ORIGINAL ARTICLE

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure

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ABSTRACT

BACKGROUND

There is concern that antidiabetic incretin-based drugs, including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) analogues, can increase the risk of heart failure. Ongoing clinical trials may not have large enough samples to effectively address this issue.

METHODS

We applied a common protocol in the analysis of multiple cohorts of patients with diabetes. We used health care data from four Canadian provinces, the United States, and the United Kingdom. With the use of a nested case–control analysis, we matched each patient who was hospitalized for heart failure with up to 20 controls from the same cohort; matching was based on sex, age, cohort-entry date, duration of treated diabetes, and follow-up time. Cohort-specific hazard ratios for hospitalization due to heart failure among patients receiving incretin-based drugs, as compared with those receiving oral antidiabetic-drug combinations, were estimated by means of conditional logistic regression and pooled across cohorts with the use of random-effects models.

RESULTS

The cohorts included a total of 1,499,650 patients, with 29,741 hospitalized for heart failure (incidence rate, 9.2 events per 1000 persons per year). The rate of hospitalization for heart failure did not increase with the use of incretin-based drugs as compared with oral antidiabetic-drug combinations among patients with a history of heart failure (hazard ratio, 0.86; 95% confidence interval [CI], 0.62 to 1.19) or among those without a history of heart failure (hazard ratio, 0.82; 95% CI, 0.67 to 1.00). The results were similar for DPP-4 inhibitors and GLP-1 analogues.

CONCLUSIONS

In this analysis of data from large cohorts of patients with diabetes, incretin-based drugs were not associated with an increased risk of hospitalization for heart failure, as compared with commonly used combinations of oral antidiabetic drugs. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT02456428.)

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The safety of incretin-based drugs, which include dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) analogues, is controversial. Although much attention has been focused on adverse pancreatic events, there are new concerns about an increased risk of heart failure.[1] Indeed, in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial,[2,3] patients who were randomly assigned to the DPP-4 inhibitor saxagliptin had a 27% increase in the risk of hospitalization for heart failure as compared with those who received placebo. In contrast, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial[4] and the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS)[5] showed no increase in the overall risk of hospitalization for heart failure among patients randomly assigned to alogliptin and sitagliptin, respectively. These and other ongoing trials are individually underpowered to effectively address this issue, and the few observational studies addressing it have yielded mixed findings.[6-10] We examined existing data from multiple cohorts of patients to determine whether the use of incretin-based drugs, as compared with oral antidiabetic-drug combinations, in routine clinical practice is associated with an increased risk of heart failure. The study was conducted as part of the Canadian Network for Observational Drug Effect Studies (CNODES).[11]

Methods

Data Sources

We obtained health care data on patients with diabetes from databases for six sites: the Canadian provinces of Alberta, Manitoba, Ontario, and Saskatchewan; the United States; and the United Kingdom. We used a common protocol to analyze these data. Data for the four Canadian provinces were obtained through data-sharing agreements between CNODES member research centers and their respective provincial governments. The Canadian databases include population-level data on physician billing claims, on diagnoses and procedures obtained from hospital discharge abstracts, and on records of prescription-drug dispensing. The Ontario data were restricted to patients who were 65 years of age or older, because prescription data were not available for younger patients. The Clinical Practice Research Datalink (CPRD), which contains the records of general-practitioner practices in the United Kingdom, was linked to the Hospital Episode Statistics database in England, which contains inpatient diagnostic and procedural data. The MarketScan database contains claims data for employees or retirees and their dependents who are covered by health insurance plans sponsored by large U.S. employers. The study was approved by the institutional review board at each participating site and by the Independent Scientific Advisory Committee of the CPRD (protocol 14_119R). The data are anonymous, and the requirement for informed consent was therefore waived.

Study Population

For each site, we assembled a base cohort that included all patients with a first-ever prescription for a noninsulin antidiabetic drug (biguanides, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 analogues, alpha-glucosidase inhibitors, meglitinides, sodium–glucose cotransporter 2 inhibitors, or combinations of these drugs) from the earliest to the last date of prescription drug information at each site. We used the date of the prescription (for the CPRD) or the dispensing date (for all other databases) for the first-ever noninsulin antidiabetic drug as the date of base-cohort entry. We then sequentially excluded, in descending order, patients who were less than 18 years of age, except in Ontario, where we excluded those who were less than 66 years of age; patients who had less than 365 days of continuous coverage, in order to exclude patients who were not new users of antidiabetic drugs; patients who had date inconsistencies; patients who had been treated with insulin at any time before or on the date of base-cohort entry; women who had a history of the polycystic ovary syndrome; and women who received a diagnosis of gestational diabetes in the year before base-cohort entry.

From this base cohort, we formed a study cohort consisting of all patients who began to receive a new antidiabetic drug during the year in which incretin-based drugs entered the market at each site or at any time thereafter. This cohort consisted of patients who were being newly treated for diabetes and those who were

taking an antidiabetic drug in a new class as a substitute for or in addition to a drug in another class. The date of study-cohort entry was defined by the prescription date of the newly prescribed drug. We excluded patients who had previously received a diagnosis of human immunodeficiency virus (HIV) infection or had received highly active antiretroviral therapy (HAART) at any time before study-cohort entry.

Two separate cohorts were created on the basis of the presence or absence of a recorded history of heart failure at any time before or on the date of study-cohort entry. Heart failure was defined by an inpatient or outpatient diagnostic code for heart failure according to the *International Classification of Diseases, 9th Revision* (ICD-9 [428.x]) or *10th Revision* (ICD-10 [I50.x]). Patients in each cohort were followed from the date of study-cohort entry until an event (defined below) occurred or data were censored, whichever occurred first. Data were censored because of death, withdrawal from the database, loss of continuous health plan or drug plan coverage, entry into a long-term care facility, a new diagnosis of HIV infection or initiation of HAART, or the end of the study period (June 30, 2014, or the last date of data availability at the study site).

CASE–CONTROL SELECTION

The two study cohorts defined above were analyzed with the use of a nested case–control analysis, in which cases were defined by hospitalization for heart failure, including fatal and nonfatal events, according to ICD-9 code 428.x or ICD-10 code I50.x. For patients who had no history of heart failure, cases were identified by the presence of a heart-failure diagnosis (principal, primary, most responsible [i.e., the diagnosis most responsible for a patient's hospital stay or responsible for the greatest proportion of the length of stay or resource use, with the terminology varying across databases], or secondary). For patients with established heart failure, the event definition excluded heart failure as a secondary diagnosis. Overall, these event definitions have been shown to have high positive predictive values[12,13] and were chosen to facilitate comparison between the present study and previous trials that defined heart failure by hospitalization.[3-5,14,15] In both study cohorts, the index date was the date of admission for heart failure.

For each hospitalization for heart failure occurring during follow-up, we used risk-set sampling to match the event with a random sample from the risk set — namely, the cohort members who were still being followed and were event-free at the time of the case event. These risk sets, which allow exposure to be measured at the time of the event occurrence, are identical to those used in a Cox proportional-hazards model. Up to 20 controls were randomly selected for each case patient and matched on the basis of sex, age (±365 days), date of study-cohort entry (±180 days), duration of treated diabetes (±90 days), and duration of follow-up. For 655 case patients (2.2%), the matching criteria were relaxed for age (maximum ±1825 days), date of study-cohort entry (±365 days), and duration of treated diabetes (±365 days) to ensure that as many case patients as possible had at least one matched control. A total of 24 case patients (0.1%) had no eligible controls and were thus excluded. The index date for each control was the same as the index date for the case patient with whom the control was matched.

EXPOSURE ASSESSMENT

We defined current exposure to an antidiabetic drug as any prescription whose duration plus a 30-day grace period included the index date. This grace period accounted for nonadherence and for the drug's biologic half-life. For both case patients and controls, current exposure was classified hierarchically with the use of the following five mutually exclusive categories: incretin-based drugs, insulin, two or more oral antidiabetic drugs used in combination, a single oral antidiabetic drug, and no current exposure to an antidiabetic drug. Oral antidiabetic drugs used in combination served as our primary reference category, since incretin-based drugs are second-line or third-line therapy and are thus used at a similar point in the management of the disease.

STATISTICAL ANALYSIS

The statistical analysis is described in detail in the Supplementary Appendix, available with the full text of this article at NEJM.org. All analyses were conducted separately for patients with and those without a history of heart failure. We used conditional logistic regression to estimate odds ratios and 95% confidence intervals for the risk of hospitalization for heart failure with incretin-based drugs as compared with oral antidiabetic-

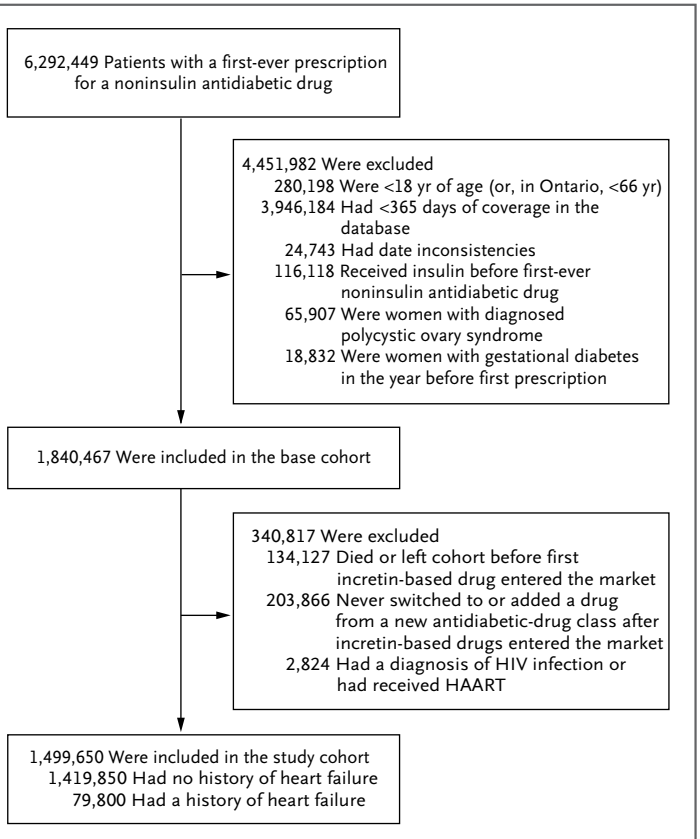

Figure 1. Numbers of Patients in the Base Cohort and Study Cohort.
HAART denotes highly active antiretroviral therapy, and HIV human immunodeficiency virus.

drug combinations. This was considered the primary analysis.

In addition to conditioning our models according to sex, age, year of study-cohort entry, duration of treated diabetes, and duration of follow-up, all of which were used to match case patients with controls, we adjusted our models for several potential confounders (specified a priori) that were measured at study-cohort entry (see the Supplementary Appendix for details). Briefly, these potential confounders included coexisting conditions, microvascular complications of diabetes, treatment with selected medications in the year before study-cohort entry, the number of hospitalizations and the number of unique nondiabetic drugs in the prior year (two proxy measures of overall health), as well as the number of antidiabetic drugs received before study-cohort entry. In the CPRD, we further adjusted for glycated hemoglobin level, body-mass index, and status with respect to smoking. By virtue of risk-set sampling, the odds ratios are unbiased estimators of the hazard ratio.[16,17]

In secondary analyses, we subclassified current treatment with incretin-based drugs according to drug class (DPP-4 inhibitor or GLP-1 analogue) and duration of current treatment (<365 days, 365 to 729 days, or ≥730 days). We also assessed status with respect to a history of myocardial infarction and duration of treated diabetes for effect modification.

We conducted seven sensitivity analyses, defined a priori, to assess the robustness of our results (see the Supplementary Appendix). In addition, for three sites (Ontario, United Kingdom [CPRD], and United States [MarketScan]), we compared incretin-based drugs with combinations of oral antidiabetic drugs in a propensity-matched cohort analysis[18] (see the Supplementary Appendix). It was not feasible to include the other three sites in the propensity-matched analysis because of the relatively low prevalence of incretin-based drug use at study-cohort entry and the small number of events at these sites. We performed a meta-analysis of all site-specific estimates, using random-effects models with inverse variance weighting and the DerSimonian and Laird approach[19]; fixed effects were used in sensitivity analyses. The amount of between-site heterogeneity was estimated with the use of the I^2 statistic,[20] which represents the proportion of the total variance in the meta-analysis that is due to between-study heterogeneity rather than within-study variability.

RESULTS

STUDY POPULATION

The cohorts included a total of 1,499,650 patients (Fig. 1), with 29,741 patients hospitalized for heart failure during 3,242,291 person-years of follow-up (crude incidence rate, 9.2 events per 1000 persons per year). Among the 1,419,850 patients with no history of heart failure, 23,205 patients were hospitalized for heart failure (crude incidence rate, 7.5 events per 1000 persons per year). There were 6536 hospitalizations for heart failure among 79,800 patients with a history of heart failure (crude incidence rate, 43.5 events per 1000 persons per year).

Among patients without a history of heart failure, case patients were more likely than con-

Table 1. Baseline Characteristics of Patients with Diabetes Who Were Hospitalized for Heart Failure (Case Patients) and Matched Controls, According to the Presence or Absence of a History of Heart Failure.*

Characteristic	No History of Heart Failure		History of Heart Failure	
	Case Patients (N=23,205)	Controls (N=435,777)	Case Patients (N=6536)	Controls (N=100,480)
Site — no. (%)				
Alberta	1,274 (5.5)	24,990 (5.5)	310 (4.7)	3,839 (4.7)
Manitoba	674 (2.9)	6,151 (2.9)	376 (5.8)	1,172 (5.8)
Ontario	1,778 (7.7)	29,716 (7.7)	1,613 (24.7)	17,785 (24.7)
Saskatchewan	138 (0.6)	944 (0.6)	116 (1.8)	352 (1.8)
United Kingdom	2,114 (9.1)	30,072 (9.1)	287 (4.4)	1,839 (4.4)
United States	17,227 (74.2)	343,904 (74.2)	3,834 (58.7)	75,493 (58.7)
Mean age — yr	68.7	68.6	74.2	74.1
Male sex — no. (%)	13,146 (56.7)	247,175 (56.7)	3,850 (58.9)	60,276 (58.9)
Mean duration of treated diabetes — yr	0.7	0.7	1.8	1.8
Coexisting conditions — no. (%)				
Alcohol-related disorder	271 (1.2)	2,327 (0.7)	78 (1.2)	883 (1.1)
Atrial fibrillation or flutter	1,195 (5.1)	9,045 (2.5)	1,425 (21.8)	9,785 (15.0)
Cancer	3,684 (15.9)	57,208 (13.5)	1,279 (19.6)	18,474 (18.9)
Chronic obstructive pulmonary disease	6,151 (26.5)	65,897 (15.6)	3,220 (49.3)	39,936 (41.2)
Coronary artery disease	9,593 (41.3)	112,849 (26.7)	5,158 (78.9)	69,336 (71.0)
Dyslipidemia	12,206 (52.6)	242,554 (56.0)	3,991 (61.1)	63,249 (62.8)
Hypertension	17,962 (77.4)	309,841 (71.8)	5,808 (88.9)	87,271 (88.5)
Peripheral vascular disease	2,823 (12.2)	30,631 (6.9)	1,204 (18.4)	17,810 (15.4)
Coronary revascularization	1,348 (5.8)	14,820 (3.6)	1,145 (17.5)	14,195 (16.1)
Myocardial infarction	3,155 (13.6)	30,485 (7.6)	2,775 (42.5)	29,352 (35.1)
Stroke	3,718 (16.0)	46,764 (10.8)	1,813 (27.7)	25,811 (25.3)
Neuropathy	735 (3.2)	7,496 (2.3)	214 (3.3)	2,165 (2.7)
Renal disease	2,381 (10.3)	20,765 (5.8)	1,872 (28.6)	14,006 (18.1)
Retinal disorders	3,774 (16.3)	57,646 (14.4)	1,295 (19.8)	17,915 (19.5)

* Cases and controls were matched for age, sex, duration of treated diabetes, year of cohort entry, and duration of follow-up. Means and percentages among controls were first weighted by the number of controls per case patient and then weighted by the number of case patients per site. Values that were based on five or fewer patients were withheld by the participating sites because of privacy restrictions; when data were collated across sites, a value of 3 was assigned in these instances. For this reason, the sums may differ slightly from the totals shown.

trols to have coexisting cardiovascular conditions and to be taking cardiovascular drugs, except for statins and aspirin (Table 1, and Table S1 in the Supplementary Appendix). In addition, case patients had a higher prevalence of diabetes-related complications and were less likely to be taking metformin at study-cohort entry. These differences were also observed among patients with a history of heart disease.

Among controls, several differences in baseline characteristics were observed between patients taking incretin-based drugs and those taking combinations of oral antidiabetic drugs (Table S2 in the Supplementary Appendix). Among patients without a history of heart failure, patients taking incretin-based drugs were younger than those taking combinations of oral antidiabetic drugs and were more likely to be women, to have coexisting cardiovascular conditions, and to be receiving cardiovascular pharmacotherapy. Among patients with a history of heart failure, patients taking incretin-based drugs were

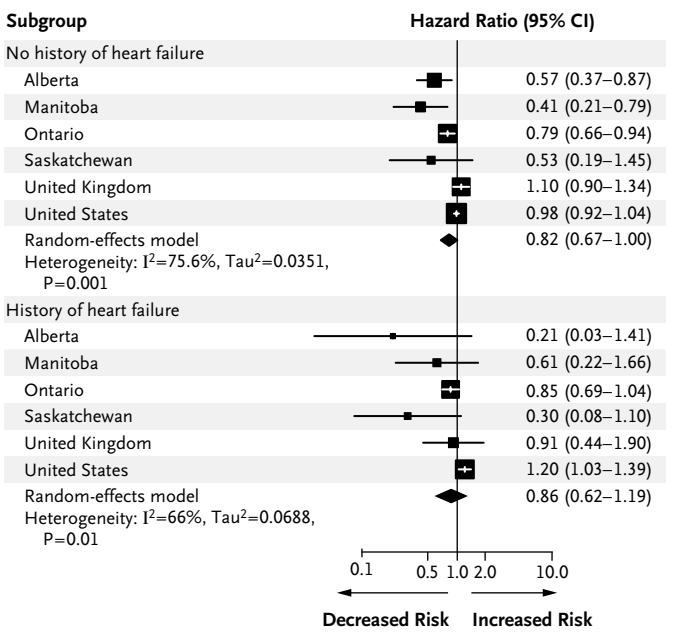

Figure 2. Association between Treatment with Incretin-based Drugs and the Risk of Hospitalization for Heart Failure among Patients with and Those without a History of Heart Failure.

The reference category was treatment with combinations of oral antidiabetic drugs. The size of the box surrounding the point estimate for each site is proportional to the weight of that site in the random-effects meta-analysis. The I^2 statistic represents the proportion of the total variance in the meta-analysis that was due to between-study heterogeneity rather than within-study variability. Tau^2 is an estimate of the between-study variance. A value of I^2 greater than 50% indicates notable heterogeneity.[20]

older than those taking oral antidiabetic-drug combinations; the patterns for other characteristics were similar to those observed among patients without a history of heart failure.

INCRETIN-BASED DRUGS AND HOSPITALIZATION FOR HEART FAILURE

Among patients without a history of heart failure, treatment with incretin-based drugs was not associated with an increased risk of hospitalization for heart failure, as compared with treatment with oral antidiabetic-drug combinations (hazard ratio, 0.82; 95% confidence interval [CI], 0.67 to 1.00) (Fig. 2). Similar results were obtained when incretin-based drugs were subcategorized according to class: hazard ratio with DPP-4 inhibitors, 0.84 (95% CI, 0.69 to 1.02) (Table 2, and Fig. S1 in the Supplementary Appendix), and hazard ratio with GLP-1 analogues, 0.95 (95% CI, 0.83 to 1.10) (Table 2, and Fig. S2 in the Supplementary Appendix). In addition, there was no evidence of a duration–response relationship (Table 2, and Fig. S3, S4, and S5 in the Supplementary Appendix) or of effect modification according to the presence or absence of a history of myocardial infarction (P=0.16 for interaction, pooled analysis) (Fig. S6 and S7 in the Supplementary Appendix) or to the duration of treated diabetes (P=0.70 for interaction, pooled analysis) (Fig. S8 and S9).

Similar results were observed with respect to the risk of hospitalization for heart failure among patients who had a history of heart failure (hazard ratio with incretin-based drug treatment vs. treatment with oral antidiabetic-drug combinations, 0.86; 95% CI, 0.62 to 1.19) (Fig. 2). The results did not differ significantly according to the class of incretin-based drugs (Table 3, and Fig. S10 and S11 in the Supplementary Appendix), duration of current use (Table 3, and Fig. S12, S13, and S14 in the Supplementary Appendix), presence or absence of a history of myocardial infarction (P=0.54 for interaction, pooled analysis) (Fig. S15 and S16 in the Supplementary Appendix), or duration of treated diabetes (P=0.75 for interaction, pooled analysis) (Fig. S17 and S18 in the Supplementary Appendix).

SENSITIVITY ANALYSES

Overall, the results of our sensitivity analyses were consistent with those of our primary analysis (Fig. S19 through S35 in the Supplementary Appendix), as were the results of our propensity-matched analysis (Fig. S36 through S43 and Tables S3 through S6 in the Supplementary Appendix). Furthermore, fixed-effects models produced results that were consistent with those of our random-effects models (Tables S7 and S8 in the Supplementary Appendix).

DISCUSSION

Our study was designed to examine the effect of incretin-based drugs on the risk of hospitalization for heart failure among patients with type 2 diabetes seen in routine clinical practice. As compared with oral antidiabetic drugs used in combination, current treatment with incretin-based drugs was not associated with an increased risk of hospitalization for heart failure. Similar results were obtained when DPP-4 inhibitors and GLP-1 analogues were considered separately, and

Table 2. Association between Treatment with Incretin-Based Drugs versus Oral Antidiabetic-Drug Combinations and Hospitalization for Heart Failure among Patients with No History of Heart Failure.*

Treatment†	Hospitalization for Heart Failure		Adjusted Hazard Ratio (95% CI)‡	I^2§
	Case Patients (N=23,205)	Controls (N=435,777)		
	no. (%)			%
Two or more oral antidiabetic drugs	3167 (13.6)	51,968 (11.9)	1.00 (reference)	
Incretin-based drugs	2457 (10.6)	42,706 (9.8)	0.82 (0.67–1.00)	75.6
DPP-4 inhibitors	2228 (9.6)	38,586 (8.9)	0.84 (0.69–1.02)	74.3
GLP-1 analogues	231 (1.0)	4,120 (0.9)	0.95 (0.83–1.10)	0.0
Duration of treatment with incretin-based drugs				
<365 days	1748 (7.5)	28,982 (6.7)	0.83 (0.66–1.05)	76.6
365–729 days	388 (1.7)	7,847 (1.8)	0.79 (0.71–0.89)	0.0
≥730 days	320 (1.4)	5,876 (1.3)	0.96 (0.75–1.22)	39.3

* Cases and controls were matched for sex, age, year of cohort entry, duration of treated diabetes, and duration of follow-up. Values that were based on five or fewer patients were withheld by the participating sites because of privacy restrictions; when data were collated across sites, a value of 3 was assigned in these instances. For this reason, the sums may differ slightly from the totals shown. DPP-4 denotes dipeptidyl peptidase 4, and GLP-1, glucagon-like peptide 1.

† Data for current treatment with insulin and single oral antidiabetic drugs and data for no current treatment (i.e., data for those who discontinued treatment with antidiabetic drugs), accounting for 17,581 case patients and 341,103 controls, are not shown in the table but were considered in the regression model for proper estimation of treatment effects.

‡ Hazard ratios were adjusted for alcohol-related disorders, coexisting conditions (atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, and previous stroke), microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy), number of hospitalizations, number of unique nondiabetic drugs in the prior year, number of antidiabetic drugs received before study-cohort entry, and treatment with the following drugs in the year before study-cohort entry: angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, statins, aspirin, and other nonsteroidal antiinflammatory drugs. For the CPRD data, hazard ratios were further adjusted for body-mass index, smoking status, and glycated hemoglobin level (≤7.0% [53 mmol per mole], 7.1 to 8.0% [54 to 64 mmol per mole], or >8.0% [64 mmol per mole]).

§ The I^2 statistic represents the proportion of the total variance of the meta-analysis that is due to between-study heterogeneity rather than within-study variability.

the results were consistent across several sensitivity analyses.

To date, three randomized, placebo-controlled trials of DPP-4 inhibitors have shown conflicting findings regarding the risk of hospitalization for heart failure.[2,3,5,14] In the SAVOR-TIMI 53 trial, saxagliptin increased the risk by 27% (hazard ratio, 1.27; 95% CI, 1.07 to 1.51).[2,3] In contrast, in the EXAMINE trial, alogliptin did not significantly increase the overall risk of hospitalization for heart failure (hazard ratio, 1.19; 95% CI, 0.90 to 1.58).[4] However, in a secondary exploratory analysis that stratified participants according to the presence or absence of heart failure at baseline, alogliptin increased the risk of hospitalization for heart failure among patients without a history of heart failure (hazard ratio, 1.76; 95% CI, 1.07 to 2.90) but not among those with a history of heart failure (hazard ratio, 1.00; 95% CI, 0.71 to 1.42).[14] It is important to note that in both trials, heart failure was a secondary end point; in the EXAMINE trial, the exploratory analysis showed no significant effect modification according to baseline heart-failure status (P=0.07 for interaction); and all these findings were subject to a type I error related to multiple testing. In TECOS, sitagliptin was not associated with heart failure (hazard ratio, 1.00; 95% CI, 0.83 to 1.20).[5]

With the use of a common protocol across all six sites, our large population-based study was specifically designed to assess the association between incretin-based drugs and heart failure in the real-world setting of clinical practice. Although our pooled estimates suggest null associations with high degrees of precision, we

Table 3. Association between Treatment with Incretin-based Drugs versus Oral Antidiabetic-Drug Combinations and Hospitalization for Heart Failure among Patients with a History of Heart Failure.*

Treatment†	Hospitalization for Heart Failure		Adjusted Hazard Ratio (95% CI)‡	I^2§
	Case Patients (N=6536)	Controls (N=100,480)		
	no. (%)			%
Two or more oral antidiabetic drugs	684 (10.5)	10,608 (10.6)	1.00 (reference)	
Incretin-based drugs	940 (14.4)	12,394 (12.3)	0.86 (0.62–1.19)	66.0
DPP-4 inhibitors	905 (13.8)	11,651 (11.6)	0.87 (0.63–1.21)	66.3
GLP-1 analogues	35 (0.5)	743 (0.7)	0.75 (0.22–2.51)	44.5
Duration of treatment with incretin-based drugs				
<365 days	664 (10.2)	9,061 (9.0)	0.68 (0.43–1.06)	81.1
365–729 days	172 (2.6)	2,012 (2.0)	1.09 (0.86–1.37)	6.5
≥730 days	103 (1.6)	1,312 (1.3)	0.95 (0.73–1.22)	0.0

* Cases and controls were matched for sex, age, year of cohort entry, duration of treated diabetes, and duration of follow-up. Values that were based on five or fewer patients were withheld by the participating sites because of privacy restrictions; when data were collated across sites, a value of 3 was assigned in these instances. For this reason, the sums may differ slightly from the totals shown.

† Data for current treatment with insulin and single oral antidiabetic drugs and data for no current treatment (i.e., data for those who discontinued treatment with antidiabetic drugs), accounting for 4912 case patients and 77,478 controls, are not shown in the table but were considered in the regression model for proper estimation of treatment effects.

‡ Hazard ratios were adjusted for alcohol-related disorders, coexisting conditions (atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction, and previous stroke), microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy), number of hospitalizations, number of unique non-diabetic drugs in the prior year, number of antidiabetic drugs received before study-cohort entry, and treatment with the following drugs in the year before study-cohort entry: angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, statins, aspirin, and other nonsteroidal antiinflammatory drugs. For the CPRD data, hazard ratios were further adjusted for body-mass index, smoking status, and glycated hemoglobin level (≤7.0% [53 mmol per mole], 7.1 to 8.0% [54 to 64 mmol per mole], or >8.0% [64 mmol per mole]).

§ The I^2 statistic represents the proportion of the total variance of the meta-analysis that is due to between-study heterogeneity rather than within-study variability.

observed important between-site heterogeneity, which may be due to differences in study populations, variations in formulary restrictions, and differences in the database structures themselves. This heterogeneity highlights the importance of replication across several databases. The pooled estimates and almost all site-specific estimates suggested either null or protective effects.

Our study has a number of strengths. With 1.5 million patients and 3.2 million person-years of observation, we had the statistical power to robustly assess this important drug safety issue. Although our study is observational in nature and thus susceptible to potential confounding, we used rigorous matching and statistical adjustment to minimize residual confounding, including adjustment for glycated hemoglobin level and body-mass index in the CPRD; the consistency of results between the CPRD and other sites suggests that confounding due to these variables was minimal. Under most reasonable assumptions, it is unlikely that unmeasured confounding is responsible for our null results (Fig. S44 in the Supplementary Appendix). Our primary reference group was patients receiving treatment with combinations of oral antidiabetic drugs. With guidelines recommending that incretin-based drugs be used as second-line or third-line therapy,[21] the use of this reference group both reduced potential confounding by indication and provided a clinically relevant treatment comparison.

Our study has some limitations. Some patients who were taking thiazolidinediones, which are known to increase the risk of hospitalization for

heart failure,[1] were included in our primary reference group. However, in one sensitivity analysis, we excluded and censored data from case patients (6440 without a history of heart failure and 1741 with a history of heart failure) and controls (114,675 and 21,982, respectively) who had a history of insulin or thiazolidinedione use, and in another sensitivity analysis, we used a reference group of patients receiving combination therapy with metformin and sulfonylureas. In both analyses, there was no increase in the risk of hospitalization for heart failure with incretin-based drugs. It is possible that our reference group, which included many patients who were taking sulfonylureas as part of combination therapy, may have had an increased risk of adverse cardiovascular effects from the sulfonylureas.[22] However, because sulfonylureas are routinely used in drug combinations as second- or third-line therapy, this represents a clinically meaningful comparison.

In addition, our definition of the study end point for patients without a history of heart failure, which included both principal and secondary diagnoses of heart failure at hospital discharge, may have resulted in some misclassification of outcome status; although cases of heart failure were not adjudicated, this approach has been validated previously.[12,13] Reassuringly, our sensitivity analysis that restricted the definition to a principal diagnosis of heart failure[12,13] produced results that were consistent with those of our primary analysis. Furthermore, without data on ejection fraction, we were not able to examine the type of heart failure that was present, nor were we able to adjust for it. Unlike the study populations in the previous trials,[2-5] most of the patients in our study population did not have long-standing diabetes and thus may have had a lower risk of heart failure. However, in a secondary analysis, the risk of heart failure with incretin-based drugs did not differ according to the duration of treated diabetes.

In conclusion, in this retrospective analysis of several large cohorts of patients with diabetes, the use of incretin-based drugs, as compared with combinations of oral antidiabetic drugs, was not associated with an increased risk of hospitalization for heart failure. This finding was consistent in separate analyses for patients with and those without a history of heart failure and for patients taking DPP-4 inhibitors and those taking GLP-1 analogues.

The opinions, results, and conclusions reported in this article are those of the authors; no endorsement by the Canadian provinces of Alberta, Manitoba (Health Information Privacy Committee no. 2014/2015–08 and Health Research Ethics Board no. H2014:236), Ontario, and Saskatchewan is intended or should be inferred.

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