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CLINICAL RESEARCH

Sitagliptin Use in Patients With Diabetes and Heart Failure

A Population-Based Retrospective Cohort Study

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ABSTRACT

OBJECTIVES The study objective was to evaluate the effects of sitagliptin in patients with type 2 diabetes (T2D) and heart failure (HF).

BACKGROUND There is uncertainty in the literature about whether dipeptidyl peptidase (DPP)-4 inhibitors cause harm in patients with HF and T2D.

METHODS We analyzed data from a national commercially insured U.S. claims database. Patients with incident HF were identified from individuals with T2D initially treated with metformin or sulfonylurea and followed over time. Subjects subsequently using sitagliptin were compared with those not using sitagliptin in the 90 days before our primary outcome of all-cause hospital admission or death using a nested case-control analysis after adjustment for demographics and clinical and laboratory data. HF-specific hospital admission or death also was assessed.

RESULTS A total of 7,620 patients with diabetes and incident HF met our inclusion criteria. Mean (SD) age was 54 years (9), and 58% (3,180) were male. Overall, 887 patients (12%) were exposed to sitagliptin therapy (521 patient years of exposure) after incident HF. Our primary composite endpoint occurred in 4,137 patients (54%). After adjustment, sitagliptin users were not at an increased risk for the primary endpoint (7.1% vs. 9.2%, adjusted odds ratio [aOR]: 0.84, 95% confidence interval [CI]: 0.69 to 1.03) or each component (hospital admission 7.5% vs. 9.2%, aOR: 0.93, 95% CI: 0.76 to 1.14; death 6.9% vs. 9.3%, aOR: 1.16, 95% CI: 0.68 to 1.97). However, sitagliptin use was associated with an increased risk of HF hospitalizations (12.5% vs. 9.0%, aOR: 1.84, 95% CI: 1.16 to 2.92).

CONCLUSIONS Sitagliptin use was not associated with an increased risk of all-cause hospitalizations or death, but was associated with an increased risk of HF-related hospitalizations among patients with T2D with pre-existing HF. (J Am Coll Cardiol HF 2014;2:573–82) © 2014 by the American College of Cardiology Foundation.

Heart failure (HF) is a frequent complication of type 2 diabetes (T2D), but how best to control blood glucose in patients with diabetes and HF is a clinically relevant question that has been the source of considerable controversy in both the research and the medical communities (1).

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ABBREVIATIONS AND ACRONYMS

aOR = adjusted odds ratio

CI = confidence interval

DPP = dipeptidyl peptidase

HF = heart failure

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

T2D = type 2 diabetes

TZD = thiazolidinedione

The antidiabetic agent metformin is currently considered first-line therapy in this population (2,3). Sulfonylureas and insulin are also treatment options; however, undesirable side effects, including fluid retention, weight gain, and hypoglycemia (2,3), often limit their use in patients with HF. Thiazolidinediones (TZDs) are contraindicated in patients with HF because of fluid retention. Thus, there is significant interest in the potential role of incretin therapies for patients with concomitant diabetes and HF.

In addition to the antihyperglycemic effects of dipeptidyl peptidase (DPP)-4 inhibitors, they have been shown to improve cardiorenal function (4). Sitagliptin has also been found to reduce cardiac apoptosis, hypertrophy, and fibrosis (5). In addition, DPP-4 inhibitors are considered weight neutral and have generally been shown to improve other cardiovascular risk factors, including low-density lipoprotein, high-density lipoprotein, and blood pressure (6,7).

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A number of recent safety analyses have suggested improved cardiovascular outcomes in sitagliptin-treated subjects, including a 52% relative risk reduction in major adverse cardiovascular events in pooled analyses (8), whereas others have found a neutral effect of DPP-4 inhibitors on cardiovascular outcomes (9,10). Of note, these studies were of short duration, enrolled highly selected patients, and were not designed with cardiovascular outcomes as the primary endpoints. The recently published SAVOR (Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes) trial suggested that saxagliptin was associated with increased risk of HF compared with placebo (11). Conversely, the EXAMINE (Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes) study with alogliptin found no significant benefit or risk related to HF in patients with T2D and a history of myocardial infarct or angina (12). Because of the recent controversies surrounding the safety of these drugs, the Food and Drug Administration has requested additional data from the SAVOR trial to further investigate the potential link between saxagliptin therapy and HF hospital admission (13).

In light of the current debate surrounding the safety of DPP-4 inhibitors in patients with existing HF, we designed this study to evaluate the effects of sitagliptin, the first marketed and most widely used DPP-4 inhibitor in North America, in patients with T2D and incident HF.

METHODS

We conducted a population-based, retrospective cohort study using a large U.S. claims and integrated laboratory database that included employed, commercially insured individuals from all 50 states (Clinformatics Data Mart, OptumInsight Life Sciences Inc.). Patient-level data included administrative and demographic information (type of insurance plan, sex, age, dates of eligibility, income) and billable medical services claims, including inpatient and outpatient visits and medical procedures (physician and facility identifier, date and place of service, cost of service, admission, and discharge dates, procedures and diagnostic codes), all laboratory tests and results (including fasting lipids, renal function, liver function, blood glucose [glycosylated hemoglobin], and complete blood count), and pharmacy claims data (prescribing physician, drug dispensed on the basis of national drug codes, quantity and date dispensed, drug strength, days supply, cost of service) (14–17). All clinical diagnoses were recorded according to the International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) codes and procedure codes.

COHORT SELECTION. We identified those individuals who had a prescription claim for metformin or sulfonylurea therapy from January 1, 2003, to December 31, 2009, and subsequently developed incident HF (i.e., any claim with ICD-9-CM code of 428.XX with no history of a diagnosis of HF in 1 year before incident HF event). These agents were chosen because they are the most commonly prescribed oral antidiabetic agents in patients with diabetes and would provide a more homogenous study population. Moreover, several studies in diabetes and HF have evaluated the effects of metformin and sulfonylurea (1). Because TZD therapy has been shown to increase the risk of HF and is contraindicated in patients with established HF, all patients were excluded if they received a TZD before HF diagnosis. Moreover, subjects not initially using TZDs but who subsequently initiated TZDs after incident HF were censored on the date they first filled a TZD prescription (**Figure 1**). Patients also had to be at least 20 years of age and had to have at least 1 year of continuous medical insurance before diagnosis of HF (so we could be certain any cases of HF were new diagnoses) to be included in our cohort. Subjects were followed from the date of incident HF until death, termination of medical insurance, or December 31, 2010 (study exit date) (**Figure 2**).

OUTCOMES. We followed our cohort after incident HF to measure their health outcomes. Our primary

outcome of interest was a composite endpoint of "all-cause hospital admission or death" with our secondary endpoints, including HF-related hospital admission or all-cause death. We also evaluated each component of our composite endpoints separately (i.e., all-cause hospital admission, all-cause death, HF-specific hospital admission). It is important to note that the incident HF event used to define our cohort of interest and our subsequent outcome of HF-related hospital admission during follow-up are 2 distinct events. Vital status was determined through linkage to the U.S. national death index files (18), although cause of death was not ascertained. Linkage to this index is highly reliable and valid (>98% specificity) and has been used in previous analyses (19,20).

NESTED CASE-CONTROL POPULATION. To reduce confounding by indication and account for time-varying changes in exposure during follow-up, we used a nested case-control approach to evaluate the effects of sitagliptin treatment in patients with HF with T2D. All subjects with the primary outcome of interest (e.g., all-cause hospital admission or death) were considered cases, with the date of all-cause death or hospital admission being considered the index date. Cases were matched on age (quartiles) and sex with up to 10 controls with no hospital

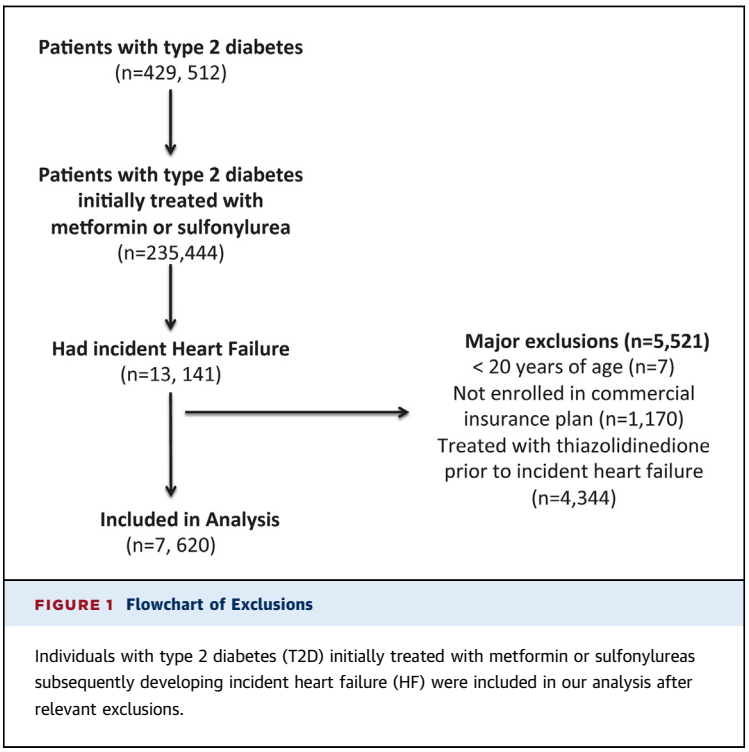

FIGURE 1 Flowchart of Exclusions

Individuals with type 2 diabetes (T2D) initially treated with metformin or sulfonylureas subsequently developing incident heart failure (HF) were included in our analysis after relevant exclusions.

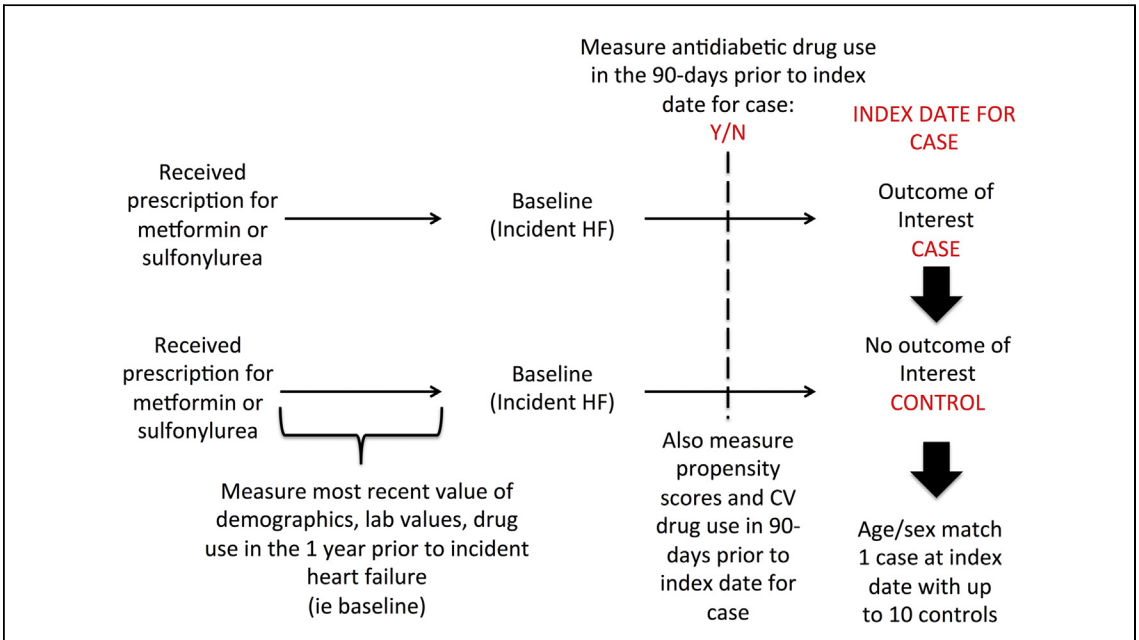

FIGURE 2 Schematic of Cohort Study Design

Patients included in our analysis were age/sex matched with up to 10 controls at the time each case arose. Drug use was measured in the 90 days before the index date for each case, and cohort characteristics were evaluated within the year before incident HF. CV = cardiovascular; HF = heart failure.

TABLE 1 Characteristics of Cases (for Primary Composite Endpoint) and Matched Controls in the 1 Year Before Incident Heart Failure

	Control (n = 41,297)	Case (n = 4,137)	p Value*
Characteristics			
Age (yrs)	54.6 ± 8.7	54.6 ± 8.7	0.97
Male	24,556 (59.5)	2,457 (59.4)	0.93
Income ($)	48,341 ± 6,262	48,316 ± 6,266	
Type of insurance			0.001
Point of service	24,874 (60.2)	2,391 (57.8)	
Exclusive provider	7,192 (17.4)	747 (18.1)	
Preferred provider	3,394 (8.2)	394 (9.5)	
Health Maintenance	4,740 (11.5)	516 (12.5)	
Independent	1,097 (2.7)	89 (2.2)	
Clinical parameters			
Mortality risk score	45.6 ± 12.8	47.8 ± 13.3	<0.001
History of cardiovascular disease			
Ischemic heart disease	17,158 (41.6)	1,703 (41.2)	0.63
Myocardial infarction	2,300 (5.6)	302 (7.3)	<0.001
Dyslipidemia	28,638 (69.4)	2,808 (67.9)	0.51
Hypertension	33,950 (82.2)	3,438 (83.1)	0.15
Arrhythmia	7,128 (17.3)	750 (18.1)	0.16
Valve disease	3,366 (8.2)	379 (9.2)	0.024
History of diabetes complications	16,459 (39.9)	1,612 (39.0)	0.27
Estimated glomerular filtration rate category (ml/min)			<0.001
<30	1,225 (3.0)	222 (5.4)	
30–<60	5,488 (13.3)	646 (15.6)	
≥60	19,983 (48.4)	1,843 (44.6)	
Total cholesterol (mg/dl)	177.1 ± 50.3	181.0 ± 55.2	0.0002
Triglycerides (mg/dl)	191.3 ± 254.7	197.6 ± 315.4	0.25
HDL cholesterol (mg/dl)	44.7 ± 13.7	44.7 ± 14.4	0.89
LDL cholesterol (mg/dl)	96.7 ± 37.1	99.7 ± 39.2	0.0059
HbA1c (%)	7.5 ± 1.7	7.8 ± 1.9	<0.001
Hemoglobin (mg/dl)	13.5 ± 1.8	13.2 ± 1.9	<0.001
Drug use			
ACE inhibitor/ARB	28,961 (70.1)	2,816 (68.1)	0.006
Statin	22,926 (55.5)	2,224 (53.8)	0.03
Beta-blocker	20,920 (50.7)	2,109 (51.0)	0.69
Dihydro calcium channel blocker	9,524 (23.1)	1,038 (25.1)	0.003
Non-dihydro calcium channel blocker	4,153 (10.1)	453 (11.0)	0.069
Nitrates	5,469 (13.2)	597 (14.4)	0.032
Diuretics	7,710 (18.7)	788 (19.1)	0.55
Anticoagulants	4,013 (9.7)	469 (11.3)	0.001
Antiplatelet agents	7,567 (18.3)	801 (19.4)	0.10

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admission and who were alive on the same index date for their given case using conventional risk set sampling (i.e., incident density sampling) (21,22). On the basis of considerations of statistical power, up to 10 controls per case were selected to provide approximately 90% power to the study. Controls were "at risk" for the outcome of interest (i.e., actively followed, alive, and event free) before the matched case index date. By convention, controls were selected one subject at a time with replacement (i.e., a subject can be a control subject for several cases across time points) and given an analogous index date as their matched case (23). This process was repeated for each endpoint assessed.

EXPOSURE TO ANTIDIABETIC DRUGS. Patients were considered exposed to an antidiabetic agent if the duration of the drug prescription, based on the dispensed days supplied, was within 90 days of the index date (i.e., time of event or pseudo date for matching controls) (24). Exposure status was classified into 5 categories that were not mutually exclusive: any sitagliptin use, any metformin use, any sulfonylurea use, other oral antidiabetic drug use (acarbose, meglitinides, pramlintide), and any insulin use as has been done previously (20). We attributed outcome events to the drugs the patient was receiving at the time of the event, and we assumed no legacy or carryover effects from remote exposures beyond 90 days with any of the glucose-lowering drugs for the primary analysis.

STATISTICAL ANALYSIS. We used conditional logistic regression to compare the effect of our drugs of interest on the primary outcome and obtained estimates of the odds ratio and 95% confidence intervals (CIs) from the regression analysis. We included each drug exposure class in the model as a dummy variable with the reference group being no exposure to that particular agent (e.g., sitagliptin use compared with no sitagliptin use in the 90 days before index date, after adjustment for the use of other antidiabetic agents).

In addition to our antidiabetic agents, covariates in our models included demographics (age, sex, and socioeconomic status [type of medical insurance and median household income according to 2010 U.S. census]) (25), most recent clinical laboratory data (glycosylated hemoglobin; low- and high-density lipoprotein cholesterol; triglycerides; estimated glomerular filtration rate stratified into ≥60, 59.9 to 30, and <30 ml/min; albuminuria; and hemoglobin concentrations), history of cardiovascular disease (ischemic heart disease, myocardial infarction, dyslipidemia, hypertension, arrhythmia, and valve disease), and prescription drug use (antiplatelet drugs, anticoagulants, statins, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates). For patients who were missing clinical laboratory information, we used the missing indicator approach (26). To further control for the clinical complexity of patients, we used specific variables and adjusted clinical groups derived from the Johns Hopkins adjusted clinical groups system (27). More specifically, we adjusted for the number of inpatient hospitalizations that patients had in the 1 year before HF diagnosis and the number

of chronic conditions. A frailty flag also was calculated on the basis of patient characteristics, including malnutrition, difficulty walking, dementia, incontinence, and barriers to access of care (27). This measure of frailty has been validated and found to accurately identify elderly populations who have the clinical characteristics of frailty and to predict adverse outcomes (28). To further control for comorbidities, we also calculated a mortality risk score based on the weighted components of the 32 adjusted diagnostic groups from the Johns Hopkins System, which has been shown to perform as well as or better than other comorbidity scores, such as the Charlson or Elixhauser scores (29). Because we did not have information available on HF severity (e.g., New York Heart Association class, brain natriuretic peptide levels, left ventricular ejection fraction), we adjusted for the location of the initial HF diagnosis as a proxy because patients with more symptomatic HF would be more likely to be hospitalized (30). We also evaluated the use of common HF drugs (i.e., agents effecting the angiotensin system, beta-blockers, spironolactone, loop diuretics, hydralazine, digoxin, and amiodarone) in the 90 days before the index date for each individual (both cases and controls).

To help control for confounding by indication, we used a generalized propensity score. Traditionally, propensity scores predict a patient's probability of receiving one treatment versus a single alternative; however, this does not reflect the real-world treatment choices for diabetic patients in whom more than 1 medication may be used. Therefore, we calculated a generalized propensity score with 4 treatment levels (metformin, sulfonylurea, insulin, or sitagliptin) in the 90 days before the index date for each individual (both cases and controls) using multinomial logistic regression (31).

SENSITIVITY ANALYSIS. We conducted several sensitivity analyses to confirm the robustness of our results. First, we evaluated the effects of combination therapy, such as metformin/sitagliptin combination, sitagliptin/sulfonylurea combination, and sitagliptin/other combination treatment all compared with metformin/sulfonylurea combination as the reference. Next, we evaluated the impact of sitagliptin therapy in patients with renal impairment (estimated glomerular filtration rate <60 ml/min). Third, we restricted our cohort to include only those who developed incident HF from 2007 to 2009 considering sitagliptin was not made available in the United States before 2007. Fourth, we excluded patients if they were exposed to insulin therapy before incident HF or during the follow-up period after HF, given that insulin treatment is most often prescribed in those with more advanced diabetes. Fifth, we restricted our analysis to those who were new users of metformin or sulfonylurea therapy before incident HF therapy in an attempt to mitigate any biases introduced to the analysis by prevalent users before the onset of HF. Next, we included those individuals who were treated with TZDs before incident HF in our analysis and did not censor individuals if they initiated TZD therapy over the follow-up. Seventh, we extended our definition of incident HF and analyzed those with no history of diagnosis of HF in the 3 years before the incident HF event. Eighth, we censored individuals if they terminated all antidiabetic drug treatment for at least 90 days after incident HF. Ninth, we considered any legacy effects of antidiabetic drug exposure by considering individuals exposed to a particular antidiabetic therapy for the remainder of the follow-up after their first prescription after incident HF, irrespective of whether the patient stopped therapy. In light of recent safety concerns, we also evaluated the effects of sitagliptin use on the risk of acute pancreatitis, although we fully acknowledge that power is extremely low for this endpoint. We also assessed whether exposure to sitagliptin affected the risk of cardiovascular-related hospital admission excluding HF (ICD-9-CM codes 410, 411, 430-438) and noncardiovascular-related hospital admission. Last, to explore the potential for unrecognized confounding, we evaluated the risk of glaucoma

TABLE 1 Continued

	Control (n = 41,297)	Case (n = 4,137)	p Value*
Health care use			
Inpatient hospital admission in year before incident HF			<0.001
0	29,957 (72.5)	2,629 (63.6)	
1	8,738 (21.2)	1,027 (24.8)	
2+	2,602 (6.3)	481 (11.6)	
Frailty	3,455 (8.4)	448 (10.8)	<0.001
Chronic conditions			<0.001
≥1	3,034 (7.4)	293 (7.08)	
2	3,400 (8.2)	290 (7.0)	
3+	34,868 (84.4)	3,554 (85.9)	
Location of HF diagnosis			
Ambulatory	164 (0.4)	5 (0.1)	0.005
Emergency department	120 (0.3)	16 (0.4)	0.28
Physician's office	19,652 (47.6)	1,167 (28.2)	<0.001
Hospital	9,339 (22.6)	1,921 (46.4)	<0.001
Outpatient facility	7,186 (17.4)	725 (17.5)	0.85
Other	4,836 (11.7)	303 (7.3)	<0.001

Values are mean ± SD or n (%). *p value is for difference in characteristics between cases and controls.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HF = heart failure; LDL = low-density lipoprotein.

TABLE 2 Characteristics in the 1 Year Before Incident Heart Failure According to Antidiabetic Drug Exposure During Follow-Up After Incident Heart Failure Diagnosis

	No Sitagliptin Exposure (n = 6,733)	Exposed to Sitagliptin (n = 887)	Exposed to Metformin (n = 3,799)	Exposed to Sulfonylurea (n = 2,954)	Exposed to Other Antidiabetic Agents† (n = 821)	p Value*
Characteristics						
Age (yrs)	54.4 ± 8.8	54.8 ± 7.6	54.3 ± 8.3	55.3 ± 8.2	53.9 ± 7.7	0.15
Male	3,902 (58.0)	538 (60.7)	1,596 (42.0)	1,850 (62.6)	468 (57.0)	0.13
Income ($)	48,337 ± 6,304	48,486 ± 6,459	48,181 ± 6,224	48,085 ± 6,110	48,196 ± 6,182	0.51
Type of insurance						0.023
Point of service	3,928 (58.3)	563 (63.5)	2,256 (59.4)	1,758 (59.5)	485 (59.1)	
Exclusive provider	1,189 (17.7)	150 (16.9)	688 (18.1)	514 (17.4)	152 (18.5)	
Preferred provider	596 (8.9)	69 (7.8)	314 (8.3)	255 (8.6)	76 (9.3)	
Health Maintenance	880 (13.1)	87 (9.8)	463 (12.2)	359 (12.2)	93 (11.3)	
Independent	140 (2.1)	18 (2.0)	78 (2.1)	68 (2.3)	15 (1.8)	
Clinical parameters						
Mortality risk score	46.3 ± 13.2	45.7 ± 11.9	44.5 ± 12.6	46.1 ± 12.4	44.6 ± 12.2	0.16
History of cardiovascular disease						
Ischemic heart disease	2,726 (40.5)	403 (45.3)	1,522 (40.1)	1,218 (41.2)	343 (41.8)	0.006
Myocardial infarction	435 (6.5)	40 (4.5)	208 (5.5)	172 (5.8)	33 (4.0)	0.02
Dyslipidemia	4,636 (68.9)	641 (72.3)	2,679 (70.5)	1,986 (67.2)	585 (71.3)	0.038
Hypertension	5,574 (82.8)	746 (84.1)	3,118 (82.1)	2,419 (81.9)	672 (81.9)	0.33
Arrhythmia	1,184 (17.6)	160 (18.0)	622 (16.4)	525 (17.8)	145 (17.7)	0.74
Valve disease	585 (8.7)	78 (8.8)	304 (8.0)	256 (8.7)	67 (8.2)	0.92
History of diabetes complications	2,622 (38.9)	429 (48.4)	1,639 (43.1)	1,393 (47.2)	337 (41.1)	0.001
Estimated glomerular filtration rate category (ml/min)						0.006
<30	274 (4.1)	17 (1.9)	12 (0.32)	70 (2.4)	17 (2.1)	
30-<60	995 (14.2)	117 (13.2)	363 (9.6)	416 (14.1)	103 (12.6)	
≥60	3,249 (48.3)	428 (48.3)	2,080 (54.8)	1,417 (48.0)	425 (51.8)	
Total cholesterol (mg/dl)	180.0 ± 53.0	173.9 ± 47.9	177.0 ± 52.5	178.8 ± 52.6	177.3 ± 62.4	0.014
Triglycerides (mg/dl)	193.5 ± 296.4	196.8 ± 198.3	197.5 ± 305.9	198.6 ± 271.3	231.7 ± 590.6	0.8
HDL cholesterol (mg/dl)	45.0 ± 13.9	43.3 ± 13.2	44.0 ± 12.3	43.5 ± 12.7	43.1 ± 11.9	0.006
LDL cholesterol (mg/dl)	99.4 ± 38.8	92.1 ± 33.1	98.0 ± 37.5	98.4 ± 36.2	96.3 ± 38.4	0.0094
HbA1c (%)	7.7 ± 1.9	7.7 ± 1.7	7.5 ± 1.7	7.6 ± 1.7	7.9 ± 1.8	0.47
Hemoglobin (mg/dl)	13.3 ± 1.9	13.6 ± 1.8	13.6 ± 1.7	13.6 ± 1.8	13.6 ± 1.7	0.012
Drug use						
ACE inhibitor/ARB	4,609 (68.5)	645 (72.7)	2,686 (70.7)	2,103 (71.2)	601 (73.2)	0.01
Statin	3,677 (54.6)	517 (58.3)	2,172 (57.2)	1,649 (55.8)	461 (56.2)	0.039
Beta-blocker	3,380 (50.2)	476 (53.7)	1,843 (48.5)	1,529 (51.8)	434 (52.9)	0.052
Dihydro calcium channel blocker	1,604 (23.8)	218 (24.6)	797 (21.0)	733 (24.8)	177 (21.6)	0.62
Non-dihydro calcium channel blocker	700 (10.4)	71 (8.0)	346 (9.1)	298 (10.1)	86 (10.5)	0.026
Nitrates	911 (13.5)	108 (12.2)	512 (13.5)	403 (13.6)	119 (14.5)	0.27
Diuretics	1,244 (18.5)	185 (20.9)	684 (18.0)	558 (18.9)	156 (19.0)	0.088
Anticoagulants	696 (10.3)	92 (10.4)	340 (9.0)	308 (10.4)	94 (11.5)	0.97
Antiplatelet agents	1,226 (18.2)	171 (19.3)	636 (16.7)	544 (18.4)	150 (18.3)	0.44
Health care use						
Inpatient hospital admission in year before incident HF						0.022
0	4,639 (68.9)	664 (74.9)	2,840 (74.8)	2,153 (72.9)	614 (74.8)	
1	1,498 (22.3)	175 (19.3)	744 (19.6)	618 (20.9)	155 (18.9)	
2+	596 (8.85)	48 (5.4)	215 (5.7)	183 (6.2)	52 (6.3)	
Frailty	644 (9.6)	73 (8.2)	324 (8.5)	233 (7.9)	88 (10.7)	0.2
Chronic conditions						0.38
≥1	489 (7.3)	62 (7.0)	286 (7.5)	234 (7.9)	67 (8.2)	
2	518 (7.7)	68 (7.7)	346 (9.1)	264 (8.9)	54 (6.6)	
3+	5,726 (85.0)	757 (85.3)	3,167 (83.4)	2,456 (83.1)	700 (85.3)	

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TABLE 2 Continued

	No Sitagliptin Exposure (n = 6,733)	Exposed to Sitagliptin (n = 887)	Exposed to Metformin (n = 3,799)	Exposed to Sulfonylurea (n = 2,954)	Exposed to Other Antidiabetic Agents† (n = 821)	p Value*
Location of HF diagnosis						
Ambulatory	22 (0.3)	3 (0.3)	13 (0.3)	5 (0.2)	4 (0.5)	0.96
Emergency department	22 (0.3)	2 (0.2)	9 (0.2)	7 (0.2)	3 (0.4)	0.61
Physician's office	2,556 (38.0)	405 (45.7)	1,652 (43.5)	1,230 (41.6)	378 (46.0)	<0.001
Hospital	2,291 (34.0)	230 (25.9)	1,084 (28.5)	919 (31.1)	216 (26.3)	<0.001
Outpatient facility	1,186 (17.6)	159 (17.9)	652 (17.2)	495 (16.8)	129 (15.7)	0.82
Other	656 (9.7)	88 (9.9)	389 (10.2)	298 (10.1)	91 (11.1)	0.87

Values are mean ± SD or n (%). *p value is for difference in characteristics between sitagliptin users and nonusers. Antidiabetic drug exposure was at any point after incident HF (ever use vs. never use). †Other antidiabetic agents can include acarbose, meglitinides, and pramlintide.

Abbreviations as in Table 1.

between sitagliptin users and nonusers (a condition chosen because it should not differ by sitagliptin exposure) (32,33).

RESULTS

Of the 7,620 diabetic patients with incident HF included in our study, the median follow-up was 1.4 years; thus, we analyzed 12,704 person years at risk. Overall, 887 patients (12%) were exposed to sitagliptin therapy (521 total patient years of exposure), 3,799 patients (49.9%) were exposed to metformin (3,383 total patient years of exposure), and 2,954 patients (38.8%) were exposed to sulfonylureas (3,107 total patient years of exposure) at any point after incident HF. The mean age was 54 (SD 8) years, and 4,440 (58%) were male.

As expected, we found that for our primary composite endpoint of all-cause hospitalization or death, cases were more likely to have a higher mortality risk score, prior hospitalizations, and a history of myocardial infarct or renal impairment, and to have been treated with cardiovascular medications before their incident HF event compared with controls (**Table 1**). Cases also had higher cholesterol and glycosylated hemoglobin levels, and were less likely to have been treated with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers before HF diagnosis.

Those exposed to sitagliptin during follow-up were similar to those not exposed to sitagliptin with respect to most covariates, including age, sex, and socioeconomic status (**Table 2**). However, those exposed to sitagliptin were more likely to have a history of diabetes complications (microvascular, macrovascular, and other) or ischemic heart disease before incident HF, slightly lower total cholesterol, and higher use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins, but fewer hospitalizations in the year before HF diagnosis compared with those who were not exposed to sitagliptin. Moreover, sitagliptin users were more likely to be diagnosed with HF in the physicians' office as opposed to the hospital setting.

By the end of follow-up, our primary composite endpoint of all-cause hospital admission or death occurred in 4,137 patients (54.3%); 4,076 patients (53.5%) were admitted to the hospital at least once (824 for HF), and 408 patients (5.4%) died. Our secondary endpoint of HF-related hospital admission or all-cause death occurred in 1,146 patients (15.0%).

Sitagliptin users demonstrated a lower crude risk of all-cause hospital admission or death compared with nonusers (7.1% vs. 9.2%), but the difference was not statistically significant after covariate adjustment (adjusted odds ratio [aOR]: 0.84, 95% CI: 0.69 to 1.03). There were no significant differences noted between sitagliptin users and nonusers for all-cause death alone or all-cause hospitalization alone (**Table 3**). In addition, we found that after adjustment, those exposed to metformin exhibited a lower risk of all-cause death or hospital admission (aOR: 0.78, 95% CI: 0.71 to 0.85), whereas users of insulin (aOR: 1.16, 95% CI: 1.05 to 1.28) or sulfonylureas (aOR: 1.10, 95% CI: 1.00 to 1.23) exhibited higher risk for our primary composite endpoint. For our secondary endpoint of interest, we found that sitagliptin use was not associated with an increased risk of HF-related hospital admission or death (9.0% vs. 9.1%, aOR: 1.34, 95% CI: 0.93 to 1.92) but was associated with an increased risk of HF-related hospital admission alone (aOR: 1.84, 95% CI: 1.16 to 2.92) (**Table 3**, **Figure 3**).

For the results of our sensitivity analyses, we found that compared with metformin and sulfonylurea

TABLE 3 Outcomes According to Antidiabetic Drug Exposure 90 Days Before Index Date for Each Outcome

Outcome	Agent	Exposed Cases/Total Exposed	Unexposed Cases/Total Unexposed	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	p Value*
All-cause death or hospital admission	Sitagliptin	113/1,588	4,024/43,846	0.75 (0.62–0.92)	0.84 (0.69–1.03)	0.10
	Metformin	756/10,734	3,381/34,700	0.64 (0.59–0.70)	0.78 (0.71–0.85)	<0.001
	Insulin	800/7,149	3,337/38,285	1.37 (1.25–1.50)	1.16 (1.05–1.28)	0.004
	Sulfonylurea	673/7,710	3,464/37,724	0.94 (0.86–1.03)	1.10 (1.00–1.23)	0.043
	Other	109/1,429	4,028/44,005	0.81 (0.67–1.00)	0.95 (0.77–1.17)	0.64
All-cause death	Sitagliptin	19/274	389/4,193	0.73 (0.45–1.18)	1.16 (0.68–1.97)	0.59
	Metformin	66/1,530	342/2,937	0.33 (0.25–0.44)	0.52 (0.37–0.71)	<0.001
	Insulin	142/1,411	266/3,056	1.18 (0.95–1.47)	1.11 (0.84–1.47)	0.46
	Sulfonylurea	73/1,247	335/3,220	0.53 (0.41–0.69)	0.83 (0.61–1.14)	0.25
	Other	13/214	395/4,253	0.63 (0.36–1.12)	0.87 (0.46–1.63)	0.66
All-cause hospital admission	Sitagliptin	112/1,489	3,964/43,274	0.80 (0.6–0.98)	0.93 (0.76–1.14)	0.46
	Metformin	750/10,556	3,326/34,207	0.65 (0.59–0.71)	0.79 (0.71–0.87)	<0.001
	Insulin	795/7,215	3,281/37,548	1.34 (1.23–1.47)	1.13 (1.03–1.25)	0.014
	Sulfonylurea	669/7,683	3,407/37,080	0.93 (0.85–1.03)	1.08 (0.97–1.19)	0.15
	Other	109/1,277	3,967/43,486	0.93 (0.76–1.13)	1.06 (0.86–1.31)	0.56
HF-related hospital admission or death	Sitagliptin	37/409	1,109/12,172	0.99 (0.70–1.41)	1.34 (0.93–1.92)	0.12
	Metformin	154/2,556	992/10,025	0.53 (0.44–0.64)	0.70 (0.57–0.86)	0.001
	Insulin	217/2,126	929/10,455	1.20 (1.01–1.42)	1.02 (0.84–1.24)	0.81
	Sulfonylurea	156/2,063	990/10,518	0.76 (0.63–0.92)	0.92 (0.75–1.13)	0.41
	Other	21/302	1,125/12,279	0.74 (0.47–1.16)	0.85 (0.53–1.36)	0.50
HF-related hospital admission	Sitagliptin	25/200	799/8,862	1.47 (0.95–2.27)	1.84 (1.16–2.92)	0.01
	Metformin	106/1,378	718/7,684	0.76 (0.60–0.96)	0.87 (0.66–1.12)	0.28
	Insulin	113/1,114	711/7,948	1.19 (0.94–1.50)	0.97 (0.75–1.27)	0.83
	Sulfonylurea	103/1,067	721/7,995	1.09 (0.86–1.39)	1.11 (0.84–1.45)	0.47
	Other	14/147	810/8,905	0.98 (0.56–1.72)	1.08 (0.59–1.96)	0.81

*p value is for adjusted odds ratio.
CI = confidence interval; HF = heart failure.

therapy, sitagliptin and metformin combination therapy was associated with a lower risk of our primary composite endpoint (aOR: 0.56, 95% CI: 0.44 to 0.82), whereas sitagliptin and sulfonylurea combination therapy was not associated with an increased risk for our primary composite endpoint (aOR: 0.90, 95% CI: 0.54 to 1.47), as was sitagliptin in combination with therapy other than metformin or sulfonylurea (i.e., sitagliptin and other combination therapies; aOR: 2.23, 95% CI: 0.74 to 6.67).

Our remaining sensitivity analyses confirmed the results of our primary analysis (results available on request). We also found that there was no increased risk of cardiovascular-related hospital admission (excluding HF) with sitagliptin use compared with nonuse (aOR: 1.12, 95% CI: 0.75 to 1.65) with a trend toward a decreased risk of noncardiovascular-related hospital admission with sitagliptin use (aOR 0.77, 95% CI: 0.58 to 1.03). Last, we found a neutral association between sitagliptin use and risk of glaucoma (aOR:1.09, 95% CI: 0.88 to 1.34, p = 0.44), suggesting there was no unrecognized confounding influencing our results.

DISCUSSION

This is the first population-based study to evaluate the effects of sitagliptin therapy in patients with T2D and HF. Although our study suggests the use of sitagliptin is not associated with significant risk of all-cause death or hospital admission in patients with T2D and HF, sitagliptin use was associated with an apparent increase in HF-related hospital admissions. The increase in HF events is likely clinically relevant (resulting in a number need to harm of 29) and may have implications for choice of add-on therapy for patients with HF and diabetes poorly controlled with other agents.

Although our results are intriguing, it is clear that additional studies are required, specifically in patients with HF, to solidify the risk:benefit picture. Indeed, even results from large-scale randomized controlled trials have not been consistent for the DPP-4 inhibitors as a whole. The recently completed SAVOR trial found saxagliptin to be noninferior for a composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke

compared with placebo (34); however, an unexpected increase in the risk of HF events was observed. Conversely, the EXAMINE trial assessing the effect of alogliptin therapy in patients with acute myocardial infarction or unstable angina compared with placebo found no effect on HF-specific events in post hoc analyses (12). Moreover, no substantial risk has been observed with sitagliptin in large population-based studies on cardiovascular endpoints in the broader diabetic population (20). Thus, the ongoing TECOS (Trial Evaluating Cardiovascular Outcomes With Sitagliptin) is key to further assessing the safety of this drug (but is not set to report until 2015). Although all of these trials enrolled patients with established cardiovascular disease or risk factors, none specifically identified individuals with established HF. Therefore, it is unlikely the upcoming results of the TECOS trial will provide evidence for the safety of sitagliptin therapy in those with preexisting HF, unless evaluate as a subgroup. As a result, observational studies, like ours, are currently the sole source of evidence regarding this important area of research.

Our study had several important strengths, including the availability of detailed clinical data (glycosylated hemoglobin, cholesterol, and markers of renal function); the use of advanced statistical techniques, such as time-varying drug exposures and calculation of propensity scores within each risk set; and large sample size, considering the agent and population under study.

STUDY LIMITATIONS. Although this was a rigorous observational study, we must still be cautious in our interpretations and conclusions because causal inferences cannot be made on the basis of observational studies alone. Despite the use of propensity scores, confounding by indication may still introduce bias. Indeed, patients at risk for HF or with asymptomatic left ventricular dysfunction will be potentially less likely to be prescribed other drugs that may make HF worse according to clinical judgment. However, we did find that sitagliptin use was not associated with risk of glaucoma, arguing against any substantial residual confounding. In addition, we were not able to control for body weight or blood pressure. The inability to adjust for these variables in our analysis may have introduced bias given that DPP-4 inhibitors are weight neutral, and thus sitagliptin may have been preferentially prescribed to those in the highest body mass index categories. Because increased body mass index has been paradoxically associated with improved outcomes in patients with HF (35), this may have resulted in lower event rates in sitagliptin-treated subjects compared with those not treated with sitagliptin; therefore, if anything, our results may underestimate the potential risks of sitagliptin. Furthermore, although we included the use of antihypertensive agents, as well as physician-assigned diagnoses of hypertension, this may not fully account for differences in blood pressure among our groups. We also did not have data available for HF severity or ventricular function. Although we attempted to account for this by adjusting for location of HF diagnosis, sitagliptin still may have had differential effects or may have been differentially prescribed in those with more or less severe HF. Finally, because sitagliptin has only recently come onto the market, the number of patients exposed to sitagliptin was relatively small and we had a relatively short duration of follow-up to detect adverse effects or potential benefits, resulting in wide CIs around our risk estimates, particularly for HF-specific events.

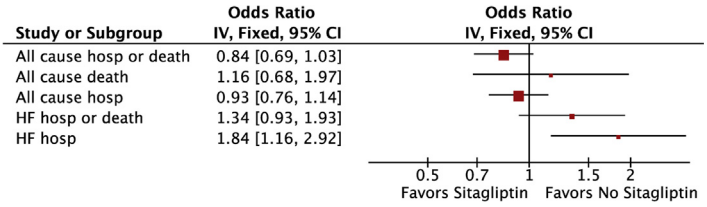

FIGURE 3 Forest Plot of Primary and Secondary Endpoints According to Sitagliptin Use

Primary and secondary endpoints after incident HF were evaluated according to sitagliptin use versus nonuse 90 days before each outcome. CI = confidence interval; HF = heart failure; hosp = hospitalization; IV = interval.

CONCLUSIONS

Current clinical practice guidelines suggest that metformin should be considered first-line therapy in patients with diabetes and HF, with the choice of second-line therapy left to the discretion of the attending physician on the basis of other patient considerations (2,3). Other studies have found that sitagliptin has a similar efficacy for lowering blood glucose compared with other agents, rarely causes hypoglycemia, and is weight neutral, whereas in the current study we found that sitagliptin therapy does not seem to be associated with increased risk of all-cause death or hospital admission. In addition, our ancillary analyses demonstrated that metformin/sitagliptin combination therapy was safer than metformin/sulfonylurea combination for our primary outcome. However, we also found that there may be

a safety signal associated with sitagliptin in terms of an excess of HF-related hospitalizations in those with established HF. Therefore, both the benefits and the potential risks of sitagliptin therapy should be weighed when choosing a second-line therapy in those with diabetes and HF.

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