Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study

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OBJECTIVE

The cardiovascular safety of saxagliptin, a dipeptidyl-peptidase 4 inhibitor, compared with other antihyperglycemic treatments is not well understood. We prospectively examined the association between saxagliptin use and acute myocardial infarction (AMI).

RESEARCH DESIGN AND METHODS

We identified patients aged ≥18 years, starting from the approval date of saxagliptin in 2009 and continuing through August 2014, using data from 18 Mini-Sentinel data partners. We conducted seven sequential assessments comparing saxagliptin separately with sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin, using disease risk score (DRS) stratification and propensity score (PS) matching to adjust for potential confounders. Sequential testing kept the overall chance of a false-positive signal below 0.05 (one-sided) for each pairwise comparison.

RESULTS

We identified 82,264 saxagliptin users and more than 1.5 times as many users of each comparator. At the end of surveillance, the DRS-stratified hazard ratios (HRs) (95% CI) were 1.08 (0.90–1.28) in the comparison with sitagliptin, 1.11 (0.87–1.42) with pioglitazone, 0.79 (0.64–0.98) with sulfonylureas, and 0.57 (0.46–0.70) with long-acting insulin. The corresponding PS-matched HRs were similar. Only one interim analysis of 168 analyses met criteria for a safety signal: the PS-matched saxagliptin-pioglitazone comparison from the fifth sequential analysis, which yielded an HR of 1.63 (1.12–2.37). This association diminished in subsequent analyses.

CONCLUSIONS

We did not find a higher AMI risk in saxagliptin users compared with users of other selected antihyperglycemic agents during the first 5 years after U.S. Food and Drug Administration approval of the drug.

Saxagliptin is an antihyperglycemic drug of the dipeptidyl-peptidase 4 (DPP-4) inhibitor class approved in 2009. To better understand the cardiovascular profiles of new antihyperglycemic treatments, regulatory agencies now require more rigorous assessments of cardiovascular risks during the pre- and postmarketing phases of the drug approval process (1–3). The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial (4)

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**A complete list of the members of the Mini-Sentinel Saxagliptin-AMI Surveillance Writing Group can be found in the APPENDIX.*

was a postmarketing cardiovascular outcomes trial initiated in 2010 to fulfill a guidance published by the U.S. Food and Drug Administration (FDA) (1).

In 2010, the FDA initiated a prospective surveillance activity in the Mini-Sentinel pilot as an additional method to monitor and detect any potential increased cardiovascular risk associated with saxagliptin use. A component of the FDA Sentinel Initiative, the Mini-Sentinel pilot was launched in 2009 to build the data and scientific infrastructure necessary for a medical product safety surveillance system as required in the FDA Amendments Act of 2007 (5,6). The envisioned system would allow the FDA to assess the safety of approved medical products within a network of electronic health care databases covering at least 100 million individuals. Specifically, it would have the capability to prospectively examine the safety of new medical products as data accrued on their use in routine clinical practice.

This prospective surveillance study was launched in 2010 to monitor the risk of acute myocardial infarction (AMI) in new users of saxagliptin after its approval. The goal of the study was to complement the placebo-controlled SAVOR-TIMI 53 trial by comparing saxagliptin with other antihyperglycemic treatments. In a previous study, we examined the associations between two DPP-4 inhibitors (saxagliptin and sitagliptin) and hospitalized heart failure within this prospective cohort (7) after the unexpected finding from the SAVOR-TIMI 53 trial (8). Here we report the results from the interim and final analyses of the AMI outcome.

RESEARCH DESIGN AND METHODS

This section summarizes the surveillance design and analytic methods. A detailed description of the design choice and rationale has previously been published (9,10).

Data Source and Study Cohort

Mini-Sentinel created a distributed network of 18 data partners (6). The data partners included national and regional health insurers and integrated delivery systems, all of which collect administrative claims data as part of their regular business. The integrated delivery systems also provide information from electronic health records. Data were converted into a standard format, periodically updated, quality checked, and stored locally under control of the data partners (11). At the final analysis of this surveillance, the distributed database included 178 million individuals and 358 million person-years of longitudinal observation time from 2000 to 2014. Mini-Sentinel was a public health surveillance activity, and this project was not under the purview of institutional review boards (12).

This study included four separate pairwise comparisons of saxagliptin with its treatment alternatives: sitagliptin, pioglitazone, second-generation sulfonylureas, and long-acting insulin. As described in more detail in the published protocol (9,10), we chose these comparators because they represented possible alternatives to saxagliptin, which was considered a second- or third-line antihyperglycemic treatment in clinical practice at the time of the protocol development in 2010 (13,14).

We identified patients aged ≥18 years who initiated treatment with saxagliptin or a comparator drug, beginning on 1 August 2009 (the day after the approval date of saxagliptin in the U.S.). New use of saxagliptin or comparator was defined as no dispensing of either drug during the previous 365 days; the index date was the date of the first dispensing of either drug (15,16). Concomitant or prior use of other antihyperglycemic drugs—including the comparators in other comparisons—was permitted and adjusted for in analyses.

To reduce chances of including patients with type 1 diabetes, we required patients to have one or more dispensing of an antihyperglycemic agent (except short-acting insulin) or one or more diabetes diagnoses during the year before the index date. Patients identified as new users of long-acting insulin were also required to have one or more prior or concomitant dispensing of an antihyperglycemic agent that was not short-acting insulin. We excluded patients who had an inpatient encounter with a principal diagnosis of AMI (ICD-9-CM codes 410.x0 or 410.x1) during the 60-day period preceding the index date because of the high potential for unmeasured confounding while recurrence risk was high. For the saxagliptin-pioglitazone comparison, we also excluded patients with a heart failure diagnosis during the 365-day baseline period because heart failure is a contraindication to pioglitazone use.

Follow-up and Outcome Identification

Each pairwise comparison included monitoring of patients from the index date until the earliest occurrence of an AMI event, discontinuation of the initiated drug, initiation of the other drug in the pair, health plan disenrollment, death, or end of the surveillance period, which varied by data partner from 30 June 2012 to 31 August 2014. We identified AMI primarily by principal hospital discharge diagnosis code 410.x0 or 410.x1, an algorithm with a positive predictive value of 86% in the Mini-Sentinel distributed database (17,18). We included additional AMI events by identifying deaths occurring on the day of or the day after an emergency department encounter associated with a diagnosis code for acute ischemic heart disease (ICD-9-CM codes 410.x0, 410.x1, 411.1, 411.8x, or 413.x) (19). Discontinuation of the initiated drug occurred when the days' supply had been exhausted for 10 days or one-third of the days' supply of the most recent dispensing, whichever was greater.

Confounding Adjustment

We identified a list of potential confounders that included patient demographics, medical history, medication use, cardiovascular risk factors, other antihyperglycemic treatments, and health services utilization measures (Table 1). We adjusted for these confounders using two separate methods—disease risk score (DRS) stratification (20) and propensity score (PS) matching (16)—for each pairwise comparison. The DRS, which was used to rank patients based on their baseline AMI risk, was developed at each data partner by estimating the associations of the prespecified confounders with AMI risk in diabetes patients identified in 2007–2008 (i.e., before saxagliptin approval) and monitored through the end of 2009 (20). We calculated the DRS for the new users in the surveillance by multiplying their covariate profiles by the regression coefficients derived from the earlier sample. We developed the DRS separately for patients with and without prior cardiovascular disease at each data partner. Within each cardiovascular disease stratum at each data partner, we ordered patients from the lowest DRS to the highest and divided them into deciles.

We estimated the PS as the probability of initiating saxagliptin by fitting logistic regression models that included all prespecified confounders. These models were run separately at each data partner for each pairwise comparison and for patients with and without prior cardiovascular disease. We used the estimated PS to match saxagliptin users with comparator users by 1:1 "greedy" matching (21) within a caliper of 0.01 within data partner, cardiovascular

Table 1—Baseline characteristics of new users of saxagliptin and comparator drugs

Covariate	Saxagliptin* (*n* = 82,264)	Sitagliptin (*n* = 220,912)	Pioglitazone (*n* = 146,045)	Second-generation sulfonylureas (*n* = 452,969)	Long-acting insulin (*n* = 262,117)
Patient demographic					
Mean age, years	57.3	59.1	58.4	59.0	59.5
Male sex	56.1	54.9	58.1	55.2	54.0
Comorbid condition†					
Asthma	6.6	7.2	6.6	8.0	9.3
Cancer	6.4	7.4	6.2	7.3	9.1
Chronic kidney disease	5.8	7.6	7.6	9.1	13.8
COPD	6.2	7.7	6.3	8.6	11.0
Dementia	1.4	2.5	1.9	2.7	3.9
Depression	9.0	10.1	9.2	11.1	14.0
ESRD	0.5	0.9	0.8	1.1	2.0
Fracture	2.8	3.4	3.1	3.3	4.3
Heart failure‡	5.3	7.5	4.5	7.8	11.8
HIV/AIDS	0.2	0.2	0.2	0.2	0.3
Hyperlipidemia	79.2	77.5	76.7	71.5	76.4
Hypertension	78.0	78.0	76.0	74.2	79.4
Hypoglycemia	4.2	5.2	5.4	6.4	10.6
Obesity or weight gain	18.8	19.3	16.9	20.1	24.0
Osteoporosis	4.3	4.8	4.2	4.4	4.6
Peripheral neuropathy	14.4	15.9	15.6	15.0	22.9
Tobacco use	7.2	7.6	7.1	10.4	12.4
Antihyperglycemic drug use					
Prior year					
Any antihyperglycemic drugs	89.2	87.0	87.6	74.9	100.0
α-Glucosidase inhibitors	0.5	0.6	0.6	0.3	1.1
Insulin, long-acting	12.6	12.6	13.2	10.2	0.0
Insulin, short-acting	4.2	4.7	5.1	3.8	7.5
Meglitinides	2.0	1.8	1.7	1.2	2.7
Metformin	73.7	71.1	70.6	64.4	80.1
Pioglitazone	20.4	19.8	0.0	10.6	21.8
Saxagliptin	0.0	2.2	2.5	2.1	4.2
Sitagliptin	20.5	0.0	15.8	10.7	21.4
Sulfonylureas, second generation	43.6	45.4	49.2	0.0	71.2
Other sulfonylureas	0.0	0.1	0.3	0.9	0.6
Other DPP-4 inhibitors	0.8	0.4	0.5	0.5	1.1
Other TZDs	3.8	3.9	15.6	1.7	2.6
Other	5.2	4.1	5.5	3.3	11.0
Concurrent					
Any antihyperglycemic drugs	100.0	100.0	100.0	100.0	100.0
α-Glucosidase inhibitors	0.3	0.3	0.4	0.2	0.6
Insulin, long-acting	8.2	8.5	9.2	7.0	100.0
Insulin, short-acting	1.9	2.4	2.8	2.0	13.9
Meglitinides	1.2	1.1	1.1	0.6	1.5
Metformin	68.6	67.7	61.6	59.1	56.5
Pioglitazone	10.2	10.9	100.0	6.7	11.2
Saxagliptin	100.0	0.8	1.8	1.5	2.5
Sitagliptin	6.5	100.0	11.8	7.6	13.0
Sulfonylureas, second generation	32.2	35.0	40.4	100.0	51.8
Other sulfonylureas	0.0	0.0	0.2	0.6	0.3
Other DPP-4 inhibitors	0.2	0.1	0.7	0.4	0.7
Other TZDs	1.1	1.3	6.5	0.7	0.8
Other	1.9	1.3	3.5	1.8	5.3
Antihypertensive drugs					
Prior year					
Any antihypertensive drugs	76.9	77.5	76.1	72.5	83.1
ACE inhibitors	45.5	47.0	48.1	43.7	53.3
Aldosterone receptor antagonists	2.3	2.6	1.7	2.4	3.7
α-Agonists	2.4	2.5	2.3	2.5	3.5
α-Blockers	1.9	2.4	26.	2.8	3.5
Angiotensin receptor blockers	26.0	24.3	22.0	19.0	22.6
β-Blockers	26.8	30.0	27.1	29.0	36.4
Calcium channel blockers	22.6	23.6	22.1	21.3	25.9

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Table 1—Continued

Covariate	Saxagliptin* (*n* = 82,264)	Sitagliptin (*n* = 220,912)	Pioglitazone (*n* = 146,045)	Second-generation sulfonylureas (*n* = 452,969)	Long-acting insulin (*n* = 262,117)
Loop diuretics	10.0	12.2	8.9	11.1	17.5
Potassium-sparing diuretics	3.1	3.3	3.1	3.2	3.1
Thiazides	31.9	31.8	31.2	29.3	32.7
Vasodilators	1.1	1.3	1.0	1.4	2.3
Concurrent					
Any antihypertensive drugs	66.8	69.2	68.3	68.0	72.4
ACE inhibitors	34.7	36.8	39.1	38.0	39.8
Aldosterone receptor antagonists	1.5	1.8	1.2	1.7	2.5
α-Agonists	1.5	1.6	1.5	1.7	2.4
α-Blockers	1.3	1.7	2.0	2.1	2.5
Angiotensin receptor blockers	21.4	20.2	18.3	15.7	17.3
β-Blockers	20.8	24.0	21.8	24.6	29.3
Calcium channel blockers	18.0	19.2	18.4	17.8	20.4
Loop diuretics	6.2	8.0	5.7	7.9	12.3
Potassium-sparing diuretics	2.0	2.1	2.1	2.2	1.9
Thiazides	24.0	24.3	24.4	23.4	23.2
Vasodilators	0.7	0.9	0.7	1.1	1.8
Lipid-lowering drugs					
Prior year	67.7	67.2	67.1	60.3	71.8
Concurrent	54.8	56.2	57.4	52.8	56.1
Health services utilization					
Any ED visit					
Prior 30 days	3.1	4.6	4.1	7.6	10.5
Prior 31–365 days	18.3	20.2	18.5	21.4	26.3
Any hospitalization					
Prior 30 days	1.7	4.6	3.1	7.2	13.3
Prior 31–365 days	9.8	12.2	9.9	12.2	17.6
Mean number of					
Outpatient visits	15.5	16.8	14.9	15.1	19.2
Unique drugs dispensed	11.8	11.8	11.2	10.5	14.1
Nonhospital institution residence§	3.6	5.9	4.2	6.2	10.0
CVD history (prior year)†					
AMI (>60 days)	0.5	0.6	0.4	0.5	0.8
Carotid revascularization	0.1	0.2	0.1	0.1	0.2
Coronary revascularization	4.6	5.9	4.3	5.7	8.2
CABG	2.3	3.0	2.1	3.0	4.4
PCI	3.0	3.7	2.7	3.6	5.2
Lower extremity revascularization	0.4	0.5	0.5	0.6	1.1
Other heart disease	18.6	22.3	17.4	21.1	27.2
Other ischemic heart disease	16.6	19.6	15.7	17.7	23.1
Peripheral arterial disease	4.0	5.3	4.1	5.4	7.6
Stroke	5.5	6.9	5.4	6.1	8.4

Data are percentages unless otherwise indicated. CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD: cardiovascular disease; ED, emergency department; ESRD, end-stage renal disease; PCI, percutaneous coronary intervention; TZD, thiazolidinedione. *Included saxagliptin users who contributed to one or more pairwise comparisons. †Recorded in inpatient or outpatient encounter, unless otherwise specified. ‡Patients with a history of heart failure were excluded from the comparisons that involved pioglitazone. §Included nursing home residence.

disease stratum, and calendar quarter of treatment initiation. Each time new data became available for surveillance, we refit the PS models to data from all new users since surveillance began and used the modeling results to match only previously unmatched patients. Once patients were matched for a pairwise comparison, they were not later rematched to simplify the sequential testing described below.

Statistical Analysis

For each pairwise comparison, we used a stratified Cox regression to *1*) estimate the hazard ratio (HR) and 95% CI of AMI for saxagliptin users versus comparator users and 2) conduct a one-sided Wald test of the null hypothesis that saxagliptin was not riskier than the comparator. We examined the association in all patients and separately in patients with and without prior cardiovascular disease. Each Cox model was stratified on data partner, calendar quarter of initiating saxagliptin, prior cardiovascular disease (for analyses that included all eligible patients), and DRS decile (for DRS-stratified analyses). For both DRS-stratified and PS-matched analyses, the stratified Cox model included only one treatment indicator variable that estimated the effect of saxagliptin on AMI risk.

We used a previously described approach that allowed patient-level data to stay behind the firewalls of data partners (22–24). This analytic approach required each site to create an aggregate-level data set that included one record per risk set. Each risk set included patients with an AMI event and comparable patients who were still at risk for the outcome at that event time. Comparable patients

were patients from the same stratum as the case in the DRS-stratified analysis or patients in the matched cohort in the PS-matched analysis. This approach has been shown via mathematical proof (22) and in empirical studies (23,24) to provide results statistically equivalent to those from a patient-level stratified Cox model. Data partners prefer this approach because it requires less granular information, thereby providing better protection for patient privacy. This risk set approach allowed us to perform all of the prespecified analyses, but certain post hoc sensitivity analyses were not possible because the information required for the analysis was not requested a priori or because the analysis could not be performed with the risk set data. We assessed treatment heterogeneity by data partner, prior cardiovascular disease, time on study drug, and calendar time.

Sequential Testing

We conducted seven sequential analyses to evaluate accumulating data and developed an "alpha-spending" plan to account for these repeated analyses of the data (25–27). We specified a flat threshold of 2.19 on the scale of the Wald z-score (log HR estimate/SE) for a safety signal, which corresponded to a one-sided *P* value of 0.014. This plan kept the overall chance of a false-positive signal below 0.05 (one-sided) for each hypothesis. Although we adjusted for the sequential nature of our analyses, we did not further adjust for multiple comparisons at each sequential analysis that arose from the use of multiple comparator drugs, use of both DRS stratification and PS matching, and stratification according to the presence of prior cardiovascular disease. A safety signal, defined as having a Wald z-score greater than 2.19, would trigger a follow-up investigation but would not stop the surveillance; we would continue to update the HR estimate after a signal. We reported the HRs and 95% CIs without adjustment for the number of hypothesis tests conducted at each sequential analysis (28). Because the main goal of the study was to assess the evidence as data accrued, we present the results from each interim analysis to show how the estimates changed sequentially (29). We performed all analyses with SAS 9.3 software (SAS Institute, Inc., Cary, NC).

Sitagliptin Surveillance

Although saxagliptin was the drug of interest, we added a parallel surveillance of sitagliptin, the first DPP-4 inhibitor approved in 2006, which was more commonly prescribed when the saxagliptin surveillance began. We summarize the design and results of the sitagliptin surveillance in the Supplementary Data.

Patient Involvement

We did not involve patients in setting the research question or the outcome measures or in interpreting or writing up of results. There are no plans to disseminate the results of this project to study patients or the relevant patient community other than making the findings available in peer reviewed publications and reports on the Sentinel website (https://www.sentinelinitiative.org/).

RESULTS

A total of 82,264 new users of saxagliptin contributed to one or more of the four pairwise comparisons. More than 1.5 times as many new users of each comparator were identified. Saxagliptin users were slightly younger (mean age 57 vs. 58 to 60 years in users of comparator drugs). For each pairwise comparison, most of the study cohort received antihyperglycemic agents other than saxagliptin or the comparator drug in the year preceding the index date. More than half of the patients were being treated with metformin at cohort entry. The prevalence of prior cardiovascular disease was similar or lower in saxagliptin users than in sitagliptin or second-generation sulfonylurea users, similar or slightly higher than in pioglitazone users, and much lower compared with long-acting insulin users (Table 1). We achieved balance in measured covariates after DRS stratification and PS matching (data not shown).

Final Results From the Surveillance

At the end of the surveillance, the average follow-up was ~8 months for saxagliptin; 7–8 months for sitagliptin, pioglitazone, and second-generation sulfonylureas; and 4 months for long-acting insulin. The incidence rates of AMI (per 1,000 person-years) ranged from 3.2 to 4.0 for saxagliptin across comparisons. The incidence rate (per 1,000 person-years) was 4.3 for sitagliptin, 3.7 for pioglitazone, 6.2 for second-generation sulfonylureas, and 8.5 for long-acting insulin. The unadjusted incidence rate ratio was <1.0 in all comparisons: 0.92 for the comparison with sitagliptin, 0.97 with pioglitazone, 0.54 with second-generation sulfonylureas, and 0.38 with long-acting insulin.

Adjustment for potential confounders increased all HRs, but none were substantially above 1.0 (Table 2). The adjusted HRs from DRS-stratified analyses in all patients were 1.08 (95% CI 0.90–1.28) in the comparison with sitagliptin, 1.11 (0.87–1.42) with pioglitazone, 0.79 (0.64–0.98) with second-generation sulfonylureas, and 0.57 (0.46–0.70) with long-acting insulin. The corresponding HRs from the PS-matched analyses were similar:

Table 2—Results from end-of-surveillance analyses

Comparison	Method of covariate adjustment	Subgroup		
		All patients	Patients with CVD	Patients without CVD
Saxagliptin vs.				
Sitagliptin	DRS	1.08 (0.90–1.28)	1.16 (0.93–1.46)	0.96 (0.72–1.27)
	PSM	0.96 (0.77–1.18)	1.10 (0.83–1.46)	0.80 (0.58–1.11)
Pioglitazone	DRS	1.11 (0.87–1.42)	1.02 (0.72–1.45)	1.20 (0.85–1.69)
	PSM	1.17 (0.86–1.57)	1.29 (0.84–1.99)	1.06 (0.70–1.60)
Sulfonylureas	DRS	0.79 (0.64–0.98)	0.89 (0.67–1.19)	0.69 (0.50–0.95)
	PSM	0.70 (0.53–0.91)	0.76 (0.52–1.10)	0.63 (0.42–0.94)
Long-acting insulin	DRS	0.57 (0.46–0.70)	0.68 (0.52–0.88)	0.44 (0.32–0.61)
	PSM	0.54 (0.41–0.71)	0.60 (0.43–0.85)	0.43 (0.27–0.70)

Shown are adjusted HRs (95% CI) of AMI events in saxagliptin users vs. comparator drug users, by pairwise comparison, baseline cardiovascular disease status, and method of covariate adjustment. CVD, cardiovascular disease; PSM, PS matching.

0.96 (0.77–1.18) with sitagliptin, 1.17 (0.86–1.57) with pioglitazone, 0.70 (0.53–0.91) with second-generation sulfonylureas, and 0.54 (0.41–0.71) with long-acting insulin. Among the 9 of 24 adjusted HRs >1.0, the highest was 1.29 and all of the 95% CIs included 1.0. There was no strong evidence to suggest that the results varied substantially by prior cardiovascular disease status.

Across subgroup analyses by data partner and period-specific analyses by time on study drug and calendar time, we found no systematic evidence that saxagliptin was associated with a higher AMI risk than the comparator drugs. Results from the parallel sitagliptin surveillance similarly showed no evidence for an elevated AMI risk compared with pioglitazone, second-generation sulfonylureas, or long-acting insulin (Supplementary Tables 1–3 and Supplementary Figs. 1–3).

Results From Interim Sequential Analyses

Each of the seven times that we updated the saxagliptin surveillance, the four pairwise comparisons were adjusted by two methods (DRS stratification and PS matching) in the following three groups: cardiovascular disease stratum, noncardiovascular disease stratum, and both cardiovascular disease strata combined. Of these $7 \times 4 \times 2 \times 3 = 168$ comparisons, all but one yielded Wald test statistics below the signaling threshold. The one analysis that signaled was the PS-matched saxagliptin-pioglitazone comparison in all patients during the fifth periodic update: the Wald test statistic was 2.32 and the HR was 1.63 (95% CI 1.12–2.37) (Table 3 and Fig. 1*B*) (interim analysis 5). When individual cardiovascular disease strata were looked at, the PS-matched HRs were 1.80 (1.05–3.06) in patients with prior cardiovascular disease and 1.48 (0.88–2.51) in patients without prior cardiovascular disease. The corresponding HRs in the DRS-stratified analyses were lower: 1.18 (0.90–1.55) in all patients, 1.29 (0.88–1.89) in patients with prior cardiovascular disease, and 1.09 (0.74–1.59) in patients without prior cardiovascular disease.

When the saxagliptin-pioglitazone comparison was reexamined later in surveillance, the Wald test statistic fell substantially below the signaling threshold, and the PS-matched HR fell to 1.19 (95% CI 0.86–1.66) at the sixth update and to 1.17 (0.86–1.57) at the seventh update. Meanwhile, the HRs from the corresponding DRS-stratified analyses at the sixth and seventh updates were 1.17 (0.90–1.52) and 1.11 (0.87–1.42), respectively. As more saxagliptin users came under surveillance, the nominal 95% CIs narrowed, and the differences between the DRS-stratified and PS-matched HR estimates also tended to narrow over time (Fig. 1).

CONCLUSIONS

In this prospective surveillance activity using electronic data collected as part of routine health care delivery, we did not observe a higher AMI risk in saxagliptin users compared with users of sitagliptin, pioglitazone, second-generation sulfonylureas, or long-acting insulin. Findings were robust under two complementary analytic approaches and in patients with and without prior cardiovascular disease. Interim results from the first five sequential analyses were available to the FDA before the publication of the SAVOR-TIMI 53 trial findings in September 2013. Final results of the surveillance were submitted to the FDA in May 2015. The delay in delivering the final results to the FDA was largely caused by the addition of a heart failure analysis (7) after the unexpected finding on hospitalized heart failure in the SAVOR-TIMI 53 trial (8).

Comparison With the SAVOR-TIMI 53 Trial and Prior Studies

The SAVOR-TIMI 53 trial provides important context for our surveillance (Supplementary Table 4). That trial found no difference in cardiovascular risk between saxagliptin and placebo during a median follow-up of 2.1 years (8). The HR was 1.00 (95% CI 0.89–1.12) in the intention-to-treat analysis and 1.03 (0.91–1.17) in the on-treatment analysis for the primary outcome of a composite of AMI, ischemic stroke, and cardiovascular death. The intention-to-treat HR was 0.95 (0.80–1.12) for AMI. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) also did not observe an increase in cardiovascular risk with saxagliptin versus placebo (30). The intention-to-treat HR in that trial was reported to be 0.98 (0.89 –1.08) for the primary composite outcome, which included cardiovascular death, nonfatal AMI, nonfatal stroke, or hospitalization for unstable angina. The HR for fatal or nonfatal AMI was reported as 0.95 (0.81–1.11). In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) noninferiority trial, the HR was 0.96 (with an upper boundary of the one-sided repeated CI of 1.16) for the primary end point—a composite of death from cardiovascular causes, nonfatal AMI, or nonfatal stroke—when alogliptin was compared with placebo (31). The HR for nonfatal AMI was 1.08 (0.88–1.33). Our findings suggest that saxagliptin was similar in AMI risk to sitagliptin and pioglitazone. The consistency in findings from the trial and real-world observational data provide additional reassurance about the safety of saxagliptin with respect to AMI.

We previously assessed the association between DPP-4 inhibitor use and the risk of hospitalized heart failure (7). The analysis was motivated by the conflicting findings from the three placebo-controlled DPP-4 inhibitor trials—the SAVOR-TIMI 53 trial (which observed an increased risk) (8), the TECOS trial (which did not report an increased risk) (30), and the EXAMINE trial (which observed an increased risk only in patients without a prior history of heart failure) (32). We did not find an increased risk of hospitalized heart failure associated with saxagliptin or sitagliptin use when we compared these two DPP-4 inhibitors individually with pioglitazone, second-generation sulfonylureas, or long-acting insulin.

Our comparisons with long-acting insulin and second-generation sulfonylureas produced adjusted HRs substantially below 1.0. We used a one-sided Wald test to determine whether saxagliptin had a higher risk of AMI than the comparator, which prevented us from drawing statistical conclusions about any potential lower risk of AMI associated with saxagliptin. However, possible reasons for the observed findings include higher AMI risks associated with these comparators or unmeasured confounding. Long-acting insulin was a potential alternative to saxagliptin at the time of our protocol development because it could be initiated after failure of two or three oral antihyperglycemic treatments to adequately control for hemoglobin A_{1c}, a clinical situation in which saxagliptin might be considered. On the one hand, the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial did not observe an increased risk in a composite end point of death from cardiovascular causes, nonfatal AMI, or nonfatal stroke (HR 1.02; 95% CI 0.94–1.11), or fatal and nonfatal AMI

Table 3—Results from prospective surveillance of AMI

Results	Interim analysis 1	2*	3*	4	5†	6	Final analysis
Data from 1 Aug 2009 through:	30 Jun 2011	31 Dec 2011	31 Dec 2011	30 Jun 2012	31 Mar 2013	31 Dec 2013	31 Aug 2014
Saxagliptin vs. sitagliptin							
DRS stratification							
HR	0.54	0.84	1.00	1.05	0.92	1.08	1.08
95% CI	0.28–1.07	0.56–1.27	0.80–1.24	0.85–1.29	0.74–1.13	0.89–1.30	0.90–1.28
Cum. AMI events							
Saxagliptin	11	31	105	122	111	145	171
Comparator	85	128	433	470	537	531	599
Signal‡	No	No	No	No	No	No	No
PS matching							
HR	0.59	1.03	0.87	0.92	0.89	1.03	0.96
95% CI	0.25–1.39	0.59–1.79	0.67–1.14	0.72–1.17	0.70–1.15	0.82–1.30	0.77–1.18
Cum. AMI events							
Saxagliptin	10	31	101	118	110	142	167
Comparator	12	22	124	137	140	145	178
Signal‡	No	No	No	No	No	No	No
Saxagliptin vs. pioglitazone							
DRS stratification							
HR	0.89	1.09	1.04	1.07	1.18	1.17	1.11
95% CI	0.44–1.84	0.67–1.75	0.77–1.41	0.81–1.42	0.90–1.55	0.90–1.52	0.87–1.42
Cum. AMI events							
Saxagliptin	9	24	77	91	85	112	136
Comparator	82	100	199	207	235	228	238
Signal‡	No	No	No	No	No	No	No
PS matching							
HR	3.24	2.07	1.15	1.21	1.63	1.19	1.17
95% CI	0.69–15.19	0.92–4.66	0.79–1.67	0.85–1.71	1.12–2.37	0.86–1.66	0.86–1.57
Cum. AMI events							
Saxagliptin	9	24	65	79	75	90	105
Comparator	2	8	50	56	44	62	75
Signal‡	No	No	No	No	Yes	No	No
Saxagliptin vs. sulfonylureas							
DRS stratification							
HR	0.37	0.62	0.68	0.70	0.89	0.79	0.79
95% CI	0.14–1.00	0.35–1.10	0.51–0.90	0.53–0.91	0.69–1.14	0.62–1.00	0.64–0.98
Cum. AMI events							
Saxagliptin	4	13	53	61	69	78	97
Comparator	239	310	781	847	941	929	1085
Signal‡	No	No	No	No	No	No	No
PS matching							
HR	0.29	0.54	0.56	0.61	0.93	0.84	0.70
95% CI	0.08–1.12	0.26–1.13	0.39–0.80	0.44–0.85	0.67–1.29	0.61–1.15	0.53–0.91
Cum. AMI events							
Saxagliptin	3	13	51	59	67	76	94
Comparator	8	16	83	89	76	84	118
Signal‡	No	No	No	No	No	No	No
Saxagliptin vs. long-acting insulin							
DRS stratification							
HR	0.34	0.49	0.51	0.54	0.59	0.58	0.57
95% CI	0.17–0.69	0.31–0.79	0.40–0.66	0.43–0.69	0.47–0.74	0.47–0.73	0.46–0.70
Cum. AMI events							
Saxagliptin	9	24	88	103	99	123	144
Comparator	136	169	380	417	560	473	531
Signal‡	No	No	No	No	No	No	No
PS matching							
HR	0.37	0.66	0.44	0.49	0.52	0.53	0.54
95% CI	0.15–0.96	0.34–1.29	0.31–0.61	0.36–0.67	0.38–0.71	0.39–0.70	0.41–0.71
Cum. AMI events							
Saxagliptin	8	21	62	73	71	92	101
Comparator	12	17	83	87	101	100	110
Signal‡	No	No	No	No	No	No	No

Events are shown for saxagliptin users vs. comparator drug users in patients with and without prior cardiovascular disease, by pairwise comparison and method of covariate adjustment. Aug, August; Cum., cumulative; Jun, June; Mar, March; Dec, December. *Interim analysis 2 and interim analysis 3 had the same end date. The difference between the two interim analyses was the addition of new data partners that joined the surveillance activity starting at interim analysis 3. †Interim analyses 1 to 4 used a slightly modified version of the outcome algorithm that included AMI events coded as nonsecondary discharge diagnosis (which included principal diagnosis and diagnosis with unknown or missing principal diagnosis status). This was because some data partners populated the principal discharge diagnosis variable differently in earlier versions of the Mini-Sentinel distributed database. The definition and extraction of the variable became stable starting in interim analysis 6. This explained the drop in the number of AMI events in some of the analyses between interim analysis 5 and interim analysis 6. ‡A signal was defined as having a Wald z-score (log HR estimate/SE) >2.19 or a one-sided P value of <0.014 based on a prespecified α-spending plan for the sequential analysis. A signal would trigger a follow-up investigation but would not stop the surveillance.

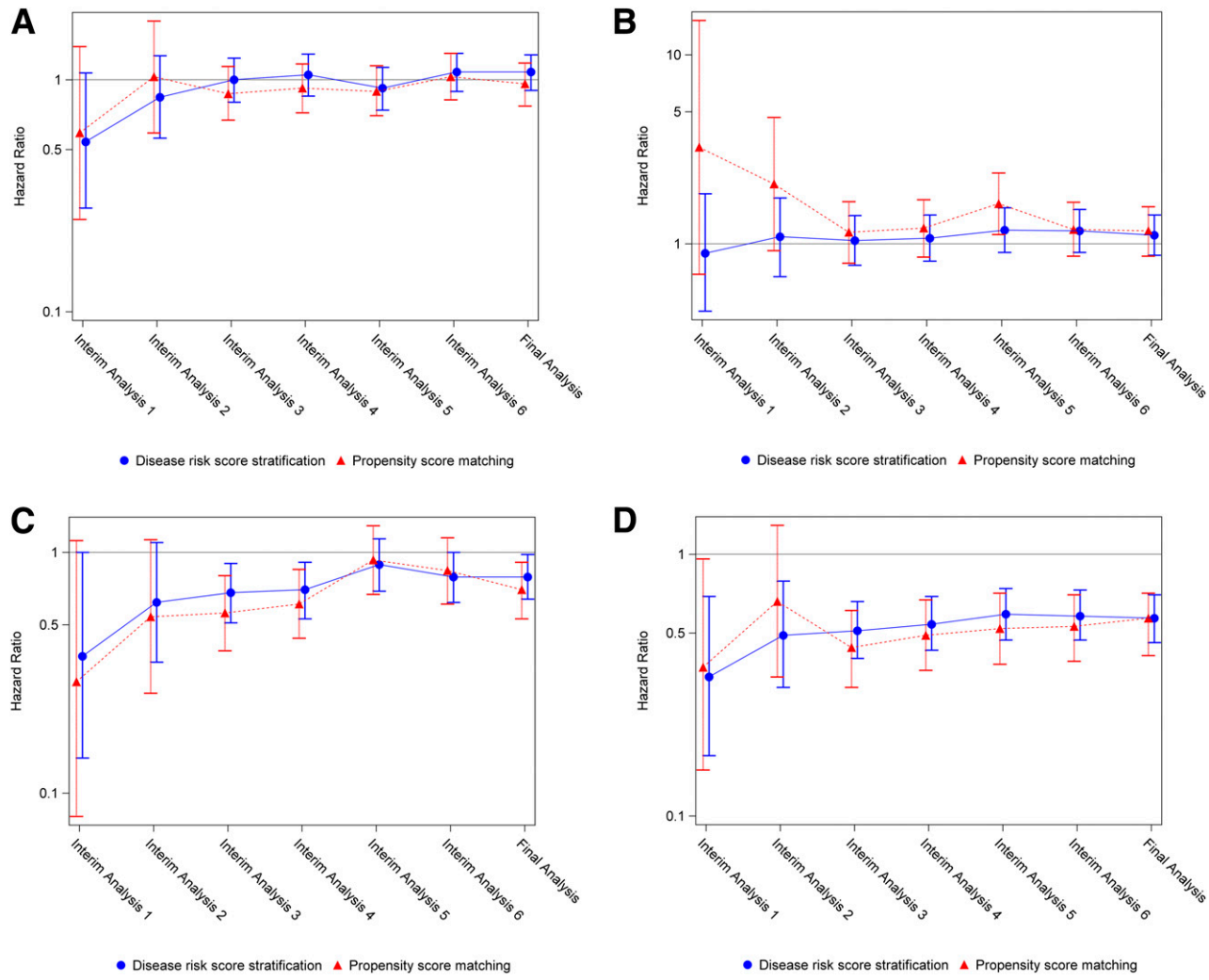

Figure 1—Results from prospective surveillance of AMI events in saxagliptin users vs. comparator drug users in patients with and without prior cardiovascular disease, by pairwise comparison and method of covariate adjustment. *A*: Saxagliptin vs. sitagliptin. *B*: Saxagliptin vs. pioglitazone. *C*: Saxagliptin vs. second-generation sulfonylureas. *D*: Saxagliptin vs. long-acting insulin.

(HR 1.02; 95% CI 0.88–1.19) with insulin glargine use compared with standard care of diabetes over a median follow-up of 6.2 years (33). On the other hand, we expected long-acting insulin users to have more severe diabetes, a longer history of diabetes, and more cardiovascular risk factors compared with saxagliptin users. Although we were able to capture medical history recorded in the year preceding the index date and use of prior and concomitant antihyperglycemic treatments as proxies for diabetes severity, we did not have information on duration or severity of diabetes. Therefore, results from the comparison of saxagliptin with long-acting insulin might be at least partly the result of unmeasured confounding.

Evidence on the cardiovascular risk of second-generation sulfonylureas is conflicting (34). Meta-analyses of randomized trials did not find a higher AMI risk with second-generation sulfonylureas compared with other antihyperglycemic agents or placebo (35,36), but the risk of major adverse cardiovascular events was higher compared with DPP-4 inhibitors. An ongoing cardiovascular outcomes trial comparing linagliptin with glimepiride could provide more definitive evidence on AMI risk for DPP-4 inhibitors versus second-generation sulfonylureas (37). The new-user design allowed us to minimize certain biases in observational studies (see below for discussion of strengths of the design), but it led to the exclusion of saxagliptin users who had previously used second-generation sulfonylureas (and vice versa). This might have resulted in a study cohort that was different from other saxagliptin or second-generation sulfonylurea users.

There are several possible explanations for the one signal identified during surveillance. Saxagliptin could be associated with a higher AMI risk than pioglitazone. The HRs from the DRS-stratified and PS-matched analyses were above 1.0 during surveillance (except for the first sequential DRS-stratified analysis). Unmeasured confounding could be another reason, but the covariate profiles of saxagliptin and pioglitazone users were overall quite similar (Table 1). The signal could also be a chance finding. The parallel DRS-stratified analysis did not produce a signal, which is worth noting.

Strengths and Limitations of the Study

A major strength of this study was the ability to prospectively analyze real-world data as they accrued. It allowed us to obtain postmarketing safety information

more quickly compared with conventional retrospective studies. We used two complementary, sophisticated analytic approaches to adjust for a large number of potential confounders and obtained comparable results. Our data came from a large number of geographically diverse, primarily commercially insured individuals. This well-defined insured population ensures nearly complete capture of medically attended events in many different practice settings. The new-user cohort design allowed us to measure confounders before treatment initiation, ensuring that the confounders were not affected by treatment (and therefore not causal mediators) (15,16,38). It allowed us to monitor patients from the date of their treatment initiation, enabling us to identify outcome events that occurred after treatment initiation to minimize biases associated with missing early events or depletion of susceptibles.

However, our findings should be interpreted within the context of several limitations. As discussed above, we might not have adequately adjusted for confounding by duration and severity of diabetes or other covariates not measured in the study. We did not account for the potential effects of prior antihyperglycemic treatments or confounders that occurred outside of the 1-year baseline period. Extending the look-back period would alleviate this concern but would reduce the number of eligible patients as a result of the requirement of a longer enrollment period. Our follow-up was short (between 4 and 8 months across various treatment groups), so we were not able to investigate the long-term effect of saxagliptin on AMI risk. The short follow-up largely reflected the limited persistence to antihyperglycemic treatments in clinical practice and limited enrollment duration caused by transitioning of individuals between health plans. Treatment discontinuation might lead to selection bias if it varied by antihyperglycemic agent and was associated with cardiovascular risk (39). We did not collect important information (e.g., time-varying predictors of treatment discontinuation) that would allow us to use appropriate methods (e.g., inverse probability weighting [40,41]) to account for selection bias resulting from differential treatment discontinuation. Finally, because of the large number of prespecified analyses, we did not further stratify the analysis by age-group, sex, race/ethnicity (which was incompletely captured in our databases), or dose.

Conclusion

In summary, consistent with the findings of a placebo-controlled randomized trial, we did not find strong evidence to suggest an increased AMI risk among patients treated with saxagliptin in the first 5 years of postmarketing experience. This Mini-Sentinel saxagliptin surveillance demonstrates a new capability to prospectively monitor the safety of approved medical products using routinely collected electronic health care data.

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The views expressed are those of the authors and do not necessarily represent the views of the FDA or the U.S. government.

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Appendix

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