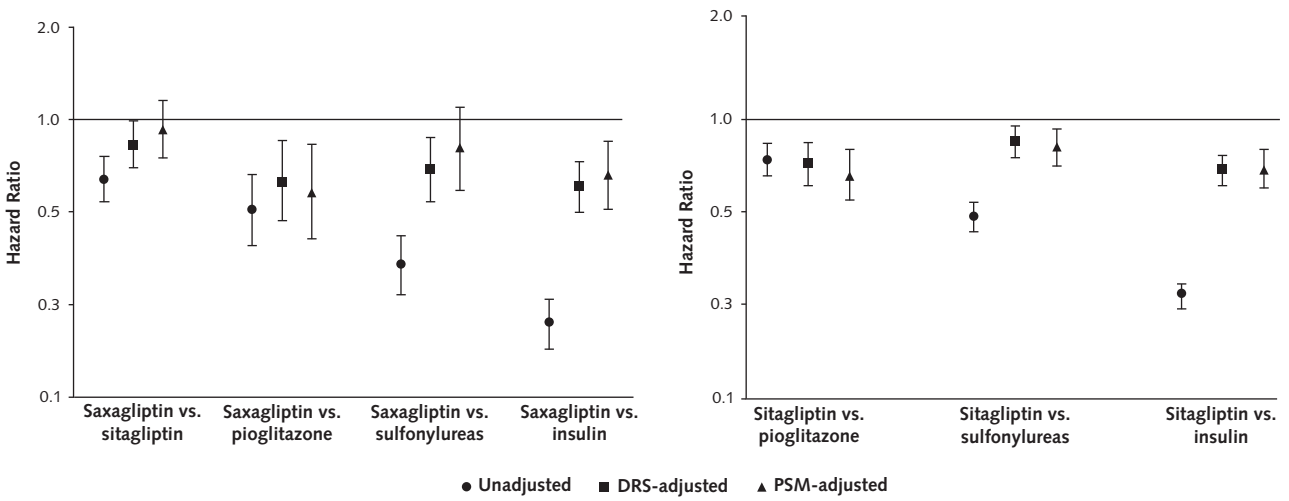
The unadjusted rate ratios were less than 1.0 and the 95% CIs excluded 1.0 in each pairwise comparison, suggesting a lower hHF risk in users of the DPP-4 inhibitor of interest (Figure 2). Some comparisons produced an unadjusted rate ratio that was well below 1.0, including saxagliptin versus sulfonylureas (0.34 [95% CI, 0.27 to 0.42]), saxagliptin versus insulin (0.22 [CI, 0.18 to 0.26]), and sitagliptin versus insulin (0.31 [CI, 0.28 to

Table 2. Selected Baseline Patient Characteristics, by Study Drug: Sitagliptin Analysis

Covariate	Sitagliptin*	Pioglitazone	Sulfonylureas	Long-Acting Insulin
New users, *n*†	298 124	252 498	613 546	342 334
Demographic characteristics				
Mean age, *y*	58.6	58.2	58.9	59.1
Male, %	54.9	57.0	54.8	53.6
Comorbid conditions, %‡				
Asthma	7.1	6.7	8.0	9.2
Cancer	7.2	6.3	7.3	9.1
Chronic obstructive pulmonary disease	7.3	6.3	8.4	10.6
Chronic kidney disease	6.4	6.3	7.5	11.9
Dementia	2.2	1.9	2.7	3.8
Depression	9.6	9.1	10.8	13.8
End-stage renal disease	0.9	0.8	1.1	2.0
Fracture	3.3	3.1	3.4	4.3
Heart failure (>60 d)§	7.1	4.7	7.5	11.4
HIV/AIDS	0.2	0.2	0.2	0.3
Hyperlipidemia	76.8	74.3	69.4	74.7
Hypertension	77.0	74.8	73.3	78.4
Hypoglycemia	4.9	5.0	5.1	9.1
Obesity or weight gain	18.0	17.1	20.2	23.6
Osteoporosis	4.7	4.0	4.1	4.4
Peripheral neuropathy	15.4	15.1	14.6	22.3
Tobacco use	7.0	7.4	10.4	12.1
Concurrent antihyperglycemic drug use, %				
Any	100.0	100.0	100.0	100.0
α-Glucosidase inhibitor	0.4	0.4	0.2	0.7
Long-acting insulin	8.3	9.0	6.7	100.0
Short-acting insulin	2.3	2.8	2.0	13.9
Meglitinide	1.5	1.2	0.6	1.7
Metformin	66.9	61.7	58.5	56.2
Pioglitazone	13.1	100.0	7.9	13.5
Saxagliptin	0.5	1.0	1.0	1.7
Sitagliptin	100.0	9.3	6.3	11.6
Second-generation sulfonylurea	35.7	42.0	100.0	53.1
Other DPP-4 inhibitor	0.1	0.3	0.2	0.4
Other thiazolidinedione	3.4	7.6	1.6	1.8
Other	1.6	3.0	1.6	5.0
CVD in prior year, %‡				
AMI (>60 d)	0.6	0.4	0.5	0.8
Carotid revascularization	0.2	0.1	0.2	0.2
Coronary revascularization	6.0	4.8	5.9	8.2
Coronary artery bypass graft surgery	3.1	2.4	3.1	4.5
Percutaneous coronary intervention	3.8	3.0	3.7	5.2
Lower-extremity revascularization	0.5	0.5	0.6	1.1
Other ischemic heart disease	19.7	16.3	17.7	22.8
Other heart disease	21.7	17.1	20.2	26.0
Peripheral arterial disease	4.1	4.1	5.4	7.8
Stroke	6.6	5.3	6.0	8.1

AMI = acute myocardial infarction; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4.
* Includes users who contributed to ≥1 pairwise comparison.
† New use with respect to the drug itself, before conducting pairwise comparisons that excluded patients who used either drug in each comparison during the baseline period.
‡ Recorded in inpatient or outpatient encounter unless otherwise specified.
§ Excluded from comparisons involving pioglitazone.

Figure 2. Hazard ratios and 95% CIs for hospitalized heart failure, by study drug and analysis.



Hazard ratio <1 indicates a lower risk for hospitalized heart failure among users of saxagliptin (*left*) or sitagliptin (*right*). DRS = disease risk score; PSM = propensity score matching.

0.33]). After adjustment for confounders using DRS-stratification or PS matching, the HRs in all comparisons generally moved closer to but were still below 1.0 (Table 3 and Figure 2). Adjustment by DRS stratification yielded results similar to those obtained with adjustment by PS matching.

We did not find strong evidence to suggest that the associations varied substantially in patients with and without prior CVD (Table 3). The HRs did not exceed 1.0 in patients who not only had prior CVD but were also in the highest 2 deciles of that stratum's DRS; they were 0.87 (CI, 0.70 to 1.09) for saxagliptin versus sitagliptin, 0.54 (CI, 0.23 to 1.29) for saxagliptin versus pioglitazone, 0.74 (CI, 0.54 to 1.00) for saxagliptin versus sulfonylureas, 0.79 (CI, 0.63 to 1.00) for saxagliptin versus insulin, 0.94 (CI, 0.62 to 1.42) for sitagliptin versus pioglitazone, 0.95 (CI, 0.84 to 1.08) for sitagliptin versus sulfonylureas, and 0.82 (CI, 0.73 to 0.92) for sitagliptin versus insulin. There was no evidence to suggest that the results differed by data partner, time receiving the study drug, or calendar time (data not shown).

DISCUSSION

In this large population-based cohort study, we did not observe an increased risk for hHF among new users of saxagliptin or sitagliptin compared with new users of pioglitazone, second-generation sulfonylureas, or long-acting insulin products. The study demonstrates the capability of Mini-Sentinel, a national medical product safety surveillance system under development, to examine emerging safety issues (21). By comparing DPP-4 inhibitor users and users of other antihyperglycemic agents who received these treatments in routine clinical practice, our study provides information that complements recently completed postmarketing placebo-controlled trials (2–4). Our findings are clinically relevant because patients and physicians often choose among various treatment alternatives (including no treatment) for T2DM in practice.

Regulatory agencies (22–24) now require more rigorous assessments of the cardiovascular risks of new antihyperglycemic treatments during the premarketing and postmarketing phases of the drug approval process. The SAVOR-TIMI 53 trial was a large cardiovascular outcomes trial conducted as a postmarketing requirement in accordance with FDA guidance recommendations (22). During a median follow-up of 2.1 years, the risk for the primary composite end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) was similar in patients randomly assigned to saxagliptin (n = 8280) and placebo (n = 8212), but the relative incidence of hHF was 27% greater in the saxagliptin group (HR, 1.27 [CI, 1.07 to 1.51]) (2). The risk seemed to be higher during the earlier follow-up period: The HR was 1.80 (CI, 1.29 to 2.55) at 6 months and 1.46 (CI, 1.15 to 1.88) at 12 months (25). Although the absolute incidence of hHF was greater among patients with a history of HF, the HR did not vary by prior HF status (1.21 among patients with prior HF vs. 1.32 among those without) (25). Hospitalization for HF was a prespecified secondary end point in SAVOR-TIMI 53, with independent, blinded adjudication of events by specialists. Given the multiple end points assessed, however, the possibility of a chance finding cannot be ruled out.

The EXAMINE trial was a second large prospective trial of cardiovascular outcomes with DPP-4 inhibitors that compared alogliptin (n = 2701) versus placebo (n = 2679), both added to background diabetes therapy, in patients with T2DM who had a recent acute coronary syndrome. Although not statistically significant, a numerical imbalance in hHF was observed for the alogliptin group (HR, 1.19 [CI, 0.90 to 1.58]), particularly in patients without a history of HF (2.2% vs. 1.3%;

HR, 1.76 [CI, 1.07 to 2.90]), during a median follow-up of 1.5 years (3). On the other hand, our results are consistent with the finding from TECOS—the most recently completed trial of cardiovascular outcomes with DPP-4 inhibitors—of no difference in the risk for hHF between sitagliptin (n = 7257) and placebo (n = 7266) during a median follow-up of 3.0 years (HR, 1.00 [CI, 0.83 to 1.20]) (4).

There are several possible explanations for the discrepant findings between our study and SAVOR-TIMI 53, including population differences and limitations inherent to our observational study design. First, although we adjusted for a wide range of variables, there could still be residual confounding, such as would occur if the DPP-4 inhibitor users were less likely to be smokers or obese, risk factors that are incompletely captured in health plan databases. We performed a sensitivity analysis to assess the effect of a strong but unmeasured risk factor for hHF. In general, the risk factor would have to also be strongly associated with the choice of antihyperglycemic drugs to fully explain the observed results (**Appendix** and **Appendix Table 4**, available at www.annals.org).

Second, our study population was drawn from patients who received antihyperglycemic treatments in routine ambulatory clinical settings, who might differ from participants in the other trials. Compared with the saxagliptin group in SAVOR-TIMI 53 (2, 25), our saxagliptin users were younger (mean age, 57 vs. 65 years), were less likely to have a history of HF (5% vs. 13%) or myocardial infarction (0.5% vs. 38%), and had less concurrent insulin use at baseline (about 10% vs. >40%). The trial also included more patients with moderate to severe renal impairment. The overall healthier profile might partially explain the lower hHF incidence rate in our study than in SAVOR-TIMI 53 (about 2 to 4 vs. about 17 per 1000 person-years).

Third, whereas we compared saxagliptin with specific antihyperglycemic agents, SAVOR-TIMI 53 compared saxagliptin with placebo. Many patients in both studies received other antihyperglycemic therapies. Risk for HF may differ among users of our comparator drugs and patients randomly assigned to placebo in SAVOR-TIMI 53; pioglitazone in particular has been linked to a higher risk for HF (26). This could have masked the elevated HF risk associated with saxagliptin if the risk was higher than among nonusers but lower than among users of pioglitazone. On the other hand, prior observational studies have suggested that sulfonylurea use was not associated with an excess risk for HF compared with no use (27, 28), except possibly in high doses (28). We expected patients placed on a regimen of long-acting insulin products to have a greater hHF risk by virtue of having more severe or longer-duration diabetes (27, 29). Therefore, any signal of an elevated hHF risk with saxagliptin relative to long-acting insulin products would be of great concern, but absence of the signal would not necessarily imply that these drugs were safe.

Table 3. Adjusted Hazard Ratios and 95% CIs for Hospitalized HF, by Study Drug

Subgroup, by Comparison	Method of Covariate Adjustment	Adjusted Hazard Ratio (95% CI)
Saxagliptin vs. sitagliptin		
All patients	DRS stratification	0.83 (0.70–0.99)
	PS matching	0.93 (0.75–1.15)
Patients with CVD	DRS stratification	0.84 (0.70–1.01)
	PS matching	1.00 (0.79–1.27)
Patients without CVD	DRS stratification	0.81 (0.52–1.24)
	PS matching	0.68 (0.42–1.12)
Patients with high HF risk*	DRS stratification	0.87 (0.70–1.09)
Saxagliptin vs. pioglitazone		
All patients	DRS stratification	0.63 (0.47–0.85)
	PS matching	0.58 (0.41–0.83)
Patients with CVD	DRS stratification	0.59 (0.41–0.87)
	PS matching	0.54 (0.34–0.84)
Patients without CVD	DRS stratification	0.70 (0.42–1.17)
	PS matching	0.66 (0.36–1.20)
Patients with high HF risk*	DRS stratification	0.54 (0.23–1.29)
Saxagliptin vs. sulfonylureas		
All patients	DRS stratification	0.69 (0.54–0.87)
	PS matching	0.81 (0.59–1.10)
Patients with CVD	DRS stratification	0.71 (0.55–0.92)
	PS matching	0.87 (0.62–1.23)
Patients without CVD	DRS stratification	0.60 (0.34–1.07)
	PS matching	0.59 (0.29–1.21)
Patients with high HF risk*	DRS stratification	0.74 (0.54–1.00)
Saxagliptin vs. insulin		
All patients	DRS stratification	0.61 (0.50–0.73)
	PS matching	0.66 (0.51–0.85)
Patients with CVD	DRS stratification	0.68 (0.56–0.83)
	PS matching	0.74 (0.56–0.98)
Patients without CVD	DRS stratification	0.36 (0.23–0.58)
	PS matching	0.40 (0.23–0.72)
Patients with high HF risk*	DRS stratification	0.79 (0.63–1.00)
Sitagliptin vs. pioglitazone		
All patients	DRS stratification	0.74 (0.64–0.85)
	PS matching	0.68 (0.58–0.81)
Patients with CVD	DRS stratification	0.68 (0.57–0.82)
	PS matching	0.66 (0.53–0.82)
Patients without CVD	DRS stratification	0.85 (0.67–1.10)
	PS matching	0.73 (0.54–0.97)
Patients with high HF risk*	DRS stratification	0.94 (0.62–1.42)
Sitagliptin vs. sulfonylureas		
All patients	DRS stratification	0.86 (0.77–0.95)
	PS matching	0.83 (0.73–0.93)
Patients with CVD	DRS stratification	0.88 (0.79–0.98)
	PS matching	0.87 (0.76–0.99)
Patients without CVD	DRS stratification	0.72 (0.55–0.95)
	PS matching	0.63 (0.46–0.87)
Patients with high HF risk*	DRS stratification	0.95 (0.84–1.08)
Sitagliptin vs. insulin		
All patients	DRS stratification	0.71 (0.64–0.78)
	PS matching	0.71 (0.63–0.81)
Patients with CVD	DRS stratification	0.75 (0.68–0.83)
	PS matching	0.76 (0.66–0.87)
Patients without CVD	DRS stratification	0.47 (0.36–0.62)
	PS matching	0.50 (0.35–0.69)
Patients with high HF risk*	DRS stratification	0.82 (0.73–0.92)

CVD = cardiovascular disease; DRS = disease risk score; HF = heart failure; PS = propensity score.
* Patients with a history of CVD who were in the 2 highest deciles of DRS.

Fourth, the average follow-up in our cohort was less than 1 year, whereas the median follow-up in SAVOR-TIMI 53 was 2.1 years. If the saxagliptin-associated hHF risk took longer to manifest, our study would not have captured it. However, the risk observed in the trial seemed to emerge within 6 months after randomization. Finally, the hHF finding in SAVOR-TIMI 53 could have been a chance finding, which highlights the importance of replicating the analysis in patients treated outside the trial setting or with another randomized trial.

Meta-analyses of trials and other observational studies provide additional information about the possible association between DPP-4 inhibitors and hHF risk. A meta-analysis of randomized trials found a greater HF risk with DPP-4 inhibitors than with placebo or active comparators (odds ratio, 1.19 [CI, 1.03 to 1.37]) (30). Drug-specific odds ratios were 1.22 (CI, 1.03 to 1.45) for saxagliptin, 0.99 (CI, 0.44 to 2.24) for sitagliptin (excluding TECOS), 1.18 (CI, 0.89 to 1.56) for alogliptin, 1.56 (CI, 0.66 to 3.65) for linagliptin, and 0.55 (CI, 0.20 to 1.53) for vildagliptin. However, the saxagliptin result (odds ratio, 0.50 [CI, 0.21 to 1.18]) did not achieve statistical significance after exclusion of SAVOR-TIMI 53, which contributed 96% of all HF events in the saxagliptin analysis and 64% in the overall analysis. Another meta-analysis of similar trials found that the risk for HF in users of DPP-4 inhibitors was higher than for placebo (relative risk, 1.17 [CI, 1.01 to 1.34]) but not an active comparator (relative risk, 0.80 [CI, 0.35 to 1.81]) (31). Prior observational studies have also yielded conflicting results. Aside from a case–control study (32) that found an increased risk for hHF among patients with diabetes and HF who used sitagliptin compared with nonusers, a cohort study of patients with kidney disease did not find an increased risk for hHF with sitagliptin use (33). Similarly, other observational studies have found no association between DPP-4 inhibitor use and HF (34–36).

Our study has several strengths. We adjusted for many potential confounders, and results were robust under 2 different, sophisticated analytic approaches. The large sample size allowed us to examine 2 commonly used DPP-4 inhibitors separately, with highly precise effect estimates. Our demographically and geographically diverse population improved the generalizability of the findings. Nevertheless, our findings should be interpreted within the context of the limitations discussed earlier.

In conclusion, in this population-based assessment of antihyperglycemic agents, saxagliptin and sitagliptin were not associated with an increased risk for hHF compared with pioglitazone, second-generation sulfonylureas, or long-acting insulin products. Additional investigations are needed to better understand the relation between DPP-4 inhibitors and hHF risk. Well-designed randomized trials with hHF as the main end point or observational studies that address the limitations of our study will help provide more definitive evidence on this topic.

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Note: Dr. Toh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix: Sensitivity Analysis to Assess the Effect of Unmeasured Confounding

Following the sensitivity analysis approach described by Schneeweiss for pharmacoepidemiologic studies (37), we examined how strongly an unmeasured confounder would have to be associated with treatment choice and hHF risk for it to explain the observed findings if the truth is that saxagliptin (or sitagliptin) does not affect hHF risk differently from the comparators. Because of the large number of analyses performed, we focused only on adjusted HRs with a 95% CI excluding the null among all patients (that is, patients with and without prior CVD combined) in Table 3. Appendix Table 4 shows how strongly an unmeasured risk factor that tripled the risk for hHF (a scenario with potential strong unmeasured confounding) would have to be associated with treatment choice for it to explain the observed findings if the truth is that saxagliptin (or sitagliptin) does not affect hHF risk differently from the comparators.

For example, we found that if the unmeasured risk factor was prevalent in 10% of the saxagliptin users, it could account entirely for the finding in the comparison of saxagliptin versus pioglitazone in the DRS-stratified analysis (adjusted HR, 0.63 [CI, 0.47 to 0.85]) if it was prevalent in 45% of the pioglitazone users. We did not present scenarios in which the prevalence of the unmeasured risk factor was higher (≥0.4) because the potential unmeasured confounding was not strong enough to fully explain the observed findings. Also of note, the prevalence of a binary confounder is symmetrical around 0.5, so we assessed only the settings with a prevalence ranging from 0.1 to 0.5.

Web-Only Reference

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Appendix Table 1. Diagnoses and Procedures Indicative of a History of Cardiovascular Disease

Diagnosis or Procedure	Codes*
Prior acute myocardial infarction (>60 d)	ICD9D: 410
Other ischemic heart disease	ICD9D: 411–414
Other heart disease	ICD9D: 402.01, 402.11, 402.91, 420–429, 440
Stroke	ICD9D: 430–434, 436
Peripheral arterial disease	ICD9D: 443.9
Coronary revascularization procedures	
Coronary artery bypass graft	ICD9D: 996.03, V45.81 ICD9P: 36.1, 36.2 CPT4: 33510–33514, 33516–33523, 33525, 33528, 33530, 33533–33536, 33560, 33570, 33572, 33575, 35600 HCPCS: S2205–S2209
Percutaneous coronary intervention	ICD9D: V45.82 ICD9P: 0.66, 17.55, 36.01–36.09, 37.22, 37.23, 88.5x CPT4: 92973, 92974, 92977, 92980, 92981, 92982, 92984, 92987, 92995, 92996 HCPCS: G0290, G0291
Carotid revascularization procedures	
Carotid endarterectomy, stenting, angioplasty, or atherectomy	ICD9P: 00.61, 00.63, 38.11, 38.12 CPT4: 35301, 35390, 35501, 35601, 35901, 0075T, 0076T, 37215, 37216 HCPCS: S2211
Carotid bypass	ICD9P: 39.28
Lower-extremity revascularization	
Lower-extremity endarterectomy, stenting, angioplasty, or atherectomy	ICD9P: 38.18, 38.19 CPT4: 35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35492, 35493, 35495, 37207, 37208, 37220–37235
Lower-extremity bypass	ICD9P: 39.25, 39.29 CPT4: 35351, 35355, 35361, 35363, 35371, 35372, 35521, 35533, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35582, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35681–35683, 35879
Lower-extremity amputation	ICD9P: 84.10–84.17 CPT4: 27295, 27590–27592, 27598, 27880–27882, 27888, 27889, 28800, 28805, 28810, 28820, 28825

CPT4 = Current Procedural Terminology; HCPCS = Healthcare Common Procedure Coding System; ICD9D = International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code; ICD9P = International Classification of Diseases, Ninth Revision, Clinical Modification procedure code.
* All diagnoses and procedures were sought for the 12-mo period before the index date.

Appendix Table 2. Baseline Patient Characteristics, by Study Drug: Saxagliptin Analysis

Covariate	Saxagliptin*	Sitagliptin	Pioglitazone	Sulfonylureas	Long-Acting Insulin
New users, *n*†	78 553	210 178	144 266	432 351	247 863
Demographic characteristics					
Mean age, *y*	57.2	59.1	58.3	58.8	59.4
Male, %	56.1	54.8	57.9	55.1	53.8
Comorbid conditions, %‡					
Asthma	6.5	7.2	6.6	7.9	9.2
Cancer	6.4	7.3	6.2	7.3	9.1
Chronic obstructive pulmonary disease	6.1	7.5	6.2	8.4	10.7
Chronic kidney disease	5.7	7.4	7.4	8.7	13.2
Dementia	1.4	2.5	1.9	2.7	3.9
Depression	9.0	10.1	9.2	11.1	14.0
End-stage renal disease	0.5	0.9	0.8	1.0	1.9
Fracture	2.8	3.3	3.0	3.3	4.3
Heart failure (>60 d)§	5.1	7.1	4.4	7.3	11.1
HIV/AIDS	0.2	0.2	0.2	0.2	0.3
Hyperlipidemia	79.2	77.5	76.6	71.3	76.2
Hypertension	77.9	77.9	75.9	74.1	79.4
Hypoglycemia	4.1	5.1	5.2	5.6	9.7
Obesity or weight gain	18.5	19.0	16.7	19.7	23.6
Osteoporosis	4.3	4.8	4.2	4.4	4.6
Peripheral neuropathy	14.4	15.8	15.4	14.8	22.6
Tobacco use	7.1	7.5	7.0	10.2	12.1
Antihyperglycemic drug use in prior year, %					
Any	89.3	87.2	87.6	74.7	100.0
α-Glucosidase inhibitor	0.5	0.6	0.6	0.3	1.2
Long-acting insulin	12.5	12.6	13.1	10.2	0.0
Short-acting insulin	4.1	4.7	5.0	3.8	7.5
Meglitinide	2.0	1.8	1.7	1.2	2.7
Metformin	73.7	71.1	70.6	64.3	80.0
Pioglitazone	21.1	20.6	0.0	11.0	22.8
Saxagliptin	0.0	2.1	2.2	2.0	4.0
Sitagliptin	20.5	0.0	15.4	10.6	21.5
Second-generation sulfonylurea	43.7	45.9	49.6	0.0	71.4
Other DPP-4 inhibitor	0.7	0.3	0.4	0.4	0.9
Other thiazolidinedione	4.0	4.1	16.0	1.8	2.7
Other	5.1	4.1	5.2	3.2	10.9
Concurrent antihyperglycemic drug use, %					
Any	100.0	100.0	100.0	100.0	100.0
α-Glucosidase inhibitor	0.3	0.4	0.4	0.2	0.6
Long-acting insulin	8.1	8.6	9.2	7.0	100.0
Short-acting insulin	1.8	2.4	2.8	2.0	13.8
Meglitinide	1.2	1.1	1.1	0.6	1.5
Metformin	68.5	67.6	61.7	58.9	56.3
Pioglitazone	10.5	11.4	100.0	6.9	11.7
Saxagliptin	100.0	0.7	1.7	1.4	2.4
Sitagliptin	6.5	100.0	11.7	7.5	13.1
Second-generation sulfonylurea	32.4	35.3	40.8	100.0	51.9
Other DPP-4 inhibitor	0.2	0.1	0.5	0.3	0.6
Other thiazolidinedione	1.2	1.4	6.6	0.8	0.9
Other	1.8	1.3	3.4	1.7	5.2
Antihypertensive drug use in prior year, %					
Any	76.9	77.6	76.1	72.4	83.0
Angiotensin-converting enzyme inhibitor	45.6	47.1	48.4	43.9	53.5
Aldosterone receptor antagonist	2.2	2.6	1.7	2.3	3.5
α-Agonist	2.3	2.5	2.3	2.5	3.6
α-Blocker	1.9	2.4	2.7	2.8	3.5
Angiotensin-receptor blocker	25.9	24.2	21.8	18.8	22.5
β-Blocker	26.8	29.9	27.1	28.7	36.1
Calcium-channel blocker	22.5	23.5	22.0	21.3	25.8
Loop diuretic	9.8	12.0	8.8	10.9	17.2
Potassium-sparing diuretic	3.1	3.3	3.1	3.3	3.2
Thiazide	31.9	31.9	31.3	29.5	32.9
Vasodilator	1.0	1.3	1.0	1.3	2.2

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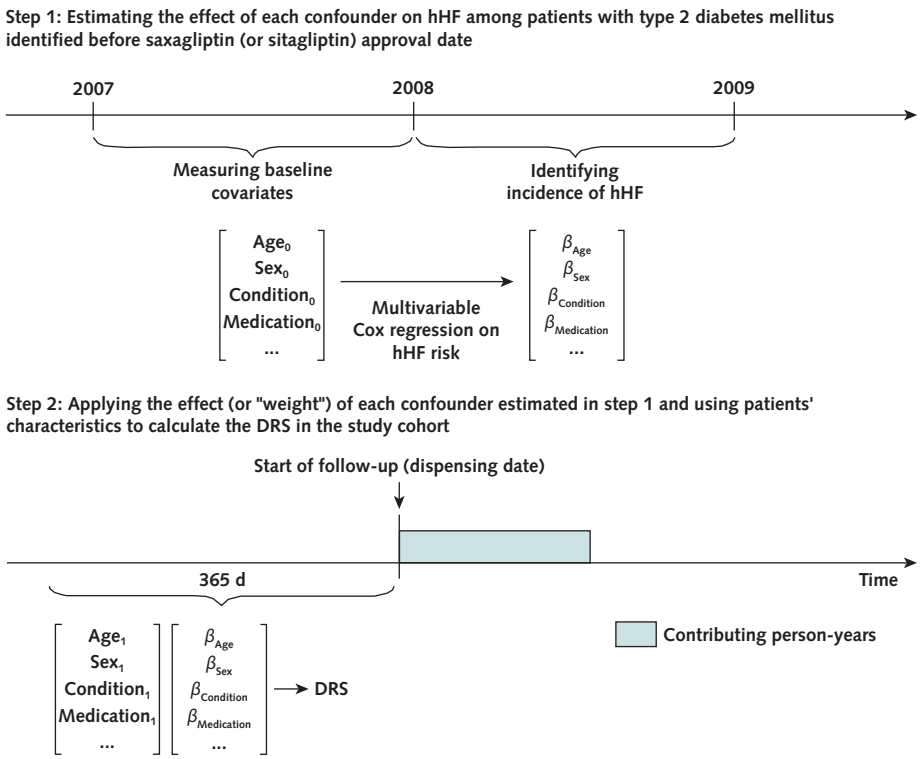
Appendix Table 2–Continued

Covariate	Saxagliptin*	Sitagliptin	Pioglitazone	Sulfonylureas	Long-Acting Insulin
Concurrent antihypertensive drug use, %					
Any	66.7	69.2	68.5	67.9	72.2
Angiotensin-converting enzyme inhibitor	34.8	36.9	39.3	38.1	39.9
Aldosterone receptor antagonist	1.5	1.7	1.2	1.7	2.4
α-Agonist	1.5	1.6	1.5	1.7	2.4
α-Blocker	1.3	1.7	2.0	2.1	2.5
Angiotensin-receptor blocker	21.3	20.2	18.2	15.4	17.2
β-Blocker	20.7	23.9	21.8	24.3	28.9
Calcium-channel blocker	17.9	19.1	18.3	17.8	20.3
Loop diuretic	6.1	7.8	5.6	7.6	11.8
Potassium-sparing diuretic	2.0	2.2	2.2	2.3	1.9
Thiazide	24.0	24.4	24.5	23.5	23.3
Vasodilator	0.7	0.9	0.7	1.0	1.7
Lipid-lowering drug use, %					
Prior year	67.8	67.4	67.2	60.1	71.7
Concurrent	54.9	56.3	57.5	52.7	55.9
Health services utilization					
Any emergency department visit, prior 30 d, %	3.0	4.4	4.1	7.3	10.1
Any emergency department visit, prior 31–365 d, %	18.2	20.0	18.3	21.0	25.8
Any hospitalization, prior 30 d, %	1.7	4.3	3.0	7.0	12.8
Any hospitalization, prior 31–365 d, %	9.7	12.1	9.9	12.1	17.4
Mean number of outpatient visits	15.5	16.8	14.8	15	19.1
Mean number of unique drugs dispensed	11.8	11.8	11.2	10.5	14.1
Nonhospital institution residence, %‖	3.4	5.7	4.1	6.0	9.8
CVD in prior year, %‡					
AMI (>60 d)	0.5	0.6	0.4	0.5	0.8
Carotid revascularization	0.1	0.2	0.1	0.2	0.2
Coronary revascularization	4.6	5.8	4.3	5.6	8.0
Coronary artery bypass graft surgery	2.2	3.0	2.1	2.9	4.4
Percutaneous coronary intervention	3.0	3.7	2.7	3.6	5.1
Lower-extremity revascularization	0.4	0.5	0.5	0.6	1.1
Other heart disease	18.5	21.9	17.2	20.6	26.5
Other ischemic heart disease	16.5	19.4	15.5	17.5	22.7
Peripheral arterial disease	4.5	5.2	4.1	5.3	7.6
Stroke	5.5	6.8	5.4	6.1	8.3

AMI = acute myocardial infarction; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4.
* Includes users who contributed to ≥1 pairwise comparison.
† New use with respect to the drug itself, before conducting pairwise comparisons that excluded patients who used either drug in each comparison during the baseline period.
‡ Recorded in inpatient or outpatient encounter unless otherwise specified.
§ Excluded from comparisons involving pioglitazone.
‖ Included nursing home residence.

Appendix Figure. DRS-stratified analysis.



DRS = disease risk score; hHF = hospitalized heart failure.

Appendix Table 3. Baseline Patient Characteristics, by Study Drug: Sitagliptin Analysis

Covariate	Sitagliptin*	Pioglitazone	Sulfonylureas	Long-Acting Insulin
New users, *n*†	298 124	252 498	613 546	342 334
Demographic characteristics				
Mean age, *y*	58.6	58.2	58.9	59.1
Male, %	54.9	57.0	54.8	53.6
Comorbid conditions, %‡				
Asthma	7.1	6.7	8.0	9.2
Cancer	7.2	6.3	7.3	9.1
Chronic obstructive pulmonary disease	7.3	6.3	8.4	10.6
Chronic kidney disease	6.4	6.3	7.5	11.9
Dementia	2.2	1.9	2.7	3.8
Depression	9.6	9.1	10.8	13.8
End-stage renal disease	0.9	0.8	1.1	2.0
Fracture	3.3	3.1	3.4	4.3
Heart failure (>60 d)§	7.1	4.7	7.5	11.4
HIV/AIDS	0.2	0.2	0.2	0.3
Hyperlipidemia	76.8	74.3	69.4	74.7
Hypertension	77.0	74.8	73.3	78.4
Hypoglycemia	4.9	5.0	5.1	9.1
Obesity or weight gain	18.0	17.1	20.2	23.6
Osteoporosis	4.7	4.0	4.1	4.4
Peripheral neuropathy	15.4	15.1	14.6	22.3
Tobacco use	7.0	7.4	10.4	12.1
Antihyperglycemic drug use in prior year, %				
Any	88.1	87.4	74.7	100.0
α-Glucosidase inhibitor	0.7	0.6	0.3	1.3
Long-acting insulin	12.5	12.8	9.8	0.0
Short-acting insulin	4.7	5.1	3.8	7.3
Metformin	71.9	70.4	63.8	80.0
Meglitinide	2.5	1.9	1.3	3.0
Pioglitazone	22.4	0.0	11.6	24.8
Saxagliptin	1.4	1.2	1.4	2.9
Sitagliptin	0.0	11.9	8.7	18.9
Second-generation sulfonylurea	46.9	50.5	0.0	72.5
Other DPP-4 inhibitor	0.2	0.2	0.3	0.7
Other thiazolidinedione	8.1	17.9	3.0	5.0
Other	5.3	5.0	3.0	10.9
Concurrent antihyperglycemic drug use, %				
Any	100.0	100.0	100.0	100.0
α-Glucosidase inhibitor	0.4	0.4	0.2	0.7
Long-acting insulin	8.3	9.0	6.7	100.0
Short-acting insulin	2.3	2.8	2.0	13.9
Meglitinide	1.5	1.2	0.6	1.7
Metformin	66.9	61.7	58.5	56.2
Saxagliptin	0.5	1.0	1.0	1.7
Sitagliptin	100.0	9.3	6.3	11.6
Pioglitazone	13.1	100.0	7.9	13.5
Second-generation sulfonylurea	35.7	42.0	100.0	53.1
Other DPP-4 inhibitor	0.1	0.3	0.2	0.4
Other thiazolidinedione	3.4	7.6	1.6	1.8
Other	1.6	3.0	1.6	5.0
Antihypertensive drug use in prior year, %				
Any	78.0	76.8	73.2	83.4
Angiotensin-converting enzyme inhibitor	47.1	49.4	45.2	54.5
Aldosterone receptor antagonist	2.6	1.6	2.3	3.5
α-Agonist	2.4	2.4	2.6	3.6
α-Blocker	2.4	2.8	3.1	3.6
Angiotensin-receptor blocker	25.1	21.7	18.4	22.3
β-Blocker	30.2	28.5	29.8	36.5
Calcium-channel blocker	23.0	21.7	21.0	25.3
Loop diuretic	12.4	9.4	11.3	17.7
Potassium-sparing diuretic	3.7	3.6	3.8	3.5
Thiazide	32.4	32.0	30.2	33.2
Vasodilator	1.1	0.9	1.3	2.1

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Appendix Table 3–Continued

Covariate	Sitagliptin*	Pioglitazone	Sulfonylureas	Long-Acting Insulin
Concurrent antihypertensive drug use, %				
Any	69.5	69.7	68.9	72.7
Angiotensin-converting enzyme inhibitor	37.1	40.6	39.5	40.9
Aldosterone receptor antagonist	1.7	1.1	1.6	2.4
α-Agonist	1.5	1.6	1.8	2.5
α-Blocker	1.7	2.1	2.4	2.6
Angiotensin-receptor blocker	20.8	18.1	15.0	16.9
β-Blocker	24.1	23.1	25.3	29.3
Calcium-channel blocker	18.7	18.2	17.7	20.0
Loop diuretic	8.0	6.1	8.0	12.3
Potassium-sparing diuretic	2.4	2.5	2.6	2.2
Thiazide	24.7	25.2	24.2	23.6
Vasodilator	0.8	0.7	1.0	1.6
Lipid-lowering drug use, %				
Prior year	67.6	66.9	60.3	71.7
Concurrent	56.3	57.4	53.1	56.0
Health services utilization				
Any emergency department visit, prior 30 d, %	4.0	4.1	7.2	9.9
Any emergency department visit, prior 31–365 d, %	19.2	18.5	20.9	25.5
Any hospitalization, prior 30 d, %	4.1	3.4	7.4	13.2
Any hospitalization, prior 31–365 d, %	12.4	10.8	12.6	17.9
Mean number of outpatient visits	16.8	14.7	14.7	18.7
Mean number of unique drugs dispensed	12	11.3	10.6	14.2
Nonhospital institution residence, %‖	5.0	3.9	5.8	9.3
CVD in prior year, %‡				
AMI (>60 d)	0.6	0.4	0.5	0.8
Carotid revascularization	0.2	0.1	0.2	0.2
Coronary revascularization	6.0	4.8	5.9	8.2
Coronary artery bypass graft surgery	3.1	2.4	3.1	4.5
Percutaneous coronary intervention	3.8	3.0	3.7	5.2
Lower-extremity revascularization	0.5	0.5	0.6	1.1
Peripheral arterial disease	4.1	4.1	5.4	7.8
Other heart disease	21.7	17.1	20.2	26.0
Other ischemic heart disease	19.7	16.3	17.7	22.8
Stroke	6.6	5.3	6.0	8.1

AMI = acute myocardial infarction; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4.
* Includes users who contributed to ≥1 pairwise comparison.
† New use with respect to the drug itself, before conducting pairwise comparisons that excluded patients who used either drug in each comparison during the baseline period.
‡ Recorded in inpatient or outpatient encounter unless otherwise specified.
§ Excluded from comparisons involving pioglitazone.
‖ Included nursing home residence.

Appendix Table 4. Sensitivity Analysis to Assess the Effect of Unmeasured Confounding

Comparison	Method of Covariate Adjustment	Apparent HR	True HR	P_1	P_0	RR_{CO}
Saxagliptin						
P_1 = 10%						
Versus sitagliptin	DRS stratification	0.83	1.00	0.10	0.22	3.0
Versus pioglitazone	DRS stratification	0.63	1.00	0.10	0.45	3.0
Versus pioglitazone	PS matching	0.58	1.00	0.10	0.53	3.0
Versus sulfonylureas	DRS stratification	0.69	1.00	0.10	0.37	3.0
Versus insulin	DRS stratification	0.61	1.00	0.10	0.48	3.0
Versus insulin	PS matching	0.66	1.00	0.10	0.41	3.0
P_1 = 20%						
Versus sitagliptin	DRS stratification	0.83	1.00	0.20	0.34	3.0
Versus pioglitazone	DRS stratification	0.63	1.00	0.20	0.61	3.0
Versus pioglitazone	PS matching	0.58	1.00	0.20	0.71	3.0
Versus sulfonylureas	DRS stratification	0.69	1.00	0.20	0.51	3.0
Versus insulin	DRS stratification	0.61	1.00	0.20	0.65	3.0
Versus insulin	PS matching	0.66	1.00	0.20	0.56	3.0
P_1 = 30%						
Versus sitagliptin	DRS stratification	0.83	1.00	0.30	0.46	3.0
Versus pioglitazone	DRS stratification	0.63	1.00	0.30	0.77	3.0
Versus pioglitazone	PS matching	0.58	1.00	0.30	0.88	3.0
Versus sulfonylureas	DRS stratification	0.69	1.00	0.30	0.66	3.0
Versus insulin	DRS stratification	0.61	1.00	0.30	0.81	3.0
Versus insulin	PS matching	0.66	1.00	0.30	0.71	3.0
Sitagliptin						
P_1 = 10%						
Versus pioglitazone	DRS stratification	0.74	1.00	0.10	0.31	3.0
Versus pioglitazone	PS matching	0.68	1.00	0.10	0.38	3.0
Versus sulfonylureas	DRS stratification	0.86	1.00	0.10	0.20	3.0
Versus sulfonylureas	PS matching	0.83	1.00	0.10	0.22	3.0
Versus insulin	Both	0.71	1.00	0.10	0.35	3.0
P_1 = 20%						
Versus pioglitazone	DRS stratification	0.74	1.00	0.20	0.45	3.0
Versus pioglitazone	PS matching	0.68	1.00	0.20	0.53	3.0
Versus sulfonylureas	DRS stratification	0.86	1.00	0.20	0.31	3.0
Versus sulfonylureas	PS matching	0.83	1.00	0.20	0.34	3.0
Versus insulin	Both	0.71	1.00	0.20	0.49	3.0
P_1 = 30%						
Versus pioglitazone	DRS stratification	0.74	1.00	0.30	0.58	3.0
Versus pioglitazone	PS matching	0.68	1.00	0.30	0.68	3.0
Versus sulfonylureas	DRS stratification	0.86	1.00	0.30	0.43	3.0
Versus sulfonylureas	PS matching	0.83	1.00	0.30	0.46	3.0
Versus insulin	Both	0.71	1.00	0.30	0.63	3.0

DRS = disease risk score; HR = hazard ratio; P_0 = prevalence of the unmeasured confounder among comparator drug users; P_1 = prevalence of the unmeasured confounder among saxagliptin or sitagliptin users; PS = propensity score; RR_{CO} = relative risk between the unmeasured confounder and hospitalized heart failure risk.