

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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This article was updated on August 25, 2016, at NEJM.org.

N Engl J Med 2016;374:1145-54.

DOI: 10.1056/NEJMoa1506115

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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) trial⁴ 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 oc-

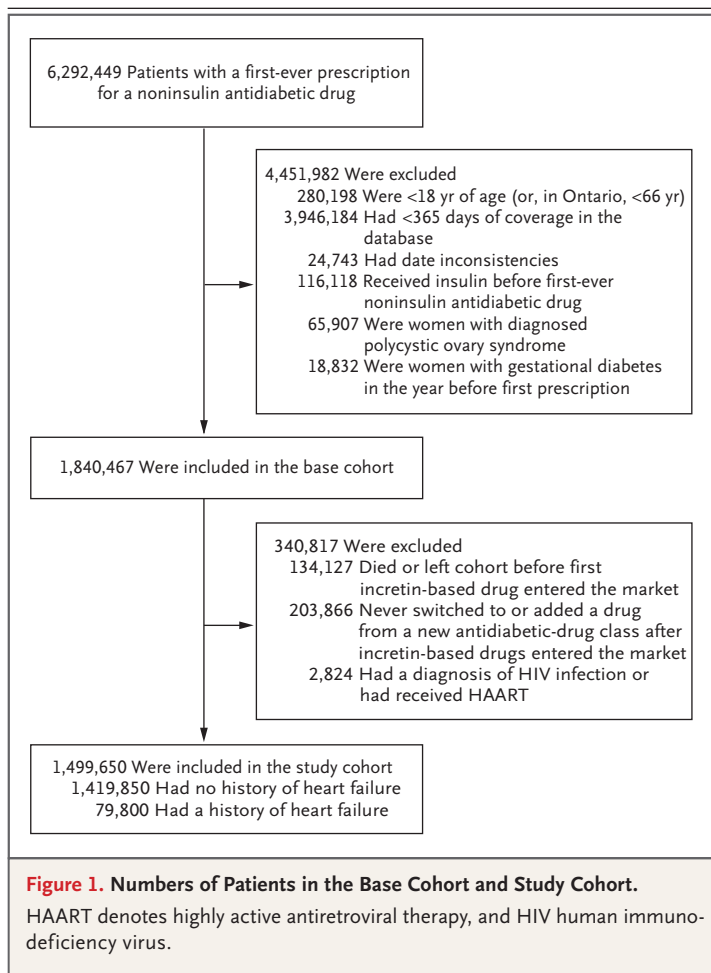
curing during follow-up, we used risk-set sampling to match the event with a random sample from the risk set — namely, the cohort members who were still being followed and were event-free at the time of the case event. These risk sets, which allow exposure to be measured at the time of the event occurrence, 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-



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 analysis¹⁸ (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 approach¹⁹; 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.

controls 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 pa-

tients 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 slightly older 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

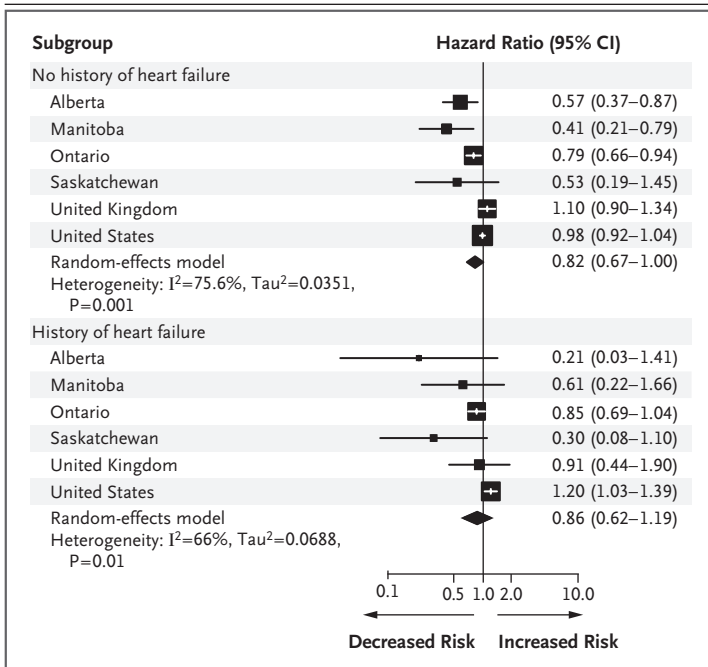


Figure 2. Association between Treatment with Incretin-based Drugs and the Risk of Hospitalization for Heart Failure among Patients with and Those without a History of Heart Failure.

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

were 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 ($\leq 7.0\%$ [53 mmol per mole], 7.1 to 8.0% [54 to 64 mmol per mole], or $> 8.0\%$ [64 mmol per mole]).

§ The I² 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 observed important between-site heterogeneity, which may be due to differences in study popu-

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 I² statistic represents the proportion of the total variance of the meta-analysis that is due to between-study heterogeneity rather than within-study variability.

lations, 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 analy-

sis, 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.

Supported by a grant from the Canadian Institutes of Health Research (DSE-111845) and by a Canadian Institutes of Health Research New Investigator Award (to Dr. Filion) and a Chercheur-National Award of Fonds de Recherche du Québec — Santé (Quebec Foundation for Health Research; to Dr. Platt).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Zhihai Ma, M.Sc., and Jianguo Zhang, M.Sc. (Alberta), Gregory A. Carney, B.Sc. (MarketScan), Janie Coulombe, M.Sc., and Hui Yin, M.Sc. (CPRD), Caixia Fangyun Wu, M.Sc., and Simon Hollands, M.Sc. (Ontario), and Shan Jin (Saskatchewan) for programming support; Corine Mizrahi, Melissa Dahan, and Laura Sang, M.P.H., at the Coordinating Center; Menglan Pang, M.Sc., from the CNODES Methods Team; Madeleine Durand, M.D., and H eloise Cardinal, M.D., Ph.D., for their contributions to the development of the study design, as well as Karine Suissa, P.Dt., M.Sc., for her assistance; and the CNODES collaborators and assistants at each site for their contributions.

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Eta Carinae

Michel Samson, M.D.

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure (March 24, 2016; 374:1145-1154). In the third paragraph of the Results (page 1149, right column), we stated, "Among patients without a history of heart failure, patients taking incretin-based drugs were younger than those taking combinations of oral antidiabetic drugs". However, among patients without a history of heart failure, patients taking incretin-based drugs were in fact slightly older than those taking combinations of oral antidiabetic drugs (68.1 years versus 67.6 years). The age distribution of patients taking incretin-based drugs and those taking combinations of oral antidiabetic drugs is correctly reported in Table S2.

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The Canadian Network for Observational Drug Effect Studies (CNODES) Investigators

The CNODES Investigators are: Samy Suissa (Principal Investigator); Colin R. Dormuth (British Columbia); Brenda R. Hemmelgarn (Alberta); Gary F. Teare (Saskatchewan); Patricia Caetano and Dan Chateau (Manitoba); David A. Henry and J. Michael Paterson (Ontario); Jacques LeLorier (Québec); Adrian R. Levy (Nova Scotia); Pierre Ernst (UK Clinical Practice Research Datalink (CPRD)); Robert W. Platt (Methods); and Ingrid S. Sketris (Knowledge Translation). CNODES, a collaborating centre of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research (Grant Number DSE-111845).

Detailed description of statistical methods

All analyses were conducted separately among patients with and without a history of HF. We used conditional logistic regression to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association between incretin-based drugs and the risk of HF; with our use of risk set sampling, these ORs are unbiased estimators of the hazard ratio (HR)¹⁻³. In addition to conditioning our models on sex, age, year of study cohort entry, duration of treated diabetes, and duration of follow-up, all of which our cases and controls were matched, we adjusted our models for several potential confounders (specified a priori) measured at study cohort entry, including comorbidities (alcohol-related disorders, atrial fibrillation, cancer [other than non-melanoma skin], chronic obstructive pulmonary disease, coronary artery disease, dyslipidemia, hypertension, peripheral vascular disease, previous coronary revascularization, previous myocardial infarction [MI], previous stroke), microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy), and use of the following drugs in the year before study cohort entry: angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), beta-blockers, calcium-channel blockers, diuretics, statins, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs). In addition, we adjusted for number of hospitalizations and number of unique non-diabetic drugs in the prior year, two proxies of overall health, as well as number of anti-diabetic drugs received prior to study cohort entry. Finally, in the CPRD, we further adjusted for glycated hemoglobin, body mass index, and smoking. All site-specific analyses were conducted independently, and sites were kept blind to the results of all other sites.

We conducted three a priori secondary analyses. First, we repeated our analyses by type of incretin-based drug (i.e., DPP-4 inhibitor vs GLP-1 analog). Second, to examine the potential presence of a duration-response relationship, we sub-classified exposure by duration of current use (≤ 365 days, 366-729 days, and ≥ 730 days). Third, we examined the potential presence of effect modification by history of MI. Site-specific effect modification was assessed via the inclusion of interaction terms into the conditional logistic regression model, and effect modification across sites was assessed via meta-regression. In a post-hoc secondary analysis, we also examined the potential presence of effect modification by duration of treated diabetes at the index date (< 5 years and ≥ 5 years).

To assess the robustness of our results, we conducted several a priori sensitivity analyses. First, we repeated our primary analysis using metformin-sulfonylureas combination therapy as the reference group. Second, we varied our definition of current exposure using grace periods of 0 and 90 days. Third, to examine the impact of insulin use and thiazolidinedione use on our estimates, we repeated our risk set sampling excluding patients with a history of use of these drugs and censoring those who initiated these drugs during follow-up. Fourth, to examine the impact of changes in health status during follow-up, we adjusted for potential confounders measured at index date rather than study cohort entry, acknowledging that some may be intermediate variables. Fifth, we further adjusted our primary analyses for anti-diabetic drugs used in the year before study cohort entry; these drugs were not included as covariates in our primary analysis due to their potential correlation with exposure. Sixth, to examine the potential effects of model over-fit in some of our smaller sites, we repeated our primary analyses using two reduced models. In the first, a composite microvascular complications variable was used instead of its individual components, categorical variables were converted to their continuous counterparts where possible, and insulin, oral antidiabetic drug monotherapy, and “not currently

exposed” were collapsed to a single “other exposure” category. In the second, our model only included exposure (current exposure to incretin-based drugs, current exposure to oral antidiabetic combinations, and other exposure) and the Deyo version of the Charlson comorbidity index⁴. Finally, in analyses restricted to our cohort of patients with no history of HF, we restricted our case definition to diagnoses in the principal (or most responsible) position.

Our nested case-control analyses were supplemented by propensity-matched cohort analyses to further assess the robustness of our findings. These analyses were conducted in the three sites (the Canadian province of Ontario, the UK CPRD, and US MarketScan) that contributed the highest numbers of cases to our nested case-control analysis. The other three sites (the Canadian provinces of Alberta, Manitoba, and Saskatchewan) were not included in these analyses; with a relatively low prevalence of incretin-based drug use at study cohort entry and a small number of events at these sites, it was not feasible to implement the propensity-matched analysis. Importantly, the three sites that participated in these propensity-matched analyses accounted for 91.0% of all cases in the nested case-control analyses among patients with no history of HF and 87.8% of all cases among patients with a history of HF. In these analyses, we identified all patients whose study cohort entry occurred due to the initiation of an incretin-based drug or oral antidiabetic drug combinations. We then estimated the probability of treatment with incretin-based drugs using a logistic regression model with a dependent variable of exposure to incretin-based drug versus exposure to oral antidiabetic drug combinations and with independent variables consisting of baseline patient characteristics (all matching variables measured at baseline, those included in our conditional logistic regression models, and up to 500 empirically identified covariates)⁵. We then matched patients who were treated with incretin-based drugs with patients who were not, but had similar model-based probabilities of being treated (maximum propensity score caliper ± 0.05). The c-statistics for the propensity score models ranged from 0.62 to 0.82 for patients with no previous history of HF and from 0.67 to 0.88 for those with a previous history of HF. Prior to matching, patients in areas of non-overlap of the propensity score distributions were trimmed. Standardized differences were estimated for the trimmed and the matched cohorts. Patients were then followed until hospitalization for HF or censoring due to the same criteria used in our nested case-control analysis or a maximum follow-up of two years, whichever occurred first. To examine the potential effects of misclassification of exposure due to the time-fixed exposure definition, we then repeated these analyses with a maximum follow-up of one year. In addition, to examine the potential consequences of the competing risk of death, we implemented the method proposed by Fine and Gray⁶ in sensitivity analyses to our cohort analyses. Sites using SAS version 9.3 used the macro by Kohl and colleagues⁷, and those using SAS version 9.4 used the *eventcode* option of *proc phreg*.

To examine the ability of unknown or unmeasured confounders to mask a true increased risk in hospitalization for HF, we used the array approach proposed by Schneeweiss⁸. In this analysis, we used the observed HR from our primary nested case-control analysis of patients with no previous history of HF, a prevalence of the confounder among users of oral anti-diabetic combinations of 0.2, and a true HR of 1.27 (the association reported in SAVOR-TIMI 53)⁹.

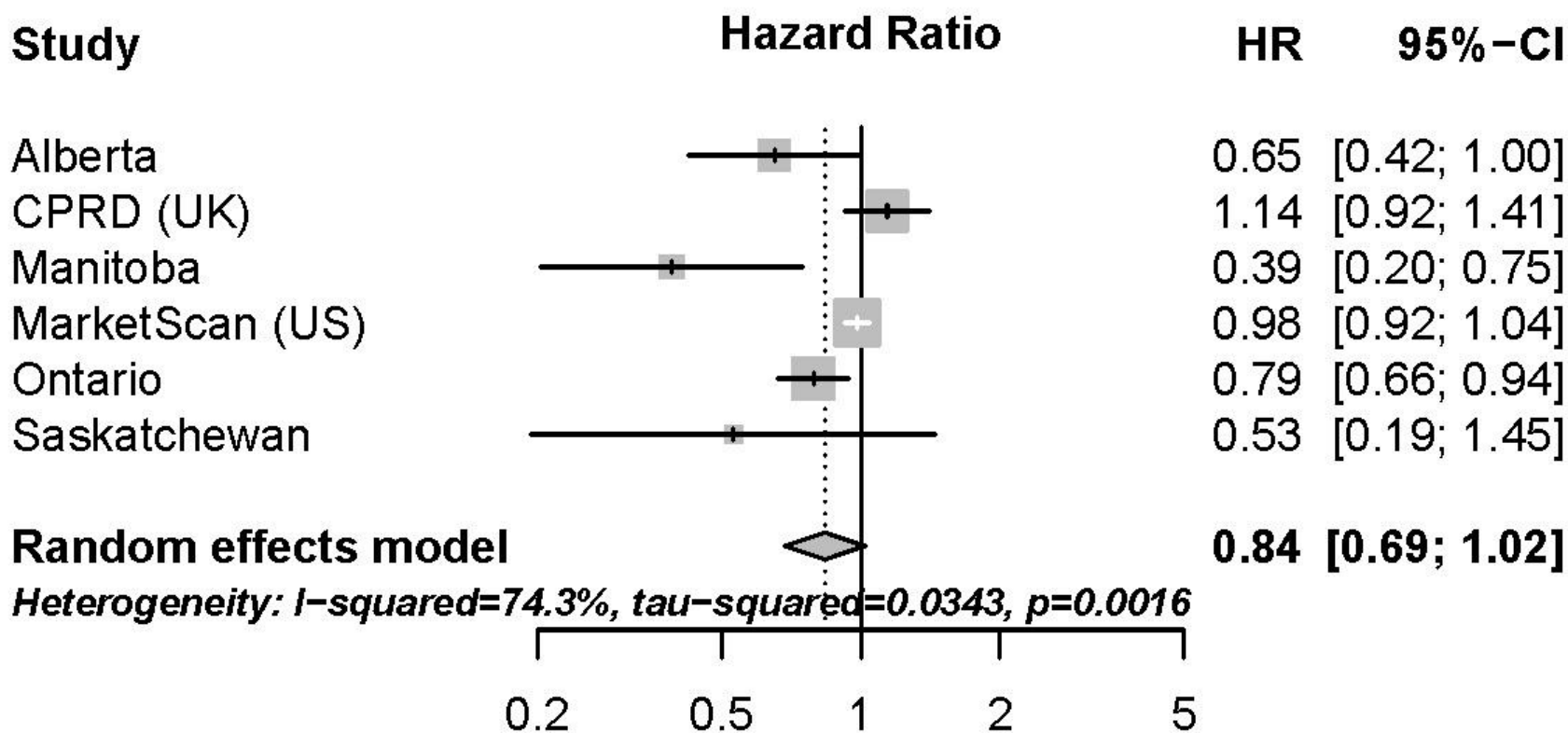
All site-specific estimates were meta-analyzed using random-effects models with inverse variance weighting and the DerSimonian and Laird approach¹⁰. The amount of between-site heterogeneity that was present was estimated using the I^2 statistic. The I^2 represents the proportion of the total variance of the meta-analysis that is due to between-study heterogeneity rather than within-study variability¹¹. In sensitivity analyses, analyses were repeated using fixed-

effects models. All site-specific analyses were conducted using SAS versions 9.3 or 9.4, and meta-analyses were conducted using R version 3.2.0.

Authors' contributions

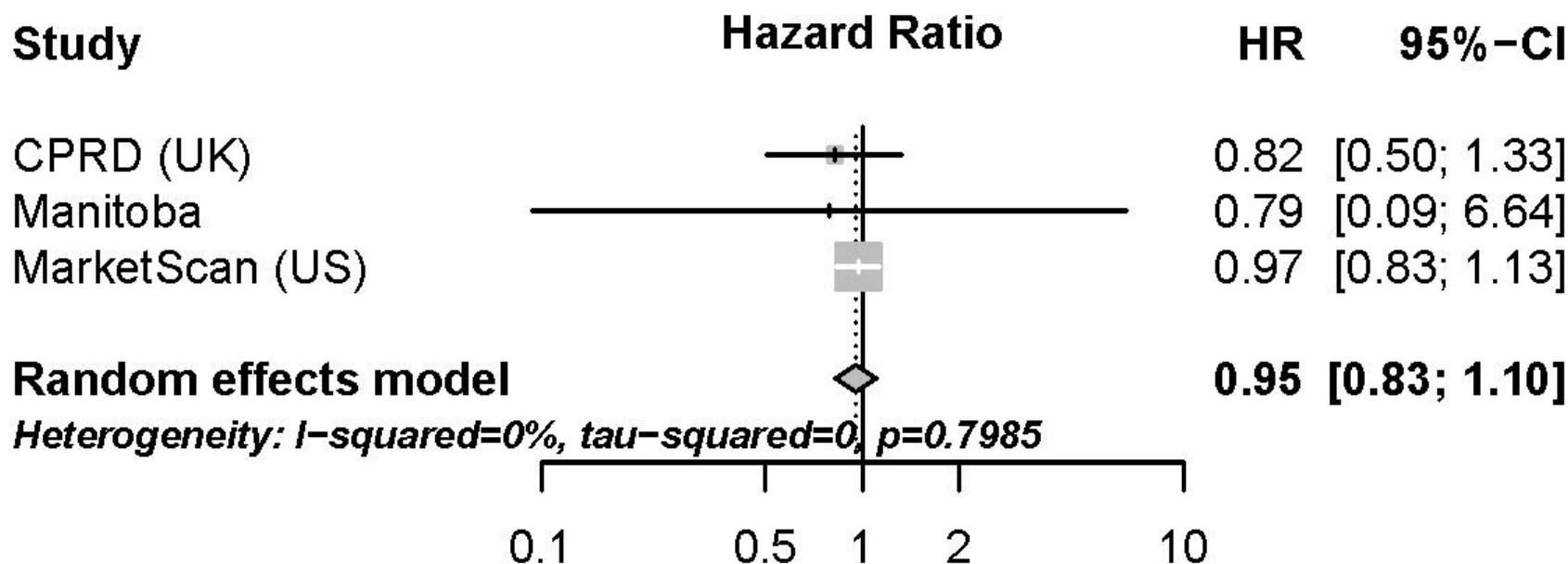
KBF drafted the manuscript and is the guarantor. KBF, LA, CRD, NH, JMP, LT, TCT, and PE supervised the analyses. MD conducted analyses at the Manitoba site. RWP conducted the meta-analyses. All authors contributed to the study design.

Figure S1. Forest plot of the association between current use of DPP-4 inhibitors and hospitalization for HF among patients with no history of HF*.



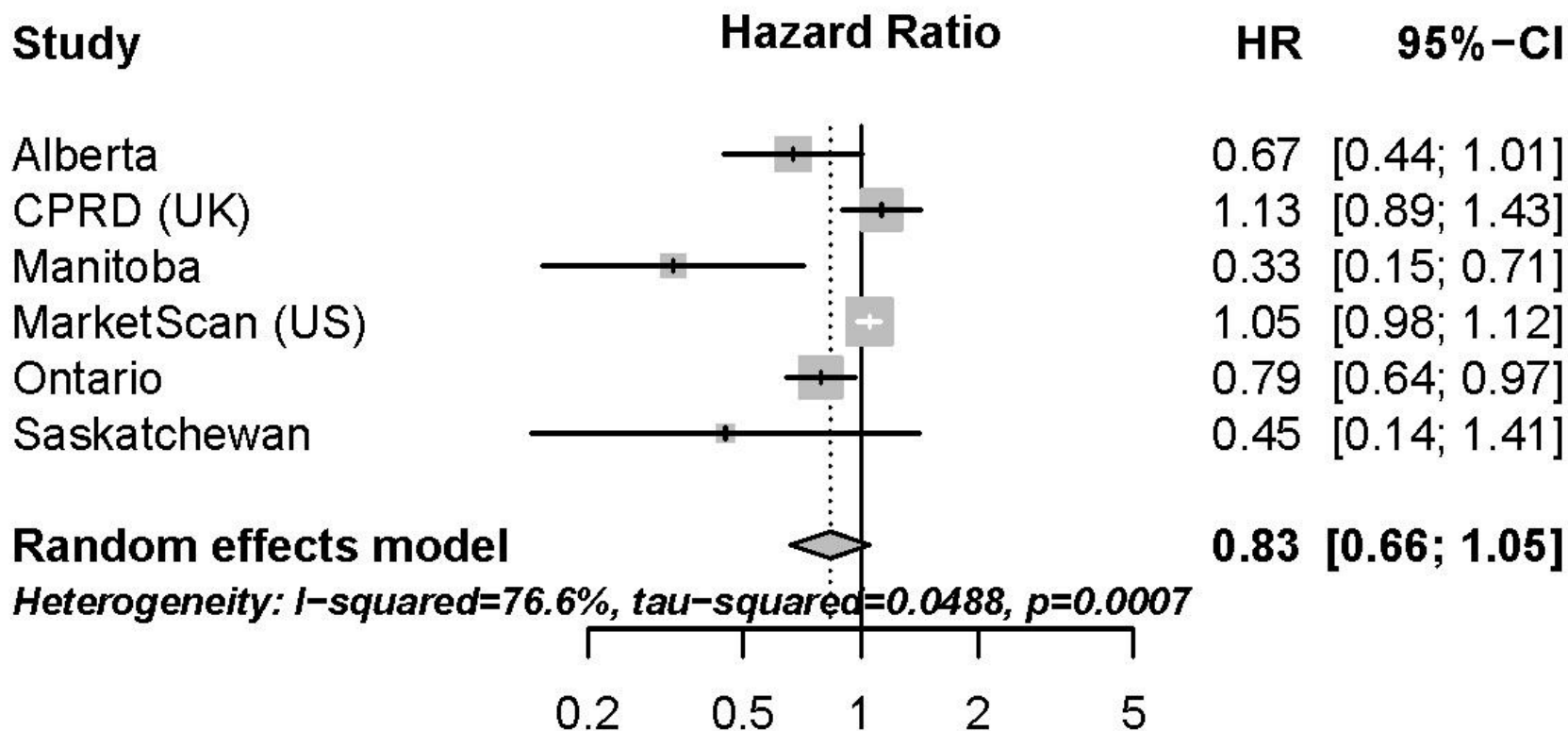
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: DPP-4, dipeptidyl peptidase-4; HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S2. Forest plot of the association between current use of GLP-1 analogs and hospitalization for HF among patients with no history of HF*.



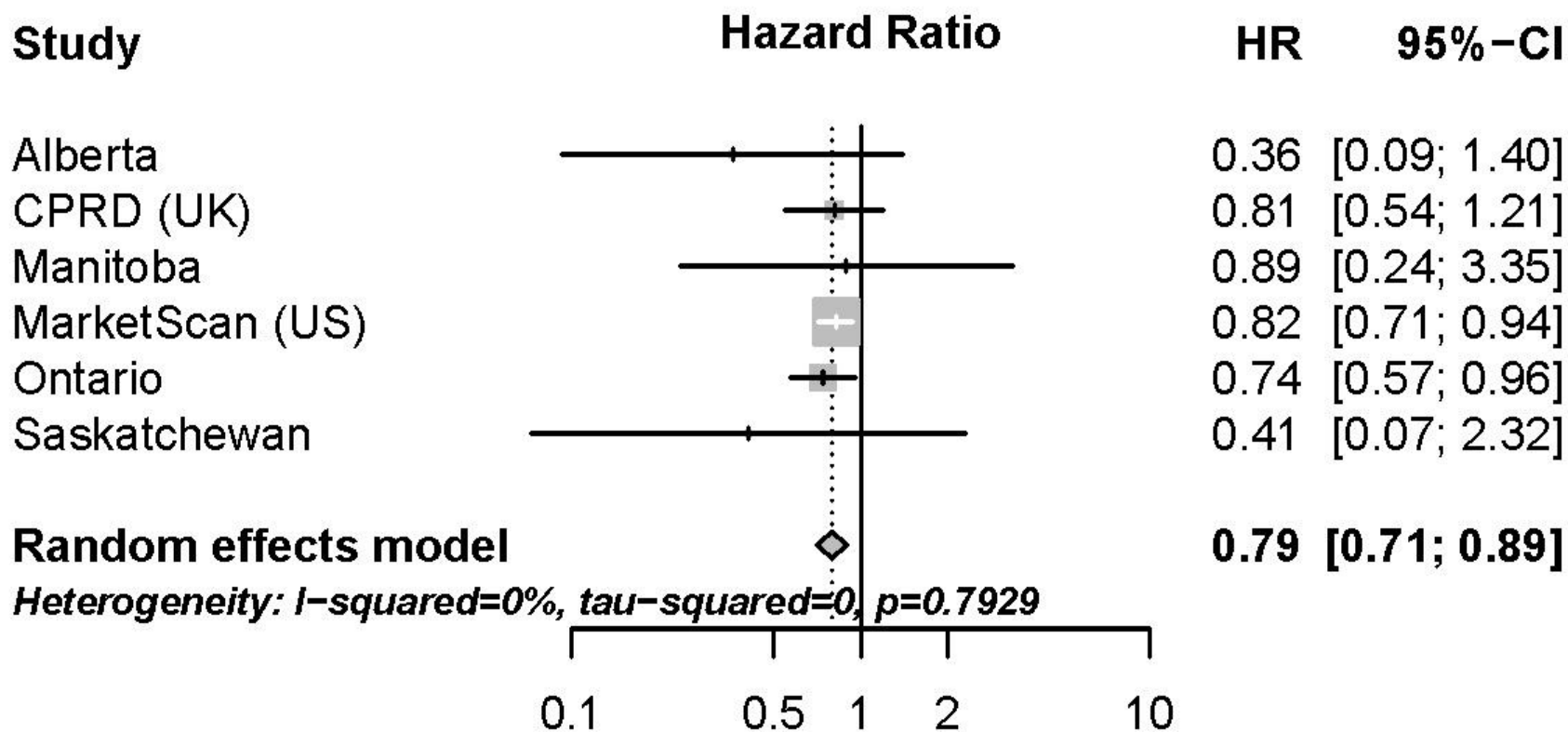
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta, Ontario, and Saskatchewan did not have GLP-1 analogs available in their jurisdiction and were thus excluded from this analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: GLP-1, glucagon-like peptide-1, HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S3. Forest plot of the association between ≤ 365 days of current use of incretin-based drugs and hospitalization for HF among patients with no history of HF*.



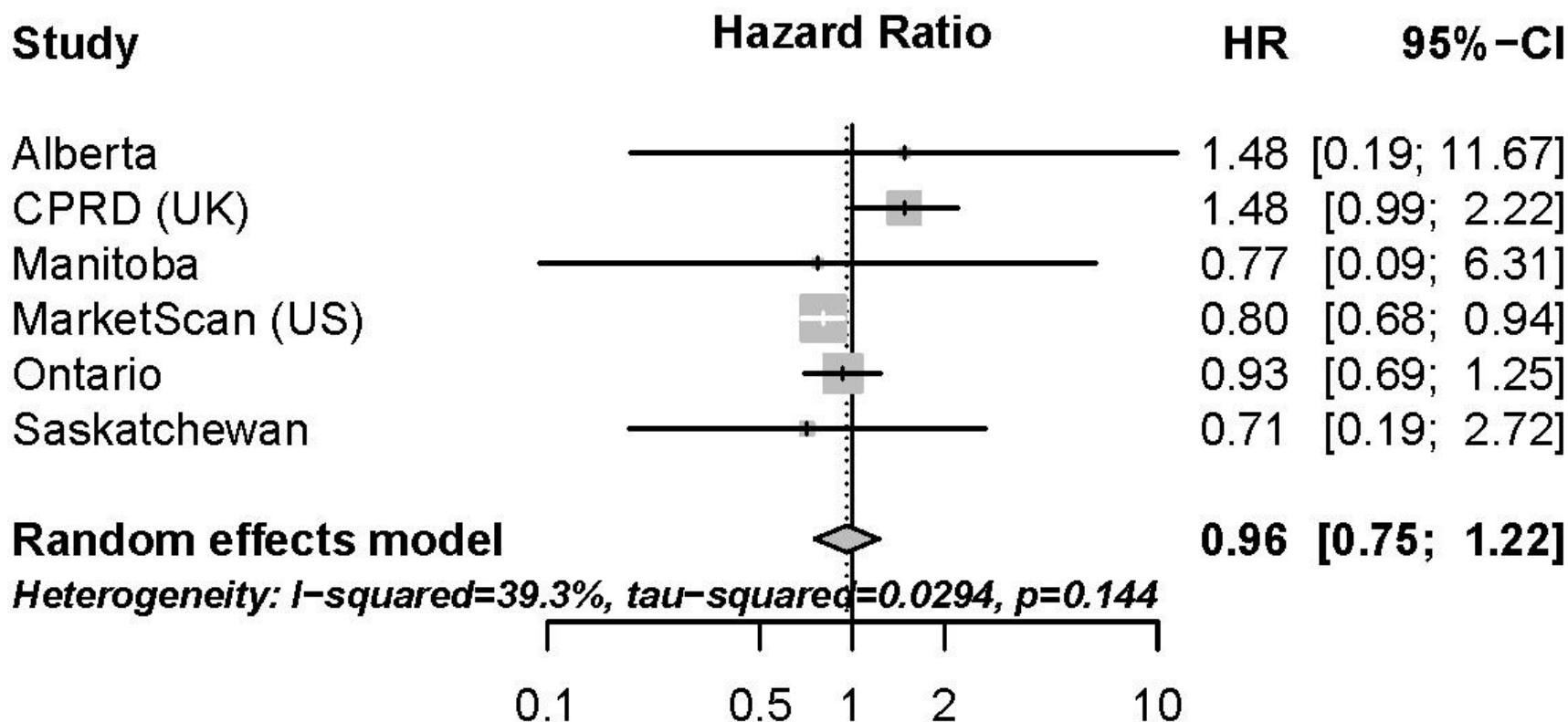
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S4. Forest plot of the association between 366-729 of current use of incretin-based drugs and hospitalization for HF among patients with no history of HF*.



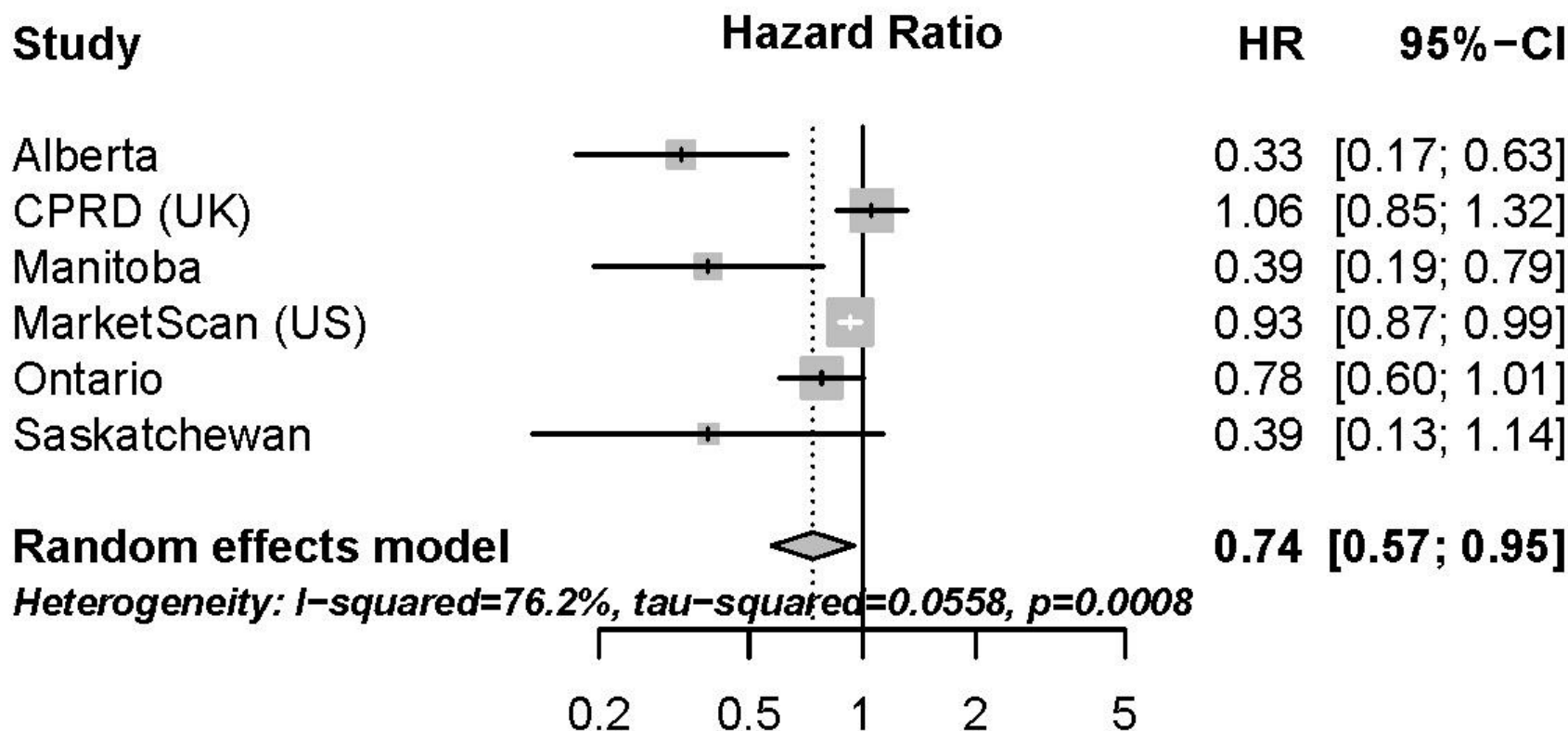
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S5. Forest plot of the association between ≥ 730 days of current use of incretin-based drugs and hospitalization for HF among patients with no history of HF*.



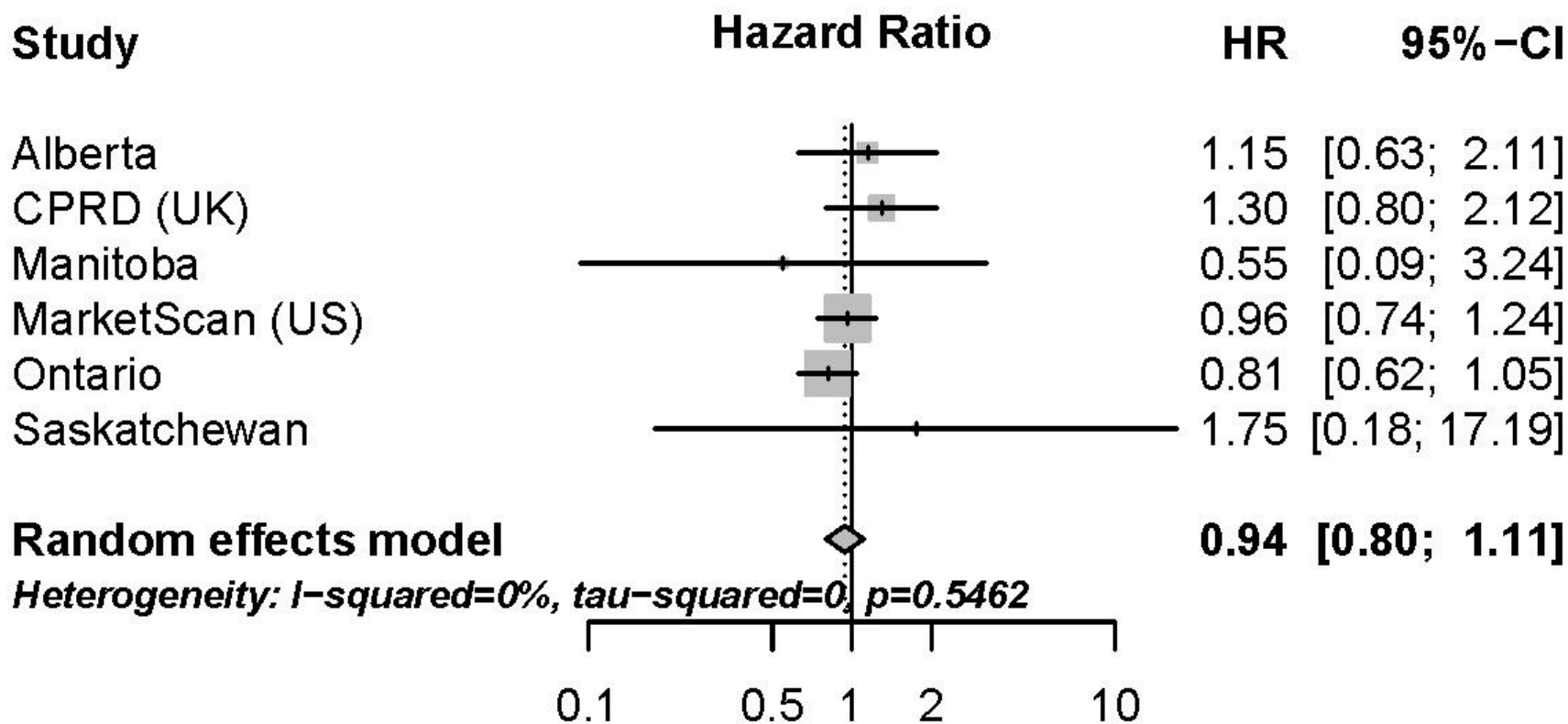
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S6. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of MI or HF*.



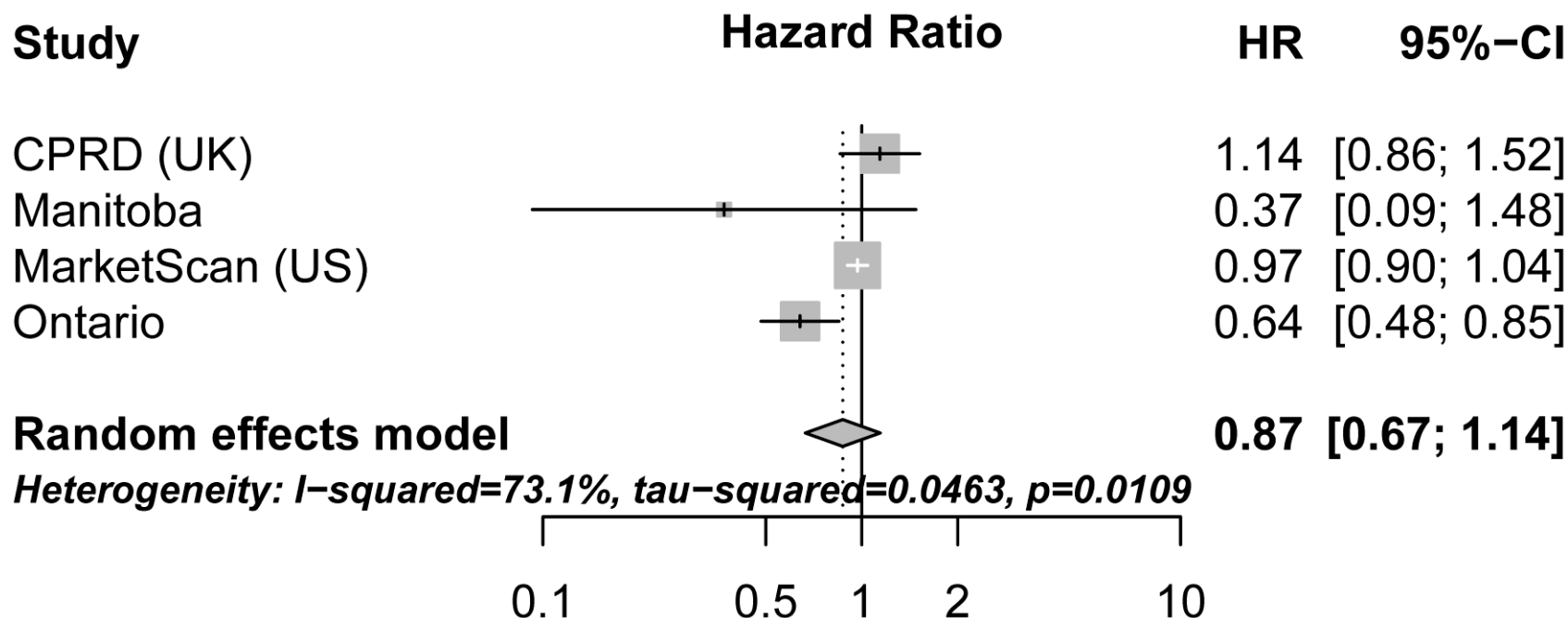
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S7. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of MI but no history of HF*.



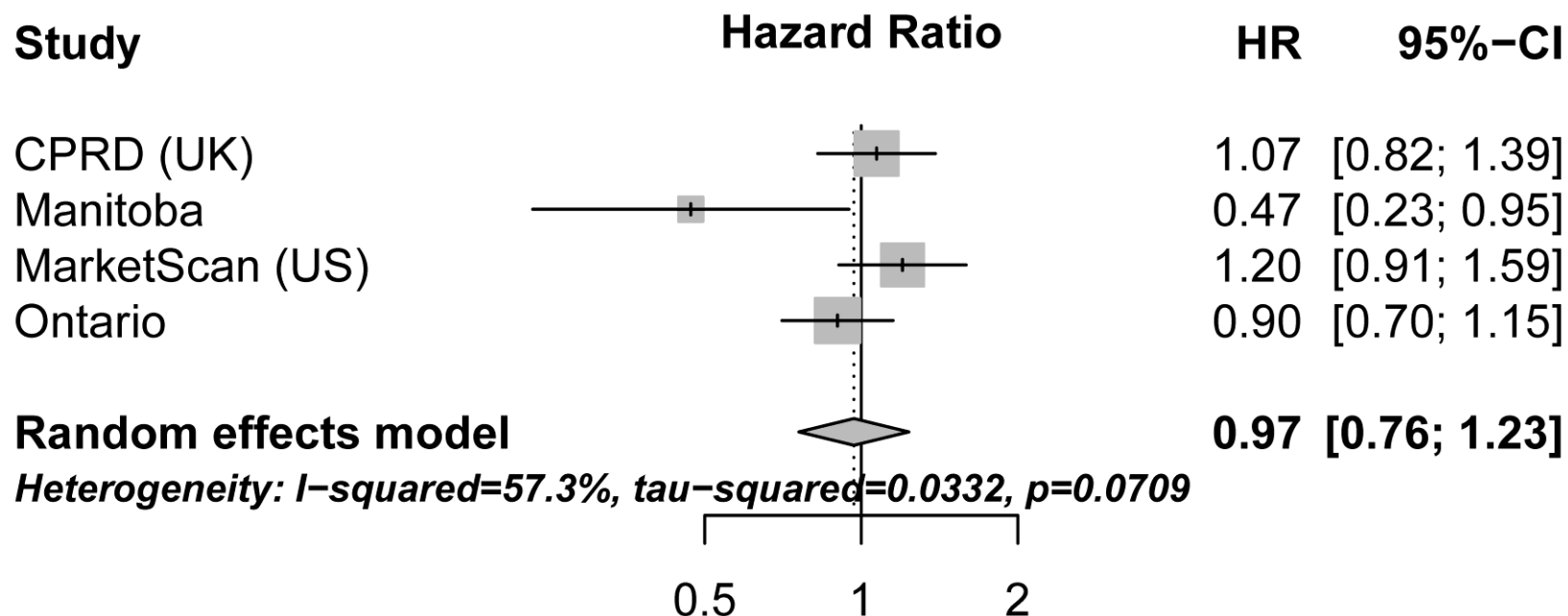
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S8. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF and a duration of treated diabetes at index date of less than five years*.



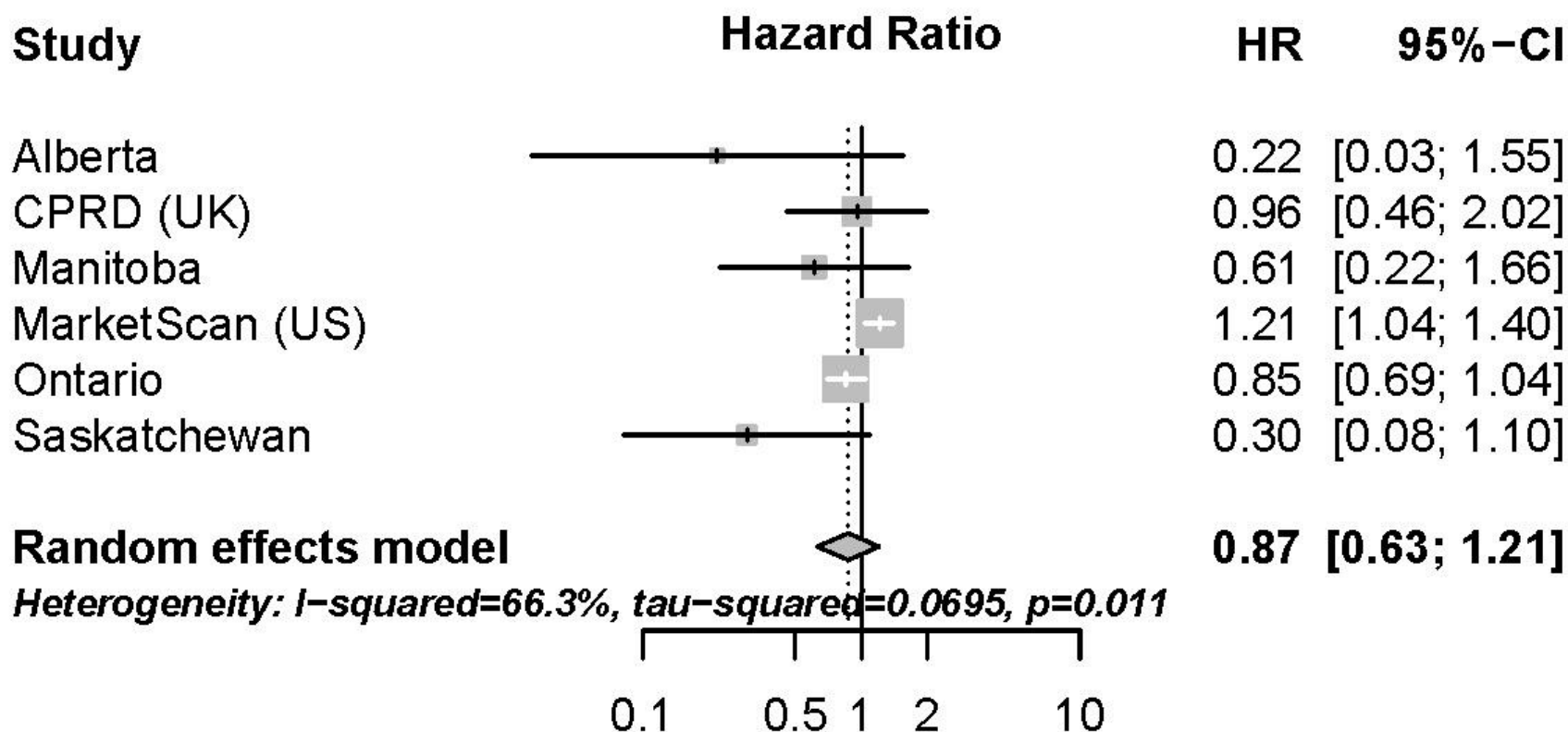
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta did not participate in this analysis as all patients had a duration of treated diabetes of less than five years, preventing the examination of the interaction. Saskatchewan was excluded due to sparse data. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S9. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF and a duration of treated diabetes at index date of five years or more*.



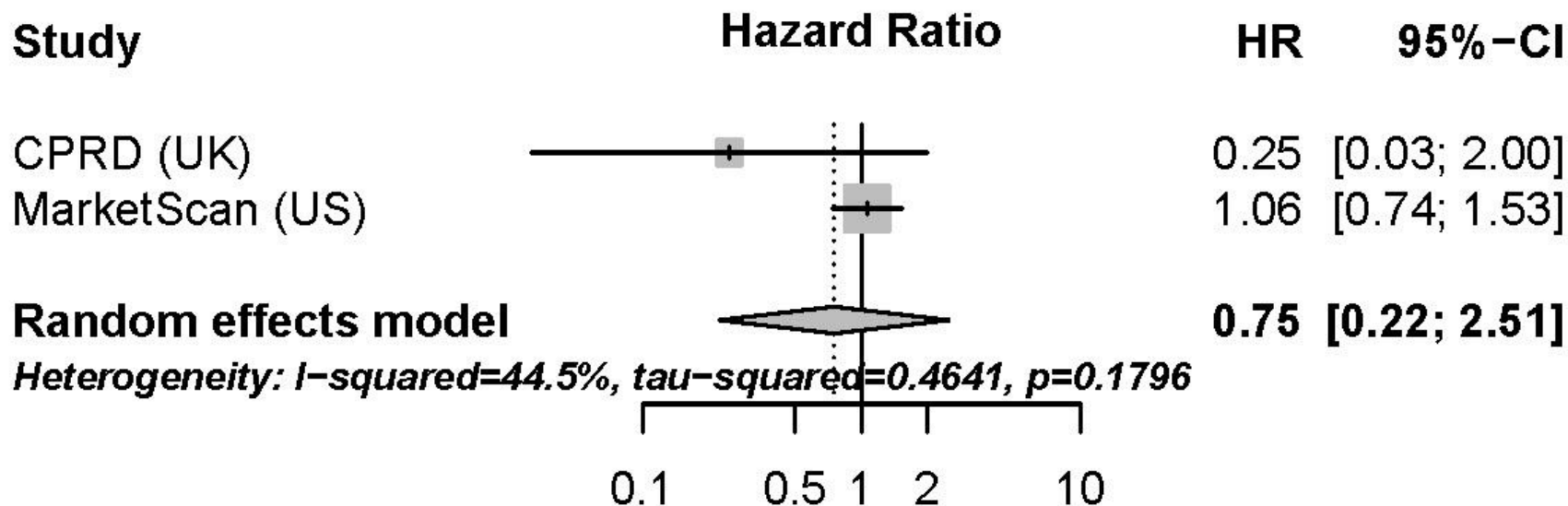
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta did not participate in this analysis as all patients had a duration of treated diabetes of less than five years, preventing the examination of the interaction. Saskatchewan was excluded due to sparse data. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S10. Forest plot of the association between current use of DPP-4 inhibitors and hospitalization for HF among patients with a history of HF*.



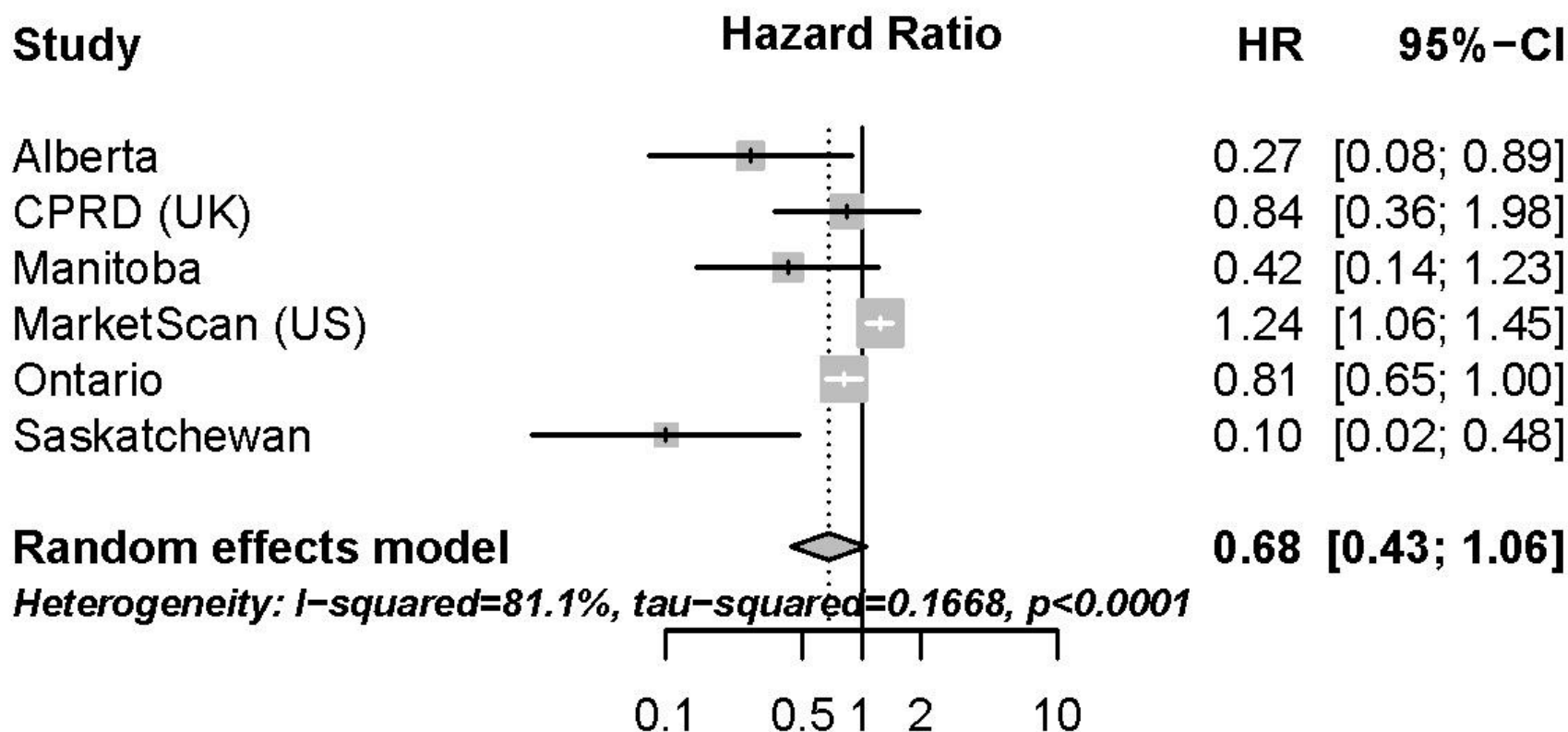
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: DPP-4, dipeptidyl peptidase-4; HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S11. Forest plot of the association between current use of GLP-1 analogs and hospitalization for HF among patients with a history of HF*.



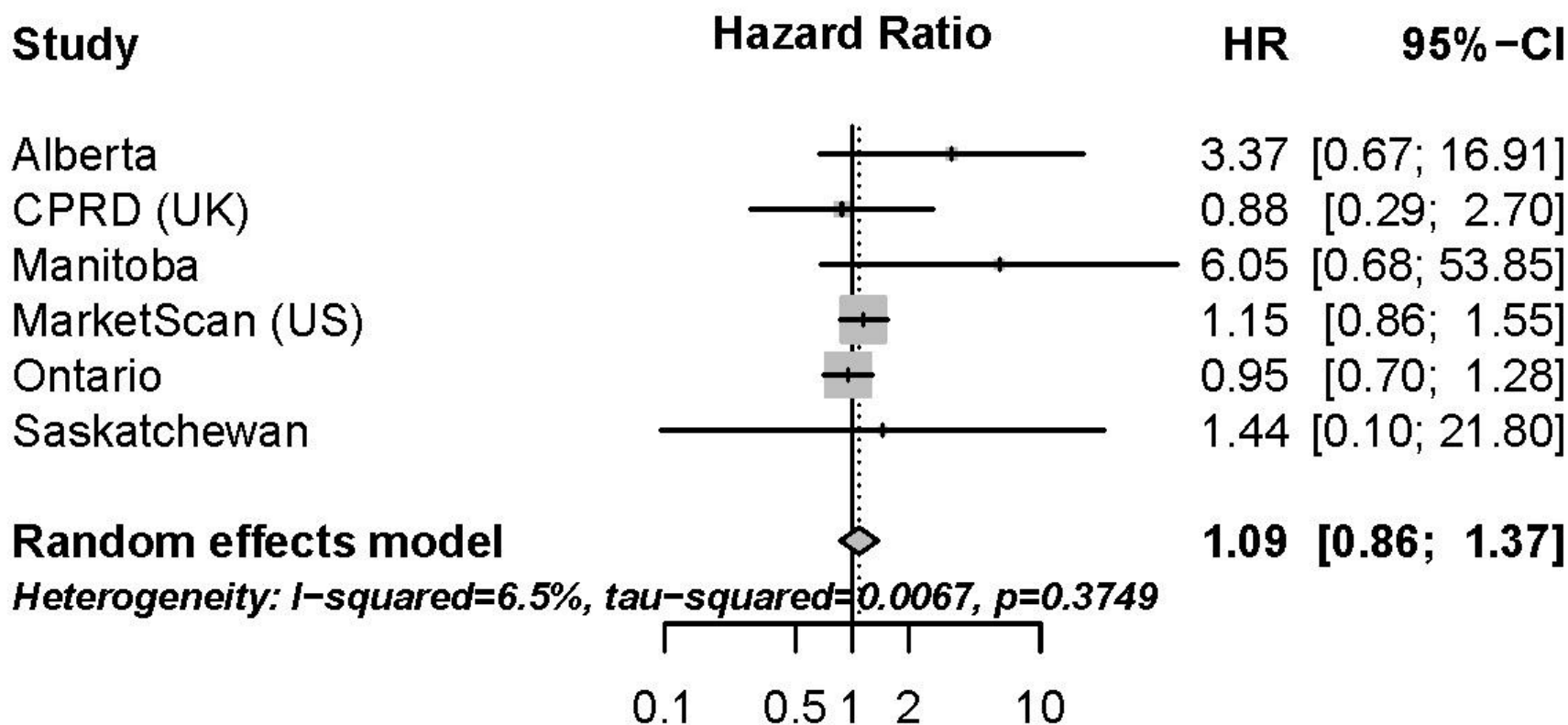
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta, Ontario, and Saskatchewan did not have GLP-1 analogs available in their jurisdiction, and the model did not converge in Manitoba. These sites were thus excluded from this analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: GLP-1, glucagon-like peptide-1, HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S12. Forest plot of the association between ≤ 365 days of current use of incretin-based drugs and hospitalization for HF among patients with a history of HF*.



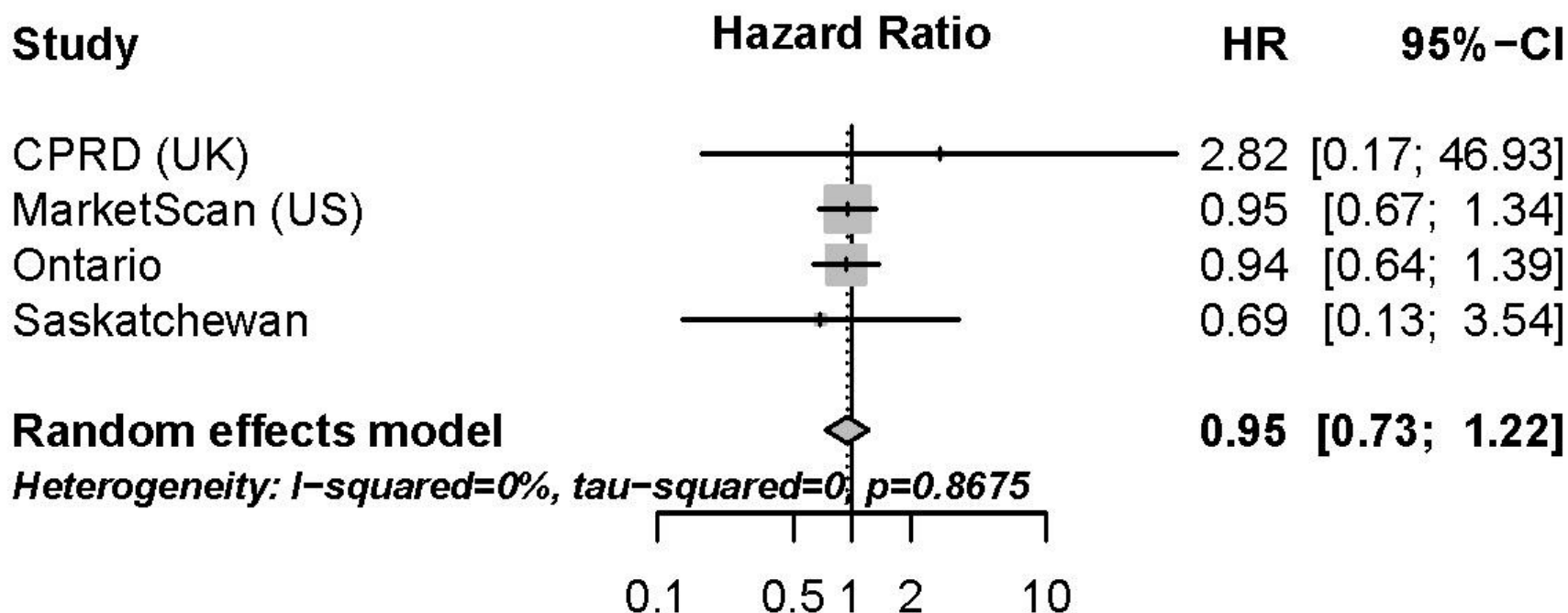
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S13. Forest plot of the association between 366-729 of current use of incretin-based drugs and hospitalization for HF among patients with a history of HF*.



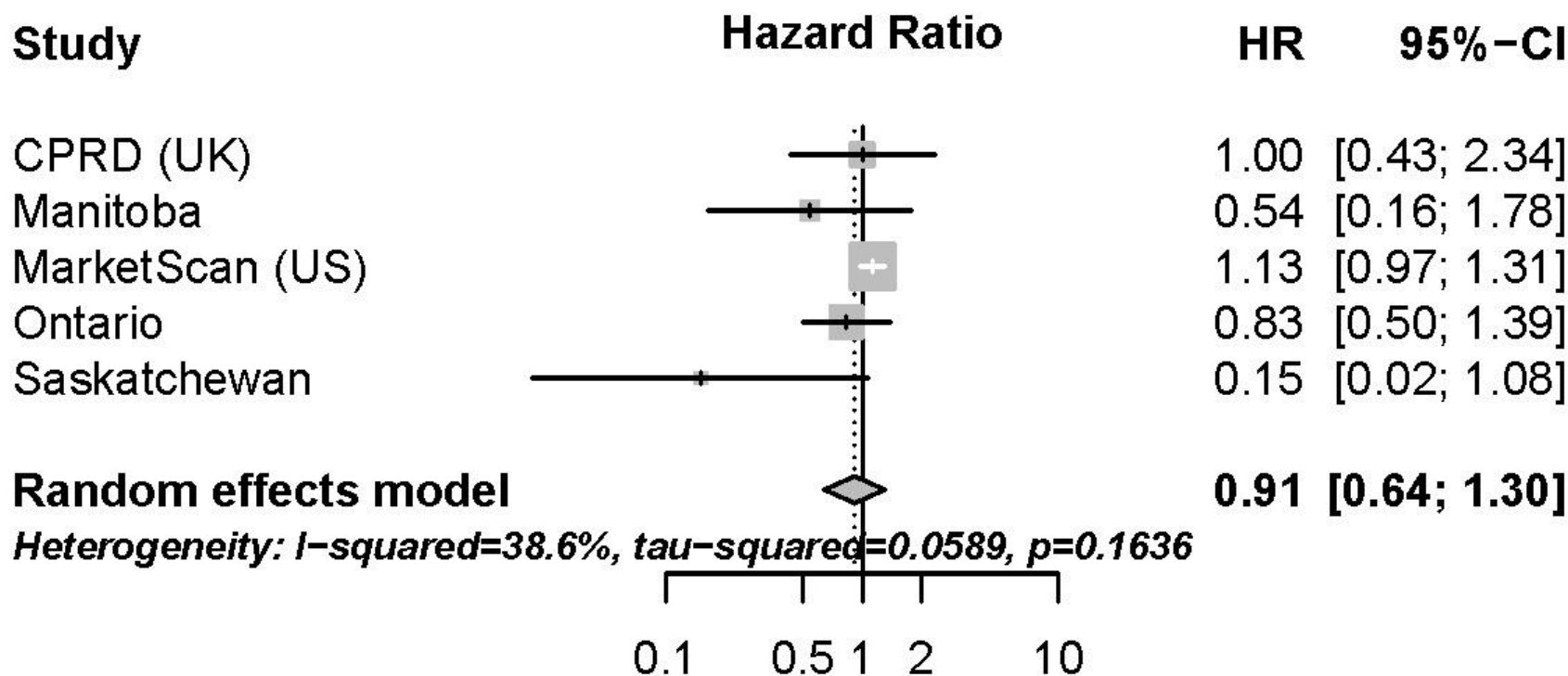
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S14. Forest plot of the association between ≥ 730 days of current use of incretin-based drugs and hospitalization for HF among patients with a history of HF*.



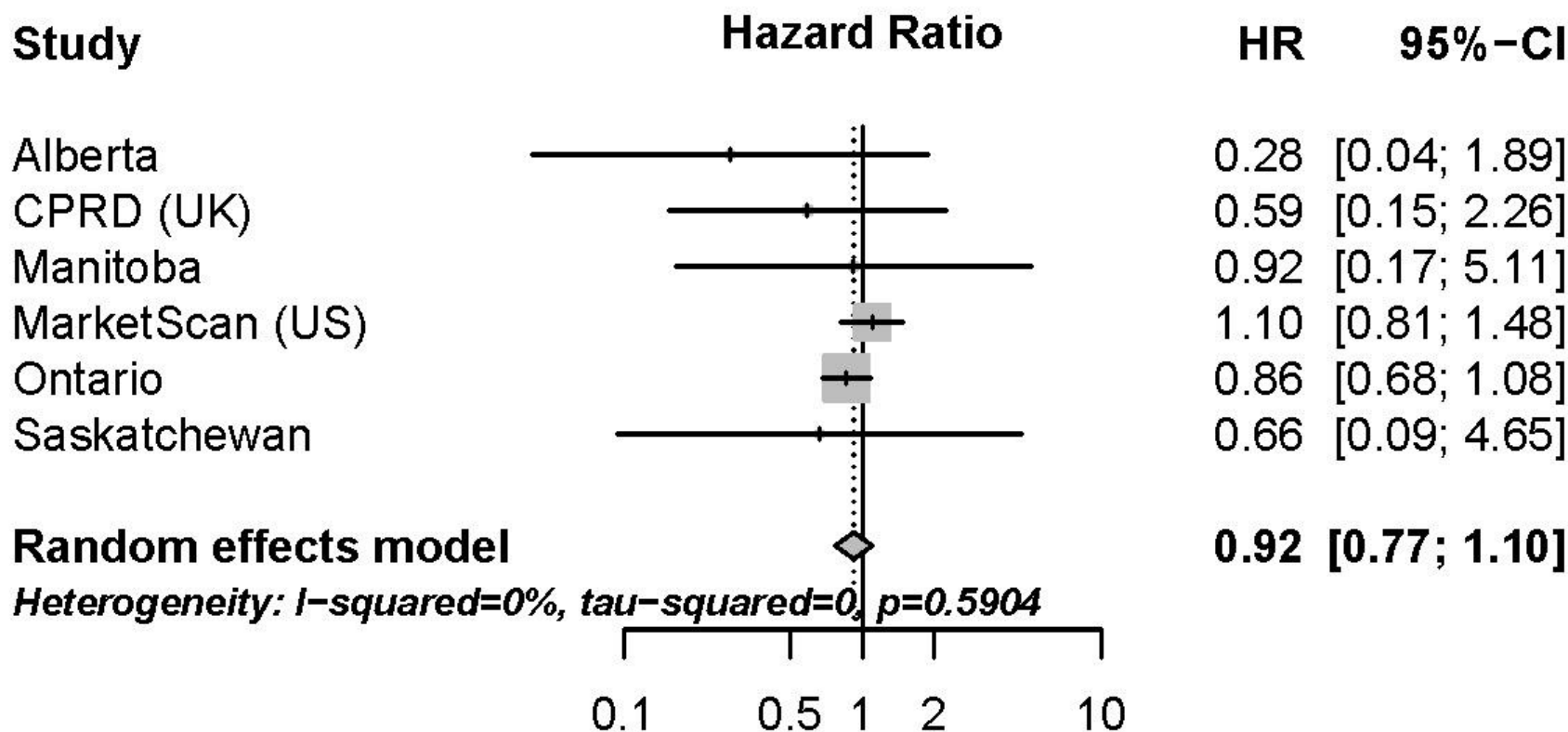
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Models in Alberta and Manitoba did not converge, and these sites were therefore excluded from this analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S15. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of MI but with a history of HF*.



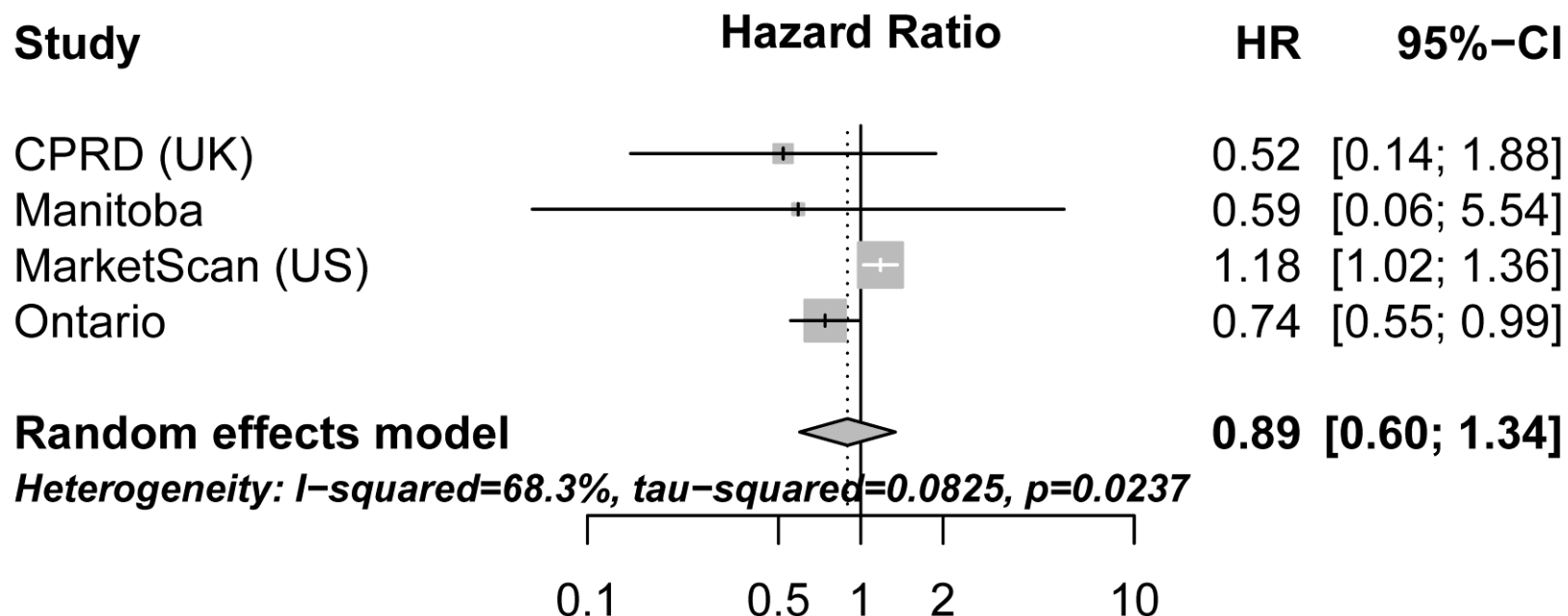
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta was excluded from this analysis as the model did not converge. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S16. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of MI and HF*.



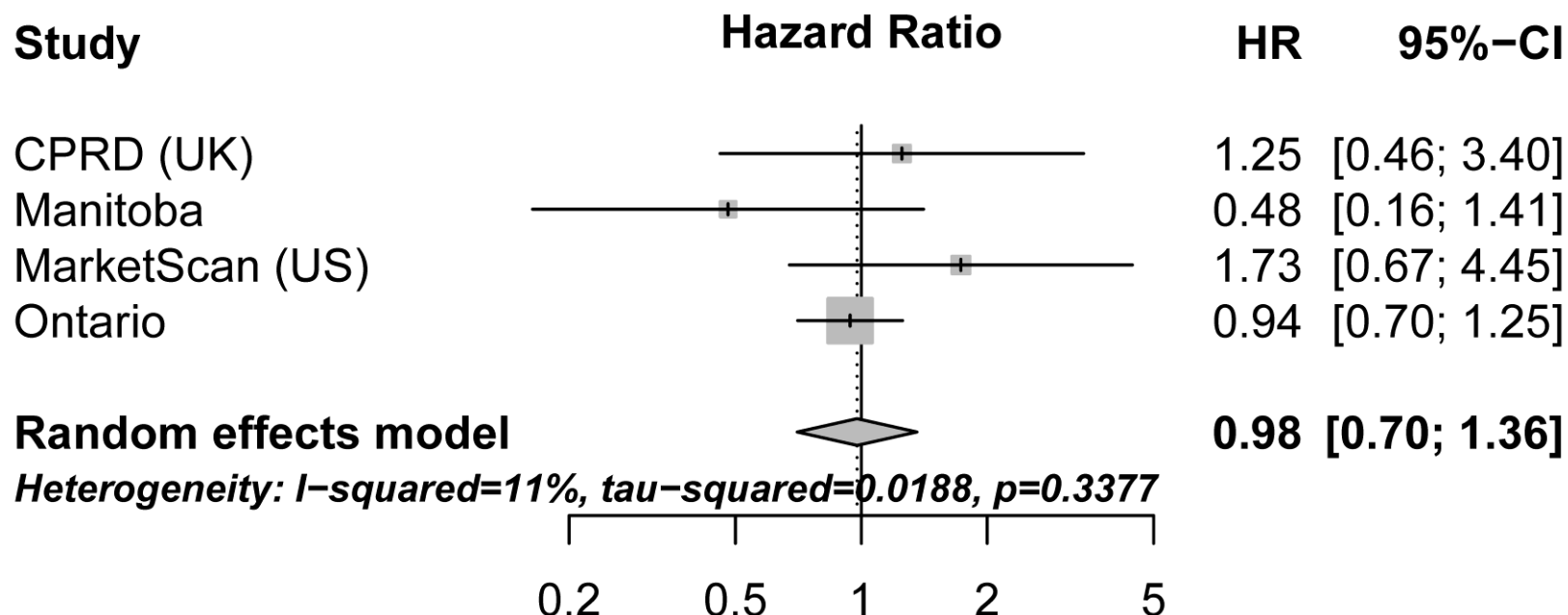
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S17. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF and a duration of treated diabetes at index date of less than five years*.



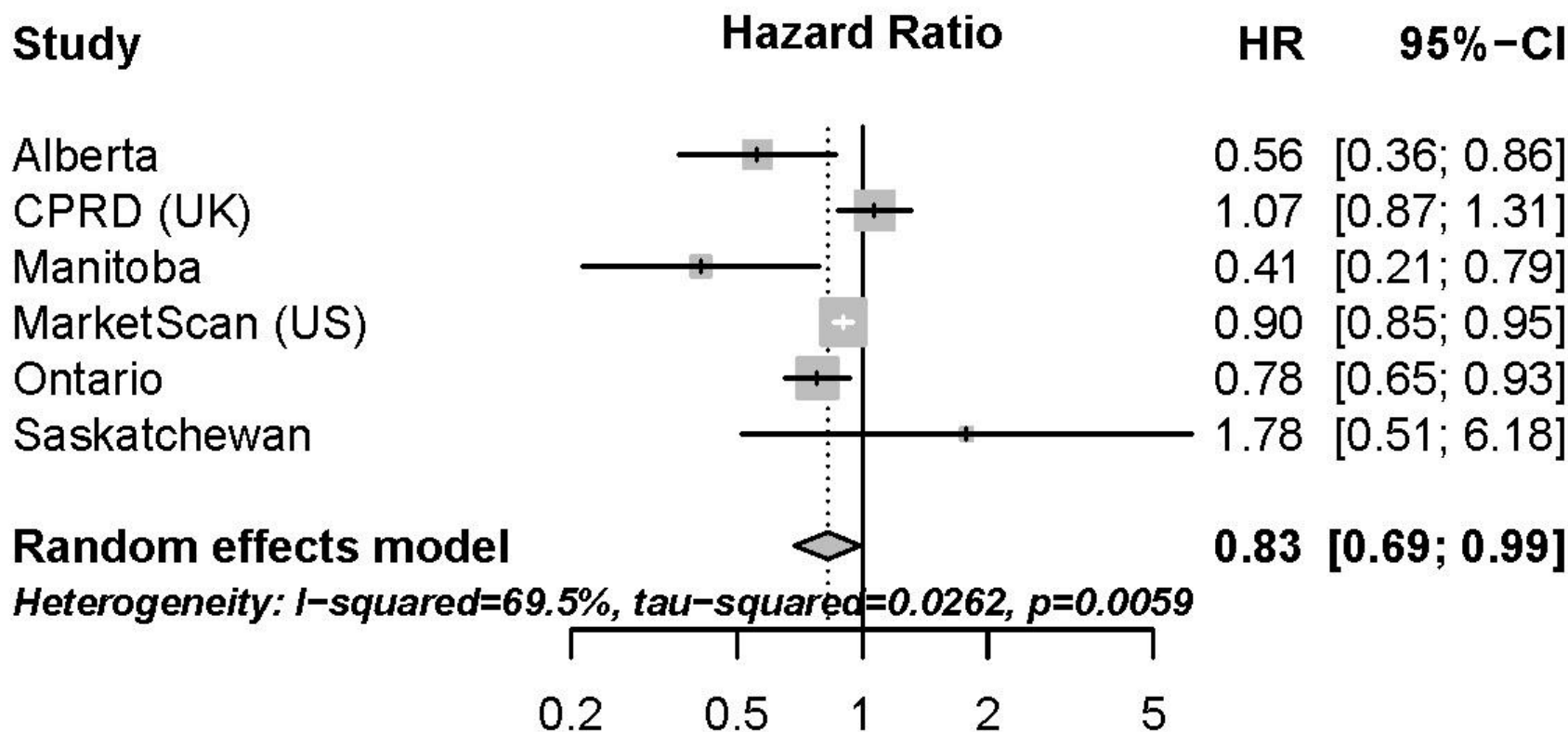
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta did not participate in this analysis as all patients had a duration of treated diabetes of less than five years, preventing the examination of the interaction. Saskatchewan was excluded due to sparse data. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S18. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF and a duration of treated diabetes at index date of five years or more*.



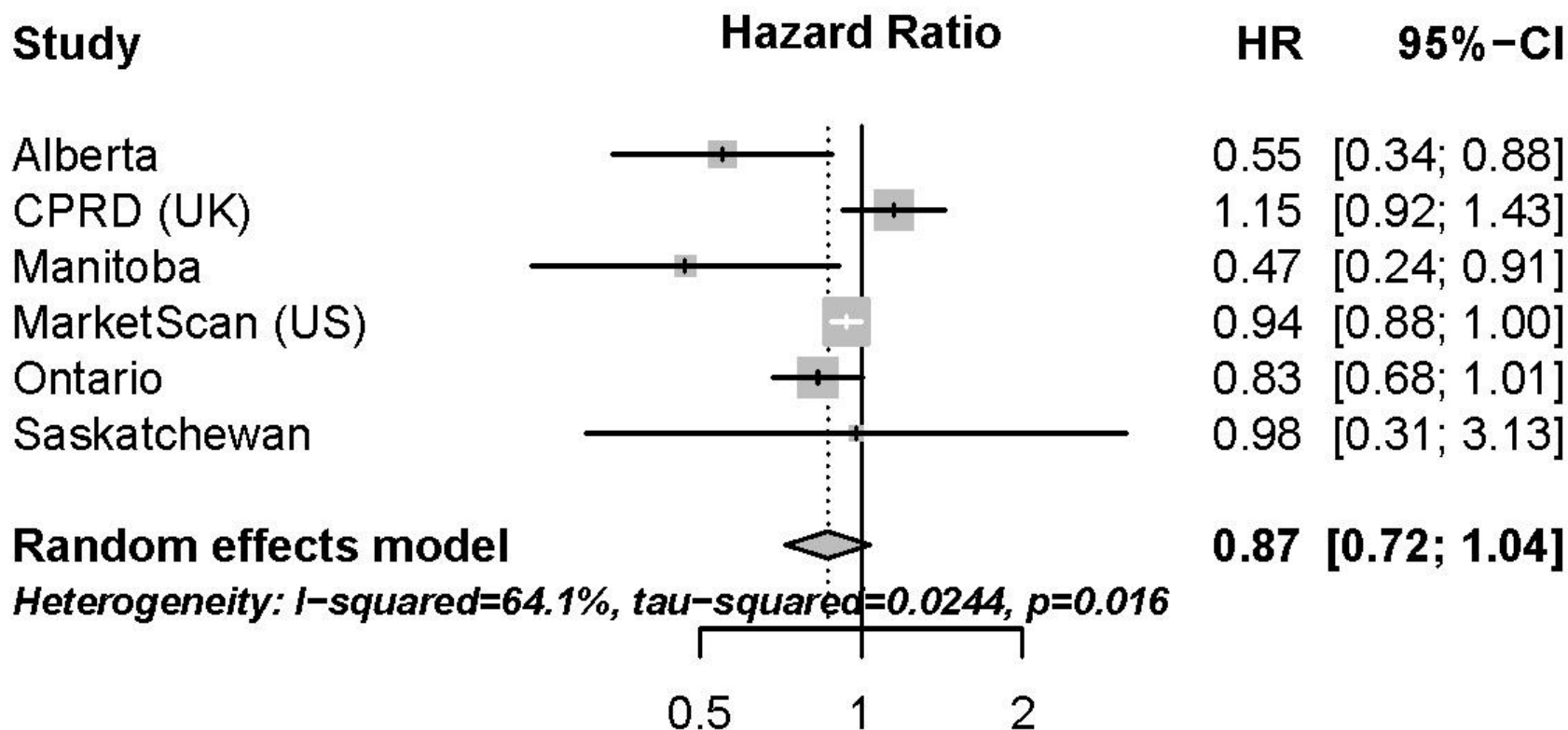
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Alberta did not participate in this analysis as all patients had a duration of treated diabetes of less than five years, preventing the examination of the interaction. Saskatchewan was excluded due to sparse data. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S19. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, using metformin-sulfonylureas combination therapy as the reference group*.



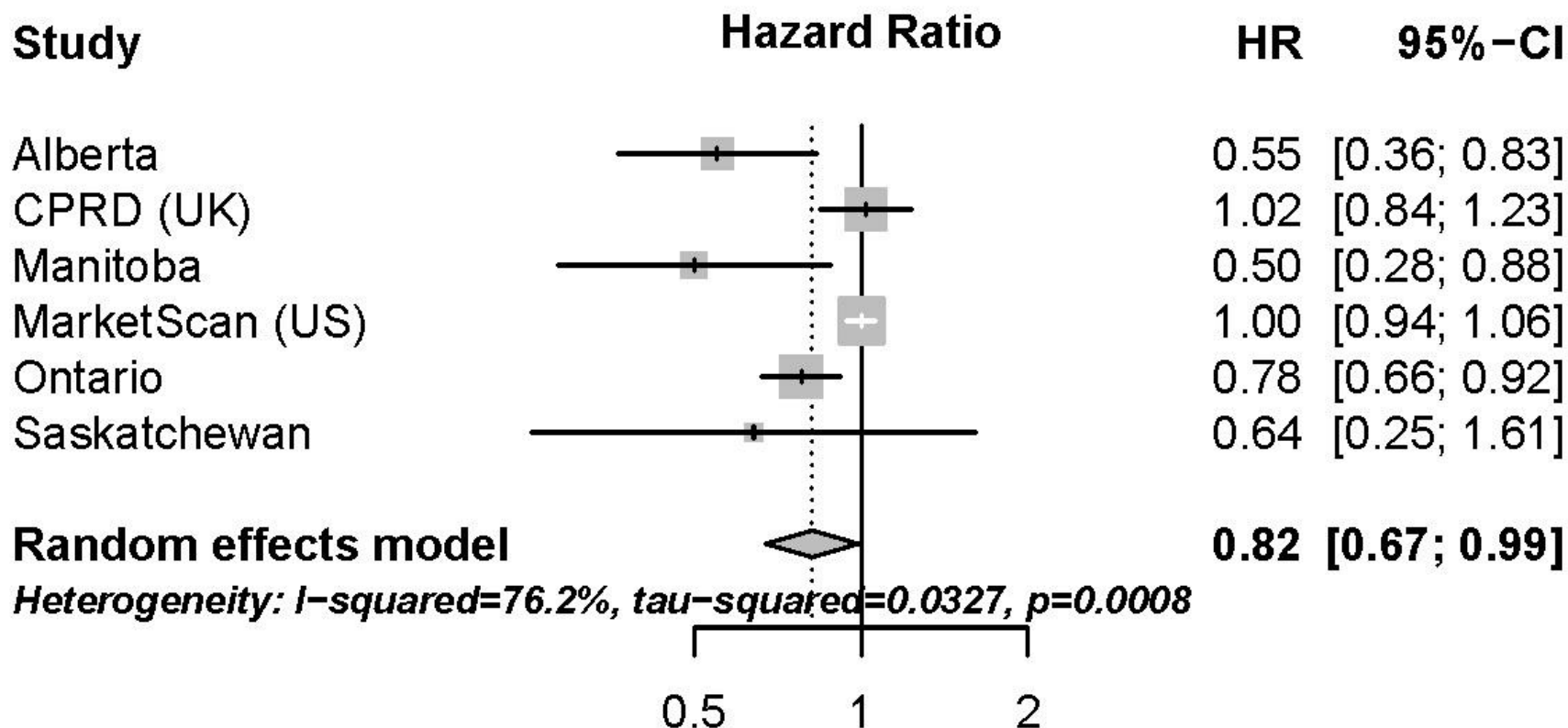
* The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S20. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, using a grace period of 0 days in our definition of current use*.



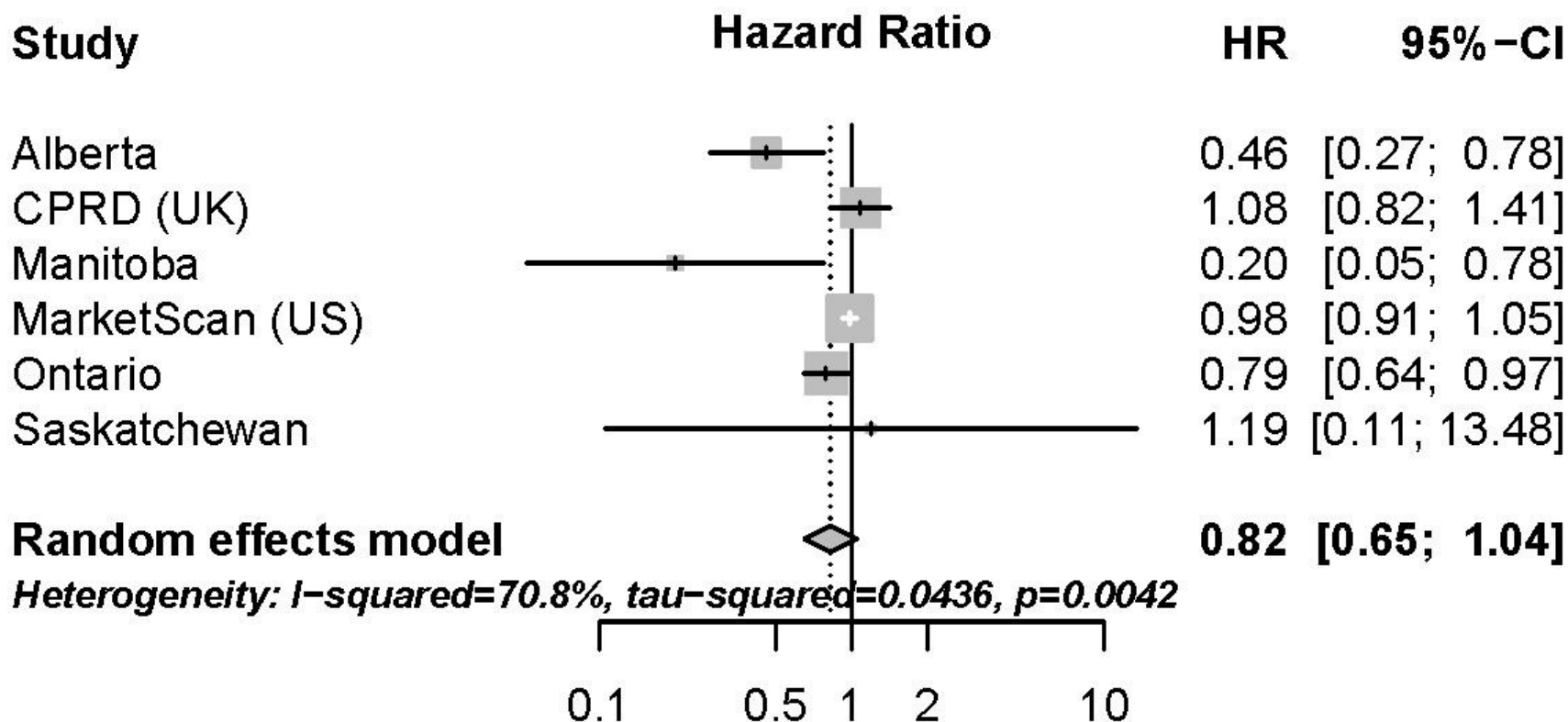
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S21. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, using a grace period of 90 days in our definition of current use*.



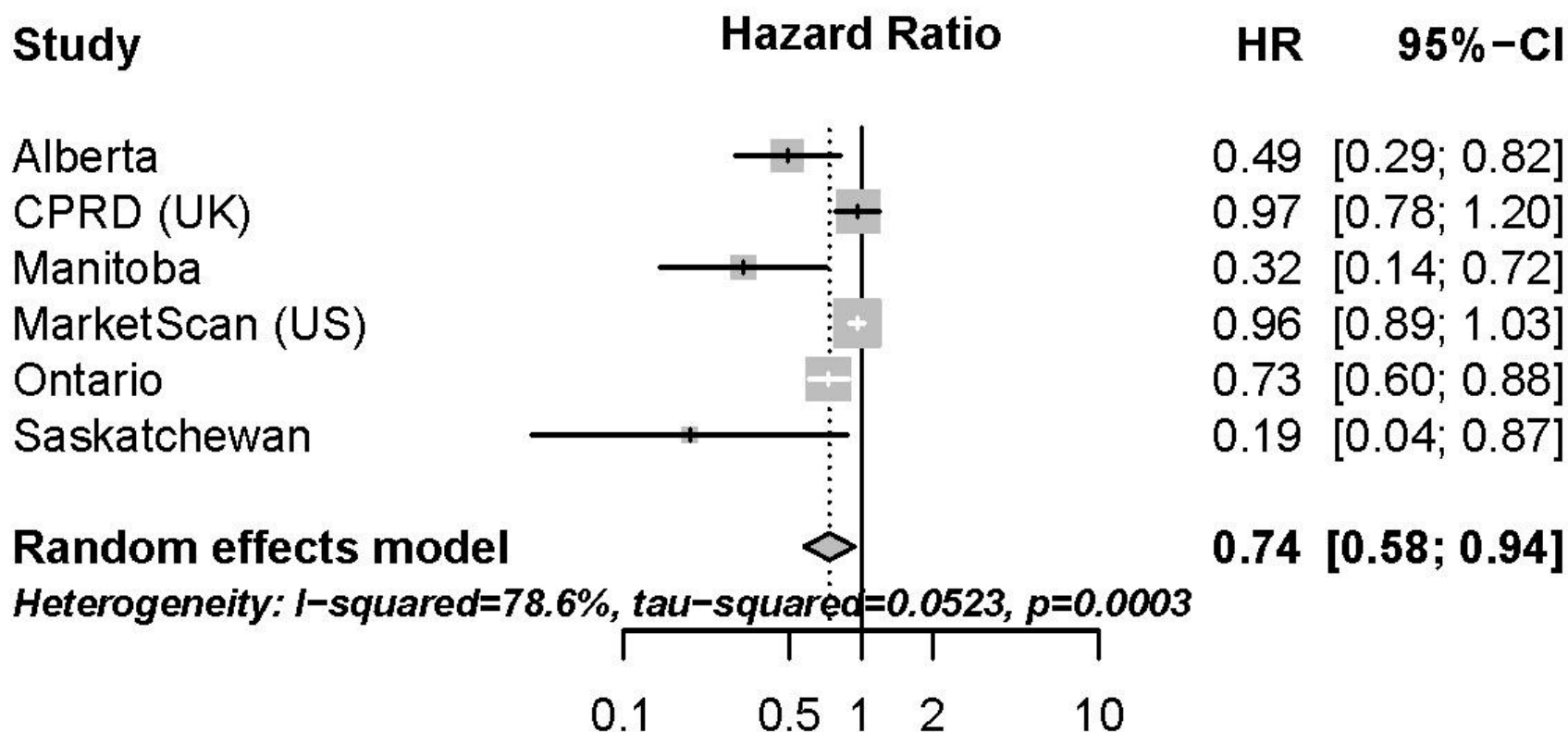
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S22. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, excluding patients with previous use of insulin or thiazolidinediones and censoring upon the use of these drugs during follow-up*.



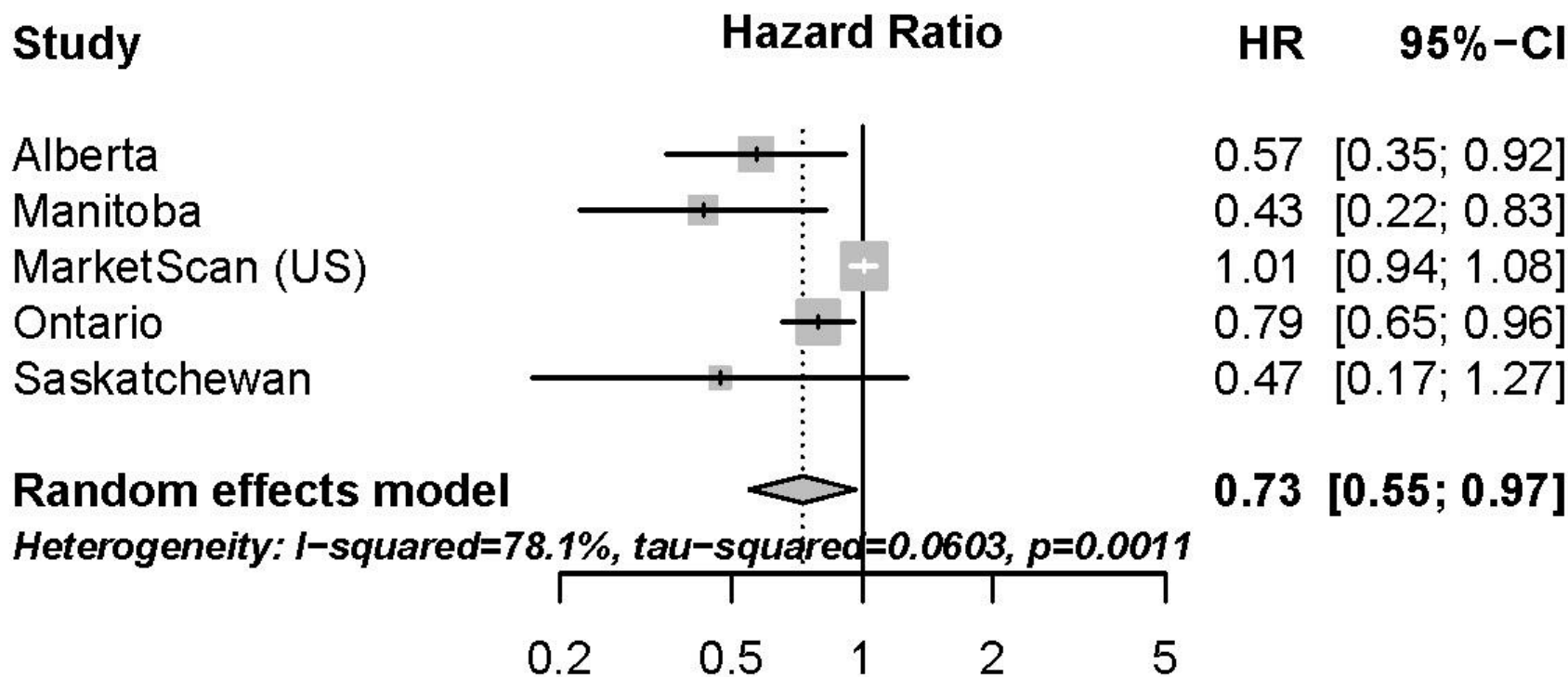
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S23. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, with adjustment for covariates at the index date rather than study cohort entry*.



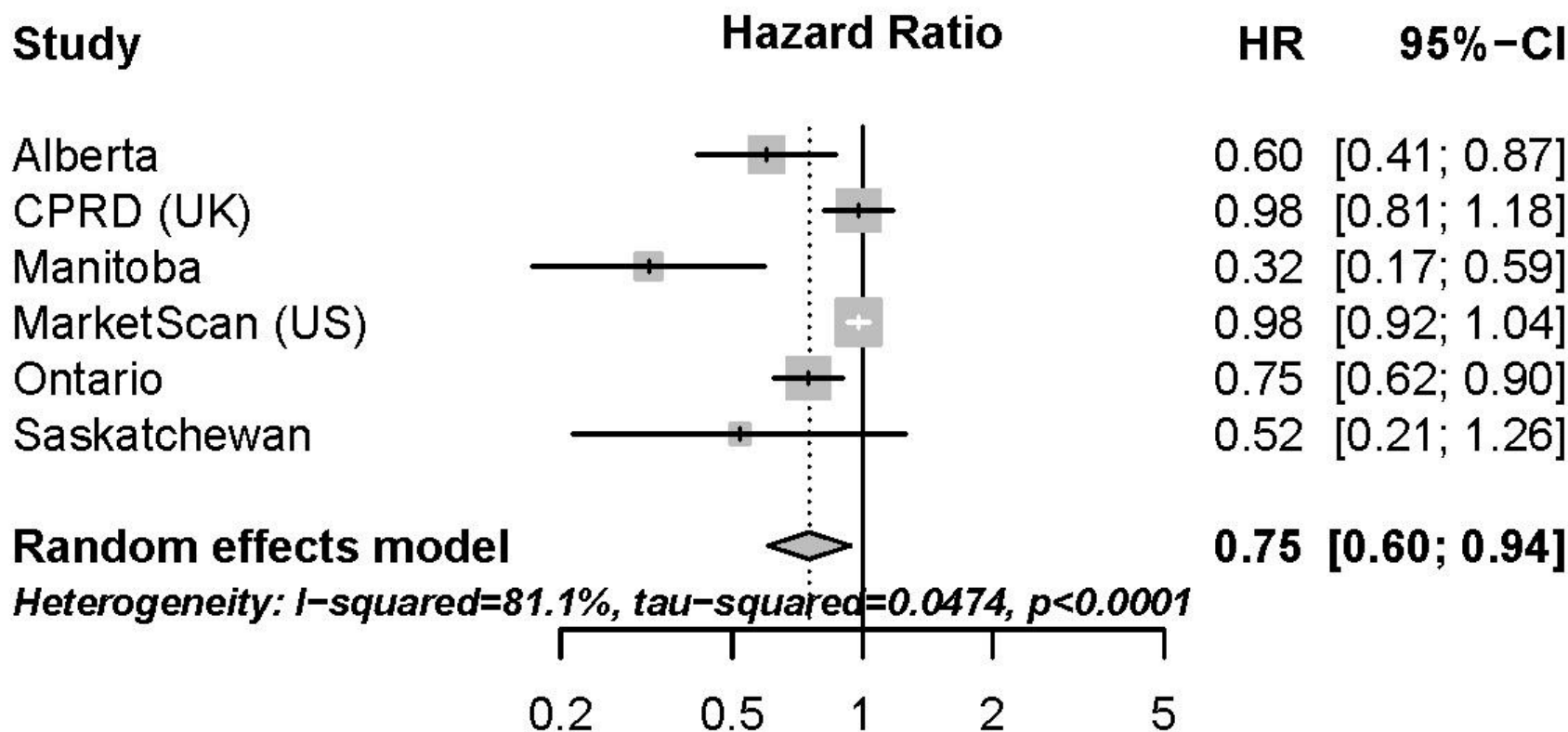
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S24. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, with further adjustment for pre-cohort entry use of antidiabetic drugs*.



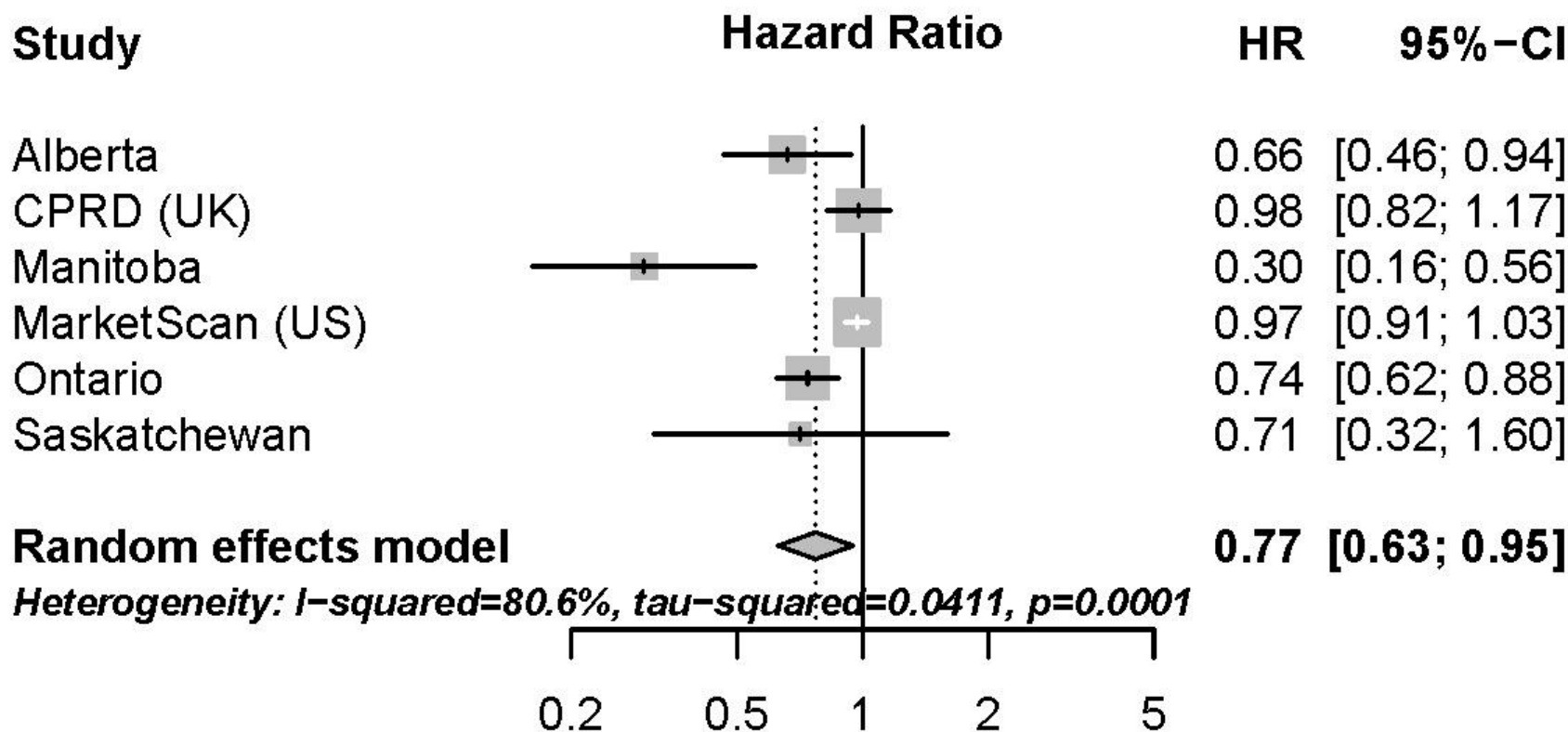
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. The model did not converge in the CPRD, which was thus excluded from this analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S25. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, with a reduced list of covariates included in the model (Reduced model #1) *.



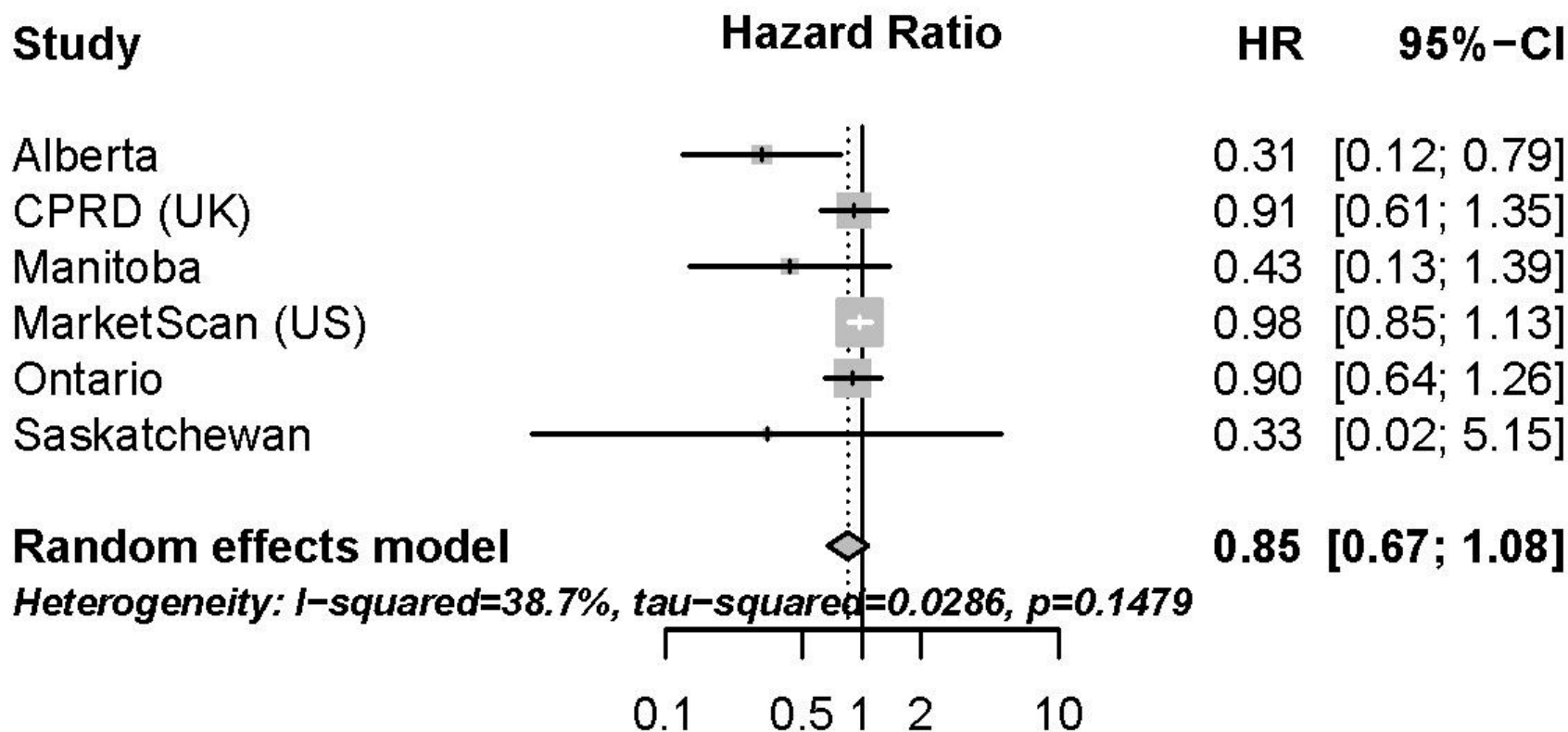
* In this reduced model, a composite microvascular complications variable was used instead of its individual components, categorical variables were converted to their continuous counterparts where possible, and insulin, oral antidiabetic drug monotherapy, and not currently exposed were collapsed to a single “other exposure” category. The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S26. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, with a reduced list of covariates included in the model (Reduced model #2) *.



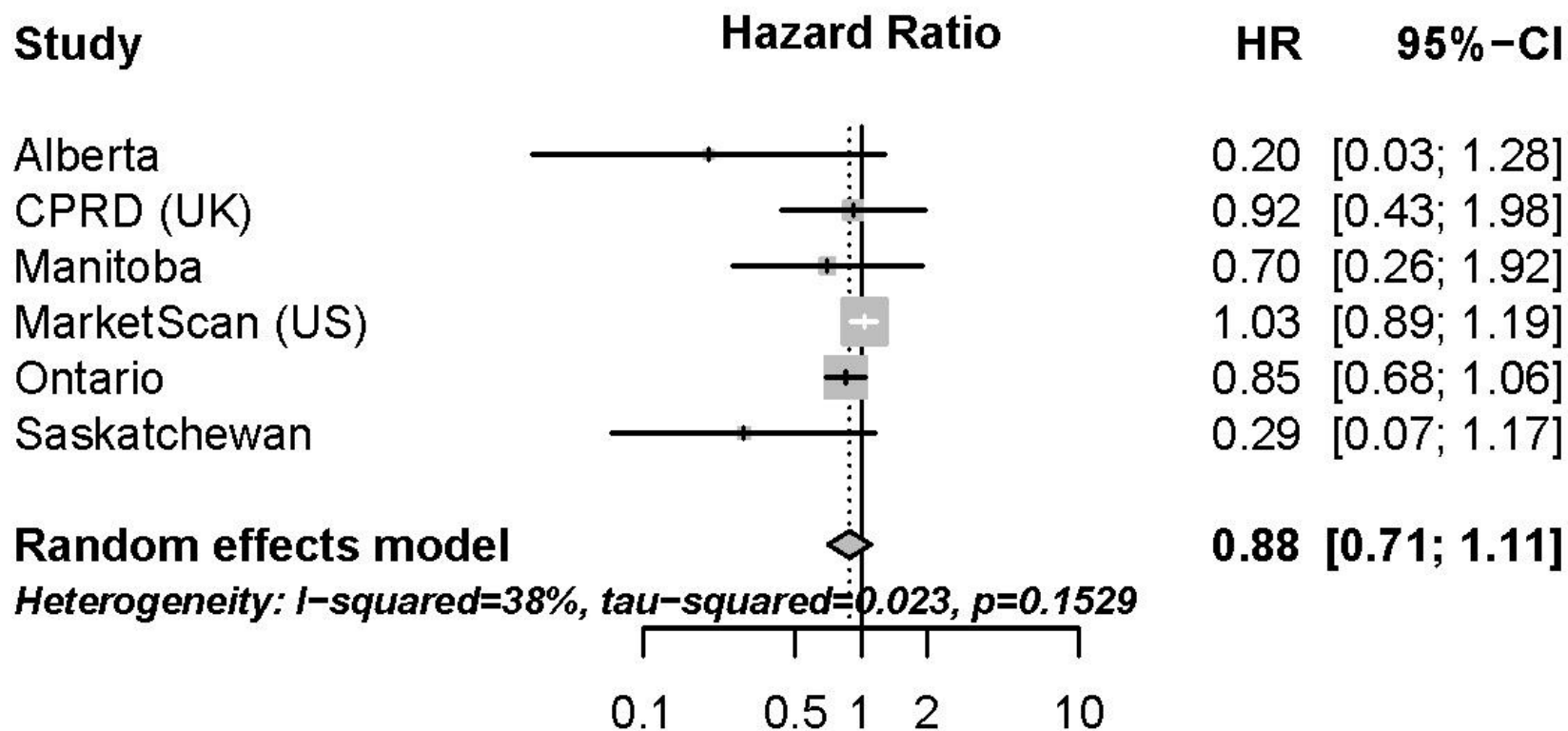
* The conditional logistic regression model only included our model only included exposure (current exposure to incretin-based drugs, current exposure to oral antidiabetic combinations, and other exposure) and the Deyo version of the Charlson comorbidity index⁴. The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S27. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, with cases restricted to those hospitalized with a primary or most responsible diagnosis of HF*.



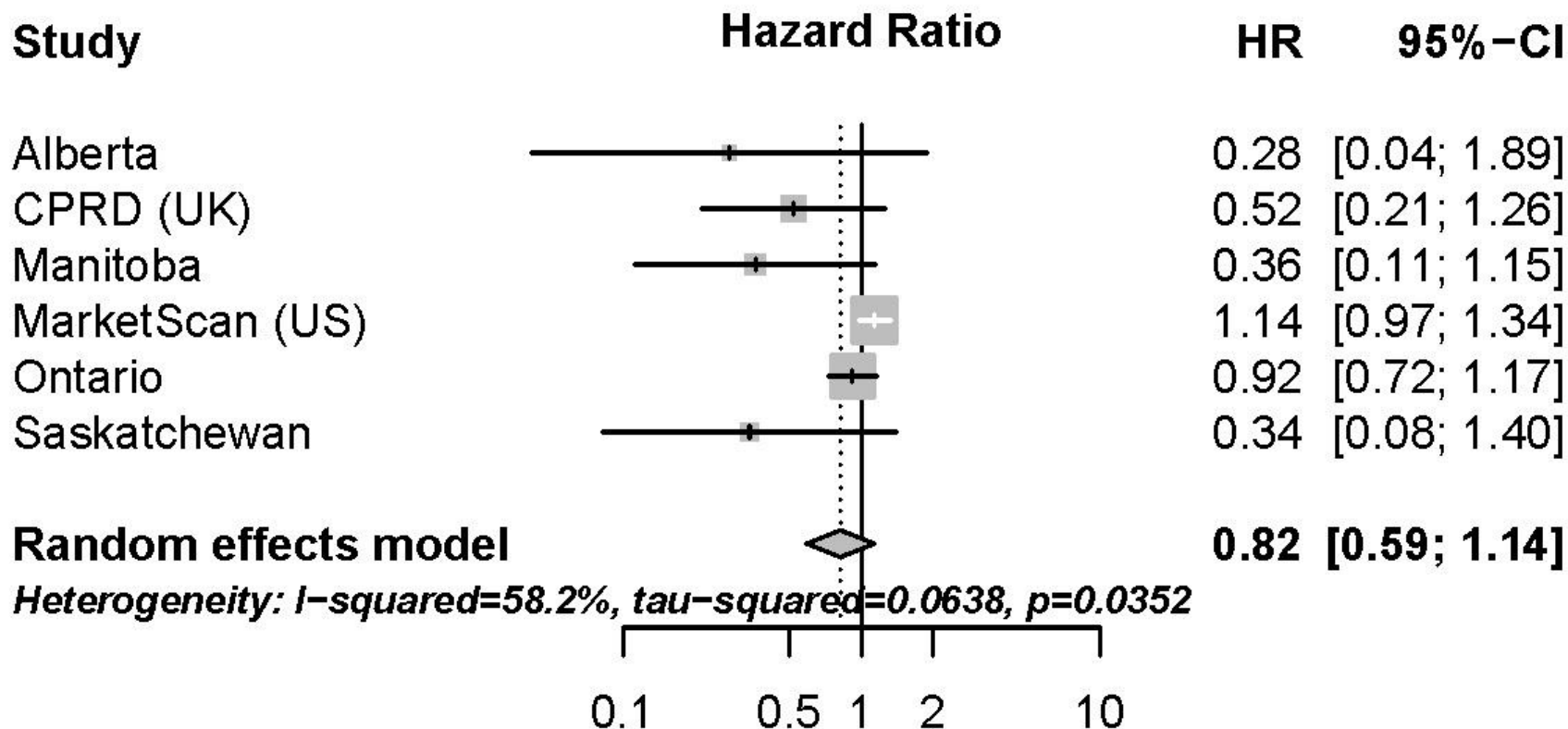
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S28. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, using metformin-sulfonylureas combination therapy as the reference group*.



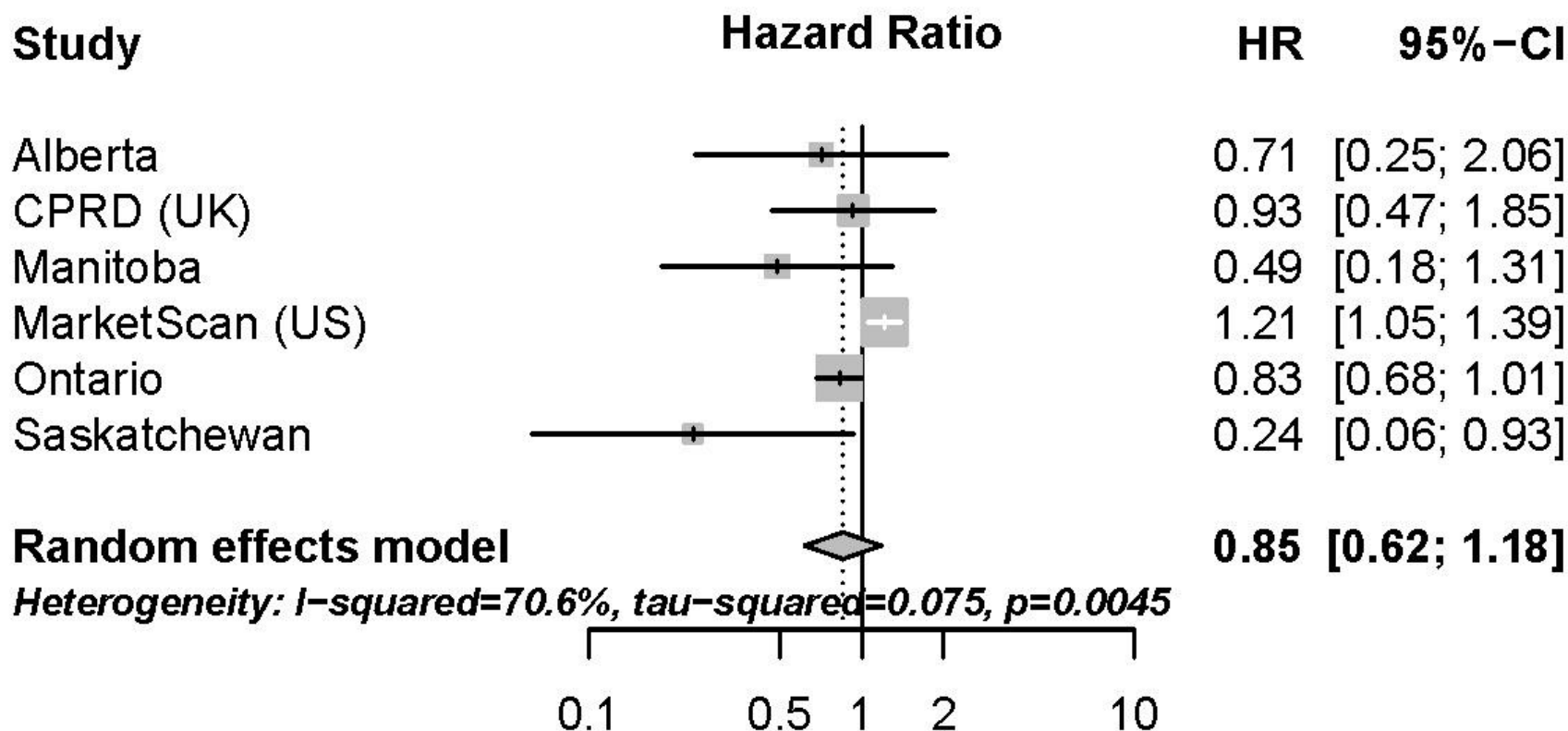
* The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S29. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, using a grace period of 0 days in our definition of current use*.



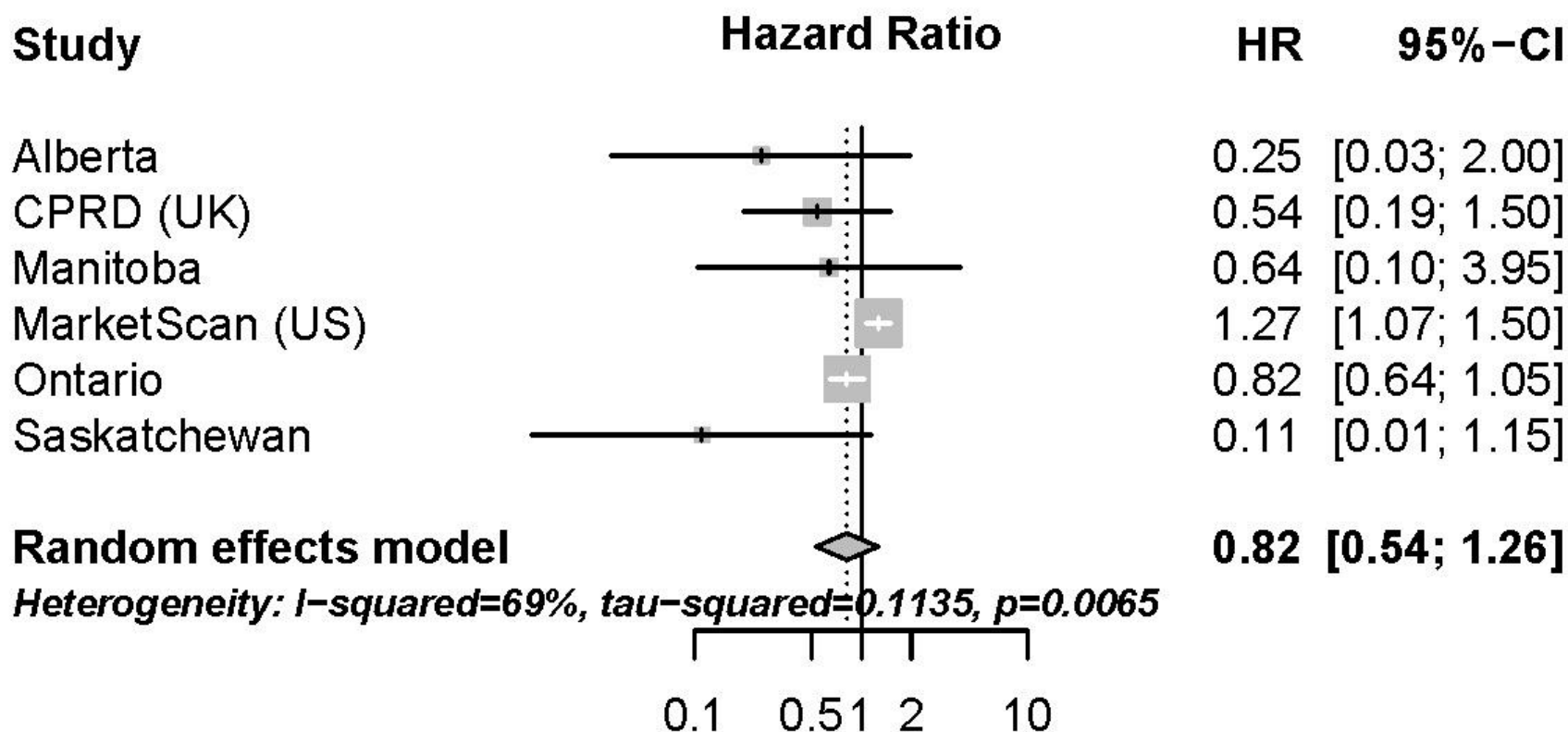
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S30. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, using a grace period of 90 days in our definition of current use*.



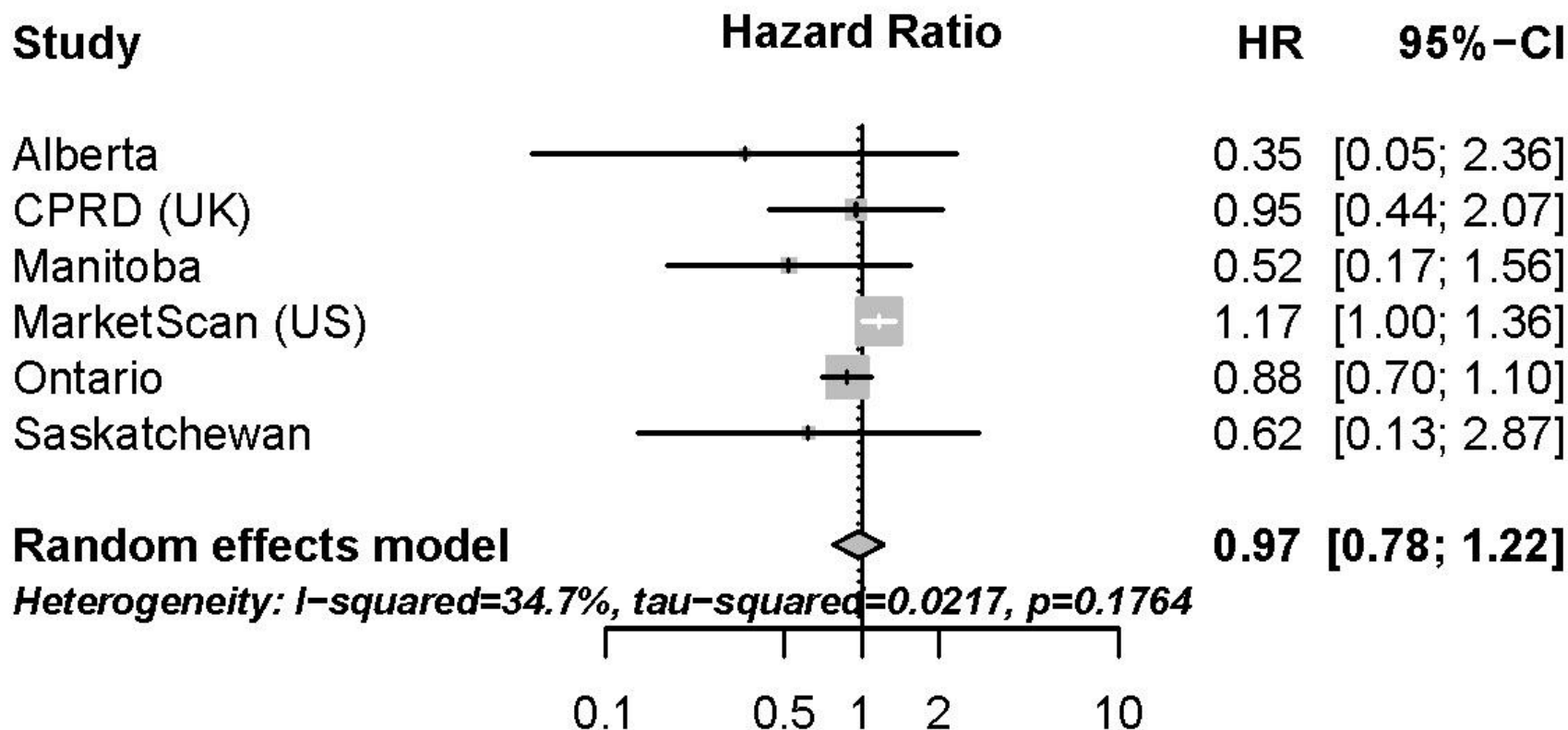
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S31. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, excluding patients with previous use of insulin or thiazolidinediones and censoring upon the use of these drugs during follow-up*.



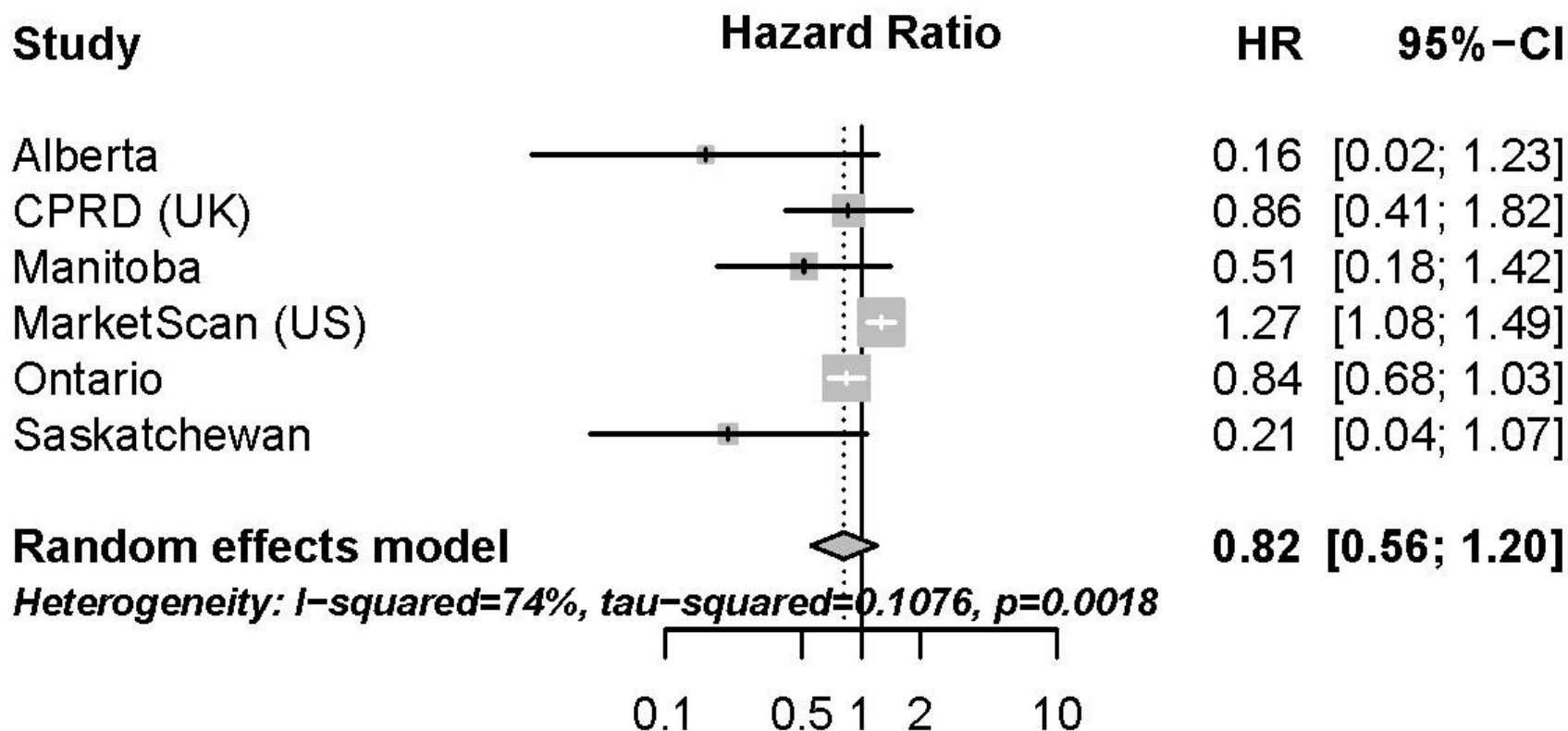
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S32. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, with adjustment for covariates at the index date rather than study cohort entry*.



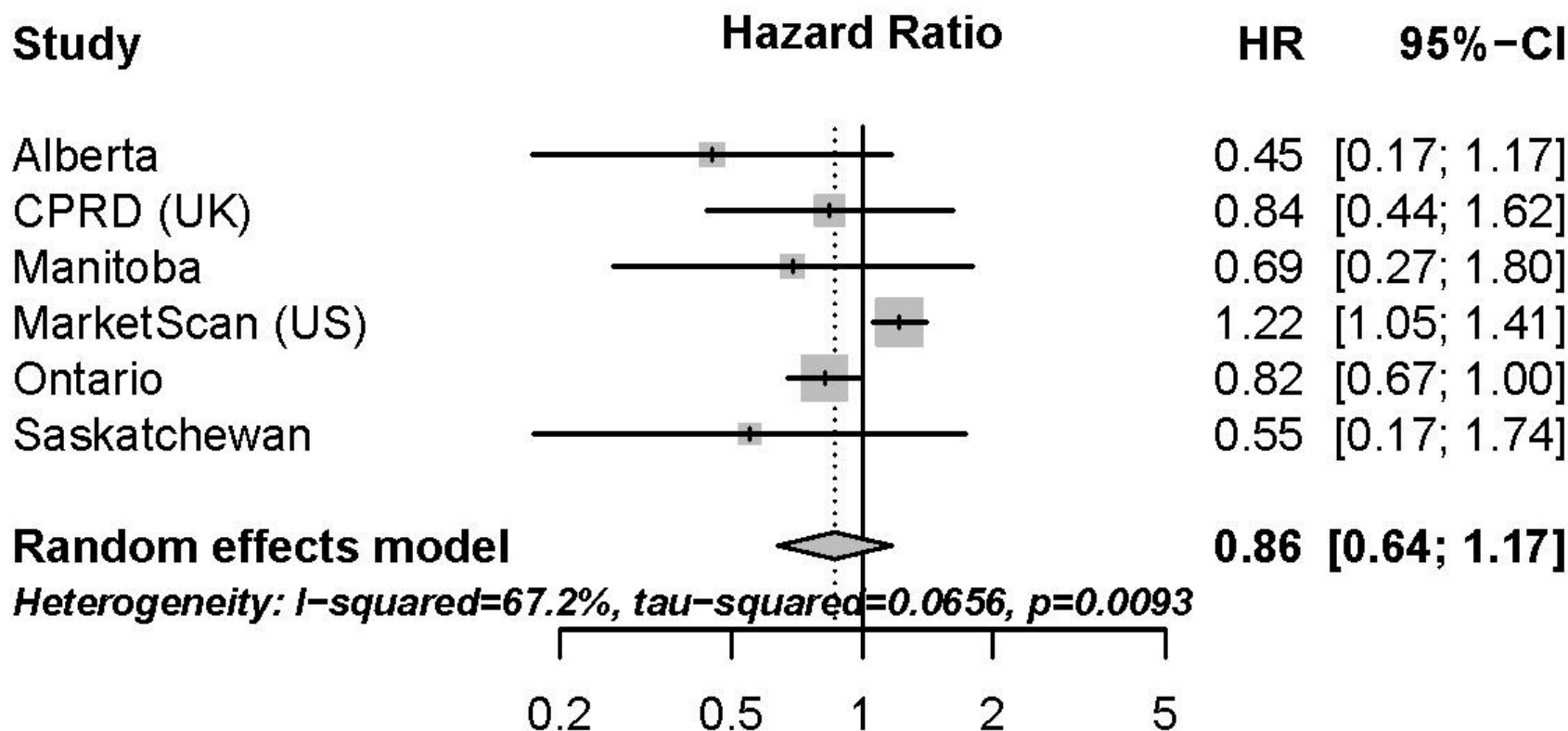
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S33. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, with further adjustment for pre-cohort entry use of antidiabetic drugs*.



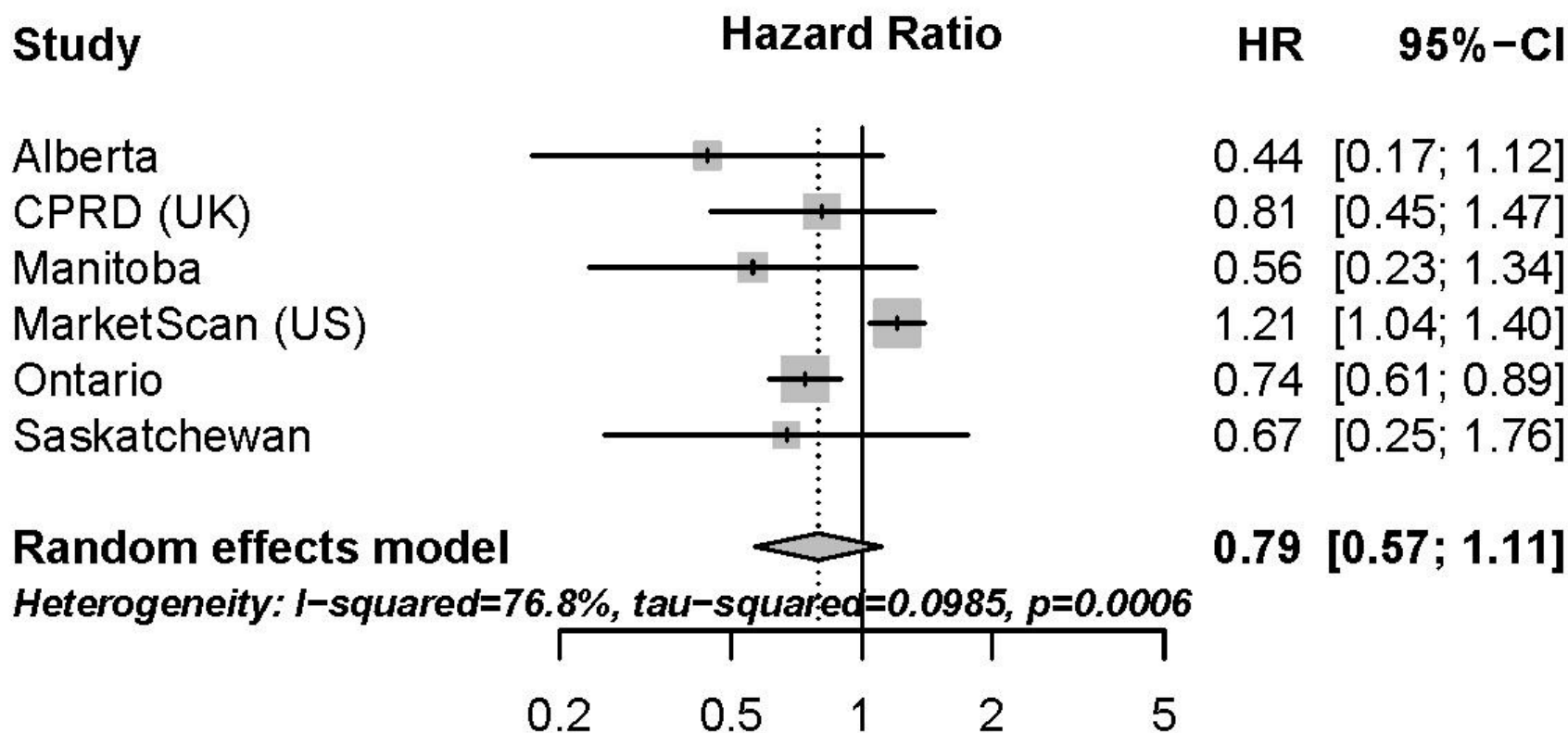
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S34. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, with a reduced list of covariates included in the model (Reduced model #1) *.



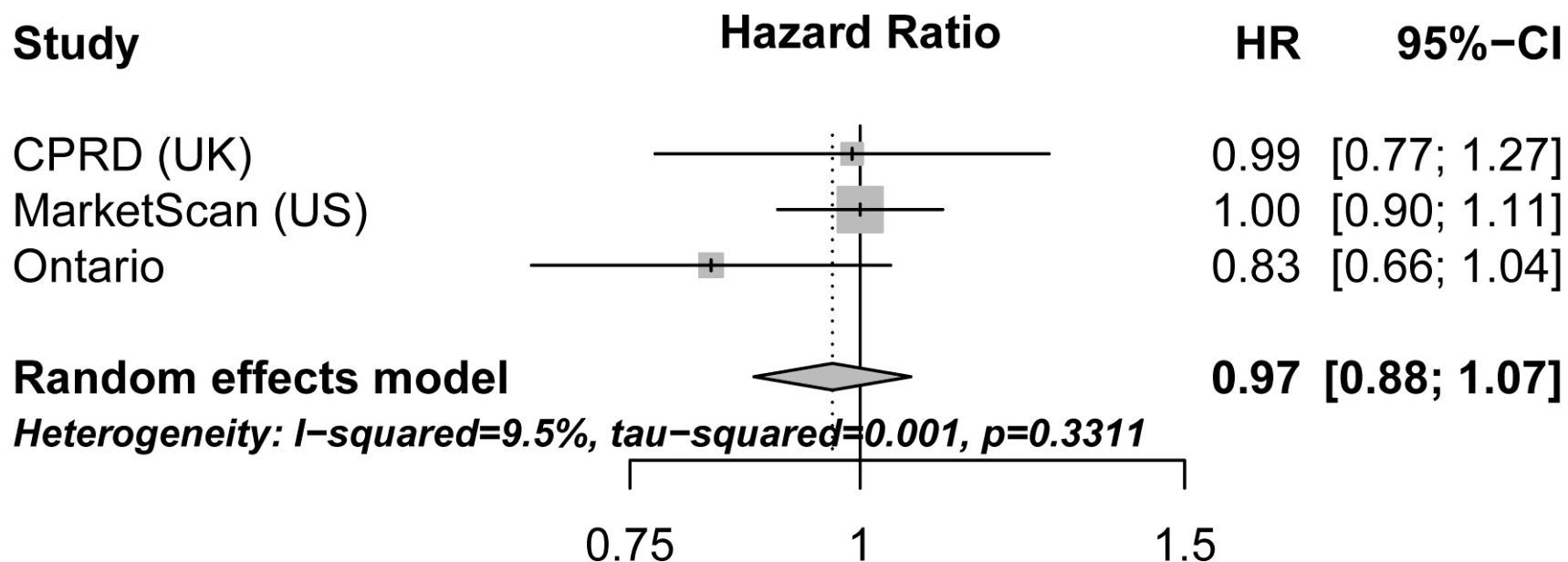
* In this reduced model, a composite microvascular complications variable was used instead of its individual components, categorical variables were converted to their continuous counterparts where possible, and insulin, oral antidiabetic drug monotherapy, and not currently exposed were collapsed to a single “other exposure” category. The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S35. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, with a reduced list of covariates included in the model (Reduced model #2) *.



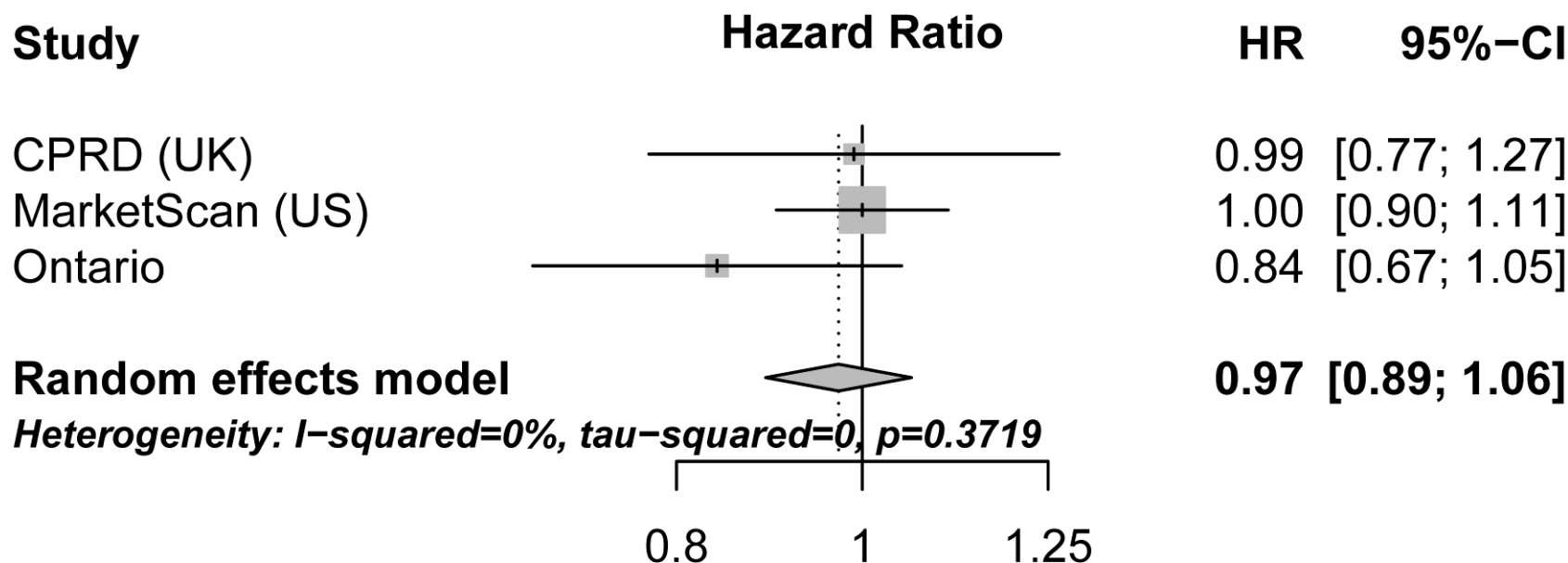
* The conditional logistic regression model only included exposure (current exposure to incretin-based drugs, current exposure to oral antidiabetic combinations, and other exposure) and the Deyo version of the Charlson comorbidity index⁴. The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S36. Forest plot of the association between use of incretin-based drugs and hospitalization for HF among patients with no history of HF in a propensity-matched cohort with a maximum follow-up of 2 years*.



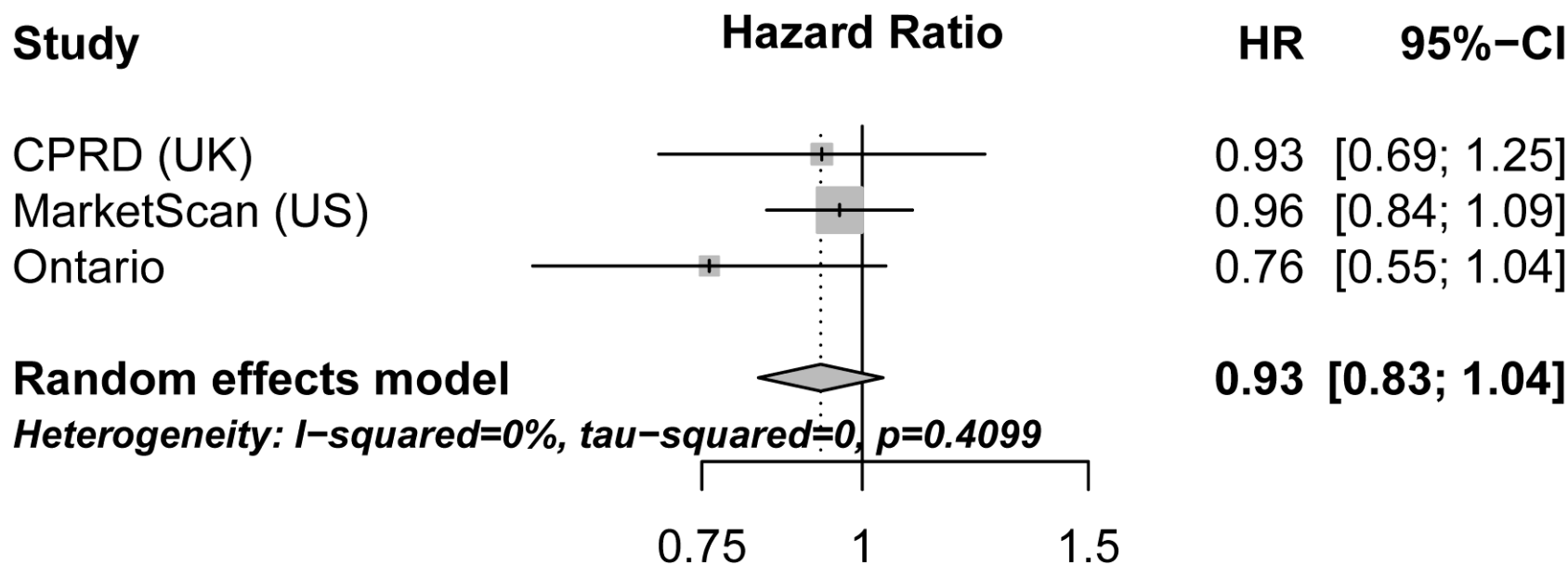
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the Cox proportional hazards models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S37. Forest plot of the association between use of incretin-based drugs and hospitalization for HF among patients with no history of HF in a propensity-matched cohort with analyses that accounted for the competing risk of mortality with a maximum follow-up of 2 years*.



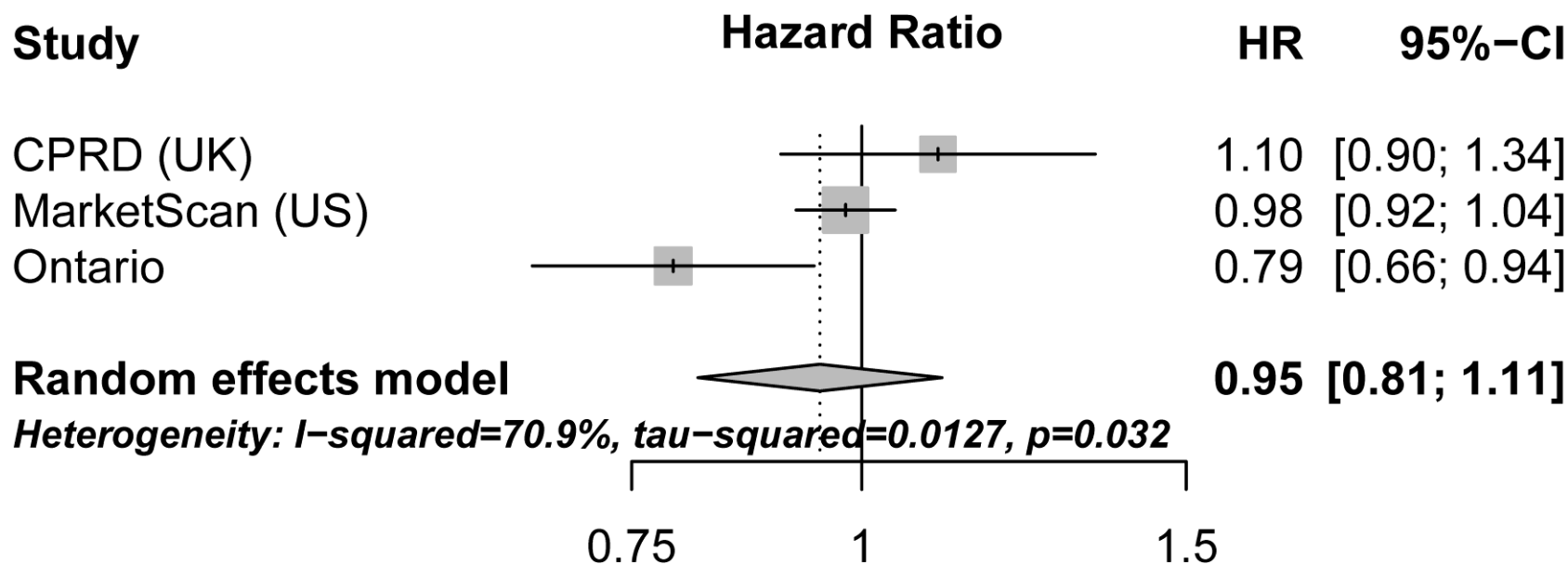
* The reference category is current use of oral antidiabetic drug combinations. Competing risks were considered using the approach described by Fine and Gray⁶. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the Cox proportional hazards models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S38. Forest plot of the association between use of incretin-based drugs and hospitalization for HF among patients with no history of HF in a propensity-matched cohort with a maximum follow-up of 1 year*.



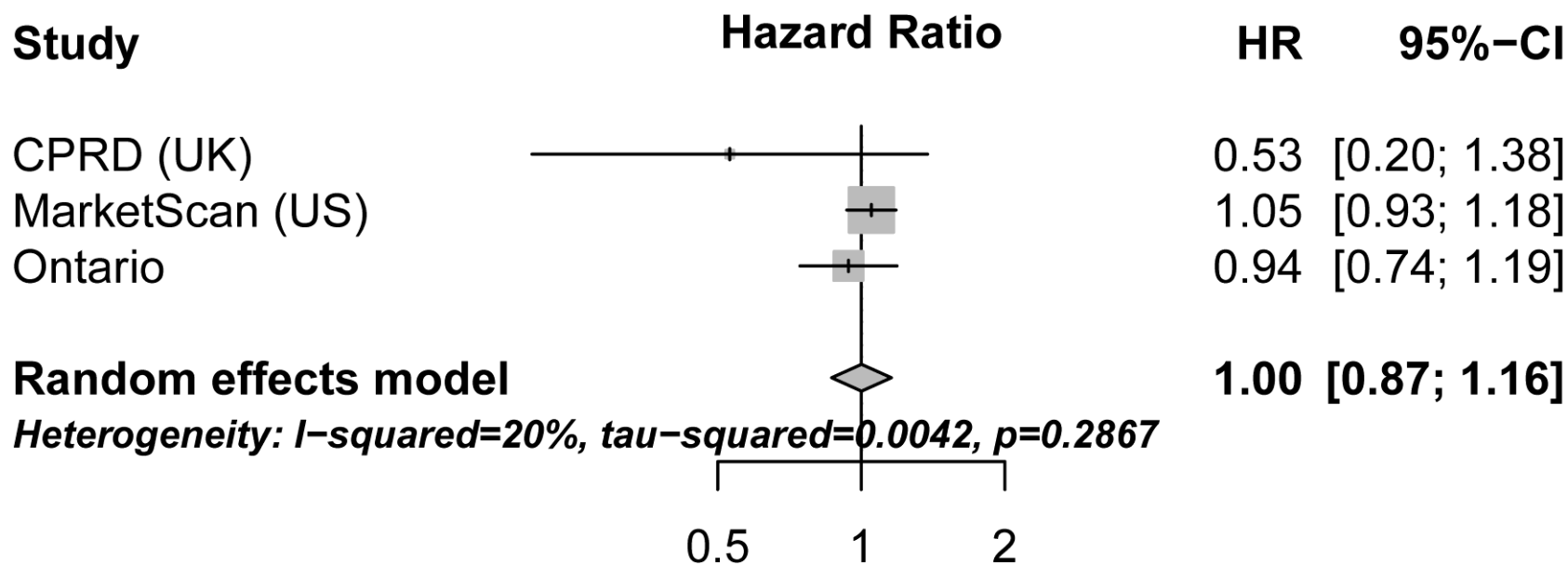
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the Cox proportional hazards models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S39. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with no history of HF, with meta-analysis of the primary nested case-control analysis restricted to the three sites participating in the propensity-matched cohort analyses*.



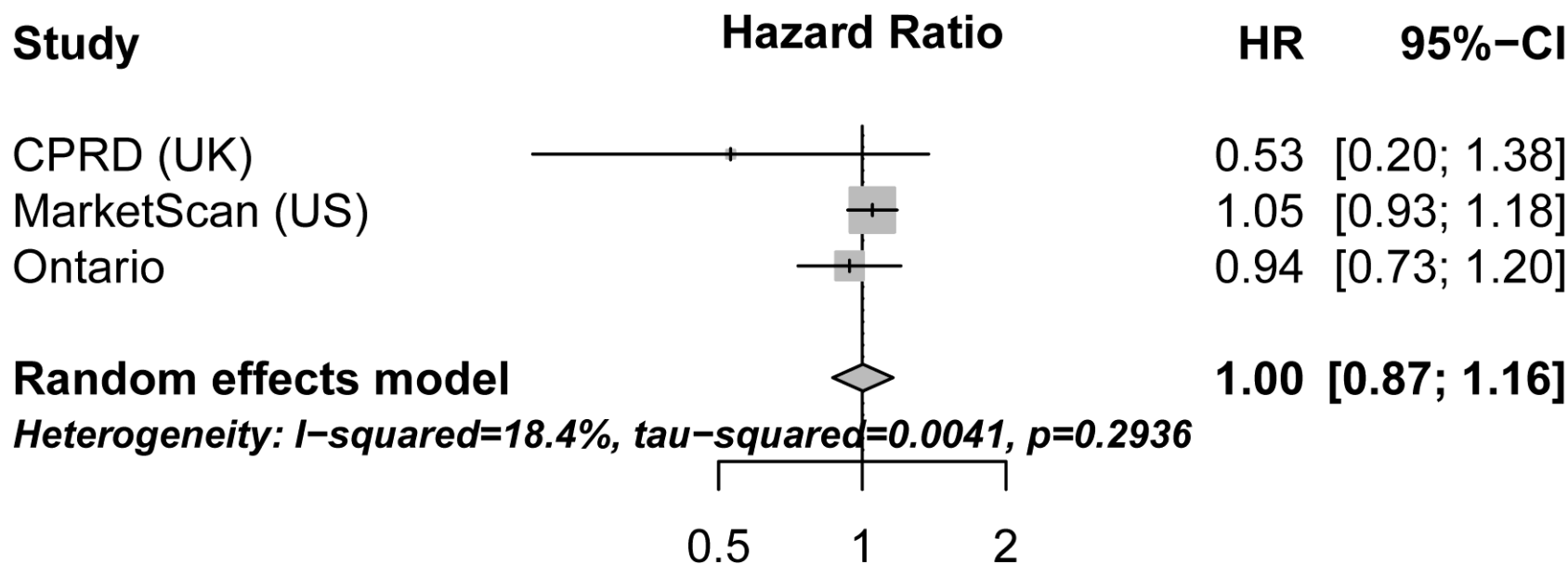
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S40. Forest plot of the association between use of incretin-based drugs and hospitalization for HF among patients with a history of HF in a propensity-matched cohort with a maximum follow-up of 2 years*.



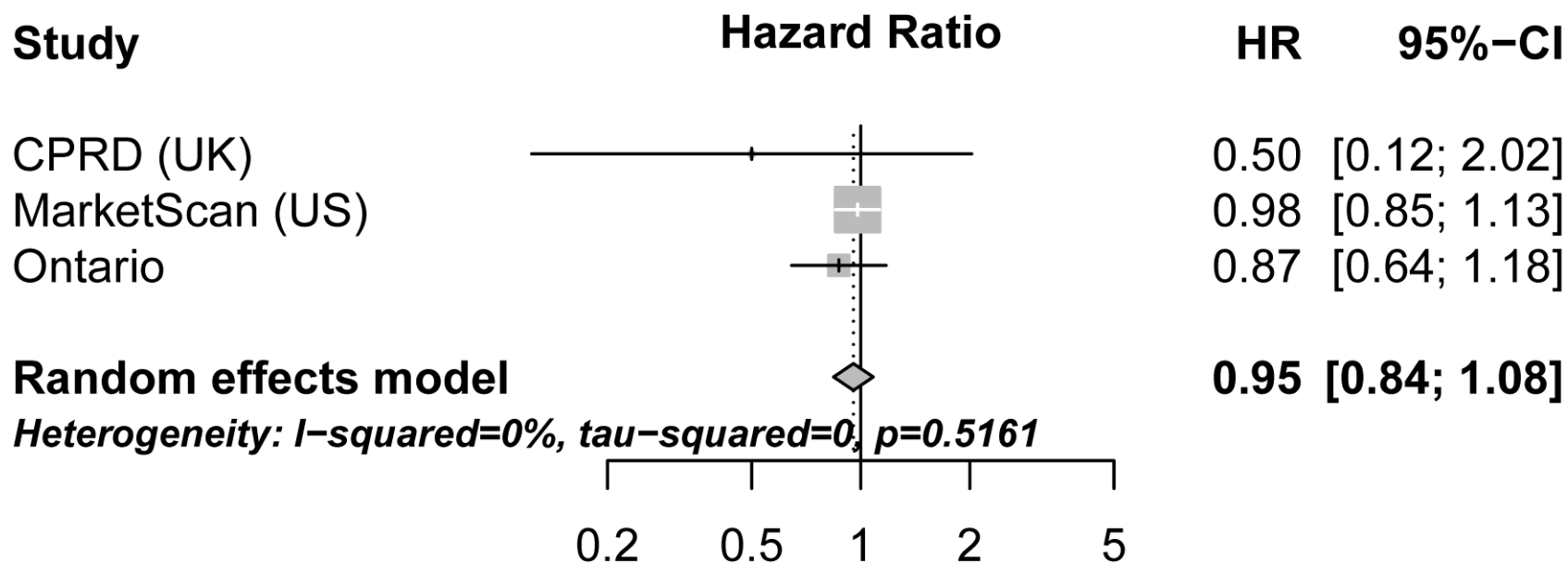
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the Cox proportional hazards models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S41. Forest plot of the association between use of incretin-based drugs and hospitalization for HF among patients with a history of HF in a propensity-matched cohort with analyses that accounted for the competing risk of mortality with a maximum follow-up of 2 years*.



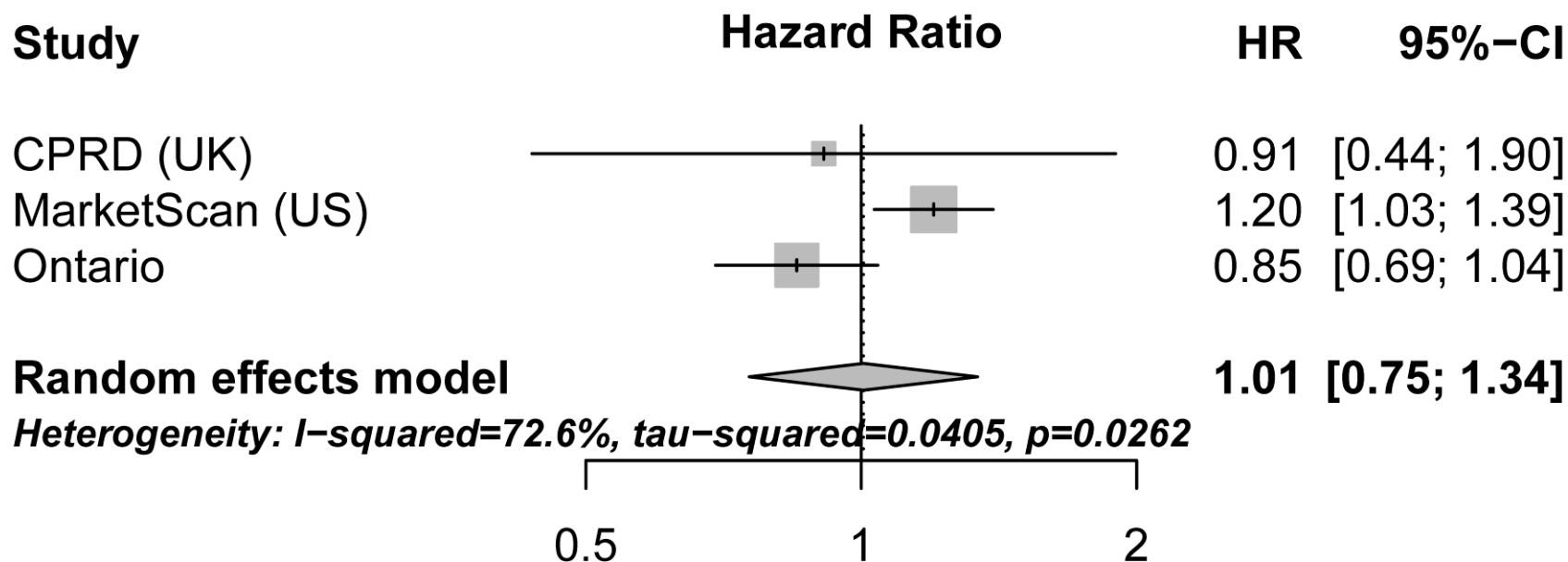
* The reference category is current use of oral antidiabetic drug combinations. Competing risks were considered using the approach described by Fine and Gray⁶. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the Cox proportional hazards models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S42. Forest plot of the association between use of incretin-based drugs and hospitalization for HF among patients with a history of HF in a propensity-matched cohort with a maximum follow-up of 1 year*.



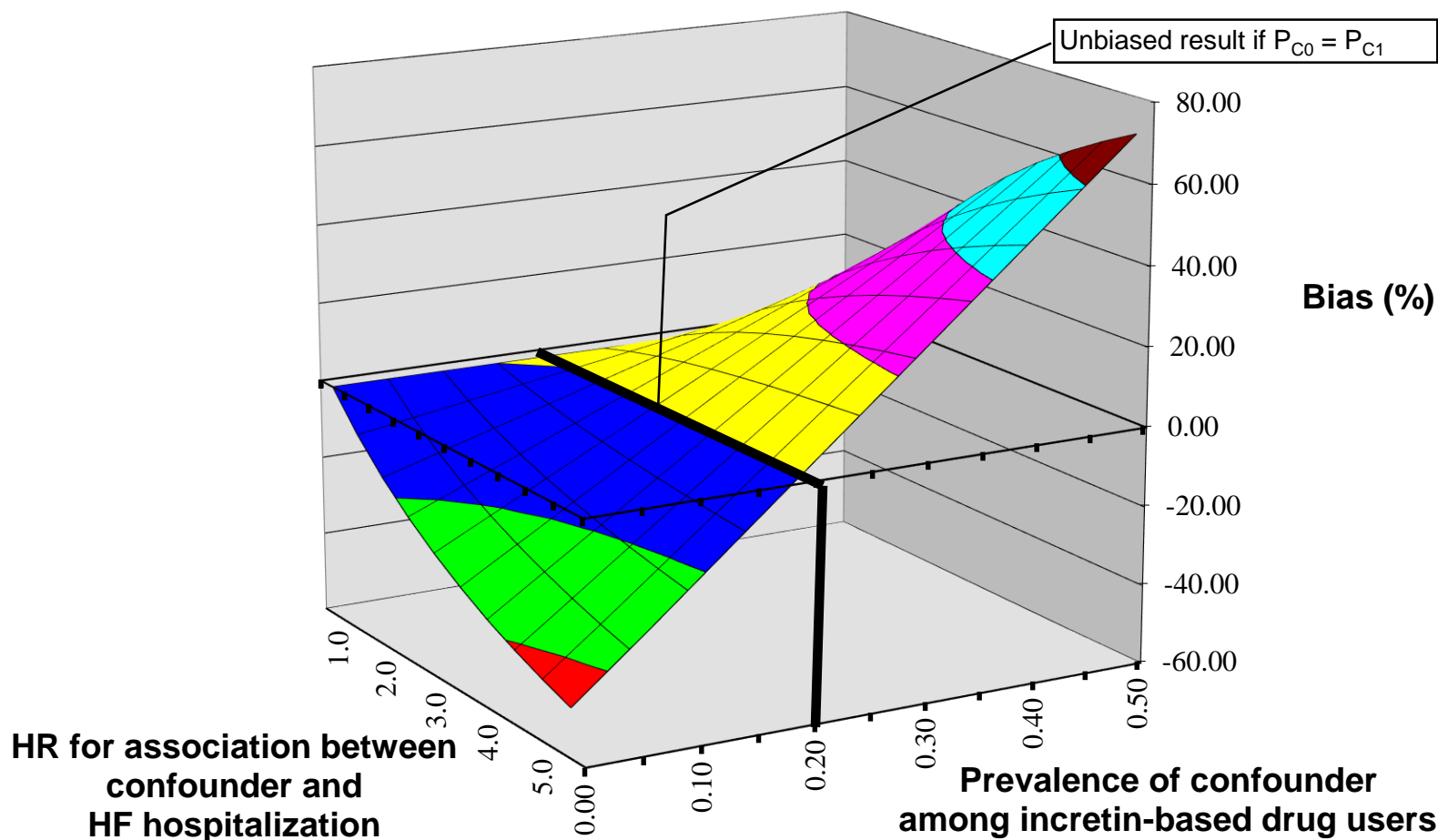
* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the Cox proportional hazards models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S43. Forest plot of the association between current use of incretin-based drugs and hospitalization for HF among patients with a history of HF, with meta-analysis of the primary nested case-control analysis restricted to the three sites participating in the propensity-matched cohort analyses*.



* The reference category is current use of oral antidiabetic drug combinations. The size of the boxes surrounding each site’s point estimate is proportional to the weight of that site in the random-effects meta-analysis. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic regression models. Abbreviations: HF, heart failure; CI, confidence interval; HR, hazard ratio; UK, United Kingdom; US, United States.

Figure S44. Sensitivity analysis examining the potential ability of an unmeasured/unknown confounder to mask an increased risk in hospitalization for HF with incretin-based drugs*.



* Analyses were conducted using the array approach suggested by Schneeweiss⁸. We assumed an observed hazard ratio of 0.82, a prevalence of the confounder among users of oral anti-diabetic combinations of 0.2, and a true hazard ratio of 1.27 (the association reported in SAVOR-TIMI 53)⁹.

Table S1. Lifestyle variables, glycemic control, hospitalizations, and prescription drug use among cases of hospitalization for HF and their corresponding matched controls among diabetic patients with and without a history of HF*

Baseline characteristics	No history of HF		With history of HF	
	Cases	Controls †	Cases	Controls †
Number	23,205	435,777	6,536	100,480
Body mass index, kg/m ² , n (%) ‡				
<25	289 (13.7)	4,266 (15.9)	54 (18.8)	245 (15.4)
25-29	623 (29.5)	11,050 (36.7)	73 (25.4)	591 (33.9)
≥30	1,150 (54.4)	13,950 (45.1)	157 (54.7)	929 (48.1)
Missing	52 (2.5)	806 (2.3)	3 (1.0)	74 (2.6)
Smoking status, n (%) ‡				
Ever	1,492 (70.6)	18,857 (62.8)	201 (70.0)	1,276 (70.8)
Never	616 (29.1)	11,080 (36.9)	85 (29.6)	559 (28.9)
Missing	6 (0.3)	135 (0.3)	1 (0.3)	4 (0.2)
Hemoglobin A1c (%), n (%) ‡				
≤7	328 (15.5)	4,646 (14.3)	65 (22.6)	349 (18.6)
7.1-8.0	579 (27.4)	9,514 (32.3)	77 (26.8)	479 (25.7)
>8	913 (43.2)	10,807 (41.0)	112 (39.0)	636 (43.4)
Missing	294 (13.9)	5,105 (12.5)	33 (11.5)	375 (12.3)
No. hospitalized episodes of care, mean **	0.4	0.2	1.1	0.7
0, n (%)	17,136 (73.8)	376,155 (85.9)	2,457 (37.6)	55,268 (55.7)
1, n (%)	4,410 (19.0)	49,175 (11.5)	2,290 (35.0)	30,802 (29.7)
2, n (%)	1,148 (4.9)	8,175 (2.0)	1,072 (16.4)	9,897 (9.7)
3, n (%)	317 (1.4)	1,605 (0.4)	388 (5.9)	2,873 (3.1)
≥4, n (%)	194 (0.8)	666 (0.2)	329 (5.0)	1,640 (1.8)
Prescription drug use, n (%)				
Angiotensin-converting enzyme inhibitors	9,506 (41.0)	156,852 (37.0)	3,488 (53.4)	46,444 (48.0)
Angiotensin receptor blockers	4,884 (21.0)	83,962 (19.6)	1,698 (26.0)	24,721 (26.8)
Beta-blockers	9,854 (42.5)	140,164 (32.1)	4,760 (72.8)	63,562 (62.6)
Calcium-channel blockers	7,830 (33.7)	110,500 (26.1)	2,393 (36.6)	34,080 (35.9)
Diuretics	11,675 (50.3)	173,458 (40.1)	5,502 (84.2)	69,681 (71.1)
Statins	12,146 (52.3)	232,086 (54.3)	4,254 (65.1)	62,688 (65.2)
Aspirin	1,899 (8.2)	23,577 (7.0)	632 (9.7)	5,296 (9.3)
Non-steroidal anti-inflammatory drugs	4,514 (19.5)	88,052 (19.9)	1,087 (16.6)	19,721 (19.4)
No. unique non-antidiabetic drugs, mean	9.7	7.9	13.6	12.3
0, n (%)	2,707 (11.7)	47,514 (10.4)	386 (5.9)	6,115 (5.1)
1, n (%)	1,052 (4.5)	22,552 (5.0)	109 (1.7)	2,366 (1.9)
2, n (%)	1,034 (4.5)	24,775 (5.6)	141 (2.2)	2,777 (2.4)
3, n (%)	1,097 (4.7)	27,619 (6.2)	131 (2.0)	2,707 (2.4)
≥4, n (%)	17,315 (74.6)	313,317 (72.4)	5,768 (88.2)	86,512 (88.3)
No. pre-study entry antidiabetic drugs, mean	0.2	0.2	0.6	0.3
0, n (%)	20,933 (90.2)	415,884 (90.1)	5,031 (77.0)	93,340 (77.0)
1, n (%)	931 (4.0)	8,199 (4.1)	520 (8.0)	2,326 (7.7)
2, n (%)	661 (2.8)	5,523 (2.6)	434 (6.6)	2,081 (6.3)
3, n (%)	377 (1.6)	3,427 (1.6)	314 (4.8)	1,452 (4.7)
≥4, n (%)	303 (1.3)	2,744 (1.6)	237 (3.6)	1,281 (4.3)
Study cohort entry drugs, n (%) §				

Baseline characteristics	No history of HF		With history of HF	
	Cases	Controls †	Cases	Controls †
Metformin	14,223 (61.3)	316,943 (69.9)	2,656 (40.6)	57,721 (50.1)
Sulfonylureas	6,655 (28.7)	85,090 (20.4)	2,389 (36.6)	29,215 (27.9)
Thiazolidinediones	1,956 (8.4)	32,457 (7.7)	238 (3.6)	5,060 (4.4)
DPP-4 inhibitors	1,963 (8.5)	32,269 (8.3)	967 (14.8)	11,889 (16.7)
GLP-1 analogs	244 (1.1)	3,512 (0.8)	33 (0.5)	720 (0.6)
Alpha-glucosidase inhibitors	79 (0.3)	1,081 (0.3)	46 (0.7)	308 (0.4)
Meglitinides	331 (1.4)	3,920 (1.0)	210 (3.2)	2,032 (2.1)
Insulins	455 (2.0)	2,043 (1.3)	446 (6.8)	1,261 (5.0)
Others	76 (0.3)	876 (0.2)	39 (0.6)	337 (0.4)

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure.

* Small cells (count ≤ 5) were suppressed by participating sites due to privacy restrictions. We assigned a value of 3 to these cells when collating data across sites. For this reason, the sum of count data may differ slightly from the presented total.

† The means and proportions among controls were weighted by the number of controls per case and then weighted by the number of cases per site.

‡ Data from the UK Clinical Practice Research Datalink; percentages based on 2,114 cases and 30,072 matched controls.

§ Non-mutually exclusive categories.

** Refers to prior hospitalizations.

Table S2. Patient characteristics of current users of incretin-based drugs and oral antidiabetic drug combinations at study cohort entry among controls^{*,†}.

Baseline characteristics	No history of HF		With history of HF	
	Incretin-based drugs	≥ 2 OHAs	Incretin-based drugs	≥ 2 OHAs
Number	42,706	51,968	12,394	10,608
CNODES site, n (%)				
Alberta	653 (1.5)	3,301 (6.4)	73 (0.6)	564 (5.3)
Clinical Practice Research Datalink (UK)	1,808 (4.2)	5,036 (9.7)	59 (0.5)	173 (1.6)
Manitoba	160 (0.4)	970 (1.9)	32 (0.3)	191 (1.8)
MarketScan (US)	30,338 (71.0)	40,042 (77.1)	7,618 (61.5)	8,273 (78.0)
Ontario	9,666 (22.6)	2,523 (4.9)	4,578 (36.9)	1,377 (13.0)
Saskatchewan	81 (0.2)	96 (0.2)	34 (0.3)	30 (0.3)
Age (years), mean	68.1	67.6	73.7	70.4
Male, n (%)	24,430 (57.2)	32,904 (63.3)	7,682 (62.0)	7,027 (66.2)
Duration of treated diabetes (years), mean	1.5	0.5	2.1	0.6
Body mass index, kg/m ² , n (%) ‡				
<25	158 (8.7)	664 (13.2)	8 (13.6)	S
25-29	484 (26.8)	1,913 (38.0)	19 (32.2)	58 (33.5)
≥30	1,135 (62.8)	2,343 (46.5)	32 (54.2)	89 (51.4)
Missing	31 (1.7)	116 (2.3)	0 (0.0)	S
Hemoglobin A1c (%), n (%) ‡				
≤7	146 (8.1)	275 (5.5)	S	14 (8.1)
7.1-8.0	548 (30.3)	1,372 (27.2)	17 (28.8)	36 (20.8)
>8	895 (49.5)	2,704 (53.7)	28 (47.5)	88 (50.9)
Missing	219 (12.1)	685 (13.6)	S	35 (20.2)
Alcohol-related disorders, n (%)	152 (0.4)	308 (0.6)	62 (0.5)	92 (0.9)
Smoking status, n (%) ‡				
Ever	1,198 (66.3)	3,342 (66.4)	39 (66.1)	135 (78.0)
Never	S	1,670 (33.2)	20 (33.9)	38 (22.0)
Missing	S	24 (0.5)	0 (0.0)	0 (0.0)
Comorbidity, n (%)				
Atrial fibrillation or flutter	985 (2.3)	907 (1.7)	1,625 (13.1)	883 (8.3)
Cancer	5,646 (13.2)	5,978 (11.5)	2,330 (18.8)	1,728 (16.3)
Chronic obstructive pulmonary disease	6,186 (14.5)	6,767 (13.0)	4,893 (39.5)	3,759 (35.4)
Coronary artery disease	12,890 (30.2)	12,646 (24.3)	9,227 (74.4)	7,166 (67.6)
Dyslipidemia	26,176 (61.3)	27,294 (52.5)	8,492 (68.5)	6,548 (61.7)
Hypertension	32,048 (75.0)	35,071 (67.5)	11,144 (89.9)	8,973 (84.6)
Peripheral vascular disease	2,813 (6.6)	3,378 (6.5)	2,020 (16.3)	1,631 (15.4)
Coronary revascularization	1,768 (4.1)	1,538 (3.0)	2,090 (16.9)	1,520 (14.3)
Myocardial infarction	5,331 (12.5)	3,154 (6.1)	4,851 (39.1)	2,752 (25.9)
Stroke	4,555 (10.7)	4,501 (8.7)	3,174 (25.6)	2,353 (22.2)
Neuropathy	794 (1.9)	1,345 (2.6)	338 (2.7)	278 (2.6)
Renal disease	2,465 (5.8)	2,452 (4.7)	2,231 (18.0)	1,163 (11.0)
Retinal disorders	5,793 (13.6)	8,128 (15.6)	2,281 (18.4)	1,828 (17.2)
Prescription drug use, n (%)				
Angiotensin-converting enzyme inhibitors	15,403 (36.1)	19,411 (37.4)	5,542 (44.7)	5,035 (47.5)
Angiotensin receptor blockers	10,545 (24.7)	8,128 (15.6)	3,649 (29.4)	2,151 (20.3)
Beta-blockers	13,405 (31.4)	14,542 (28.0)	7,648 (61.7)	6,307 (59.5)

Baseline characteristics	No history of HF		With history of HF	
	Incretin-based drugs	≥ 2 OHAs	Incretin-based drugs	≥ 2 OHAs
Calcium-channel blockers	11,608 (27.2)	11,449 (22.0)	4,469 (36.1)	3,089 (29.1)
Diuretics	17,047 (39.9)	17,388 (33.5)	8,458 (68.2)	6,727 (63.4)
Statins	24,781 (58.0)	25,730 (49.5)	8,442 (68.1)	5,990 (56.5)
Aspirin	2,012 (4.7)	3,547 (6.8)	649 (5.2)	504 (4.8)
Non-steroidal anti-inflammatory drugs	8,512 (19.9)	7,956 (15.3)	2,429 (19.6)	1,801 (17.0)
No. hospitalized episodes of care, mean**	0.1	0.1	0.5	0.6
0, n (%)	37,707 (88.3)	45,696 (87.9)	7,822 (63.1)	6,088 (57.4)
1, n (%)	4,228 (9.9)	5,230 (10.1)	3,165 (25.5)	3,267 (30.8)
2, n (%)	620 (1.5)	799 (1.5)	983 (7.9)	863 (8.1)
3, n (%)	116 (0.3)	180 (0.3)	285 (2.3)	253 (2.4)
≥4, n (%)	37 (0.1)	63 (0.1)	143 (1.2)	141 (1.3)
No. unique non-antidiabetic drugs, mean	8.0	5.8	12.2	9.8
0, n (%)	5,670 (13.3)	11,436 (22.0)	917 (7.4)	1,464 (13.8)
1, n (%)	2,220 (5.2)	3,979 (7.7)	340 (2.7)	487 (4.6)
2, n (%)	2,071 (4.8)	3,818 (7.3)	364 (2.9)	416 (3.9)
3, n (%)	2,400 (5.6)	3,612 (7.0)	276 (2.2)	509 (4.8)
≥4, n (%)	30,346 (71.1)	29,121 (56.0)	10,499 (84.7)	7,734 (72.9)
No. pre-study entry antidiabetic drugs, mean	0.5	0.1	0.7	0.2
0, n (%)	33,693 (78.9)	47,406 (91.2)	8,978 (72.4)	9,523 (89.8)
1, n (%)	2,518 (5.9)	2,912 (5.6)	749 (6.0)	674 (6.4)
2, n (%)	2,616 (6.1)	1,253 (2.4)	1,081 (8.7)	293 (2.8)
3, n (%)	2,087 (4.9)	270 (0.5)	821 (6.6)	65 (0.6)
≥4, n (%)	1,792 (4.2)	123 (0.2)	765 (6.2)	54 (0.5)
Study cohort entry drugs, n (%) §				
Metformin	19,741 (46.2)	35,367 (68.1)	3,524 (28.4)	6,705 (63.2)
Sulfonylureas	5,617 (13.2)	21,234 (40.9)	1,514 (12.2)	5,149 (48.5)
Thiazolidinediones	3,208 (7.5)	9,889 (19.0)	423 (3.4)	1,447 (13.6)
DPP-4 inhibitors	21,444 (50.2)	976 (1.9)	8,344 (67.3)	242 (2.3)
GLP-1 analogs	1,518 (3.6)	108 (0.2)	384 (3.1)	16 (0.2)
Alpha-glucosidase inhibitors	71 (0.2)	205 (0.4)	15 (0.1)	63 (0.6)
Meglitinides	326 (0.8)	679 (1.3)	115 (0.9)	232 (2.2)
Insulins	131 (0.3)	0 (0.0)	68 (0.5)	0 (0.0)
Others	39 (0.1)	209 (0.4)	1 (0.0)	74 (0.7)

Abbreviations: CNODES, Canadian Network for Observational Drug Effect Studies; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HF, heart failure; OHA, oral hypoglycemic agent; S, suppressed value; UK, United Kingdom; US, United States.

* The exposure categories above are based on the number of matched controls currently exposed to incretin-based drugs and oral antidiabetic drug combinations at index date.

† Small cells (count ≤ 5) were suppressed by participating sites due to privacy restrictions. We assigned a value of 3 to these cells when collating data across sites. For this reason, the sum of count data may differ slightly from the presented total.

‡ Data from the UK Clinical Practice Research Datalink; percentages based on 2,005 current users of incretin-based drugs and 5,450 current users of ≥ 2 oral hypoglycemic agents.

§ Non-mutually exclusive categories.

** Refers to prior hospitalizations.

Table S3. Patient characteristics of users of incretin-based drugs and oral antidiabetic combination among patients with no history of HF before and after matching on propensity score*.

Baseline characteristics	Unmatched			Propensity score-matched		
	Incretin-based drugs	≥2 OHAs	Standardized differences (range)	Incretin-based drugs	≥2 OHAs	Standardized differences (range)
Number	105,329	114,740		73,622	73,622	
CNODES site, n (%)						
UK Clinical Practice Research Datalink	4,301 (4.1)	13,383 (11.7)		4,287 (5.8)	4,287 (5.8)	
US MarketScan	83,274 (79.1)	95,160 (82.9)		64,067 (87.0)	64,067 (87.0)	
Ontario	17,754 (16.9)	6,197 (5.4)		5,268 (7.2)	5,268 (7.2)	
Age (years), mean	58.6	55.7	0.01 - 0.11	56.2	55.9	0.01 - 0.03
18-25, n (%)	630 (0.6)	669 (0.6)	0.01 - 0.04	508 (0.7)	477 (0.6)	0.00 - 0.03
26-35, n (%)	3,935 (3.7)	4,934 (4.3)	0.02 - 0.03	3,147 (4.3)	3,156 (4.3)	0.00 - 0.00
36-45, n (%)	13,676 (13.0)	17,598 (15.3)	0.01 - 0.04	10,841 (14.7)	10,931 (14.8)	0.00 - 0.01
46-55, n (%)	27,222 (25.8)	34,808 (30.3)	0.03 - 0.05	21,340 (29.0)	21,830 (29.7)	0.01 - 0.02
56-65, n (%)	28,751 (27.3)	34,873 (30.4)	0.00 - 0.01	22,300 (30.3)	22,570 (30.7)	0.00 - 0.01
66-75, n (%)	15,889 (15.1)	13,090 (11.4)	0.01 - 0.11	9,169 (12.5)	8,708 (11.8)	0.00 - 0.03
≥76, n (%)	15,226 (14.5)	8,768 (7.6)	0.00 - 0.11	6,317 (8.6)	5,950 (8.1)	0.00 - 0.03
Male, n (%)	53,966 (51.2)	69,718 (60.8)	0.02 - 0.22	40,993 (55.7)	40,669 (55.2)	0.01 - 0.04
Cohort entry year						
2007	9,834 (9.3)	18,594 (16.2)	0.00 - 0.18	9,618 (13.1)	9,044 (12.3)	0.01 - 0.03
2008	14,988 (14.2)	26,625 (23.2)	0.00 - 0.21	14,459 (19.6)	14,423 (19.6)	0.00 - 0.00
2009	13,167 (12.5)	21,837 (19.0)	0.01 - 0.15	12,614 (17.1)	12,805 (17.4)	0.01 - 0.01
2010	14,143 (13.4)	14,398 (12.5)	0.00 - 0.12	9,981 (13.6)	9,751 (13.2)	0.00 - 0.01
2011	20,611 (19.6)	14,933 (13.0)	0.01 - 0.16	11,959 (16.2)	12,046 (16.4)	0.00 - 0.02
2012	20,108 (19.1)	10,763 (9.4)	0.03 - 0.25	8,867 (12.0)	9,218 (12.5)	0.01 - 0.02
2013	12,409 (11.8)	7,393 (6.4)	0.00 - 0.23	6,062 (8.2)	6,263 (8.5)	0.00 - 0.01
2014	69 (0.1)	197 (0.2)	0.03 - 0.03	62 (0.1)	72 (0.1)	0.02 - 0.02
Duration of treated diabetes (years), mean	1.1	1.3	0.00 - 0.37	0.4	0.4	0.00 - 0.01
Body mass index, kg/m ² , n (%) †						
<25	507 (11.8)	1,545 (11.5)	0.01 - 0.01	452 (10.5)	503 (11.7)	0.04 - 0.04
25-29	1,319 (30.7)	4,159 (31.1)	0.01 - 0.01	1,365 (31.8)	1,308 (30.5)	0.03 - 0.03
≥30	2,401 (55.8)	7,409 (55.4)	0.02 - 0.02	2,384 (55.6)	2,391 (55.8)	0.00 - 0.00
Missing	74 (1.7)	270 (2.0)	0.02 - 0.02	86 (2.0)	85 (2.0)	0.00 - 0.00
Hemoglobin A1c (%), n (%) †						

Baseline characteristics	Unmatched			Propensity score-matched		
	Incretin-based drugs	≥2 OHAs	Standardized differences (range)	Incretin-based drugs	≥2 OHAs	Standardized differences (range)
≤7	678 (15.8)	2,133 (15.9)	0.01 - 0.01	682 (15.9)	672 (15.7)	0.01 - 0.01
7.1-8.0	1,176 (27.3)	3,673 (27.4)	0.01 - 0.01	1,184 (27.6)	1,165 (27.2)	0.01 - 0.01
>8	1,749 (40.7)	5,510 (41.2)	0.02 - 0.02	1,792 (41.8)	1,781 (41.5)	0.01 - 0.01
Missing	698 (16.2)	2,067 (15.4)	0.00 - 0.00	629 (14.7)	669 (15.6)	0.03 - 0.03
Alcohol-related disorders, n (%)	520 (0.5)	995 (0.9)	0.01 - 0.04	451 (0.6)	416 (0.6)	0.00 - 0.01
Smoking status, n (%) †						
Ever	2,674 (62.2)	8,401 (62.8)	0.01 - 0.01	2,700 (63.0)	2,665 (62.2)	0.02 - 0.02
Never	1,618 (37.6)	4,944 (36.9)	0.00 - 0.00	1,576 (36.8)	1,605 (37.4)	0.01 - 0.01
Missing	9 (0.2)	38 (0.3)	0.00 - 0.00	11 (0.3)	17 (0.4)	0.02 - 0.02
Comorbidity, n (%)						
Atrial fibrillation or flutter	2,233 (2.1)	2,410 (2.1)	0.01 - 0.03	1,315 (1.8)	1,251 (1.7)	0.00 - 0.02
Cancer	9,901 (9.4)	7,826 (6.8)	0.01 - 0.10	5,891 (8.0)	5,383 (7.3)	0.01 - 0.03
Chronic obstructive pulmonary disease	13,449 (12.8)	11,165 (9.7)	0.01 - 0.08	8,404 (11.4)	7,718 (10.5)	0.01 - 0.04
Coronary artery disease	23,071 (21.9)	17,520 (15.3)	0.00 - 0.12	13,415 (18.2)	11,684 (15.9)	0.00 - 0.08
Dyslipidemia	67,490 (64.1)	59,841 (52.2)	0.00 - 0.22	43,078 (58.5)	43,440 (59.0)	0.01 - 0.03
Hypertension	74,419 (70.7)	69,771 (60.8)	0.01 - 0.17	48,200 (65.5)	47,939 (65.1)	0.01 - 0.01
Peripheral arterial or vascular disease	4,804 (4.6)	4,113 (3.6)	0.01 - 0.08	3,295 (4.5)	2,904 (3.9)	0.00 - 0.03
Previous coronary revascularization	3,461 (3.3)	2,715 (2.4)	0.02 - 0.03	1,853 (2.5)	1,765 (2.4)	0.00 - 0.04
Previous myocardial infarction	9,704 (9.2)	5,426 (4.7)	0.02 - 0.03	3,917 (5.3)	3,796 (5.2)	0.01 - 0.02
Previous stroke	7,325 (7.0)	5,432 (4.7)	0.02 - 0.08	4,344 (5.9)	3,863 (5.2)	0.00 - 0.04
Neuropathy	1,826 (1.7)	2,869 (2.5)	0.01 - 0.02	1,488 (2.0)	1,307 (1.8)	0.02 - 0.03
Renal disease	5,356 (5.1)	4,948 (4.3)	0.01 - 0.07	3,001 (4.1)	2,760 (3.7)	0.00 - 0.02
Retinal disorders	9,199 (8.7)	9,667 (8.4)	0.00 - 0.04	6,180 (8.4)	5,839 (7.9)	0.00 - 0.02
Prescription drug use, n (%)						
Angiotensin-converting enzyme inhibitors	31,979 (30.4)	42,191 (36.8)	0.01 - 0.19	23,606 (32.1)	23,005 (31.2)	0.00 - 0.02
Angiotensin receptor blockers	23,536 (22.3)	16,434 (14.3)	0.02 - 0.17	13,177 (17.9)	12,637 (17.2)	0.01 - 0.03
Beta-blockers	24,102 (22.9)	22,653 (19.7)	0.00 - 0.06	16,056 (21.8)	15,171 (20.6)	0.00 - 0.04
Calcium-channel blockers	22,333 (21.2)	20,585 (17.9)	0.02 - 0.05	14,052 (19.1)	13,151 (17.9)	0.02 - 0.03
Diuretics	35,549 (33.8)	33,236 (29.0)	0.00 - 0.07	23,053 (31.3)	22,315 (30.3)	0.01 - 0.03
Statins	50,092 (47.6)	49,192 (42.9)	0.03 - 0.15	31,868 (43.3)	31,091 (42.2)	0.01 - 0.02
Aspirin	3,546 (3.4)	6,083 (5.3)	0.01 - 0.01	2,344 (3.2)	2,327 (3.2)	0.00 - 0.01
Non-steroidal anti-inflammatory drugs	21,079 (20.0)	17,856 (15.6)	0.01 - 0.09	13,751 (18.7)	13,197 (17.9)	0.01 - 0.03
No. hospitalized episodes of care, mean ††	0.1	0.1	0.00 - 0.21	0.1	0.1	0.01 - 0.03
0, n (%)	94,554 (89.8)	101,882 (88.8)	0.01 - 0.22	65,358 (88.8)	66,075 (89.7)	0.00 - 0.04
1, n (%)	8,717 (8.3)	10,497 (9.1)	0.00 - 0.17	6,714 (9.1)	6,124 (8.3)	0.00 - 0.03
2, n (%)	1,513 (1.4)	1,716 (1.5)	0.00 - 0.10	1,119 (1.5)	1,046 (1.4)	0.00 - 0.01

Baseline characteristics	Unmatched			Propensity score-matched		
	Incretin-based drugs	≥2 OHAs	Standardized differences (range)	Incretin-based drugs	≥2 OHAs	Standardized differences (range)
3, n (%)	368 (0.3)	427 (0.4)	0.01 - 0.06	281 (0.4)	254 (0.3)	0.00 - 0.02
≥4, n (%)	177 (0.2)	218 (0.2)	0.00 - 0.04	148 (0.2)	123 (0.2)	0.01 - 0.02
No. unique non-antidiabetic drugs, mean	7.5	5.3	0.02 - 0.38	6.8	5.9	0.03 - 0.16
0, n (%)	15,819 (15.0)	29,867 (26.0)	0.02 - 0.28	14,217 (19.3)	14,507 (19.7)	0.01 - 0.02
1, n (%)	6,256 (5.9)	9,378 (8.2)	0.00 - 0.08	5,357 (7.3)	5,514 (7.5)	0.01 - 0.03
2, n (%)	6,523 (6.2)	9,145 (8.0)	0.02 - 0.07	5,602 (7.6)	5,542 (7.5)	0.00 - 0.00
3, n (%)	6,741 (6.4)	8,527 (7.4)	0.00 - 0.04	5,496 (7.5)	5,305 (7.2)	0.00 - 0.01
≥4, n (%)	69,990 (66.4)	57,823 (50.4)	0.01 - 0.34	42,950 (58.3)	42,754 (58.1)	0.01 - 0.01
No. pre-study entry antidiabetic drugs, mean	0.4	0.1	0.00 - 0.77	0.2	0.1	0.00 - 0.04
0, n (%)	88,785 (84.3)	105,523 (92.0)	0.01 - 0.05	67,752 (92.0)	67,804 (92.1)	0.00 - 0.03
1, n (%)	5,105 (4.8)	5,761 (5.0)	0.03 - 0.78	3,658 (5.0)	3,625 (4.9)	0.01 - 0.01
2, n (%)	4,914 (4.7)	2,592 (2.3)	0.01 - 0.06	1,716 (2.3)	1,756 (2.4)	0.01 - 0.02
3, n (%)	3,647 (3.5)	622 (0.5)	0.00 - 0.54	348 (0.5)	323 (0.4)	0.00 - 0.03
≥4, n (%)	2,878 (2.7)	242 (0.2)	0.00 - 0.57	148 (0.2)	114 (0.2)	0.01 - 0.07

Abbreviations: CNODES, Canadian Network for Observational Drug Effect Studies; UK, United Kingdom; US, United States; S, suppressed value.

* Small cells (count ≤ 5) were suppressed by participating sites due to privacy restrictions. We assigned a value of 3 to these cells when collating data across sites. For this reason, the sum of count data may differ slightly from the presented total.

† Data from the UK Clinical Practice Research Datalink; percentages based on 4,301 users of incretin-based drugs and 13,383 users of oral antidiabetic combinations before matching and 4,287 of each after matching.

‡ Refers to prior hospitalizations.

Table S4. Patient characteristics of users of incretin-based drugs and oral antidiabetic combination among patients with a history of HF before and after matching on propensity score*.

Baseline characteristics	Unmatched			Propensity score-matched		
	Incretin-based drugs	≥2 OHAs	Standardized differences (range)	Incretin-based drugs	≥2 OHAs	Standardized differences (range)
Number	10,749	5,982		4,444	4,444	
CNODES site, n (%)						
UK Clinical Practice Research Datalink	325 (3.1)	818 (13.7)		318 (7.2)	318 (7.2)	
US MarketScan	5,410 (50.3)	3,285 (54.9)		2,900 (65.3)	2,900 (65.3)	
Ontario	5,014 (46.6)	1,879 (31.4)		1,226 (27.6)	1,226 (27.6)	
Age (years), mean	72.3	68.0	0.02 - 0.30	67.7	67.6	0.01 - 0.06
18-25, n (%)	S	S	0.01 - 0.04	0 (0)	S	0.08 - 0.08
26-35, n (%)	S	S	0.00 - 0.06	27 (0.6)	S	0.01 - 0.13
36-45, n (%)	252 (2.3)	248 (4.1)	0.00 - 0.08	189 (4.3)	182 (4.1)	0.00 - 0.11
46-55, n (%)	933 (8.7)	847 (14.2)	0.02 - 0.13	628 (14.1)	665 (15.0)	0.01 - 0.18
56-65, n (%)	1,710 (15.9)	1,451 (24.3)	0.03 - 0.16	1,156 (26.0)	1,104 (24.8)	0.02 - 0.20
66-75, n (%)	2,468 (23.0)	1,345 (22.5)	0.06 - 0.09	973 (21.9)	988 (22.2)	0.00 - 0.11
≥76, n (%)	5,336 (49.6)	2,054 (34.3)	0.03 - 0.28	1,471 (33.1)	1,476 (33.2)	0.01 - 0.05
Male, n (%)	5,945 (55.3)	3,532 (59.0)	0.05 - 0.09	2,631 (59.2)	2,641 (59.4)	0.01 - 0.03
Cohort entry year						
2007	597 (5.6)	585 (9.8)	0.01 - 0.11	437 (9.8)	419 (9.4)	0.02 - 0.02
2008	878 (8.2)	866 (14.5)	0.04 - 0.19	638 (14.3)	654 (14.7)	0.00 - 0.09
2009	859 (8.0)	826 (13.8)	0.02 - 0.16	660 (14.9)	639 (14.4)	0.01 - 0.09
2010	1,897 (17.6)	1033 (17.3)	0.00 - 0.08	696 (15.7)	717 (16.1)	0.01 - 0.02
2011	2,692 (25.0)	1357 (22.7)	0.04 - 0.14	975 (21.9)	972 (21.9)	0.00 - 0.05
2012	2,603 (24.2)	882 (14.7)	0.08 - 0.20	687 (15.5)	692 (15.6)	0.00 - 0.05
2013	1,215 (11.3)	416 (7.0)	0.03 - 0.22	S	343 (7.7)	0.00 - 0.05
2014	8 (0.07)	17 (0.3)	0.04 - 0.04	S	8 (0.2)	0.07 - 0.07
Duration of treated diabetes (years), mean	3.4	1.8	0.07 - 0.47	1.6	1.6	0.00 - 0.03
Body mass index, kg/m ² , n (%) †						
<25	38 (11.7)	88 (10.8)	0.02 - 0.02	44 (13.8)	S	0.11 - 0.11
25-29	94 (28.9)	267 (32.6)	0.03 - 0.03	100 (31.4)	99 (31.1)	0.01 - 0.01
≥30	186 (57.2)	448 (54.8)	0.04 - 0.04	166 (52.2)	183 (57.5)	0.11 - 0.11
Missing	7 (2.2)	15 (1.8)	0.08 - 0.08	8 (2.5)	S	0.12 - 0.12
Hemoglobin A1c (%), n (%) †						
≤7	41 (12.6)	117 (14.3)	0.10 - 0.10	51 (16.0)	48 (15.1)	0.03 - 0.03
7.1-8.0	100 (30.8)	230 (28.1)	0.07 - 0.07	70 (22.0)	92 (28.9)	0.16 - 0.16
>8	126 (38.8)	338 (41.3)	0.01 - 0.01	137 (43.1)	135 (42.5)	0.01 - 0.01

Baseline characteristics	Unmatched			Propensity score-matched		
	Incretin-based drugs	≥2 OHAs	Standardized differences (range)	Incretin-based drugs	≥2 OHAs	Standardized differences (range)
Missing	58 (17.8)	133 (16.3)	0.02 - 0.02	60 (18.9)	43 (13.5)	0.15 - 0.15
Alcohol-related disorders, n (%)	103 (1.0)	97 (1.6)	0.02 - 0.06	52 (1.2)	47 (1.1)	0.01 - 0.08
Smoking status, n (%) †						
Ever	209 (64.3)	522 (63.8)	0.01 - 0.01	207 (65.)	213 (67.0)	0.04 - 0.04
Never	S	S	0.02 - 0.02	111 (34.9)	213 (67.0)	0.04 - 0.04
Missing	S	S	0.10 - 0.10	0 (0)	0 (0)	0.00 - 0.00
Comorbidity, n (%)						
Atrial fibrillation or flutter	1,773 (16.5)	844 (14.1)	0.01 - 0.09	507 (11.4)	527 (11.9)	0.01 - 0.03
Cancer	1,971 (18.3)	901 (15.1)	0.04 - 0.15	677 (15.2)	664 (14.9)	0.00 - 0.07
Chronic obstructive pulmonary disease	4,271 (39.7)	2,012 (33.6)	0.00 - 0.14	1,545 (34.8)	1,531 (34.5)	0.00 - 0.12
Coronary artery disease	7,946 (73.9)	3,749 (62.7)	0.02 - 0.16	2,946 (66.3)	2,858 (64.3)	0.02 - 0.07
Dyslipidemia	7,588 (70.6)	3,763 (62.9)	0.00 - 0.10	2,934 (66.0)	2,925 (65.8)	0.00 - 0.03
Hypertension	9,905 (92.1)	5,183 (86.6)	0.06 - 0.10	3,879 (87.3)	3,893 (87.6)	0.02 - 0.08
Peripheral arterial or vascular disease	1,557 (14.5)	718 (12.0)	0.01 - 0.15	600 (13.5)	610 (13.7)	0.00 - 0.09
Previous coronary revascularization	2,054 (19.1)	966 (16.1)	0.03 - 0.16	686 (15.4)	684 (15.4)	0.01 - 0.07
Previous myocardial infarction	4,901 (45.6)	2,018 (33.7)	0.01 - 0.10	1,445 (32.5)	1,449 (32.6)	0.00 - 0.01
Previous stroke	2,673 (24.9)	1,232 (20.6)	0.07 - 0.15	922 (20.7)	917 (20.6)	0.01 - 0.04
Neuropathy	333 (3.1)	244 (4.1)	0.00 - 0.02	146 (3.3)	141 (3.2)	0.03 - 0.04
Renal disease	2,374 (22.1)	942 (15.7)	0.01 - 0.29	575 (12.9)	613 (13.8)	0.00 - 0.09
Retinal disorders	1,851 (17.2)	894 (14.9)	0.00 - 0.15	648 (14.6)	634 (14.3)	0.01 - 0.02
Prescription drug use, n (%)						
Angiotensin-converting enzyme inhibitors	4,883 (45.4)	2,925 (48.9)	0.07 - 0.14	2,074 (46.7)	2,089 (47.0)	0.01 - 0.07
Angiotensin receptor blockers	3,394 (31.6)	1355 (22.7)	0.02 - 0.17	1,043 (23.5)	1,038 (23.4)	0.00 - 0.07
Beta-blockers	6,587 (61.3)	3,294 (55.1)	0.02 - 0.11	2,512 (56.5)	2,520 (56.7)	0.01 - 0.01
Calcium-channel blockers	4,166 (38.8)	2,005 (33.5)	0.03 - 0.08	1,432 (32.2)	1,429 (32.2)	0.00 - 0.03
Diuretics	7,359 (68.5)	3,711 (62.0)	0.04 - 0.10	2,816 (63.4)	2,836 (63.8)	0.02 - 0.06
Statins	7,511 (69.9)	3,735 (62.4)	0.03 - 0.11	2,695 (60.6)	2,723 (61.3)	0.00 - 0.18
Aspirin	679 (6.3)	507 (8.5)	0.03 - 0.11	254 (5.7)	244 (5.5)	0.00 - 0.03
Non-steroidal anti-inflammatory drugs	2,164 (20.1)	1,072 (17.9)	0.03 - 0.15	827 (18.6)	835 (18.8)	0.00 - 0.10
No. hospitalized episodes of care, mean ††	0.56	0.6	0.05 - 0.32	0.6	0.6	0.01 - 0.18
0, n (%)	6,700 (62.3)	3,477 (58.1)	0.00 - 0.35	2,607 (58.7)	2,621 (59.0)	0.01 - 0.15
1, n (%)	2,674 (24.9)	1,676 (28.0)	0.03 - 0.21	1,261 (28.4)	1,237 (27.8)	0.02 - 0.09
2, n (%)	907 (8.4)	569 (9.5)	0.01 - 0.16	394 (8.9)	411 (9.2)	0.01 - 0.07
3, n (%)	278 (2.6)	158 (2.6)	0.05 - 0.12	123 (2.8)	110 (2.5)	0.00 - 0.08
≥4, n (%)	190 (1.8)	102 (1.7)	0.02 - 0.11	59 (1.3)	65 (1.5)	0.02 - 0.11
No. unique non-antidiabetic drugs, mean	12.71 (-)	10.2	0.03 - 0.40	11.2	10.2	0.02 - 0.16

Baseline characteristics	Unmatched			Propensity score-matched		
	Incretin-based drugs	≥2 OHAs	Standardized differences (range)	Incretin-based drugs	≥2 OHAs	Standardized differences (range)
0, n (%)	582 (5.4)	656 (11.0)	0.05 - 0.25	455 (10.2)	456 (10.3)	0.00 - 0.11
1, n (%)	195 (1.8)	216 (3.6)	0.02 - 0.11	158 (3.6)	132 (3.0)	0.01 - 0.13
2, n (%)	255 (2.4)	249 (4.2)	0.00 - 0.09	179 (4.0)	171 (3.8)	0.02 - 0.04
3, n (%)	223 (2.1)	228 (3.8)	0.01 - 0.11	163 (3.7)	156 (3.5)	0.00 - 0.14
≥4, n (%)	9,494 (88.3)	4,633 (77.4)	0.03 - 0.34	3,480 (78.3)	3,519 (79.2)	0.01 - 0.09
No. pre-study entry antidiabetic drugs, mean	1.1	0.5	0.03 - 0.94	0.4	0.4	0.03 - 0.05
0, n (%)	6,194 (57.6)	4,065 (68.0)	0.02 - 0.08	3,284 (73.9)	3,285 (73.9)	0.02 - 0.06
1, n (%)	1,017 (9.5)	1,268 (21.2)	0.10 - 0.93	665 (15.0)	672 (15.1)	0.01 - 0.14
2, n (%)	1,351 (12.6)	544 (9.1)	0.02 - 0.02	399 (9.0)	402 (9.0)	0.03 - 0.15
3, n (%)	1,115 (10.4)	71 (1.2)	0.03 - 0.63	62 (1.4)	59 (1.3)	0.03 - 0.07
≥4, n (%)	1,072 (10.0.973)	34 (0.6)	0.00 - 0.68	34 (0.8)	26 (0.6)	0.05 - 0.06

Abbreviations: CNODES, Canadian Network for Observational Drug Effect Studies; UK, United Kingdom; US, United States; S, suppressed value.

* Small cells (count ≤ 5) were suppressed by participating sites due to privacy restrictions. We assigned a value of 3 to these cells when collating data across sites. For this reason, the sum of count data may differ slightly from the presented total.

† Data from the UK Clinical Practice Research Datalink; percentages based on 325 users of incretin-based drugs and 818 users of oral antidiabetic combinations before matching and 318 of each after matching.

‡ Refers to prior hospitalizations.

Table S5. Summary table of propensity-matched cohort analyses of the association between use of incretin-based drugs and hospitalization for HF among patients with no history of HF*.

Exposure	Patients[†]	Events[†]	Person-years	Incidence Rate (95% CI) [per 1,000/ year]	HR (95% CI)	I² (%)[§]
<u>PS-matched analysis (2 years)</u>						
≥2 oral antidiabetic drugs	73,622.0	961	106,790.6	9.0 (8.4-9.6)	1.0 (Reference)	9.5
Incretin-based drugs	73,622.0	938	107,817.3	8.7 (8.2-9.3)	0.97 (0.88-1.07)	
<u>PS-matched (2 years with competing risk)[‡]</u>						
≥2 oral antidiabetic drugs	73,622.0	961	106,790.6	9.0 (8.4-9.6)	1.0 (Reference)	0.0
Incretin-based drugs	73,622.0	938	107,817.3	8.7 (8.2-9.3)	0.97 (0.89-1.06)	
<u>PS-matched (1 year)</u>						
≥2 oral antidiabetic drugs	73,622.0	563	63,177.4	8.9 (8.2-9.7)	1.0 (Reference)	0.0
Incretin-based drugs	73,622.0	524	63,410.7	8.3 (7.6-9.0)	0.93 (0.83-1.04)	

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, propensity score.

* Analyses were restricted to the CPRD, MarketScan, and Ontario. For comparative purposes, the primary nested control analysis resulted in a HR: 0.95 (95% CI: 0.81-1.11) when restricted to these three sites (see Figure S39).

[†] Small cells (count ≤ 5) were suppressed by participating sites due to privacy restrictions. We assigned a value of 3 to these cells when collating data across sites. For this reason, the sum of count data may differ slightly from the presented total.

[‡] Using this approach described by Fine and Gray⁶.

[§] The I² represents the proportion of the total variance of the meta-analysis that is due to between-study heterogeneity rather than within-study variability.

Table S6. Summary table of propensity-matched cohort analyses of the association between use of incretin-based drugs and hospitalization for HF among patients with a history of HF*.

Exposure	Patients †	Events †	Person-years	Incidence Rate (95% CI) [per 1,000/ year]	HR (95% CI)	I ² (%) §
<u>PS-matched analysis (2 years)</u>						
≥2 oral antidiabetic drugs	4,444	626	6,016.8	104.0 (96.1-112.4)	1.00 (Reference)	20.0
Incretin-based drugs	4,444	636	6,037.8	105.3 (97.4-113.8)	1.00 (0.87-1.16)	
<u>PS-matched analysis (2 years with competing risk) ‡</u>						
≥2 oral antidiabetic drugs	4,444	626	6,016.8	104.0 (96.1-112.4)	1.00 (Reference)	18.4
Incretin-based drugs	4,444	636	6,037.8	105.3 (97.4-113.8)	1.00 (0.87-1.16)	
<u>PS-matched analysis (1 year)</u>						
≥2 oral antidiabetic drugs	4,444	457	3,624.4	126.1 (114.9-138.1)	1.00 (Reference)	0.0
Incretin-based drugs	4,444	437	3,638.6	120.1 (109.2-131.8)	0.95 (0.84-1.08)	

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, propensity score.

* Analyses were restricted to the CPRD, MarketScan, and Ontario. For comparative purposes, the primary nested control analysis resulted in a HR: 1.01 (95% CI: 0.75-1.34) when restricted to these three sites (see Figure S43).

† Small cells (count ≤ 5) were suppressed by participating sites due to privacy restrictions. We assigned a value of 3 to these cells when collating data across sites. For this reason, the sum of count data may differ slightly from the presented total.

‡ Using this approach described by Fine and Gray⁶.

§ The I² represents the proportion of the total variance of the meta-analysis that is due to between-study heterogeneity rather than within-study variability.

Table S7. Sensitivity analysis comparing meta-analytic results of the association between incretin-based drugs and hospitalization for HF among patients with no history of HF comparing random- and fixed-effects models*.

	HR (95% CI)		I ² (%) ^{††}
	Random-effects	Fixed-effects	
<u>Nested-case-control analyses:</u>			
Incretin-based drugs	0.82 (0.67-1.00)	0.95 (0.90-1.01)	75.6
Duration of current use			
≤ 365 days	0.83 (0.66-1.05)	1.01 (0.95-1.07)	76.6
366-729 days	0.79 (0.71-0.89)	0.79 (0.71-0.89)	0.0
≥ 730 days	0.96 (0.75-1.22)	0.88 (0.77-1.00)	39.3
DPP-4 Inhibitors	0.84 (0.69-1.02)	0.95 (0.90-1.01)	74.3
GLP-1 analogs	0.95 (0.83-1.10)	0.95 (0.83-1.10)	0.0
History of MI			
Yes	0.94 (0.80-1.11)	0.94 (0.80-1.11)	0.0
No	0.74 (0.57-0.95)	0.91 (0.86-0.97)	76.2
Duration of treated diabetes at index date [†]			
< 5 years	0.87 (0.67-1.14)	0.95 (0.89-1.02)	73.1
≥ 5 years	0.97 (0.76-1.23)	1.00 (0.86-1.16)	57.3
<u>Sensitivity Analyses</u>			
Metformin-sulfonylureas as reference	0.83 (0.69-0.99)	0.89 (0.85-0.94)	69.5
No grace period (0 days)	0.87 (0.72-1.04)	0.93 (0.88-0.99)	64.1
Varied grace period (90 days)	0.82 (0.67-0.99)	0.96 (0.91-1.01)	76.2
Insulin or TZDs: exclusion or censoring	0.82 (0.65-1.04)	0.95 (0.89-1.01)	70.8
Covariates adjusted at index date	0.74 (0.58-0.94)	0.91 (0.85-0.97)	78.6
Adjust for anti-diabetic drugs [‡]	0.73 (0.55-0.97)	0.96 (0.90-1.02)	78.1
Reduced model 1 [§]	0.75 (0.60-0.94)	0.94 (0.89-0.99)	81.1
Reduced model 2 [£]	0.77 (0.63-0.95)	0.93 (0.88-0.98)	80.6
Primary or most responsible diagnosis [€]	0.85 (0.67-1.08)	0.93 (0.83-1.05)	38.7
<u>Propensity-matched cohort analyses[¥]:</u>			
Maximum follow-up: 2 years	0.97 (0.88-1.07)	0.97 (0.89-1.06)	9.5
Maximum follow-up: 2 years (competing risk) ^{**}	0.97 (0.89-1.06)	0.97 (0.89-1.06)	0
Maximum follow-up: 1 year [‡]	0.93 (0.83-1.04)	0.93 (0.83-1.04)	0

Abbreviation: HF, heart failure; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1, MI, myocardial infarction; TZDs, thiazolidinediones.

* The reference category for all analyses was current use of oral anti-diabetic combinations unless otherwise specified. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic models.

† Alberta did not participate in this analysis as all patients had a duration of treated diabetes of less than five years, preventing the examination of the interaction. Saskatchewan was excluded due to sparse data.

‡ With additional adjustment for the anti-diabetic drugs used in the year prior to study cohort

§ In this reduced model, a composite microvascular complications variable was used instead of its individual components, categorical variables were converted to their continuous counterparts where possible, and insulin, oral antidiabetic drug monotherapy, and not currently exposed were collapsed to a single “other exposure” category.

‡ The conditional logistic regression model only included exposure (current exposure to incretin-based drugs, current exposure to oral antidiabetic combinations, and other exposure) and the Deyo version of the Charlson comorbidity index⁴.

€ The case series was restricted to those with the HF diagnosis in most responsible or primary position.

¥ Analyses were restricted to the CPRD, MarketScan, and Ontario. For comparative purposes, the random-effects meta-analysis of the primary nested control analysis resulted in a HR: 0.95 (95% CI: 0.81-1.11) when restricted to these three sites (see Figure S39). The fixed-effects meta-analysis resulted in a HR: 0.97 (95% CI: 0.81-1.11).

** Using this approach described by Fine and Gray⁶.

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

Table S8. Sensitivity analysis comparing meta-analytic results of the association between incretin-based drugs and hospitalization for HF among patients with a history of HF comparing random- and fixed-effects models*.

	HR (95% CI)		I ² (%)**
	Random-effects	Fixed-effects	
<u>Nested-case-control analyses:</u>			
Incretin-based drugs	0.86 (0.62-1.19)	1.03 (0.92-1.16)	66.0
Duration of current use			
≤ 365 days	0.68 (0.43-1.06)	1.03 (0.91-1.16)	81.1
366-729 days	1.09 (0.86-1.37)	1.08 (0.88-1.32)	6.5
≥ 730 days	0.95 (0.73-1.22)	0.95 (0.73-1.22)	0.0
DPP-4 Inhibitors	0.87 (0.63-1.21)	1.04 (0.93-1.17)	66.3
GLP-1 analogs	0.75 (0.22-2.51)	1.02 (0.71-1.45)	44.5
History of MI			
Yes	0.92 (0.77-1.10)	0.92 (0.77-1.10)	0.0
No	0.91 (0.64-1.30)	1.08 (0.94-1.24)	38.6
Duration of treated diabetes at index date †			
< 5 years	0.89 (0.60-1.34)	1.07 (0.94-1.21)	68.3
≥ 5 years	0.98 (0.70-1.36)	0.96 (0.74-1.25)	11.0
<u>Sensitivity Analyses</u>			
Metformin-sulfonylureas as reference	0.88 (0.71-1.11)	0.95 (0.85-1.07)	38.0
No grace period (0 days)	0.82 (0.59-1.14)	1.02 (0.90-1.16)	58.2
Varied grace period (90 days)	0.85 (0.62-1.18)	1.04 (0.93-1.16)	70.6
Insulin or TZDs: exclusion or censoring	0.82 (0.54-1.26)	1.07 (0.93-1.23)	69.0
Covariates adjusted at index date	0.97 (0.78-1.22)	1.05 (0.92-1.18)	34.7
Adjust for anti-diabetic drugs ‡	0.82 (0.56-1.20)	1.05 (0.93-1.19)	74.0
Reduced model 1 §	0.86 (0.64-1.17)	1.03 (0.92-1.15)	67.2
Reduced model 2 £	0.79 (0.57-1.11)	0.97 (0.87-1.08)	76.8
<u>Propensity-matched cohort analyses</u> €:			
Maximum follow-up: 2 years	1.00 (0.87-1.16)	1.02 (0.92-1.13)	20.0
Maximum follow-up: 2 years (competing risk) ¥	1.00 (0.87-1.16)	1.02 (0.92-1.13)	18.4
Maximum follow-up: 1 year †	0.95 (0.84-1.08)	0.95 (0.84-1.08)	0.0

Abbreviation: HF, heart failure; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; MI, myocardial infarction; TZDs, thiazolidinediones.

* The reference category for all analyses was current use of oral anti-diabetic combinations unless otherwise specified. Please refer to the detailed description of statistical methods in the Supplementary Appendix for a list of covariates included in the conditional logistic models.

† Alberta did not participate in this analysis as all patients had a duration of treated diabetes of less than five years, preventing the examination of the interaction. Saskatchewan was excluded due to sparse data.

‡ With additional adjustment for the anti-diabetic drugs used in the year prior to study cohort.

[§] In this reduced model, a composite microvascular complications variable was used instead of its individual components, categorical variables were converted to their continuous counterparts where possible, and insulin, oral antidiabetic drug monotherapy, and not currently exposed were collapsed to a single “other exposure” category.

[£] The conditional logistic regression model only included exposure (current exposure to incretin-based drugs, current exposure to oral antidiabetic combinations, and other exposure) and the Deyo version of the Charlson comorbidity index⁴.

[€] Analyses were restricted to the CPRD, MarketScan, and Ontario. For comparative purposes, the random-effects meta-analysis of primary nested control analysis resulted in a HR: 1.01 (95% CI: 0.75-1.34) when restricted to these three sites (see Figure S43). The fixed-effects meta-analysis resulted in a HR: 1.06 (0.94-1.19).

[¥] Using this approach described by Fine and Gray⁶.

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

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