Incretin-Based Drugs and the Risk of Congestive Heart Failure

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Diabetes Care 2015;38:277–284 | DOI: 10.2337/dc14-1459

OBJECTIVE

To determine whether the use of incretin-based drugs, including GLP-1 analogs and dipeptidyl peptidase-4 inhibitors, is associated with an increased risk of congestive heart failure (CHF) among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The U.K. Clinical Practice Research Datalink, linked to the Hospital Episode Statistics database, was used to conduct a cohort study with a nested case-control analysis among patients newly prescribed antidiabetic drugs between 1 January 2007 and 31 March 2012 and no prior history of CHF. Case subjects were defined as patients hospitalized for a first CHF and matched with up to 20 control subjects on age, duration of treated diabetes, calendar year, and time since cohort entry. Conditional logistic regression was used to estimate odds ratios (ORs) with corresponding 95% CIs of incident CHF comparing current use of incretin-based drugs with current use of two or more oral antidiabetic drugs.

RESULTS

The cohort consisted of 57,737 patients followed for a mean 2.4 years, during which time 1,118 incident cases of hospitalized CHF were identified (incidence rate 8.1/1,000 person-years). Current use of incretin-based drugs was not associated with an increased risk of CHF (adjusted OR 0.85 [95% CI 0.62–1.16]). Secondary analyses revealed no duration-response relationship (*P* trend = 0.39).

CONCLUSIONS

In our population-based study, incretin-based drug use was not associated with an increased risk of CHF among patients with type 2 diabetes. These findings provide some reassurance, but will need to be replicated in other large-scale studies.

Incretin-based drugs, which consist of dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 analogs, were first approved by the U.S. Food and Drug Administration in 2006 for the treatment of type 2 diabetes. Both DPP-4 inhibitors and GLP-1 analogs improve glycemic control by increasing plasma levels of endogenous and exogenous GLP-1, respectively. This increase in GLP-1 stimulates insulin secretion and inhibits glucagon secretion (1).

The cardiovascular safety of incretin-based drugs is currently under debate. This debate stems from a secondary analysis of the randomized controlled trial SAVOR-TIMI 53, in which saxagliptin was associated with an increased risk of congestive heart failure (CHF) (hazard ratio [HR] 1.27 [95% CI 1.07–1.51]) (2). In contrast, the EXAMINE trial found no association between alogliptin and CHF (HR 1.07 [95% CI 0.79–1.46]) (3). A subsequent meta-analysis of randomized controlled trials found an increased risk of CHF with DPP-4 inhibitors (relative risk 1.16 [95% CI 1.01–1.33]) (4), but these results were driven by those of SAVOR-TIMI 53. Although the safety

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Received 13 June 2014 and accepted 16 August 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-1459/-/DC1.

A slide set summarizing this article is available online.

See accompanying article, p. 183.

signal for an increased CHF risk is currently limited to saxagliptin, incretin-based drugs in general may be associated with an increased risk of CHF as increasing plasma GLP-1 level has previously been associated with impaired left-ventricular function (5). To date, no observational study has been conducted to determine whether incretin-based drugs are associated with an increased risk of incident CHF in the real-world setting.

Given the limited and conflicting data available regarding the effect of these drugs on the risk of CHF, there remains a need to further examine the CHF signal identified in SAVOR-TIMI 53 and examine the CHF effects of incretin-based drugs in general. The objective of this study was therefore to determine whether the use of incretin-based drugs, including DPP-4 inhibitors and GLP-1 analogs, is associated with an increased risk of CHF among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data Sources

This study was conducted using the U.K. Clinical Practice Research Datalink (CPRD) linked to the Hospital Episode Statistics (HES) database. The CPRD is a large electronic database with data on >13 million patients enrolled in >680 general practices; these patients are representative of the U.K. population (6). The CPRD contains medical information including demographic data, medical diagnoses, procedures, and deaths that are documented by trained general practitioners. Prescriptions and diagnoses collected in the CPRD are regularly audited and have been shown to be valid and of high quality (7–10). The HES database records hospital admission dates, primary and secondary diagnoses (coded using the ICD-10 classification), and related procedures and has been shown to have good accuracy (11).

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol number 13_034RA2) and the Research Ethics Board of the Jewish General Hospital, Montreal, Quebec, Canada.

Study Population

Base Cohort

A base cohort of patients newly treated with noninsulin antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, α-glucosidase inhibitors, guar gum, meglitinides, and incretin-based drugs) between 1 January 1988 and 31 March 2012 was assembled. To be included, patients were required to be at least 18 years of age and have at least 1 year of CPRD medical history prior to the first noninsulin antidiabetic prescription. Women with a diagnosis of polycystic ovary syndrome, another known indication for metformin, at any time prior to this first prescription were excluded. Patients were also excluded if they were initially treated with insulin as such patients are more likely to have type 1 diabetes or an advanced form of type 2 diabetes. Patients who later required insulin during follow-up were eligible for inclusion. Patients who were not linkable to HES were excluded.

Study Cohort

Using this base cohort, we identified a study cohort of all new users of an antidiabetic drug between 1 January 2007, the year the first DPP-4 inhibitor was licensed in the U.K., and 31 March 2012. New users were defined as those newly treated with an antidiabetic drug (e.g., those receiving a first-ever antidiabetic prescription after 2007), as well as those who added on or switched to an antidiabetic drug not previously used in the patient's treatment history. Cohort entry was defined by the date of this new antidiabetic drug. Patients previously diagnosed with CHF (including inpatient or outpatient records found in either the CPRD or HES) at any time prior to cohort entry were excluded, as were those with <1 year of HES data prior to cohort entry. Patients were followed until the study outcome (HES-defined hospitalization for CHF, ICD-10 codes: I50.x, in primary or secondary position), death from any cause, end of registration with the general practice, end of linkability to HES, or end of study period (31 March 2012), whichever came first.

Case-Control Selection

A nested case-control analysis was conducted within the study cohort described above. Case subjects were defined by hospitalization for CHF, and up to 20 control subjects per case were randomly selected using risk set sampling, matched on duration of follow-up, age (±1 year), duration of treated diabetes (i.e., time from first-ever noninsulin prescription to date of study cohort entry; ±90 days), and calendar year of study cohort entry. For 35 (3.1%) case subjects without any control subjects, we relaxed the calipers for age, duration of treated diabetes, and cohort entry year until all case subjects had at least one control (maximum calipers of ±5, ± 1, and ±3 years, respectively). The day of hospital admission for CHF defined the index date for case subjects, and control subjects inherited their index date from their matched case. The nested case-control analysis represents a computationally efficient approach relative to a full cohort analysis with a time-dependent Cox proportional hazards model and produces odds ratios (ORs) that are unbiased estimators of the incidence rate ratio (12,13).

Exposure Assessment

For all case subjects and their matched control subjects, exposure to insulin and noninsulin antidiabetic drugs was identified, and current use was classified hierarchically using the following five mutually exclusive categories: incretin-based drugs (including both DPP-4 inhibitors [sitagliptin, vildagliptin, and saxagliptin] and GLP-1 analogs [exenatide and liraglutide], alone or in combination with other antidiabetic drugs), insulins (alone or in combination with other antidiabetic drugs), ≥2 oral antidiabetic drugs, single oral antidiabetic drug, or no current exposure. Current use was defined by prescription duration plus a 30-day grace period (to account for nonadherence and the biological half-lives of these drugs) overlapping with the index date. As incretin-based drugs are considered second- to third-line treatments (14), the reference group for the primary analyses was current use of ≥2 oral antidiabetic drugs.

Statistical Analysis

Descriptive statistics were used to summarize the baseline demographic and clinical characteristics of case subjects and matched control subjects. The crude incidence rate with 95% CIs based on the Poisson distribution of the CHF outcome was calculated by dividing the total number of case subjects by the total person-years of follow-up in the study cohort. Conditional logistic regression was used to estimate ORs and corresponding 95% CIs of CHF, comparing

current use of incretin-based drugs to current use of ≥2 oral antidiabetic drugs. The latter was considered the primary analysis.

In addition to conditioning on the matching variables (i.e., duration of follow-up, age, duration of treated diabetes, and calendar year of cohort entry), all models were adjusted for the following potential confounders measured prior to study cohort entry: sex, BMI (last measure prior to cohort entry), excessive alcohol use (defined as alcohol-related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure, and other related disorders), smoking status, HbA_{1c} level (≤7.0% [53 mmol/mol], 7.1–8.0% [54–64 mmol/mol], and >8.0% [64 mmol/mol]; last measure prior to cohort entry [median time from last HbA_{1c} measurement to cohort entry: 14 days; interquartile range 7–35 days]), comorbidities such as neuropathy, renal disease, retinopathy, atrial fibrillation, cancer (other than nonmelanoma skin cancer), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), dyslipidemia, hypertension, previous myocardial infarction (MI), peripheral arteriopathy, peripheral vascular disease, previous coronary revascularization, and previous stroke, all measured at any time prior to cohort entry. We also adjusted for the number of prescriptions, number of physician visits, and use of the following drugs in the year before cohort entry: ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, fibrates, statins, aspirin, and other nonsteroidal anti-inflammatory drugs. Antidiabetic drugs (insulins, metformin, sulfonylureas, thiazolidinediones, and others [α-glucosidase inhibitors, guar gum, and meglitinides]) used in the year before cohort entry were not included in the primary analysis due to their high correlation with exposure during follow-up. However, adjustment for these drugs was considered in a sensitivity analysis.

Secondary Analyses

We performed five secondary analyses. First, we repeated the primary analysis with current exposure to incretin-based drugs subclassified by duration of current exposure, with tertile-defined duration categories (i.e., 1–83 days, 84–265 days, and >265 days). Second, we stratified current exposure to incretin-based drugs by type and by pharmaceutical. Third, the analyses were repeated by subclassifying current use of incretin-based drugs using the following hierarchy: incretin-based drug with insulin (with or without other oral antidiabetic drugs), incretin-based drug with oral antidiabetic drugs, and incretin-based drug as monotherapy. Finally, in the last two secondary analyses, we examined potential effect measure modification by history of cardiovascular disease (defined as MI, stroke, coronary revascularization, CAD, peripheral vascular disease, or atrial fibrillation) and by duration of treated diabetes (<5 vs. ≥5 years).

Sensitivity Analyses

We also performed nine sensitivity analyses to assess the robustness of the results. First, we excluded patients with a history of insulin or thiazolidinedione use prior to cohort entry and censored patients upon receiving these medications during follow-up, given their reported association with an increased risk of CHF (15–17). Second, the use of metformin is not recommended in patients with renal insufficiency. Consequently, we repeated our primary analyses excluding patients with a history of renal disease (i.e., defined as having acute kidney injury, chronic renal failure, or dialysis-related procedures any time prior to cohort entry) to examine the impact of this contraindication on our results. Third, we repeated the primary analysis with case subjects restricted to those in whom CHF was the primary diagnosis and censoring those with CHF recorded as a secondary diagnosis. Fourth, we repeated the analysis using an alternate reference group consisting of patients currently exposed to

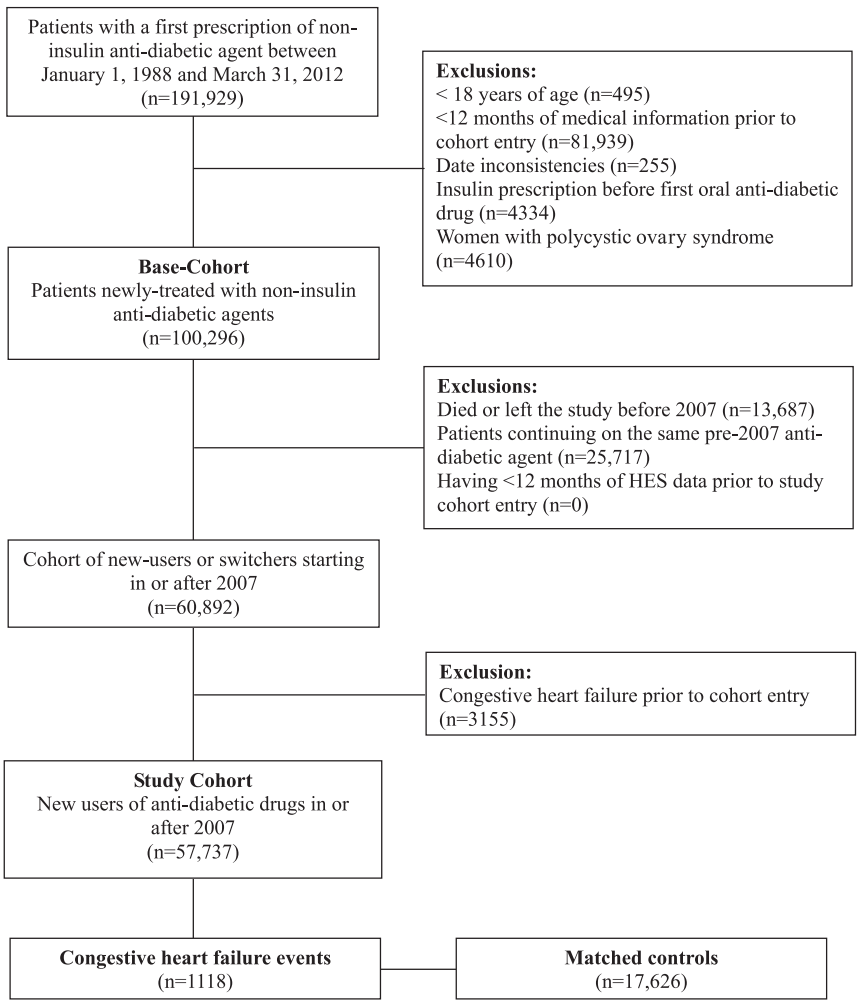

Figure 1—Study flow chart showing the assembly of the base and study cohorts.

metformin-sulfonylurea combinations, the most common treatment combination in type 2 diabetes (18,19). Fifth, we also used a reference category of current exposure to ≥1 oral antidiabetic drug to examine the impact of requiring current use of (and thus adherence to) two drugs in the reference group of our primary analysis. Sixth, we repeated the analysis using patients currently exposed to any nonincretin-based drugs as the reference category to facilitate comparison with SAVOR-TIMI 53 (2) and EXAMINE (20); in these trials, the active drugs or placebo was added to a heterogeneous background of antidiabetic agents. Seventh, we repeated the analysis adjusting for covariates measured at index date rather than at cohort entry. With potential adjustment for intermediates, this analysis provides an overly conservative risk estimate (21). Eighth, we varied the grace period used for current exposure to 0 and 90 days. Finally, we further adjusted our risk estimates for antidiabetic drugs prescribed in the year before cohort entry. All analyses were two-tailed, with $P < 0.05$ considered statistically significant, and were all conducted with SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 57,737 patients met the study inclusion criteria (Fig. 1). The mean (SD) age at cohort entry was 61.6 (13.4) years, and 56.8% were males. The mean (SD) duration of treated diabetes was 2.3 (3.5) years. At cohort entry, the vast majority of patients received metformin monotherapy (67.1%), followed by sulfonylurea monotherapy (13.0%), 5.7% incretin-based drugs (either in monotherapy or in combination with other agents), while the remainder (14.2%) received other drugs. With a mean (SD) follow-up of 2.4 (1.5) years, there were a total of 1,118 case subjects with a first-ever hospitalization for CHF over 138,833 total person-years of follow-up (incidence rate: 8.1 [95% CI 7.6–8.5 per 1,000 person-years]).

Table 1 shows the characteristics of the 1,118 case subjects and 17,626 matched control subjects. Case subjects were more likely to be obese, with a higher prevalence of comorbidities, including renal disease, atrial fibrillation, CAD, COPD, hypertension, history of MI, and peripheral arteriopathy. Case

Table 1—Baseline characteristics of CHF case subjects and matched control subjects[a]

Characteristics	CHF case subjects	Control subjects
Number of patients	1,118	17,626
Age (years), mean (SD)	73.3 (11.0)	73.2 (10.9)
Duration of treated diabetes (years), mean (SD)	2.3 (3.5)	2.3 (3.5)
Males, *n* (%)	650 (58.1)	9,274 (52.5)
Year of study cohort entry, *n* (%)		
2007	418 (37.4)	6,846 (37.7)
2008	281 (25.1)	4,412 (25.3)
2009	223 (19.9)	3,418 (19.7)
2010	136 (12.2)	2,064 (11.9)
2011	S	863 (5.2)
2012	S	23 (0.2)
Number of distinct prescriptions, *n* (%)[b,c]		
0–8	305 (27.3)	8,955 (46.4)
9–16	495 (44.3)	6,877 (42.0)
≥17	318 (28.4)	1,794 (11.5)
Number of physician visits, *n* (%)[b]		
0–10	163 (14.6)	4,847 (26.4)
11–20	407 (36.4)	7,563 (43.2)
≥21	548 (49.0)	5,216 (30.4)
Excessive alcohol use, *n* (%)[b]	181 (16.2)	2,102 (12.3)
Smoking status, *n* (%)[b]		
Ever	793 (70.9)	10,768 (61.5)
Never	S	6,754 (38.0)
Unknown	S	104 (0.5)
BMI, *n* (%)[d]		
≤24.9 kg/m^2	164 (14.7)	2,676 (16.5)
25–29.9 kg/m^2	338 (30.2)	6,454 (37.0)
≥30 kg/m^2	591 (52.9)	8,012 (43.9)
Unknown	25 (2.2)	484 (2.5)
HbA_{1c}, *n* (%)[d]		
≤7.0% [53 mmol/mol]	173 (15.5)	2,598 (13.9)
7.1–8.0% [54–64 mmol/mol]	289 (25.8)	5,611 (32.2)
>8.0% [64 mmol/mol]	494 (44.2)	6,803 (42.0)
Unknown	162 (14.5)	2,614 (11.9)
Antidiabetic drugs, *n* (%)[b]		
Insulins	S	51 (0.8)
Metformin	358 (32.0)	3,811 (30.9)
Sulfonylureas	215 (19.2)	1,860 (19.1)
Thiazolidinediones	80 (7.2)	740 (6.6)
Other	S	58 (0.8)
None	667 (59.7)	12,894 (59.5)
Other drugs, *n* (%)[b]		
ACE inhibitors	573 (51.3)	7,503 (44.9)
Angiotensin receptor blockers	189 (16.9)	2,765 (16.6)
β-Blockers	403 (36.0)	5,018 (28.6)
Calcium channel blockers	499 (44.6)	5,978 (35.2)
Diuretics	656 (58.7)	7,302 (42.0)
Fibrates	25 (2.2)	285 (1.9)
Statins	769 (68.8)	11,473 (68.2)
Aspirin	590 (52.8)	7,729 (46.2)
Other nonsteroidal anti-inflammatory drugs	200 (17.9)	3,270 (18.0)
Comorbidities, *n* (%)[e]		
Neuropathy	201 (18.0)	2,622 (17.5)
Renal disease	385 (34.4)	4,005 (26.1)
Retinopathy	327 (29.2)	4,195 (28.4)
Atrial fibrillation	238 (21.3)	1,626 (9.6)
Cancer	218 (19.5)	2,777 (16.1)
COPD	314 (28.1)	2,409 (14.1)
Coronary arterial disease	542 (48.5)	5,333 (31.6)
Coronary revascularization	109 (9.7)	1,064 (6.3)

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Table 1—Continued

Characteristics	CHF case subjects	Control subjects
Dyslipidemia	413 (36.9)	5,446 (32.5)
Hypertension	851 (76.1)	12,100 (70.0)
MI	204 (18.2)	1,398 (8.6)
Peripheral arteriopathy	197 (17.6)	1,409 (9.0)
Peripheral vascular disease	171 (15.3)	1,282 (7.9)
Stroke	112 (10.0)	1,209 (7.3)

S, suppressed as at least one cell has a count <5. [a]Case and control subjects were matched on the duration of follow-up, age, duration of treated diabetes, and calendar year of cohort entry. [b]Measured in the year prior to study cohort entry. [c]Number of prescriptions refers to the number of drug classes prescribed. [d]Last measure prior to cohort entry. [e]Comorbidities measured any time before study cohort entry.

subjects were also more likely to be prescribed β-blockers, calcium channel blockers, and diuretics and have a higher number of distinct prescriptions and physician visits.

Table 2 presents the characteristics of the current users of incretin-based drugs and those who received ≥2 oral antidiabetic drugs in the control group. Compared with current users of ≥2 oral antidiabetic drugs, incretin-based drug users were slightly younger, more likely to be obese, and had more distinct prescriptions and physician visits. Overall, both groups were comparable with respect to comorbidities and medication use at baseline.

The results of the primary analysis are presented in Table 3. Compared with current use of ≥2 oral antidiabetic drugs, current use of incretin-based drugs was not associated with an increased risk of CHF (OR 0.85 [95% CI 0.62–1.16]). In a secondary analysis, the risk did not appear to vary with type or duration of use, with all ORs of the duration categories at or under the null value (Table 3). Our analysis by pharmaceutical was inconclusive due to sparse data (Supplementary Table 1). When exposure to incretin-based drugs was subclassified by concomitant antidiabetic therapy use, no association was observed when compared with users of ≥2 antidiabetic drugs, though estimates were accompanied by wide 95% CIs (Supplementary Table 2). Finally, there was no effect measure modification by history of cardiovascular disease (no prior history, OR 1.13 [95% CI 0.74–1.74]; prior history, OR 0.67 [95% CI 0.43–1.04]; *P* for interaction = 0.29) or by duration of treated diabetes (<5 years, OR 0.69 [95% CI 0.41–1.15]; ≥5 years, OR 0.97 [95% CI 0.65–1.43]; *P* for interaction = 0.18).

Sensitivity Analyses

When patients with a history of insulin or thiazolidinedione use prior to cohort entry were excluded and those who received these prescriptions during follow-up were censored, the OR remained nonsignificant and moved closer to 1 (Supplementary Table 3). Similarly, sensitivity analyses that excluded patients with a history of renal disease resulted in an OR that was closer to 1 (Supplementary Table 4). All other sensitivity analyses produced results that were consistent with those of our primary analyses (Supplementary Tables 5–11).

CONCLUSIONS

The results of this large, population-based study indicate that the use of incretin-based drugs is not associated with an increased risk of hospitalization for CHF. Similar results were obtained in secondary analyses that considered type and duration of incretin-based drug use. Moreover, these results remained consistent in several sensitivity analyses. Overall, these results should provide reassurance in light of the safety signal raised by the SAVOR-TIMI 53 trial (2).

There are several possible explanations for why our study did not replicate the increased risk of CHF observed in the SAVOR-TIMI 53 trial. First, the SAVOR-TIMI 53 trial included patients with a history of cardiovascular disease, including pre-existing CHF, whereas our study excluded patients with a history of CHF at cohort entry. Second, the duration of diabetes in patients enrolled in the SAVOR-TIMI 53 trial was longer compared with patients included in this study (10.3 vs. 2.3 years, respectively). However, we did not observe any effect modification by history of cardiovascular disease and duration of treated diabetes (≥5 years) on the association between incretin-based drug use and the risk of CHF. Nonetheless, these were secondary analyses and thus should be interpreted with caution. Third, the SAVOR-TIMI 53 trial examined saxagliptin rather than incretin-based drugs as a class. It is therefore possible that the increased risk observed in the randomized controlled trial is specific to saxagliptin, though it is unclear why their biological effects would differ with respect to CHF. Finally, the increased risk of CHF observed in SAVOR-TIMI 53 may be a spurious finding due, in part, to the statistical consequences of examining multiple end points.

While the SAVOR-TIMI 53 trial reported an increased CHF risk with incretin-based drugs, some clinical studies have suggested that incretin-based drugs may play a protective role in the pathogenesis of CHF (22,23). For example, studies demonstrated that B-type natriuretic peptide, a cardiac marker that is elevated in the presence of CHF (24), was decreased in patients treated with liraglutide (25) or exenatide (26). Another study showed that GLP-1 improved ventricular function in patients with chronic CHF (22), although this was not observed in another study (27). A recent population-based cohort study conducted in patients with both diabetes and CHF found an increased risk of hospitalization for CHF with sitagliptin, but a heterogeneous reference category makes these results difficult to interpret, particularly with included sensitivity analyses, demonstrating that their risk estimates differ greatly depending on their choice of comparator (28). Taken together, these studies suggest that incretin-based drugs should have a neutral or possibly beneficial effect on the incidence of CHF.

This study has a number of strengths. First, our large study population provided sufficient power to study the association between incretin-based drugs and hospitalization for CHF. Second, our study population was unrestricted and thus was representative of patients with type 2 diabetes of varying age, disease stage, and severity. Third, the CPRD and HES databases used in this study have

Table 2—Baseline characteristics of current users of incretin-based drugs and oral antidiabetic drug combinations among matched control subjects[a]

Characteristics	Current use of incretin-based drugs	Current use of oral antidiabetic combinations
Number of patients	923	4,198
Age (years), mean (SD)	67.7 (8.9)	69.6 (9.5)
Duration of treated diabetes (years), mean (SD)	3.5 (3.3)	2.7 (2.7)
Males, *n* (%)	515 (55.8)	2,441 (58.1)
Year of study cohort entry, *n* (%)		
2007	263 (28.5)	2,131 (50.8)
2008	200 (21.7)	1,062 (25.3)
2009	255 (27.6)	603 (14.4)
2010	133 (14.4)	299 (7.1)
2011	72 (7.8)	100 (2.4)
Number of distinct prescriptions, *n* (%)[b,c]		
0–8	380 (41.2)	2,074 (49.4)
9–16	436 (47.2)	1,745 (41.6)
≥17	107 (11.6)	379 (9.0)
Number of physician visits, *n* (%)[b]		
0–10	245 (26.5)	1,238 (29.5)
11–20	406 (44.0)	1,878 (44.7)
≥21	272 (29.5)	1,082 (25.8)
Excessive alcohol use, *n* (%)[b]	126 (13.7)	502 (12.0)
Smoking status, *n* (%)[b]		
Ever	580 (62.8)	2,708 (64.5)
Never	S	1,472 (35.1)
Unknown	S	18 (0.4)
BMI, *n* (%)[d]		
≤24.9 kg/m^2	84 (9.1)	550 (13.1)
25–29.9 kg/m^2	273 (29.6)	1,617 (38.5)
≥30 kg/m^2	555 (60.1)	1,954 (46.5)
Unknown	11 (1.2)	77 (1.8)
HbA_{1c}, *n* (%)[d]		
≤7.0% [53 mmol/mol]	85 (9.2)	280 (6.7)
7.1–8.0% [54–64 mmol/mol]	269 (29.1)	1,318 (31.4)
>8.0% [64 mmol/mol]	508 (55.0)	2,240 (53.4)
Unknown	61 (6.6)	360 (8.6)
Antidiabetic drugs, *n* (%)[b]		
Insulins	S	5 (0.1)
Metformin	532 (57.6)	2,182 (52.0)
Sulfonylureas	264 (28.6)	939 (22.4)
Thiazolidinediones	158 (17.1)	311 (7.4)
Other	S	23 (0.5)
None	319 (34.6)	1,491 (35.5)
Other drugs, *n* (%)[b]		
ACE inhibitors	429 (46.5)	1,932 (46.0)
Angiotensin receptor blockers	178 (19.3)	649 (15.5)
β-Blockers	259 (28.1)	1,148 (27.3)
Calcium channel blockers	309 (33.5)	1,337 (31.8)
Diuretics	342 (37.1)	1,572 (37.4)
Fibrates	20 (2.2)	84 (2.0)
Statins	703 (76.2)	3,085 (73.5)
Aspirin	425 (46.0)	1,971 (47.0)
Other nonsteroidal anti-inflammatory drugs	190 (20.6)	767 (18.3)
Comorbidities, *n* (%)[e]		
Neuropathy	203 (22.0)	769 (18.3)
Renal disease	180 (19.5)	826 (19.7)
Retinopathy	302 (32.7)	1,335 (31.8)
Atrial fibrillation	58 (6.3)	270 (6.4)
Cancer	141 (15.3)	609 (14.5)
COPD	141 (15.3)	537 (12.8)
Coronary arterial disease	248 (26.9)	1,126 (26.8)
Coronary revascularization	63 (6.8)	215 (5.1)

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Table 2—Continued

Characteristics	Current use of incretin-based drugs	Current use of oral antidiabetic combinations
Dyslipidemia	337 (36.5)	1,309 (31.2)
Hypertension	638 (69.1)	2,796 (66.6)
MI	62 (6.7)	277 (6.6)
Peripheral arteriopathy	78 (8.5)	334 (8.0)
Peripheral vascular disease	76 (8.2)	282 (6.7)
Stroke	53 (5.7)	237 (5.6)

S, suppressed as at least one cell has a count <5. [a]Case and control subjects were matched on the duration of follow-up, age, duration of treated diabetes, and calendar year of cohort entry. [b]Measured in the year prior to study cohort entry. [c]Number of prescriptions refers to the number of drug classes prescribed. [d]Last measure prior to cohort entry. [e]Comorbidities measured any time before study cohort entry.

been validated extensively to ensure data accuracy (11,29). Moreover, the CPRD collects information on potentially important confounders, such as HbA_{1c} and BMI. Fourth, using a base cohort of patients receiving noninsulin antidiabetic agents between 1988 and 2012 allowed for an accurate assessment of the duration of treated diabetes, a potentially major confounder. Finally, our nested case-control analysis allowed for a time-dependent assessment of exposure while matching on key potential confounders.

Our study has some potential limitations. First, the CPRD does not capture prescriptions written by specialists. However, with both the exposed and reference group identified by prescriptions written by general practitioners, we believe that this had a minimal effect on our results. Second, the CPRD only contains information on the prescriptions issued and not filled, which may result in some minor misclassification. Third, with an average follow-up that was relatively short (mean of 1.8 years for case subjects and control subjects), changes in health status since baseline may have resulted in some residual confounding. However, in sensitivity analyses, we adjusted for covariates at index date, producing results that were similar to those of our primary analysis. In addition, we were unable to adjust for diet and physical activity, though we believe that these variables were not differentially distributed between the exposure groups and correlate well with others included in our adjustment (e.g., BMI). Fourth, to our knowledge, the end point of HES-defined hospitalization for CHF has not been previously validated. However, consistent results were obtained when restricting to case subjects with a primary diagnosis of CHF. Our case definition was restricted to hospitalized CHF rather than patients with either an inpatient or outpatient diagnosis to obtain a more homogeneous, highly specific, and clinically relevant case series. Nonetheless, our overall CHF rate compares favorably to previously reported CHF rates among patients with type 2 diabetes (30). Fifth, as incretin-based drugs are most commonly used as second- or third-line therapies (14), the optimal choice of comparator is unclear. While we used ≥2 oral antidiabetic drugs as our main comparator, we conducted sensitivity analyses in which we used metformin and sulfonylurea combination therapy as well as an additional sensitivity analysis in which we censored upon prescription of insulin or a thiazolidinedione. Regardless of comparator, we found no evidence of an increased risk with incretin-based drugs. Finally, although we had sufficient power for our primary analyses, statistical power was modest in some secondary analyses, including our analyses by type of incretin-based drug (i.e., DPP-4 inhibitor and GLP-1 analog) and by pharmaceutical. For example, with fewer than five case and control subjects prescribed saxagliptin, we were unable to draw strong conclusions

Table 3—Crude and adjusted ORs of hospitalization for CHF, comparing incretin-based drugs to combinations of oral antidiabetic drugs[a]

Current exposure[b]	Case subjects (n = 1,118)	Control subjects (n = 17,626)	Crude OR (95% CI)	Adjusted OR[c] (95% CI)
≥2 oral antidiabetic drugs, n (%)	267 (23.9)	4,198 (23.8)	1.00 (Reference)	1.00 (Reference)
Incretin-based drugs, n (%)	64 (5.7)	923 (5.2)	0.98 (0.73–1.33)	0.85 (0.62–1.16)
DPP-4 inhibitors	54 (4.8)	808 (4.6)	0.96 (0.70–1.32)	0.88 (0.63–1.22)
GLP-1 analogs	10 (0.9)	115 (0.7)	1.18 (0.59–2.39)	0.67 (0.32–1.42)
Duration of incretin-based drug use,[d] n (%)				
1–83 days	25 (2.2)	310 (1.8)	1.18 (0.74–1.89)	1.01 (0.62–1.63)
84–265 days	18 (1.6)	299 (1.7)	0.86 (0.51–1.44)	0.79 (0.46–1.36)
>265 days	21 (1.9)	314 (1.8)	0.92 (0.56–1.50)	0.75 (0.45–1.25)
				P trend = 0.39

[a]Case and control subjects were matched on the duration of follow-up, age, duration of treated diabetes, and calendar year of cohort entry. [b]Current users of insulins, single oral antidiabetic drugs, and noncurrent users of antidiabetic drugs are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects (representing 787 case subjects and 12,505 control subjects). [c]Adjusted for sex, BMI, excessive alcohol use, smoking status, HbA_{1c} level (≤7.0% [53 mmol/mol], 7.1–8.0% [54–64 mmol/mol], >8.0% [64 mmol/mol]), comorbidities (neuropathy, renal disease, retinopathy, atrial fibrillation, cancer [other than nonmelanoma skin cancer], COPD, CAD, dyslipidemia, hypertension, previous MI, peripheral arteriopathy, previous coronary revascularization, peripheral vascular disease, and previous stroke), number of prescriptions, number of physician visits, and use of the following drugs in the year prior to cohort entry: ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, diuretics, fibrates, statins, aspirin, and other nonsteroidal anti-inflammatory drugs. [d]Duration categories based on tertiles.

regarding its pharmaceutical-specific CHF risk. Further, large-scale studies are needed to definitively assess such risks.

In summary, this is the first large, population-based observational study that assessed the risk of incident CHF among patients with type 2 diabetes that were treated with incretin-based drugs. In this study population, incretin-based drugs were not associated with an increased risk of CHF. These results should provide reassurance regarding the cardiovascular effects of incretin-based drugs in patients with type 2 diabetes.

Funding. This study was funded in part by research grants from the Canadian Institutes of Health Research. K.B.F. is a Canadian Institutes of Health Research New Investigator. L.A. is the recipient of a Chercheur-Boursier career award from the Fonds de Recherche du Québec-Santé. S.S. is the recipient of the James McGill Chair.

Duality of Interest. A.M. receives consultation and speaker fees from Merck, Sanofi, AstraZeneca, Bristol-Myers Squibb, Servier, and Novo Nordisk. S.S. has received research grants and participated in advisory board meetings and/or as a speaker at conferences for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, and Novartis. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. O.H.Y.Y. was responsible for study conception and design, drafting the manuscript, interpretation of data, and critical revision of the manuscript for important intellectual content. K.B.F. and L.A. were responsible for study conception and design, supervising the conduct of the statistical analyses, interpretation of data, and critical revision of the manuscript for important intellectual content. V.P. performed the statistical analyses, interpretation of data, and critical revision of the manuscript for important intellectual content. A.M. was responsible for interpretation of data and critical revision of the manuscript for important intellectual content. S.S. was responsible for study conception and design, acquiring the data, supervising the conduct of the study, interpretation of data, and critical revision of the manuscript for important intellectual content. S.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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